ИНФОРМАЦИЯ ЗА:

Наименование на заболяването

Селективен дефицит на имуноглобулин А (IgA)

Синонимно изписване: Селективен ИгА дефицит

Определение на заболяването

Дефиниция

Селективният дефицит на имуноглобулин А представлява най-честият антитялов първичен имунен дефцит и се храктеризира с изолирани липсващи нива (<0.07 g/L) на имуноглобулин А (IgA) при пациенти на възраст над 4 години. Като парциален ИгА дефицит се означават състояния, при които има откриваемо ниво на IgA в серума, но то е под две стандартни отклонения от средната стойност за съответната възрастова група.

Епидемилогия

Счита се, че честотата на селективния ИгА дефицит варира значително между популациите и е значително по-чест при Кавказката раса. Честота варира от 1:150 до 1:18500 в проучванията от различни страни. Честотата на селективния ИгА дефицит е значително по-висока при пациенти с глутенова ентеропатия и захарен диабет тип I. Мъжкият пол е по-често засегнат от женския.

Етиология

Генетичните основи на селективния ИгА дефицит не са напълно разкрити. Той често се съобщава в асоциасия с различни цитогенетични аберации като анеуплоидии на хромозоми 4p, 8, 21, 22, делеции на 17p11.2 и 22q11.2. В последните 10 години големи проучвания показаха асоциация с полиморфизми с повече от 10 не-HLA локуса като *CLEC16A*, *CTLA4*, *ICOS*, *AICDA*, *TNFAIP3*, *PVT1*, *FAS*, *IL6*, *IL10*, *CDH23* и *TM7SF3*, но до този момент механизмът на тези полиморфизми върху развитието на ИгА дефицит не е изяснен.

Патогенеза

От имунологична гледна точка селективният ИгА дефицит може да е свързан с фундаментален дефект в изотипното превключване на имуноглобулиновите гени, терминалната диференциация на IgA+ плазмабластите в секретиращи плазмоцити или в дългосрочната преживяемост на последните. Неясна остава причината за голямата честота на асимптоматични лица с дефицита.

Клинична картина

Счита се, че около от 85-90% от лицата със селективен ИгА дефицит са асимптомни. Основаната изява на дефицита са повтарящи се синопулмонални инфекции, причинявани най-често от *Str. pneumoniae* и *H. influenzae*. Пациентите със съпътстващ IgG2 дефицит са с по-голям риск от развитие на хронични инфекции и бронхиектазии. Характерни са и чести изяви от страна на гастро-интестиналния тракт като малабсорбция, лактозна непоносимост, глутенова ентеропатия, болест на Крон, интестинална лимфоидна хиперплазия и малигнена трансформация. Различни видове алергични реакции могат да се диагностицират при 50-60% от пациентите, като са по-чести в детска възраст. Най-чести са бронхиалната астма, атопичния дерматит и хранителните алергии. При възрастни пациенти зачестява клиничната изява на заболяването с автоимунни реакции. Най-честите автоимунни заболявания са имунната тромбоцитопения, автоимунната хемолитична анемия, ювенилния хроничен артрит, тиреоидит и системен лупус еритематозус. Някои пациенти развиват анти-ИгА антитела от клас ИгЕ, които могат да отключат тежки реакции на свръхчувствителност при трансфузии на кръвни продукти. В много редки случаи се съобщава развитие на солидни тумори и хематологични неоплазии особено при пациенти в напреднала възраст.

Лечение

Основата на терапевтичното поведение при селективен ИгА дефицит е лечение на свързаните патологични състояния. При склонност за чести инфекции е препоръчително приложението на антибиотици ежедневно или интермитентно. При съчетаване с дефицит на други субкласове имуноглобулини особено благоприятен ефект има интермитентното прилжоение на имуноглобулинови

препарати. В тези случаи е необходимо пациентите да бъдат изследвани за наличие на анти-ИгА антитела поради риска от тежки анафилактични реакции.

Първична профилактика

Поради съобщаването на случаи на фамилно клъстериране на заболяването при всички пациенти се препоръчва насочено изследване за серумни нива на имуноглобулини при родственици от първа линия, особено при положителна анамнеза за инфекциозни и автоимунни или алергични заболявания. Препоръчва се периодичното изследването на всички пациенти за наличие на анти-ИгА антитела. Препоръчва се носенето на обозначителни знаци от такива пациенти с цел минимизиране на риска от алергични реакции при необходимост от хемотрансфузии по спешност. При планови трансфузии е препоръчително използване на промити еритроцити по възможност от пациент с ИгА дефицит.

Четирицифрен код на заболяването по МКБ-10 (ако такъв е наличен)

D80.2

Код на заболяването по **Orpha code**

ORPHA: 69127

Епидемиологични данни за заболяването в Република България

По данни на националния регистър на пациенти с първични имунни дефицити, функциониращ на територията на УМБАЛ ”Александровска”, до 2016 г. не е вписани 14 пациента със селективен ИгА дефицит. Този брой е значително по-нисък от реалния очакван въз основа на данните за честота на дефицита в Кавказката популация.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Наумова, Е., et al. "Регистър на първичните имунни дефицити в България и създаване на експертни центрове." Социална медицина 1.1 (2016): 22-23.

Стоименов, А., et al. Автоимунни цитопении при възрастни пациенти с първични имунни дефицити: два „типични случая”. Девета национална конференция за редки болести и лекарства сираци, 31 август – 1 септември 2018 г., Пловдив, България.

Епидемиологични данни за заболяването в Европейския съюз

Счита се, че в повечето Европейски страни честота варира от 1:200 до 1:1000 души от общата популация. При население от 7 млн. и пенетрантност от 15%, това би означавало наличие на около 1000-5000 случая у нас, които очевидно остават неразпознати поради неспецифичната клинична картина и ниската изпозлваемост на имунологични изследвания в българската клинична практика. Може да се очаква, че при адекватно лечение на съпътстващите инфекциозни, автоимунни и алергични прояви на заболяването качеството на живот на засегнатите пациенти е близко до това на незасеганата популация. Едно голямо ретроспективно проучване от Швеция обаче показва повишен риск от смърт при пациенти с ИгА дефицит през първите 10 години след диагнозата.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

Yel, Leman. "Selective IgA deficiency." Journal of clinical immunology 30.1 (2010): 10-16.

Yazdani, R., et al. "Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management." Scandinavian journal of immunology 85.1 (2017): 3-12.

Ludvigsson, Jonas F., M. Neovius, and L. Hammarström. "IgA deficiency & mortality: a population-based cohort study." Journal of clinical immunology 33.8 (2013): 1317-1324.

Оценка на съответствието на заболяването с дефиницията за рядко заболяване съгласно **§ 1,** т**. 42** от допълнителните разпоредби на Закона за здравето

Заболяването съответства на определената в Закона за здравето дефиниция за рядко заболяване, а именно разпространение под 5:10 000 души сред населението на ЕС, включително и в България.

Критерии за диагностициране на заболяването

Понастоящем одобрените от Европейското дружество за имунни дефицити (ESID) критерии за диагноза на селективния ИгА дефицит са:

Поне един от следните критерии**:**

- повишена склонност към инфекции
- автоимунни изяви
- засегнат член на семейството

И диагностициране след 4-тата година
И неоткриваем серумен IgA (когато се мери чрез нефелометрия под 0.07 g/L), но но нормални серумни нива на IgG и IgM (измерени поне два пъти)
И изключени вторични причини за хипогамаглобулинемия
И нормален IgG антитялов отговор към всички ваксинации
И Изключен Т-клетъчен дефект

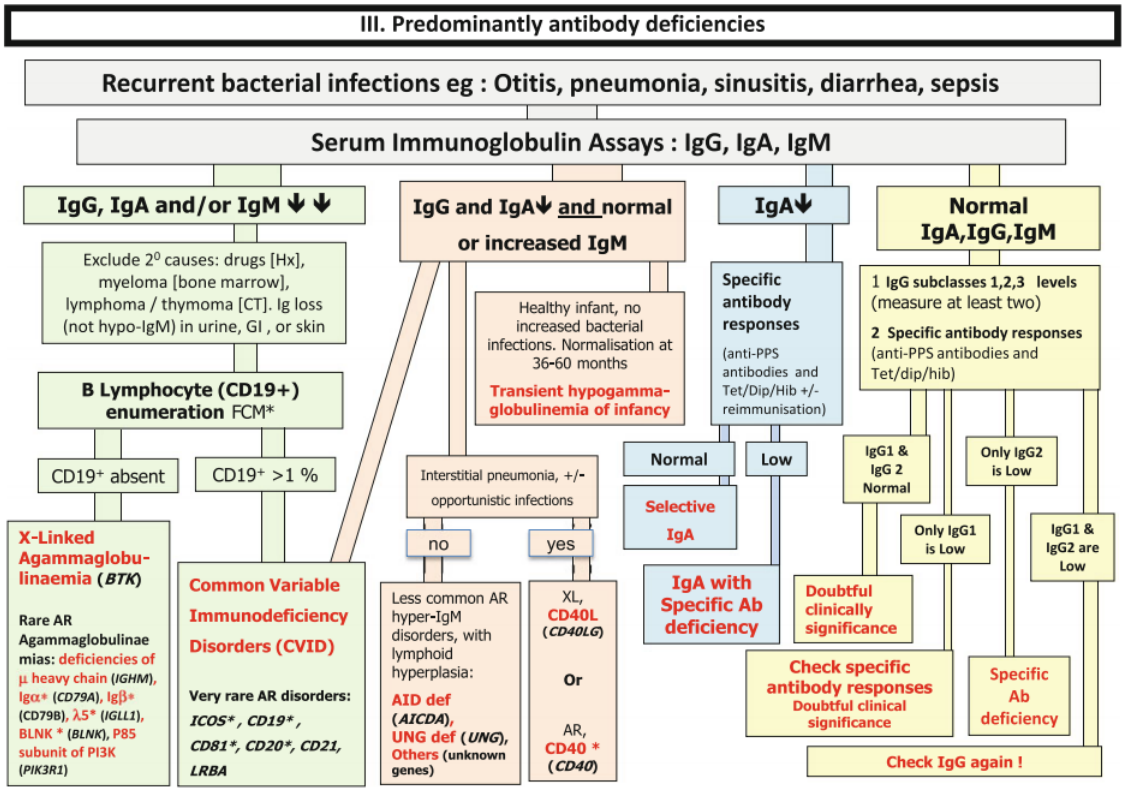
В т.ч. научни публикации от последните пет години и приложена библиографска справка

Edgar, D., and S. Ehl. "ESID Registry-Working definitions for clinical diagnosis of PID, 2014."

Bousfiha AA, Jeddane L, Ailal F, Al Herz W, Conley ME, Cunningham-Rundles C,Etzioni A, Fischer A, Franco JL, Geha RS, Hammarström L, Nonoyama S, Ochs HD, Roifman CM, Seger R, Tang ML, Puck JM, Chapel H, Notarangelo LD, Casanova JL. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013 Aug;33(6):1078-87.

Алгоритми за диагностициране на заболяването

С цел диагностика на първичните имунни дефциити с преоладаващ антитялов дефект при възрастни е препоръчително придържане към алгоритъма, предложен от Международния съюз на имунологичните дружества (IUIS), който е представен на фигурата по-долу. Използвани съкращения Ab: Антитяло; Anti PPS: Анти-пневмококови полизахариди антитела: AR: Автозомно рецесивно унаследяване; CD: Клъстер на диференциация; CVID: Общ вариабилен имунен дефицит; CT: Компютърна томография; Dip: Дифтерия; FCM: При наличие флоуцитометрия; GI: Гастро-интестинални; Hib: Haemophilus influenzae серотип b; Hx: анамнеза; Ig: имуноглобулин; subcl: IgG субклас; Tet: тетанус; XL: Х-свързано унаследяване. Фигурата е от следната публикация: Bousfiha AA, Jeddane L, Ailal F, Al Herz W, Conley ME, Cunningham-Rundles C,Etzioni A, Fischer A, Franco JL, Geha RS, Hammarström L, Nonoyama S, Ochs HD, Roifman CM, Seger R, Tang ML, Puck JM, Chapel H, Notarangelo LD, Casanova JL. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013 Aug;33(6):1078-87.



В т.ч. научни публикации от последните пет години и приложена библиографска справка

Bousfiha AA, Jeddane L, Ailal F, Al Herz W, Conley ME, Cunningham-Rundles C,Etzioni A, Fischer A, Franco JL, Geha RS, Hammarström L, Nonoyama S, Ochs HD, Roifman CM, Seger R, Tang ML, Puck JM, Chapel H, Notarangelo LD, Casanova JL. A phenotypic approach for IUIS PID classification and diagnosis: guidelines for clinicians at the bedside. J Clin Immunol. 2013 Aug;33(6):1078-87.

Алгоритми за лечение на заболяването

Симптоматичните пациенти със селективен ИгА дефицит налагат следната плеяда от терапевтични мерки:

1. Лечение на свързаните с дефицита алергични и автоимунни изяви. По принцип поведението при тези състояния не се отличава от общото поведение при автоимунни и алергични заболявания.
2. Опит с профилактична употреба на антибиотик. При пациенти с рецидивиращи синопулмонални инфекции е препоръчително да се направаи опит за намаляване на честотата и тежестта на тези инфекции с профилактична употреба на антибиотик особено през зиминте месеци. В идеалния случай изборът на антибиотик трябва да се основава на известната чувствителност на изолирания причинител.
3. Приложение на пневмококова ваксина. Препоръчва се във всички слуаи, особено при пациенти със съпътващ дефицит на IgG2 и IgG3.
4. Ако пациентите са приемали профилактично антибиотично лечение и са получили пневмококова ваксина, но все още страдат от рецидивиращи синопулмонални инфекции се препоръчва опит за лечение с интравенозни имуноглобулинови препарати. В повечето клинични насоки се препоръчва ежемесечно приложение на ИгГ преапарати в доза 0.4-0.6 g/kg/месец с цел поддържане на най-ниски серумни нива на ИгГ около 6-8 g/L. По правило приложението на ИгГ препарати трябва да става внимателно с предпочитане на продукти с ниско съдържание на IgA.

В т.ч. научни публикации от последните пет години и приложена библиографска справка

библиографска справка
Yel, Leman. "Selective IgA deficiency." Journal of clinical immunology 30.1 (2010): 10-16. Yazdani, R., et al. "Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management." Scandinavian journal of immunology 85.1 (2017): 3-12.
Алгоритми за проследяване на заболяването
Обучението и периодичното проследяване на пациентите със селективен ИгА дефицит са от основно значение за намаляване на риска от алергични реакции, свързани с трансфузии на кръвни продукти. Препоръчва се пациентите да носят обозначаващи гривни или други лесно откриваеми документи, че страдат от такъв дефицит. Препоръчва се проследяване на асимптомните пациенти на всеки 4-6 месеца. Препоръчва се и епизодично изследване на пациентите за наличие на анти-ИгА антитела. При наличие на такива антитела трабва да се прилагат само кръвни продукти с ниско съдържание на ИгА като промити еритроцити или плазма, получена от пациенти с ИгА дефицит. Има единични съобщения за успешна хипосенсибилизация на пациенти с анти-ИгА антитела с имуноглобулинови препарати.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
Yel, Leman. "Selective IgA deficiency." Journal of clinical immunology 30.1 (2010): 10-16. Yazdani, R., et al. "Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management." Scandinavian journal of immunology 85.1 (2017): 3-12.
Алгоритми за рехабилитация на заболяването
Препоръчва се оказване на психосоциална помощ на засегнатите индивиди чрез точно обяснение на естеството на заболяването, естествения му ход, риска от усложнения, възможностите за терапевтично повлияване и прогнозата. Необходимо е бързото насочване на пациентите към профилни специалисти при данни за специфични медицински проблеми, свързани с основния имунен дефицит.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
Yel, Leman. "Selective IgA deficiency." Journal of clinical immunology 30.1 (2010): 10-16. Yazdani, R., et al. "Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management." Scandinavian journal of immunology 85.1 (2017): 3-12.
Необходими дейности за профилактика на заболяването **(**ако такива са приложими**)**
Поради неясните генетични основи на заболяването не е възможно извършване на генетичен скринг на близки родственици на засегнатите пациенти. Във всеки случаи обаче е необходимо снемане на насочена фамилна анамнеза и по възможност разширено изследване за нива на имуноглобулини и евентуално клетъчен имунен статус.
В т.ч. научни публикации от последните пет години и приложена библиографска справка
Yel, Leman. "Selective IgA deficiency." Journal of clinical immunology 30.1 (2010): 10-16. Yazdani, R., et al. "Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management." Scandinavian journal of immunology 85.1 (2017): 3-12.
Предложения за организация на медицинското обслужване на пациентите и за финансиране на съответните дейности**,** съобразени с действащата в страната нормативна уредба
Лечението на пациенти с доказани ПИД - деца и възрастни, се покрива от НЗОК по Клинична пътека, включена в пакета дейности, гарантиран от бюджета на НЗОК. Според нас е необходима ревизия на звената, които могат да извършват дейността по тази пътека поради хетерогенността на клиничната

ИНФОРМАЦИЯ ЗА:

Наименование на заболяването

Селективен дефицит на имуноглобулин М (IgM)

Синонимно изписване: Селективен ИгМ дефицит

Определение на заболяването

Дефиниция

Селективният дефицит на имуноглобулин М представлява рядка форма на дисгаммаглобулинемия и се храктеризира с изолирани ниски нива на имуноглобулин М (IgM). При този дефицит обикновено се съобщават нива на IgM от 0.4 g/L до напълно неоткриваеми нива. Счита се, че точната дефициниция на дефицита предполага нива на IgM под две стандартни отклонения от средната стойност за съответната възрастова група. Освен това нивата на останалите класове имуноглобулини трябва да са в референтни граници.

Епидемилогия

По настоящем не съществуват точни данни за честотата на заболяването въз основа на широкомащабни епидемиологични проучвания. Единственото по-широко мащабно проучване датира от средата на 1970-те години и съобщава честотата от 0.03%.

Етиология

Съществуват единични съобщения на няколко члена на отделни фамилии с данни за селективен ИгМ дефицит, но до този момент не е установен точен начин на унаследяване на заболяването. Епизодично се съобщават единични случаи с хромозомни аберации, но единствената системно съобщавана аберация е делеция на 22q11.2. Не са установени и гени, свързани с това заболяване.

Патогенеза

От имунологична гледна точка е трудно да бъде обяснено намаленото количество на ИгМ при запазване на нормални нива на останалите класове имуноглобулини. Възможните обяснения на този феномен включват понижена Т-хелперна функция или нарушена терминална диференциация на В-лимфоцити в специфични IgM-секретиращи плазмоцити. Малко вероятно е дефицитът да се дължи на понижена траскрипция на локуса за μ-тежка верига.

Клинична картина

Клиничната изява на този антитялов дефицит може да е разнообразна и включва единични или комбинация от рекурентни инфекции, алергични и автоиммуни заболявания. Без да се представя пълен списък най-честите инфекции са инфекции на горните дихателн пътища, възпаление на средното ухо, сино-пулмонални инфекции (вкл. пневмонии). Алергичните изяви включват алергична астма, алергичен ринит и атопичен дерматит. От автоиммунните изяви на заболяването често се съобщават – системен лупус, ревматоиден артрит, автоимунна хемолитична анемия. В много редки случаи се съобщава развитие на солидни тумори и хематологични неоплазии.

Лечение

Логичното заместително лечение при този дефицит е използване на ИгМ обогатени имуноглобулинови препарати. Към този момент обаче такива липсват. В отделни случаи обаче вливането на конвенционални имуноглобулинови препарати има благоприятен ефект. Необходимо е адекватно третиране на всички инфекциозни и автоимунни прояви на забоялването. Част от пациентите имат също адекватен отговор към поливаленти пневмококови ваксини, което е в полза препоръка на тяхното профилактично приложение с цел намаляване на риска от инвазивни пневмококови инфекции.

Първична профилактика

Поради съобщаването на случаи на фамилно клъстериране на заболяването при всички пациенти се препоръчва насочено изследване за серумни нива на имуноглобулини при родственици от първа линия, особено при положителна анамнеза за инфекциозни и автоимунни заболявания.

картина на ПИД. Лекарствени продукти за Извънболничното заместително лечение на пациентите с наследствени имунофедицити се осигурява по изисквания на НЗОК с протоколи на комисии от специалисти. Предвижда се да се повиши информираността на обществото и медицинската общност и да се повиши вниманието на правителствствени структури и НЗОК към първичните имунни дефицити за съществуването на ПИД с оглед разработване на програма за профилактично изследване на имунната система в различни възрастови периоди свързани със съзряването и остаряването на имунната система. Създаване на клинични процедури за високо-специализирана диагностика на ПИД, с продължителност 12 до 24 часа, и на по-ниска цена от КП. Те биха покрили лабораторните изследвания, необходими за протокола за заместителна терапия в извънболничната помощ, което би намалило разходите за болнична помощ.

Описание на опита с конкретни пациенти със съответното рядко заболяване (ако има такъв)

През м.04,2018 г. в Отделение по хематология на УМБАЛ „Софиямед" беше диагностицирана Пациентката със селективен IgA дефицит, имуннна неутропения и глутенова ентропатия. Та беше изследвана за наличие на анти-IgA антитела, които биха увеличили риска от НЛР при трансфузия на кръвни продукти. Понастоящем Лабораторията по Трансфузионна хематология е единственото място в България, където се извършва такова изследване. Бяха дадени препоръки за по-нататъшно поведение в амбулаторни условия. Пациентката с IgA дефицит беше насочена към специалист-диетолог и специалисти по репродуктивна медицина. Пациентката се проследява активно в Кабинет по имунология и Кабинет по хематология към ДКЦ „Софиямед".

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Selective IgA Deficiency

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Abstract
Introduction Immunoglobulin A (IgA) deficiency is the most common primary immunodeficiency defined as decreased serum level of IgA in the presence of normal levels of other immunoglobulin isotypes. Most individuals with IgA deficiency are asymptomatic and identified coincidentally. However, some patients may present with recurrent infections of the respiratory and gastrointestinal tracts, allergic disorders, and autoimmune manifestations.
IgA and Its Functions Although IgA is the most abundant antibody isotype produced in the body, its functions are not clearly understood. Subclass IgA1 in monomeric form is mainly found in the blood circulation, whereas subclass IgA2 in dimeric form is the dominant immunoglobulin in mucosal secretions. Secretory IgA appears to have prime importance in immune exclusion of pathogenic microorganisms and maintenance of intestinal homeostasis. Despite this critical role, there may be some compensatory mechanisms that would prevent disease manifestations in some IgA-deficient individuals.
Pathogenesis In IgA deficiency, a maturation defect in B cells to produce IgA is commonly observed. Alterations in transmembrane activator and calcium modulator and cyclophilin ligand interactor gene appear to act as disease-modifying mutations in both IgA deficiency and common variable immunodeficiency, two diseases which probably lie in the same spectrum. Certain major histocompatibility complex haplotypes have been associated with susceptibility to IgA deficiency.
Conclusion The genetic basis of IgA deficiency remains to be clarified. Better understanding of the production and function of IgA is essential in elucidating the disease mechanism in IgA deficiency.

Keywords IgA · function · immunodeficiency · pathogenesis

Introduction

Immunoglobulin (Ig) A deficiency (OMIM 137100) is defined as decreased or absent level of serum IgA in the presence of normal serum levels of IgG and IgM in a patient older than 4 years of age, in whom other causes of hypogammaglobulinemia have been excluded [1, 2]. In general, serum IgA level of less than 7 mg/dL (0.07 g/L) is considered as *selective IgA deficiency* since this concentration is the lowest detectable limit established by most of the laboratories. When serum IgA level is higher than 7 mg/dL but two standard deviations below normal for age, the condition may be referred to as *partial IgA deficiency*, which is quite common. The threshold of 4 years of age is used to avoid premature diagnosis of IgA deficiency which may be transient in younger children due to delayed ontogeny of IgA system after birth.

In here, selective IgA deficiency, with an emphasis on functions of IgA and disease pathogenesis, along with its epidemiology, clinical manifestations, disease associations, treatment approaches, and prognosis will be reviewed.

Immunoglobulin A and Its Functions

First described in serum in 1953, IgA is the most abundant antibody isotype produced in the body [3–7]. It is the second dominant isotype in the blood circulation following IgG. It can be found in both monomeric and polymeric forms.

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Circulating IgA is in monomeric form, whereas secretory IgA, in the mucosal secretions of respiratory, intestinal, and genitourinary systems, is dimeric [4, 6, 7]. The monomeric structure of serum IgA has two heavy chains, each consisting of one variable and three constant regions, and two light chains, each of which is made up of one variable and one constant region. In humans, there are two subclasses of IgA: IgA1 and IgA2, constant heavy chains of which are encoded by two separate α1 and α2 genes on chromosome 14 [5–7]. The main structural difference between them is that IgA2 has a shorter hinge region which may render this isotype more resistant to bacterial proteases in the lumen of gastrointestinal or respiratory systems [8].

The function of serum IgA in the systemic immune response has not been clearly understood. Monomeric IgA in the circulation does not fix the classical pathway of the complement. However, it may have a role in activation of phagocytic system by means of the FcRα receptors [5, 7, 9]. It has been proposed that serum IgA binds to FcRα receptor on the monocytes and granulocytes; thereby, immune complexes formed by foreign antigens and IgA are cleared from the circulation by the phagocytic system without activating the complement system and without causing inflammation [10, 11]. Serum IgA may also have a role in controlling the immune system through inhibition of neutrophil chemotaxis by binding to other inhibitory proteins such as α-1-antitrypsin and forming complexes [5, 7].

IgA, which is mostly in dimeric form, is the dominant immunoglobulin in luminal secretions comprising more than two thirds of total IgA production in the body [8, 12, 13]. Being more resistant to proteolytic activity of the bacteria, IgA2 is the main IgA subclass found in secretions, although

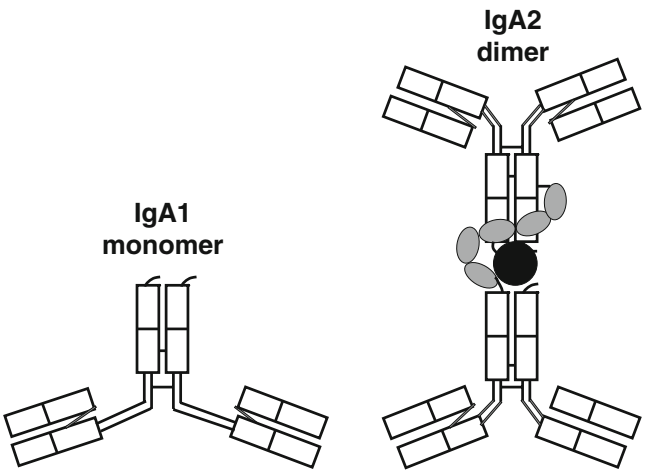

Fig. 1 Models of a monomeric IgA (*left*) and a dimeric secretory IgA (*right*). The monomer contains IgA1 subclass, whereas the dimer comprises two IgGA2 subclass monomers. The *black circle* denotes the joining (J) chain. The *gray chain of five oval links* indicates the secretory piece. Note the shorter hinge region in IgA2 [8]. Modified from [22]

both IgA subclasses can form dimers by covalent interaction with a joining (J) chain attached to the terminal constant region on the Fc portion. The secretory IgA dimer contains a secretory component which is actually the secreted component of the polymeric immunoglobulin receptor located on the basolateral surface of the mucosal epithelial cell [13, 14] (Fig. 1). More than 95% of secretory IgA is produced locally. In the gastrointestinal system, organized Payer's patches or isolated lymphoid follicles as well as nonorganized lamina propria can be sites for local IgA production by T cell-dependent as well as T cell-independent mechanisms [15–17]. Intestinal epithelial cells, dendritic cells, and local stromal cells may be contributing to T cell-independent production of IgA locally by secreting thymic stromal lymphopoietin, interleukin (IL)-6, interleukin-10, tumor necrosis factor-alpha, transforming growth factor beta (TGF-β1), B-cell activating factor (BAFF), and a proliferation-inducing ligand (APRIL) [16].

Mucosal membranes in the body cover an approximate area of 200–400 m^2 harboring an estimate of 15,000–36,000 species and 1,800 genera of microbiota [18–21]. Thus, the total number of prokaryotic cells exceeds the total number of eukaryotic cells in the body. Bacteria endogenous to the intestinal tract, oral cavity, and respiratory and genital tracts are coated with secretory IgA. As a result, the epithelial adherence and penetration of bacteria are limited, and the bacteria are confined to the mucosal surfaces [20]. The IgA coating of bacteria is traditionally considered to be through adaptive immunity by Fab-mediated antigen-specific binding. Recently, it has been proposed that there is a link between the specific antibody-dependent protection and the innate glycan-mediated mucosal immunity by means of *N*- and *O*-glycans of secretory IgA. It is likely that glycan-mediated interactions in concert with Fab-mediated polyreactivity enforce protective functions of secretory IgA [19, 20, 22, 23]. Despite this critical role of secretory IgA, surprisingly, some individuals with selective IgA deficiency are asymptomatic. The diagnosis of IgA deficiency depends on the measurement of IgA concentration in serum. Secretory IgA level is not determined; therefore, it is possible that the individuals diagnosed with selective IgA deficiency may still have some IgA in the mucosal systems enough to provide some protective functions. In addition, in most IgA-deficient patients, seemingly as a compensatory mechanism, production of secretory IgM is increased [24, 25]. IgA and IgM have evolutionary, structural, and functional similarities: homologies between the primary constant chain domains and the tail pieces, presence of a J chain in both, formation of polymers, ability to bind the basolateral polymeric Ig receptor on mucosal epithelial cell, and thereby forming secretory immunoglobulin molecule that contains the epithelial secretory component. The glycan moieties are

also similar in IgA and IgM molecules [26–28]. However, there are also some IgA-deficient patients who do not exhibit compensatory increase in secretory IgM [29].

Most of the commensal bacteria are located in the gastrointestinal tract [15, 16]. Therefore, maintenance of intestinal homeostasis is of prime importance. This homeostasis is achieved by means of immune defense mechanisms, in which secretory IgA has a central role. Growing body of evidence suggests that protective role of secretory IgA in the gastrointestinal system is not only through immune exclusion of bacteria [16–20]. In mice, it has been shown that secretory IgA is also critical in regulating bacterial communities of the intestinal lumen. Excessive expansion of anaerobic bacteria in the entire proximal intestinal system due to lack of secretory IgA has been reported in activation-induced cytidine deaminase knockout mice [30]. Similar aberrant anaerobic expansion is also observed in other mice with IgA deficiency, e.g., RAG2 −/−, SCID mice [31, 32]. This type of change in the intestinal microbial ecology may cause activation of mucosal immune cells including intraepithelial lymphocytes, cells of the isolated lymphoid follicles, Peyer's patches, and mesenteric lymph nodes. In addition, this activation status may become systemic and involve lymphocytes of all germinal centers and lymphoid tissues. Secretory IgA may also play a role in creating a noninflammatory host–microbial relationship as a consequence of its inability to fix the complement and the lack of proinflammatory IgA receptors on the intestinal macrophages.

Pathogenesis of IgA Deficiency

In IgA-deficient patients, the common finding is a maturation defect in B cells to produce IgA [6, 33]. The defect appears to involve the stem cells since IgA deficiency can be transferred by bone marrow transplantation [34]. The constant $\alpha 1$ and $\alpha 2$ genes are generally normal except for rarely described cases of heavy chain gene deletions involving various segments on chromosome 14 [35]. This may be the case in sporadic IgA-deficient patients who have associated IgG2, IgG4, and IgE deficiencies [36–38]. In IgA deficiency, B cells express IgA; however, they are of immature phenotype with the coexpression of IgM and IgD, and they cannot fully develop into IgA-secreting plasma cells [39, 40]. An intrinsic B cell defect, T helper cell dysfunction, and suppressor T cells have all been reported in IgA deficiency. Abnormalities in the cytokine network such as lack of IL-4, IL-6, IL-7, IL-10, TGF-β, and most recently IL-21 have also been proposed to play a role in IgA deficiency [6, 41–43]. It is interesting that IL-21 stimulation has been shown to induce class switch recombination to IgG and IgA and differentiation of IgA and IG secreting plasma cells with restoration of immunoglobulin production *ex vivo* in patients with IgA deficiency and common variable immunodeficiency (CVID) [43].

There is a not well-defined genetic susceptibility in IgA deficiency. The pedigrees of IgA-deficient individuals show familial clustering with no distinct Mendelian inheritance pattern. Autosomal recessive, autosomal dominant, and sporadic transmission patterns have all been observed [44]. In view of the variation in the inheritance patterns and the lack of an identified primary genetic defect, it is likely that IgA deficiency represents a heterogeneous group of genetic abnormalities such as CVID. Mutations in transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI, TNFRSF13B) have been found both in a subset of patients with IgA deficiency or CVID [45]. TACI, B-cell surface ligand for BAFF and APRIL, has a role in isotype switching in B cells. The same TACI mutation may be present in individuals with either IgA deficiency or CVID in the same family. However, it is controversial whether TACI mutations have a cause–effect relationship with IgA deficiency or CVID [46, 47]. Recently, a shared cytotoxic T lymphocyte-associated protein-4-inducible costimulator risk locus in IgA deficiency and CVID has been defined [48]. It is also known that IgA deficiency may progress to CVID, supporting the notion that IgA deficiency and CVID lie in the spectrum of the same disease [49, 50].

Associations between IgA deficiency and certain major histocompatibility complex (MHC) class I, II, and III haplotypes have been proposed [6, 51–54]. In IgA deficiency and type 1 diabetes mellitus, HLA-B8 frequency was found to be increased in earlier studies. HLA-B8 frequency was also higher in IgA deficiency and autoimmune disorders. However, these findings may be secondary to the presence of diabetes mellitus or autoimmune disorders rather than IgA deficiency itself. In another study in IgA-deficient individuals, HLA B8 allele was not related to history of autoimmunity; however, IgA-deficient patients who had HLA B8 were found to have significantly higher pneumococcal vaccination responses [55]. A recent study questioning the frequently implied higher risk for IgA deficiency with the HLA8 DR3 haplotype has shown that IgA deficiency is not associated with a distinct haplotype; rather, the risk is conferred by the common extended MHC haplotype HLA A1, B8, DR3, and DQ2 (the 8.1 haplotype) acting in a multiplicative manner [56]. An amino acid substitution at position 57 of the HLA-DQ beta chain gene has also been associated with susceptibility to IgA deficiency [57].

Epidemiology

Selective IgA deficiency is considered as the most common primary immunodeficiency. The worldwide incidence

varies depending on the ethnic background: 1:143 in the Arabian peninsula [58], 1:163 in Spain [59], 1:252 in Nigeria [60], 1:875 in England [61], and 1:965 in Brazil [62]. The incidence is lower among Asian populations, e.g., from 1:2,600 to 1:5,300 in China [63] and from 1:14,840 to 1:18,500 in Japan [64]. In general, IgA deficiency is more common in Caucasians. In the USA, the frequency is estimated to be from 1:223 to 1:1,000 in community studies and from 1:333 to 1:3,000 among healthy blood donors [6]. These numbers may in fact be higher because some individuals with IgA deficiency are asymptomatic, and there is no established routine screening program for IgA deficiency. The variation in incidence may also arise from the fact that the definition of selective IgA deficiency may differ in each study or registry.

Clinical Manifestations

There is a wide spectrum of clinical findings in IgA deficiency. Patients with IgA deficiency may be identified among blood bank donors, without any clinical findings [6]. In fact, 85–90% of IgA-deficient individuals are asymptomatic. This high percentage is interesting and still remains a puzzle to be solved since IgA is such a significant immunoglobulin in immune defense. Some patients with IgA deficiency have a tendency to develop recurrent sinopulmonary infections, gastrointestinal infections and disorders, allergies, autoimmune conditions, and malignancies.

Recurrent Sinopulmonary Infections Infections of the respiratory system are the most common findings in individuals with IgA deficiency [6, 55, 65]. These infections are mostly due to bacteria, e.g., *Haemophilus influenzae* and *Streptococcus pneumoniae*. Some patients may develop end organ damage such as bronchiectasis secondary to recurring or chronic infections [66]. Patients with associated antibody deficiency such as IgG2 subclass deficiency have a higher chance of having more severe infections and complications.

Gastrointestinal Infections/Disorders IgA-deficient individuals have a tendency to develop infections and disorders of the gastrointestinal tract [6, 44, 55]. Giardiasis, malabsorption, lactose intolerance, celiac disease, ulcerative colitis, nodular lymphoid hyperplasia, and malign proliferation are among the associated diseases. Since the protective barrier of the gastrointestinal system is impaired in IgA deficiency, protozoa such as *Giardia lamblia* can adhere to the epithelium, proliferate, and cause infection [67]. Malabsorption may ensue secondary to structural damage to the intestinal villi. Even in the absence of infection, some molecules may enter the subepidermal and submucosal tissue because of the impaired mucosal clearance of macromolecules and proteins. This process may facilitate antibody production against certain antigens and intolerance to certain foods [68]. For instance, patients with IgA deficiency have a higher chance of developing celiac disease [69]. Patients with IgA deficiency are not expected to develop IgA isotype antibodies against gliadin, tissue transglutaminase, or endomysium; however, they may have IgG isotype antibodies against those antigens. Inflammatory bowel diseases, mostly ulcerative colitis, have also been reported in association with selective IgA deficiency [6, 55, 70, 71].

Allergic Disorders Allergic disorders appear to be common in patients with IgA deficiency [6, 55, 65]. The reported frequency of allergies varies according to the definitions of both IgA deficiency and allergy and also by the evaluation methods. In an earlier study, atopy was reported in 58% of pediatric and adult patients with IgA deficiency [72]. However, in a later study that surveyed 127 IgA-deficient patients between ages of 2 and 67 years, 13% of patients, a figure which was probably not higher than in the general population, was noted to have a history of allergy and asthma [55]. History of allergy was more common among younger patients (median age 10.5 years). In 126 Brazilian children and adolescents with IgA deficiency, 48% had respiratory allergies and atopic dermatitis [70]. In a recent prospective Swedish study in children, IgA-deficient patients were found to have an increased risk of pseudocroup at year 1 and parentally reported food hypersensitivity at year 4, both of which were possibly not IgE-mediated, as compared to children with normal serum levels of IgA [65]. In a more recent report, in which allergy status was determined more reliably by clinical presentation and skin prick testing using 14 common standard allergens, allergic manifestations including asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, urticaria, drug allergy, and food allergy were noted in 84% of patients (age range 4–32 years) with selective IgA deficiency [71]. In 40.5% of the patients, allergic manifestations were the presenting symptoms. It is thought that 25% of patients with IgA deficiency are identified during evaluation for allergic disorders [6].

Autoimmunity Autoimmune diseases are among the most important clinical manifestations in IgA deficiency [6, 55, 70]. Autoantibodies, such as antibodies against sulfatide, Jo-1, cardiolipin, phosphatidylserine, and collagen can be detected in IgA-deficient patients even if overt clinical disease is not the case [73]. It has been long known that several autoimmune disorders may occur in association with IgA deficiency. In a 2004 study, the second most common association with IgA deficiency after recurrent infections was autoimmunity (28%) [55]. Autoimmunity was more prevalent in adults (median age 29 years) and in

females (24 autoimmune conditions in females versus 14 in males in a total of 34 subjects). The most common autoimmune condition was idiopathic thrombocytopenic purpura followed by hemolytic anemia, juvenile rheumatoid arthritis, thyroiditis, systemic lupus erythematosus, and presence of various autoantibodies. In a younger population, autoimmune disorders, i.e., thyroid disease, arthropathy, celiac disease, anemia, and systemic lupus erythematosus, were detected in 19% of patients. This figure varies from 20% to 30% based on the age range of studied populations [71, 74]. In addition, autoimmune conditions were found to be higher among relatives of IgA-deficient patients. Of the first-degree relatives of IgA-deficient patients, 10% had autoimmunity compared to an estimate of 5% in the general population.

IgA-deficient patients may develop anti-IgA antibodies which have a potential to cause anaphylactic reactions upon transfusion of any blood product, such as red blood cells or platelets, which contains trace amounts of IgA [75, 76]. The anti-IgA antibody capable of causing a type I hypersensitivity reaction would be of IgE isotype. Therefore, testing for the IgE isotype antibodies against IgA would be meaningful in determining the possibility of a blood transfusion reaction in an IgA-deficient patient. However, this testing is not readily available in most of the laboratories. Instead, IgG anti-IgA antibodies may be measured as a screening tool.

Malignancy The association of IgA deficiency and malignancies have been reported in sporadic cases, particularly at older ages. Those are usually of lymphoid and gastrointestinal origins [55, 77].

