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Ocena występowania autoprzeciwciał oraz swoistych przeciwciał klasy IgE u pacjentów z pierwotnymi niedoborami odporności

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1. **Pieniawska-Śmiech, K.,** Lewandowicz-Uszyńska, A., Zemelka-Wiacek, M., & Jutel, M. (2022). Serum Allergen-Specific IgE among Pediatric Patients with Primary Immunodeficiency. *Children (Basel, Switzerland)*, *9*(4), 466. DOI:10.3390/children9040466
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2. **Pieniawska-Śmiech, K.,** Lewandowicz-Uszyńska, A., Zemelka-Wiacek, M., & Jutel, M. (2023). Assessment of autoantibodies in paediatric population with primary immunodeficiencies: a pilot study. *BMC Immunology.* DOI: 10.1186/s12865-023-00543-6
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3. **Pieniawska-Śmiech, K.,** Pasternak, G., Lewandowicz-Uszyńska, A., & Jutel, M. (2022). Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation. *Journal of clinical medicine*, *11*(14), 4220. DOI:10.3390/jcm11144220
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Oświadczenia współautorów określający ich wkład w powstanie poszczególnych prac stanowi załącznik 2 niniejszej rozprawy doktorskiej.

Wykaz stosowanych skrótów

AAb – autoprzeciwciała
AMA-M2 – przeciwciała przeciwmitochondrialne typ M2
AN - autoimmunologiczna neutropenia
ANA – przeciwciała przeciwjądrowe
Anti-Scl-70 – przeciwciała przeciwko topoizomerazie I
A-T - ataksja–telangiektazja
CENP-B – przeciwciała przeciwko białkom centromerów
CIDs – złożone niedobory odporności
CVID – pospolity zmienny niedobór odporności (ang. common variable immunodeficiency)
DGP – deamidowane peptydy gliadynowe
dsDNA – dwuniciowy kwas dezoksyrybonukleinowy (DNA)
Hgb – hemoglobina
HLA – główny układ zgodności tkankowej (ang. human leukocyte antigen)
IEI – wrodzone błędy odporności (ang. inborn errors of immunity)
IF – czynnik wewnętrzny
IFN- γ – interferon gamma
Ig A/E/G/M – immunoglobulina klasy A/E/G/M
IUIS – Międzynarodowa Unia Towarzystw Immunologicznych (ang. International Union of Immunological Societies)
MPO - mieloperoksydaza
NGS – sekwencjonowanie nowej generacji (ang. next generation sequencing)
no - numer
p – prawdopodobieństwo testowe
PAD – niedobór odporności z przeważającym defektem przeciwciał
PCNA – jądrowy antygen komórek proliferujących (ang. proliferating cell nuclear antigen)
PLT – liczba płytek krwi
PM/Scl-100 – antygen PM/Scl-100
PR3 – proteinaza 3
PNO – pierwotny niedobór odporności (ang. primary immunodeficiency PID)
sIgAD – selektywny niedobór IgA
sIgE – swoiste przeciwciała klasy E

SS-A – antygen A związany z zespołem Sjogrena (kompleks małocząsteczkowego RNA i dwóch białek o ciężarze cząsteczkowym 52 i 60 kDa)

SS-B – antygen B związany z zespołem Sjogrena (fosfoproteina o ciężarze cząsteczkowym 48 kDa wspomagająca RNA-polimerazę III)

Sm – antygen Smith

Th – limfocyty T pomocnicze

tIgE – stężenie IgE całkowitego

TG - tyreoglobulina

TPO – peroksydaza tarczycowa

Treg – limfocyty T regulatorowe

tTG – transglutaminaza tkankowa

WBC – liczba leukocytów

WSS – Wojewódzki Szpital Specjalistyczny

XLA – agammaglobulinemia sprzężona z chromosomem X

Streszczenie w języku polskim

Wprowadzenie: Pierwotne niedobory odporności (PNO), określane aktualnie jako wrodzone błędy odporności (ang. inborn errors of immunity, IEI) to heterogenna grupa chorób o podłożu genetycznym. Poszczególne jednostki chorobowe wchodzące w skład tej grupy występują rzadko, jednak zdecydowanie częściej niż pierwotnie sądzono. Wszystkie przypadki PNO jako całość stanowią istotny problem zdrowotny. W chwili obecnej scharakteryzowano ponad 400 PNO, wynikających z defektu jednego lub kilku elementów układu odpornościowego. Postęp jaki dokonał się w ich rozpoznawaniu i klasyfikacji przyczynił się także do ich lepszej charakterystyki. Klinicznie PNO różnią się ciężkością przebiegu, ale zwykle cechują je nawracające lub przewlekłe infekcje. Alergia, choroby autoimmunologiczne i autozapalne, brak prawidłowego rozwoju fizycznego czy zwiększona podatność na określone nowotwory mogą również stanowić objawy wiodące u pacjenta z PNO, a nawet być pierwszą manifestacją choroby lub jej komplikacją. Zaburzenia regulacji immunologicznej, rozumiane jako zaburzenia funkcji kontroli molekularnej procesów zachodzących w układzie odpornościowym, wydają się obecnie tak samo ważne w definiowaniu PNO jak zwiększona podatność na infekcje.

Cel: Głównym celem niniejszego cyklu prac oraz rozprawy doktorskiej było zwrócenie uwagi na inne niż infekcyjne objawy towarzyszące PNO, ze szczególnym uwzględnieniem chorób alergicznych i autoimmunologicznych a także na trudności diagnostyczne w zakresie ich rozpoznawania. Cele szczegółowe to: (1) ocena występowania swoistych przeciwciał IgE (sIgE) u pacjentów z PNO poniżej 18. roku życia oraz ich korelacja z danymi klinicznymi, (2) ocena występowania autoprzeciwciał w populacji pacjentów pediatrycznych z PNO, (3) omówienie wyzwań diagnostycznych u pacjentów z PNO ze szczególnym uwzględnieniem zaburzeń regulacji immunologicznej na bazie istniejącej literatury.

Materiały i metody: Grupę badaną we wszystkich analizach stanowili pacjenci ze zdiagnozowanymi PNO w wieku 1-17 lat, będący pacjentami Oddziału Immunologii Klinicznej i Pediatrii Wojewódzkiego Szpitala Specjalistycznego im. J. Gromkowskiego we Wrocławiu w okresie od lipca 2020 do lutego 2021 roku. Grupa badana, wśród której oceniano występowanie sIgE, liczyła 72 osoby (publikacja nr 1). Od badanych pobierano próbki krwi, w których oceniano takie parametry jak stężenie sIgE, IgE całkowitego i IgG, eozynofilię krwi obwodowej. sIgE oznaczano za pomocą metody immunoenzymatycznej – testu Polycheck (Biocheck GmbH, Münster, Germany), zgodnie z instrukcją producenta. Punkt odcięcia, powyżej którego stężenie sIgE uznano za podwyższone wynosił 0.35 kU/L. Dane laboratoryjne

analizowano w oparciu o dostępne dane kliniczne, uzyskane na podstawie medycznej dokumentacji pacjentów oraz autorskiego kwestionariusza. W publikacji nr 2 grupa badana składała się z 58 osób. Grupę kontrolną stanowiły dopasowane wiekowo osoby immunokompetentne (n=14). W pobranych próbkach krwi za pomocą ilościowej metody immunoenzymatycznej (Polycheck) wykrywano autoprzeciwciała w klasie IgG przeciwko 17 autoantygenom, a otrzymane wyniki korelowano ze stężeniem głównych klas immunoglobulin oraz podklas IgG, a także parametrów morfologii krwi takich jak stężenie hemoglobiny, liczba leukocytów oraz płytek krwi. Za punkt odcięcia, powyżej którego stężenie autoprzeciwciał uznano za pozytywne przyjęto ≥ 0.80 kU/L. Zebrane wyniki laboratoryjne analizowano w odniesieniu do zebranych danych klinicznych oraz dokumentacji medycznej pacjentów.

W publikacji nr 3 dokonano analizy istniejącej literatury poruszającej temat metod diagnostycznych oraz towarzyszącym im wyzwaniom u pacjentów z PNO w kontekście chorób alergicznych, autoimmunologicznych, nienowotworowej limfoproliferacji oraz chorób nowotworowych.

Wyniki: Podwyższone sIgE stwierdzono u 50% pacjentów w grupie badanej, co korelowało z występowaniem klinicznych objawów alergii ($p < 0.0001$). W czasie trwania badania, u 61.1% pacjentów obserwowano objawy alergii, z czego u 77.27% stwierdzono podwyższone stężenie co najmniej jednego sIgE. Stężenie całkowitego IgE było podwyższone u 18.06% pacjentów w grupie badanej i statystycznie również korelowało z objawami klinicznymi alergii ($p=0.004$). W grupie pacjentów otrzymujących leczenie substytucyjne preparatami immunoglobulin nie obserwowano podwyższonych stężeń całkowitego IgE. Na podstawie dokumentacji medycznej pacjentów uzyskano informacje o zdiagnozowanych wcześniej chorobach alergicznych takich jak: astma oskrzelowa u 18.06% pacjentów, alergiczny nieżyt nosa u 20.84%, alergia pokarmowa u 23.61%, atopowe zapalenie skóry u 25%. Autoprzeciwciała przeciwko co najmniej jednemu autoantygenowi stwierdzono we krwi 24.14% pacjentów w grupie badanej. Najczęściej wykrywanymi autoprzeciwciałami były przeciwciała przeciwko peroksydazie tarczycowej (anty-TPO), które obecne były u 13.8% pacjentów w grupie badanej. Statystycznie częściej stwierdzano je u pacjentów z dodatnim wywiadem rodzinnym w kierunku chorób autoimmunologicznych ($p=0.04$). Spośród czterech pacjentów w grupie badanej, u których wykryto podwyższone stężenie przeciwciał przeciwko deamidowanemu peptydowi gliadyny (anty-DGP), u dwóch postawiono po raz pierwszy rozpoznanie choroby trzewnej. Na podstawie przeprowadzonych badań nie stwierdzono różnic istotnych statystycznie w zakresie występowania autoprzeciwciał pomiędzy grupą badaną a grupą kontrolną.

Wnioski: Wykazano, że częstość występowania chorób alergicznych w populacji pediatrycznej z PNO jest wysoka. Stężenie sIgE oraz całkowitego IgE mogą być wiarygodnym narzędziem diagnostycznym u pacjentów z IEI. Stężenie całkowitego IgE nie jest przydatnym markerem w diagnostyce alergii u pacjentów otrzymujących substytucyjne leczenie immunoglobulinami. Pacjenci z PNO powinni być uważnie monitorowani pod kątem ryzyka alergii i autoimmunizacji. Populacja pediatryczna z PNO wymaga szczegółowej oceny statusu immunologicznego, ponieważ autoimmunizacja często rozwija się we wczesnym okresie życia. Wybrane autoprzeciwciała (tj. anty-tTG, anty-DGP) mogą być przydatne w badaniach przesiewowych wśród pacjentów z PNO. Ich powszechna ocena pomogłaby uniknąć opóźnienia rozpoznania choroby. Zasadne jest przeprowadzenie analizy opłacalności z uwzględnieniem czynników ryzyka i nasilenia choroby. Wczesna i trafna diagnoza może zapewnić podjęcie leczenia, zanim dojdzie do poważnych uszkodzeń narządów.

Streszczenie w języku angielskim

Introduction: Primary immunodeficiency disorders (PIDs), now known as inborn errors of immunity (IEI), are a heterogeneous group of diseases with a genetic background. If most PID are individually rare, they are collectively more common than generally thought. All cases of PID as a whole represent a significant health problem. Today, more than 400 PID have been characterized, resulting from a defect in one or more components of the immune system. The progress that has been made in the recognition and classification of PIDs has also contributed to their better characteristics. Clinically, PIDs vary in severity, but are usually characterized by recurrent or chronic infections. Allergy, autoimmune and autoinflammatory diseases, disturbances of physical development or increased susceptibility to nonmalignant lymphoproliferative and specific malignant manifestations may also be leading symptoms in a patient with PID, and may even be the first manifestation of the disease or its complication. Disturbances of immune regulation, understood as a breakdown or malfunction of molecular control of immune system processes, now seem to be as important in defining IEI as increased susceptibility to infections.

Aim: The main purpose of this series of publications and the doctoral dissertation was to draw attention to other than infectious symptoms accompanying PID, with particular emphasis on allergic and autoimmune diseases, as well as diagnostic difficulties in their diagnosis. Specific goals are: (1) assessment of the prevalence of specific IgE (sIgE) in PID patients under 18 years of age and their correlation with clinical data; (2) assessment of autoantibodies in paediatric population with primary immunodeficiencies; (3) discussion of diagnostic challenges in patients with PID with particular emphasis on immune dysregulation based on the existing literature.

Materials and methods: The study group in all analyses consisted of patients diagnosed with PID aged 1-17 years, who were patients of the Clinical Immunology and Pediatric Ward of the J. Gromkowski Provincial Hospital in Wroclaw from July 2020 to February 2021. The study group, among which the occurrence of sIgE was assessed, consisted of 72 people (publication no. 1). A blood samples were collected from the subjects and such parameters as sIgE, total IgE and IgG levels and peripheral blood eosinophilia were assessed. sIgE were measured by quantitative enzyme immunoassay—the Polycheck ® test (Biocheck GmbH, Münster, Germany), according to the manufacturer's instructions. The threshold for a positive result for sIgE, which was indicative of sensitization, was ≥0.35 kUa/L. Laboratory data were analyzed in the context of available clinical data obtained from the patients' medical records and

a proprietary questionnaire. In the publication no. 2, the study group consisted of 58 people. Age-matched immunocompetent individuals constituted the control group (n=14). Autoantibodies were measured by means of a quantitative enzyme immunoassay – the Polycheck ® test (Biocheck GmbH, Munster, Germany). In the collected blood samples, IgG autoantibodies against 17 autoantigens were detected and the obtained results were correlated with the concentration of the main immunoglobulin classes and IgG subclasses, as well as blood count parameters such as haemoglobin level, the number of white blood cells and platelets. The threshold for a positive result was ≥ 0.80 kU/L. The collected laboratory results were analyzed in relation to the collected clinical data and medical records of the patients.

Publication no. 3 analyzed the existing literature in terms of diagnostic methods and the accompanying challenges in patients with PID in the context of allergic, autoimmune, non-malignant lymphoproliferative and malignant manifestations.

Results: Serum sIgE was detected in the blood of 50% of the patients in the study group, which significantly correlated ($p < 0.0001$) with clinical symptoms of allergy. During the period of the study, 61.1% of the patients showed symptoms of allergy, with 77.27% of them having tested positive for sIgE. The total IgE level was elevated in 18.06% of the patients and correlated with clinical symptoms of allergy ($p = 0.004$). An elevated total IgE level was not observed in children receiving immunoglobulin replacement therapy (IRT). Based on the patients' medical records, information about previously diagnosed allergic diseases was confirmed, asthma was previously diagnosed in 18.06% of patients, allergic rhinitis in 20.84%, food allergy in 23.61%, atopic dermatitis in 25%. Autoantibodies against one or more antigens were detected in the sera of 24.14% (n=14) subjects in the study group. The most frequent were anti-thyroid peroxidase (anti-TPO) antibodies (n=8; 13.8%). Anti-TPO antibody levels were elevated more often in PID patients with a positive family history of autoimmune diseases ($p=0.04$). Four patients in the study group had elevated levels of antibodies against deamidated gliadin peptide (anti-DGP), two of them were diagnosed with celiac disease for the first time. There was no statistically significant difference between the study and the control group in terms of the autoantibodies prevalence.

Conslusions: The conducted studies revealed that the prevalence of allergic diseases in the pediatric population with PID is high. The study showed that serum sIgE and total IgE might be a plausible diagnostic tool for these patients. However, for patients with IRT, the assessment of total IgE is not useful in the diagnostics of allergy. PID patients should be carefully monitored with regard to their risk of allergy and autoimmunity. The pediatric population with PID requires a detailed assessment of immune status, as autoimmunity often develops at an early

age. Selected autoantibodies (i.e. anti-tTG, anti-DGP) may be useful for the screening of PID patients. Their widespread assessment would help avoid a delay in diagnosis. Cost-effectiveness analysis should be considered along with the risk factors and severity of the disease. Early and proper diagnosis can provide the initiation of treatment before serious organ damage occurs.

Wprowadzenie

Pierwotne niedobory odporności (PNO), określane aktualnie jako wrodzone błędy odporności (ang. inborn errors of immunity) to heterogenna grupa chorób o podłożu genetycznym. W celu zapewnienia jednolitej i prostszej terminologii, w niniejszej rozprawie posługiwać się będę skrótem PNO. Poszczególne jednostki chorobowe wchodzące w skład tej grupy występują rzadko, jednak zdecydowanie częściej niż pierwotnie sądzono. Wszystkie przypadki PNO jako całość stanowią istotny problem zdrowotny. Według szacunków na świecie żyje około sześć milionów chorych na PNO, z czego 70-90% pozostaje niezdiagnozowanych [1-3]. W chwili obecnej scharakteryzowano ponad 400 jednostek chorobowych należących do PNO, wynikających z defektu jednego lub kilku elementów układu odpornościowego [2]. Postęp, jaki dokonał się w ich rozpoznawaniu i klasyfikacji przyczynił się także do ich lepszej charakterystyki. Warto podkreślić, że badania nad PNO nie tylko pomagają w znalezieniu odpowiedniej terapii, ale co równie ważne, pozwalają na pogłębienie wiedzy na temat funkcjonowania układu odpornościowego, stanowią także doskonały model łączący określone defekty monogenowe z klinicznymi fenotypami zaburzonej regulacji immunologicznej [2].

PNO są spowodowane przez mutacje często pojedynczego genu, która skutkuje specyficznym upośledzeniem prawidłowego rozwoju i funkcji układu odpornościowego [2]. Progres, jaki dokonał się w ostatnich latach szczególnie w dziedzinie genetyki, umożliwił zarówno rozwój technologii sekwencjonowania DNA w celach diagnostycznych, jak i wykorzystywania terapii genowej w leczeniu chorób wrodzonych. Rozwój sekwencjonowania nowej generacji (ang. next generation sequencing – NGS) zapoczątkował rewolucję w wielu dziedzinach medycyny, w tym immunologii klinicznej. NGS uważane jest za przełom, zwłaszcza w sytuacji sekwencjonowania więcej niż kilku genów, co często ma miejsce, biorąc pod uwagę zróżnicowanie genetyczne tak powszechne w PNO [3]. Dzięki intensywnym badaniom naukowym, w klasyfikacji PNO z 2022 roku uwzględniono ponad 400 defektów odpowiedzialnych za wrodzone błędy odporności i ukazano ogromną różnorodność fenotypową PNO [2]. Zgodnie z klasyfikacją Międzynarodowej Unii Towarzystw Immunologicznych (ang. International Union of Immunological Societies; IUIS) obowiązującą w 2022 roku istnieje 10 głównych kategorii, do których należą poszczególne jednostki chorobowe zaliczane do wrodzonych błędów odporności: 1) niedobory odporności z defektem komórkowej i humoralnej odpowiedzi immunologicznej; 2) złożone niedobory odporności z dodatkowymi lub układowymi objawami; 3) niedobory z dominującymi zaburzeniami

produkcji przeciwciał; 4) zaburzenia regulacji immunologicznej; 5) wrodzone defekty liczby lub funkcji fagocytów; 6) zaburzenia odporności wrodzonej; 7) choroby autozapalne; 8) niedobory dopełniacza; 9) zaburzenia związane z niewydolnością szpiku kostnego; 10) fenokopie wrodzonych niedoborów odporności. Pomimo że zaburzenia regulacji immunologicznej stanowią osobną kategorię w klasyfikacji IUIS, w praktyce klinicznej także pacjenci z zaburzeniami odporności humoralnej, komórkowej czy wrodzonej wykazują zwiększone ryzyko chorób autoimmunologicznych lub autozapalnych.