Laboratory Evaluation

IgA deficiency should be a consideration in a patient with recurrent respiratory and gastrointestinal infections, allergies, and autoimmune disorders [1, 2]. Immunologic evaluation for IgA deficiency is also warranted in case of anaphylaxis secondary to a blood product transfusion, celiac disease, and a family history of IgA deficiency and/or CVID. It would be prudent to take into account the medications that may cause decreased serum levels of IgA in the patient. Evaluation of a suspected IgA deficiency would generally include a complete blood count with differential, quantitative serum immunoglobulin levels, serum IgG subclasses, specific antibody response to protein and polysaccharide antigens, and lymphocyte subsets. In addition, pertinent laboratory testing for the associated conditions, e.g., recurrent infections, allergies, or celiac disease, should be performed. Celiac disease screening should include IgG isotype antibodies against gliadin and tissue transglutaminase since IgA isotype antibodies may not be detected because of the IgA deficiency.

Management

IgA-deficient patients who are diagnosed coincidentally and/or who do not have any symptoms do not need any treatment. However, awareness and education are of prime importance, particularly to prevent a potential anaphylactic reaction secondary to blood transfusion. In this regard, patients with selective IgA deficiency should be recommended to wear a medical alert bracelet. In case of a blood transfusion requirement, the patient, ideally, should be screened for anti-IgA antibodies. The blood product should be prepared from an IgA-deficient individual, or saline-washed red blood cells should be the choice. All blood products should be given with caution, and the staff should be prepared to treat a potential anaphylactic reaction.

In IgA deficiency, the mainstay of treatment is the treatment of associated diseases. If the patient experiences recurrent infections, daily prophylactic antibiotics on a continuous or seasonal intermittent basis may be beneficial. In case of associated IgG subclass deficiency and/or specific antibody deficiency, immunoglobulin treatment via venous or subcutaneous route with a product that contains minimal IgA may be given. Standard treatment approach is entertained in case of an associated allergic disorder or autoimmune condition.

Prognosis

The prognosis is good in patients with IgA deficiency if it is not associated with a significant disease. IgA deficiency in children may resolve over time. However, it is also known that IgA deficiency may progress into CVID, which has a less favorable outcome. Therefore, a patient with IgA deficiency, once identified, would deserve a regular follow-up of clinical and immunological findings.

In summary, although IgA deficiency is the most common primary immunodeficiency recognized for almost a half century, its genetic basis remains to be defined, and the cellular and molecular mechanisms involved in IgA physiology and functions as well as in disease pathogenesis need to be further elucidated. Molecular mechanisms of physiological and pathological actions are discussed in the accompanying review by Dr. Renato Monteiro.

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РЕГИСТЪР НА ПЪРВИЧНИТЕ ИМУННИ ДЕФИЦИТИ В БЪЛГАРИЯ И СЪЗДАВАНЕ НА ЕКСПЕРТНИ ЦЕНТРОВЕ

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REGISTER OF PRIMARY IMMUNE DEFICIENCIES IN BULGARIA AND PROMOTION OF EXPERT CENTERS

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Резюме. *Първичните имунни дефицити (ПИД) са редки вродени генетично-обусловени заболявания. През последните 10 г. Българската асоциация по клинична имунология (БАКИ) създаде Регистър на тези заболявания, разработи алгоритми за тяхната диагноза и лечение, започна създаването на Експертни центрове по този проблем.*

Summary. *Primary immune deficiencies (PID) are rare diseases with genetic etiology. During the last 10 years the Bulgarian association of clinical immunology (BACI) developed a Register of these diseases, algorhythms for their diagnosis and treatment and initiated the development of Expert centers for this problem.*

Key words: Primary immune deficiencies, register, expert centers

Една от главните задачи на Българската Асоциация по клинична имунология (БАКИ) от самото ѝ основаване през 2005 г. е да повиши вниманието на медицинските специалисти (общопрактикуващи лекари, хематолози, педиатри, клинични имунолози, отоларинголози, алерголози, генетици), широката общественост, правителствените структури, пациентските организации и НЗОК към първичните имунни дефицити (ПИД). Основна характеристика на тези вродени генетични заболявания е наличието на дефекти в имунната система, вследствие на което се наблюдават чести, рецидивиращи, хронични инфекции, автоимунни и онкологични заболявания, а при наследствения ангиоедем (НАЕ) – отоци в различни части на тялото, които нямат алергична или автоимунна генеза.

Исторически данни

Първият случай на ПИД в България (20 годишен мъж с над 50 пневмонии) е съобщен от пловдивския педиатър – проф. Вапцаров през 1965 г. Състоянието е описано като дисгамаглобулинемия с липса на серумни ИгА и ИгМ при намалени ИгГ.

Първото наблюдение на наследствен ангиоедем (НАЕ) в България е направено от проф. Б. Божков, проф. П. Кирчев и д-р И. Владимиров през 1973 г. и е представено на II национален конгрес по оториноларингология в Пловдив през 1975 г. [1, 2].

Изследването на плазмената концентрация и функционалната активност на С1-инхибитора е въведено в България от проф. Марта Балева и доц. Красимир Николов през 1981 г., което позволи фенотипизацията на болните от НАЕ. Повечето от изследваните пациенти са с количествен дефицит на С1-инхибитора (НАЕ I тип) и малка част от пациентите с качествен дефицит на С1-инхибитора (НАЕ II тип).

Към 1993 г. са описани 72 фамилии с 1238 члена, 283 от които болни от НАЕ [3]. Извършени са имунологични и генетични проучвания на болните с НАЕ от проф. Б. Божков, проф. М. Балева, проф. И. Кременски, проф. В. Ганев, доц. А. Савов, доц. К. Николов, д-р М. Угърчински и доц. М. Стаевска в МУ – София [4, 5, 6, 7, 12].

През 1997 г. е диагностициран първият случай у нас с общ вариабилен имунен дефицит (Common variable immunodeficiency-CVID) от проф. Е. Наумова при 51-годишна жена с хипогамаглобулинемия, чести синопулмонарни инфекции, гастроинтестинална симптоматика и хепатоспленомегалия.

През 2005 г. България се включва в т.нар. J project за ПИД, координиран от проф. Ласло Мароди от Дебрецен, Унгария.

БАКИ съвместно с други организации е била домакин на четири работни срещи по проекта, проведени в София, Цигов чарк, Слънчев бряг, Златни пясъци. Гост-лектори бяха проф. Л. Мароди от Унгария, проф К. Варнац от Германия и д-р К. Пикард от Франция.

Активността на БАКИ относно ПИД е свързана и с участията на българските имунолози в инициативите на Института по редки болести в Пловдив. Включването чрез тази организация на пловдивски имунолози и специалисти по редки болести в работната мрежа за НАЕ (HAENETWORK project) през периода 2005-2008 г., позволи добри професионални контакти с проф. Хенриета Фаркас от Унгарския център по наследствен ангиоедем при Института „Земелвайс" в Будапеща.

В рамките на Националните конференции по редки болести в Пловдив през 2009-2015 г. бяха организирани поредица от работни срещи и кръгли маси на БАКИ за ПИД.

През септември 2012 г. на 3-та Национална конференция по редки болести, в Пловдив, се обсъдиха възможностите за изграждане на Експертни центрове за ПИД в страната.

Създадоха се и пациентските организации за НАЕ (с председател Йорданка Павлова) и Общ вариабилен имунен дефицит (с председател отец Стоил Лазаров), чийто представители участват активно във всички мероприятия, свързани с ПИД.

През 2010 г. се създаде Национална работна група за ПИД и се разработиха алгоритми за диагностика и лечение на основните ПИД.

Създаде се и се актуализира периодично Национален регистър за ПИД (***Таблица 1***).

Лечението на пациенти с доказани ПИД – деца и възрастни, се финансира чрез НЗОК по Клинична пътека 306 (от 2016 г. – Клинична пътека 110), разработена от група български имунолози и педиатри от София и Пловдив и утвърдена с Постановление № 5 на МЗ от 10.01. 2013 г. [8].

Извънболничното заместително лечение на пациентите с наследствени имунодефицити се осигурява по изисквания на НЗОК с протоколи на комисии от специалисти. Общо по клиничната пътека и в извънболничната помощ са обхванати 40 пациента.

Изградени са два експертни центъра за ПИД в УМБАЛ „Александровска" и УМБАЛ „Св. Георги" – Пловдив [9]. Експертният център в УМБАЛ „Александровска" – София е част от националната референтна мрежа на центровете за редки болести и е утвърден с решение на Министерство на здравеопазването.

Регулярно се публикуват данни за редки клинични наблюдения и лечение на ПИД [10-15, 17]

Въведе се обучение на пациенти и родители за провеждане на терапия със субкутанен гамаглобулин в Клиниката по педиатрия и в Клиниката по клинична имунология – УМБАЛ „Александровска" в София, както и в Клиниката по педиатрия на УМБАЛ „Св. Георги" Пловдив.

Ангажираността на обществото за каузата ПИД се повишава чрез организираните пресконференции в медицинските университети и болниците в София, Пловдив и Плевен всяка година на 29 април и по време на Международна имунологична седмица, посветена на ПИД, която се провежда също в края на м. април.

През 2015 г. в УМБАЛ „Александровска" – София се регистрира Център за обучение на пациенти с ПИД тип „Джефри Моделс" с ръководител проф. д-р Е. Наумова.

През април 2016 г. в почивната база на МУ – Пловдив в Цигов чарк се проведе първото за страната обучение за ПИД на възрастни пациенти с тези заболявания. Специален акцент се постави на приложението на заместителна терапия с интравенозни и субкутанни имуноглобулини. Организатори на съвместната инициатива бяха БАКИ, МУ – Пловдив и Експертният център за ПИД в София.

Таблица 1. *Регистър на пациентите с ПИД в България*

Диагноза	***Брой пациенти – 164***
HAE (Hereditary angioedema)	77
CVID (Common variable immune deficiency)	22
XLA (X-linked agammaglobulinemia)	4
Transient hypogammaglobulinemia	3
Selective IgA deficiency	14
Hypogammaglobulinemia	4
Hyper-IgE syndrome (Job's syndrome)	4
Omenn's syndrome	2
SCID (Severe combined immune deficiency)	2
MHC class II deficiency	1
Predominant T-cell deficiency	1
22q11.2deletion syndrome	5
Ataxia telangiectasia	5
Nijmegen breakage syndrome	3
CGD (Chronic granulomatous disease)	3
LAD (Leucocyte adhesion deficiency)	2
ALPS (Autoimmune lymphoproliferative syndrome)	1
PFAPA syndrome (periodic fevers with aphthous stomatitis, pharyngitis and adenitis)	3
CHARGE синдром	1
Други	7

Предстоящи инициативи

Бъдещите задачи на БАКИ за подобряване на диагностиката и терапията на ПИД са:

- Въвеждане на скрининг програма при новородените (TREC screening) за тежки имунни дефицити (SCID) и Т-клетъчна лимфопения.
- Въвеждане на реимбурсирането на други скъпоструващи медикаменти за заместителна терапия на ПИД – напр. интерферон-гама и GM-CSF.
- Създаване на клинични процедури за високо-специализирана диагностика и лечение на ПИД, с продължителност 12 до 24 часа, и на по-ниска цена от клиничната пътека. Те биха покрили лабораторните изследвания, необходими за протокола за заместителна терапия в извънболничната помощ; проследяването и обучението на пациентите, които реално се извършват в болничната, а не в извънболничната среда. Подобна дейност съществува за пациенти с хемофилии и таласемии.
- Регистриране на експертни центрове за ПИД и създаване на референтна мрежа за ПИД съгласно НАРЕДБА № 16 на МЗ от 30 юли 2014 г. [16].
- Съобразяване с политиката на трансгранично национално сътрудничество според Директива 2011/24/ЕС за правàта на пациентите при трансгранично здравно обслужване.

Заключение

Първичните имунни дефицити са редки заболявания. Досега в България са регистрирани 164 пациента, което означава честота 2/100 000. Като се вземе предвид, че ИгА дефицитът е с честота 1/500, а общият вариабилен имунен дефицит се среща средно 1/30000, може да се направи заключение, че има голям процент недиагностицирани случаи, а следователно и нелекувани. Ето защо е необходимо активно взаимодействие с другите медицински дружества, сдружение на общопрактикуващите лекари, НЗОК, МЗ и други организации с оглед осигуряване на достъп до ранна и адекватна диагноза и лечение на деца и възрастни с първични имунни дефицити.

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Human serum immunoglobulin concentrations: Prevalence of immunoglobulin deficiencies

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Classical antibody deficiency syndromes, such as sex-linked agammaglobulinemia, are rare and relatively homogeneous in presentation. In the present investigation an unselected group of 3,213 individuals from a community health study was examined in an attempt to estimate the prevalence of the commoner and largely unclassified examples of immunoglobulin deficiencies defined by the lower 2.5 per cent of the population. The prevalence of selective IgA deficiency (an isolated absence of IgA) was 0.097 per cent and that for selective IgM deficiency was 0.03 per cent. No isolated absence of IgG was found. In addition to these deficiency syndromes, concentrations of each of the immunoglobulins were found to be highly correlated to each other.

Defective immunologic surveillance as a consequence of immune deficiency is thought to play a central role in the pathogenesis of many diseases.[1] Although immunodeficiencies may be more common than would be expected,[2] interpretation of the comparative frequency of the antibody deficiency syndromes in disease states depends upon a firm knowledge of their prevalence in the general population. In the present study data on immunoglobulin concentrations in 3,213 unselected persons from a single community have been examined for the prevalence of immunoglobulin deficiencies and for interrelationships between immunoglobulin classes. Data on the International Reference Standard have been included so that studies of individuals with specific diseases can be compared to these values in order to determine the significance, if any, of a postulated finding of immunoglobulin deficiency.

MATERIALS AND METHODS

Study group

A total of 3,213 consecutive sera were obtained in a community health study in Tecumseh, Michigan (42° N. latitude, 83° W. longitude) from May, 1968, to April, 1969. All individuals were of the white race. Sera were divided aseptically into aliquots and stored at 4° C.; they

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TABLE I. Means and bounds of the 2.5 per cent extremes of the age-corrected serum immunoglobulin concentration distribution

Immunoglobulin	Males			Females		
	Lower (mg./ml.)	Mean (mg./ml.)	Upper (mg./ml.)	Lower (mg./ml.)	Mean (mg./ml.)	Upper (mg./ml.)
IgA	0.55	1.64	4.86	0.58	1.53	4.05
IgG	6.32	11.17	19.76	6.42	11.45	20.43
IgM	0.23	0.74	2.34	0.32	1.02	3.28

TABLE II. Classification of patterns of serum immunoglobulin concentrations at the 2.5 per cent level distributed by age for males

Serum concentration			Total cases		Frequencies by age group in years (range/mean)					
IgA	IgG	IgM	No.	%	4-16 12	16-32 23	32-40 37	41-46 43	46-56 51	56-87 66
N	L	L	8	0.52	3	1	2	1	1	0
L	N	L	1	0.07	0	0	0	0	1	0
N	N	L	30	1.97	7	3	7	2	7	4
L	L	N	5	0.33	2	0	1	0	0	2
N	L	N	39	2.56	9	4	9	5	5	7
L	N	N	23	1.51	6	7	2	1	3	4
N	N	N	1,341	87.9	218	224	220	233	222	224
H	N	N	20	1.31	2	2	6	4	4	2
N	H	N	20	1.31	6	5	2	1	1	5
H	H	N	2	0.13	1	0	0	1	0	0
N	N	H	32	2.10	0	7	4	5	10	6
H	N	H	2	0.13	0	1	0	1	0	0
N	H	H	3	0.20	0	0	1	0	0	2
Total			1,526		254	254	254	254	254	256

L, low; N, normal; H, high.

were either assayed within a week or frozen at –70° C. until analysis. An additional 921 consecutive sera from the same study were included in estimates of the frequency of selective IgA deficiency.

Preparation of purified immunoglobulins and antisera

IgG was prepared from Cohn Fraction II (American Red Cross, Bethesda, Maryland) by diethylaminoethyl (DEAE) cellulose (Carl Schleicher & Schuell Co., Keen, New Hampshire) chromatography with 0.0175 M phosphate buffer, pH 6.3.[3] IgA was prepared from myeloma sera by starch block electrophoresis in 0.075 M barbital buffer, pH 8.6,[4] and Sephadex G-200 (Pharmacia, Uppsala, Sweden) filtration with 1 M NaCl in 0.1 M Tris-HCl buffer, pH 8.2.[5] IgM was isolated from macroglobulinemic sera by plasmapheresis, euglobulin precipitation,[6] and Sephadex G-200 filtration. Light chains were isolated from urines of patients with myeloma by precipitation with 60 per cent ammonium sulfate at 4° C. followed by gel permeation chromatography on Sephadex G-100. The specificity of the isolated immunoglobulins and light chains was monitored by double diffusion in gel[7] and by immunoelectrophoresis[8] against antisera to each of the immunoglobulins and to whole serum. Antisera prepared in rabbits with specific immunoglobulins emulsified in Freund's complete adjuvant (Difco Laboratories, Detroit, Michigan) were cross-adsorbed with purified immunoglobulins and light chains.

Preparation of standard sera

The purified immunoglobulins were assayed for protein nitrogen by a micro-Kjeldahl procedure,[9] and approximate Svedberg constants were determined by analytical ultracentrifuga-

TABLE III. Classification of patterns of serum immunoglobulin concentrations at the 2.5 per cent level distributed by age for females

Serum concentration			Total cases		Frequencies by age group in years (range/mean)					
IgA	IgG	IgM	No.	%	4-17 12	17-32 24	32-40 36	40-46 43	46-57 51	57-92 67
L	L	L	1	0.06	0	0	0	0	1	0
N	L	L	1	0.06	0	0	1	0	0	0
L	N	L	3	0.18	1	1	0	0	0	1
N	N	L	24	1.42	3	5	3	2	5	6
H	N	L	1	0.06	0	0	1	0	0	0
L	L	N	5	0.30	2	0	1	1	0	1
N	L	N	32	1.90	5	5	5	5	7	5
L	N	N	39	2.31	15	2	4	4	4	10
N	N	N	1,478	88.1	237	249	248	250	251	243
H	N	N	26	1.54	6	6	5	4	3	2
L	H	N	1	0.06	1	0	0	0	0	0
N	H	N	29	1.72	6	6	2	5	4	6
H	H	N	3	0.18	0	0	0	1	1	1
L	N	H	1	0.06	0	0	0	0	1	0
N	N	H	36	2.13	4	7	9	7	4	5
N	H	H	4	0.24	0	0	1	1	0	2
H	H	H	3	0.18	1	0	1	1	0	0
			1,687		281	281	281	281	281	282

L, low; N, normal; H, high.

tion in 0.02 M phosphate, 0.12 M NaCl, pH 7.2, to be $7S°_{20,w}$ for IgG and IgA and $19S°_{20,w}$ for IgM.[10] A set of working standards consisted of 4 dilutions of serum from a healthy donor stored in aliquots at -70° C. Immunoglobulin concentrations in these standards were determined by comparison to the purified immunoglobulin standards and to International Reference Preparation 67/95.[11] International units per milligram of protein were computed for IgG as 10.4, IgA 56.4, and IgM 12.2. Antisera used in this study were compared to two commercially available preparations and produced comparable linear assays.

Quantitation of immunoglobulins in test sera

Immunoassay was performed by a modification of the radial diffusion method,[12] in 0.8 per cent Ionagar No. 2 (Consolidated Laboratory, Chicago Heights, Illinois) in Tris-HCl buffer, $\Gamma = 0.1$, pH 7.2. After incubation of the plates at 4° C. for 18 to 22 hours, a period of time determined experimentally to be within the linear relationship between area of precipitation and concentration of antigen, the perpendicular diameters of the precipitin rings were measured on a micrometer stage of a microscope and averaged. Four dilutions of the standard serum were included on each test plate. The concentration of immunoglobulin was read from a line plotted from the standards which was valid for the following ranges: IgG 3 to 16 mg. per milliliter, IgA 0.5 to 2.5 mg. per milliliter, and IgM 0.3 to 2.0 mg. per milliliter. High and low immunoglobulin concentrations were verified by repeated examination. Sera with low immunoglobulin content were reassayed by the electroimmunodiffusion method of Laurell,[13] which has a lower limit of sensitivity of 0.01 mg. per milliliter. Sera with immunoglobulin concentrations in excess of the highest standard values were diluted so that concentration could be evaluated on the linear portion of the scale.

Reproducibility of radial immunodiffusion

The coefficient of variation for repeated measurements of a standard serum during a 2-year period was computed with the formula $100t_{n-1}$ (S.D./mean) in order to obtain the 95 per cent confidence limits for each assay. These values were ±17 per cent for IgG, ±20 per cent for IgA, and ±27 per cent for IgM. Corresponding values for interplate variation during a single day's experiments were ±10 per cent for IgG, ±13 per cent for IgA, and ±16 for IgM.

TABLE IV. Number of cases with low, normal, or high serum immunoglobulin concentrations for each age-sex group defined by the extreme 2.5 per cent tails of the distribution

Age group (yr.)	IgA			IgG			IgM		
	L	N	H	L	N	H	L	N	H
Males:									
4-16	8	243	3	14	233	7	10	244	0
16-32	7	244	3	5	244	5	4	242	8
32-40	3	245	6	12	239	3	9	240	5
41-46	1	247	6	6	246	2	3	245	6
46-56	4	246	4	6	247	1	9	235	10
56-87	6	248	2	9	240	7	4	244	8
Females:									
4-17	19	255	7	7	266	8	4	272	5
17-32	3	272	6	5	270	6	6	268	7
32-40	5	269	7	7	270	4	5	265	11
40-46	5	270	6	6	267	8	2	270	9
46-57	6	271	4	8	268	5	6	270	5
57-92	12	267	3	6	267	9	7	268	7

L, low; N, normal; H, high.

TABLE V. The range of the "normal" serum immunoglobulin concentrations defined by the central 95 per cent of the distribution for each age-sex group

Age-sex group range (yr.)	IgA range (mg./ml.)	IgG range (mg./ml.)	IgM range (mg./ml.)
Male 4-16	0.30-3.26	5.33-18.92	0.24-1.72
Female 4-17	0.32-3.08	6.10-19.07	0.34-2.69
Male 16-32	0.41-4.60	6.52-19.17	0.27-2.41
Female 17-32	0.57-3.80	6.15-21.88	0.37-3.46
Male 32-40	0.68-4.71	6.22-19.84	0.24-2.58
Female 32-40	0.64-3.91	6.30-20.00	0.34-3.56
Male 41-46	0.72-4.71	6.56-18.80	0.23-2.59
Female 40-46	0.69-3.82	6.46-20.44	0.36-3.37
Male 46-56	0.59-5.76	6.63-19.70	0.23-2.43
Female 46-57	0.68-4.13	6.63-20.09	0.26-3.43
Male 56-87	0.76-5.72	6.65-21.63	0.21-2.27
Female 57-92	0.72-5.15	6.86-20.94	0.28-3.10

Statistical methods

All statistical analyses were performed on $\log_e$ transformed data which represented serum concentrations for IgG, IgA, or IgM expressed as milligrams per milliliter. As logarithmic transformations were not possible for concentrations of 0.00 mg. per milliliter, these undetectable levels were considered to be 0.01 mg. per milliliter for the purposes of this study.

In order to classify the sera according to immunoglobulin concentrations, the $\log_e$ immunoglobulin values for each subject were extrapolated to values corresponding to the age of 40 years by using regression formulas computed on the three immunoglobulin concentrations segregated by sex.[14] The absence of an age effect in the extrapolated data was confirmed by correlation analysis. The data sets were then categorized for each immunoglobulin into low, normal, or high values based upon the ± 1.960 S.D. percentage points which excluded 2.5 per cent of the values at each extreme of the distribution (Table I). The grouped data were then classified into the 27 possible combinations of variations in serum immunoglobulin levels from hypogammaglobulinemia to hypergammaglobulinemia (Tables II and III). The frequency data for each category were further distributed among age groups as described below.

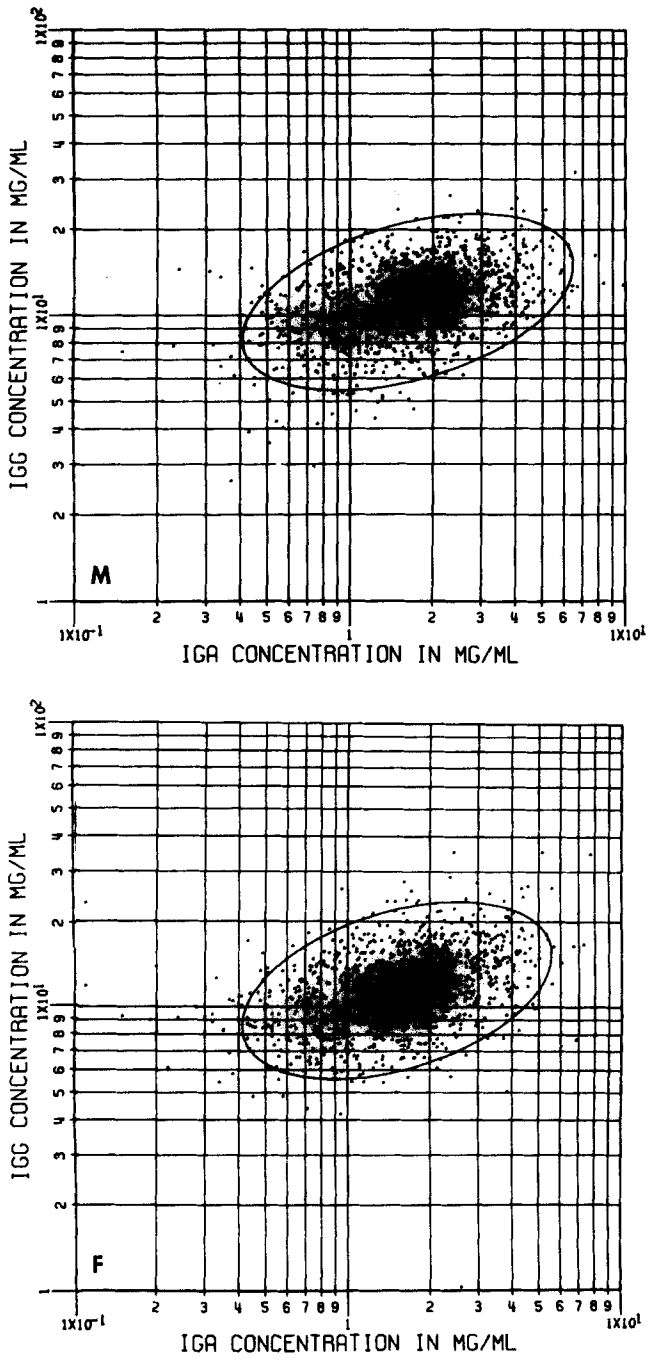

FIG. 1. Correlation plots for IgG and IgA for 1,526 males (**M**) and 1,687 females (**F**). The ellipse describes the 95 per cent confidence limits of the analyses. Correlation coefficients and Z/S values are, respectively, 0.3765 and 15.455 for males and 0.4097 and 17.860 for females.

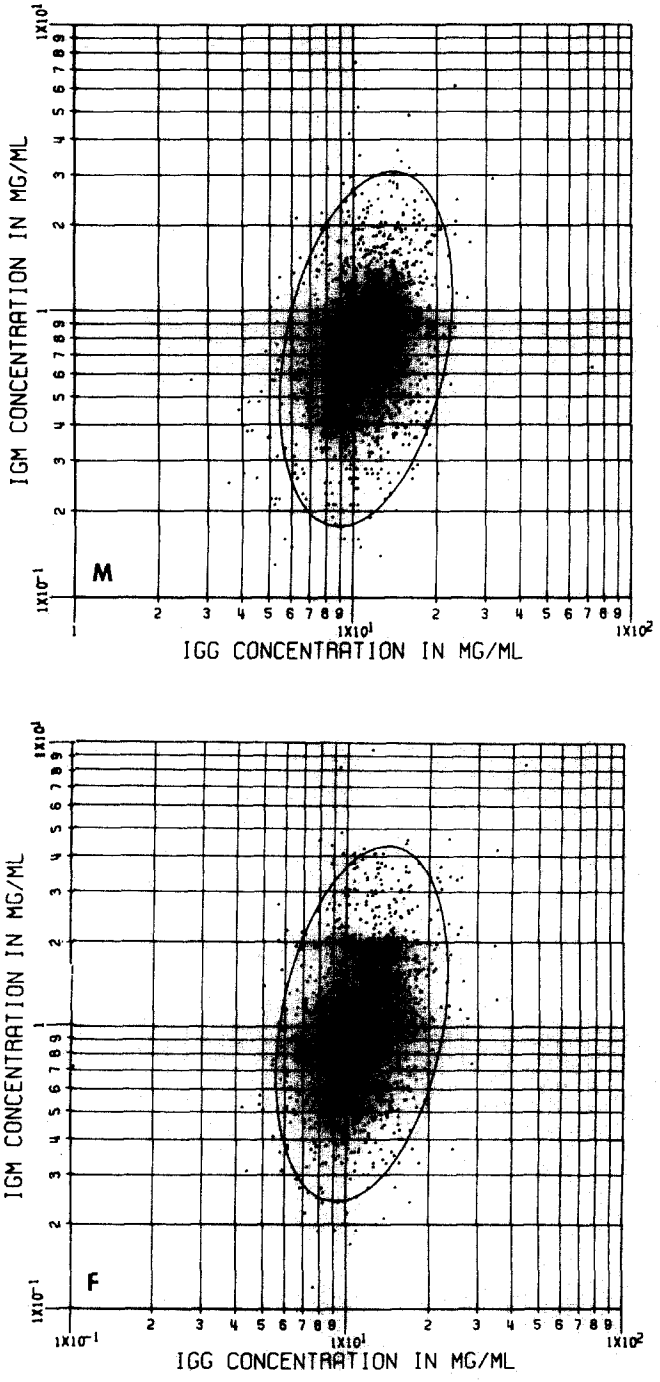

FIG. 2. Correlation plots for IgM and IgG for 1,526 males (**M**) and 1,687 females (**F**). Correlation coefficients and Z/S values are, respectively, 0.3001 and 12.085 for males and 0.2991 and 12.660 for females.

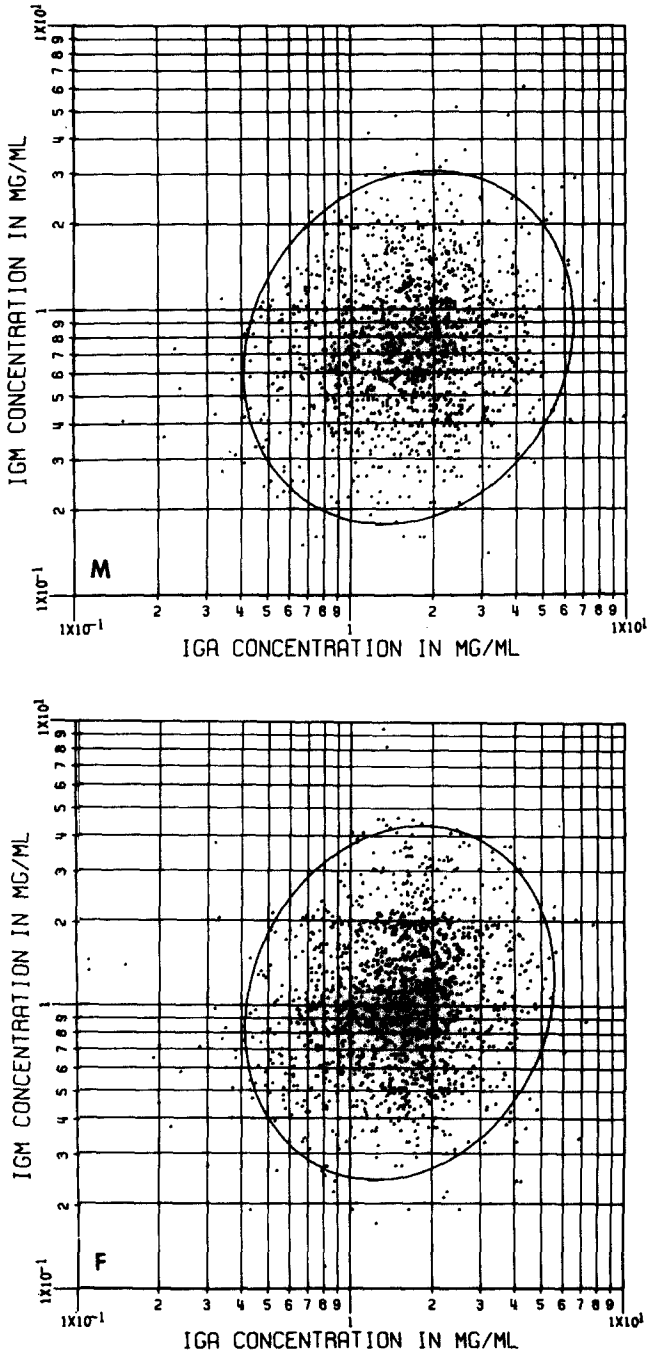

FIG. 3. Correlation plots for IgM and IgA for 1,526 males (**M**) and 1,687 females (**F**). Correlation coefficients and Z/S values are, respectively, 0.1576 and 6.203 for males and 0.1589 and 6.576 for females. The partial correlation coefficient and Z/S value for IgA and IgM with the effect of IgG removed are 0.0243 and 1.394.

In order to evaluate the age effect upon the classification, the age-corrected data set was subdivided by age into six groups of 535 individuals, 254 males and 281 females, except for the last group of 538, which included 256 males and 282 females. Each age-sex group was analyzed separately for low, normal, or high values as described above, using the percentage points computed for the total population. A summary table was constructed and significant departures from the predicted frequencies were tested by a chi-square analysis (Table IV).[15]

To provide clinically useful ranges of normal immunoglobulin levels for the six age groups, however, the original $\log_e$ data were subdivided by age into the above six groups of approximately equal size. For each group, the distribution was characterized, and the percentage points excluding 2.5 per cent of the sample at each extreme were determined. The range of normal values is defined by the limits of the central 95 per cent of the distribution (Table V).

Correlation coefficients among immunoglobulin concentrations were calculated using the complete data set of 3.213 subjects.[14] Partial correlations were computed in order to test pairwise interaction of serum immunoglobulin classes. Similar correlations were computed using data which were within the central 95 per cent of the distribution for all immunoglobulins (2,819 subjects). Determination of significance was based upon standard tests at the 5 per cent level of confidence after converting the correlation coefficient to the variable $Z = \frac{1}{2} \ln (1+r/1-r)$, which is normally distributed with mean zero and standard deviation, $s = \sqrt{1/n-3}$.[14] The ratio of Z to S identifies the percentage point in standard deviation units corresponding to the level of confidence (e.g., 1.960 is equivalent to a p value of 0.025). Contour ellipses for all simple correlations which include 95 per cent of the population were computed (Figs. 1 to 3).

RESULTS

Reference serum immunoglobulin concentrations

Table I lists the means and bounds of the central 95 per cent range for the age-corrected serum immunoglobulin concentrations used to construct the data in Tables II to IV. Table V lists the bounds of the 95 per cent range for non–age-corrected immunoglobulin concentrations derived by analysis of the actual distribution of values for each of the 12 age-sex groups. Although these ranges would not have provided a valid basis for analyzing an age-related effect on hypogammaglobulinemia or hypergammaglobulinemia for the purposes of this paper, they do indicate the approximate values of the "normal" age-sex distribution for each of the three immunoglobulins.

Prevalence of immunoglobulin deficiencies

Twenty-seven combinations of low, normal, or high serum concentrations of IgA, IgG, or IgM taken simultaneously are theoretically possible. Tables II and III list the non-null combinations that were found in the data extrapolated to the age of 40 years. Deficiency of an immunoglobulin's concentration was arbitrarily defined as one that was included in the lower 2.5 per cent of values predicted in this study. Hypergammaglobulinemia was defined in the opposite manner as a concentration that was included in the upper 2.5 per cent of values.

Only 18 of the possible 27 immunoglobulin concentration patterns were found. Of the 27 combinations, 19 represented patterns of immunoglobulin deficiency, e.g., characterized by at least one immunoglobulin whose concentration was less than the limits of normality as defined. Ten such deficient patterns existed for females and six for males. Deficiency of a single immunoglobulin was more common than combined deficiencies. Deficiency of IgG alone was most com-

mon and occurred in 2.21 per cent of subjects, IgA in 1.93 per cent, and IgM in 1.68 per cent. IgG deficiency in any combination occurred in 2.83 per cent of cases, IgA deficiency in 2.46 per cent, and IgM deficiency in 2.15 per cent.

Certain potential immunoglobulin deficiency syndromes were not represented. There were no sera counted in the groups representing low IgA, low IgG, high IgM; low IgA, high IgG, low IgM; low IgA, high IgG, high IgM; normal IgA, low IgG, high IgM; normal IgA, high IgG, low IgM; high IgA, low IgG, low IgM; high IgA, low IgG, normal IgM; high IgA, low IgG, high IgM; and high IgA, high IgG, low IgM.

Hypergammaglobulinemia occurred in 5.7 per cent of the subjects. Increase in concentration of a single immunoglobulin was distinctly more common than increases in more than one immunoglobulin. Discordant combinations of complex patterns containing both high and low values were uncommon. The largest number of sera were found in the (N,N,N) category which represented subjects with normal or average serum immunoglobulin concentrations. For the 2.5 per cent level of confidence, 95 per cent of the sera would be included in the central area of the distribution curve for each immunoglobulin concentration. For the three immunoglobulins taken simultaneously, 85.7 per cent of the total sera would be included and judged as normal (e.g., 0.95^3). The actual frequency found in this study was 87.9 per cent for males and 88.1 per cent for females.

Age of the individuals with immunoglobulin deficiency patterns

Table IV lists the number of low, normal, or high combinations of sera at the 2.5 per cent level of confidence for six age groups. Analysis of these data does not indicate any statistically significant deviation of one group from another for an increased frequency of immunoglobulin deficiency either for the entire group of cases for each immunoglobulin or for only the 2.5 per cent tails. The finding of low IgA values in the youngest and oldest age groups and high IgA values in the middle group approached significance. Similarly, the asymmetry in IgM frequencies for males approached significance.

Prevalence of selective immunoglobulin deficiencies

The prevalence of selective IgA deficiency was 0.097 per cent and that for selective IgM deficiency was 0.03 per cent. Four sera were contained in the initial study of 3,213 subjects that had undetectable levels of an immunoglobulin ($<$ 0.01 mg. per milliliter). These selective deficiencies were verified by re-examining each serum for qualitative abnormalities by immunoelectrophoresis and for an undetectable level of the specific immunoglobulin by double diffusion in gel against monospecific antisera to either IgA or IgM.

Three sera represented selective IgA deficiency and one selective IgM deficiency. Data on these sera are shown in Table VI. Three of these individuals were essentially normal on examination. One subject with undetectable serum IgA had mental retardation and a past history of frequent upper respiratory tract infections. An additional 921 consecutive sera were assayed for IgA. One serum was found with undetectable IgA which was from a 14-year-old boy who had had a history of transient arthritis at the age of 6 years.

TABLE VI. Subjects with selective immunoglobulin deficiencies

Age	Sex	Serum concentrations (mg./ml.) IgG	IgA	IgM	Associated findings
11	M	13.00	< 0.01	0.42	Penicillin reaction
14	M	17.90	< 0.01	0.91	Arthritis at 6 years of age
17	M	7.50	< 0.01	0.23	Retarded; arrested hydrocephalus; drug reaction; frequent sino-pulmonary infections; hepatitis
50	M	18.50	< 0.01	0.46	
56	F	5.80	0.57	< 0.01	

Correlations of serum immunoglobulin concentrations

Figs. 1 to 3 depict correlation plots of the serum immunoglobulin concentrations on the non–age-corrected complete data set. All simple correlation coefficients were highly significant except that between IgA and IgM, which was judged not significant on the basis of a partial correlation. There appeared to be no sex difference detected in these immunoglobulin interrelationships.

Correlation coefficients and Z/S values were also computed for the set which included cases within the central 95 per cent region of all three immunoglobulins (e.g., N,N,N in Tables II and III). Values for males were 0.3629 and 13.829 for IgG and IgA; 0.2331 and 8.637 for IgG and IgM; and 0.0499 and 1.816 for IgA and IgM. The partial correlation coefficients and Z/S values were respectively 0.3617 and 13.780, 0.2310 and 8.557, and –0.0383 and 1.394. Similar values for females were 0.3926 and 15.906, 0.2321 and 9.064, and 0.1144 and 4.405. The partial relationships were 0.3788 and 15.285, 0.2049 and 7.967, and 0.0260 and 0.997.