Klinicznie PNO różnią się ciężkością przebiegu, ale zwykle cechują je nawracające lub przewlekłe infekcje. Niektóre zaburzenia wpływają na kluczowe szlaki immunologiczne, skutkując podatnością zarówno na powszechne jak i oportunistyczne patogeny, podczas gdy inne mogą powodować podatność na wąskie spektrum drobnoustrojów i ujawniać się w różnym wieku [4,5]. Co ciekawe, liczne obserwacje wskazują, że defekty genów związanych z układem odpornościowym mogą prowadzić także do fenotypów klinicznych niezwiązanych z podatnością na infekcje. Alergia, choroby autoimmunologiczne i autozapalne, brak prawidłowego rozwoju fizycznego czy zwiększona podatność na określone nowotwory mogą również stanowić objawy wiodące u pacjenta z PNO, a nawet być pierwszą manifestacją choroby lub jej komplikacją. Zaburzenia regulacji immunologicznej, rozumiane jako zaburzenia funkcji kontroli molekularnej procesów zachodzących w układzie odpornościowym, wydają się obecnie tak samo ważne w definiowaniu PNO jak zwiększona podatność na infekcje.

Prawidłowe funkcjonowanie układu odpornościowego zależy od balansu pomiędzy aktywacją (by bronić organizm przed obcymi, inwazyjnymi patogenami) a kontrolą (by różnicować pomiędzy antygenami własnymi a obcymi). Alergia rozwija się z powodu zaburzenia funkcji układu odpornościowego. W pierwotnych niedoborach odporności układ odpornościowy z jednej strony funkcjonuje niedostatecznie, prowadząc do zwiększonej predyspozycji do zakażeń, z drugiej zaś umożliwia rozwój reakcji alergicznej, która jest nadmierną odpowiedzią immunologiczną przeciwko swoistym alergenom [6-8]. Dzięki badaniom naukowym coraz lepiej rozumiane są mechanizmy leżące u podłoża tego zjawiska, między innymi zaburzenia tolerancji centralnej w grasicy, zaburzenia równowagi między funkcją komórek T efektorowych a regulatorowych, zaburzenia produkcji interferonu gamma (IFN- γ), zaburzona produkcja cytokin, a także możliwe różnice w kolonizacji bakteryjnej [8-10].

W przeszłości PNO i choroby autoimmunologiczne uważane były za swoje przeciwieństwa. Dziś, dzięki zastosowaniu analizy genetycznej i lepszemu zrozumieniu immunologicznych mechanizmów regulatorowych i sygnalizacyjnych, złożone powiązania i zależności pomiędzy PNO a chorobami autoimmunologicznymi są coraz lepiej charakteryzowane. Mutacje genetyczne mogą mieć wpływ na liczne komórki i molekuły układu odpornościowego, w związku z czym PNO i choroby autoimmunologiczne nie tylko nie wykluczają się wzajemnie, ale często ze sobą współistnieją [11]. Potencjalne mechanizmy związane z patogenezą autoimmunizacji to zaburzone różnicowanie komórek B, zmieniona centralna lub obwodowa tolerancja komórek T, niekontrolowana proliferacja i różnicowanie limfocytów, zaburzenia równowagi komórek T regulatorowych i Th17 (Treg/Th17), zaburzenia układu dopełniacza i aktywacji odporności wrodzonej, upośledzone usuwanie patogenów [12,13]. Dane naukowe sugerują, że zjawiska autoimmunizacyjne mogą dotyczyć znaczącego odsetka pacjentów z PNO [14].

Rozpoznawanie pierwotnych niedoborów odporności zarówno w Polsce jak i na świecie stanowi wciąż wyzwanie kliniczne, a dostępne dane z literatury światowej pozwalają stwierdzić, że ponad połowa przypadków pozostaje niezdiagnozowana lub opóźnienie w diagnostyce wynosi wiele lat. Objawy różnią się w zależności od rodzaju jednostki chorobowej, jednak istnieje kilka objawów alarmowych wskazujących na potencjalny pierwotny niedobór odporności [Tabela 1].

Tabela 1. Objawy alarmowe PNO według Jeffrey Modell Foundation

Cztery lub więcej zakażeń uszu w ciągu roku
Dwa lub więcej zapaleń zatok w ciągu roku
Trwająca dwa miesiące lub dłużej antybiotykoterapia z niewielką poprawą stanu klinicznego
Dwa lub więcej zapaleń płuc w ciągu roku
Brak przyrostu masy ciała i zahamowanie prawidłowego rozwoju
Powtarzające się głębokie ropnie skórne lub narządowe
Przewlekła grzybica jamy ustnej lub skóry u dzieci po 1. roku życia
Konieczność długotrwałego leczenia zakażeń dożylnymi antybiotykami
Dwa lub więcej zakażeń tkanek miękkich, w tym posocznica
Wywiad rodzinny wskazujący na występowanie pierwotnych niedoborów odporności

Powyższe 10 objawów alarmowych sugerujących PNO w dużym stopniu przyczyniło się do rozpowszechnienia wiedzy na temat wrodzonych zaburzeń odporności wśród lekarzy różnych specjalności. Warto jednak zauważyć, że rzadziej występujące objawy kliniczne, zwłaszcza dotyczące zaburzeń regulacji immunologicznej, nie zostały w niej uwzględnione. Pacjenci z mniej charakterystycznymi manifestacjami klinicznymi, nierzadko z towarzyszącymi objawami chorób alergicznych, autoimmunologicznych bądź nowotworowych, stanowią bardzo często wyzwanie diagnostyczne. Biorąc pod uwagę, że schorzenia te w większości są stosunkowo rzadkie, zasadne wydaje się zgromadzenie jak największej ilości danych na temat częstości występowania powikłań alergicznych, autoimmunologicznych, autozapalnych oraz nowotworowych w tej szczególnej grupie chorych. Jest to istotne również dlatego, że czynniki takie jak rasa, grupa etniczna, miejsce zamieszkania czy szerokość geograficzna mogą mieć wpływ na częstość ich występowania.

Cele i założenia rozprawy doktorskiej

Głównym celem niniejszego cyklu prac oraz rozprawy doktorskiej było zwrócenie uwagi na inne niż infekcyjne objawy towarzyszące IEI, ze szczególnym uwzględnieniem chorób alergicznych i autoimmunologicznych, a także na trudności diagnostyczne w zakresie ich rozpoznawania.

Celem pracy nr 1 była ocena występowania swoistych przeciwciał IgE (sIgE) u pacjentów z PNO poniżej 18. roku życia oraz ich korelacja z danymi klinicznymi.

Celem pracy nr 2 była ocena występowania autoprzeciwciał w populacji pacjentów pediatrycznych z PNO.

Celem pracy nr 3 było omówienie wyzwań diagnostycznych u pacjentów z PNO ze szczególnym uwzględnieniem zaburzeń regulacji immunologicznej.

Materiały i metody

Na przeprowadzenie badań wchodzących w skład prac oryginalnych (praca nr 1 i 2) uzyskano zgodę Komisji Bioetycznej Uniwersytetu Medycznego im. Piastów Śląskich we Wrocławiu (nr 333/2020). Wszyscy pacjenci powyżej 16. roku życia oraz rodzice/opiekunowie prawni małoletnich pacjentów przed przystąpieniem do badania wyrazili na nie świadomą i pisemną zgodę.

W pracy nr 1 grupę badaną stanowiło 72 pacjentów (n=46 płci męskiej; n=26 płci żeńskiej) w wieku 1-17 lat (mediana wieku = 7; średnia wieku = 7.7) ze zdiagnozowanym i udokumentowanym pierwotnym niedoborem odporności. Większość stanowili pacjenci z przeważającym defektem przeciwciał (n=51; 70.83%). 26.39% (n=19) pacjentów było w trakcie terapii substytucyjnej immunoglobulinami, pozostałe 73.61% (n=53) grupy badanej nie otrzymywało terapii substytucyjnej. Pacjenci byli hospitalizowani na Oddziale Immunologii Klinicznej i Pediatrii Wojewódzkiego Szpitala Specjalistycznego (WSS) im. J.Gromkowskiego we Wrocławiu w okresie od lipca 2020 do lutego 2021. W tym czasie pobierano od nich próbki krwi, w których oznaczano jednorazowo 1) stężenie sIgE przeciwko 18 alergenom pokarmowym takim jak: mleko krowie, alfa-laktoalbumina, beta-laktoglobulina, surowica albuminy wołowej, kazeina, białko jaja kurzego, żółtko jaja kurzego, dorsz, mąka-mix, soja, orzech ziemny, orzech laskowy, marchew, ziemniak, jabłko, kakao, kurczak; 2) stężenie sIgE przeciwko 11 alergenom wziewnym takim jak: pyłek 6 traw-mix, pyłek brzozy, pyłek bylicy, naskórek psa, naskórek kota, naskórek konia, Cladosporium herbarum, Aspergillus fumigatus, Alternaria alternta, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae;* 3) stężenie IgG; 4) eozynofilię krwi obwodowej; 5) stężenie całkowitego IgE. Na podstawie dokumentacji medycznej pacjentów zgromadzono takie dane jak: 1) udokumentowana diagnoza choroby alergicznej postawionej przez alergologa/pulmonologa; 2) choroba alergiczna w rodzinie; 3) występowanie nawracających infekcji dróg oddechowych w wywiadzie; 4) występowanie wyprysku skórnego; 5) przyjmowane leki, w tym antyhistaminowe; 6) niedobór masy ciała i/lub wzrostu; 7) miejsce zamieszkania (wieś, miasto).

Za pomocą kwestionariusza uzyskano dane na temat występowania objawów alergii wziewnej takich jak kichanie, katar, świąd nosa/oczu, potrzeba pocierania nosa/oczu, łzawienie oczu, niedrożność nosa z/bez świądem twarzy, wyciek z nosa, zmniejszone odczuwanie zapachu, problemy z oddychaniem z zamkniętymi ustami. Oceniano także objawy alergii pokarmowej takie jak świąd, zaczerwienienie, pokrzywka, obrzęk naczynioruchowy, nastrzyknięcie

spojówek, łzawienie, obrzęk powiek, objawy ze strony jamy ustnej i gardła, objawy alergii ze strony układu oddechowego, objawy ze strony układu pokarmowego takie jak nudności/wymioty, kurczowy ból brzucha, przelewania, biegunka, objawy anafilaksji. Dane na temat występowania astmy oskrzelowej i/lub atopowego zapalenia skóry były uzyskane głównie na podstawie specjalistycznej dokumentacji medycznej pacjentów.

sIgE były oznaczane za pomocą ilościowego testu immunoenzymatycznego – metody Polycheck® (Biocheck GmbH, Münster, Germany) zgodnie z instrukcją producenta. Punktem odcięcia dla wyniku pozytywnego było stężenie sIgE ≥0.35 kUa/L. Stężenie IgG i stężenie IgE całkowitego były oznaczane za pomocą metody immunoturbidymetrycznej, wyniki zostały zinterpretowane w stosunku do norm dla wieku pacjentów. Podwyższone IgE całkowite definiowano jako stężenie IgE powyżej normy dla wieku.