DISCUSSION

The data summarized in this report are derived from analyses of serum immunoglobulin concentrations in 3,213 subjects, who ranged in age from childhood to late adult life, from a community health study. Racial admixture and large deviations in socioeconomic levels were not important aspects of this population group. These data provide clinically useful parameters for comparison to observations made on patients with specific diseases derived from a population of similar background and characteristics. The method of analysis of immunoglobulin concentration based upon radial diffusion assay is comparable to that in general use in clinical laboratories. Our data have also been related to the World Health Organization's Immunoglobulin Reference Preparation.[17] As a consequence, information from this study can be used by any laboratory whose methods are standardized to a comparable serum.

Immunoglobulin deficiency was defined in this study as failure of an individual to manifest a serum concentration of a specific immunoglobulin greater than a statistically defined value, the 2.5 per cent level of confidence computed from the actual distribution curves of the serum IgA, IgG, and IgM. The immunoglobulin concentrations of each individual were classified into 27 groups based upon serum concentrations. These data provide an estimate of the frequency and kinds of aberrations that can occur and define reference points for

the heterogeneity of immunoglobulin levels in the general population. At the 2.5 per cent level of confidence, ten types of immunoglobulin deficiencies were found in 6.7 per cent of the subjects. Humoral immunoglobulin deficiency was therefore a relatively common event. Selective deficiencies of IgA and IgM were the only clearly defined syndromes. The numbers of subjects classified as normal at this level of confidence compared favorably with the theoretical estimates. These similarities between determined and calculated values attested to the adequacy of the model that was used. Analysis of our data at the 5 per cent level of confidence rejected the possibility that there was an age-related effect in any of the observed deviations from normality. The data did not support the contention that aging was related to the development of hypogammaglobulinemia.

Buckley and Dorsey,[18] in an analysis of 819 subjects, found that elevated IgM, low IgA, low IgG, low IgM, and elevated IgA were the commonest changes observed at the ±2.0 S.D. level. Only 16 of the possible 27 combinations were recorded. Eight of the 11 combinations that were not found in their study were also not found in the present investigation; furthermore, only four subjects accounted for the remaining three categories in our study. One category (IgA-H, IgG-L, IgM-N) was found in their investigation and not in ours.

Serum immunoglobulin concentrations were significantly related to each other in the present study. The 95 per cent elipses in Figs. 1 to 3 indicate graphically that the major contribution to these associations was the grouping of values within the midrange of concentration. This analysis indicated also that the relationship between IgA and IgM was based upon an interdependence with IgG. Similar interactions were found by us in a study of children with juvenile rheumatoid arthritis.[19] These relationships are normal, therefore, and not specific for that disease. Buckley and Dorsey[18] found the same general relationships. Significant dependent changes in their analyses were associated with concurrence of high or low values of IgG and IgA, and IgG and IgM, and low values of IgA and IgM.

Five persons were found in the present investigation with selective immunoglobulin deficiency, a finding based entirely upon the sensitivity of the methods used. Serum immunoglobulins are detectable in a majority of individuals even with extreme hypogammaglobulinemia,[20] and evidence of antibody formation has been found in some of these patients.[21] One of the subjects with selective IgA deficiency in the present report had a medical history that included frequent sinopulmonary infections. Another had a past history of presumed juvenile rheumatoid arthritis. Both associations have been observed previously in our studies and those of other investigators.[22, 23] However, these former reports started with patients and investigated for immunologic deficiencies, a procedure that can lead to errors of overascertainment.

Selective IgA deficiency is the only well-defined absence of a single immunoglobulin.[24] Various estimates of its prevalence have been computed. In Sweden a frequency of 0.13 per cent was found for selective IgA deficiency in 6,995 adults who were otherwise healthy.[25] Hobbs[26] found a frequency of 0.2 per cent. The association of IgA deficiency with certain diseases, especially those with an autoimmune background, may have pathogenic significance. Selective IgA deficiency has been reported in ataxia telangiectasia,[27-29] in families of pa-

tients with hypogammaglobulinemia,[30, 31] and in patients with systemic lupus erythematosus,[32, 33] rheumatoid arthritis,[34-36] steatorrhoea,[37] alcoholic cirrhosis,[38] and recurrent infection.[39] Other studies have described its occurrence in a variety of diseases including epilepsy, mental retardation, congenital rubella syndrome, malabsorption, allergy, and nephritis,[40] and hypersplenism and Sjögren's syndrome.[26] IgA deficiency has been reported rarely in normal adult males[41] and in their families.[42] One of the subjects of the original report[41] has had a striking increase in his IgG concentration,[43] which suggests that this type of immune deficiency may only with great reservation be considered "normal." Abnormalities of chromosome No. 18 were recently found in patients with undetectable serum IgA.[44]

Selective IgM deficiency has been reported much less commonly, and estimates of its expected frequency in a general population are not available.[31] IgM deficiency was found in 37 per cent of adults with celiac disease and in even higher frequency in children with the same disorder.[45] The subjects of these reports had very low IgM but none had an undetectable serum level. In some individuals the serum value returned to normal after treatment with a glutein-free diet. Nodular lymphoid hyperplasia has been described with severe combined IgA and IgM deficiency.[46] Low levels of IgM have been found in infants with generalized nonprogressive vaccinia[47] and with meningococcal septicemia.[48]

Preliminary studies indicate that the less well-defined immunoglobulin deficiencies that have been described in this report are idiopathic or primary, as any contribution from recognized secondary disease such as the nephrotic syndrome or gastrointestinal loss is known to be minor in this population study. The majority fall into the current nomenclature of variable, largely unclassified immunodeficiencies.[49] At this time it is not possible to be certain of the biologic significance of these categories of serum immunoglobulin concentrations as immunoglobulin deficiency and functional antibody deficiency are not necessarily equatable. The fact that many are of relatively common occurrence is of importance in studies of individuals with autoimmune or inflammatory diseases. A postulated unique pathogenic role of hypogammaglobulinemia or hypergammaglobulinemia in such diseases is significant only in relation to their expected frequency in an unselected, general population.

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Answers for Allergy Foundation of America Self-Assessment Program

The correct answers to questions in this Journal issue are as follows:

Question 1 (p. 9): C, see Visser, H. K. A.: Physiology of the adrenal cortex in childhood, Scand. J. Resp. Dis. (Suppl.) **68**: 22, 1969.

Question 2 (p. 15): D, see Tuft, L., and Mueller, H. L.: Allergy in children, ed. 1, Philadelphia, 1970, W. B. Saunders Company, pp. 81 and 354.

Question 3 (p. 24): E, see Heimlich, E. M.: Asthmatic hyper-responsiveness, Pediatr. Clin. North Am., vol. 1, p. 14, 1969.

ESID Registry – Working Definitions for Clinical Diagnosis of PID

These criteria are only for patients with **no genetic diagnosis***.
*Exceptions: Atypical SCID, DiGeorge syndrome – a known genetic defect and confirmation of criteria is mandatory

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Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Agammaglobulinaemia	Annarosa Soresina, Nizar Mahlaoui, Hans Ochs, Isabella Quinti	Fewer than 2% circulating B cells (CD19 and CD20), preferably in two separate determinations and a normal number of T cells (CD3, CD4 and CD8) **AND** serum IgG levels below: -200 mg/dl in infants aged < 12 months -500 mg/dl in children aged > 12 months **OR** normal IgG levels with IgA and IgM below 2SD **AND** onset of recurrent infections before 5 years of age **OR** positive maternal family history of agammaglobulinaemia	For patients with normal B cells and agammaglobulinaemia, please consider "**Unclassified antibody deficiency"**.
Asplenia syndrome (Ivemark syndrome)	Nizar Mahlaoui David Edgar Stephan Ehl, Capucine Picard, Jean-Laurent Casanova	Asplenia or hyposplenia **AND** Documentation of Howell-Jolly bodies on blood smears **AND** radiological findings evidencing asplenia (US, CT scan, scintigraphy) **AND** heterotaxia defects (dextrocardia, situs inversus, other…) or other heart and great vessel defects	
Ataxia telangiectasia (ATM)	Nizar Mahlaoui David Edgar Stephan Ehl, Richard Gatti, Dominique Stoppa-Lyonnet	Ataxia **AND at least two of the following :** • Oculocutaneous telangiectasia • Elevated alphafetoprotein (tenfold the upper limit of normal) • Lymphocyte A-T caryotype (translocation 7;14) • Cerebellum hypoplasia on MRI	

Autoimmune lymphoproliferative syndrome (ALPS)	David Edgar, Stephan Ehl, Frederic Rieux-Laucat and Benedicte Neven	**At least one of the following:**
		• splenomegaly
		• lymphadenopathy (>3 nodes, >3 months, non-infectious, non-malignant)
		• autoimmune cytopenia (>/= 2 lineages)
		• history of lymphoma
		• affected family member
		AND at least one of the following:
		• TCRab+CD3+CD4-CD8- of CD3+ T cells>6%
		• elevated biomarkers (at least 2 of the following):
		  • sFASL > 200pg/ml
		  • Vitamin B12 > 1500ng/L
		  • IL-10 > 20pg/ml
		  • Impaired FAS mediated apoptosis
			For patients with lymphoproliferation and/or autoimmunity who do not fulfil these criteria, please consider the following diagnoses:
			• CVID
			• Unclassified combined immunodeficiencies
			• Unclassified disorders of immune dysregulation

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
APECED / APS1 with CMC - Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)	Nizar Mahlaoui, Frank.vandeVeerdonk (Radboud), Desa Lilic	**Look for at least 2 of the following:** • chronic mucocutaneous candidiasis (oral, oesophageal (difficulty swallowing) genital, skin, nails) – confirm with culture • autoimmune hypoparathyroidism / hypocalcemia • autoimmune adrenocortical failure (Addison's disease) • other autoimmune: hypergonadotropic hypogonadism, alopecia, vitiligo, autoimmune hepatitis, type 1 diabetes, gastrointestinal dysfunction • other: ectodermal dystrophy: dental enamel hypoplasia, nail dystrophy **Diagnostic tests (specific for APECED / APS1):** • organ-specific autoantibodies (parathyroid, adrenal, gonads, islet cell) • anti-cytokine autoantibodies (IFNα & ω and/or IL17A /IL17F/ IL22) [comment: sensitivity & specificity >95% (Kisand et al, Eur J Immunol 2011), can replace AIRE genotyping as >70 known mutations]	
Barth syndrome	Nizar Mahlaoui, Jean Donadieu, Ch. Klein	Male **AND** Cardiac features (Heart failure, dilated cardiomyopathy, left ventricular non-compaction, endocardial fibroelastosis, and serious disturbances of heart rhythm such as ventricular fibrillation or tachycardia **AND** Chronic Neutropenia **AND at least one of the following** • Neuromuscular features such as skeletal myopathy, hypotonia, delayed motor milestones, exercise intolerance, and abnormal fatigability. • Distinctive facial gestalt (most evident in infancy) • Growth delay is common in childhood	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Bloom syndrome	Markus Seidel, Beata Wolska, Corry Waemes, Andy Gennery	Short stature **AND** • immunodeficiency (hypogammaglobulinemia, variably reduced lymphocyte proliferation, lower respiratory tract infections) • Cytogenetics: high sister-chromatid exchange rate, chromosomal breaks **AND at least one of the following** • Skin: photosensitivity, butterfly erythema, café-au-lait maculae • Head: microcephaly, dolichocephaly, prominent ears and nose • Hands: syndactyly, polydactyly, fifth finger clinodactyly • Malignoma: leukemia, lymphoma, adenocarcinoma, squamous cell carcinoma	
Cartilage hair hypoplasia (CHH)	Nizar Mahlaoui, Bobby Gaspar, Andrew Gennery	Short stature **AND** immunodeficiency (combined immunodeficiency (variable T and B cell lymphopenia), **AND AT LEAST one of the following:** • radiographical manifestations of CHH (metaphyseal chondrodysplasia, • light-coloured hypoplastic hair / fine silky hair • gastrointestinal malabsorption or Hirschsprung's , • hematological abnormalities (bone marrow dysplasia, pure red cell aplasia), • granulomatous inflammation (skin lesions,…), • EBV driven lymphoproliferative disease • Malignancies **AND** no sign of other immune-osseous dysplasia (Schimke disease)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Chronic mucocutaneous candidiasis (CMC)	Nizar Mahlaoui, Frank.vandeVeerdonk (Radboud), Desa Lilic	**Look for:** • chronic, persistent or recurrent non-invasive mucocutaneous Candida or dermatophyte infections (oral, oesophageal (difficulty swallowing, oesophageal cancer) genital, skin, nails) – confirm with culture • other infections: skin (boils, abscesses, eczema, rosacea) lungs (chest infections, bronchiectasis) eyes (styes, blepharitis, conjunctivitis) • autoimmunity: hypothyroidism, vitiligo, alopecia, autoimmune hepatitis • vasculopathy (intracranial aneurisms, brain vascular anomalies) • family history / early age of onset **Exclude secondary causes:** • predisposing conditions: HIV, diabetes, iron deficiency, neutropenia, dentures • predisposing treatments: antibiotics, immunosuppressive drugs, inhaled steroids, PPIs • exclude isolated recurrent vulvo-vaginal candidiasis (RVVC) [Comment: Informative tests (where available): i. Th-17 & Th-22 cells and production ii. Low CD4 and B cell counts (combined immune deficiency) iii. Low iron]	
Complement component 2 deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (recurrent pyogenic) • Discoid lupus • SLE • Family history of symptomatic C2 Deficiency **AND** CH50 or CH100 activity less than 10% of control activity **AND** Absent C2 with normal C3 and C4 complement levels	
Complement component 3 deficiency (C3)	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisseria or streptococcal) • Glomerulonephritis • Family history of symptomatic C3 Deficiency **AND**	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
		CH50/CH100 and AP50/AP100 less than 10% of control activity **AND** Absent immunochemical C3 with normal Factor H and I levels	
CSR defects and HIGM syndromes	Stephan Ehl, Anne Durandy, Teresa Espanol	**At least one of the following:** • increased susceptibility to infections (recurrent and/or opportunistic, including cryptosporidium) • immune dysregulation (autoimmunity, lymphoproliferation, sclerosing cholangitis) • cytopenia (neutropenia or autoimmune) • malignancy (lymphoma) • affected family member **AND** marked decrease of IgG (measured at least twice) **AND** normal or elevated IgM (measured at least twice) **AND** defined causes of hypogammaglobulinemia have been excluded **AND** no evidence of profound T-cell deficiency, defined as 2/3 of the following (mo=month, y=year of life): • CD4 numbers/microliter: 0-6mo <1000, 6mo-1y <800, 1-2y <500, 2-6y <300, 6-12y <250, >12y <200 • % naive CD4: 0-2y <30%, 2-6y <25%, 6-16y <20%, >16y 10% • T cell proliferation absent **AND** no evidence of Ataxia telangiectasia (cafe-au lait spots, ataxia, telangiectasia, raised AFP)	
Chediak Higashi syndrome (CHS)	Nizar Mahlaoui, David Edgar Stephan Ehl, Genevieve de Saint Basile, Despina Moshous	**At least one of:** • recurrent bacterial infections • episode of hemophagocytic lymphohistiocytosis (HLH) • Neutropenia • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND one of:** • Typical hair shaft abnormalities • Presence of intracytoplasmic typical giant granules on blood or bone marrow smears	Immunodeficiency with partial albinism

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Chronic granulomatous disease (CGD)	Maria Kanariou, Reinhard Seger	**At least one of the following:** • deep seated infection due to bacteria and/or fungi (abscesses, osteomyelitis, lymphadenitis) • recurrent pneumonia • lymphadenopathy and/or hepatomegaly and/or splenomegaly • obstructing/diffuse granulomata (gastrointestinal or urogenital tract) • chronic inflammatory manifestations (colitis, liver abscess and fistula formation) • failure to thrive • affected family member **AND** absent/significantly decreased respiratory burst (NBT or DHR, measured at least twice)	
Clericuzio-type poikiloderma with neutropenia syndrome	Nizar Mahlaoui, Jean Donadieu, Ch. Klein	Chronic neutropenia, **AND** Poikiloderma, **AND** Recurrent infections, **AND** Pachyonychia, **OR** Palmo-plantar hyperkeratosis	
COHEN syndrome	Nizar Mahlaoui, Jean Donadieu, Ch. Klein	Chronic neutropenia. **AND at least 2 of the followings:** • intellectual deficiency (ID), • microcephaly, • facial dysmorphism, • slender extremities, • obesity, • progressive chorioretinal dystrophy	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Combined immunodeficiency (CID)	Stephan Ehl, Maria Kanariou, Alain Fischer	**At least one of:** • at least one severe infection (requiring hospitalization) • one manifestation of immune dysregulation (autoimmunity, IBD, severe eczema, lymphoproliferation, granuloma) • malignancy • affected family member **AND** 2 of 4 T cell criteria fulfilled: • reduced CD3 or CD4 or CD8 T cells (using age-related reference values) • reduced naive CD4 and/or CD8 T cells • elevated g/d T cells • reduced proliferation to mitogen or TCR stimulation **AND** HIV excluded **AND** exclusion of clinical diagnosis associated with CID (e.g. defined syndromic diseases, DKC, AT, CHH)	
Common variable immunodeficiency disorders (CVID)	Vojtech Thon, Natalia Martinez, Maria Kanariou, Klaus Warnatz, Isabella Quinti, Helen Chapel	**At least one of the following:** • increased susceptibility to infection • autoimmune manifestations • granulomatous disease • unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency **AND** marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age); **AND** at least one of the following: • poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination where defined • low switched memory B cells (<70% of age-related normal value) **AND** secondary causes of hypogammaglobulinaemia have been excluded (see separate list) **AND** diagnosis is established after the 4th year of life (but symptoms may be present before) **AND** no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life): • CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200 • % naive CD4: 2-6y <25%, 6-16y <20%, >16y <10% • T cell proliferation absent	For patients <4 years old or patients with incomplete criteria please consider "**Unclassified antibody deficiency"**. For patients with evidence of profound T-cell deficiency, please consider **Unclassified combined immunodeficiencies**.

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Congenital neutropenia	Nizar Mahlaoui, Jean Donadieu	Neutropenia below 0.5 g/L measured on at least 3 occasions **OR** Neutropenia below 1 g/L measured on at least 3 occasions with at least one of the following: • deep seated infection due to bacteria and/or fungi • recurrent pneumonia • buccal and/or genital aphtous lesions or ulcerations • omphalitis • affected family member **AND e**xclusion of secondary causes of neutropenia	For other patients with chronic neutropenia, please consider **Unclassified phagocytic disorders**.
Cyclic neutropenia	Nizar Mahlaoui David Edgar Stephan Ehl, Jean Donadieu	Cyclic fluctuation of Neutrophil counts (every 16 to 28 days) During these neutropenic episodes, symptoms are **at least one of the following**: • Increased susceptibility to infections • Oral apthae • Abdominal pain episodes	
Defects of TLR/NFkappa-B signalling	Nizar Mahlaoui, Capucine Picard, Jacinta Bustamante	Recurrent and/or severe infections **AND at least 2 of the following:** • normal T- and B-cell responses • mild inflammatory reaction • polysaccharide-specific serum antibodies deficiency • anhidrotic ectodermal dysplasia features in some patients	
Defects with susceptibility to mycobacterial infection (MSMD)	Nizar Mahlaoui, Capucine Picard, Jacinta Bustamante	Infections caused by weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria, tuberculosis, salmonellosis, candidiasis, other intramacrophagic bacteria, fungi, or parasites, **AND** Altered IFN-γ mediated immunity tests or Altered IL-12 mediated immunity tests **AND** no IFN-γ auto-antibodies	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Deficiency of specific IgG (Specific antibody deficiency - SPAD)	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (recurrent or severe bacterial) **AND** normal serum/plasma IgG, A and M and IgG subclass levels **AND** Profound alteration of the antibody responses to *S.* pneumoniae (or other polysaccharide vaccine) either after documented invasive infection or after test immunization. **AND** Exclusion of T cell defect	**Unclassified antibody deficiencies**
DiGeorge syndrome	Nizar Mahlaoui David Edgar Stephan Ehl	Documented microdeletion 22q11 or 10p **AND** signs of immunodeficiency (i.e. infections and/or immune dysregulation)	
Dyskeratosis congenita	Nizar Mahlaoui David Edgar Stephan Ehl, Inderjeet Dokal	**At least two of the following:** • Skin pigmentation abnormalities • Nail dystrophy • Mucosal leucoplakia • Bone marrow failure **AND** Very short telomeres	
Factor D deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (recurrent pyogenic including Neisseria) • Family History of symptomatic Factor D Deficiency **AND** AP50/AP100 activity less than 10% of control value with normal CH50/CH100 activity **Or** Absent Factor D activity in serum in functional or immunochemical assessment	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Familial hemophagocytic lymphohistiocytosis syndromes (FHLH)	Stephan Ehl, Genevieve de Saint Basile, Gritta Janka	**At least one of the following:** • at least 1 episode of HLH (at least 5/8 criteria as defined by the Histiocyte Society) • affected family member **AND at least one of the following:** • recurrent disease (>4 weeks after initiating treatment for first episode) • persistent disease (no full remission can be achieved) • partial albinism • absent or significantly decreased Perforin expression in flow cytometry • at least one assay with absent degranulation (NK or CTL) or two assays with reduced degranulation • at least 2 assays with absent NK cell cytotoxicity	For patients with incomplete criteria, please consider **Unclassified disorders of immune dysregulation**.
FOXP3 deficiency (IPEX)	Nizar Mahlaoui David Edgar Stephan Ehl, Hans Ochs, Benedicte Neven	**At least one of** • Severe and protracted enteropathy with villous atrophy in a male infant • Severe, often multiple endocrinopathies **AND** Exclusion of hypogammaglobulinaemia **AND at least one of the following:** • Low or absent Foxp3 expression by CD4+CD25+ on flow analysis • No overt T cell defect (proliferations are normal) • Elevated IgA and IgE levels • Normal CD25 expression	Combined immunodeficiency
Glycogen storage disease type 1b (GS1b)	Nizar Mahlaoui David Edgar Stephan Ehl, Jean Donadieu	Recurrent infections **AND** Fasting intolerance **AND** Hypoglycaemic attacks **AND** Hyperlactacidemia **AND** Glycogen accumulation in the liver **AND** colitis mimicking Crohn's disease **AND one of:** • neutrophil function alterations • neutropenia	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Griscelli syndrome type 2	Nizar Mahlaoui, David Edgar Stephan Ehl, Genevieve de Saint Basile, Despina Moshous	**At least one of the following:** • episode of hemophagocytic lymphohistiocytosis (HLH) • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND** Typical hair shaft abnormalities **AND** Absence of giant granules on blood smear	Immunodeficiency with partial albinism
Hereditary Angioedema (C1inh)	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Recurrent angioedema without urticaria • Recurrent abdominal pain and vomiting • Laryngeal oedema • Family history of angioedema **AND** Low complement C4 (< 2.S.D of the mean) between or during angioedema attacks **AND** Absent C1 esterase protein (Type 1 HAE) or absent C1 esterase inhibitor function (Type 2 HAE) **AND** Normal C1q level	
Hermansky-Pudlak syndrome (type 2)	Nizar Mahlaoui, Stephan Ehl	Oculocutaneous albinism **AND** Chronic neutropenia **AND at least one of the following:** • bleeding diathesis • recurrent infections • hemophagocytic lymphohistiocytosis (HLH) **AND** Defective cytotoxicity caused by impaired degranulation	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
HLA class I deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following:** • Predisposition to recurrent and/or opportunistic infections • Granulomatous skin lesions **AND at least one of the following:** • Predisposition to recurrent and/or opportunistic infections • Necrotizing granulomatous skin lesions • Low T-CD8 or lymphopenia • Absence of Ab production in response to antigens • Absence of T cell proliferation in response to antigens **AND** Reduced or absent HLA A,B,C expression at the surface of resting and PHA/Cytokine activated T-cells	
HLA class II deficiency (MHC2)	Nizar Mahlaoui, David Edgar Stephan Ehl, Capucine Picard, Amos Etzioni	**One of the following:** • Recurrent and/or opportunistic infections • Autoimmunity **AND one of the following:** • Hypogammaglobulinaemia • Lymphopenia • Low T-CD4 count • absence of Ab production in response to antigens or absence of T cell proliferations in response to antigens **AND** Reduced or absent HLA DR expression at the surface of B cells and/or monocytes	Combined immunodeficiency
Hoyeraal-Hreidarsson syndrome	Nizar Mahlaoui David Edgar Stephan Ehl, Inderjeet Dokal	**At least four of the following criteria:** • Microcephaly and/or neurocognitive impairment • Cerebellar hypoplasia • Bone marrow failure • Immune deficiency including B cell lymphopenia • Severe enteropathy • Severe failure to thrive This can be substantiated by undertaking telomere length analysis (usually very short)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Hyper IgE syndrome (HIES)	Beata Wolska, David Edgar, Bodo Grimbacher, Steven Holland	IgE > 10 times the norm for age **AND** pathologic susceptibility to infectious diseases **AND** no evidence of T-cell deficiency (low T cell numbers, low naive T cells, reduced proliferation) **AND** no evidence of B cell deficiency (low B cell numbers, hypogammaglobulinaemia)	• For patients with evidence of T-cell deficiency, please consider: **Unclassified combined immunodeficiencies**. • For patients with evidence of B-cell deficiency, please consider **Unclassified antibody deficiency**. • For other patients, please consider **Unclassified immunodeficiencies**.
IgA with IgG subclass deficiency	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (recurrent or severe bacterial) **AND** Undetectable serum/plasma IgA level (with normal/lowish IgG and IgM levels) **AND** Low levels in one or more IgG subclass (documented twice) **AND** normal IgG antibody response to some vaccinations **AND** Exclusion of T cell defect	**Unclassified antibody deficiencies**
Immunodeficiency centromeric instability facial anomalies syndrome (ICF)	Markus Seidel, Beata Wolska, Corry Waemes, Capucine Picard	Immunodeficiency (variable hypogammaglobulinemia, variably reduced T, B, and NK cells, bacterial and opportunistic infections) **AND** • Head: microcephaly, hypertelorism, epicanthal folds, flat face, micrognathia, macroglossia, tongue protrusion, small upturned nose • Cytogenetics: Centromeric instability of chromosomes 1, 9 and 16 with increased somatic recombination and formation of multibranched/-radial configurations **AND at least two of the following** • Short stature • Neurologic: variable mental retardation • Malabsorption, diarrhea • Sinusitis, upper and lower respiratory tract infections	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
IPEX-like disease	Nizar Mahlaoui David Edgar Stephan Ehl, Hans Ochs, Benedicte Neven	**At least one of** • Severe and protracted enteropathy with villous atrophy in a male infant • Severe, often multiple endocrinopathies **AND** Exclusion of hypogammaglobulinaemia **AND at least one of the following:** • Normal Foxp3 expression by CD4+CD25+ on flow analysis • No overt T cell defect (proliferations are normal) • Elevated IgA and IgE levels	Combined immunodeficiency
Isolated IgG subclass deficiency	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (recurrent or severe bacterial) **AND** normal IgG, A and M serum/plasma levels **AND** Low levels in one or more IgG subclass (documented twice) **AND** Normal IgG antibody response to some vaccinations **AND**Exclusion of T cell defect	**Unclassified antibody deficiencies**
Isolated congenital asplenia	Nizar Mahlaoui David Edgar Stephan Ehl, Capucine Picard, Jean-Laurent Casanova	Asplenia or hyposplenia **AND** Documentation of Howell-Jolly bodies on blood smears **AND** radiological findings evidencing asplenia (US, CT scan, scintigraphy) **AND** exclusion of any over developmental defect such as heterotaxia (dextrocardia, situs inversus, other…) or other heart and great vessel defects	
Mannose-binding lectin deficiency (MBL)	Matthew Buckland, Sofia Grigoriadou, Ania Manson	Infections (severe recurrent bacterial) **AND one of the following:** Mannose binding lectin <75 µg/L: Correlates with homozygous variant alleles and non-functional MBL which is associated with the greatest risk of infection. **OR** 75 - 399.9 µg/L: Correlates with functional MBL deficiency associated with increased risk of infection. **OR** 400 - 1300 µg/L: Correlates with heterozygous varient alleles and may show mild deficiency associated with some increased risk of infection.	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
		NB: Patients should be classified as Homozygous, Functional or Heterozygous Deficient as appropriate.	
Nijmegen breakage syndrome	Markus Seidel, Beata Wolska, Corry Waemes, Andy Gennery	Microcephaly **AND** reduced T cell number and/or elevated percentage of memory CD4 and CD8 cells and/or reduced T cell function **AND at least two of the following** • Typical facial appearance • Variable hypogammaglobulinemia, dysgammaglobulinemia and/or reduction of B cells - opportunistic and/or chronic, recurrent infections, predominantly of the respiratory tract • Skin: Café-au-lait spots and/or hypopigmented areas and/or skin granulomas • lymphoma/leukemia or other malignancy • Chromosomal instability (especially chrom. 7 and 14), increased sensitivity towards ionizing radiation and alkylating agents	
Omenn syndrome	Nizar Mahlaoui, Annarosa Soresina, Anna Villa, Alain Fischer	Desquamating erythroderma in the first year of life **AND** one of the following: • lymphoproliferation • failure to thrive • chronic diarrhoea • recurrent pneumonia **AND** eosinophilia or elevated IgE **AND** T-cell deficiency (low naïve cells, reduced proliferation, oligoclonality) **AND** maternal engraftment excluded **AND** HIV excluded	For other patients with severe erythroderma, please consider: • SCID • IPEX • Unclassified disorders of immune dysregulation • Unclassified defects in innate immunity.

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Partial albinism and immunodeficiency syndrome	Nizar Mahlaoui, Stephan Ehl	Partial oculo-cutaneous albinism **AND at least one of of the following:** • recurrent bacterial infections • episode of hemophagocytic lymphohistiocytosis (HLH) • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND** Exclusion of Chediak Higashi Syndrome and Griscelli Syndrome type 2	
Properdin P factor complement deficiency (PFC)	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (recurrent pyogenic including Neisseria) • Family History (X-linked inheritance pattern **AND** AP50/AP100 activity in at least the bottom 10% of control value with normal CH50/CH100 activity **AND** Absent Properdin (type I/II) or activity (type III) in serum in functional or immunochemical assessment	
Schimke disease	Nizar Mahlaoui David Edgar Stephan Ehl	Predominantly T cell defects (low T cell counts, low T cell proliferations) **AND** osseous dysplasia (metaphyseal usually) **AND** kidney dysfunction	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Seckel syndrome	Markus Seidel, Beata Wolska, Corry Waemes, Andy Gennery	Short stature (pre- and postnatal growth retardation), severe microcephaly **AND at least three of the following:** • Head: downward slanting palpebral fissures, sloping forehead, face asymmetry, prominent beaked nose, selective tooth agenesis • Hematology: pancytopenia • Cytogenetics: increased sister chromatid exchange • Neurology: mental retardation, seizures, and CNS structural abnormalities • Skeletal: fifth finger clinodactyly, hip and radius head dislocation, hypoplasia of proximal radius and proximal fibula, 11 ribs, scoliosis	
Selective CD4 cell deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	$CD4^+$ T cell less than 350/µl (patient more than 4 years of age) or less than 20% of circulating T-lymphocytes at any age **AND** OKT4 Deficiency Excluded **AND** Normal or increased CD8, CD19 and CD56 **AND** HIV Negative **And** Other primary causes of lymphopenia excluded	
Selective IgA deficiency	Vojtech Thon, Natalia Martinez, Maria Kanariou, Klaus Warnatz, Isabella Quinti	**At least one of the following:** • increased susceptibility to infection • autoimmune manifestations • affected family member **AND** diagnosis after 4th year of life **AND** undetectable serum IgA (when measured with nephelometry less than 0.07 g/L) but normal serum IgG and IgM (measured at least twice) **AND** secondary causes of hypogammaglobulinaemia have been excluded. **AND** normal IgG antibody response to all vaccinations **AND** Exclusion of T-cell defect	• For patients with abnormal vaccine responses, please consider **Deficiency of specific IgG (SPAD)**. • For other patients, please consider **Unclassified antibody deficiency**.

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Selective IgM deficiency	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (either invasive or recurrent, usually bacterial) **AND** Low IgM serum/plasma level (with normal IgG and IgG subclasses and IgA plasma level) **AND** Normal IgG antibody response to all vaccinations **AND** Exclusion of T-cell defect	**Unclassified antibody deficiencies**
Severe combined immunodeficiency (SCID)	Stephan Ehl, Alain Fischer	**At least one of the following:** • invasive bacterial, viral or fungal/opportunistic infection • persistent diarrhoea and failure to thrive • affected family member **AND** manifestation in the first year of life **AND** HIV excluded **AND** 2 of 4 T cell criteria fulfilled : • low or absent CD3 or CD4 or CD8 T cells • reduced naive CD4 and/or CD8 T cells • elevated g/d T cells • reduced or absent proliferation to mitogen or TCR stimulation	For other (e.g. older) patients with T-cell deficiency, consider **Unclassified combined IDs**.
Shwachman-Diamond-syndrome	Nizar Mahlaoui, Jean Donadieu	Neutropenia **AND** Exocrine pancreatic failure **AND at least one of the following:** • enlargement of metaphyseal zones on bone X-rays • cognitive retardation or Behavioral problems	
Thymoma with immunodeficiency	David Edgar, Helen Chapel	Presence of thymoma **AND** reduced serum IgG (< 2SD below the mean reference for age)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Transient hypogamma-globulinaemia of infancy	David Edgar, Maria Kanariou, Esther de Vries	IgG below age-related normal value detected in the first three years of life (measured at least twice) **AND** defined causes of hypogammaglobulinaemia have been excluded **AND** spontaneous resolution approx. after the 4th birthday NB: Patients will initially be registered as **Unclassified antibody deficiency,** in the registry and moved to **THI**, if there is spontaneous resolution before age 4.	
Warts hypogammaglobulinemia infections and myelokathexis (WHIM)	Jean Donadieu, Sarah, Beaussant Cohen, Bodo Grimbacher	Neutropenia **AND** lymphopenia **AND** monocytopenia **AND** Evidence of myelokathexis on bone marrow smear; **AND at least one of the following:** • Recurrent and severe HPV infections • Recurrent bacterial infections • Mycobacterial infection(s). • Mild hypogammagobulinemia	
Wiskott-Aldrich syndrome (XLT/WAS)	Annarosa Soresina, Natalia Martinez, Michael Albert, Adrian Thrasher	**At least one of the following:** • eczema • recurrent bacterial or viral infections • autoimmune diseases (incl. vasculitis) • malignancy • reduced WASP expression in a fresh blood sample • abnormal antibody response to polysaccharide antigens and/or low isohaemagglutinins • positive maternal family history of XLT/WAS **AND** male patient with thrombocytopenia (less than 100,000 platelets/mm3) (measured at least twice) **AND** small platelets (platelet volume < 7,5 fl)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
X-linked lymphoproliferative syndrome (XLP)	Nizar Mahlaoui, Stephan Ehl	Male individual (or female with severely skewed X-chromosome inactivation) **AND two of the following:** • at least 1 episode of HLH (according to the Histiocyte Society criteria) • affected family member • abnormal EBV response • Hypogammaglobulinemia • Inflammatory Bowel Disease • Vasculitis • Lymphoid Neoplasm, especially if EBV-associated **AND at least one of the following minor criteria:** • decreased or absent SAP (for XLP1) or XIAP (for XLP2) expression assessed by Flow Cytometry • reduced frequency of iNKT cells (< 0.02% of T cells) • Normal Perforin expression in flow cytometry • Normal degranulation (NK or CTL) assays or Normal NK cell cytotoxicity assays **AND** No partial albinism **AND** Normal work-up for metabolic diseases	
Unclassified antibody deficiency	Esther de Vries, Nizar Mahlaoui, David Edgar, Isabella Quinti, Helen Chapel	**At least 1 of the following 4:** • Recurrent or severe bacterial infections • Autoimmune phenomena (especially cytopenias) • Polyclonal lymphoproliferation • Affected family member **AND at least one of the following**: • marked decrease of at least one of total IgG, IgG1, IgG2, IgG3, IgA or IgM levels • failure of IgG antibody response(s) to vaccines **AND** secondary causes of hypogammaglobulinaemia have been excluded (infection, protein loss, medication, malignancy) **AND** no clinical signs of T-cell related disease **AND** does not fit **any** of the other working definitions (**ex**cluding 'unclassified immunodeficiencies')	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Unclassified phagocytic disorders	Nizar Mahlaoui, Capucine Picard, Jacinta Bustamante	**At least one of the following:** • deep seated infection due to bacteria and/or fungi • recurrent severe pneumonia • buccal and/or genital aphtous lesions or ulcerations • omphalitis • chronic inflammatory manifestations (e.g. colitis, fistula formation) • affected family member • BCGitis or BCGosis **AND** normal to subnormal respiratory burst (NBT or DHR, assessed at least twice)	
Unclassified disorders of immune dysregulation	Stephan Ehl, Maria Kanariou	**At least one of the following:** • autoimmune manifestations • lymphoproliferation • severe eczema • inflammatory bowel disease • granuloma • vasculitis • HLH-like disease **AND** at least one numeric or functional abnormal finding upon immunological investigation **AND** no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life): • CD4 numbers/microliter: 0-6mo <1000, 6mo-1y <800, 1-2y <500, 2-6y <300, 6-12y <250, >12y <200 • % naive CD4: 0-2y <30%, 2-6y <25%, 6-16y <20%, >16y 10% • T cell proliferation absent **AND** no evidence of B-cell deficiency (low B cell numbers, hypogammaglobulinaemia	• For patients with evidence of profound T-cell deficiency, please register these as **Unclassified combined immunodeficiencies**. • For patients with evidence of B-cell deficiency, please register as **Unclassified antibody deficiency**.
Unclassified defects in innate immunity	Nizar Mahlaoui, Maria Kanariou, Capucine Picard, Jacinta Bustamante	**At least one of the following:** • onset of disease before 5 y of age • pyogenic bacterial infections • unusual infections and/or atypical clinical course **AND** the dominant abnormal immunological finding concerns the innate immune system (excluding defects in phagocyte number or function) i.e. NF-κB-dependent TLR and IL-1R immunity **AND** functional spleen (no Howell-Jolly bodies on blood smears)	For patients with evidence of profound defect of phagocytes, please consider **Unclassified phagocytic disorders**.

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Unclassified complement deficiencies	Annarosa Soresina, Matthew Buckland, David Edgar	**At least one of the following:** • one episode of bacteraemia, meningitis or systemic Neisserial infection • recurrent respiratory infections **AND** persistent defect of CH50 or AP50 (in three determinations in 6 months) **AND** no evidence of other conventional immunological defects	
Unclassified autoinflammatory diseases	David Edgar, Beata Wolska, Helen Lachmann	Recurrent fever (temperature >38 degrees Celsius) having occurred on at least 6 occasions. **AND** exclusion of other known infective / inflammatory autoimmune disorders **AND** documented evidence of increased inflammatory markers (ESR/CRP) **AND** age of onset under 40 years **AND** predominantly but not exclusively systemic symptoms	
Unclassified syndromic immunodeficiencies	Stephan Ehl	**At least one of the following:** • dysmorphic features such as short stature, facial abnormalities, microcephaly, skeletal abnormalities • other organ manifestations such as albinism, hair or tooth abnormalities, heart or kidney defects, hearing abnormalities, primary neurodevelopmental delay, seizures **AND** at least one numeric or functional abnormal finding upon immunological investigation **AND** exclusion of secondary causes for immunological abnormalities (infection, malignancy)	
Unclassified immunodeficiencies	Stephan Ehl, Alain Fischer	**At least one of the following:** • at least one major infection • abnormal course or frequency of minor infections • at least one manifestation of immune dysregulation • failure to thrive • affected family member **AND** at least one numeric or functional abnormal finding upon immunological investigation **AND** exclusion of secondary causes for immunological abnormalities (infection, protein loss, medication, malignancy) **AND** does not fit **any** of the other working definitions (**in**cluding 'unclassified syndromic immunodeficiencies')	For patients with syndromic manifestations, consider **Unclassified syndromic IDs**.

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REVIEW
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Selective IgM Deficiency—An Underestimated Primary Immunodeficiency

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Although selective IgM deficiency (SIGMD) was described almost five decades ago, it was largely ignored as a primary immunodeficiency. SIGMD is defined as serum IgM levels below two SD of mean with normal serum IgG and IgA. It appears to be more common than originally realized. SIGMD is observed in both children and adults. Patients with SIGMD may be asymptomatic; however, approximately 80% of patients with SIGMD present with infections with bacteria, viruses, fungi, and protozoa. There is an increased frequency of allergic and autoimmune diseases in SIGMD. A number of B cell subset abnormalities have been reported and impaired specific antibodies to *Streptococcus pneumoniae* responses are observed in more than 45% of cases. Innate immunity, T cells, T cell subsets, and T cell functions are essentially normal. The pathogenesis of SIGMD remains unclear. Mice selectively deficient in secreted IgM are also unable to control infections from bacterial, viral, and fungal pathogens, and develop autoimmunity. Immunological and clinical similarities and differences between mouse models of deficiency of secreted IgM and humans with SIGMD have been discussed. Patients with SIGMD presenting with recurrent infections and specific antibody deficiency responses appear to improve clinically on immunoglobulin therapy.