W pracy nr 2 grupę badaną stanowiło 58 pacjentów (n=36 płci męskiej, n=22 płci żeńskiej) w wieku 1-17 lat, ze zdiagnozowanym wcześniej PNO, będących pod stałą/ okresową opieką Oddziału Immunologii Klinicznej i Pediatrii WSS im. J. Gromkowskiego. Większość (n=46; 79.31%) stanowili pacjenci z przeważającym defektem przeciwciał. 13.79% (n=8) było w trakcie leczenia substytucyjnego immunoglobulinami. Do grupy kontrolnej zakwalifikowano 14 pacjentów (n=7 płci męskiej; n=7 płci żeńskiej) niespełniających kryteriów rozpoznania PNO, z jedynie sporadycznymi lub łagodnymi nawracającymi infekcjami dróg oddechowych. Od pacjentów w grupie badanej pobierano próbki krwi, w których oznaczano 1) stężenie IgG przeciwko antygenom takim jak Ro/SS-A 52, La/SS-B, Scl-70, PM/Scl-100, Sm, PCNA, dsDNA, ribosomal P protein, CENP-B, AMA M2, MPO, PR3, TPO, TG, deamidowane peptydy gliadyny (DGP), tkankowa transglutaminaza (tTG), czynnik wewnętrzny (IF);

2) stężenie hemoglobiny (Hgb); 3) liczbę leukocytów (WBC); 4) liczbę płytek krwi (PLT); 5) stężenie IgG i podklas IgG; 6) anty-tTG IgA u części pacjentów w grupie badanej. Anty-tTG IgA i anty-DGP IgA razem z stężeniem całkowitego IgA oraz autoprzeciwciała w klasie IgG były oznaczane w grupie kontrolnej zgodnie z rekomendacjami dla pacjentów immunokompetentnych. Autoprzeciwciała były oznaczane ilościową metodą immunoenzymatyczną, za pomocą testu Polycheck ® (Biocheck GmbH, Munster, Germany). Za punkt odcięcia, powyżej którego wyniki uznano za pozytywne przyjęto ≥ 0.80 kU/L. Czułość testu według charakterystyki produktu wynosiła 96.4%, zaś swoistość 97%. Stężenie całkowitego IgG oznaczano za pomocą immunoturbidymetrii, podczas gdy stężenia podklas IgG za pomocą metody nefelometrycznej. Stężenia immunoglobulin, hemoglobiny, liczbę leukocytów i płytek krwi porównywano z normami ustalonymi dla wieku pacjentów.

Dokonano analizy dokumentacji medycznej pacjentów, biorąc pod uwagę przede wszystkim takie dane jak dotychczas postawiona diagnoza choroby autoimmunologicznej oraz choroby alergicznej, wywiad rodzinny w kierunku chorób autoimmunologicznych, występowanie nawracających infekcji dróg oddechowych, powikłania PNO, obecność hepato-/splenomegalii i/lub limfadenopatii, przyjmowane leki, wyniki badań przeprowadzonych przed włączeniem pacjenta do leczenia immunoglobulinami (jeśli były dostępne) oraz miejsce zamieszkania.

Analizy statystycznej dokonano za pomocą programów Microsoft Office Excel (Microsoft Corp., Washington, DC, USA) oraz Statistica v.13 – dla danych jakościowych użyto testu chi-kwadrat Pearsona, dla danych ilościowych nieparametrycznych – testu U Manna-Whitneya. Poziom istotności statystycznej wynosił $\alpha = 0,05$. Wartość p poniżej 0.05 była uważana za statystycznie istotną.

Praca nr 3 miała charakter poglądowy. Celem jej przygotowania dokonano analizy baz oraz publikacji anglojęzycznych ze szczególnym uwzględnieniem zaburzeń regulacji immunologicznej.

Wyniki i wnioski

Dzięki szerokiemu zastosowaniu sekwencjonowania całego genomu, na świecie dokonał się olbrzymi postęp w zakresie rozpoznawania i charakterystyki nowych PNO, zaś ich liczba podwoiła się w latach 2009-2019 [15]. Z uwagi na fakt, że niektóre jednostki chorobowe wchodzące w skład PNO występują niezwykle rzadko, niekiedy jako kilka przypadków na świecie, przeprowadzenie badań na szeroką skalę jest niezwykle trudne. Dane na temat populacji pediatrycznej z PNO są ograniczone oraz często różnią się w zależności od pochodzenia grupy badanej oraz rozbieżności geograficznych. W ostatnich latach szczególnym zainteresowaniem badaczy cieszą się objawy inne niż infekcyjne, które to zostały dobrze zdefiniowane i scharakteryzowane. Poza 10 objawami alarmowymi PNO, znajdującymi się w Tabeli 1, uwagę zwraca się na manifestacje alergiczne, autoimmunologiczne, autozapalne oraz nowotworowe. Niewielka liczba opublikowanych prac naukowych powoduje, że dane z poszczególnych krajów dotyczące populacji pediatrycznej stanowią cenne źródło informacji, a niekiedy są wstępem do dalszych, wieloośrodkowych badań.

W niniejszej pracy doktorskiej przeprowadzono badania określające częstość występowania autoprzeciwciał oraz sIgE u pacjentów z PNO. sIgE stwierdzono u 50.0% (n=36) pacjentów, wykazując korelację z obecnością klinicznych objawów alergii wziewnej i/lub pokarmowej ($p<0.0001$). U większości pacjentów z dodatnim wynikiem (n=20; 27.78% pacjentów z PNO) stężenie sIgE mieściło się w przedziale 0.35-3.5 kU/L, podczas gdy u 16 pacjentów (22.22% pacjentów z PNO) sIgE wynosiło ≥3.5 kU/L. U 22.22% (n=16) pacjentów z PNO stwierdzono sIgE jedynie przeciwko jednemu alergenowi, podczas gdy u 18.06% (n=13) stwierdzono sIgE przeciwko trzem lub więcej alergenom. Najczęściej wykrywano podwyższone sIgE przeciwko alergenom pokarmowym (25%, n=18). U 12.5% (n=9) pacjentów podwyższone sIgE dotyczyło jedynie alergenów wziewnych. Spośród 21 pacjentów (29.17%) pacjentów, u których stwierdzano stały lub okresowy wyprysk skórny, większość (n=16) miało podwyższone sIgE ($p=0.003$). Nie stwierdzono istotnej korelacji pomiędzy występowaniem nawracających zakażeń dróg oddechowych a stężeniem sIgE ($p=0.55$). Podwyższone stężenie sIgE przeciwko alergenom wziewnym korelowało z podwyższonym całkowitym stężeniem IgE ($p=0.0002$), natomiast nie korelowało z eozynofilią krwi obwodowej ($p=0.85$), nawracającymi infekcjami dróg oddechowych ($p=0.23$), pozytywnym wywiadem rodzinnym w kierunku chorób alergicznych ($p=0.99$). Nie stwierdzono również różnicy w zakresie sIgE pomiędzy płciami ($p=0.39$). W przypadku sIgE przeciwko alergenom pokarmowym, nie stwierdzono statystycznie istotnej różnicy pomiędzy ich stężeniem a stężeniem całkowitego IgE ($p=0.14$),

eozynofilią krwi obwodowej (p=0.31), niedoborem masy ciała (p=0.87), niedoborem wzrostu (p=0.65), dodatnim wywiadem rodzinnym w kierunku chorób alergicznych (p=0.53), stosowaniem leków, w tym przeciwhistaminowych (p=0.54).

Analizując stężenie sIgE bez rozróżniania w zakresie rodzaju alergenów, przeciwko którym sIgE były skierowane, wykazano różnice pomiędzy ilością sIgE a miejscem zamieszkania (p=0.047). Podczas gdy 25% pacjentów mieszkających na wsi miało podwyższone stężenie sIgE, ponad dwukrotnie częściej (57.14%) zjawisko to dotyczyło pacjentów mieszkających w mieście. Różnice obserwowano także w zakresie stężenia sIgE: u żadnego pacjenta mieszkającego na wsi stężenie sIgE nie przekroczyło 3.5 kU/l, natomiast u 26.79% pacjentów z terenów miejskich obserwowano stężenie sIgE≥ 3.5 kU/L.

Stężenie IgE całkowitego u większości pacjentów z podwyższonym stężeniem sIgE mieściło się w zakresie normy (69.44%, *n* = 25). Wśród pacjentów z podwyższonym stężeniem IgE całkowitego (n=13), 11/13 (84.62%) pacjentów miało również podwyższone stężenie sIgE. Podwyższonego stężenia IgE całkowitego nie zaobserwowano u żadnego pacjenta będącego w trakcie terapii substytucyjnej immunoglobulinami.

Eozynofilię krwi obwodowej odnotowano u 15.28% (n=11) pacjentów z grupy badanej. Nie korelowała ona ze stężeniem sIgE (p=0.74), stężeniem całkowitego IgE (p=-.66), klinicznymi objawami alergii (p=0.62), wypryskiem skórnym (p=0.85), nawracającymi infekcjami układu oddechowego (p=0.29).

Na podstawie dokumentacji medycznej pacjentów uzyskano informacje o zdiagnozowanych wcześniej chorobach alergicznych takich jak astma oskrzelowa u 18.06% pacjentów, alergiczny nieżyt nosa u 20.84% pacjentów, alergia pokarmowa u 23.61% pacjentów, atopowe zapalenie skóry u 25%.