Keywords: autoimmunity, specific antibody deficiency, CD4 Treg, CD8 Treg, Breg

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INTRODUCTION

During ontogeny, IgM is the first immunoglobulin to be expressed on the surface of B cells (1), and the first immunoglobulin isotype secreted during an initial immune response to an exogenous antigen. Mature naïve B cells in response to antigens undergo clonal expansion and differentiation into Ig-secreting cells. In the germinal center (GC) of secondary lymphoid organs, two important events take place. A subset of activated IgM+ B cells undergo a process of heavy chain isotype switching resulting in the production of antibodies of different isotypes such as IgG, IgA, and IgE, upon engagement of CD40 with CD40L and interaction with cytokines, and somatic hypermutation in v region results in the selection of high affinity antibody producing B cells (2, 3). In contrast to secreted IgG, IgM comes in two flavors, pre-immune or without exposure to exogenous antigen also know as "natural IgM" that is spontaneously produced, and the second type is exogenous antigen-induced or "immune" IgM antibodies. The majority of circulating IgM is comprised of natural IgM antibodies. It has been established from studies of mutant mice deficient in IgM secretion that both natural and immune IgM are important in responses to pathogens and self-antigens (4, 5). The two prominent features of natural IgM are polyreactivity and autoreactivity,

which are attributed to the germline configuration of their v region structures. The natural IgM antibodies are reactive with many conserved epitopes that are shared by microbes and self-antigens. The production of natural IgM appears to be triggered by interaction with self-antigens. In addition to providing early defense against microbes, natural IgM plays an important role in immune homeostasis, and provide protection from consequences of autoimmunity and inflammation (6–9). It also appears that the specificity to bind to components of self-antigen is critical for protecting effect of natural IgM against autoimmunity. In mice, B1 cell-derived plasma cells are the major source of natural IgM, and natural IgM promotes the T cell-dependent antibody response by conventional B2 cells (10). The immune IgM antibodies are selected for antigen-specificity that are usually produced in response to pathogens, and serve as a first line of defense against microbial infections and also provide protection from autoimmune diseases (4, 6).

Selective IgM Deficiency (SIGMD) is disorder with serum IgM below two standard of mean, and normal IgG, and IgA and T cell functions. In 1967, Hobbs et al. (11) first described children with SIGMD (type V dysgammaglobulinemia) presenting with meningococcal meningitis. Since then, a number of patients with SIGMD have been reported [reviewed in Ref. (12)]. There are no large-scale studies reported for the prevalence of SIGMD. In an unselected community health screening survey, a prevalence of 0.03% of "complete" SIGMD was reported (13). Recently, in screening of more than 3,000 healthy adult blood bank blood donors in Iran, the prevalence of SIGMD was 0.37% (14). A prevalence of 0.07–2.1% in Immunology and immunodeficiency clinics has been reported (15, 16).

GENETICS

Although occasional symptomatic familial cases of SIGMD deficiency have been reported (11, 17), no definitive inheritance pattern is known for SIGMD. In our immunology clinic, we are also following a mother and daughter with symptomatic SIGMD and specific antibody deficiency; both have similar clinical and immunological profile. SIGMD has been reported in a number of chromosomal abnormalities, including that of chromosome 1,18 and 22q11.2 (18–22). The most common association of SIGMD has been with 22q11.2 deletion syndrome (18–20, 23–25).

CLINICAL FEATURES

Similar to other primary immunodeficiency disorders, patients with SIGMD commonly present with recurrent infections with common microbes, and increased frequency of allergic and autoimmune diseases. These clinically features have been reviewed in detail (12). Recurrent infections as the presenting manifestation occur in more than 80% of patients with SIGMD. Some of these bacterial infections may result in serious life-threatening infections (11, 17, 21, 22). The clinical infectious presentations of SIGMD include recurrent otitis media, chronic sinusitis, bronchitis, bronchiectasis, pneumonia, urinary tract infections, cellulitis, meningitis, sepsis, etc. Some of the common microbial organisms include *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Aspergillus fumigatus*, *Giardia lamblia*; many of these organisms express epitopes of phosphorylcholine in their cell walls that are similar to those expressed on apoptotic cells, and recognized by natural IgM.

Although IgG levels are normal in SIGMD, increased susceptibility to infections in SIGMD may be due to associated impaired IgG-specific antibody response to T-independent polysaccharide antigens (26). These observations are analogous to mutant mice deficient in secreted IgM, in that immunoglobulin isotype switching to IgG is normal; however, these animals are also unable to control viral, bacterial, and fungal infections due to impaired induction of a protective specific IgG antibody response, and lack of serum IgM (4, 27, 28).

In children with SIGMD, allergic and autoimmune diseases are infrequent (29), whereas in adults, allergic and autoimmune diseases are frequently present (15, 26). Almost 40% of patients with SIGMD display allergic manifestations. Several investigators have reported association between atopic diseases and SIGMD (15, 26, 30, 31). The frequency of asthma and allergic rhinitis in SIGMD in reported cases ranged from 30 to 45%.

Similar to other primary antibody deficiency disorders (32), autoimmunity and autoimmune diseases (**Table 1**) are more common in patients with SIGMD than in the general population (33–39). Goldstein et al. (15) reported positive ANA in 13% and arthritis and SLE in 14% of patients with SIGMD. In our current cohort of 55 patients with SIGMD, we have observed Hashimoto's thyroiditis in 8, SLE in 3, Myasthenia gravis in 2, and Addison's disease in 1 patient (unpublished observations). Mice genetically generated to be deficient in secreted IgM spontaneously develop ANA, anti-ds-DNA, and anti-ss-DNA antibodies and autoimmune diseases like arthritis and "lupus-like" diseases (6, 40, 41). In mice deficient in secreted IgM, the prevalence of autoimmune diseases increases as mice age (6). In SIGMD, autoimmune diseases are more frequent in adults as compared to children with SIGMD (12, 15, 29). Paradoxically, levels of autoreactive IgM are elevated in patients with autoimmune diseases (42, 43). This could reflect a compensatory mechanism by which IgM inhibits inflammation and promotes clearance of apoptotic cells. Mice mutants for FcμR are impaired in IgG antibodies against T-dependent

TABLE 1 | Autoimmune diseases associated with SIGMD.

Addison's disease
Autoimmune glomerulonephritis
Autoimmune hemolytic anemia
Autoimmune thrombocytopenia
Celiac disease
Crohn's disease
Hashimoto's thyroiditis
Myasthenia gravis
Polymyositis
Rheumatoid arthritis
Sjogren's syndrome
Systemic lupus erythematosus
Vitiligo

and T-independent antigens, develop autoimmunity as they age, however, have increased levels of IgM (44). Although the precise mechanism of IgM-mediated regulation of tolerance is unclear, a number of mechanisms have been proposed: (a) cross-linking of FcμR and BCR by IgM autoantibodies-self-antigen complexes resulting in the induction of anergy or deletion of B cells; (b) loss of central tolerance as a result of BCR editing at the level bone marrow; (c) loss of peripheral tolerance secondary to a deficiency of isotype-specific regulatory lymphocytes; (d) impaired clearance of apoptotic cells/bodies (self antigens). In SIGMD patients, we did not observe any significant changes in the expression of FcμR on any of B cell subsets except low-level expression on MZ B cells (45). Therefore, it is unlikely that changes in FcμR or peripheral tolerance play a significant role in the development of autoimmunity in SIGMD. Patients with SIGMD also have decreased proportions of CXCR3$^+$ B cells (46). Recently, a deficiency of CXCR3$^+$ B cells has been linked to autoimmune diseases (47).

IMMUNE RESPONSES IN SIGMD

A number of abnormalities in lymphocyte numbers and functions have been reported in SIGMD. In contrast, innate immune responses appear to be preserved.

Lymphocyte Phenotype

B Lymphocytes

The proportions and numbers of surface IgM$^+$ B cells or CD19$^+$/CD20$^+$ B cells are normal in the majority of patients with SIGMD (15, 26, 48–51). However, low to complete lack of sIgM$^+$, CD19$^+$, or CD20$^+$ B cells have been reported (23, 52–54). Recently, we have performed an extensive analysis of B cell subsets in 20 patients with SIGMD (46). A significant increase in CD21^{low}, and IgM memory B cells, and a significant decreased in GC B cells, and CXCR3$^+$ naïve and memory B cells were observed in SIGMD. Lau et al. (55) have demonstrated that CD21^{low} cells are recent GC graduates that represent a distinct population from CD27$^+$ memory cells, are refractory to GC reentry, and are predisposed to differentiate into long-lived plasma cells. Therefore, a deficiency of CD21^{low} cells may be responsible for decreased differentiation to plasma cells and decreased Ig production. However, it cannot explain defects in selective production of IgM. CD21^{low} are increased in patients with CVID with autoimmunity, and systemic lupus erythematosus (53, 54, 56). Impaired polysaccharide response early life is believed to be secondary to low expression of CD21 on B cells. A significant increase in the proportions of CD21^{low} B cells in our patients with SIGMD may explain both increased autoimmunity and impaired anti-polysaccharide antibody responses in SIGMD.

A role of CXCR3 in T cells and T-cell-mediated autoimmunity has been well established (57); however, its role in B cell trafficking and antibody-mediated autoimmunity is beginning to emerge (58). Patients with SLE have decreased number of CXCR3$^+$ B cells (45). We have observed decreased expression of CXCR3 on both naïve and memory B cells in SIGMD (46). A role of decreased expression of CXCR3 on B cell subsets in SIGMD and autoimmunity associated with SIGMD remains to be investigated.

T Lymphocytes

Number and functions of T cell and T cell subsets are normal in the majority of patients with SIGMD (26, 29, 46, 48–50, 59) except in the syndrome of SIGMD, T cell deficiency, and MAC infection (12, 60, 61).

Upon antigenic stimulation, naïve CD4$^+$ and CD8$^+$ T cells undergo clonal expansion, differentiation, and distinct homing patterns. Based upon their functions and homing patterns, both CD4$^+$ and CD8$^+$ T cells have been classified into naïve (T_N), central memory (T_{CM}), effector memory (T_{EM}), and terminally differentiated effector memory (T_{EMRA}) subsets (62–64). Patients with SIGMD are reported to have normal distribution of T_N, T_{CM}, T_{EM}, and T_{EMRA} subsets of CD4$^+$ and CD8$^+$ T (46, 50). In contrast, T_N and T_{CM} subsets of both CD4$^+$ and CD8$^+$ T cells were decreased, whereas T_{EMRA} subset of CD4$^+$ and CD8$^+$ T cells were markedly increased in patients with syndrome of SIGMD, T cell deficiency, and MAC infection (60, 61).

Regulatory Lymphocytes

Although a role of CD4$^+$ Treg in immune tolerance is well established (65), it is only recently there has been an interest in the role of Breg (66) and CD8Treg (67, 68) in immune homeostasis, and tolerance.

Breg have shown to regulate various immune responses including regulation of generation of CD4$^+$ Treg; deficiency of Breg results in experimental autoimmune diseases, and more recently, Breg were shown to regulate the generation of peripheral CD4$^+$ Treg cells (66, 69–72). We have reported significant increase in Breg in patients with SIGMD (46). It is unclear whether increase in Breg and CD8$^+$ Treg (see below) are compensatory changes to control the development of autoimmunity and autoimmune diseases in SIGMD, or they contribute to disease phenotype. If increased Breg contribute to SIGMD by suppressing directly B cell differentiation to Ig-secreting plasma cells remains to be investigated.

A role of CD8 Treg cells in immune homeostasis has been demonstrated in a number of experimental models and their alterations have been observed in human diseases (67, 68, 73–75). In our cohort of patients with SIGMD, CD8 Treg cells (CD8$^+$CCR7$^+$CD183$^+$CD45RA$^-$) were increased (46).

Lymphocyte Proliferative Response

The lymphocyte transformation in response to mitogens phytohemagglutinin, concanavalin A, and pokeweed mitogen, recall antigens, *Candida albicans*, mumps, and tetanus toxoid, and alloantigens appears to be intact in SIGMD (26, 48), demonstrating normal functioning T cells. Yamasaki (48) observed impaired B cell proliferation in six patients with SIGMD in response to *Staphylococcus aureus* Cowan (SAC) strain I (a B cell activator), suggesting B cell functional defect in SIGMD. Mensen et al. (50) examined the expansion of B cells and antibody secreting cells following stimulation of peripheral blood mononuclear cell (PBMC) or non-T cells with a cocktail of B cell stimuli.

A decreased expansion/survival of all subsets of B cells in five of six patients, and decreased IgM secreting B cells in two of six patients were observed.

Serum Immunoglobulins and Specific Antibody Responses

Serum Immunoglobulins

By definition, SIGMD is characterized by serum IgM levels below 2 SD of mean for a laboratory with normal serum IgG and IgA. However, patients with complete absence (≤3 mg/dl) of serum IgM have been reported in SIGMD. In our cohort of 55 patients with SIGMD, 4 patients have complete absence of serum IgM. IgG subclass deficiency has been reported in few cases of SIGMD (26, 76). IgG subclass deficiency is not restricted to any particular subclass. This would be analogous to association of IgG subclass deficiency with selective IgA deficiency. Because of small cohort of cases, it is difficult to determine the clinical significance of IgG subclass deficiency in patients with SIGMD. Patients with SIGMD have increased prevalence of allergic diseases, therefore, it is not surprising that serum IgE levels are increased in a subset of SIGMD (26, 48, 59, 76, 77).

Specific Antibody Responses

Specific antibody responses to T-dependent protein antigens (e.g., tetanus, diphtheria), and T-independent antigens (anti-polysaccharide antigens) have been studied in a small number of patients with SIGMD. Antibody response to diphtheria and tetanus in a small number of patients with SIGMD studied are reported to be normal (25, 26), except impaired response in the syndrome of SIGMD, T cell deficiency, and mycobacterial infection (60, 61). A role of specific antibodies in mycobacterial defense is discussed (61). The response to T-independent antigens appeared to be impaired (18, 22, 25, 26, 78). We reported impaired antibody responses against *S. pneumoniae* following Pneumovax-23 vaccination in 45% of SIGMD (26). In our current cohort of 55 patients with SIGMD, more than 45% have impaired anti-pneumococcal antibody responses (unpublished observations). Al-Herz et al. (18) and Guill et al. (30) reported decreased IgM Isohemagglutinins titers in a subset of patients with SIGMD.

PATHOGENESIS OF SIGMD

The pathogenesis of SIGMD remains unclear. A number of mechanisms have been proposed (**Table 2**). Since the majority of patients have normal surface IgM$^+$ B cells, investigators have focused their studies on the analysis of helper T cells, regulatory (suppressor) cells, and intrinsic defects of B cells. A deficiency of helper T cells (59), increased IgM isotype-specific suppressor T cells (49, 79–81), intrinsic B cell defects (48, 52), and reduced secreted μ mRNA transcripts (82) have been reported as possible pathogenic mechanisms for SIGMD. De la Concha et al. (59) reported that B cells from SIGMD patients could produce normal amounts of IgM, IgG, and IgA when coculture *in vitro* with T cells from healthy controls, suggesting a defect in T-helper cell function. However, this defect was not IgM isotype specific. In contrast, Matsushita et al. (80) reported the presence of radiosensitive IgM-specific suppressor T cells in a patient with SIGMD and giant leiomyoma of the stomach. Inoue et al. (79) using *in vitro* cocultures revealed an increased IgM isotype-specific suppressor T cell activity in all seven patients with SIGMD. Ohno et al. (49), in a recombination plaque assay, observed increased isotype IgM-specific (one case) and non-specific (one case) suppressor activity in patients with SIGMD. We have observed that CD8 Treg *in vitro* suppress immunoglobulin secretion by purified B cells (unpublished personal observations); therefore, increased CD8$^+$ Treg in SIDMD (46) may play a role in the pathogenesis of SIGMD.

In contrast, Karsh et al. (52) failed to observe any defect in T helper or T suppressor activity in SIGMD and suggested a possible intrinsic B cell defect. Takeuchi and associates (33) demonstrated that *in vitro* stimulation of PBMCs from a patient with SIGMD and systemic lupus erythematosus with IL-2 and SAC (a B cell activator) did not increased IgM synthesis, suggesting an intrinsic B cell defect. Furthermore, sequence analysis of μ heavy chain, and the IgM mRNA did not reveal any mutation or deletion. Mensen et al. (50), in a T-dependent B cell activation experimental system and using ELISA spot assay, observed decreased number of IgM-secreting cells in two of six patients with SIGMD as compared to healthy controls. Yamasaki (48) analyzed T and B cells from six patients with SIGMD. Purified B cells from SIGMD patients following *in vitro* stimulation with *SAC* in the presence of T cells from healthy controls secreted decreased amounts of IgM as compared to B cells from healthy controls. Furthermore, stimulation of patient's B cells with SAC and B cell differentiation factor (BCDF) did not increase IgM secretion. These data suggest an intrinsic B cell defect, and not of helper T cell defect or impaired BCDF production in SIGMD. We have observed increased proportion of Breg in SIGMD (46).

Whether increased Breg contribute to SIGMD by suppressing directly B cell differentiation to Ig-secreting plasma cells remains to be investigated. Since membrane bound IgM$^+$ B cells are normal, we propose there is a likelihood of gene defect(s) responsible for transport of secreted proteins, including IgM.

TABLE 2 | Proposed mechanisms for the pathogenesis of SIGMD.

Mechanisms	Reference
Decreased T helper cell activity	(59)
Increased isotype specific suppressor T cells	(49, 79, 80)
Increased CD8 Treg cells	(46)
Intrinsic B cell defect	(48, 52)
Increased Breg	(46)
Defective secretion of μ mRNA transcripts	(82)
[a]Mutations in protein transport gene(s)	

[a]*Proposed by authors.*

IMMUNOGLOBULIN THERAPY

The replacement of IgM would be an ideal therapy for SIGMD patient. Hurez et al. (83) reported that passive transfer of IgM

enriched (90%) preparation from normal human donors, in a dose-dependent manner, inhibited *in vitro* binding of a variety of autoantibodies to target autoantigens, and *in vivo* prevented the onset of experimental autoimmune uveitis in rats. Warrington et al. (84) demonstrated that the administration of recombinant human monoclonal IgM that binds to oligodendrocytes-induced remyelination in mice with chronic virus-induced demyelination, a model of chronic progressive multiple sclerosis. Vassilev and colleagues (85) demonstrated that the administration of highly enriched IgM (more than 90%) from pooled plasma of healthy donors inhibited experimental myasthenia gravis in SCID mice model that was associated with marked decreased in anti-choline receptor antibodies. However, there are no commercial immunoglobulin preparations available that is highly enriched in IgM. Since more than 45% of patients with SIGMD have an impaired specific anti-pneumococcal IgG antibody response (a defect also observed in mice with mutations in IgM FcμR), current immunoglobulin preparations may be beneficial in this subsets of clinically symptomatic patients with SIGMD. Yel et al. (26) reported favorable response to intravenous immunoglobulin in SIGMD patients with regard to frequency and severity of infections. Stoelinga et al. (35) and Fallon (86) also observed beneficial effects of IVIG in SIGMD. Goldstein and associates (87), in a retrospective chart analysis, observed clinical improvement in four patients with a triad of SIGMD, bronchiectasis, and asthma using high dose IVIG. However, in these patients no information is provided for specific antibody responses. Recently, Patel and colleagues (78) reported a patient with SIGMD and non-protective pneumococcal antibody titers, and recurrent multiple infections who responded to subcutaneous immunoglobulin therapy. Therefore, symptomatic SIGMD patients with specific antibody deficiency may be considered candidates for immunoglobulin treatment.

SUMMARY

Selective IgM deficiency is more common than previously recognized and is likely a heterogeneous disorder. Patients with SIGMD may be asymptomatic; however, commonly present with chronic and recurrent infections; some of them could be serious and life threatening. Interestingly, patients with common variable immunodeficiency with low serum IgM are clinically worse than those with normal IgM levels. There is an increased frequency of allergic and autoimmune manifestations in SIGMD. Autoimmunity in SIGMD and in mice deficient in secreted IgM and FcμR mutations, and the notably prevention of experimental autoimmune diseases by IgM supports an important immunomodulatory role of IgM. The genetic basis of SIGMD is currently unclear; however, whole exome sequencing, GWAS, and NGS may reveal gene(s) responsible for SIGMD. Patients with SIGMD should undergo a thorough immunological evaluation, particularly with history of recurrent/severe infections. A definitive diagnosis of SIGMD, especially in children, should be established after follow-up for months to a year as in few undocumented cases serum IgM levels have normalized, and after excluding any known cause of secondary SIGMD including drug (e.g., Clozapine) induced IgM deficiency (88). Furthermore, immunoglobulin treatment is a beneficial therapeutic approach for symptomatic patients with SIGMD who also have specific IgG antibody deficiency. Finally, highly enriched IgM preparations may be most desirable therapeutic modality for SIGMD with possible antimicrobial, and immunomodulatory effects on autoimmune manifestations of SIGMD.

AUTHOR CONTRIBUTIONS

AG collected and reviewed published material and wrote first draft. SG edited and proof read the manuscript.

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Truly selective primary IgM deficiency is probably very rare

Short/running title: selective IgM deficiency

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Keywords: primary selective IgM deficiency, IgM deficiency, immunodeficiency, unclassified antibody deficiency, primary immunodeficiency.

Abbreviations: ANA, antinuclear antibodies; ESID, European Society for Immunodeficiencies; ICD, International Classification of Diseases; IVIG, intravenous immunoglobulin substitution; JBZ, Jeroen Bosch Hospital; RAST, radioallergosorbent test; sIgMdef, selective IgM deficiency; SPAD, deficiency of specific IgG - specific antibody deficiency; unPAD, unclassified primary antibody deficiency.

SUMMARY

Isolated decreased serum-IgM has been associated with severe and/or recurrent infections, atopy and autoimmunity. However, the reported high prevalence of clinical problems in IgM-deficient patients may reflect the skewed tertiary center population studied so far. Also, many papers on IgM-deficiency have included patients with more abnormalities than just IgM-deficiency. We studied truly selective primary IgM deficiency according to the diagnostic criteria of the European Society for Immunodeficiencies ESID (*true sIgMdef)* by reviewing the literature (261 patients with primary decreased serum-IgM in 46 papers) and retrospectively analyzing all patients with decreased serum-IgM in a large teaching hospital in ‘s-Hertogenbosch, the Netherlands (1-July-2005 to 23-March-2016; n=8,049 IgM<0.4g/l; n=2,064 solitary [IgG+IgA normal/IgM<age-matched reference]). 359/2064 (17%) cases from our cohort had primary isolated decreased serum-IgM, proven persistent in 45/359 (13%) cases; their medical charts were reviewed. Our main finding is that true sIgMdef is probably very rare. Only 6/261 (2%) literature cases and 3/45 (7%) cases from our cohort completely fulfilled the ESID criteria; 63/261 (24%) literature cases also had other immunological abnormalities and fulfilled the criteria for unclassified antibody deficiencies (*unPAD*) instead. The diagnosis was often uncertain (*possible sIgMdef*): data on IgG-subclasses and/or vaccination responses were lacking in 192/261 (74%) literature cases and 42/45 (93%) cases from our cohort. Our results also illustrate the clinical challenge of determining the relevance of a serum sample with decreased IgM; a larger cohort of true sIgMdef patients is needed to fully explore its clinical consequences. The ESID online Registry would be a good tool for this.

INTRODUCTION

IgM deficiency is on the one hand reported to be associated with a wide range of clinical presentations including severe or recurrent infections, atopy, autoimmunity and malignancy (1). On the other hand, there are doubts about its clinical significance (2); studies in healthy populations have shown that genetic polymorphisms as well as environmental factors may influence serum IgM levels (2,3). Previous studies on the clinical significance of IgM deficiency have been affected by selection bias towards 'disease', as mostly symptomatic patients from tertiary center cohorts have been described (4–6).

The European Society for Immunodeficiencies (ESID) Registry defines primary selective IgM deficiency (sIgMdef) as a serum IgM level repeatedly below 2 SDs of normal with normal levels of serum IgA, IgG and IgG-subclasses, normal vaccination responses, absence of T-cell defects and absence of causative external factors (http://www.esid.org). Many previously published articles that report on 'IgM deficiency' do not fulfill these criteria (7,8).

To facilitate a clear discussion, we define three categories in our study: (1) truly selective primary IgM deficiency (true sIgMdef) - the ESID criteria are *completely* fulfilled, which means serum IgM levels are repeatedly decreased and IgG, IgA, IgG-subclasses and vaccination responses have been determined and were normal for age; we consider the absence of *clinical* signs suggesting a T-cell defect sufficient; (2) possible selective primary IgM deficiency (possible sIgMdef) - the diagnosis of true sIgMdef is *uncertain*, which means that the ESID criteria are not completely fulfilled, because data on IgG-subclasses and/or vaccination responses are lacking; and (3) *unclassified* primary antibody deficiency (unPAD) - other abnormalities in antibodies are also present: IgG-subclass deficiency, below-normal levels of IgG or IgA, and/or impaired vaccination responses.

The aim of our study was to learn more about the clinical significance of true sIgMdef. Therefore, we first conducted a scoping review to identify all previously published patients with decreased serum IgM. Second, we analyzed decreased serum IgM identified through the laboratory files of the Jeroen Bosch Hospital in 's-Hertogenbosch, the Netherlands, a large teaching hospital (secondary centre). Finally, we analyzed whether these fulfilled the criteria for true sIgMdef.

MATERIALS AND METHODS

Literature search

The PubMed database was searched for articles concerning 'IgM deficiency' published until May 10, 2017 (no starting date). The search query was defined as {selective OR isolated} AND {IgM OR Immunoglobulin M} AND {deficiency OR low} AND {immunodeficiency syndromes}. We also screened the reference lists of articles identified by our search strategy and added those articles that reported about decreased serum IgM (snowball method). Our search strategy is described in detail in Supplementary Figure 1. We considered decreased serum IgM to be secondary in combination with the use of immunosuppressive agents, malignancy (e.g. clear cell sarcoma, promyelocytic leukemia, multiple myeloma) or gastrointestinal loss (e.g. enteropathy through Crohn's or coeliac disease). Only papers that (also) contained patients with *primary* decreased serum IgM were included in the study. We analysed whether these patients fulfilled the criteria for *true* sIgMdef.

Our cohort

Patient selection

All serum immunoglobulin levels determined between July 1, 2005, and March 23, 2016, in the Jeroen Bosch Hospital (JBZ) in 's-Hertogenbosch, the Netherlands (encachment area 350,000; 500,000 outpatient visits & 32,000 admissions per year), were obtained (n=38,149; 5,342 (14%) samples from children and 32,509 (85%) samples from adults, missing age values in 298 samples). Of these, all samples with serum IgM values <0.4 g/l were selected (n=8,049, details in Supplementary Figure 2). Samples were excluded if serum IgM levels were normal according to age-matched reference values (these were all young children) (9). To identify all *patients* with isolated decreased serum IgM, samples with decreased age-matched IgA- and/or IgG values as well as follow-up samples of serum-IgM were excluded. The medical charts were screened regarding patient history and medication use to exclude the samples from those patients in whom decreased serum IgM could be *secondary* (caused by external factors; definition see literature review above). Patients with cystic fibrosis (n=3) were excluded because their clinical symptoms would be difficult to interpret. Laboratory data of all primary cases were analyzed to identify patients in whom serum IgM level was determined only once and in whom serum IgM level was repeatedly determined, but had normalized. Only the medical charts of patients with *persistent* decreased serum IgM levels were reviewed in detail; this patient group comprises both *possible* and *true* primary sIgMdef (definitions see Introduction). The Medical Ethical Committee Brabant approved the study.

Data collection

Data on demographics, clinical features, laboratory results and treatment, conclusions written by medical specialists and ICD-10-codes were derived from our electronic patient system. For clinical evaluation, we collected the type of medical specialist who discovered the decreased serum IgM, reason(s) for determining serum IgM, and clinical problems that could be related to antibody deficiency. We considered the following clinical problems to be possibly related to antibody deficiency: infections, atopic and/or autoimmune manifestations, inflammation of the gastrointestinal tract, long-lasting fatiguedepression and malignancies. Pneumonia required confirmation by thoracic X-ray. Allergic diseases (allergic rhinoconjunctivitis, food allergy, allergic urticaria, allergic anaphylaxis) required confirmation by skin prick testing or RAST. For immunological evaluation, we collected data on serum IgM, IgG and IgA levels and - if determined - data on IgG subclasses, T-cell subsets and function, antibody responses to vaccinations, isohemagglutinin levels, antinuclear antibodies (ANA) and specific serum IgE directed against inhalant allergens. For interpretation of serum immunoglobulins and lymphocyte subpopulations age-matched reference values were used (10). Because our laboratory cut-off for serum IgM levels is 0.2 g/l, a value of <0.2 g/l was replaced by 0.1 g/l for calculating mean serum IgM level (n=4). For interpretation of pneumococcal antibody responses laboratory specific reference values were used (11). The follow-up period was defined as the date of the first serum sample with decreased IgM until the date of data extraction. All patient data were encrypted and saved on a protected server using Research Manager software developed by Cloud9 Health Solutions (Deventer, the Netherlands).

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 21. Descriptive statistics were used to compute frequencies of categorical variables and mean (with SD) or median (with IQR) of continuous variables depending on the distribution.

RESULTS

Literature search

Supplementary Table 1 gives an overview of the identified relevant literature. 261 patients with primary decreased serum IgM were described in 46 papers. 8 patients (2 adults and 6 children) fulfilled the criteria for *combined* immunodeficiency, these were excluded. Only 6/261 patients (2.3%, 3 adults and 3 children) completely fulfilled the ESID criteria for *true* sIgMdef; 63/261 (24.1%; 44 adults and 19 children) fulfilled the criteria for *unclassified* antibody deficiency. In 192/261 patients (73.6%, 164 adults and 28 children) the diagnosis was uncertain (*possible* sIgMdef), due to incomplete laboratory data (Figure 1).

Clinical and laboratory features of the published adult and pediatric cases with true or possible sIgMdef are summarized in Tables 1 and 2. Over two-thirds of both adults and children were male (57/85 adults, 67% vs. 23/31 children, 74%). Many patients presented with infectious problems (30/62 adults, 48% vs. 14/15 children, 93%). In 3/62 (5%) of the reported adults decreased IgM was identified "by accident" as part of laboratory evaluation for ischemic heart disease, hypertension and visual disturbance. 13/62 (21%) of the reported adults and 1/15 (7%) child were asymptomatic; this boy was detected during family screening. Serum IgM values were reported in 86 adults and 14 children (mean 0.23 g/l, range 0.004-0.45 g/l for adults vs. mean 0.18 g/l, range 0.00-0.36 g/l for children). Undetectable serum IgM levels were reported in two children (12,13) and four adults (14). Three adults and one baby were treated with intravenous immunoglobulin substitution (IVIG).

Our cross-sectional retrospective cohort

2,064 patients with isolated decreased serum IgM were identified in the laboratory system of the JBZ (July 1, 2005, to March 23, 2016): 2,034 adults and 17 children aged 6-18 years (13 children <6 years were excluded because the age-matched reference value was lower than the cut-off value of the test). The patient selection process is shown in detail in Supplementary Figure 2. 1,685/2,034 adults (83%) and 7/17 (41%) children had secondary isolated decreased serum IgM. 349/2,034 (17%) adults and 10/17 (59%) children had a *primary* form; of these, serum IgM levels were determined more than once in only 49/349 (14%) adults and 3/10 (30%) children. In 7/49 (14%) of the adults the serum IgM level normalized, yielding *persistent* isolated decreased serum IgM (*possible* or *true* sIgMdef cases) in 42 adults and 3 children.

More than half of the adults (54.8%) and all the children were male. Mean age at the date of the first serum sample with decreased IgM was 61 (range 33-86) years in the adults and 16 (range 16-17) years in the children. Mean follow-up time was 74.8 (range 20-133) months in the adults and 102.7 (range 82-119) months in the children.

Clinical and laboratory features are described in Tables 2 (3 children) and 3 (42 adults). The onset and duration of symptoms could not be determined accurately in the medical files. 24% of the adults and two of the three children were analyzed for suspected

potential immunodeficiency. The others were detected during analysis for other problems, however, 22% of these adults and the one child had a history of symptoms that could be related to antibody deficiency (mainly infections). The majority (72%) of adults without such symptoms remained asymptomatic during follow-up; 28% developed symptoms that could be related to antibody deficiency. In none of the patients a family history of immunodeficiency was found in the medical charts. Only 7% (2 adults and 1 child) completely fulfilled the ESID criteria for true sIgMdef.

The first serum IgM level in possible or true sIgMdef cases ranged from <0.2 to 0.39 g/l (mean 0.30 ± 0.84) in the adults and from 0.28 to 0.38 g/l (mean 0.34 ± 0.05) in the children. First serum IgA levels were increased (>4.0 g/l) in 7 adults (17%). Serum IgE levels were determined in 6 adults and 1 child (mean 133 ± 182 U/ml; range 5-410 U/ml); they were elevated (>90 U/ml) in 2 adults. None of the patients were treated with IVIG or prophylactic antibiotics.

DISCUSSION

We studied true sIgMdef (according to the ESID diagnostic criteria) by reviewing the literature and by analyzing decreased serum IgM in our secondary hospital population. Our main finding is that *true* sIgMdef is probably very rare. Unfortunately, when a decreased serum IgM level is found, it is rarely fully analyzed. In most cases in our cohort serum IgM levels were determined only once (86%). When proven persistently decreased, further immunological analysis is often not performed (data on IgG-subclasses and/or vaccination responses were lacking in 74% of the literature cases and 93% of the cases in our cohort). Also, different criteria for 'selective IgM deficiency' are used in the literature; in a quarter of the cases, the deficiency is not 'selective', other immunological abnormalities were present. Eight literature cases even showed clinical and/or laboratory signs fitting combined immunodeficiency; these should not be classified as a form of 'predominantly antibody deficiency'. Sixty-three (24%) literature cases fitted the ESID classification 'unclassified antibody deficiency'. These patients with concomitant defects in specific antibody production (SPAD) and/or IgG-subclass deficiencies may be at risk of more severe and frequent infections, comparable to the increased number of lower respiratory tract infections and bronchiectasis in patients with IgA deficiency in combination with IgG-subclass deficiency and/or SPAD (15). Patients with recurrent and/or severe infections and decreased serum IgM levels in combination with SPAD, have been described to benefit from immunoglobulin treatment (4,16).

Routine determination of serum IgM is advised in many medical protocols, mainly for adults; we showed in our cohort that this leads to many incidental findings of decreased serum IgM. The relatively common finding of a low serum IgM level in – immunologically speaking – asymptomatic adults (see Table 3), often not followed by further evaluation, warrants reevaluation of these medical protocols. In our cohort, secondary decreased serum IgM was 5 times more prevalent in adults and 2.5 times more prevalent in children than the primary form. Hobbs et al. reported that secondary decreased IgM was 20 times more prevalent than the primary form in 1975 (17). This may be explained by the fact that age-related reference values have changed over the years, as the sensitivity of the methods used to measure serum IgM increased (Hobbs et al. <0.47 g/l >3 years, our cohort <0.21 g/l <6 years, <0.13 g/l <16 years and <0.40 g/l ≥16 years). Anyway, the first reaction to finding a low IgM should be to exclude a secondary cause.

The fact that only a few incidental findings of decreased serum IgM were followed by further evaluation in our cohort, suggests that the perceived medical problems were mild. Most of our incidentally diagnosed cases with true or possible sIgMdef did not have a history of symptoms related to antibody deficiency (76%), and that often remained to be the case during follow-up (72%) (on the other hand, 28% later developed symptoms that could be related to antibody deficiency). The higher prevalence of various associated diseases in the

literature cases (1) is probably related to the fact that these patients had been referred to specialized allergy and immunology clinics (4–6).

Interestingly, possible or true sIgMdef was more frequently observed in males in our cohort. This parallels the observed male predominance in the literature. However, also among healthy controls low IgM levels are more common in males (18–21), and there are some reports of low serum IgM levels among fathers of patients (22,23). It would be of interest to investigate this gender difference further.

The limitation of our study is of course its retrospective design. We collected our cohort data from the medical files, which were not collected with a research purpose in mind. Therefore, we could not correct for environmental factors and genetic polymorphisms that may influence serum IgM levels (3). However, although very interesting on a population basis, these factors are probably not very helpful in directing decisions regarding individual patient care in the doctor's consulting room.

In conclusion, our review of the literature and retrospective secondary center cohort study on decreased serum IgM, illustrate the challenge of determining the clinical significance of a serum sample with decreased IgM. The diagnosis could rarely be made with certainty, but *truly selective primary* IgM deficiency is probably very rare. Our strict definitions and thorough analysis of the available information have yielded the largest cohort study so far. Still a larger cohort of true sIgMdef patients is needed to fully explore the clinical consequences; the ESID online Registry would be a good tool for this.

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L.M.A.J. and E.d.V. designed the study and wrote the manuscript. L.M.A.J. acquired the data and carried out statistical analyses. E.d.V. supervised and critically reviewed all data collection. T.M., M.C.W.C., J.F.M.P., and J.J.J.E. critically reviewed the results and contributed to the final version of the manuscript; all authors approved the final manuscript as submitted.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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Figure legends

Figure 1. Patients with truly selective primary IgM deficiency in the literature (according to the ESID Registry clinical diagnosis criteria).

Abbreviations: PAR, pneumococcal antibody response; sIgMdef, selective IgM deficiency; unPAD, unclassified primary antibody deficiency.

Supplementary Figure 1. Identification of papers that report on patients with decreased serum IgM (date: 10 May 2017).

Abbreviations: sIgMdef, selective IgM deficiency; unPAD, unclassified primary antibody deficiency.

Supplementary Figure 2. Patient selection.

Abbreviations: CF, cystic fibrosis; Ig, immunoglobulin; pt, patient; sIgMdef, selective IgM deficiency.

Table 1. Adult patients from the literature. The 3 adults with *true* and 164 adults with *possible* selective primary IgM deficiency from the literature (definition of true selective IgM deficiency (sIgMdef) according to the ESID registry clinical diagnosis criteria).

Year	Reference	Reported patients[a]	Age Years/gender	Clinical manifestation(s) that could be related to antibody deficiency[b]	Familial cases	Serum IgM level (g/l)	IVIG (yes/no)
ESID criteria completely fulfilled (*true* sIgMdef)							
2009	(4)	3	79/M	Asthma, myalgia, fatigue	No	0.18	No
			39/F	Recurrent respiratory infections, allergic rhinitis, asthma,	No	0.16	No
				myalgia	No	0.39	No
			55/M	Recurrent shingles, myalgia, arthralgia, fatigue			
ESID criteria not completely fulfilled: data on IgG subclasses and/or pneumococcal antibody responses lacking (*possible* sIgMdef)							
1967	(22)	5	Adult/M	Asymptomatic	Yes	0.40	No
			Adult/M	Asymptomatic	Yes	0.40	No
			Adult/M	Asymptomatic	Yes	0.45	No
			Adult/M	Asymptomatic	Yes	0.30	No
			Adult/F	Asymptomatic	Yes	0.30	No
1970	(24)	10	20/M	Bacterial infections, asthma	n.r.	0.36	No
			23/M	Allergic rhinitis	n.r.	0.41	No
			28/M	Bacterial infections, asthma	n.r.	0.42	No
			30/M	Bacterial infections, asthma, atopic dermatitis	n.r.	0.41	No
			31/M	Bacterial infections, asthma	n.r.	0.35	No
			33/M	Bacterial infections, atopic dermatitis	n.r.	0.24	No
			48/M	Asthma	n.r.	0.41	No
			50/M	Asthma	n.r.	0.43	No
			56/M	Asthma	n.r.	0.41	No
			75/M	Bacterial infections, asthma	n.r.	0.35	No
1973	(25)	2	22/M	CMV hepatitis	Yes	0.28	No
			20/M	Psittacosis	Yes	0.33	No
1975	(17)	70	n.r.[c]	Recurrent respiratory infections(59%), asymptomatic (19%)	n.r.	n.r.	No
1976	(26)	2	72/M	No	No	0.15	No
			60/M	Tuberculosis pneumonia	No	0.04	No
1978	(27)	1	48/M	Pneumonia, sepsis, rheumatic heart disease	n.r.	0.21	No
1981	(28)	1	21/M	Smallpox, pneumonia, died from infection	No	0.20	No
1981	(29)	1	85/M	No	n.r.	0.17	No
1982	(30)	1	65/M	No	n.r.	0.01	No
1984	(31)	1	66/M	Stomach leiomyoma	n.r.	0.08	No
1986	(32)	7	58/M	Urinary tract infection, pulmonary tuberculosis	n.r.	0.20	No

			73/F	Urinary tract infection, respiratory infection	n.r.	0.14	No
			71/F	Urinary tract infection, pneumonia	n.r.	0.11	No
			53/F	Urinary tract infection, rheumatoid arthritis	n.r.	0.17	No
			29/F	Urinary tract infection, respiratory infection, SLE	n.r.	0.25	No
			30/M	Urinary tract infection, SLE	n.r.	0.06	No
			48/M	Pneumonia	n.r.	0.10	No
1987	(33)	4	44/F	SLE-like	n.r.	0.26	No
			62/F	Asthma	n.r.	0.23	No
			60/F	Lymphoma	n.r.	0.08	No
			51/F	SLE	n.r.	0.10	No
1992	(34)	6	50/M	Liver abscess, cholangitis, dermatitis	No	0.18	No
			57/M	Diabetes mellitus	No	0.06	No
			22/M	Streptococcal infection	No	0.32	No
			34/M	Chronic tonsillitis, bronchitis, psoriasis pustulosa	No	0.01	No
			57/M	Diabetes mellitus, polyarthritis	No	0.004	No
			37/F	Asymptomatic	No	0.34	No
2004	(35)	1	23/M	Recurrent respiratory infections, allergic rhinitis, asthma	No	0.28	Yes
2006	(5)	23	Unknown[d]	n.a.	No	0.32	No
2009	(4)	5	69/M	Asthma, rhinorrhea	No	0.39	No
			44/F	Chronic sinusitis	No	0.27	Yes
			44/F	Recurrent sinus infections, allergic rhinitis, rash	No	0.28	No
			76/M	Recurrent respiratory infections	No	0.30	No
			46/F	Recurrent respiratory infections, rheumatoid arthritis	No	0.39	No
2009	(36)	2	n.r.	n.r.	n.r.	n.r.	n.r.
2015	(37)	1	52/M	CEP, pericarditis, allergic rhinitis, asthma, celiac disease	No	0.32	No
2016	(2)	11	57/M	Asymptomatic	No	0.19	No
			45/M	Urinary tract infection (2x)	No	0.29	No
			48/M	Atopic dermatitis, allergic rhinitis, food allergy	No	0.27	No
			50/F	Atopic dermatitis, allergic rhinitis	No	0.25	No
			32/M	Atopic dermatitis	No	0.27	No
			55/F	Asymptomatic	No	0.23	No
			63/M	Asymptomatic	No	0.27	No
			57/M	Asymptomatic	No	0.19	No
			48/M	Asymptomatic	No	0.29	No
			50/M	Asymptomatic	No	0.16	No
			30/M	Asymptomatic	No	0.26	No

2016	(14)	10	Unkown[e]	n.r.		n.r.	Unknown	n.r.

Abbreviations: CEP, chronic eosinophilic pneumonia; CMV, cytomegalovirus; ESID, European Society for Immunodeficiency; F, female; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; M, male; n.a., not applicable; n.r., not reported; SLE, systemic lupus erythematosus.

a)Only reported patients fulfilling the criteria for reported *true* or *possible* primary sIgMdef are described in this table.

b)The difference between "asymptomatic" and "no" is that "no" refers to patients who were screened for problems not related to antibody deficiency in contrast to asymptomatic patients, who had no clinical problems at all.

c)70 patients were reported without specific age indications or exact IgM levels in this paper.

d)Clinical manifestations of patients were not separately described in this paper. Mean age at diagnosis of the whole group was 54 years; 11 males, 12 females. One patient was treated with IVIG because of refractory asthma.

e)Patient data were not separately described in this paper. Of the twenty described patients, 50% had also specific antipolysaccharide antibody deficiency, and fulfilled the criteria for 'unclassified antibody deficiency'. Therefore, these 10 patients were not included in this table. Age range of the whole group: 24 years-56 years, F:M ratio 1.1:1.0, serum IgM range: 0.04 g/l to 0.32 g/l.

Table 2. Paediatric patients from the literature and our cohort. The 3 paediatric patients from our cohort and 31 paediatric patients with *true* or *possible* selective primary IgM deficiency (sIgMdef) from the literature.

Year	Reference	Reported patients	Age Years/gender	Clinical manifestations that could be related to antibody deficiency	Serum IgM level (g/l)	IVIG (yes/no)
ESID criteria completely fulfilled (*true* sIgMdef)						
Our cohort			16/M	URTI, growth retardation, verrucae vulgares, RLS	0.36	No
2008	(6)	2	10/M	Recurrent otitis media	0.21	No
			12/M	Pneumonia	0.30	No
2009	(38)	1	6/M	Multiple recurrent impetigo	0.21	No
Data on IgG subclasses present, but no data on pneumococcal antibody responses (*possible* sIgMdef)						
No cases						
Data on pneumococcal antibody responses present, but no data on IgG subclasses (*possible* sIgMdef)						
2013	(39)	16	Unknown[a]	n.r.	n.r.	n.r.
No data on pneumococcal antibody responses and no data on IgG subclasses (*possible* sIgMdef)						
Our cohort			16/M	Recurrent infections, asthma, verrucae vulgares	0.28	No
Our cohort			17/M	Depression, long-lasting fatigue	0.38	No
1967	(22)	1	5/M	Meningococcal meningitis, died from infection	0.12	No
1971	(13)	1	0/M	Recurrent pseudomonas infections	0.00	No
1973	(40)	1	2/F	Recurrent otitis media, laryngitis, meningitis	0.08	No
1973	(25)	1	13/M	CMV hepatitis	0.26	No
1973	(41)	2	4/M	Meningitis	0.34	No
			1/M	Asymptomatic	0.36	No
1986	(42)	1	16/F	Disseminated molluscum contagiosum	0.04	No
1989	(12)	1	3/M	Recurrent infections	0.00	No
2001	(43)	1	10/M	Recurrent sinusitis, pneumonia, chronic staphylococci blepharitis	0.23	No
2005	(23)	1	0/M	Pseudomonas septicemia	0.12	Yes
2009	(44)	1	6/M	Chronic recurrent multifocal osteomyelitis	0.20	No
2010	(45)	1	16/M	Refractory giardiasis	0.21	No

Abbreviations: CMV, cytomegalovirus; F, female; Ig, immunoglobulin; IVIG, intravenous immunoglobulin; M, male; n.a., not applicable; n.r., not reported; URTI, upper respiratory tract infection; RLS, Raynaud-like symptoms.

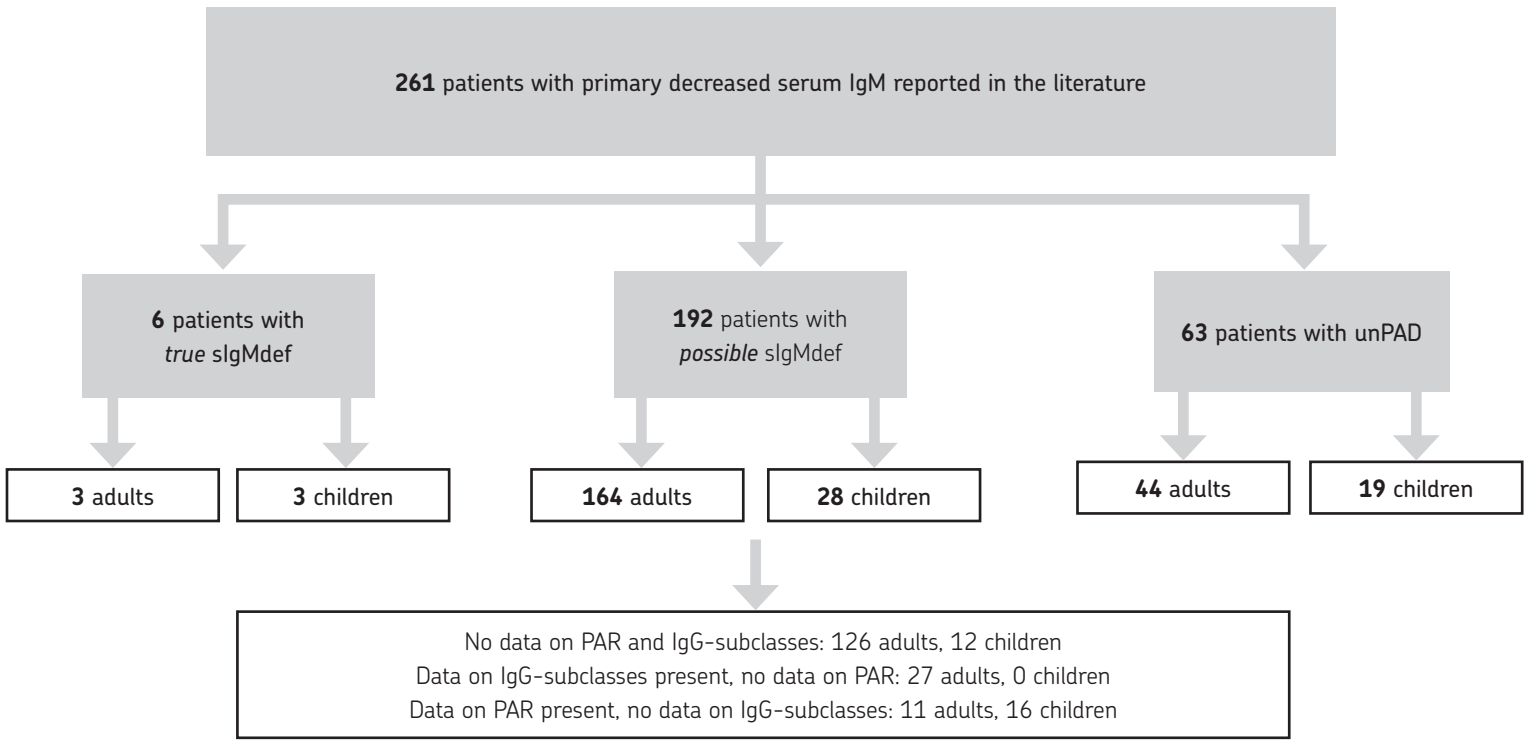
a)Patients were not separately described in this paper. Median age at diagnosis was 4.2 years; 10 males, 6 females.

Table 3. Adult patients from our cohort. The 42 adult patients with *true* or *possible* selective primary IgM deficiency (sIgMdef) from our cohort.

Patient	Age Years/gender	Reason(s) for determining serum IgM level	Manifestation(s) *during follow-up* that could be related to antibody deficiency	First serum IgM level (g/l)	Last serum IgM level (g/l)
10 adults analysed for potential immunodeficiency					
ESID criteria completely fulfilled (true sIgMdef)					
1	54/F	Recurrent respiratory infections, asthma, AR	Long-lasting fatigue, keratitis	0.26	0.27
2	41/M	Recurrent respiratory infections, asthma	-	0.23	0.26
Data on IgG subclasses present, but no data on pneumococcal antibody responses (possible sIgMdef)					
3	33/M	Recurrent respiratory infections, asthma	-	0.29	0.24
4	33/F	Recurrent vaginal candidiasis, weight loss	-	0.24	0.24
5	68/F	Pneumonia	CREST-syndrome, ABPA	0.37	0.30
6	73/F	Recurrent pneumonia, bronchiectasis, AR	Chronic sinusitis	0.36	0.29
Data on pneumococcal antibody responses present, but no data on IgG subclasses (possible sIgMdef)					
7[a]	34/M	Arthralgia	Erysipelas	<0.20	<0.20
No data on pneumococcal antibody responses and no data on IgG subclasses (possible sIgMdef)					
8	53/F	Recurrent UTI, sinusitis	Inflammatory nodular hand osteoarthritis	0.26	0.24
9	71/M	Pneumonia, bronchiectasis	-	0.26	0.22
10	76/F	Non-healing ulcer on feet	Depression, bronchiectasis, UTI	<0.20	<0.20
7 adults diagnosed during analysis for other problems; history of symptoms that could be related to antibody deficiency					
No data on pneumococcal antibody responses and no data on IgG subclasses (possible sIgMdef)					
serum IgM ordered by a neurologist					
11	45/M	Migraine	-	0.24	0.25
12	79/M	Polyneuropathy	Psoriasis	0.39	0.32
serum IgM ordered by an internist					
13	55/F	Liver test abnormalities	-	0.38	0.31
14	58/F	Liver test abnormalities	-	0.35	0.32
15	60/M	Collapsed vertebra	-	0.23	0.23
16	73/M	Renal insufficiency	Chronic Q fever	<0.20	0.21
17	51/M	Long-lasting fatigue, Q fever infection	-	0.26	0.33
25 adults diagnosed during analysis for other problems; no history of symptoms that could be related to antibody deficiency					
No data on pneumococcal antibody responses and no data on IgG subclasses (possible sIgMdef)					
serum IgM ordered by a rheumatologist					
18	68/M	Arthralgia, RLS	Cholecystitis, pharyngitis, infected hematoma	0.28	0.27

19	65/M	Arthralgia, myalgia	-	0.28	0.26
20	75/F	Raynaud-like symptoms	Basal cell carcinoma	<0.20	0.22
21	51/M	Arthritis urica	Inflammatory arthritis	0.38	0.30
serum IgM ordered by an internist					
22	67/F	Hypoparathyroidism, hypothyroidism	Abscess in thigh, infection of right hip	0.27	0.27
23	70/M	Liver test abnormalities	-	0.26	<0.2
24	62/F	Weight loss	-	0.37	0.30
25	52/F	Micro-albuminuria, hypothyroidism	Chronic Q fever	0.22	0.27
26	43/F	Splenic infarcts, abdominal pain	-	0.38	0.23
27	55/M	Haematuria, recurrent kidney stones	UTI, respiratory infection, cervical lymphadenopathy	0.35	0.37
28	71/F	Renal insufficiency	-	0.32	0.31
29	45/M	Renal insufficiency	-	0.37	0.32
30	69/M	Renal insufficiency	-	0.37	0.32
serum IgM ordered by a neurologist					
31	66/M	Polyneuropathy	-	0.36	0.31
32	67/F	Polyneuropathy	-	0.32	0.31
33	68/M	Polyneuropathy	Nodular basal cell carcinoma	0.39	0.37
34	72/F	Polyneuropathy	-	0.39	0.39
35	73/F	Polyneuropathy	-	0.32	0.36
36	74/F	Polyneuropathy	-	0.37	0.36
37	74/M	Polyneuropathy	-	0.33	0.37
38	58/F	Polyneuropathy	-	0.36	0.39
39	84/M	Polyneuropathy	-	0.37	0.36
40	86/M	Polyneuropathy	-	0.32	0.36
41	46/M	Polyneuropathy	-	0.32	0.23
42	63/M	Polyneuropathy	-	0.35	0.27

Abbreviations: ABPA, allergic bronchopulmonal aspergillosis; AR, allergic rhinitis; CREST, calcinosis, raynaud's phenomenon, esophageal dysmotility, sclerodactyly, teleangiectasia; ESID, European society for immunodeficiencies; F, female; Ig, immunoglobulin; M, male; RLS, Raynaud-like symptoms; UTI, urinary tract infection.
a)This patient was diagnosed during analysis for rheumatoid arthritis. He was referred to a university centre elsewhere for analysis for potential immunodeficiency when a persistent decreased IgM level was discovered.



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Primary Selective IgM Deficiency: An Ignored Immunodeficiency

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Abstract Immunoglobulin M (IgM) provides the initial response to foreign antigen and plays a regulatory role in subsequent immune response development, accelerating the production of high-affinity IgG. Though selective IgM deficiency was described more than 45 years ago in children with fulminant meningococcal septicemia, it has been largely an ignored primary immunodeficiency. It appears to be more common than originally realized. Selective IgM deficiency is observed in both children and adults with no gender bias. The most common clinical manifestation of selective IgM deficiency is infections with extracellular and intracellular bacteria, viruses, and fungi. Allergic diatheses are the second commonest presentation of selective IgM deficiency. There is an increased prevalence of autoimmune diseases, which in both humans and mice appear to be secondary to selective IgM deficiency rather IgM deficiency secondary to autoimmune diseases. Selective IgM deficiency, in some cases, is associated with 22q11.2 chromosome deletion and few familial cases of selective IgM deficiency have been reported. Innate immunity is relatively intact. T cells, T cell subsets, and T cell functions are normal. However, several patients with selective IgM deficiency and T cell and NK cell defects with *Mycobacterium avium intracellulare* infections have been reported. In a subset of patients with selective IgM deficiency circulating IgM+ B cells are decreased or completely lacking. Specific IgG antibody responses against pneumococcus polysaccharides are impaired in a subset of patients with selective IgM deficiency. The pathogenesis of selective IgM deficiency is unclear; decreased T helper activity, increased isotype-specific suppressor T cell activity, and intrinsic B cell defects have been reported. Patients with selective IgM deficiency and impaired pneumococcal antibody responses appear to respond to immunoglobulin therapy.

Keywords IgM deficiency · Autoimmunity · Malignancy · Specific antibody deficiency

Introduction

During B cell development, the pre-B cell is the first cell that synthesizes immunoglobulin peptide. The rearranged Ig heavy chain gene is transcribed to produce a primary transcript that includes rearranged VDJ complex and proximal (μ and δ) C genes. Subsequent processing of RNA leads to splicing out the intervening sequences between VDJ complex and Cμ gene, resulting in a functional mRNA for μ heavy chain, which is then transcribed to produce a μ chain protein in Pre-B cells. This is a membrane form of μ chain; however, most of it remains within the cytoplasm because chaperone proteins associated with newly synthesized μ chain, restrict their movement out of the cell. Most of the cytoplasmic μ chain in the pre-B cell is degraded and only a small amount is expressed on the cell surface in association with a surrogate light chain to form the pre-B cell receptor. During next stage of maturation, each developing cell also rearranges κ or λ light chain, which associates with μ heavy chain to produce a complete IgM protein, which is expressed on the surface of immature B cells. During the next stage of development to the mature B cell, the cells co-express μ and δ heavy chain in association with κ or γ light chain, thereby producing both membrane IgM and IgD. Both surface Igs have same V region, and therefore, the same specificity. Mature naïve B cells are antigen

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responsive, and respond to both protein and non-protein antigens to undergo proliferation, and a few of these cell differentiate into Ig secreting cells. IgM is the first Ig produced and is the immunoglobulin that is predominantly produced in response to T-independent antigens such as polysaccharides and lipid. Activated T cells secrete cytokines and express CD40L. A small progeny of activated IgM+IgD+ B cells upon engagement of CD40 and cytokines undergo the process of heavy chain isotype (class) switching resulting in the production of antibodies of different isotypes such as IgG, IgA, and IgE [1]. Class switch occurs in peripheral lymph nodes. In the germinal center of lymph nodes, Ig V genes undergo point mutation (somatic hypermutation) leading high affinity antibody producing B cells [1, 2]. The importance of "antigen-induced" IgM antibody in protection against infection and autoimmune diseases has been established in mice deficient in IgM secretion [3, 4]. In addition to "antigen-induced" IgM antibodies, serum IgM in healthy individuals is also comprised of a majority of "natural" autoantibodies that exhibit self reactivity [5]. These antibodies appear to arise naturally without actual antigen stimulation as they are present in human cord blood and in mice housed in germ-free conditions. Natural autoantibodies are unmutated and typically polyreactive. These natural autoantibodies provide early defense against pathogens [6] and play an important role in immune homeostasis and modulation of innate and adaptive immune responses, and clearance of apoptotic cells (self antigens), thereby conferring protection from autoimmune and inflammatory injuries [7]

Prevalence

The true prevalence of primary selective IgM deficiency is unknown. The prevalence of complete primary selective IgM deficiency in children in a community-based survey was reported in 1970s to be 0.03 % [8]. The prevalence of deficient but detectable levels of IgM was reported to be 0.1 % to 3.8 % in hospitalized patients [9–12], 1.68 % in unselected community health screening [4], and 0.07 % in an Allergy and Clinical Immunology clinic [13]. In a more recent study of long-term follow-up [14], two of 421 children with primary immunodeficiency had persistent selective IgM deficiency (0.5 %). Ozen et al. [15] reported 3 children with selective IgM deficiency among 131 children with primary immunodeficiency (2.1 %). In our Primary Immunodeficiency clinic, among 451 patients with primary immunodeficiency, we are currently following 25 adult symptomatic patients with persistent primary selective IgM deficiency (6 %); 15 were previously reported [16]. The selective IgM deficiency appears to be equally distributed among male and female.

Genetics

No definitive inheritance pattern has been reported in patients with selective IgM deficiency. However, only a few family studies have been reported. Since some of these patients are asymptomatic, and therefore, serum immunoglobulins have not been performed on family members. Few familial cases, however, have been reported. Yocum et al. [17] reported selective IgM deficiency in three generation of males in one family. We have a mother and daughter with selective IgM deficiency and specific antibody deficiency who presented with recurrent infections (unpublished data). Selective IgM deficiency has also been reported with a genetic disorder Russell–Silver syndrome, a growth disorder, which possibly involving hypomethylation of H19 and IGF2 [18]. A number of chromosomal abnormalities, including of chromosome 1, 18, and 22q11.2 have also been reported in patients with selective IgM deficiency [19–21]. Kung et al. [21] described selective IgM deficiency in two patients with 22q11.2 deletion syndrome, a 6-year-young boy who presented with chronic rhinitis and recurrent sinusitis and pneumonia, and a 14-year-young girl who presented with failure to thrive and mucopurulent discharge from nostrils. No cardiac, pulmonary, or neurological abnormalities were present. Al-Herz et al. [22] also reported selective IgM deficiency in a 15-year-young girl with 22q11.2 deletion syndrome. Others have also reported selective IgM deficiency with 22q11.2 deletion syndrome [23, 24]. Gennery et al. [23] reported low IgM levels in 3 of 32 patients with 22q11.2. However, through careful analysis of these cases, it appears that two of these cases are likely to be of common variable immunodeficiency and only one case is of selective IgM deficiency. It has been proposed that since the genetic sites of the V, J, and C regions of λ light chain are in 22q11.2 region, it may be responsible for decreased immunoglobulin synthesis [22]; however, it cannot explain selective IgM deficiency with normal IgG and IgA. Nevertheless, it would be of interest to examine a large cohort of 22q11.2 patients for selective IgM deficiency.

Clinical Features

Although selective immunodeficiency has been associated with various infections (Table 1) including upper and lower respiratory tract infection such as recurrent otitis media, chronic sinusitis, bronchitis, bronchiectasis, pneumonia, deep tissue and liver abscess, cellulitis, meningitis, sepsis, diarrhea, cholangitis, hepatitis, chronic moniliasis, and allergic rhinitis/asthma or anaphylaxis [9, 11–13, 16, 17, 24–33], it may also occur in asymptomatic individuals [12]. In children with selective IgM deficiency, infectious manifestations are more common and allergic and autoimmune diseases and malignancies are infrequent [34],

Table 1 Clinical presentations in selective IgM deficiency

Upper respiratory tract infections
Otitis media
Sinusitis
Bronchitis
Pneumonia
Allergic rhinitis
Allergic asthma
Atopic dermatitis
Anaphylaxis
Diarrhea
Liver abscess
Cholangitis
Chronic moniliasis
Sepsis
Meningitis
Vaccinia
Fibromyalgia
Vericella zoster infection
Cellulitis
Recurrent impetigo
Pyelonephritis

Table 2 Infections in primary selective IgM deficiency

Staphylococcus aureus
Psuedomonas aerugenosa
Sterptoccocus pneumniae
Neisseria Meningitides
Hemophilus influenza
Mycobacterium tuberculosis
Mycobacterium avium icomplex (MAC)
Listeria monocytogenes
Brucella abortus
Giardia lamblia
Aspergillus fumigates
Pneumocystis carinii
Varicella zoster
Cytomegalovirus
Molluscum contagiosum

whereas in adults with selective IgM deficiency, though recurrent upper and lower respiratory tract infections are common, allergic and autoimmune diseases are also frequently present [13, 16]. Patients with selective IgM deficiency may present with a variety of dermatological manifestations including deep skin abscesses, recurrent impetigo, pyoderma, siddeminated molluscum contageosum, CD34+ cutaneous lymphoproliferative disorder, and epidermaldysplasia verruciformis [13, 29, 35–38]. A number of autoimmune diseases and malignancies have also been reported in association with selective IgM deficiency,

Infections More than 80 % of patients present with recurrent infections [13, 16]. Infections may be caused by a variety of extracellular and intracellular bacteria, protozoan, viruses, and fungi (Table 2); some of these bacterial infections resulting in meningitis and sepsis could be life-threatening. Infection with *Aspergillus* species is intriguing [16]. Kutukchular and Gulez [14] reported a long-term follow-up (34.1±22 months) of 37 children (mean age 51.5± 25.8 months) with symptomatic hypogammaglobulinemia among 421 children who were diagnosed with primary immunodeficiency. The commonest clinical presentations included upper and lower respiratory tract infections, urinary tract infections, and gastroenteritis. In several of these patients, spontaneous correction of various immunoglobulin deficiencies (IgG, IgA, and IgM) was observed. However, two children remained selective IgM deficient. Therefore, a diagnosis of selective IgM in children should be established after a follow-up of their immunoglobulin levels.

These observations support that IgM is an important component of host defense against various microorganisms. It also appears that normal serum levels of IgG, i.e., secondary antibody response, cannot compensate for the defective IgM response at least under certain circumstances. However, one cannot conclude a cause–effect relationship between low IgM levels and recurrent infections. Despite normal IgG levels, specific antibody response to polysaccharide antigens may be defective. This association is shown as impaired antibody response to pneumococcal polysaccharide antigens in 45 % of 11 tested patients [16]. All of those patients presented with recurrent or severe, life-threatening infections. Nevertheless, our data do not support the opinion that the specific antibody defect in patients with IgM deficiency per se would be the cause of susceptibility to infections, since 5 out of 6 patients whose specific antibody production appeared to be intact experienced recurrent infections as well. Therefore, susceptibility to infections in IgM deficiency is probably due to a number of contributing factors of which specific antibody deficiency appears to be important factor.

Naïve B cells from mutant mice deficient in IgM secretion, following antigen stimulation, undergo Ig isotype switching to other immunoglobulin isotypes; however, these animals are unable to control viral, bacterial, and fungal infections due to lack of serum IgM and inefficient induction of a protective IgG antibody response [3, 39, 40], which is analogous to patients with selective IgM deficiency.

Allergic Diseases In our experience of adult patients with selective IgM deficiency, approximately 25 % of patients have allergic rhinitis/asthma [16]. In our series, the second most common manifestation was allergic disorders (33 %);

this is in parallel with the results of Goldstein et al. [13] in adults who found the frequency of asthma and allergic rhinitis to be 47 % and 36 %, respectively. The association of IgM deficiency and atopy was described previously in 10 patients with asthma by Kaufman and Hobbs [41]. Some other reports have also noted an association between atopic diseases and selective IgM deficiency [25]. However, it is not easy to explain the mechanism of this association since it is not clear why and how a low IgM would cause a shift from Th1 towards a Th2 response, which is the basic mechanism in allergic disorders. In addition, not all of these atopic patients had elevated serum IgE levels and/or eosinophilia. It is also important to keep in mind that the prevalence of atopic disorders can be as high as 20–25 % in the general population.

Autoimmune Diseases A number of autoimmune diseases (Table 3) have been described in association with selective IgM deficiency [42–51]. Though selective IgM deficiency has been considered secondary to autoimmune disorders, there is no evidence to support this notion. A possibility should be entertained that autoimmune disorders associated with selective IgM deficiency are secondary to primary selective IgM deficiency because patients with other primary immunodeficiency diseases also have higher incidence and prevalence of autoimmune diseases [52]. There are no large long-term follow-up studies of patients with selective IgM deficiency. In long-term follow-up of our patients, we have observed development of autoimmune diseases in 2 of 25 patients with selective IgM deficiency a few years following the diagnosis of selective IgM deficiency (unpublished data). Antar et al. [46] described an adult patient with selective IgM deficiency and recurrent infections who later developed autoimmune glomerulonephritis. These observations suggest that autoimmune diseases may be secondary manifestations of primary selective IgM deficiency. A role of both "natural" and "antigen-induced" IgM in protection against autoimmunity and autoimmune diseases is well established in mice deficient in secreted IgM [3, 53]. Autoimmune pathology associated with IgG autoantibodies is exacerbated in mutant mice with deficient secreted IgM, possibly because of impaired clearance of autoantigen expressing apoptotic cells [4, 46]. Ehrenstein et al. [54] demonstrated that mice deficient in serum IgM have an increased propensity to spontaneous autoimmunity as evidenced by the development of serum IgG anti-DNA antibodies and the renal deposition of IgG and complement. These mice exhibit increased anti-DNA IgG production on exposure to lipopolysaccharide. More recently, several investigators have demonstrated that effector functions of IgM with regard to enhancement of antibody responses and suppression of autoimmunity are mediated via interaction of IgM with Fcμ receptor. Ochida et al. [55] reported that phenotype of FcμR-deficient mice is similar to but not as severe as CD19-deficient mice [56] in terms of decreased marginal zone B cells, impaired germinal center formation, and reduced antibody production to T-independent and T-dependent antigen, and impaired memory response. In addition, they observed that these mice, both male and female, produced elevated levels of IgG autoantibodies (anti-dsDNA, rheumatoid factor, and antinuclear antibodies) as they aged. It is interesting to note that autoimmune diseases are more common in adult patients with selective IgM deficiency than children with selective IgM deficiency. Although the precise mechanism of IgM-mediated suppression of autoimmunity is unclear, one of the possibilities that have been entertained is that the IgM–autoantigen complex may cross-link FcμR and BCR on autoreactive B cells and trigger their deletion/anergy. The phenotype of FcμR-deficient mice resembles that of mice lacking secreted IgM with regard to reduced specific antibody responses and development of autoantibody production [3, 53, 57]. Thus, deficiency in serum IgM may explain a paradox of diminished responsiveness to foreign antigens (therefore, increased susceptibility to infections) and increased responsiveness to self-antigen resulting in autoimmunity and autoimmune diseases in patients with selective IgM deficiency.

In addition, to effector function of IgM in self tolerance, other mechanisms of autoimmunity in patients with selective IgM deficiency may be explored. A possibility of lost tolerance either at the level of bone marrow (receptor editing) and/or in the periphery secondary to a deficiency of isotype-specific regulatory T cells may be entertained. In addition, selective IgM deficiency might also have decreased or absence of natural IgM autoantibodies, resulting in impaired clearance of apoptotic cells (self antigens) leading to the development of autoimmune diseases. These possibilities are currently under investigation in our laboratories.

Malignancies There are only few cases of malignancy with selective IgM deficiency that have been reported [38, 58–60]. These include clear cell sarcoma, multiple

Table 3 Autoimmune diseases associated with selective IgM deficiency

Systemic lupus erythematosus
Rheumatoid arthritis
Hashimoto's thyroiditis
Autoimmune hemolytic anemia
Crohn's disease
Celiac disease
Vitligo
Polymyositis
Autoimmune glomerulonephritis
Chronic idiopathic thrombocytopenic purpura

myeloma, non-Hodgkin's lymphoma, primary cutaneous anaplastic large cell CD30+ lymphoma, promyelocytic leukemia, hepatocellular carcinoma, and stomach Leiomyoma. Any cause and effect relationship remains unclear. These malignancies may be just coincidental findings, or secondary to B cell defects (in B cell malignancies), or due to an increased susceptibility to malignancies as in other primary Immunodeficiency diseases. One patient with selective IgM deficiency and angioedema developed non-Hodgkin's lymphoma one year after the diagnosis of selective IgM deficiency [16]. It is still possible that it might have been a low grade lymphoma therefore explaining the delay in the diagnosis of lymphoma, and the selective IgM deficiency being secondary to lymphoma. In a patient with clear cell carcinoma, co-culture of mononuclear cells in vitro suppressed IgM secretion by normal B cells, suggesting increased suppressor cell activity may be responsible for selective IgM deficiency [58].

Immune Response in Selective IgM Deficiency

Various abnormalities in T and B cell numbers and functions have been reported in selective IgM deficiency [16, 17, 35, 36, 61–66]. In contrast, innate immune responses appear to be preserved, including a number of polymorphonuclear leucocytes, natural killer cells, and monocytes [65]. Neutrophil functions, including chemotaxis, phagocytosis, bactericidal killing, and levels of complement components are normal [36, 63, 65].

Lymphocyte Phenotype

In the majority of patients with selective IgM deficiency, surface IgM+ B cells (sIgM+), CD19+ B cells, and CD20+ B cells are normal (16, 17. 64). However, low to complete lack of sIgM+ or CD19+ or CD20+ B cells has been reported [16, 64, 65]. We observed decreased number of peripheral blood CD19+ B cells in 2 of 15 subjects and complete lack of CD19+ B cells in one of 15 patients with selective IgM deficiency [16]. Inoue et al. [61] reported three patients with decreased B cells; however, two of them also had decreased expression of sIgM, sIgG, and sIgA. In only one patient, selective sIgM+ expression was decreased. Ideura et al. [65] reported decreased number of memory B cells in a single patient with selective IgM deficiency who presented with bronchial polyp. Belgemen et al. [36] observed decreased class-switched memory B cells in a patient with selective IgM deficiency. In IgM-deficient mice as well as FcμR mutant mice, there is an impaired germinal center formation and decreased memory cells [55].

Serum Immunoglobulins and Specific Antibody Responses

Serum Immunoglobulins

Serum IgM levels in selective IgM deficiency ranged from undetectable (complete absence) to levels below 2 SD of the mean (partial deficiency). IgM deficiency was first described by Hobbs et al. [11] in 1967, when 2 male children with fulminant meningococcal septicemia were found to have low levels of IgM. In our 15 cases, IgM levels ranged between 14 and 39 mg/dl [20]. Since this publication, we have an additional ten patients with selective IgM deficiency in whom serum IgM levels ranged from 3 to 47 mg/dl (unpublished data). IgG and IgA levels are normal. However, a few cases of associated low IgG subclasses have been reported [16, 65], a condition very similar to selective IgA deficiency, which is also occasionally associated with IgG subclass deficiency. We reported one of 15 patients with primary selective IgM deficiency with IgG3 subclass deficiency [16]. Ideura et al. [65] reported IgG4 subclass deficiency in a patient with selective IgM deficiency who presented with fibroepithelial bronchial polyp and possibly drug-induced exanthema. The clinical significance of associated IgG subclass deficiency with selective IgM deficiency is unclear since these patients did not have any difference clinical course than those who had no IgG subclass deficiency. Interestingly, elevated serum IgE levels have been observed more frequently than deficiency of IgG subclasses in patients with selective IgM deficiency [16, 17, 63, 66, 67]. Yamasaki [66] observed elevated IgE in 2 of 7 patients with selective IgM deficiency. Yel et al. [16] had one of 10 patients with elevated IgE. Inoue et al. [61, 67] reported 2 of 7 patients with elevated IgE. Though atopic manifestations are the second most common presentation in patients with selective IgM deficiency, there is no correlation between elevated IgE levels and presence or absence of atopic diseases or positivity of skin tests to allergens, and no correlation was observed between elevated IgE levels and deep skin abscesses or pneumonia, which are commonly observed in hyperimmunoglobulinemia E syndrome.

Specific Antibody Responses

Natural isohemagglutin (IgM) are diminished in a subset of patients with selective IgM deficiency [22, 25]. We reported normal protective levels of tetanus IgG antibody titers in all 10 patients with selective IgM Deficiency [16]. Kung et al. [21] also reported protective specific antibody titers against tetanus and diphtheria in 2 children with selective IgM reported. In contrast, they observed that these patients had impaired protective antibody titers against pneumococcus polysachharides 7/12 and 4/12 serotypes. Yel et al. [16] reported specific antibody response to pneumococcal

polycassharides in 11 adults with selective IgM deficiency following Pneumovax-23 vaccination. Three patients, two of whom had recurrent infections, had adequate pneumococcal antibody response at baseline and therefore, no Pneumovax-23 vaccination was administered. Five (45 %) of 8 remaining patients, who all presented with recurrent/severe infections, had impaired pneumococcal antibody responses following Pneumavx-23 administration, which demonstrates a specific antibody deficiency.

Lymphocyte Proliferative Response

The lymphocyte transformation in response to mitogens phytohemagglutin, concanvalin A, and pokeweed mitogen, recall antigens, *Candida albicans*, mumps, and tetanus toxoid, and alloantigens appear to be intact in selective IgM deficiency [16, 17, 66].

Pathogenesis of Primary Selective IgM Deficiency

It is possible that IgM deficiency represents a heterogeneous disorder as evident by complete absence to partial deficiency of serum IgM, normal to complete absence of circulating B cells, normal to severely impaired specific antibody responses against pneumococcal polysaccharides, and chromosomal association.

The pathogenesis of selective IgM remains to be defined. De la Concha et al. [63] observed that the IgM-deficient patients' B cells produced normal amounts of IgM in vitro when co-cultured with normal T cells, whereas the patients' T cells demonstrated a decreased helper activity for IgM, IgG, and IgA production. They proposed that a defect in T-helper cell function was the most likely cause of decreased IgM production. On the other hand, Matsushita et al. [67] and Endoh et al. [68] hypothesized that in IgM deficiency, terminal differentiation of B lymphocytes into IgM-secreting cells in vitro was impaired, as observed in patients with selective IgA deficiency. They demonstrated presence of isotype-specific increased suppressor activity in IgM-deficient patients. These findings were also reproduced in 2 other studies, with a significant number of patients having decreased CD4/CD8 ratios [61, 62]. Raziuddin et al. [69] also observed increased IgM-specific T suppressor activity in in vitro immunoglobulin synthesis assay. Yamasaki et al. [66] and Karsh et al. [64] did not observe any defect in T helper or T suppressor activity, suggesting an intrinsic B cell defect. Kondo et al. [70] reported reduced secreted μ mRNA transcript in selective IgM deficiency associated with Bloom syndrome. However, it is unlikely that decreased μ chain transcript is responsible for selective IgM deficiency since other immunoglobulins are normal in patients with selective IgM deficiency.

Selective IgM Deficiency with T Cell Deficiency—A Distinct Syndrome?

Selective IgM deficiency is commonly associated with normal T cell functions. Recently, we described three adult patients with selective IgM deficiency with severe T cell lymphopenia (predominantly shared by CD4+ T cells), T cell functional defects, and Natural killer cell function deficiency [71]. All three patients had *Mycobacterium avium complex* (MAC) infections. Furthermore, severity of MAC infection correlated with severity of CD4 lymphopenia and T cell functions; disseminated MAC infection was associated with more severe CD4 lymphopenia and T cell functional deficiency as compared to those with relatively mild MAC infection. These functional defects and low serum IgM persisted even after successful treatment of MAC. However, a role of IgM deficiency (if any) in this clinical complex remains unclear. All these patients were negative for HIV infection. Does this represent a distinct syndrome remain to be determined? Raziuddin et al. [69] reported a 9-year-old girl with selective IgM deficiency (complete lack of serum IgM) with *Brucella abortus* infection who had almost complete absence of CD4 during acute phase of infection. Following 5 weeks of therapy, patients CD4+ T cells returned to normal and serum IgM was detectable; however remained low on further follow-up.

Immunoglobulin Therapy

The treatment of patients with IgM deficiency is challenging. Patients who do not have adequate response to polysaccharide pneumococcal vaccine may benefit from vaccination with the conjugated pneumococcal vaccine. In theory, immunoglobulin replacement would be ideal. However, there is no immunoglobulin product that renders IgM antibodies. Therefore, it is not easy to supplement these patients with immunoglobulin products which mainly provide immunoglobulin of the IgG isotype. Nonetheless, other constituents of the immunoglobulin preparations, such as cytokines and growth factors, may act as adjuvants to the impaired immune system. In our published series, among five IgM-deficient patients with susceptibility to infections, four with associated specific antibody deficiency, were treated with intravenous immunoglobulin [16]. The outcome in all patients was favorable in regard to frequency and severity of infections. However, no changes in serum IgM were observed, excluding the possibility that cytokines or growth factors in immunoglobulin preparations may somehow help IgM levels. Since our publication [16], we have now treated five additional symptomatic adult patients with selective IgM deficiency associated with specific antibody deficiency with intravenous immuonoglobulin resulting in significant reduction in the frequency and severity of infections.

Stoelinga et al. [45] reported beneficial effect of Ig therapy in a boy with selective IgM deficiency with specific antibody deficiency. Fallon [72] also treated patient with selective IgM deficiency with immunoglobulin. Therefore, an association of specific antibody deficiency may be taken as an indication for immunoglobulin treatment in IgM deficiency.