Nieprawidłowo funkcjonujący układ odpornościowy u pacjentów z PNO zwykle nie zapewnia ochrony organizmu przed zewnętrznymi patogenami, jednocześnie pozwalając na nadmierne reakcje nadwrażliwości. Rozwój alergii u pacjentów z PNO może być spowodowany zaburzeniem równowagi pomiędzy komórkami T efektorowymi a regulatorowymi układu odpornościowego, zaburzeniem tolerancji centralnej grasicy, zaburzeniem produkcji IFN- γ [8,9]. Dodatkowo pewną rolę mogą pełnić różnice w kolonizacji mikrobami oraz wzorce infekcji. Sama obecność sIgE nie jest równoznaczna z klinicznym rozpoznaniem alergii, a wyniki badań diagnostycznych muszą być zawsze interpretowane w kontekście historii klinicznej pacjenta. Definitywna diagnoza alergii IgE-zależnej wymaga wykazania sIgE i klinicznych objawów alergii po ekspozycji na konkretny alergen. U pacjentów z PNO, którzy prawdopodobnie są bardziej predysponowani do chorób alergicznych niż populacja ogólna,

diagnostyka może jednocześnie sprawiać więcej trudności. U pacjentów z niektórymi zaburzeniami syntezy przeciwciał (np. CVID, XLA) wyniki badań serologicznych opartych na IgE mogą mieć charakter fałszywie ujemny. Pacjenci z CVID często wykazują ekstremalnie niskie stężenia całkowitego IgE, a w badaniu Lawrence i wsp. sIgE były niewykrywalne u 96.5% pacjentów z CVID. W takich przypadkach w sytuacji klinicznego podejrzenia alergii wskazane jest wykonanie innych testów diagnostycznych, takich jak np. próba prowokacyjna [16,17]. W niniejszej pracy podwyższone sIgE wykazano u 2 spośród 3 pacjentów z CVID, jednak stężenie to było stosunkowo niskie (0.35-0.70 kU/L), choć korelowało z objawami klinicznymi alergii. Pomocne w praktyce klinicznej byłoby określenie wartości odcięcia dla swoistych IgE wśród pacjentów z pierwotnymi niedoborami odporności. W tym celu pomocne byłoby przeprowadzenie badań na szeroką skalę z dobrze zdefiniowaną, reprezentacyjną grupą badaną, przy użyciu także innych metod diagnostycznych, w tym prób prowokacji.

Autoprzeciwciała przeciwko co najmniej jednemu antygenowi stwierdzono u 24.14% (n=14) pacjentów w grupie badanej, z czego większość była skierowana przeciwko jednemu (n=7) lub dwóm (n=4) antygenom. Najczęściej (13.8%; n=8) stwierdzano podwyższone stężenie przeciwciał przeciwko peroksydazie tarczycowej (anty-TPO). Anty-TPO statystycznie częściej były podwyższone wśród pacjentów z dodatnim wywiadem rodzinnym w kierunku chorób autoimmunologicznych (p=0.044). 2 spośród 8 pacjentów z podwyższonymi anty-TPO było podczas trwania badania w trakcie terapii substytucyjnej immunoglobulinami. Wykazano różnicę statystyczną w zakresie stężenia anty-TPO pomiędzy grupą pacjentów otrzymującą immunoglobuliny (IRT +) a pacjentami nie będącymi w trakcie terapii (IRT (-); p=0.0009). Wyższe stężenia anty-TPO obserwowano w tej drugiej grupie (IRT -). Nie wykazano różnicy statystycznej pomiędzy obecnością przeciwciał przeciwjądrowych (p=0.551) oraz anty-TPO (p=0.609) pomiędzy grupą badaną a grupą kontrolną. Istotnej statystycznie różnicy nie stwierdzono także pomiędzy obiema grupami w zakresie występowania przeciwciał anty-DGP – pomimo, że wykazano je u 6.9% (n=4) pacjentów w grupie badanej, podczas gdy w grupie kontrolnej nie wykazano obecności anty-DGP. Obecność autoprzeciwciał nie korelowała z występowaniem niedokrwistości (p=0.358), leukopenii (p=0.664), czy neutropenii (p=0.526). Na podstawie dokumentacji medycznej pacjentów zgromadzono dane na temat dotychczas zdiagnozowanych chorób autoimmunologicznych. Spośród 58 pacjentów w grupie badanej, jedynie 8.62% (n=5) miało wcześniej uzyskaną diagnozę choroby autoimmunologicznej, takiej jak celiakia (n=2), małopłytkowość immunologiczna (n=2), neutropenia autoimmunologiczna (n=1). Przeprowadzone badanie umożliwiło identyfikację dwóch kolejnych, dotychczas

niezdiagnozowanych, przypadków celiakii (za pomocą kolejnych badań diagnostycznych). U 18.97% pacjentów z PNO (n=11) na podstawie dokumentacji medycznej odnotowano obecność hepato- i/lub splenomegalii i/lub limfadenopatii, które częściej dotyczyły płci męskiej (n=10) niż żeńskiej (n=1; p=0.025). Limfoproliferacja była obecna u wszystkich pacjentów z CVID (n=3), u dwojga pacjentów była to przyczyna diagnostyki w kierunku PNO.

Współwystępowanie niedoboru odporności i autoimmunizacji stanowi istotne pole do badań, a równoległe występowanie stanu hipo- i hiperimmunizacji czyni je niezwykle interesującym. Badanie złożonych mechanizmów regulacji immunologicznej w połączeniu z badaniami genetycznymi pozwoliło na ujawnienie złożonych relacji pomiędzy chorobami autoimmunologicznymi a PNO. Postulowane mechanizmy biorące udział w patogenezie tych chorób to zaburzone usuwanie patogenów, zaburzone różnicowanie komórek B, zachwiana tolerancja centralna i obwodowa komórek T, niekontrolowana proliferacja i różnicowanie limfocytów, zaburzenia równowagi limfocytów T regulatorowych i limfocytów Th17, zaburzona aktywacja układu dopełniacza i odporności wrodzonej [12,13].

Dotychczas przeprowadzono niewielką liczbę badań na temat występowania autoprzeciwciał oraz chorób autoimmunologicznych u pacjentów z PNO, zwłaszcza w populacji pediatrycznej. Największe dotychczas badanie przeprowadzono we Francji [14]. Co najmniej jedno powikłanie autoimmunologiczne i/lub zapalne odnotowano u 26.2% wszystkich pacjentów z PNO. W badaniu podkreślono zwiększone ryzyko rozwoju nieswoistych zapaleń jelit i zapalenia stawów u dzieci z PNO w porównaniu z populacją ogólną. W badaniu Tahiat i wsp. u 32.4% pacjentów z PNO pochodzących z Algierii i 15.8% badanych w grupie kontrolnej stwierdzono obecność autoprzeciwciał, a różnica ta była istotna statystycznie ($p < 0.0005$) [18]. Najczęściej stwierdzonymi autoprzeciwciałami były przeciwciała przeciwjądrowe (ANA), które występowały u 10% grupy badanej, a następnie przeciwciała przeciwko transglutaminazie tkankowej (8.4%). W analizie badań z różnych ośrodków naukowych w kontekście PNO warto wziąć pod uwagę wiek badanych pacjentów, udział poszczególnych jednostek chorobowych należących do PNO, szerokość geograficzną, możliwość występowania różnic etnicznych oraz odsetek pacjentów, których przodkowie byli ze sobą spokrewnieni, gdyż wszystkie te czynniki mogą mieć wpływ na uzyskiwane wyniki. Stąd niezwykle ważne jest zgromadzenie jak największej liczby danych z jak największej liczby ośrodków na świecie. Choć autoprzeciwciała występują także w populacji ludzi zdrowych, a ich obecność nie jest wystarczająca do postawienia klinicznej diagnozy, w tak szczególnej populacji jaką są dzieci i młodzież z PNO ich wykrycie wymaga uwagi, a w pewnych sytuacjach również monitorowania. Niezwykle fascynujący jest fakt, że niektórzy pacjenci z PNO z jednej strony

mogą nie wytwarzać specyficznych przeciwciał np. po szczepieniu, zaś z drugiej strony w ich krwi stwierdza się obecność autoprzeciwciał.

Poważne i/lub uporczywe nawracające infekcje oraz niewyjaśniona śmierć członka rodziny są coraz lepiej rozpoznawanymi objawami alarmowymi PNO, jednak warto zwrócić uwagę, że objawy zaburzonej regulacji immunologicznej także mogą być manifestacją lub komplikacją tej grupy chorób. Rokowanie u pacjentów z PNO z towarzyszącymi powikłaniami autoimmunizacyjnymi jest gorsze niż u pacjentów bez tych powikłań, wobec czego ich odkrycie u pacjentów z już rozpoznanym niedoborem odporności może prowadzić do istotnych zmian w strategii obserwacji i podejściu terapeutycznym. Z drugiej strony, rozpoznanie PNO u dziecka ze zdiagnozowaną już chorobą autoimmunologiczną również pozwala na odpowiednie leczenie choroby podstawowej (terapia immunoglobulinami, HSCT, terapia genowa) i/lub uniknięcie lub zmodyfikowanie leczenia immunosupresyjnego, co może mieć kluczowe znaczenie dla powodzenia danej terapii.

Pediatryczna populacja pacjentów z PNO wymaga dokładnej oceny statusu immunologicznego, ponieważ autoimmunizacja zaczyna się nierzadko przed osiągnięciem pełnoletności. Należy rozważyć czy wybrane autoprzeciwciała np. charakterystyczne dla choroby trzewnej, nie powinny znaleźć się w zestawie badań screeningowych dla pacjentów z wybranymi chorobami należącymi do PNO. Wczesna i trafna diagnoza oraz idąca za nią odpowiednia terapia mogą zapobiec wystąpieniu powikłań narządowych oraz polepszyć rokowanie pacjentów. Z uwagi na fakt, że obecnie badania te obarczone są istotnymi kosztami, należy przeprowadzić analizę opłacalności, biorąc pod uwagę czynniki ryzyka oraz nasilenie choroby.

Nowoczesne spojrzenie na PNO, jednocześnie korzystające z coraz lepszych i bardziej dokładnych narzędzi diagnostycznych, jak i oparte na wieloletnim klinicznym doświadczeniu, pozwoli na prawidłowe diagnozowanie i monitorowanie chorych, a także umożliwi opracowanie precyzyjnych strategii leczniczych, które mogą mieć wpływ na długość i jakość ich życia.