In summary, selective IgM deficiency is more common than previously recognized. Selective IgM deficiency may be associated with often serious life-threatening infections. Interestingly, patients with common variable immunodeficiency with low serum IgM are clinically worse than those with normal IgM levels. Autoimmunity may be secondary to primary selective IgM deficiency rather than selective IgM deficiency secondary to autoimmune diseases. Patients with selective IgM deficiency should undergo a thorough immunological evaluation, particularly in the presence of recurrent/severe infections. Furthermore, immunoglobulin treatment is a beneficial therapeutic approach for patients with selective IgM deficiency who present with recurrent infections in the presence of an associated defective specific antibody response to pneumococcal and/or other antigens.

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ORIGINAL RESEARCH

IgA Deficiency & Mortality: A Population-Based Cohort Study

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Abstract IgA deficiency has been linked to increased morbidity but data on mortality is lacking. In this population-based prospective cohort study we examined mortality in patients with IgA deficiency compared with the general population. Through six university hospitals in Sweden we identified 2,495 individuals with IgA deficiency (IgA deficiency≤0.07 mg/L) diagnosed between 1980 and 2012. Each patient with IgA deficiency was matched on age, sex, place of residence, and year of diagnosis with up to 10 general population controls (n=24,509). Data on education level and emigration status were obtained from Statistics Sweden. Our main outcome measure was all-cause mortality retrieved from the nationwide Causes of Death Register, which includes >99 % of all deaths in Sweden. We used Cox regression to estimate mortality hazard ratios conditioned on the matching factors and adjusted for education level. During 25,367 person-years of follow-up (median 8.3), there were 260 deaths in the IgA deficiency group versus 1, 599 deaths during 257,219 person-years (median 8.6) in the general population controls (102 versus 62 deaths per 10,000 person-years; incidence rate difference, 40, 95%CI 28–53, $P<.001$). This corresponded to a conditional mortality hazard ratio of 1.8 (95%CI 1.6–2.1, $P<.001$). Relative mortality varied by follow-up time ($P<.001$) from a hazard ratio of 3.6 (95%CI 2.5–5.3; $P<.001$) during the first year to 1.9 (95%CI 1.5–2.4; $P<.001$) year 1–4; 1.9 (95%CI 1.4–2.4; $P<.001$) year 5–9; 1.5 (1.0–2.2; $P=.054$) year 10–14.9; and 1.1 (0.7–1.6; $P=.66$) year 15–25. Effect modification was also seen by age in each stratum of follow-up time, with higher relative mortality in younger than older patients ($P<.001$). In conclusion, patients with IgA deficiency are at increased risk of death in the first 10 to 15 years after diagnosis.

Keywords Autoimmune · death · IgA deficiency · immunoglobulin · mortality

Introduction

Selective IgA deficiency is the most common form of immunodeficiency in the western world. It has been reported to affect 0.15–0.5 % of the population [1] corresponding to 0.5–1.5 million US citizens. While most individuals with IgA deficiency lack symptoms, this diagnosis has been linked to an excess risk of comorbidity [2] such as autoimmune disease [3, 4] and respiratory tract infections [1, 5]. Mellemkjaer et al. reported an increased risk of lymphoma and possibly also gastrointestinal cancers in patients with immunodeficiency [6], but IgA deficiency did not appear to be associated with an increased risk of cancer overall.

Despite earlier reports of increased co-morbidity in IgA deficiency, we are not aware of any population-based study that has examined mortality in this patient population. We linked population-based data on IgA deficiency with mortality data and examined the risk of death associated with the disease. We hypothesized that IgA deficiency was associated with excess mortality compared to general population controls without IgA deficiency.

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Methods

Through the unique personal identity number [7] assigned to each Swedish resident, we performed a register linkage of patients with IgA deficiency, as well as matched general population controls, to mortality data from the nationwide Causes of Death Register and the education register.

Study Participants

Individuals with IgA deficiency were identified from laboratory data from 1980 through 2012 at six university hospitals in Sweden (Karolinska Hospital in Stockholm, Sahlgrenska hospital in Gothenburg, the University hospital in Lund, the University hospital in Linköping, the University hospital in Umeå and the Academic hospital in Uppsala). These university hospitals cater for both urban and rural areas. The samples were collected from healthy blood donors, routinely screened for IgA deficiency at 12 different blood transfusion centers in Sweden, patients referred to the above six major clinical immunology laboratories in Sweden for screening for gastrointestinal symptoms (anti-tissue transglutaminse, tTG) where IgA levels are routinely measured, and patients referred to the outpatient clinic for individuals with an increased infection proneness at the Karolinska University hospital Huddinge.

IgA Deficiency

We defined IgA deficiency as having an IgA value≤0.07 mg/L, with normal IgM and IgG levels, in individuals ≥4 years of age in accordance with the recommendations of *the International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies* [8]. In the current study we required that all participants had an IgA value≤0.07 g/L recorded after the age of 10 years. Only if levels are persistently low after the age of 10 years can IgA deficiency be established with confidence since younger children may still have transiently low IgA values between 4 and 10 years of age [1]. In Sweden, most laboratories use nephelometry to measure total IgA levels.

Controls

Through the government agency Statistics Sweden, each patient with IgA deficiency was matched on age, sex, place of residence, and year of diagnosis with up to 10 controls from the general population. We did not have data on IgA levels in controls.

Outcome

Data on overall and cause-specific mortality were retrieved from the Swedish Causes of Death Register [9, 10]. The register contains data since 1961 and covers more than 99 % of all deaths in Sweden [11]. According to relevant international classification of disease (ICD) codes, we specifically examined the following contributory causes of death (death from cancer [ICD8/9 140–239; ICD10 C00-D48], cardiovascular disease [ICD8/9 390–459; ICD10 I00-I99), respiratory disease [ICD8/9 460–519; ICD10 J00-J99], and death from other causes).

Follow-Up

We began follow-up at the date of first IgA deficiency value (corresponding date in controls), or when the IgA measurement took place in early childhood, at the age of 10 years since we required an IgA value≤0.07 g/L after that age for inclusion in the study cohort. Follow-up ended with death, first emigration, or August 31, 2012, whichever came first.

Covariates

Data on education were collected through the government agency Statistics Sweden, and a priori categorized as follows: ≤9, 10–12, >12 years, and missing (separate category).

Statistics

To illustrate the absolute mortality rates in IgA deficiency patients and matched controls from the general population, incidence rates (deaths per 10,000 person-years) and Kaplan-Meier curves are presented. We used Cox regression to estimate conditional hazard ratios for overall mortality. In this analysis we compared IgA deficiency individuals and their matched controls stratum-wise, thereby eliminating the influence of the matching factors (age, sex, calendar year of birth, and county). Additionally, we adjusted for highest attained level of education.

The proportional hazards assumption was examined by interacting IgA deficiency status with observation time, and calculating hazard ratios by different periods of follow-up (0–0.9, 1–4.9, 5–9.9, 10–14.9 and 15–25 years). The attributable death fraction (the proportion of all deaths in individuals with IgA deficiency that can be explained by the underlying disease) was calculated as 1-1/hazard ratio).

In pre-specified analyses we examined overall mortality according to sex, age at IgA deficiency diagnosis (10–39, 40–59, and ≥60 years), and calendar year of diagnosis (1980–2004 versus 2005–2012). For these subgroup analyses we restricted our Kaplan-Meier curves to the first 10 years of follow-up due to low number of events thereafter. Interaction terms between IgA deficiency status and sex, as well as age, were also tested.

Statistics were calculated using SAS (version 9.3) and graphs drawn using Stata (version 11). *P*-values<.05 were considered statistically significant.

Results

We identified 2,533 individuals who had been diagnosed with IgA deficiency at any of the participating university hospitals. Of these individuals, 10 had incorrect personal identity numbers, and another 7 were excluded by the government agency Statistics Sweden due to potential data irregularities. An additional 6 had re-used or changed their personal identity numbers, and 3 had suspicious diagnosis dates, leaving 2,508 IgA deficiency patients. Of these, 13 had no matched controls, while the remaining 2,495 had on average 9.8 controls each ($n_{controls}$=24,509; Fig. 1).

Patient Characteristics

Fifty-six percent of the IgA deficiency patients were women, and the mean age at identification was 37 years (range: 10–89 years; median age: 36 vs 35 year in IgAD vs controls; Table I). Of the included patients, 72 % had their first registration between 2000 and 2012, while another 11 % were registered in the 1980s. A large number of individuals were diagnosed at the age of 10–15 years (*n*=410; 16 %), consistent with our case definition that only those aged 10 years or above with a low IgA value could be included in the study.

Mortality and Follow-Up

During 25,367 person-years of follow-up there were 260 deaths among patients with IgA deficiency compared with 1,599 deaths during 257,219 person-years among matched general population controls (102 versus 62 deaths per 10,000 person-years; incidence rate difference, 40, 95%CI 28–53, *P*<.001; conditional mortality hazard ratio, 1.8, 95%CI 1.6–2.1, *P*<.001; Table II).

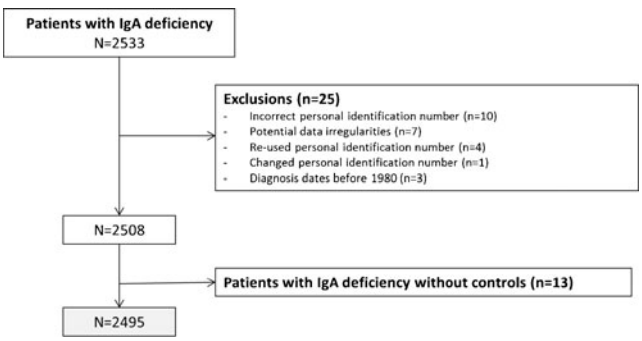

Fig. 1 Flow chart

Table I Participant characteristics

	IgA patients *n*=2495	Matched controls *n*=24,509
Women, n (%)	1404 (56 %)	13,793 (56 %)
Age at identification,[a] years		
Mean (SD)	37 (19)	37 (19)
Median (25th-75th percentile)	36 (20–52)	35 (20–52)
Minimum-maximum	10–89	10–89
Age categories, n (%)		
10–39 years	1423 (57 %)	14,005 (57 %)
40–59 years	676 (27 %)	6640 (27 %)
≥60 years	396 (16 %)	3864 (16 %)
Education level,[b] n (%)		
≤9 years	582 (23 %)	5861 (24 %)
10–12 years	982 (39 %)	9501 (39 %)
>12 years	736 (29 %)	7236 (30 %)
Missing	195 (8 %)	1911 (8 %)
Identification period, n (%)		
1980–2004	1506 (60 %)	14,797 (60 %)
2005–2012	989 (40 %)	9712 (40 %)

[a] Minimum age by definition: 10 years

[b] Highest reported level based on data from 1990, 1995, 2000, 2005, and 2009

The absolute mortality risks are shown in Fig. 2, illustrating a violation of the proportional hazards assumption (P for interaction between IgA deficiency status and time with regards to mortality was<*.001*). During the first year after identification, the mortality hazard ratio was close to 4. From the 1st to 10th year it was close to 2, but thereafter continued to decline, and no statistically significant mortality difference was detected versus the general population controls from the 10th year of follow-up.

Table II Person-years of observation and deaths

	IgA (*n*=2495)	Matched controls (*n*=24,509)
Observation years		
Sum	25,367	257,219
Median	8.3	8.6
Deaths, n	260	1599
Cancer	70 (27 %)	470 (29 %)
Cardiovascular causes	66 (25 %)	531 (33 %)
Respiratory causes	21 (8 %)	99 (6 %)
Other causes	103 (40 %)	499 (31 %)
Death rate (per 10,000 person-years)	102	62
Death rate difference (95%CI)	40 (28–53)	
P-value	*P*<.001	
Attributable death fraction (95%CI)	39 % (31–47 %)	

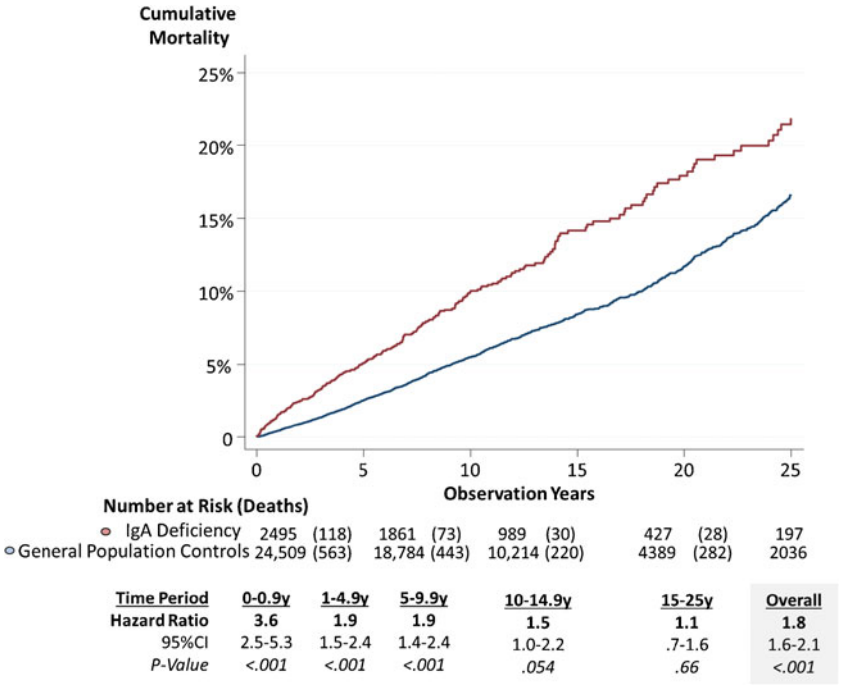

Fig. 2 Kaplan-Meier failure functions and conditional mortality hazard ratios by follow-up time. Number at risk and deaths given for 0–4.9, 5–9.9, 10–14.9, and 15–25 year intervals

Causes of Death

Cancer was the most common cause of death in IgA deficiency patients, closely followed by cardiovascular disease (Table II). The patient group and the matched controls differed in cause of death distribution ($P=.01$; Table II). This difference was due to lower percentage of cardiovascular deaths among IgA deficiency patients ($P=.01$), while overall cancer mortality was similar in the two cohorts ($P=.42$). Among IgA deficiency patients dying from cancer, the most common causes of death were prostate cancer (14.3 % of cancer deaths versus 9.4 % in controls); colon cancer (10.0 % versus 5.1 %), and lung cancer (8.6 % versus 20.3 %).

Subgroup Analyses

Sex Men had higher mortality rate than women in both IgA deficiency patients and controls (Fig. 3a). Compared to controls, male IgA deficiency patients had higher mortality over the 1st year of follow-up, 1–4.9 y, and 5–10 y, while no difference was seen in women between year 5 and 10.

Age As expected, large differences were seen between the ≥60, 40–59, and 10-39-year age-groups (Fig. 3b). The association of IgA deficiency and mortality appeared to be modified by age in each follow-up period investigated (P for interaction 0–0.9 y<$.001$; 1–4.9 y<$.001$; 5–10 y<$.001$). Hazard ratios were higher in the younger age-groups.

Calendar Period of Identification No differences were seen between patients identified in the period 1980–2004 compared to those identified 2005–2012 (Fig. 3c).

Discussion

This population-based cohort study of almost 2,500 individuals with IgA deficiency and matched controls from the general population found an increased risk of death in IgA deficiency. This excess mortality was seen in both men and women and independently of age at diagnosis as well as period of diagnosis. The absolute mortality excess risk was 40/10,000 person-years. We are not aware of any prior large-scale study on mortality in IgA deficiency.

We observed a doubled mortality rate in IgAD patients compared to the general population over the 1–4.9 and 5–9.9 y follow-up periods, while excess mortality was reduced to 1.5 and was only borderline significant during the 10–14.9 y follow-up period. Beyond 15 years of follow-up, no difference was detected. This may be due to a milder phenotype developing with time in the patients as is seen in several other forms of primary immunodeficiency disorders, but it can also be due to secondary disorders contributing both to IgA testing and excess mortality, especially in the early follow-up.

Previous Research

Prior literature suggests that individuals with IgA deficiency suffer an increased risk of a variety of diseases. Most notably,

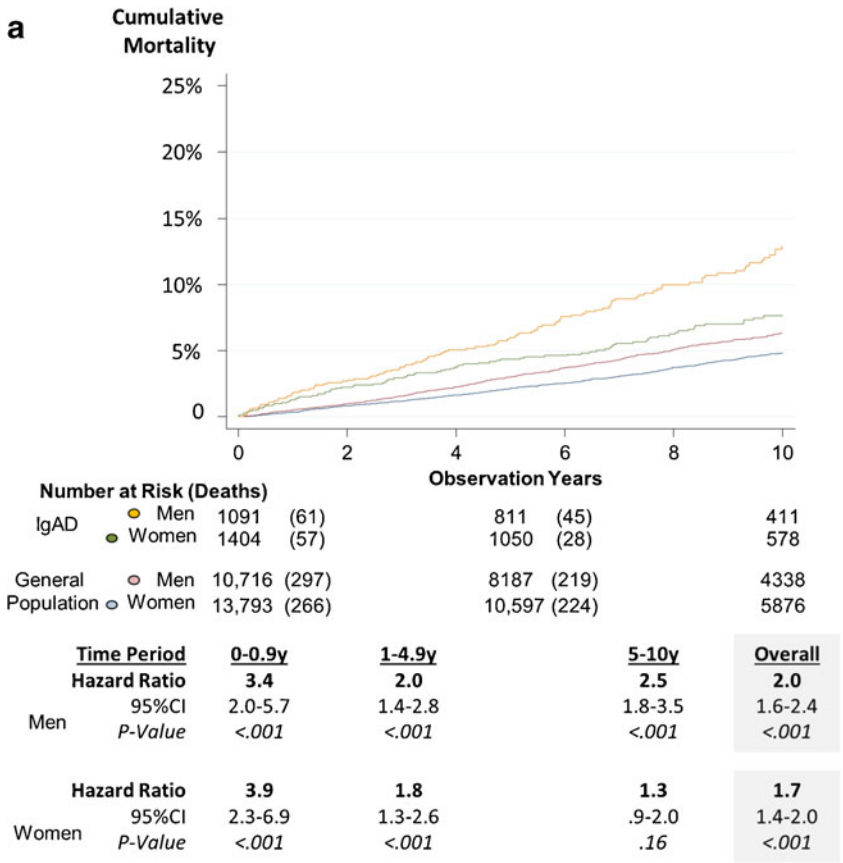

Fig. 3 **a** Kaplan-Meier failure functions by sex. Overall hazard ratios: full observation time (not only 0–10 years). Number at risk and deaths given for 0–4.9 and 5–10 year intervals. *IgAD* IgA deficiency. **b** Kaplan-Meier failure functions by age. Overall hazard ratios: full observation time (not only 0–10 years). Number at risk and deaths given for 0–4.9 and 5–10 year intervals. *IgAD* IgA deficiency. **c** Kaplan-Meier failure functions by period. Number at risk and deaths given for 0–4.9 and 5–10 year intervals. *IgAD* IgA deficiency. **Legend Fig. 3c**: Of individuals diagnosed with IgAD in 2005–2012, 436 entered the follow-up period "5–10 years" but none of these had 10 years of follow-up. At the same time 69 % (989 out of 1,425) of IgAD patients diagnosed 1980–2004 who entered the follow-up period "5–10 years" remained in the study 10 years after IgAD diagnosis. This explains why the proportion of deaths during the observation period was similar in the early (1980–2004) and the late (2005–2012) cohorts and the Kaplan-Meier curves are similar for the early and late IgA cohorts

these patients have been reported to be at increased risk of autoimmune disease [12] including Grave's disease, systemic lupus erythematosus, type 1 diabetes, coeliac disease, myasthenia gravis and rheumatoid arthritis. Several of these comorbidities [13–15] have been linked to excess mortality, and it is possible that secondary disorders have contributed to the increased risk of death that we observed.

However, comorbidity with autoimmune disease may not be the only explanation for the increased risk of death in our patient group. Lack of IgA allows bacteria to colonise the respiratory tracts. Cunningham-Rundles and Bodian [4] reported that in 248 patients with common variable immunodeficiency 77–78 % had an earlier diagnosis of pneumonia, and up to 98 % a history of recurrent bronchitis, sinusitis or otitis. Similarly a recent case–control study from Iceland reported that 25 % of IgA deficiency patients had experienced a pneumonia versus 1.6 % of controls [2]. Although the term common variable immunodeficiency is not restricted to IgA (these patients may also have low levels of IgM or IgG), the extremely high proportion of individuals with recurrent respiratory infections suggests that this trait is also relevant for IgA deficiency patients, potentially explaining the increased risk of death seen in our study. Unfortunately limited power did not allow us to distinguish between infectious and non-infectious causes of death.

Strengths

The main strengths of our study are the large number of study participants, and that the diagnosis had been confirmed through measurement of actual IgA levels. Earlier studies on complications in IgA deficiency or combined variable immunodeficiency have been based on few patients with only one study involving more than 300 patients [6]. In contrast, we identified almost 2,500 individuals, and were able to calculate age-specific hazard ratios for IgA deficiency, finding a high relative mortality risk especially in young people. We were

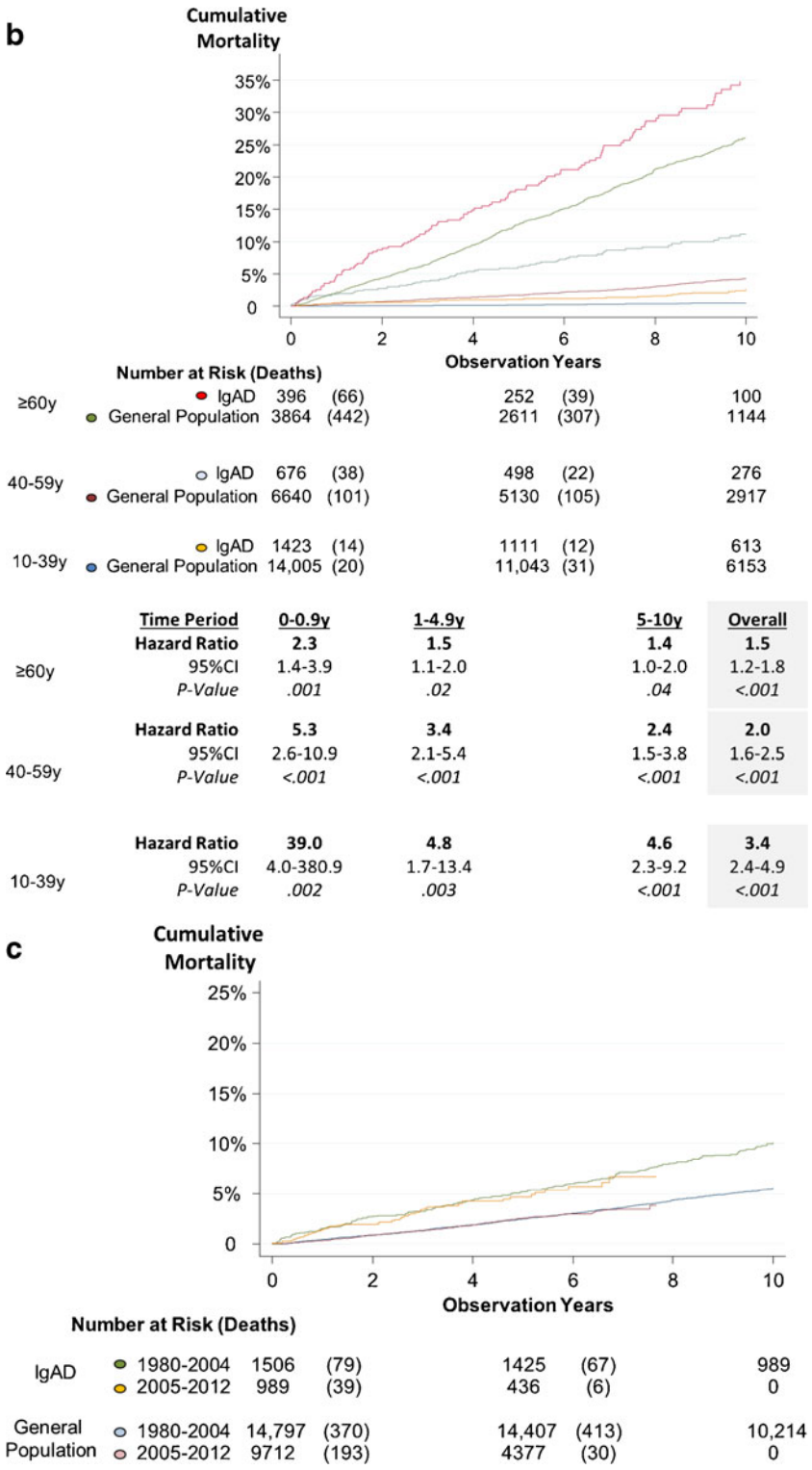

Fig. 3 (continued)

also able to stratify for sex, showing consistently increased relative risks over strata, although we noted an interaction between sex and risk of death with male IgA deficiency patients being at greater risk of death. We did not observe any differences in mortality by the different calendar periods of identification that we investigated.

All Swedish residents are assigned a unique personal identity number [7]. Through this number, most residents can be

followed over long periods of time with virtually no loss to follow-up (in our case, the IgA deficiency cohort was followed for approximately 25,000 person-years versus 250,000 person-years for the reference cohort). We ascertained death through the nationwide Swedish Causes of Death Register [9, 10]. The register is regularly audited against the mortality data from the National Tax Office to ensure a near 100 % coverage of all deaths in Sweden. Only in some 1.8 % of all deaths in Sweden in 2011 [16] did the National Board of Health and Welfare not receive any death certificate and hence there were no data on the underlying cause of death, only the date of death.

Limitations

We were unable to calculate mortality hazard ratios according to presence of symptoms, and cannot rule out that our patients were more symptomatic (and therefore tested) than the average IgA deficiency patient. Another limitation is the lack of data on serum IgG, T-cell response to phytohemagglutinin, or the percentage of peripheral B-cells (all of which have been linked to higher mortality in common variable immunodeficiency [4]). We also did not have data on smoking. Although smoking is an important risk factor for death from cardiovascular and respiratory disease, it is unlikely to confound the results of this study since the vast majority of patients with IgA deficiency lack IgA since birth or early childhood, and we are not aware of any data showing that smoking would be more common in IgA deficiency patients than in the general population.

The lack of data on symptoms meant that we were unable to calculate mortality risks in asymptomatic vs. symptomatic IgAD patients.

IgA levels are usually measured as part of a clinical investigation for coeliac disease, or in individuals with signs and symptoms suggestive of immunodeficiencies. There is therefore a risk that some individuals in our cohort had other comorbidities that contributed to the excess mortality, which could explain why we observed the highest hazard ratios during the first year after diagnosis. It is also possible that a milder phenotype develop with time in the IgAD patients as is seen in several other forms of primary immunodeficiency disorders since we found no excess mortality after 15 years of follow-up.

However, the mortality hazard ratios remained elevated beyond the first year after IgA deficiency testing indicating that this potential detection bias is unlikely to explain our finding of increased mortality.

Finally we cannot rule out that some controls had undiagnosed IgA deficiency, since Swedish residents are not routinely screened for low IgA levels. However, even if up to 1:200 of the general population have an undetected deficiency (the highest prevalence reported so far, and then mostly in children [1]), false-negative controls are unlikely to influence any risk estimate since 99.5 % of the control population would have normal IgA levels.

Conclusion

In this population-based study, we found an increased risk of death in individuals with IgA deficiency compared to matched general population controls. The relative risk of death was highest the year after detection, but remained increased over up to 10 years of follow-up.

Acknowledgments

Competing Interest Statement The authors (JFL, MN, LH) declare that they have no conflicts of interest relevant to the contents of this manuscript.

Ethical Approval This project (2011/69-31/3) was approved by the Regional Ethical Review Board in Stockholm on Feb 23, 2011. This was a register-based study and therefore all data were anonymised prior to analysis, and we were not allowed to contact the patients.

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Details of Contributors

Dr Ludvigsson and Dr Neovius had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ludvigsson
Acquisition of data: Hammarström and Ludvigsson
Drafting of the manuscript: Ludvigsson, Neovius
Critical revision of the manuscript for important intellectual content: Hammarström, Ludvigsson, Neovius
Statistical analysis: Ludvigsson, Neovius
Obtained funding: Hammarström
Study supervision: Ludvigsson

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Selective IgA deficiency: Epidemiology, Pathogenesis, Clinical Phenotype, Diagnosis, Prognosis and Management

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Running title: Selective IgA deficiency

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Abstract

Selective immunoglobulin A deficiency (SIgAD) is the most common primary antibody deficiency. Although more patients with SIgAD are asymptomatic, selected patients suffer from different clinical complications such as pulmonary infections, allergies, autoimmune diseases, gastrointestinal disorders and malignancy. Pathogenesis of SIgAD is still unknown, however, a defective terminal differentiation of B-cells and defect in switching to IgA-producing plasma cells are presumed to be responsible. Furthermore, some cytogenic defects and monogenic mutations are associated with SIgAD. There is no specific treatment for patients with symptomatic IgA deficiency; although prophylactic antibiotic therapy along with circumstantial immunoglobulin replacement with justification and supportive care (using a product that contains minimal IgA) could be helpful for patients with a severe phenotype. The epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis, management and treatment in patients with SIgAD have been reviewed.

Key words: Selective immunoglobulin A deficiency, pathogenesis, clinical phenotype, diagnosis, prognosis, management, treatment

Introduction

Selective immunoglobulin A deficiency (SIgAD) was first described in children with ataxia–telangiectasia [1], but this deficiency was later identified in other patients with isolated immunologic manifestations and populations of normal subjects. SIgAD is characterized by serum IgA level of <7 mg/dl in individuals older than 4 years old in the presence of normal levels of both immunoglobulin G (IgG) and immunoglobulin M (IgM) and exclusion of other causes of hypogammaglobulinemia and T-cell defect as well as normal IgG antibody response to all vaccinations [2, 3].

IgA deficiency comprises a heterogeneous group of diseases ranging from asymptomatic patients whom are diagnosed coincidentally in laboratory screening of normal individual [4, 5] to symptomatic patients are presented by different clinical phenotypes including mild recurrent sinopulmonary infection [6], allergy [7], autoimmunity [8] and associated group with severe complications [5]. The latest group is prone to progress in common variable immunodeficiency (CVID) [5, 9, 10]. Although SIgAD is the most common primary immunodeficiency (PID), due to the rarity of symptomatic SIgAD, very large groups of patients with SIgAD have not been studied.

Therefore, SIgAD presents a challenge for clinicians and researchers. Based on different clinical phenotypes and associated varieties in immunological abnormalities of patients with IgA deficiency, knowing pathogenesis along with appropriate management, treatment and monitoring should be considered for these patients.

Epidemiology

The prevalence of SIgAD varies in different ethnicities across the world (**Fig1**). Based on the Jeffrey Modell Centers network (4), a global distribution of 8437 diagnosed SIgAD patients, prevalence of SIgAD in the European, North American, Latin American, Asian, and African countries has been reported to be 5492, 1704, 1050, 115 and 76 patients, respectively [11]. Indeed, the worldwide incidence of SIgAD varies, depending on ethnic background; 1:651 in Iran [12], 1:143 in the Arabian peninsula [13], 1:163 in Spain [14], 1:252 in Nigeria [15], 1:875 in England [16], and 1:965 in Brazil [17]. These reports could be higher because more individuals with SIgAD are asymptomatic, and there is no established routine screening program for IgA deficiency. In countries with high rates of consanguineous marriage, the rate of multiple cases in a family is more than the other countries [18, 19]. Factors associated with

the prevalence of IgAD include a family history of SIgAD and the country of origin. Family studies using SIgAD blood donors as probands indicate that first-degree relatives have a 7.5% prevalence rate of SIgAD, which is 38-fold higher than that of unrelated donors [20]. Based on our recent study on first-degree relatives of symptomatic SIgAD patients with consanguineous marriage 10.8 % had one type of primary antibody deficiency specially SIgAD or subclass deficiency [21].

Pathogenesis of IgA deficiency

Although several investigations have performed to determine the etiology of SIgAD, the exact pathogenesis of SIgAD is unknown yet. Since SIgAD has a heterogeneous nature, suggesting that different etiologies might be involved in cause the disease. SIgAD has been associated with an intrinsic B-cell lymphocyte defect, T-cell abnormalities and most recently in impairment in cytokine networks [22, 23].

It has been found that patients with SIgAD have a defect in immunoglobulin class switching, terminal differentiation of IgA^+ plasmablasts into secretory cells, or the long-term survival of the IgA-secreting plasma cells [24-27]. It seems that main defect in patients with SIgAD is changing IgA-bearing B lymphocytes into IgA-secreting plasma cells [2, 28]. Furthermore, there are reduced (but not absent) counts of IgA-bearing B-cells in the peripheral circulation in these patients [28], that bear an immature phenotype; that is, IgA-bearing B-cells that also are positive for IgM and IgD [29]. It seems to be a defect in stem cells, as IgA deficiency can be transferred by bone marrow engraftment [30]. Furthermore, a defect in the internal B-cell signaling pathways downstream of different cytokines in the secondary lymphoid organs' germinal centers, selected co-stimulatory molecules in double-strand breakage DNA repair have been also suggested that involve in the pathogenesis of SIgAD [31-33]. Moreover, increased apoptosis during an immune response could be involved in the reduction of survival, growth and differentiation of B-cells and also their inability in produce normal levels of IgA immunoglobulin [34]. Genetically, impaired rearrangement of the switch (S) μ to Sα in peripheral B-cells has been described in SIgAD. The low expression of both secreted and membrane forms of complete mRNA in IgA-switched B- cells and defective IgA switching in SIgAD have been also identified [35]. In addition, isotype switching and terminal differentiation of stimulated B lymphocyte with antigen under the influence of TGF-b into IgA-secreting plasma cells indicates a key role of cytokine in this process. Furthermore, a defect in several cytokines including IL-4, IL-6, IL-7, IL-10 and most newly

IL-21 have been found in SIgAD [31, 36-38]. On the other hand, defective antibody production may be due to a decreased or impaired helper T-cell activity in some SIgAD patients [39, 40].

Cytogenic defects and monogenic mutations associated with SIgAD

The heterogeneous nature of SIgAD recommends that different etiologies and/or modifier genes may cause the disease [36].

Chromosomal abnormalities and cytogenetic defects have been frequently reported in patients with IgAD including 4p monosomy, trisomy 8, trisomy 10p, translocation of 10q to 4p, 17p11.2 deletions, 18q-syndrome, trisomy 21, monosomy 22, and 22q11.2 deletion syndrome [41-45].

Recently, we have reviewed monogenic mutations that are associated with selective IgA deficiency [46]. Mutations in genes affecting cellular and humoral immunity (e.g. *JAK3, RAG1, DCLRE1C, CD27* and *LRBA*), in genes of combined immunodeficiencies with syndromic features (e.g. *ATM, NBS1, RAD50, MLH1, DNMT3B, ZBTB24, MECP2, PMS2, RNF168, CHD7, RMRP, DKC1, TINF2, PNP, TTC7* and *WAS*), in genes predominantly associated with antibody deficiencies (e.g. *BTK, TACI, TWEAK, MSH6, MSH2, PIK3R1* and *CARD11*), in genes associated with phagocytotic defects (e.g. *RAC2, CYBB, NCF1* and *SBDS*), in genes associated with immune dysregulation (e.g. *IFIH1* and *XIAP*), in genes associated with defects in intrinsic and innate immunity (e.g. *CXCR4, STAT1* and *IL12RB1*) and in gene associated with complement deficiencies (e.g. *C3*) could manifest as immunological problem with low IgA [46]. It is anticipated that by identification of the underlying genetic defect(s) in IgAD patients, the precise pathophysiology will be discovered, and subsequently, treatment strategies, especially in patients with severe clinical complications, will be adjusted based on the findings of molecular studies.

Clinical manifestations in patients with SIgAD

Although most of the individuals with SIgAD are asymptomatic, some patients develop various clinical manifestations such as pulmonary infections, allergies, autoimmune diseases, gastrointestinal disorders and malignancy.

Pulmonary diseases

Recurrent pulmonary infections are the most common diseases associated with SIgAD. Previous studies demonstrated that about 40–90% of the first presentation of symptomatic IgA-deficient patients included infectious manifestations as the only or the dominant manifestation at the time of diagnosis [47]. Most infections are caused by extracellular encapsulated bacteria (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*) [2]. Sinopulmonary infections are more likely to present in individuals with SIgAD who have IgG subclass deficiency especially IgG2, and IgG3 [48-50]. In this sense, in one study, we have shown a correlation between IgG3 and serum IgA concentrations in IgA deficient individuals [4], indicating the varied clinical manifestations related to antibody deficiency. Patients with SIgAD have a compensatory increase in IgM-bearing B-cells due to the absence of IgA [51], however, secretory IgM does not completely replace IgA functionally, particularly not in the upper respiratory tract [52]. Recurrent sinopulmonary infections might be presented only in the form of upper respiratory tract infection, or of more severe forms that end up with sequels such as bronchiectasis or obliterative bronchiolitis [53]. It has been demonstrated that even IgA deficiencies could be associated with bronchiectasis that indicating the importance of follow-up of individuals with selective IgA deficiency [54]. Since the defect in IgA antibodies is associated with the pulmonary damages, determination of IgA antibody levels and evaluation for pulmonary alterations is essential in SIgAD patients with recurrent sinopulmonary infections.

Allergic diseases

Several studies have demonstrated IgA deficiency and allergy are associated, as allergic diseases may be the first and/or only clinical manifestation in some patients with SIgAD. There is a high prevalence of allergic diseases in SIgAD patients [5, 55], as it has been estimated that 25–50% of SIgAD patients are recognized by evaluation of allergic diseases that may increase during the disease course [36]. It has been indicated that allergy is more common in SIgAD comparing with subjects with normal concentrations of IgA [5, 56], however, the findings are not conclusive, as some studies demonstrate no increased frequency of allergies in patients with SIgAD [57-59]. The allergic diseases most commonly associated with IgAD are allergic conjunctivitis, rhinitis, urticaria, eczema, food allergy and asthma [6, 36, 60]. IgE concentrations are often increased in selective IgA deficiency, which may be due to a compensatory mechanism for low secretory IgA level and lack of IgM compensation,

especially in atopic children [61]. Indeed, the secretory IgA helps to prevent the absorption of allergens into the bloodstream, thus, IgA in mucosal barriers plays a significant role in the prevention of allergy. Since severe anaphylactoid transfusion reactions are seen (of course rare) in patients with SIgAD, these individuals are considered to be at increased risk of anaphylaxis when they receive blood products that contain some IgA. This is thought to be due to IgG (or possibly IgE) anti-IgA antibodies, which may be found in some IgA-deficient individuals [62-64].

Autoimmunity

It has been demonstrated that a number of autoimmune diseases are associated with selective IgA deficiency, as the prevalence of this disorders in SIgAD patients varies from 5 to 30%, based on studied populations [25, 47, 55, 65]. This difference might be due to the age-related autoimmune presentation, as patients with a history of autoimmunity were older than others, particularly in their second decade of life [47]. Some autoimmune diseases including idiopathic thrombocytopenic purpura, Graves' disease, autoimmune hemolytic anemia, type 1 diabetes mellitus, rheumatoid arthritis, thyroiditis, systemic lupus erythematosus and celiac disease are more common in SIgAD patients [8]. Several immunological mechanisms have been suggested in the development of autoimmunity in SIgAD patients. Secretory IgA has an important role in the protection of mucosal surfaces, as environmental antigens can easily penetrate the mucosa in the absence IgA. Molecular mimicry and cross-reaction with self-antigens might cause the formation of auto-reactive antibodies [36, 66], as an increase in autoantibody levels has been shown in patients with SIgAD [36, 65]. The association between SIgAD and abnormal T-cell regulation, especially in $CD4^{+}CD25^{+}Foxp3^{+}$ regulatory T-cells (Treg) could also explain the association between SIgAD and autoimmunity due to the breakdown of immune tolerance [39, 67]. Researchers suggest that there is a complex association between genetic susceptibility and development of IgAD autoimmune diseases, as it has been reported an association between certain human leukocyte antigen (HLA) haplotypes especially HLA-A1, -B8, -DR3 and DQ2 and manifestation of SIgAD [8]. Furthermore, it has been shown that the sera of patients with SIgAD often contain autoantibodies, even in the absence of clinical autoimmune manifestations. Antibodies against thyroglobulin, red blood cells, thyroid microsomal antigens, basement membrane, smooth muscle cells, pancreatic cells, nuclear proteins, cardiolipin, human collagen, and adrenal cells have been recognized. Although the detection and level of specific autoantibodies in these patients do not predict the development of autoimmune disorders, it

can be suggestive of future diseases [41]. Furthermore, a significant part of individuals with SIgAD have serum anti-IgA antibodies that may cause infusion reactions if traces of IgA are given parenterally [68, 69].