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Article

Serum Allergen-Specific IgE among Pediatric Patients with Primary Immunodeficiency

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Abstract: Background: Allergy is a clinical condition that reflects a deviated function of the immune system. The purpose of this study was to evaluate serum allergen-specific IgE (sIgE) along with clinical manifestations of allergy in patients with diagnosed primary immunodeficiency (PID). Methods: 72 patients, aged 1–17 years, diagnosed with PID and hospitalized between July 2020 and February 2021 were included in the study. Blood samples were obtained by venipuncture. sIgE (30 allergens), blood eosinophil count, as well as total IgE and IgG were measured and assessed in relation to a detailed medical examination. Results: Serum sIgE was detected in the blood of 50% of the patients in the study group, which significantly correlated ($p < 0.0001$) with clinical symptoms of allergy. During the period of the study, 61.1% of the patients showed symptoms of allergy, with 77.27% of them having tested positive for sIgE. The total IgE level was elevated in 18.06% of the patients and correlated with clinical symptoms of allergy ($p = 0.004$). An elevated total IgE level was not observed in children receiving immunoglobulin replacement therapy. Conclusion: The study showed that serum sIgE and total IgE together might be a plausible diagnostic tool for PID patients. However, for patients receiving immunoglobulin replacement therapy, the assessment of total IgE is not useful.

Keywords: allergy; inborn errors of immunity; immunoglobulin E (IgE); primary immunodeficiency (PID); specific IgE (sIgE)

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1. Introduction

Inborn errors of immunity (IEI) are a heterogeneous group of inherited diseases associated with genetic susceptibility, often stemming from a single-gene mutation. In the past, their prevalence was estimated at approximately 1:10,000–1:50,000. Due to novel diagnostic procedures, new nosologic units have been described and classified as primary immunodeficiencies (PID). The description of clinical phenotypes is being continuously updated [1,2]. Currently, the prevalence of IEI is estimated at 1:1000–1:5000 [3]. More than 400 diseases have been classified as PID. In most cases, they result from a single-gene mutation causing impaired development and function of the immune system. Regardless of their exact prevalence, PIDs are regarded as an unprecedented model, connecting defined monogenic defects with clinical manifestations of incorrect immune regulation. Immune dysregulation is a term used to characterize an array of autoimmune and inflammatory conditions [4]. In practice, IEI are associated with increased susceptibility to infection (especially severe, atypical, and/or recurrent infections), autoimmunity, allergy, and malignancy [3,5]. Immune dysregulation seems to be as important as susceptibility to infection in defining inborn errors of immunity nowadays. The International Union of Immunodeficiency Societies

(IUIS) regularly provides an overview of IEI. In current IUIS classification, there are 10 IEI categories according to their underlying molecular defect, and one of them is called 'diseases of immune dysregulation'. Within these IUIS classifications, each disorder is only listed once; therefore, these overviews do not feature phenotypic overlaps. However, it has been shown that other patients classified as having B-cell, T-cell, or innate immune system deficiencies are also at risk of autoimmune or inflammatory conditions [6].

Allergy develops due to a deviated function of the immune system. The occurrence of allergy in the context of PID has always been a compelling issue. Several PIDs are frequently associated with allergies. Moreover, common allergic reactions (eczema, allergic rhinitis, asthma, and food allergies) are exaggerated immune responses that may be manifestations of an underlying PID [7]. Appreciation of allergy as a manifestation of immune dysregulation should also stimulate the involvement of allergy specialists [8]. The misdiagnosis of PID as allergy has been described and may be complicated by the comorbidity of allergic diseases [8].

Atopic dermatitis (AD), in association with an elevated level of total IgE, constitutes a clinical feature of the hyper-IgE syndrome, Omenn syndrome, and Netherton syndrome. In the Wiskott–Aldrich syndrome (WAS), features of eczema are indistinguishable from those of atopic eczema. Selective IgA deficiency (sIgAD) often coexists with asthma, allergic rhinitis (AR), AD, and food allergy (FA) [9,10]. Allergic diseases, including food and drug allergies, are also present in other types of PID [11].

Studies on the prevalence of allergy in several PID disorders have shown mixed results. The reported differences might be due to differences in methodological approaches, as well as to ethnic and geographical diversity [12,13]. Thus, data on the prevalence of FA in patients with PID are very limited. The purpose of this study was to evaluate the prevalence of clinical manifestations of allergy and serum allergic-specific IgE (sIgE) in patients with PID.

2. Materials and Methods

The study was consented by the Bioethical Commission of the Wroclaw Medical University. Patients included in the study were previously diagnosed with PID (according to IUIS criteria and classification and ICD-10) and hospitalized in the Clinical Immunology and Pediatric Ward of the J. Gromkowski Provincial Hospital in Wroclaw from July 2020 to February 2021. All parents/legal guardians and patients over 16 years signed an informed consent before inclusion in the study.

The study group included 72 subjects (n = 46 boys, n = 26 girls) aged 1–17 years (median age = 7; mean age = 7.7). The baseline characteristics of the patients are presented in Table S1. Patients with predominantly antibody deficiencies (PAD; n = 51; 70.83%) constituted most of the study group, followed by patients with combined immunodeficiencies associated with syndromic features (n = 11; 15.28%). In addition, the study group was divided into two groups depending on the treatment received: a group of patients received permanent immunoglobulin (Ig) substitution therapy (n = 19; 26.39%), and a group did not receive Ig substitution therapy (n = 53; 73.61%) at the time of the study. The group of patients receiving Ig replacement therapy (IRT) included patients with X-linked agammaglobulinemia (n = 1), common variable immunodeficiency (CVID; n = 3), IgG subclass deficiency (n = 1), four patients with other hypogammaglobulinemias such as IgG deficiency (n = 3) and IgG subclass plus IgM deficiency (n = 1), one patient with Kabuki syndrome plus IgG subclass deficiency, one patient with PRKDC mutation with IgG subclass deficiency, two patients with severe combined immunodeficiency (SCID; one of them was enrolled before hematopoietic stem cell transplantation (HSCT), and the other was enrolled four years after HSCT), three patients with Nijmegen breakage syndrome (NBS), three patients with ataxia–telangiectasia (A-T). Doses of Ig were individualized and were within 0.2–0.8 g/kg (Table S2). In all cases, substitution therapy had started before the initiation of the current study. Patients with hyper-IgE syndrome, Omenn syndrome,

Netherton syndrome, WAS, which are associated with an elevated level of IgE, were not included in the study because they were not represented in our database.

During the study, a detailed medical history of the patients was collected, in particular: (1) a documented diagnosis of allergic disease performed by a trained allergist/pulmonologist, (2) family history of allergic diseases, (3) recurrent respiratory tract infections, (4) skin eczema, (5) medications taken, especially antihistamine drugs, (6) weight and/or height deficiency, (7) place of residence (village, town, city).

The following parameters were assessed by venous blood analysis: (1) concentration of sIgE against 18 food allergens: egg white, egg yolk, cow's milk, alpha-lactalbumin, beta-lactoglobulin, casein, bovine serum albumin (BSA), codfish, flour mix, rice, soybean, peanut, hazelnut, carrot, potato, apple, cacao, chicken; (2) concentration of sIgE against 11 inhalant allergens: 6 grass mix, birch pollen, mugwort pollen, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat epithelia, horse epithelia, dog epithelia, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Alternaria alternata*; (3) IgG concentration; (4) blood eosinophilia; (5) total IgE level.

Clinical symptoms were assessed by a questionnaire including questions on inhalant allergy: sneezing, rhinorrhea, nose/eyes itching, need to rub nose/eyes, watery eyes, nasal obstruction, with or without facial itching, nasal congestion, reduced sense of smell, trouble breathing with mouth closed. Symptoms of IgE-mediated food allergy (like pruritus, flushing, urticaria, angioedema, conjunctival injection, lacrimation, periorbital edema, oropharyngeal symptoms, allergy symptoms from the respiratory tract, gastrointestinal symptoms like nausea/vomiting, abdominal cramping, bloating, diarrhea, signs of anaphylaxis) were assessed separately. Assessment of asthma and atopic dermatitis was mainly based on specialists' consultations obtained from medical documentation.

sIgE were measured by quantitative enzyme immunoassay—the Polycheck ® test (Biocheck GmbH, Münster, Germany), according to the manufacturer's instructions. The threshold for a positive result for sIgE, which was indicative of sensitization, was $\geq$0.35 kUa/L. Subjects with at least one positive sIgE were considered to be sensitized. IgG and total IgE concentrations were measured by immunoturbidimetry. The total IgG and IgE reference ranges depended on the age of the individual. Elevated total IgE was defined as total IgE concentration above the age-related reference ranges.

Statistical analysis of the data was conducted using the spreadsheet of Microsoft Office Excel (Microsoft Corp., Washington, DC, USA) and Statistica v.13—for qualitative data—Pearson's chi-squared. The significance level was accepted as α = 0,05. A p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Allergen-Specific IgE

sIgE $\geq$ 0.35 kUa/L were detected in the sera of 50.0% (n = 36) of the PID patients (n = 72), which correlated ($p < 0.0001$) with the presence of clinical symptoms of inhalant and/or food allergy (Table S3). During the period of the study, 61.11% (n = 44) of the children with PID reported subjective symptoms of allergy, and in this group, 77.27% (n = 34) tested positive for sIgE. In most cases, there was a correlation between reported symptoms and positive sIgE. In 17 patients, the correlation was more evident, notably if there were symptoms of inhalant allergy (n = 12).

sIgE concentrations in the majority of allergic patients (n = 20; 27.78% of PID patients) ranged from 0.35 to 3.5 kU/L, while in 22.22% (n = 16) of the patients, sIgE concentration was $\geq$3.5 kU/L (Table 1 and Table S4). sIgE against only one allergen was observed in 22.22% (n = 16) of the PID patients, while in 18.06% (n = 13), sIgE against three and more allergens were observed. In most cases, sIgE were against food allergens (n = 18; 25%), whereas in 9 children (12.5%), they were only against inhalant allergens, and in other 9 children (12.5%) they were against both inhalant and food allergens.