Gastrointestinal Disorders

Although secretory IgA is considered as a major antibody in the intestinal mucosa, the rate of gastrointestinal disorders in SIgAD patients is not high. It seems that IgM antibody could compensate the absence of IgA in the intestine by its transportation from the mucosa into the intestinal lumen. However, an association between SigAD and several gastrointestinal disorders such as celiac disease, giardiasis, nodular lymphoid hyperplasia (NLH), ulcerative colitis, Crohn's disease, pernicious anemia, and gastric and colonic adenocarcinoma has been reported [70].

Among gastrointestinal disorders, celiac disease is more common and it has been found that the incidence of IgA deficiency in patients with celiac disease is somewhere between 2 and 3%, indicating an increase 10 to 15 times over the normal IgA level subjects [71]. Secretory IgA can bind to some proteins (e.g., transglutaminase, gliadin, and prolamin) in the gastrointestinal tract, and the lack of IgA may result in abnormal processing of these antigens. Furthermore, the association between celiac disease and SIgAD may have a genetic basis like shared some HLA haplotypes such as HLA-A1, Cw7, B8, DR3, and DQ2 [72-75]. The histopathology of celiac disease such as elevated counts of intraepithelial lymphocytes, villous shortening or flattening, crypt hyperplasia, and infiltration of the lamina propria with lymphoid cells are similar in patients with or without SIgAD, however a distinguishing feature is the lack of IgA-secreting plasma cells in intestinal biopsy specimens in patients with SIgAD [76-78]. Since celiac disease is most commonly identified by the presence of IgA antibodies against above-mentioned proteins (e.g., transglutaminase, gliadin, prolamin), and defect of IgA antibody in SIgAD patients, identification of IgG against deamidated gliadin peptides is suggested for screening test because has a high specificity to reliably diagnose celiac disease in patients with SIgAD [79, 80]. Thus, results of tests based on IgA in celiac disease may be falsely negative and the results of tests based on IgG should be considered as valuable and clinically significant.

Giardia lamblia as gastrointestinal disorders has been also reported in patient with SIgAD [81]. *Giardia lamblia* cysts produce trophozoites that colonize the small intestine and leads to bloating, cramping, excessive flatus, and watery diarrhea. Diagnosis is based on examining

the stool for cysts or trophozoites of *Giardia lamblia*, or by examination of duodenal aspirates that can yield more determinate results. The parasitic load can be unremitting in patients with SIgAD, despite treatment with metronidazole. Since the protective barrier of the gastrointestinal system is defective in SIgAD, protozoa such as *Giardia lamblia* can attach to the epithelium, proliferate, and cause infection; however, mouse models have suggested that clearance is T-cell mediated [82]. As mentioned above, other gastrointestinal disorders reported in SIgAD patients include pernicious anemia [83, 84], Crohn's disease, and ulcerative colitis [85-88].

Malignancy

The association of SIgAD and malignancies have been identified in sporadic cases such as carcinoma (particularly adenocarcinoma of the stomach) and lymphoma (usually of B-cell origin) [89, 90], particularly at older ages. Moreover, other cancers found in SIgAD patients are carcinoma of the colon, ovarian cancer, lymphosarcoma, melanoma and thymoma [91]. A recent report described 63 Israeli children with SIgAD followed for 10 years, with malignancies diagnosed in 3 children (4.8%) [55]. It seems that some gastrointestinal disorders could involve in increased incidence of cancer, as the absence of secretory IgA has been hypothesized to compromise the defense against infection with *Helicobacter pylori*, which is thought to be a cause of stomach cancer [92], although the role of secretory IgA in this defense has been questioned. However, the prevalence of malignancy is not high in patients with SIgAD.

Diagnosis

In general, the diagnosis of SIgAD depends on the measurement of IgA concentration in the serum. Based on new ESID criteria, SIgAD is diagnosed by increased susceptibility to infection, and/or autoimmune manifestations, and/or affected family member; diagnosis after 4th year of life; undetectable serum IgA (when measured with nephelometry less than 0.07 g/L) but normal serum IgG and IgM (measured at least twice); secondary causes of hypogammaglobulinaemia have been excluded; normal IgG antibody response to all vaccinations and exclusion of T-cell defect. Although in SIgAD patients, secretory IgA level is not determined, it is possible that the individuals diagnosed with SIgAD may still have some IgA in the mucosal systems enough to provide some protective functions. Thus, despite this critical role of secretory IgA, some individuals with SIgAD are asymptomatic. According

to the first report of International Union of Immunological Societies (IUIS) on Primary Immunodeficiency Diseases in 1999, primary IgA deficiency were categorized as selective immunoglobulin deficiency among the main form of predominantly antibody deficiencies [93]. During the updates on the recent finding on the SIgAD patients the IUIS decides to separate these patients into two separate subtypes including IgA deficiency associated with IgG subclass deficiency and selective IgA deficiency and it was constantly reported from 2007 till 2014 [94, 95]. However surprisingly in the recent release of the IUIS classification in 2015 the IgA deficiency was not included and unfortunately the reason of this exclusion was not explained in the report [96].

Classification

Classification of SIgAD could be done based on laboratory and clinical data. In general, limited studies evaluated B-cell subpopulation in SIgAD patients. One study reported that there is no significant difference in some B-cell subsets such as naive, IgM memory, switched memory or $IgM^{+}CD21^{-}$ B-cells in SIgAD patients in compression to healthy controls [97]. However, in one study, we demonstrated that SIgAD patients could be classified into two groups (I and II) [25]. In this study, the percentage of switched memory B-cells was more than 0.4% in all healthy controls, but in patients who were classified as group I, the percentage of switched memory B-cells was less than 0.4% (0.34 ± 0.06), while patients in group II had not reduction in switched memory B-cells (1.74±0.12%) [25]. Patients in group I demonstrated a higher rate of pneumonia, autoimmunity, and hepatosplenomegaly as well as specific antibody and IgG subclass deficiencies than other SIgAD patients [25]. Later, Nechvatalova et al. confirmed the reduction in terminally differentiated B-cell subsets in patients with SIgAD [98].

On the other hand, in a recent review, we proposed a classification for SIgAD patient into five clusters (asymptomatic, minor infection, allergy, autoimmune and severe phenotype) based on clinical phenotype [47]. Severe forms and allergy clinical phenotypes tend to present at childhood, while mild infections and autoimmunity phenotype would be diagnosed at middle age. It is possible that during the course of the disease, asymptomatic SIgAD might develop to other symptomatic phenotypes including minor infectious, allergic and autoimmune. In contrast, symptomatic patients (even with dramatic response to routine treatments and controlled condition) could not shift back and re-categorize as an

asymptomatic phenotype. Patients with minor infection phenotype could also progress to allergy, autoimmunity and severe phenotypes. However, patients with allergy and autoimmunity cannot be re-classified as minor infectious phenotype even in the absence of active complications, but they might progress to severe phenotype.

Management of patients with SIgAD

There is no recommended specific treatment for patients with SIgAD and based on recognized condition, patients should be managed individually. However, some patients gradually develop normal levels of IgA without treatment. In contrast a few patients with IgA deficiency can progress to common variable immunodeficiency (CVID) [9], this tended to occur in adolescence or young adulthood.

Management of patients with SIgAD consists different modalities including education, periodic monitoring, treatment of associated allergic or autoimmune conditions, prolonged or even prophylactic antibiotics, administration polyvalent pneumococcal vaccines and administration of intravenous or subcutaneous immunoglobulin replacement therapy.

1- Education and periodic monitoring

Patient awareness and education are of prime importance, especially to prevent a potential anaphylactic reaction secondary to transfusion of blood and/or its product. In this regard, patients with SIgAD should be recommended to wear a medical alert bracelet [2]. It is recommended that all patients even asymptomatic patients should be monitored periodically every 4-6 months. In those patients with undetectable serum IgA level and also in patients with past infusion reactions to plasma-containing blood products, it is recommended to perform screening test for anti-IgA antibodies to better assess patients' risk for future infusion reactions to blood products. If these antibodies are identified, various steps can be taken to prevent recurrent reactions, depending upon the blood product needed. For these patients, the blood products should be prepared from an IgA-deficient individual, or saline-washed red blood cells should be the choice. In these patients, all blood products should be given with caution, and the staff should be prepared to treat a potential anaphylactic reaction. For patients with SIgAD subcutaneous immunoglobulin, infusion is a safe procedure to prevent anaphylaxis. Desensitization to blood products is another approach that may be appropriate in specific circumstances. A case report described desensitization of a patient with SIgAD who

experienced anaphylaxis to blood products, but subsequently required numerous infusions of various blood products in the context of a liver transplant. The patient was successfully desensitized to a gammaglobulin preparation, which was then administered weekly to maintain the desensitized state [99].

2- Treatment of associated allergic and autoimmune conditions

Patients with chronic and recurrent respiratory infection should be evaluated for other conditions that predisposing patients to upper and lower respiratory tract infections such as allergic rhinitis, asthma and chronic rhinosinusitis. If one of these conditions is identified, appropriate treatment reduces symptoms and prevents recurrent reactions. Management of the allergies associated with SIgAD is similar to management of allergies in general. The main issue in the management of autoimmune disorders associated with SIgAD is the early diagnosis independent from detection of IgA antibody tests however the treatment of these disorders is similar to the autoimmune in healthy individuals particularly Graves disease, systemic lupus erythematosus, type 1 diabetes, celiac disease, myasthenia gravis and rheumatoid arthritis.

3- A trial of prophylactic antibiotics

In patients with recurrent and chronic sinopulmonary infections despite aggressive management for conditions such as allergic rhinitis/asthma, chronic rhino sinusitis, a trial of prophylactic antibiotics particularly in winter months should be started. Ideally, antibiotic therapy should be targeted at the specific organism causing the infection. Unfortunately, it is not always possible to isolate and identify these microorganisms and their antibiotic sensitivities precisely, therefore the use of broad-spectrum antibiotics may be necessary.

4-Administration of pneumococcal vaccine

It is suggested that in some patients additional immunization with pneumococcal vaccines should be used to increase immunity. Patients with a decreased ability to make anti polysaccharide antibodies should be immunized with polysaccharide-protein conjugate vaccines, such as *Haemophilus influenzae* type b (HIB) with diphtheria-tetanus. The conjugated protein allows anti-HIB antibodies to develop, though 2 or 3 doses are usually required. In this sense, it has been demonstrated that administration of pneumococcal vaccine

in patients with associated IgG2 and IgG3 deficiency led to developed protective antibody levels to the conjugated pneumococcal vaccine with a subsequently decreased rate of infections [100, 101].

5-A trial of intravenous or subcutaneous immunoglobulin replacement therapy

In patients who have received pneumococcal vaccine and regular prophylactic antibiotics still suffer from refractory infection may require intravenous immunoglobulin (IVIg). First, this trial could be started in winter months, but if patients continue to experience an infection in spring and summer, administration of regular monthly immunoglobulin replacement therapy should be considered. Patients receiving IgG therapy should have regular monitoring of IgG trough levels, blood cell counts, and serum chemistry. The adequacy of IgG replacement is detected by the trough (pre-infusion) or steady-state IgG level in association with the clinical course [102]. In most of the practice guidelines, a starting dosage of IgG between 400 and 600 mg/kg/monthly is recommended to achieve a serum trough IgG level of 600 to 800 mg/dL. Furthermore, for each 100 mg/kg of IVIg infused, peak serum IgG levels rise by 250 mg/dL [103, 104] and trough levels increase by approximately 100 mg/dL. Immunoglobulin replacement therapy can be used in bolus doses by IV route every 21 to 28 days or the same dose can be divided into daily, weekly, or biweekly doses to administrate by SC route after using the coefficient factor to correct the dose (some use a 1:1 conversion) [105]. In general, immunoglobulin replacement should be done cautiously with a product low in IgA (including lyophilized Gammagard, Gammaplex, Vigam, Iveegam, Polygam and Nanogam with IgA <10 mg/ml) [10]. In this situation, usually, IVIg therapy can be given safely.

Prognosis

Prognosis of SIgAD is principally dependent on the presence of SIgAD phenotype and associated immune abnormalities. SIgAD is usually life-long, but not associated with severe infections or a reduced quality of life. Rare cases of spontaneous recovery have been recorded, particularly in young patients [106-108]. A rare patient may evolve into CVID [9, 10, 109]. The fact that the disease may progress over a period of time makes the regular observations a necessity among patients of this group every 4–6 months after accidental diagnosis.

Conclusion

The clinical phenotype classification of SIgAD has shown that more patients with SIgAD are without any clinical complications except selected patients with infections and noninfectious immunologic manifestations. The presence of clinical manifestations in SIgAD patients demonstrate which it is essential to understand exact pathogenesis, clinical manifestations and treatment of patients with SIgAD. There are many questions about SIgAD diseases and there is a long way for reach to answers of these questions, thus it is necessary to investigate more about this disease on SIgAD patients with different genetic backgrounds and number of patients around the world.

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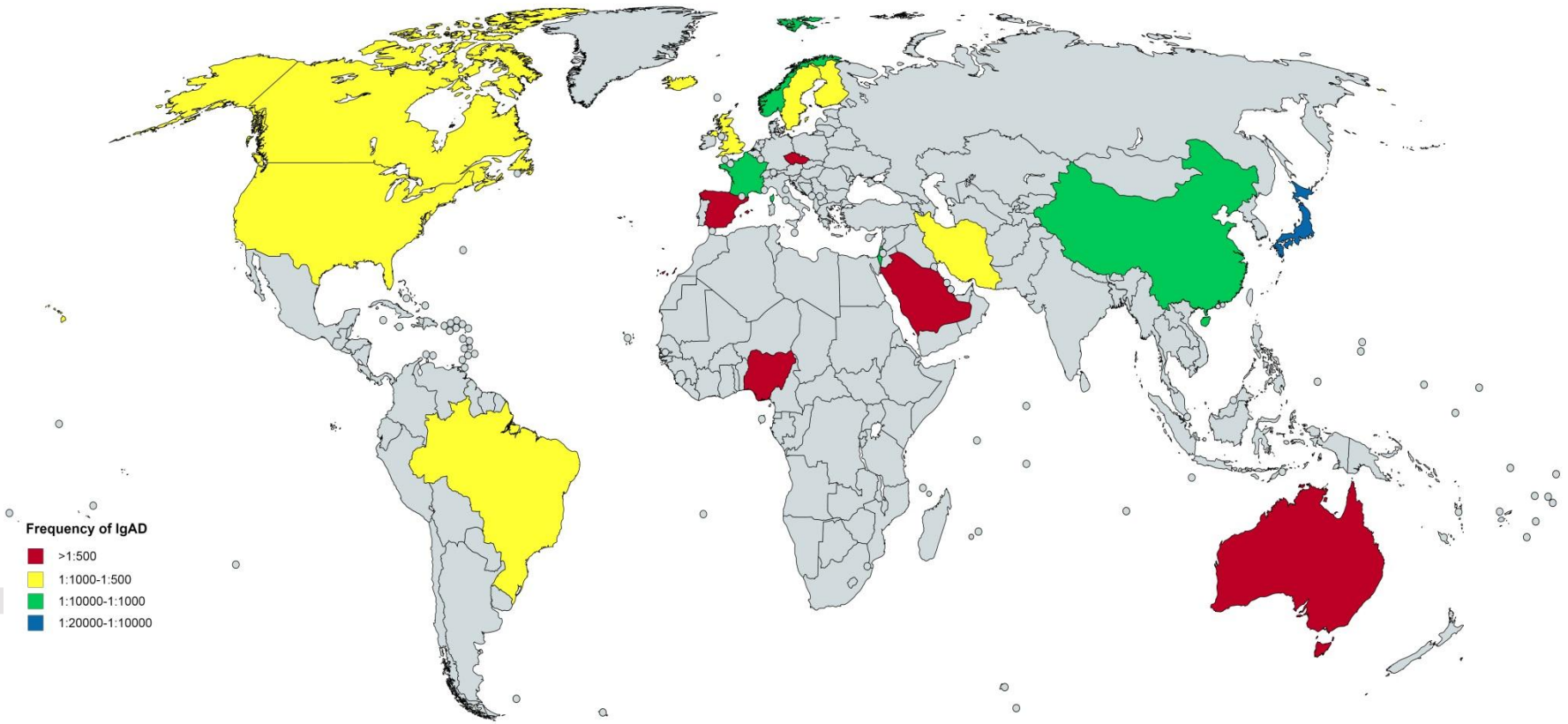
Figure 1- Frequency of IgA deficiency in normal population across the world. The map has been made based on the data extracted from repots of following countries: Austria [110, 111], USA [112-114], France [115], Spain [116], China [117], Sweden [118], Japan [119], Canada [120], Nigeria[15], Australia [121], Iran [4], Saudi Arabia [13], Norway [122], Finland [123], Czech [124], Brazil [125, 126], Iceland [127].



ДЕВЕТА НАЦИОНАЛНА КОНФЕРЕНЦИЯ ЗА РЕДКИ БОЛЕСТИ И ЛЕКАРСТВА СИРАЦИ

31 август – 1 септември 2018 г.

Гранд хотел „Пловдив“

ПОД ПАТРОНАЖА НА

Комисия по здравеопазване към 44-то Народно събрание

В сътрудничество с:

Българско медицинско сдружение по хематология

БАМО Българска асоциация по медицинска онкология

С подкрепата на:

NOVARTIS — Платинен спонсор

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Уважаеми колеги и приятели,

Имам удоволствието и честта да Ви поканя на 9-та Национална конференция за редки болести и лекарства сираци, която ще се проведе на 31 август – 01 септември 2018 г. в Гранд Хотел Пловдив.

Основна тема на събитието ще бъдат редките болести в онкология и хематология. Ще бъдат представени най-новите постижения в профилактиката, диагностиката, лечението, рехабилитацията и социалните грижи за хората с редки онкологични и хематологични заболявания. Утвърдени специалисти в областта на онкологията и хематологията ще споделят своя опит и актуални новости.

Конференцията се организира и провежда съвместно с Българската Асоциация по Медицинска Онкология (БАМО) и Българското медицинско сдружение по хематология.

Надявам се на Вашата подкрепа и участие в 9-та Национална конференция за редки болести и лекарства сираци.

Проф. Румен Стефанов, дм
От името на Организационния комитет

РЕЗЮМЕТА НА ПЛЕНАРНИ ДОКЛАДИ

УСТОЙЧИВОСТ И ЕФЕКТИВНОСТ НА ПОЛИТИКАТА ЗА РЕДКИ БОЛЕСТИ В БЪЛГАРИЯ И ЕС

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През последните десетилетия здравните системи в цял свят са подложени на редица изпитания в резултат на нарастващите разходи за медицински услуги. Дългосрочната устойчивост и ефективност на този сектор са под въпрос вследствие на застаряването на населението и навлизането на нови скъпоструващи здравни технологии. Тези проблеми са особено актуални в областта на редките болести, където са в сила някои специфични особености.

Здравнополитическите решения по отношение на редките заболявания са изключително деликатни предвид конфликта между принципите на благодеяние (да се помогне на всеки отделен индивид) и справедливост (всеки отделен индивид да получи равна по качество помощ). Предвид факта, че никоя страна или система не е в състояние да се справи сама с редките болести, това медико-социално и здравнополитическо предизвикателство изисква глобален подход, основан на колаборация и консенсус.

В началото на 2017 г. станахме свидетели на стартирането на 24 Европейски референтни мрежи (ЕРМ). Повече от 15 г. минаха от зараждането на тази концепция, но днес ЕРМ са факт и са водещ приоритет в европейската политика в областта на редките болести. От сега е ясно, че ЕРМ ще играят основа роля за развитието на тази проблематика. Устойчивостта на медико-социалната рамка на редките болести днес до голяма степен зависи от това дали самите ЕРМ ще съумеят да се превърнат в устойчиви и ефективни структури. Потенциалът на тези инфраструктури е значителен, но и предизвикателствата не са никак малко.

ИНОВАЦИИТЕ В ОНКОХЕМАТОЛОГИЯТА – ТРУДНОСТИ И НАДЕЖДИ

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Тенденциите при одобрение на нови лекарства и биологични агенти са категорични - 30 % от тези продукти за периода 2010-2013 са в областта на онкохематология (ОХ) и онкология като ръстът е в геометрична прогресия! За 10-годишен период (2010-2020 г.) се очаква цената на лечението в тези сфери да се удвои в световен мащаб. ОХ има примери за задоволени медицински нужди с постигнат впечатляващ терапевтичен ефект (хроничната миелоидна левкемия, ХМЛ). Това е резултат на прецизна диагностика, ранен достъп до съвременна терапия и ангажимент на държавата. Прилага се и концепцията за спиране на терапията при ХМЛ след спазване на строги критерии. ОХ разполага в доказателства за значително подобрена петгодишна обща преживяемост при болест на Ходжкин, неХоджкинови лимфоми, множествен миелом, хронична лимфоцитна левкемия, остеомиелофиброза. За съжаление има незадоволени медицински нужди при важни нозологии като острата миелоидна левкемия, рецидивиращи/ рефрактерни лимфоми и др. Модерната молекулярна биология идентифицира много нови потенциални таргети за малигнени заболявания. Лекарствените взаимодействия с тези таргети е възможна като клиничните ползи зависят от значимостта на таргета и евентуалната необходмост от инхибиране на няколко таргета. Направените сериозни терапевтични пробиви в таргетната, имунна и генна терапия дават основание за реален оптимизъм и в ОХ.

ОЦЕНКА НА СТОЙНОСТТА НА ИНОВАТИВНИТЕ ТЕРАПИИ В ОНКОЛОГИЯТА И ХЕМАТОЛОГИЯТА – ПИЛОТНИ РЕЗУЛТАТИ

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Въведение. Оценката на иновативни терапии в онкологията и хематологията и вземането на решение за тяхното заплащане е комплексен процес, който зависи от множество фактори и засегнати страни. Редица проучвания показват, че тези терапии са по-вероятно да бъдат реимбурсирани от здравни технологии в други клинични области предвид високия обществен интерес и социална значимост на онкохематологичните заболявания.

Цел. Настоящето проучване има за цел да оцени стойността на иновативните терапии в онкологията и хематологията.

Материал и методи. Проведено е анкетно проучване сред 230 лекари със специалност в областта на онкологията и хематологията. Изследването е проведено онлайн в периода май-юли 2018 г. Участниците трябва да оценят два практически казуса, свързани с минимално удължаване на преживяемостта и максимално заплащане при подобрено качество на живот.

Резултати. Относителният дял на участвалите е 34,8%. При оценка на иновативните терапии в областта на онкологията и хематология лекарите дават предимство на удължаването на преживяемостта спрямо повишаването на качеството на живот. Инкременталното съотношение на разходите за единица QALY е съответно 96 186 и 93 500 евро в тези два случая. Мнозинството от анкетираните не са склонни да отчитат специфични съображения при оценката на тези терапии, като индикация за педиатрична популация или редки болести.

Обсъждане. Проведеното проучване е пилотно за България. Изведените инкрементални съотношения са сравнително високи, но съпоставими със сходни проучвания от други европейски страни. Мнението и нагласите на медицинските специалисти са важни и следва да бъдат вземани под внимание при оценката на иновативни терапии.

Ключови думи: оценка на здравни технологии, разходна ефективност, качество на живот, готовност за заплащане.

ТРОЙНО НЕГАТИВЕН КАРЦИНОМ НА ГЪРДАТА ПРИ МЛАДА ЖЕНА – ДИАГНОСТИЧНИ И ТЕРАПЕВТИЧНИ ПРОБЛЕМИ

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Въведение. Тройно-негативният карцином на гърдата е част от групата подтипове на рака на гърдата, характеризиращ се с липса или оскъдно количество естрогенови, прогестеронови и HER2 рецептори, което го прави резистентен към хормонална терапия. Съставлява около 20% от случаите на рак на гърдата и обикновено засяга пременопаузални жени. Установена е и генетична предиспозиция в част от случаите. Съвременните изследвания целят да изучат по-подробно тройно-негативният карцином на гърдата и да го разделят на отделни подтипове.

Представяме случай на жена на 38 години, диагностицирана с тройно-негативен карцином на гърдата.

Извършена е оперативна интервенция с ексцизия на тумора, биопсично, имунохистохимично и генетично изследване.

Резултати. Касае се за жена на 38 години, постъпила в хирургично отделение по повод на фебрилитет, болки, подуване и зачервяване в областта на лява гърда. При извършените процедури и изследвания се установява тройно-негативен инвазивен дуктален карцином, Ki-67 положителен, с положителна BRCA1 мутация.

Дискусия. Тройно-негативният карцином на гърдата е заболяване, което може да бъде разделено на подтипове с различна прогноза. Хистологично най-често е базално-подобен, по-рядко може да е секреторен, адено-кистичен, адено-сквамозен, които са с по-добра прогноза. Имунохистохимичното изследване показва липса или оскъден брой естрогенови, прогестеронови и HER2 рецептори.

Генетичният анализ сочи, че част от пациентките са положителни за BRCA1 мутация. Съвременните изследвания целят по-подробно проучване на това заболяване и разделянето му на подтипове с цел оптимизиране на провежданата терапия.

EPAS1 P.M535T МУТАЦИЯ ПРИ БЪЛГАРСКА ФАМИЛИЯ С КОНГЕНИТАЛНА ЕРИТРОЦИТОЗА

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Цели. През последното десетилетие откриването на вродени мутации на няколко гена като EPOR, VHL, EGLN1 и EPAS1 доведе до дефинирането на няколко различни подтипа фамилна (конгенитална) еритроцитоза. Като редки заболявания те често остават неразпознати или погрешно диагностицирани, което налага съобщаването на новооткритите случаи.

Методи. Приложихме генетичен подход, включващ пълно екзомно секвениране и секвениране по Sanger за идентифициране на каузалната вродена мутация при една българска фамилия с конгенитална еритроцитоза.

Резултати. Открихме EPAS1 (HIF2A) p. M535T хетерозиготна мутация при четирима членове на фамилията от три поколения. Тук представяме също така обширно описание на клиничните характеристики на засегнатите членове на фамилията.

Обсъждане. EPAS1 p.M535T мутацията се открива при различни популации като каузален вариетет при фамилна еритроцитоза тип 4. Нашите резултати подкрепят идеята, че засегнаните пациенти се представят с разнообразни клинични характеристики и ход на заболяването. Освен това стриктното проследяване с извършване на флеботомии при нужда и редовен прием на ниски дози антикоагуланти/антиагреганти превентира развитието на сериозни усложнения като тромбемболични събития и пулмонална хипертония.

Заключение. Това е първото описание на цяла фамилия с EPAS1 p. M535T мутация, което разширява познанията относно клиничните характеристики на заболяването.

ЕФЕКТ НА ПОЛИМОРФИЗМА C677T В MTHFR ГЕНА ОТ ПЪТЯ НА МЕТОТРЕКСАТ ВЪРХУ ТОКСИЧНОСТТА И СЕРУМНИТЕ МУ НИВА ПРИ ВЪЗРАСТНИ СЪС ОНКОХЕМАТОЛОГИЧНИ ЗАБОЛЯВАНИЯ ПРЕДВАРИТЕЛНИ РЕЗУЛТАТИ

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Фармакогенетиката на метотрексат (MTX) допринася за междуиндивидуалните разлики в токсичността и серумните му нива. Целта ни е да оценим въздействието на C677T полиморфизма в MTHFR гена върху MTX-индуцираната токсичност и серумните нива на MTX по време на лечението при български възрастни с пациенти с онкохематологични заболявания. До този момент шест пациента са генотипизирани за C677T полиморфизма в MTHFR гена преди началото на терапия с високи дози MTX. Пет от тях са хетеро или хомозиготи по C677T полиморфизма. Средното плазмено ниво при тях на 24 час след инфузията е 4.34 μmol/l докато при пациента с нормален генотип е 0.16 μmol/l. Приложението на калциев фолинат не преодолява ефекта на полиморфизма върху степента на метаболизиране на метотрексат. Едно от ограниченията на изследването е малкият брой проби. Изследването на по-голям брой пациенти, ще допринесе до по-надеждни резултати. Идентифицирането на полиморфизма C677T в MTHFR гена от пътя на метотрексата е подходящ и полезен метод за подобряване на терапевтичните стратегии при възрастни със онкохематологични заболявания.

ФАРМАКОГЕНЕТИЧНИ ВАРИНАТИ ПРИ НДКБК И ФПТК

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Фармакогенетиката е наука, която изучава ролята на редки генетични дефекти за променения отговор на пациента към действието на лекарствата. Като стандартно лечение за пациенти с недребноклетъчен белодробен карцином (НДКБК) и папиларен тироиден карцином (ПТК) се използва платина базирана химиотерапия. Определянето на нови фармакогенетични варианти при НДКБК и ПТК, е изключително важно за определяна на по добри отговор към лечението.

Материали и методи. Изследвани са 18 туморни проби от НДКБК и 12 кръвни проби от ПТК. Изолирането на ДНК от НДКБК беше проведено с кит QIAamp DNA FFPE Tissue Kit, а от кръвните проби с QIAamp DNA Blood Mini Kit. Пробите бяха секвинирани с NGS технологията на инструмент Illumina-MiSeq, използвайки TruSight Cancer Sequencing Panel за 94 гени и 284 SNPs варианта. Резултатите са анализират според база данни pharmgkb (https://www.pharmgkb.org/) за SNP варианти, свързани с чувствителността към определени лекарства.

Резултати. Открити са 7 фармакогенетични варианти, от които 4 се откриват при двата типа карциноми - rs1042522 в TP53, rs2228001 в XPC, rs2227983 в EGFR и rs1318 в ERCC2. Открои се вариант rs1799793 в ERCC2 гена при НДКБК. Откриха се два варианта - rs1799939 в RET гена и rs17655 ERCC5 гена при ПТК. Фармакогенетичните варианти rs13181, rs1042522 и rs2228001 са чувствителни към цисплатина. Вариантът rs227983 в EGFR се асоциира с чувствителни към тирозинкиназни инхибитори.

Заключение. Секвенирането на ДНК-и от туморни проби и кръвни проби с TruSight Cancer Sequence панел може да определи соматични и герминативни фармакогенетични варианти, свързани с неефективна платина базирана химиотерапия или определящи токсично действие при химиотерапия.

МОЛЕКУЛНА ДИАГНОСТИКА НА ОНКОЛОГИЧНИ ЗАБОЛЯВАНИЯ С РАЗЛИЧЕН ГЕНЕТИЧЕН ТАРГЕТ

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Въведение. Малигнените заболявания представляват глобален медико-социален проблем в Света. Обикновено имат полигенен характер и включват множество генетични фактори с по-слабо или силно изразена фенотипна изява, както и с адитивен ефект в комбинация с факторите на средата и начина на живот.

Молекулната им диагностика е насочена към: доказване на наследствена предиспозиция, определяне риска от развитие в бъдещи поколения, ранна диагностика и молекулно профилиране относно клинично поведение и отговор към терапия.

Чрез молекулен анализ на вариабилни генетични дефекти: точкови мутации, микро/макроделеции, генна амплификация, транслокации, промяна в генната експресия, епигенетични флуктуации доказваме и профилираме множество онкозаболявания: рак на гърдата, множествена ендокринна неоплазия тип 1/ 2, неврофиброматоза тип 1/ 2, синдром на Hippel-Lindau, комплекс туберозна склероза тип 1/ 2, синдром на Линч, фамилна аденоматозна полипоза, фамилна ювенилна полипоза, невробластом, простатен карцином и др.

Генните дефекти преимуществено засягат гени, кодиращи важни регулаторни фактори, свързани със сигналните каскади за: апоптоза, клетъчна пролиферация, диференциация и др. Вследствие на различни мутационни събития, контрола върху тези процеси се губи и настъпва туморогенеза, последваща инвазия, прогресия. Все по-често, като биоиндикатори се използват некодиращи РНКи или мутации в некодиращи генни последователности. Потвърждава се хипотезата, че при някои неоплазми, причината е по-скоро в нарушената финна регулация на гените, а не в кодиращата им функция.

За молекулно профилиране на онкогенетичните заболявания се борави със съвременни методи: изолиране на ДНК/РНК, RT-PCR, Real-time PCR, MLPA, директно секвениране. Пациентите с изброените онкозаболявания в България имат възможност за ранна диагностика, превенция, терапевтичен скрининг по световните стандарти за високо експертно ниво на молекулната диагностика и интерпретация на резултатите.

ГЕНЕТИЧНИ ВАРИАНТИ В ДРЕВНИ ДНК ПРОБИ, АСОЦИИРАНИ С ПРЕДРАЗПОЛОЖЕНОСТ КЪМ ЗАБОЛЯВАНИЯ

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Прабългарите и Траките имат основна роля за произхода на съвременните българи. Техният геном повлиява генетичния спектър на съвременните българи.

Целта на изследването е да се анализират генетични варианти в митохондриалния геном, изолиран от тракийски костни останки от 3-то хилядолетие пр.хр. и от прабългарски, датирани от 8-10 век. Анализа и обработката на материалите е направен посредством Sanger метода и NGS – технологии.

Идентифицирани са 21 варианти, които асоциират със заболявания при съвременни популации: полиморфизъм T16189C (в две от прабългарските проби) асоциира с кардиомиопатии, рак на ендометриума, метаболитен синдром и меланома; 8 варианти (8 прабългарски и 3 тракийски проби) са свързани с повишен риск за меланома; 6 варианта (в 10 прабългарски и 5 тракийски проби) създават риск за рак на простата; вариант T310C (в две тракийски проби) асоциира с риск за Паркинсон и Фридрих атаксия; вариант T16519C (в 4 тракийски проби) асоциира с оптична невропатия на Лебер, загуба на слух, хипертриглицериемия, инфаркт, атаксия на Фридрих, някои форми на рак, основно на яйчниците; четири варианта (4 прабългарски пробии една тракийска) са свързани с намален риск за на рак на гърдата.

Получени са първи резултати за генетични варианти в древни ДНК проби на траки и прабългари, които определят предразположеност към заболявания.

Данните за вариантите на прабългарските и тракийски проби са представени в следните статии:

1. Nesheva, D.V., et al. Human Biology. 2015Vol. 87, 1

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ЕПИДЕМИОЛОГИЯ НА СИСТЕМНАТА МАСТОЦИТОЗА

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Мастоцитозата представлява хетерогенна група от заболявания, характеризиращи се с пролиферация и натрупване на неопластични мастоцити в един или повече органи или системи. Актуалната класификация на мастоцитозите на Световната здравна организация от 2016 г. разделя тези заболявания на кожна мастоцитоза, системна мастоцитоза и локализирани мастоцитни тумори. Системната мастоцитоза от своя страна се диференцира на индолентна, тлееща, със свързана хематологична неоплазия (с немастоцитна клетъчна линия), агресивна и мастоклетъчна левкемия.

Изучаването на епидемиологията на системната мастоцитоза и нейните подварианти е изключително трудно поради редица обективни фактори. Това са група от заболявания със сравнително хетерогенна клинична картина. Класификацията на подвариантите на системна мастоцитоза и съответните диагностични алгоритми търпят непрекъснато развитие и допълване. Поставянето на диагноза често изисква мултидисциплинарно сътрудничество между експерти с опит в областта на мастоцитозите. Значителна част от пациентската популация при системната мастоцитоза са възрастни пациенти, при които по презумпция се наблюдават множество коморбидности.

СУБЕПЕНДИМНИ ГИГАНТОКЛЕТЪЧНИ АСТРОЦИТОМИ ПРИ ТУБЕРОЗНА СКЛЕРОЗА

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Туберозната склероза (Tuberous Sclerosis Complex, TSC) е рядко автозомно-доминантно заболяване, характерезиращо се мултиорганно засягане на ЦНС, кожа, бъбреци, черен дроб и бял дроб, сърце, изразяващо се с повишена склонност към туморообразуване. Причината за това са мутации в двата гена – TSC1 и TSC2, имащи функция на тумор-супресори. Продукт на тези два гена е хамартин-туберинов белтъчен комплекс, водещ до подтискане на mTOR синалния път. При мутации в един или в двата гена настъпва дисрегулация на процесите на подтискане на туморния растеж, поради което се образуват тумори в различни органи. Редица проучвания доказват значително по-неблагоприятна клинична картина при пациентите с мутация в TSC2-гена.

Субепендмните гигантоклетъчни астроцитоми (SEGA) представляват доброкачествени туморни образувания, които се асоциират най-често с TSC. Според различни проучвания се срещат в 10-20% от пациентите. Обичайно се разрастват от стената на латералните вентрикули, в близост до форамен Монро. Имат бавен растеж, основно в детско-юношеска възраст и нерядко могат да съдържат калциеви отлагания, подобно на субепендимните нодули. Когато са с малки размери са практически асимптомни, но при нарастването им могат да причинят хидроцефалия с клинични изяви на интракарниална хипертензия – спешно състояние, налагащо неврохирургична интервенция. Провеждане на контролни проследяващи МРТ на главен мозък могат да покажат наличие и/или динамиката в размрите на SEGA. От м.май 2018г в България е регистриран медикамена Вотубиа /еверолимус, mTOR-киназен инхибитор/, разрешен за употреба и в детска възраст с оглед превенция нарастването на мозъчните SEGA, както и повлияване на бъбречните лезии – ангиомиолипоми.

В клиниката по нервни болести за деца са регистрирани 52 пациента с клинична диагноза ТСК, като 20 от тях имат и генетична верификация с оглед уточняване на засегнатия ген респ. оценка и прогностична стойност за тежестта и хода на заболяването. При 9 от децата (17%) се установява наличие и на SEGA. Три деца приемат еверолимус, като и при трите се отчита редукция в размерите на астроцитома. Едно от тези деца беше и със значително бъбречно засягане – също с много значима редукция в размерите на бъбречните лезии.

МОНОГЕНЕН ЗАХАРЕН ДИАБЕТ ПРИ ДЕТЕ И НЕГОВАТА МАЙКА С УСТАНОВЕНА НОВА МУТАЦИЯ В HNF1A ГЕНА

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Въведение. Около 5% от захарния диабет в популацията се дължи на единични генни дефекти. Провеждането на генетичен тест при пациентите с подозиран моногенен диабет и поставянето на точна диагноза е важно за лечението и прогнозата на заболяването. Представяме клиничен случай на захарен диабет при дете и неговата майка, носители на неизвестна досега мутация в гена за MODY -3 (Maturity-onset diabetes of the young type 3).

Методи и материали. Момче на 14 години с дебют на захарен диабет на 10 годишна възраст и майка, диагностицирана с неинсулинозависим захарен диабет на 37 години. Поради отрицателните маркери за автоимунен диабет и фамилната обремененост се проведе генетичен анализ с Next –Generation sequencing (NGS) метод на панел от пет подозирани гени за MODY на майката, пробанда и неговата сестра.

Резултати. Детето и майката са хетерозиготи за p.G69S (c. 205>A) на мутация с неуточнена значимост в HNF1A гена, който кодира транскрипционния хепатоцитен нуклеарен фактор 1-алфа. Направи се опит за преминаване по протокол от интензифицирано инсулиново лечение при детето към лечение със сулфанилуреен препарат Диапрел. На фона на перорално лечение не се постигна спиране или намаляване на инсулиновата доза.

Дискусия. Установената мутация в HNF1A гена представлява аминокиселинна замяна в първи екзон на гена и не е описвана досега сред пациенти със захарен диабет. Поради съчетанието на клинично изявен захарен диабет и мутация в HNF1A гена при майката и сина, вероятно се касае за моногенен диабет. Дефектите в този ген са причина за MODY 3, който може да се изяви във всяка възраст. Пубертетната фаза на развитие с физиологично изявена инсулинова резистентност е възможна причина за липсата на терапевтичен отговор към лечението със сулфанилуреен препарат.

ЛЕКАРСТВО-СВЪРЗАНИ ПРОБЛЕМИ ПРИ ПАЦИЕНТИ С ХРОНИЧНА МИЕЛОИДНА ЛЕВКЕМИЯ

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Въведение. Съвременното лечение с тирозин-киназни инхибитори (ТКИ) осигурява подобрено качество на живот и удължена преживяемост на пациентите с хроничната миелоидна левкемия (ХМЛ).

Цел. Целта е да се представят основните видове лекарство-свързани проблеми (ЛСП), които могат да бъдат идентифицирани и предотвратени от фармацевтите в хода на отпускането на лекарствата и проследяването на състоянието на пациентите с ХМЛ.

Материали и методи. Извършен е систематичен преглед на съществуващата научна медицинска литература, касаеща лекарствената терапия с ТКИ на пациенти с ХМЛ.

Резултати. Изборът на оптимална терапия се базира не само на ефикасността, но и на безопасността на лекарствения продукт и съобразяване с индивидуалните характеристики като възраст и съпътстващи заболявания. Nilotinib и Dasatinib са втора линия ТКИ, предписвани при терапевтичен неуспех с Imatinib, за които е необходимо стриктно мониториране на потенциални сериозни нежелани лекарствени реакции като ретенция на урина и плеврална ефузия. Безопасността, ефикасността и оптималното дозиране на терапията при пациенти с хипотиреоидизъм вследствие на лечението с ТКИ следва да бъдат оценени индивидуално. Приложението на лекарства индуктори или инхибитори на CYP3A4 ензима може да причини сериозни взаимодействия. Едновременното приложение на иматиниб и симвастатин води до увеличение на максималната плазмена концентрация на симвастатин, което се дължи на инхибирането на ензим CYP3A4 от иматиниб. Проучвания сочат сравнително ниски нива на придържане към терапията с иматиниб сред пациентите с ХМЛ поради пропускане на приема, грешка при предписване, поява на странични ефекти и др.

Заключение. Комплексната грижа за пациентите с ХМЛ, в която е включен и фармацевтът, осигурява проследяемост, контрол и предотвратяване на проблемите, свързани с лекарствената терапия.

ПРОУЧВАНЕ ЗА ДОСТЪПА НА ЛЕКАРСТВА СИРАЦИ В БЪЛГАРИЯ И ВРЕМЕТО ЗА ТЯХНОТО ВКЛЮЧВАНЕ В ПЛС

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Въведение. В Европейското законодателство рядко заболяване се дефинира като животозастрашаващо или инвадизиращо състояние с честота 5 пациента или по-малко на 10 000 човека. Поради ниската честота на тези заболявания, разработването на лечение обикновено не се счита за икономически интересно за дадена компания.

Материали и методи. Основната цел на изследването да бъде установена бройката лекарства сираци, които се срещат в ПЛС Приложение 1 и Приложение 2), както и в регистъра на Пределните ценМ, публикувани на официалната страница на Националния съвет по цени и реимбурсация. Допълнителна задача на изследването е да се изчисл средния период от време, необходим за регистрирането на цена на лекарствея продукт в България, след получаването на разрешение за употреба по централизирана процедура. Вторичнаа цел, която изследователския екип си постави е да бъде провереа на броя клинични изпитвания, регистрирани в базата данни на ClinicalTrials.gov на продуктите, които се срещат в гореспоменатите списъци.

Резултати. Според официалния списък на сайта на EMA (European Medicine Agency) 119 лекарствени продукти са кандидатствали по централизираната процедура като лекарства сираци, като 7 от тях са отхвърлени. В Списъка с Пределни цени се срещат 4.46% от тях, в Приложение 1 се срещат 8.93% от тях , а в Приложение 2 от ПЛМ се срещат 25%. При средно половината от достъпните в България лекарства сираци са провеждани и клинични изпитвания в България.

Дискусия. Малък брой лекарства сираци, при това за значителен период от време, се появяват на пазара в България, което създава бариери при лечението на редки заболявания.

РЕХАБИЛИТАЦИЯ ПРИ ОНКОЛОГИЧНИ ЗАБОЛЯВАНИЯ

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Рехабилитационното поведение при онкологични заболявания има своите специфики.

Според съвременните схващания физиорехабилитационните (в това число и кинезитерапевтичните) средства са насочени към промоцията на здраве, превенция на заболявания и рехабилитация на пациентите с цел осигуряване на по-добро качество на живот.

Възможностите на рехабилитационната медицина могат и трябва да бъдат обосновано и пълноценно използвани за въздействие върху функционалния дефицит, психо-емоционалните промени, самостоятелността в ежедневието и качеството на живот на пациентите с онкологични заболявания. Важно е да се отбележи, че рехабилитационната терапия е финансово изгодна, неинвазивна и лесно приложима.

Рехабилитационното поведение при тези пациенти е комплекс от съвместно провеждани медицински, социални, педагогически и професионални мероприятия, което е необходимо условие за постигане на адекватна ресоциализация на индивида.

Материал и методи. Представяме няколко конкретни рехабилитационни програми при онкопациети, с цел да демонстрираме мястото и възможностите на рехабилитационното леченипри пациенти със онкологични заболявания.

Резултати. Традиционното становище, че онкопациентите не са показани за физиорехабилитационно лечение, отдавна подлежи на преоценка.

Дискусия. Изграждането и провеждането на една индивидуализирана, целесъобразна, оптимална за клиничния стадий, форма и придружаващи заболявания, мултидисциплинарна рехабилитационна програма е необходимо условие за оптимален резултат за качеството на живот на пациентите с онкозаболявания.

Ключови думи. рехабилитация, онкологични заболявания, качество на живот, рехабилитационен потенциал

РЕЗЮМЕТА НА ПОСТЕРИ

ПОСТЕР 1
РАЗХОДИ ЗА НЕФОРМАЛНИ И ФОРМАЛНИ ГРИЖИ ЗА ПАЦИЕНТИ С РЕДКИ БОЛЕСТИ – ЛИТЕРАТУРЕН ОБЗОР

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Въведение. Предвид инвалидизиращия характер на повечето редки болести (РБ), диагностицираните пациенти се нуждаят както от специализирани формални грижи, така и от неформални грижи, осигурени от член на семейството. Определянето на цялостната социална и икономическа тежест на РБ е от значение за очертаване на бъдещите насоки за развитие в областта.

Цел. Целта на проучването е да се представят и анализират разходите за неформални и формални грижи за пациенти с РБ.

Материали и методи. Извършен е систематичен преглед на публикувани проучвания в PubMed и Scopus по ключови думи formal care, informal care, rare diseases, costs. От 25 открити публикации са подбрани 22, които са систематизирани по заболявания и държави.

Резултати. López-Bastida et al. анализират социалната, икономическата тежест и качеството на живот на пациенти с РБ, като заключават, че индиректните разходи, породени от загуба на производителност, и разходите за формалните и неформалните грижи са много по-високи от директните медицински разходи. Angelis et al. изчисляват, че делът на разходите за неформални грижи за пациентите с муковисцидоза в Обединеното кралство са най-високи – 44.1%. Разходите за неформални грижи за пациентите с мускулна дистрофия в Германия са 27% от общите, а за пациенти с хемофилия в Италия – 95% от директните немедицински. 74,8% от всички разходи за пациенти с булозна епидермолиза са директни немедицински, от които значителен дял са тези за неформални грижи.

Заключение. Повечето проучвания сочат, че независимо от съществения дял на разходите за формални и неформални грижи, пациентите с РБ имат нужда от здравна и социална грижа, в която да са включени медицински специалисти, квалифицирани социални работници и обучени техни близки.

ПОСТЕР 2
СЛУЧАЙ НА BCR-ABL ПОЗИТИВЕН ПАЦИЕНТ С ХИПЕРДИПЛОИДИЯ („A CASE OF A BCR-ABL POSITIVE PATIENT WITH HYPERDIPLOIDY“)

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Въведение. ХМЛ е честа злокачествена хематологична болест и представлява 15-20% от случаите на левкемия. Честотата на ХМЛ е 1.6/100000. Цитогенетичният маркер на ХМЛ е наличието на Филаделфийска хромозома при повече от 95% от пациентите. Тя е реципрочна транслокация между дългите рамена на хромозоми 9 и 22. Транслокацията включва гена ABL на хромозома 9 в т.нар. breakpoint cluster region и гена BCR на хромозома 22, което води до образуване на фузионен ген. Той кодира тирозин-киназа с дерегулаторна активност, която играе важна роля в развитието на ХМЛ.

Ние показваме случай на 83 годишна жена Р.М., която е насочена за цитогенетичен и молекулярно-генетичен анализ със суспекция за Ph(+).

Материали и методи. Извършено е кариотипиране след 24-часова култивация на материал от костен мозък. Получени са хромозоми, които са оцветени чрез G-техника. Отделно е използвана около 4 мл венозна кръв за количествен PCR анализ с цел детектиране на брой копия на фузионния ген BCR-ABL.

Количественият PCR е извършен с изцяло автоматизирана система GeneXpert (Cepheid). Аналитичната чувствителност на този тест е 0.01% BCR/ABL:ABL.

Резултати. Резултатът от цитогенетичния анализ показва наличие на главен патологичен Ph(+) клон, както и допълнителен хипердиплоиден Ph(+) клон: 46,XX,t(9;22)(q34;q11)[3]/46,XX,t(9;22)(q34;q11),+8,+10,+12[9]. Количественият RT-PCR анализ показва наличие на BCR/ABL транскрипт на ниво от 120% IS.

Заключение. Цитогенетичните особености играят важна роля при прогностичната оценка на ХМЛ. Освен Ph хромозома, с това заболяване са асоциирани различни други хромозомни аберации. 5-10% от случаите показват сложни транслокации с участие на други хромозоми. Има само един случай в литературата, при който Ph(+) пациент показва 51 хромозоми с тризомия по хромозоми 6, 10, 13, 19. Нашата пациентка е също Ph(+) с допълнителен хипердиплоиден клон в кариотипа с тризомия на 8, 10 и 12 хромозомни. Наличието на хипердиплоиден кариотип може да бъде лош прогностичен фактор. В момента пациентката е на терапия с Tasigna (Nilotinib) и ще бъде проследен ефекта от терапията. Случаят показва значимостта на цитогенетичните аномалии за прогнозата на ХМЛ.

ПОСТЕР 3
ПРОГНОСТИЧНО ЗНАЧЕНИЕ НА КАРИОТИПНИ НАХОДКИ С НАРУШЕНИЯ В ХРОМОЗОМА 20 ПРИ БОЛНИ С МИЕЛОДИСПЛАСТИЧЕН СИНДРОМ

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Въведение. Миелодиспластичните синдроми са хетерогенна група заболявания произхождащи от хемопоетичните стволови клетки, които се характеризират с неефективна хемопоеза, костно-мозъчна дисплазия и периферна цитопения с повишен риск за трансформация в остра миелоидна левкемия. Кариотипните промени заедно с процента бласти в костния мозък и засегнатите от цитопения кръвни редове са важна част от прогностичната скала IPSS (International Prognostic Score System),имаща за цел предвиждане на еволюцията на заболяването и средната преживяемост.

Цел. Цел на проучването е сравнение на прогностичното значение на кариотипните находки за преживяемостта на болните.

Материали и методи. Представяме три случая на многократно пролежали пациенти с миелодиспластичен синдром насочени към лабораторията по Медицинска генетика от клиника по Клинична Хематология към УМБАЛ „Св.Марина“ Варна. Проведен е цитогенетичен анализ върху 20 метафази за всеки пациент,които са получени чрез краткосрочно клетъчно култивиране на костен мозък и оцветени чрез GTG бендинг диференциално оцветяване на резолюция 150 - 200 бенда. Хромозомните аномалии са описани съгласно International System for Human Cytogenomic Nomenclature (ISCN 2013).

Резултати. Анализът показа наличие на структурна хромозомна аберация del(20)(q11 q13) и в трите случая:самостоятелно системно хромозомно нарушение,дериватна изохромозома по дългото рамо на 20-та хромозома с налична интерстициална делеция 46,XY,ider(20)(q10)del(20)(q11q13); в комплексен кариотип с различни структурни аберации в различни хромозоми, в това число и делеция на дългото рамо на 20-та хромозома (45,XY,del(7)(p12),inv(11)(q21q23),-18,del(20)(q11q13),del (22)(q12)).

Заключение. Пациентите с изолирана del(20q)попадат в категорията за добра прогноза базирана на прогностичната скала (IPSS). Наличието на ider(20q) и комплексен кариотип е свързано с по-кратка преживяемост и слаб терапевтичен отговор.

ПОСТЕР 4
АНАЛИЗ НА СПОДЕЛЕНА НАСЛЕДСТВЕНОСТ ПРИ НЕВРОЛОГИЧНИ И ПСИХИЧНИ БОЛЕСТИ

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Генетичната предразположеност към заболявания се определя от действието на множество генетични фактори. Често различни заболявания имат споделена генетична основа. Това се дължи на участието на множество гени в едни и същи молекулни патогенетични механизми.

Определянето на споделена наследственост е актуален проблем, който изисква провеждането на мащабни геномни изследвания и анализи на големи бази данни.

Анализирани са данните за 25 неврологични и психични болести от цялостни геномни асоциативни проучвания на 265 218 пациенти и 784 643 контроли.

Високата степен на генетична корелация сред психичните разстройства добавя допълнителни доказателства, че техните съвременни клинични фенотипи не отразяват отделните молекулни патогенетични процеси на генетично ниво. От друга страна, са установени доказателства, че няма съществено припокриване на геномно ниво между неврологични болести, както и между неврологични и психични разстройства.

В заключение, широко-мащабни геномни изследвания могат да подобрят съществено диагнозата и лечението на заболявания с генетична предразположеност.

ПОСТЕР 5
НАЦИОНАЛЕН РЕГИСТЪР ЗА ПАЦИЕНТИТЕ С РЕДКИ БОЛЕСТИ – ПОЛЗА И ПРЕДИЗВИКАТЕЛСТВА

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Националният регистър за пациентите с редки болести в РБългария (НРПРБ) е изграден в рамките на проект „Подобряване на контрола и информационните системи за превенция на риска в здравеопазването“ по програма BG07 “Инициативи за обществено здраве”. От май 2017 г. НРПРБ работи на национално ниво. Той е система за наблюдение, чиято основна цел е да се получат епидемиологични данни за редките заболявания в страната и да се подкрепят разработването на политики и планирането на здравните услуги. В доклада са представени основните възможности и функции на регистъра, изведени са някои базови статистически справки върху въведената информация за пациентите с редки болести.

ПОСТЕР 6
РЯДЪК СЛУЧАЙ НА ЕКСТРАСКЕЛЕТЕН ОСТЕОСАРКОМ НА БЕДРОТО ПРИ МЛАДА ЖЕНА

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Екстраскелетният остеосарком е изключително рядък тумор, представляващ 4% от всички остеосаркоми и 1-2% от мекотъканните саркоми. До днес в литературата са описани по-малко от 300 случая.

Представяме случай не ЕСОС на 36 - годишна жена, приета в клиниката по Ортопедия по повод болка и подуване в областта на лява тазобедрена става, придружено от затруднено ходене. Направените изследвания показват наличието на туморна формация латерално на ляво бедро, която е отстранена оперативно. След хистологично и имунохистохимично изследване окончателната диагноза е екстраскелетен остеосарком. Извършена е имунохистохимична типизация на тумора.

Екстраскелетният остеосарком е тумор от мезенхимен произход, който произвежда остеоид и кост (понякога се придружава и от хрущял). Разполага се в меките тъкани без да има връзка със скелетните кости. Тези негови особености

правят важно разграничаването му от други мекотъканни тумори (доброкачествени или злокачествени). Познаването на характеристиките на тумора правят възможно правилното му диагностициране и последващо терапевтично поведение.

Ключови думи: екстраосален остеосарком, диагноза, имунохистохимия

ПОСТЕР 7
КАРЦИНОСАРКОМИ НА МАТОЧНОТО ТЯЛО – ДИАГНОСТИЧНИ И МОРФОЛОГИЧНИ АСПЕКТИ

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Смесените Малигнени Мюлерови Тумори (ММMТ) са 2 до 8 % от всички злокачествени новообразувания на матката. Имат агресивен растеж и лоша прогноза. Срещат се предимно при жени в постменопауза. Основен клиничен симптом е гениталното кървене.

ММMТ по хистологичен строеж могат да бъдат хомоложни и хетероложни. Наричат се още карциносаркоми, защото са съставени от епителна и мезодермална компонента. Тяхната хистогенеза в литературата остава неизяснена.

Някои доказателства предполагат, че Смесените Малигнени Мюлерови Тумори (ММMТ) показват сходства със саркоматоиден карцином – тумор, възникващ на екстрагентални места, който също има смесен хистологичен вид. За да коментираме хистогенетичните механизми при тези тумори, ние сме изследвали чрез имунохистохимия 4 случая на ММMТ на маточното тяло.

Освен рутинно оцветяване с хематоксилин-еозин, хистохимично и имунохистохимично оцветяване сме използвани за доказване на диагнозата. Имунохистохимичното изследване е извършено с антитела на Фирма DAKO. Използван е стрептавидин-биотин имунопероксидазен метод. Панела от антитела включва: Виментин, Цитокератин 7, Цитокератин 20, Дезмин, Гладко мускулен актин, Епително мембранен антиген (EMA), p 53 и S-100 протеин.

Ключови думи: карциносаркоми, маточно тяло, диагностични методи

ПОСТЕР 8
РЯДКА ЛОКАЛИЗАЦИЯ НА КАЛЦИФИЦИРАЩ ЕПИТЕЛИОМ НА МАЛЕРБ НА ДЯСНОТО КОЛЯНО

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Калцифициращият епителиом на Малерб, наричан още Пиломатриксом, е доброкачествен тумор, произлизащ от космените фоликули. За пръв път е описан от Малерб и Шенанте през 1880 година, които му дават наименованието „калцифициращ епителиом“, взимайки името на първия от двамата.

Обичайната локализация е на главата, врата и горните крайници. По-рядко се среща в областта на торса и долните крайници. Предимно се наблюдава в млада възраст, като съотношението жени:мъже е около 1,5:1. Представяме случай с мъж на 63 години с туморно образувание на дясното коляно, неболезнено, но затрудняващо клякането. Рентгенографски и оперативно се установява туморна формация с големина на лешник, белезникава. След хистологично изследване се диагностицира като калцифициращ епителиом на Малерб.

Пиломатриксомът е рядка лезия, произлизаща от матриксните клетки в основата на космените фоликули. Доказва се единствено хистологично. Туморът обикновено е единичен, плътен, с големина около 2см.

Честотата на локализация по долните крайници варира, но в литературата е описана около 5%.

Ключови думи: пиломатриксом, диагноза, редки локализации

ПОСТЕР 9
ТРАНЗИТОРЕН МИЕЛОПРОЛИФЕРАТИВЕН СИНДРОМ ПРИ НОВОРОДЕНИ СЪС СИНДРОМ НА ДАУН – ПРЕДСТАВЯНЕ НА ДВА СЛУЧАЯ

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Въведение. Транзиторният миелопролиферативен синдром засяга предимно новородени деца със синдром на Даун и се характеризира с неконтролируема пролиферация на миелобласти в периферна кръв и костен мозък. Между 4% и 10% от новородените с тризомия 21 развиват транзиторен миелопролиферативен синдром, в повечето случаи със спонтанна регресия след 3-7 месеца, но в около 20-30% от засегнатите е свързан с развитието на остра миелоидна левкемия.

Материал и методи. Представяме два неродствени случая на деца със синдром на Даун и транзиторен миелопролиферативен синдром. М.С.И. е новородено от високорискова, непроследявана 13-та бременност, родено в тежка асфиксия, с малформативни стигми за синдром на Даун, с масивна левкоцитоза, тромбоцитопения с проявен хеморагичен синдром и хепатоспленомегалия. Впоследствие е установен мозъчен кръвоизлив и въпреки проведеното интензивно лечение, детето екзитира. Б.Е.Б. е дете на едномесечна възраст от втора нормално протекла бременност, първо раждане, с мекониално оцветени околоплодни води, с морфологични стигми за тризомия 21, хиперлевкоцитоза, хепатоспленомегалия и тромбоцитопения без проявен хеморагичен синдром. В резултат от проведената терапия общото състояние на детето се подобрява и се отбелязва редукция на органомегалията.

Резултати. Проведеният цитогенетичен анализ на култивирани лимфоцити от периферна кръв и костен мозък разкрива свободна тризомия 21 и при двата случая. При флоуцитометричното изследване на материал от периферна кръв се установява патологична миелоидна прекурсорна популация. Миелограмата показва хиперплазия на миелоидната клетъчна линия.

Заключение. Съчетанието на тризомия 21 и транзиторен миелопролиферативен синдром е рядко срещано състояние в педиатричната практика, което поставя диагностични предизвикателства, изисква диференциран подход за лечение и играе важна роля в развитието на остра миелоидна левкемия при пациенти със синдром на Даун.

ПОСТЕР 10
КАЧЕСТВО НА ЖИВОТ ПРИ ПАЦИЕНТИ С НАРУШЕНИЯ В КОАГУЛАЦИЯТА: HAEMO-QOL

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Въведение. При провеждането на научни проучвания все повече нараства необходимостта да се изследва степента на възприемане на заболяването от пациента, за да се оцени неговото качество на живот. Според дефиницията на Световната здравна организация за понятието качество на живот, то включва личните цели и очаквания на пациента, т.е. отношението му към неговото състояние и лечение.

Цел. Да се анализират данните от публикации, изследващи приложението на Haemo-Qol, като инструмент за оценка качеството на живот при деца с хемофилия.

Материал и методи. Проведено е систематично търсене в базите данни с научна литература на всички налични публикации до юли 2018 г., които описват въпросника Haemo-Qol.

Резултати. Въпросникът Haemo-Qol се прилага в 17 държави валидизиран и в 7 частично валидизиран. Научните изследвания са проведени при деца с хемофилия и родителите им на национално и международно ниво. При децата, данните до момента доказват повишаване на качеството на живот при засилена профилактика и подчертават ролята на семейството за благополучието на пациентите.

Дискусия. Изследванията потвърждават, че съвременните методи на лечение на деца с хемофилия водят до високо качество на живот, въпреки че има опции за усъвършенстване. Напредък може да бъде постигнат чрез осигуряване на среда, в която пациентите и родителите се чувстват разбрани и добре информирани и тяхната психосоциална адаптация към състоянието се счита за водеща.

Заключение. Специфичен въпросник за оценка качеството на живот, насочен едновременно към деца и родители, дава на семействата възможност да изразят възгледите си за хемофилията и представлява актуален способ за лечение на хемофилията.

ПОСТЕР 11
СЪВРЕМЕННИ МЕТОДИ ЗА ЛЕЧЕНИЕ НА ТУМОРИ ПРИ СИНДРОМ НА ФОН ХИПЕЛ ЛИНДАУ

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Синдромът на Фон Хипел Линдау е автозомно доминантно заболяване с честота 1:36 000, характеризиращо се с растеж на тумори като: хемангиобластома в ЦНС, Хемангиобластома на ретината, Феохромоцитома, Рак на бъбреците и др.

Диагнозата се потвърждава след неврологичен и офталмологичен преглед, компютърна томография или магнитен резонанс на мозъка и гръбначния стълб, ултразвук или СТ бъбреците, панкреаса, надбъбречните жлези, генетична диагноза.

Лечение чрез хирургични ексцизия на хемангиобластома е показано в случаите, когато туморът е симптоматичен. Ако размерът на туморите е не повече от 3 см, е възможна лъчева терапия. При тумор в ретината се препоръчва спешно лазерна фотокоагулация или криотерапия.

Проучват се редица експериментални терапии, например, инхибитори на васкуларния ендотелен растежен фактор (анти-VEGF). Такова лечение намалява отока на вътреочните структури, подобряване на зрението на пациенти, страдащи от ретинната ангиома.

Поради това, ранната диагностика и терапия на този синдром са от изключително значение за преживяемостта на пациентите. В миналото тя е била до 50 годишна възраст, но новите методи за диагностика и лечение удължават значително тази възраст и осигуряват по-високо качество на живот за пациентите.

ПОСТЕР 12
КЛИНИЧЕН СЛУЧАЙ СЪС СИНДРОМА НА LANGER–GIEDION И НАСЛЕДСТВЕНИ ОСТЕОХОНДРОМИ

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Синдромът на Langer–Giedion (LGS), OMIM 150 230, е автозомно доминантно генетично заболяване, дължащо се на делеция 8q23.2–q24.1, включваща TRPS1 и EXT1 гена, при което се установяват трихо-, рино-, фалангеални аномалии в съчетание с доброкачествени костни тумори – остеохондроми.Използвани са следните основни и физикални клинични методи на изследване, радиологични и генетични методи. MLPA анализът е извършен със Salsa® MLPA® kit P215. Амплификацията на кодиращите екзони на EXT1 (екзон 1-11) и EXT2 (екзон 2-14) е извършена по Clines et al. (Genome Res. 7(4):359-67, 1997). Проведени са консултации с детски невролог, офталмолог, уролог, ортопед, детски хирург, психолог и др.Авторите представят момче на възраст 4 години и 8 месеца, при което се установяват интелектуален дефицит, лицев дизморфизъм (дизпластични уши, удължен септум, дълъг филтрум, гъсти вежди), скелетни аномалии (пектус екскаватус, брахидактилия, високо небце, хипоплазия на десния радиус, ставна хипереластичност), хипоспадиес с фистула неоуретре, умбиликална херния в съчетание с множествени остеохондроми. Резултатът от MLPA анализа, показва делеция на целия EXT1 ген и потвърждава клиничната диагноза.

Представеният рядък клиничен случай показва асоциацията на доброкачествени костни тумори с генетични аномалии.

ПОСТЕР 13

СЛУЧАЙ НА ИДИОПАТИЧНА АРТЕРИАЛНА КАЛЦИНОЗА НА НОВОРОДЕНО С АНОМАЛИИ НА ВЪТРЕШНИТЕ ОРГАНИ

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Въведение. Идиопатичната артериална калциноза на новороденото (ИАКН) е рядко автозомно рецесивно заболяване, характеризиращо се с отлагането на калций по вътрешната еластична мембрана на артериите, придружено от фиброиране на интимата, което причинява стесняване на лумена.

Материал и методи. Представен е случай на ИАКН със situs inversus и сърдечни аномалии на дете родено в 39 г.с. чрез цезарово сечение. Новороденото постъпва в инрензивен сектор на 24 час след раждане с клиника на дихателна недостатъчност. През целия период на хоспитализация е на апаратна вентилация. Въпреки проведената КПР детето екзитира на 45-я ден след раждане.

Резултати. Резултатите от аутопсия показват вродената аномалия на вътрешните органи: голям междупредсърден дефект и излизащи от дясната камера трункус пулмоналис и аорта; атретична лява камера, както и situs inversus на коремните органи: стомах и черен дроб разположени от ляво и слезка с десностранно разположение. На този фон стените на артериални съдове на мозъка, белите дробове, бъбреците, надбъбреците са с наличие на калциеви депозити.

Дискусия. ИАКН трябва да се има предвид при всяко новородено с персистираща белодробна хипертония, тежка системна хипертония и ехогенни съдове. Калцификациите на големи и средни артерии са важни диагностични находки и трябва активно да се търсят на ехографско изследване.

Ключови думи: Идиопатичната артериална калциноза на новороденото , аномалии.

ПОСТЕР 14

КЛИНИЧЕН СЛУЧАЙ НА POEMS СИНДРОМ ПРИ ПАЦИЕНТКА С JAK2 V617F ПОЗИТИВНА МИЕЛОПРОЛИФЕРАТИВНА НЕОПЛАЗИЯ

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POEMS синдромът е добре известен, но рядко срещан паранеопластичен синдром, свързан с подлежаща плазмоклетъчна дискразия. Първоначално във медицинската литература той беше описван чрез пентадата: полиневропатия, органомегалия, ендокринопатия, моноклонално плазмоклетъчна неоплазия, и кожни промени. Освен това той често е свързан с еритроцитоза и тромбоцитоза. Костния мозък при него често показва изразена мегакариоцитна пролиферация с формиране на клъстери. Не се откриват обаче признаци на фиброза и пациентите не носят JAK2 V617F мутация. От друга страна първичната миелофиброза може да бъде свързана с наличие на моноклонален имуноглобулин. Тук описваме пациентка в напреднала възраст с постполицитемична миелофиброза, при която беше доказана IgM карра парапротеинемия. Обстойната клинична оценка показа, че пациентката покрива последните международно признати критерии за POEMS синдром. Доколкото ни е известно това е първият съобщен случай на POEMS синдром при пациент с верифицирана JAK2 V617F позитивна миелопролиферативна неоплазия (МПН), поставящ определени диагностични предизвикателства в контекста на съвременните диагностични критерии за двете заболявания. Този случай потвърждава, че двете заболявания не са взаимно изключващи се и оправдава изследването за мутации, свързани с МПН, при пациенти с POEMS синдром, особено в случаите, представящи се с еритроцитоза и тромбоцитоза.

ПОСТЕР 15
ПРИМЕРЕН АЛГОРИТЪМ ЗА ТАРГЕТНА ТЕРАПИЯ ПРИ ПАЦИЕНТИ С ХРОНИЧНА МИЕЛОИДНА ЛЕВКЕМИЯ, РЕЗИСТЕНТНИ НА ПЪРВО ПОКОЛЕНИЕ ТИРОЗИН КИНАЗНИ ИНХИБИТОРИ

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Иматиниб революционизира възможностите за лечение на хронична миелоидна левкемия (CML). Въпреки това около 3-4% от пациентите в хронична фаза развиват резистентност към иматиниб и наличието на точкови мутации в BCR-ABL киназения домейн са една от главните причините за това. Прилагането на второ поколение тирозин киназни инхибитори (TKI) (дазатиниб и нилотиниб) може да бъде съпроводено със скрининг на мутации в BCR-ABL киназния домейн (ABL-KD). Целта е създаване на алгоритъм/протокол за ранно откриване на прилежащите мутации, за да може да се осигури най-подходящата прицелна терапия. Откриването на наличните или появявили се в хода на лечението определени точкови мутации ще допринесе за прецизиране на терапията с определен TKI. Доказано е, че мутациите V299L, T315A, F317L / V / I / C водят до намалена чувствителност към дазатиниб, докато E255K / V, Y253H, F359V / C / I значително намаляват чувствителността към нилотиниб. Идентифицирането на мутация T315I, която е силно резистентна към иматиниб, дазатиниб и нилотиниб, е показание за задължителното прилагане на единствения перорален TKI, който инхибира T315I мутанта - понатиниб.

Препоръчително е идентифицирането на прилежащите мутации при пациенти с хронична миелоидна левкемия, които показват липса или субоптимален отговор на TKI от първо поколение, за да може да им се осигури най-подходящата таргетна терапия.

ПОСТЕР 16
ЕСТЕЗИОНЕВРОБЛАСТОМ С ЧЕРНОДРОБНА МЕТАСТАТИЧНА БОЛЕСТ

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Въведение. Естезионевробластома или олфакторен невробластом е много рядък злокачествен тумор на невроепителa. Среща се предимно във възрастта 11-20 години или 51- 60 години, засяга по-често мъже. Характеризира се с бавен, но интензивен растеж, чести рецидиви, рядко дава далечни метастази. Поради раритета на патологията липсва консенсус за лечение и се налага интердисциплинарен подход.

Клиничен случай. Касае се за бяла жена на 30 години. През 2016 год. по повод на ринорея и главоболие е направен ЯМР на главен мозък – данни за туморна формация в носна кухина. След биопсия се верифицира хистологично нискодиференциран естезионевробластом. Проведено оперативно лечение (09.16г.) с последващо лъчелечение в областта на засегнатите структури (носна кухина, ляв максиларен синус, етмоидални клетки, сфеноидален синус и фронтален синус) до ООД 60 Гр. На пореден контролен ЯМР от 11.17г. се описва рецидивна формация в областта на носната преграда дорзално. След ексцизия е насочена за лъчелечение до толеранс на тъканите. За остатъчната формация на първичния тумор е реализирана стереотактична роботизирана радиохирургия с Кибернож. На КТ през май месец 2018 г. се доказват множествени чернодробни метастази. Извършена е ТАБ и лезиите се верифицират като свързани с основното заболяване. Преценена от ОКОК за започване на системно ПХТ лечение по протокол Cisplatin/ Etoposide (4-6 курса), предстоят рестадиращи изследвания с ПЕТ-КТ.

Заключение. Алгоритъмът на терапевтичното поведение при естезионевробластома се базира на ретроспективни проучвания като липсва съвременен терапевтичен стандарт. С доказана ефективност са радикалната оперативна интервенция с последваща дефинитивна лъчетерапия. Системната химиотерапия има роля в случаите, когато туморът се разпространява извън носна кухина и дава далечни метастази. Платина- базираните режими са средство на избор като първа линия на лечение, особено при високодиференцираните тумори.

ПОСТЕР 17
ПРЕВЕНЦИЯ НА ВТОРО ЗЛОКАЧЕСТВЕНО ЗАБОЛЯВАНЕ

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Преболедувалите от онкологично заболяване имат повишен риск за второ малигнено заболяване (ВМЗ). То може да бъде солиден тумор или хематологична неоплазия и винаги е резултат на независимо генетично събитие.

Според преобладаващия етиологичен фактор ВМЗ могат да бъдат свързани с проведена антинеопластична терапия, с генетични синдроми или в резултат на сложни взаимодействия на множество фактори. Свързаните с лъчетерапия ВМЗ се характеризират с дълъг латентен период и тенденция за поява в облъчената или гранична зона. Миелоидната левкемия като ВМЗ има каузална връзка с химиотерапията и се появява след кратък латентен период. Приема се, че има генетична предиспозиция към увреждания, свързани с антинеопластичната терапия: герминативни мутации в гени, свързани с канцерогенезата (BRCA1 и BRCA2); гени, контролиращи възстановяване на увредената ДНК молекула или метаболизма на медикаменти. Идентифицирани са гени, отговорни за наследствени варианти на миелоидни неоплазми - RUNX1, CEBPA, GATA2 гени. Взаимодействие на множество фактори - генетични, специфични за индивида (възраст, пол, хормонален баланс, имунна дисрегулация) и фактори от околната среда създава риск от ВМЗ.

Познанията ни за сложната етиология на ВМЗ са основа за превенция. Принципите на първична и вторична превенция в онкологията важат и за ВМЗ. В подобни случаи важна е ролята на генетичната консултация и генетично тестуване, резултатите от които могат да променят терапевтичния план. Хемопревенцията включва диетични правила и препоръчителни хранителни добавки. Най-важно в първичната превенция на ВМЗ остава преценка на интензивността на цитостатичната терапия, както и избягване на лъчетерапията при пациенти с нисък риск от рецидив. Разработват се и специфични персонализирани програми за диспансерно наблюдение.

ПОСТЕР 18
РЕИМБУРСИРАНЕ НА ИНОВАТИВНИТЕ ЛЕКАРСТВЕНИ ПРОДУКТИ ПРЕЗ 2018

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Цели. На 14 декември 2017 г. българският парламент гласува бюджета на Националната здравно-осигурителна каса (НЗОК) за 2018 година, в рамките на който върху 21 иновативни лекарствени продукта беше наложен мораториум по отношение заплащането им с публични средства за срок от една година (за 2018 г.). След противопоставяне от страна на обществеността, неправителствените организации и индустрията, забраната беше отменена в края на декември 2017 г. В резултат на това отпадна ограничението към българските пациенти с редки заболявания, които потенциално биха били засегнати от мораториума. МЕТОДИ

Въз основа на публикуван на 01 юни 2018 г. списък на продуктите, заплащани с публични средства от НЗОК е направен анализ на реимбурсния статус на всички 21 лекарствени продукта, обект на мораториума от края на декември 2017 г.

Определени са редките заболявания и лекарствата сираци сред забранените с цел определяне броя на редки заболявания и тяхната значимост.

Резултати. Въз основа на резултатите от публикувания на 01 юни 2018 г. списък на продуктите, заплащани с публични средства от НЗОК 20 от 21 продукта (50% предназначени за амбулаторно и 50% предназначени за болнично лечение) се реимбурсират, с изключение на Trametinib, за който има отрицателна оценка на здравните технологии, като 7 от тези продукти имат статут на лекарства сираци, предназначени за лечение на редки заболявания.

Изводи. Въз основа на окончателното политическо решение от края на декември 2017 г. пациентите с редки заболявания не са лишени от възможни нови лечения и могат да извлекат полза от политиките на реимбурсация.

ПОСТЕР 19

ТЕЖКА АЗАТИОПРИН-ИНДУЦИРАНА МИЕЛОСУПРЕСИЯ ПРИ ПАЦИЕНТ С ЮВЕНИЛЕН ИДИОПАТИЧЕН АРТРИТ И НАСЛЕДСТВЕНА КСАНТИНУРИЯ

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Описваме уникален случай на асоциация между ювенилен идиопатичен артрит (ЮИА) и наследствена ксантинурия (НК) тип II при 19-годишен пациент, който разви тежка миелосупресия след лечение с азатиоприн (АЗА). Пълните хематологични, биохимични, генетични и имунологични изследвания показаха склонност към АЗА-индуцирана токсичност поради подлежащата НК тип II и частичен IgA дефицит. Спирането на лечението с АЗА и поддържащото лечение доведоха до пълно възстановяване на острата костно-мозъчна недостатъчност. Това е първият от по-малко от 10 случаи на НК тип II при пациент с ЮИА и първият случай с документирана АЗА-индицирана токсичност. Най-вероятният механизъм за токсичност е вторичното инхибиране на ензима тиопурин-S-метил трансфераза поради натрупването на тиоксантин. Считаме, че е препоръчително включването на НК като абсолютно противопоказание в кратката характеристика на АЗА. Изследването на нивото на пикочната киселина може да спомогне за откриването на такива случаи и предотвратяването на животозастрашаващи нежелани реакции.

ПОСТЕР 20

МУТАЦИИ НА КАЛРЕТИКУЛИН ПРИ БЪЛГАРСКИ ПАЦИЕНТИ С МИЕЛОПРОЛИФЕРАТИВНИ НЕОПЛАЗИИ

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Соматичните мутации на гените JAK2, MPL и CALR се откриват при повечето пациенти с миелопролиферативни неоплазии (МПН) без Филаделфийска хромозома. В това проучване приложихме четири различни молекулярно-генетични метода за откриване на мутации в екзон 9 на CALR гена, включително високоразделителен мелтинг анализ (HRM), директно ДНК секвениране по Sanger, секвениране на панел от таргетни гени с полупроводникова платформа, и пълно екзомно секвениране. В проучването бяха включени общо 78 пациенти с миелоидни неоплазии. Открихме 14 пациенти с мутации в екзон 9 на CALR. Всички пациенти с мутации бяха с потвърдена МПН, както следва: ПМФ (n = 7) или ЕТ (n = 7). Девет случая бяха с тип 1 мутации, а 5 случая – с тип 2 мутации. Мутациите в екзон 9 на CALR, екзон 10 на MPL и JAK2 p. V617F мутацията бяха взаимно изключващи се. Нямаше статистически значими разлики в хематологичните параметри между случаите с CALR или JAK2 или MPL мутации. И четирите техники показаха идентични резултати по отношение на детекцията на CALR мутации. Това проучване е едно от малкото съобщения за честотата на мутациите на CALR в Югоизточна Европа. Нашето проучване показва, че честотата и профилът на CALR мутациите са идентични с тези при пациенти от развитите страни. Освен това то демонстрира ползата от четири различни метода за тяхното откриване.

ПОСТЕР 21

АВТОИМУННИ НЕУТРОПЕНИИ ПРИ ВЪЗРАСТНИ ПАЦИЕНТИ С ПЪРВИЧНИ ИМУННИ ДЕФИЦИТИ: ДВА „ТИПИЧНИ" СЛУЧАЯ

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Автоимунните заболявания са честа изява на първичните имунни дефицити (ПИД) при възрастни пациенти. Те могат да бъдат както системни заболявания така и орган-специфични. Към последните се отнасят и изолираните автоимунни цитопении. Поради ниската си честота ПИД често остават неглижирана причина за автоимунни цитопении, Тук описваме два подобни случая, които илюстрират ролята на ПИД като фактор за развитие на автоимунни цитопении.

Случай 1: Пациентка на 33 години с рецидивиращи синопулмонални инфекции беше насочена поради тежка неутропения. Имунологичните изследвания показаха ниски нива на IgA и IgG4. Поради това беше поставена диагнозата селективен IgA дефицит. Пациентаката се повлия от ниски дози КС, което предполага наличието на антинеутрофилни антитела. Освен това при пациентиката беше доказана глутенова ентеропатия с висок титър на анти-ТТГ антитела. На фона безглутенова диета пациентката поддържа неутрофилен брой над 1.5 Г/л в продължение на 6 месеца.

Случай 2: 32 годишен мъж с тежка хемолотична анемия, смесен тип, и генерализирана лимфаденомегалия и спленомегалия, с дългогодишна анамнеза за чести синопулмонални инфецкии, псориазис и тиреоидит на Хашимото. Биопсията на ингвинален лимфен възел показа фоликуларна хиперплазия, а костно-мозъчната пункция – изразена еритробластна хиперплазия без данни за инфилтративен процес. Имунологичните изследвания показаха понижени нива на IgM и C3, поради което беше поставена диагнозата селективен IgM дефицит. Беше проведено лечение с високи дози кортикостероиди с последващо титриране на дозата до пълното им спиране след четири месеца. Пациентът показа нормализиране на хематологичните показатели и долногранични нива на общия IgM. Отчете се слабо повлияване на лимфаденомегалията.

Тези два случая показват, че автоимунните цитопении могат да бъдат изява на ПИД при възрастни пациенти и извършването на основни изследвания за хуморалния и клетъчния имунитет рано в диагностичния процес може да доведе до бърза диагноза и правилно терапевти чно поведение.