Table 1. Characteristics of patients with sIgE concentration ≥ 3.5 kU/L.

Patient No	Age	Gender	PID Type	Previous Diagnosis of Allergic Disease	Reported Allergy Symptoms	sIgE [kU/L]	Total IgE [IU/mL]	Correlation between sIgE and Allergy Symptoms	Eosinophil Count [10^3/uL]	Antihistamines
1	8	M	IgM, IgG subclass deficiency	A, AR, FA	Nasal obstruction Sneezing Nose/eyes itching Trouble breathing with mouth closed Recurrent bronchitis	6 Grass mix = 2.9 *D. pteronyssinus* > 100 *D. farinae* > 100 Cat = 33.0 Dog = 0.89 *A. alternata* = 12	587 [0.5–393]	Yes	1.77	Yes
2	14	M	IgM deficiency	AR, FA	Rhinorrhea Diarrhea	*D. pteronyssinus* = 13.0 *D. farinae* = 65.0 Cat = 0.81 BSA = 0.5	207 [1.9–170]	Possible	0.12	No
3	13	M	IgA deficiency	AD	Nose/eyes itching Eczema Pruritus	Horse = 0.53 Cow's milk = 2.0 BSA = 38.0	34,2 [1.9–170]	Possible	0.17	No
4	7	M	IgM and IgG subclass deficiency	No	Sneezing	*D. pteronyssinus* > 100 *D. farinae* > 100 Cat = 1.2 Dog = 2.2 Horse = 0.45	328 [0.5–393]	Yes	3.75	No
5	6	F	IgG subclass deficiency	A, AD, FA	Eczema Pruritus Sneezing Nose/eyes itching Trouble breathing with mouth closed	6 Grass mix > 100 Birch pollen > 100 Mugwort pollen = 0.86 *D. pteronyssinus* = 4.5 *D. farinae* = 48 Cat = 0.27 Dog = 74 *C. herbarum* = 1.9 *A. alternata* = 5.0 Egg white = 0.94 Cow's milk = 0.94 Casein = 0.36 Flour Mix 0.46 Rice = 0.86 Peanut = 54.0 Hazelnut = 0.91 Carrot = 0.77 Potato = 1.8 Apple = 0.99	823.5 [0.5–393]	Yes	0.32	Yes

Table 1. *Cont.*

Patient No	Age	Gender	PID Type	Previous Diagnosis of Allergic Disease	Reported Allergy Symptoms	sIgE [kU/L]	Total IgE [IU/mL]	Correlation between sIgE and Allergy Symptoms	Eosinophil Count [10^3/uL]	Antihistamines
6	12	F	IgG subclass deficiency	AR	Sneezing Nose/eyes itching Watery eyes Need to rub eyes/nose Nasal obstruction	6 Grass mix > 100 Birch pollen = 3.5 Mugwort pollen = 0.81 *D. pteronyssinus* = 1.3 *D. farinae* = 11 Cat = 4.1 Dog = 0.6 *A. alternata* = 1.2 Flour Mix = 0.43 Rice = 0.48 Carrot = 0.50	466 [1.9–170]	Yes	0.17	Yes
7	6	M	IgA deficiency	A, AR	Sneezing Nose/eyes itching Watery eyes Need to rub eyes/nose Nasal obstruction Nasal congestion Rhinorrhea Abdominal cramping Recurrent bronchitis	*D. pteronyssinus* > 100 *D. farinae* > 100 BSA = 4.8 Cow's milk = 0.44	699 [0.5–393]	Yes	0.35	Yes
8	4	F	IgG subclass deficiency	A	Sneezing Nose/eyes itching Watery eyes Need to rub eyes/nose Recurrent bronchitis	Birch pollen = 1.3 Cat = 15	38.4 [0.4–351]	Yes	0.72	Yes
9	6	F	IgA and IgG subclass deficiency	AD, AR, FA	Sneezing Nose/eyes itching Watery eyes Need to rub eyes/nose Rhinorrhea Nasal obstruction Eczema	6 Grass mix = 60 Birch pollen = 1.7	134 [<90]	Yes	0.12	Yes
10	10	F	IgG subclass deficiency	AR	Rhinorrhea	6 Grass mix > 100 Birch pollen = 0.63 Mugwort pollen = 0.64	227 [<200]	Yes	0.22	No

Table 1. *Cont.*

Patient No	Age	Gender	PID Type	Previous Diagnosis of Allergic Disease	Reported Allergy Symptoms	sIgE [kU/L]	Total IgE [IU/mL]	Correlation between sIgE and Allergy Symptoms	Eosinophil Count [10^3/uL]	Antihistamines
11	16	M	IgM deficiency	AD, AR	Eczema Rhinorrhea	6 Grass mix > 100 Birch pollen = 0.50 Mugwort pollen = 0.51 Cow's milk = 0.54 BSA = 4.9	1157 [1.5–100]	Possible	0.17	Yes
12	9	M	PRKDC mutation, IgG subclass deficiency	AD, AR, FA	Eczema Nasal congestion Cough Sneezing Nose/eyes itching	6 Grass mix = 4.1 Birch pollen = 0.36 Mugwort pollen = 0.88 Cat = 0.96 Dog = 0.63	131 [0.5–393]	Yes	0.23	Yes
13	3	F	Complement deficiency	AD	Eczema Pruritus Excoriatio Rhinorrhea Cough	Dog = 0.37 Horse = 0.36 BSA = 9.9 Cow's milk = 0.73	10.5 [<60]	Possible	0.2	No
14	2	M	Phagocyte number/function deficiency	U	Urticaria	Cow's milk = 0.77 BSA = 7.0	17.3 [<60]	Possible	0.22	No
15	7	F	Congenital asplenia	AR	Rhinorrhea Nose/eyes itching	6 Grass mix = 4.0 Horse = 0.72 *A. alternata* = 9.4	47.3 [0.5–393]	Yes	0.27	Yes
16	10	F	Lymphocyte T deficiency	U	Urticaria Flushing	6 Grass mix = 2.7 Birch pollen = 0.36 Mugwort pollen = 0.58 *D. pteronyssinus* = 0.81 *D. farinae* = 0.94 Cow's milk = 0.52 BSA = 4.4 Flour Mix = 0.37 Rice = 0.44 Carrot = 0.39 Potato = 0.93 Apple = 1.00	908 [1.9–170]	Possible	0.19	Yes

Abbreviations: A—asthma; AC—allergic conjunctivitis; AD—atopic dermatitis; AR—allergic rhinitis; BSA—bovine serum albumin; F—female; FA—food allergy; Ig—immunoglobulin; M—male; No—number; PID—primary immunodeficiencies; PRKDC—Protein Kinase, DNA-Activated, Catalytic Subunit; U—urticaria.

The presence of sIgE (≥0.35 kU/L) against BSA in 33.33% (n = 24) of patients with PID was an interesting finding. In most of these cases (n = 20; 83.33%), it correlated with clinical symptoms of milk allergy at the time of the study or in the past. sIgE against BSA showed low values (<0.7 kU/L; n = 12). A higher concentration of sIgE against BSA was observed in patients without Ig replacement therapy than in patients receiving Ig substitution therapy, and the difference between these two groups was statistically significant (p = 0.03; Figure 1).

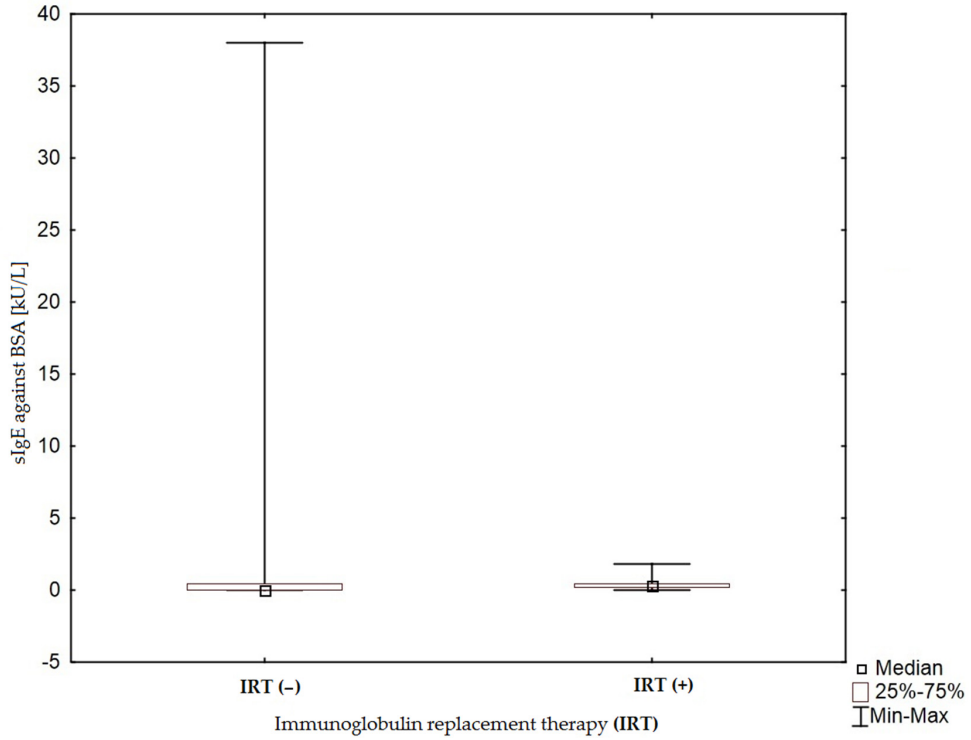


Figure 1. Concentration of sIgE against BSA (bovine serum albumin) in PID patients during immunoglobulin replacement therapy (IRT+) and not receiving IRT (IRT−) (p = 0.03).

Twenty-one (29.17%) patients showed chronic or recurrent skin eczema, and the majority of them (n = 16) had a significantly increased sIgE level (p = 0.003).

There was no significant correlation between the prevalence of recurrent respiratory tract infections and the serum sIgE level (p = 0.55).

The levels of sIgE against inhalant allergens correlated with an elevated total IgE (p = 0.0002). However, no correlation with blood eosinophilia (p = 0.85), recurrent respiratory tract infections (p = 0.23), family history of allergic diseases (p = 0.99) was observed. There was no significant difference between males and females (p = 0.39).

The levels of sIgE against food allergens did not correlate with eosinophilia (p = 0.31), total IgE (p = 0.14), weight deficiency (p = 0.87), height deficiency (p = 0.65), positive family history of allergy (p = 0.53). There was no effect of the treatment with antihistamine medications (p = 0.54).

Although 72.22% (n = 26) of the patients with increased sIgE were males, the difference between the sexes was not significant (p = 0.14). In addition, there was no significant difference between different groups of PID (Table 2).

Table 2. Prevalence of sensitization to food allergens, skin eczema, clinical symptoms of allergy, elevated total IgE and sIgE levels in the recruited patients with PID.

Type of PID (*n* = 72) / Selected Parameter	Clinical Symptoms of Allergy (*n* = 44)	sIgE ≥ 0.35 kUa/L (*n* = 36)	Elevated Total IgE (*n* = 13)	Sensitization to Food Allergens (sIgE ≥ 0.35 kUa/L) + Clinical Symptoms (*n* = 23)	Skin Eczema (*n* = 21)
SCID (*n* = 2)	*n* = 0 (0.00%)	*n* = 1 (50.00%)	*n* = 0 (0.00%)	*n* = 0 (0.00%)	*n* = 0 (0.00%)
Ataxia-telangiectasia (*n* = 4)	*n* = 3 (75.00%)	*n* = 3 (75.00%)	*n* = 0 (0.00%)	*n* = 2 (50.00%)	*n* = 1 (25.00%)
Nijmegen syndrome (*n* = 3)	*n* = 1 (33.33%)	*n* = 1 (33.33%)	*n* = 0 (0.00%)	*n* = 1 (33.33%)	*n* = 1 (33.33%)
DiGeorge syndrome (*n* = 2)	*n* = 1 (50.00%)	*n* = 1 (50.00%)	*n* = 0 (0.00%)	*n* = 1 (50.00%)	*n* = 0 (0.00%)
Kabuki syndrome (*n* = 1)	*n* = 0 (0.00%)	*n* = 0 (0.00%)	*n* = 0 (0.00%)	*n* = 0 (0.00%)	*n* = 0 (0.00%)
PRKDC mutation (*n* = 1)	*n* = 1 (100.00%)	*n* = 1 (100.00%)	*n* = 0 (0.00%)	*n* = 0 (0.00%)	*n* = 1 (100.00%)
Predominantly Ab deficiency (*n* = 51):	*n* = 31 (60.78%)	*n* = 24 (47.06%)	*n* = 12 (23.53%)	*n* = 15 (29.41%)	*n* = 16 (31.37%)
CVID (*n* = 3)	*n* = 2 (66.67%)	*n* = 2 (66.67%)	*n* = 0 (0.00%)	*n* = 2 (66.67%)	*n* = 1 (33.33%)
X-linked agammaglobulinemia (*n* = 1)	*n* = 1 (100.00%)	*n* = 1 (100.00%)	*n* = 0 (0.00%)	*n* = 1 (100.00%)	*n* = 1 (100.00%)
other hypo-gammaglobulinemia's (*n* = 20)	*n* = 12 (60.00%)	*n* = 10 (50.00%)	*n* = 4 (20.00%)	*n* = 4 (20.00%)	*n* = 6 (30.00%)
IgG subclass deficiency (*n* = 20)	*n* = 12 (60.00%)	*n* = 7 (35.00%)	*n* = 6 (30.00%)	*n* = 5 (25.00%)	*n* = 7 (35.00%)
selective IgA deficiency (*n* = 7)	*n* = 4 (57.14%)	*n* = 4 (57.14%)	*n* = 2 (28.57%)	*n* = 3 (42.86%)	*n* = 1 (14.29%)
Congenital defects of phagocyte number, function or both (*n* = 3)	*n* = 2 (66.67%)	*n* = 1 (33.33%)	*n* = 0 (0.00%)	*n* = 1 (33.33%)	*n* = 0 (0.00%)
Complement deficiency (*n* = 2)	*n* = 2 (100.00%)	*n* = 2 (100.00%)	*n* = 0 (0.00%)	*n* = 2 (100.00%)	*n* = 1 (50.00%)
Others (*n* = 3)	*n* = 3 (100.00%)	*n* = 2 (66.67%)	*n* = 1 (33.33%)	*n* = 1 (33.33%)	*n* = 1 (33.33%)

Abbreviations: Ab—antibody; CVID—common variable immunodeficiency; *n*—number of cases; sIgE—allergen-specific immunoglobulin class E; PID—primary immunodeficiencies; PRKDC—Protein Kinase, DNA-Activated, Catalytic Subunit; SCID—severe combined immunodeficiency; X-linked—gene is located in the X chromosome.

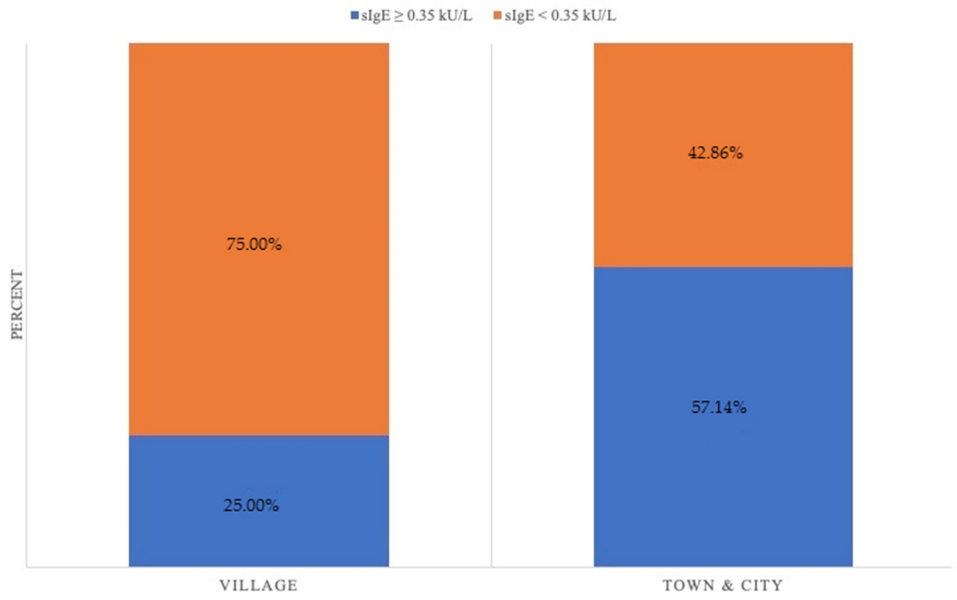
An increased sIgE level was observed in 47.17% (25/53) of patients not receiving IRT and in 57.89% (11/19) of patients undergoing IRT, but the difference between these two groups was not statistically significant ($p = 0.42$).

A statistically significant difference ($p = 0.047$) was observed with regard to rural or urban residence (Figure 2): 25% of patients living in the countryside had increased sIgE. Increased sIgE was found in the serum of 57.14% of children living in an urban area, while 26.79% of children from urban environments showed an sIgE level ≥ 3.5 kU/L, and none of the individuals from the countryside had sIgE levels ≥ 3.5 kU/L ($p = 0.047$; Figure 2B).

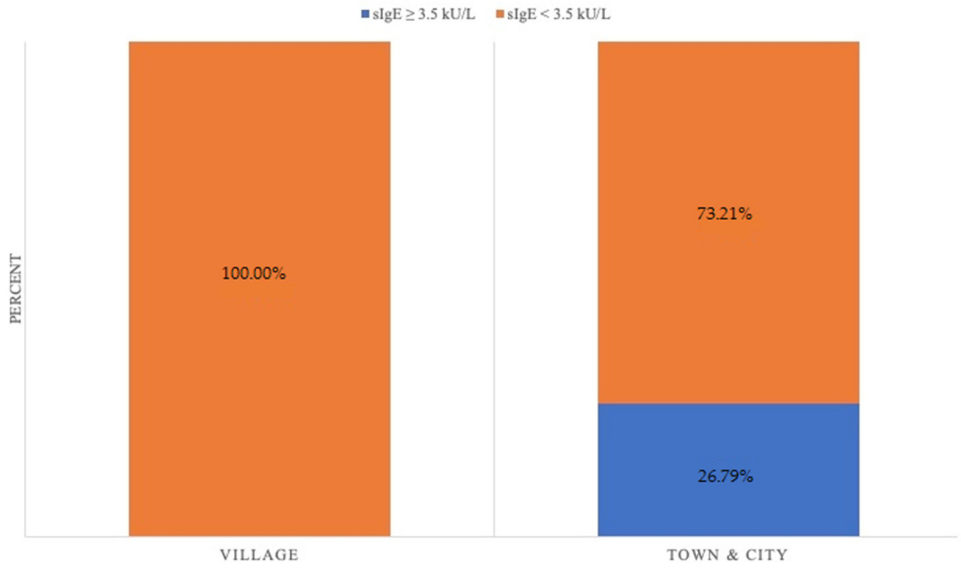
3.2. Total IgE Level

The total IgE level was normal in the majority (69.44%, $n = 25$) of the 36 children with increased (≥0.35 kU/L) sIgE. On the other hand, 84.62% ($n = 11$) of the 13 patients (18.06% of all 72 recruited patients) with an elevated total IgE level had increased sIgE concentration as well. There was a statistically significant correlation between sIgE and total IgE levels ($p = 0.014$). Furthermore, an elevated level of total IgE correlated with clinical symptoms of allergy in this particular group ($p = 0.004$; Table S3) but did not correlate with skin eczema ($p = 0.31$).

There was a statistically significant difference ($p = 0.04$) between PID patients treated with Ig and PID patients who were not undergoing Ig therapy (Figure 3). While the total IgE level was elevated in 24.53% ($n = 13$) of patients not receiving IRT, such deviation was not observed in those patients ($n = 0$) who were undergoing IRT.



A



B

Figure 2. (**A**). sIgE level depending on the living place ($p = 0.047$). (**B**). Prevalence of allergen-specific IgE concentration ≥ 3.5 kU/L depending on the living place (village vs. town and city; $p = 0.047$).

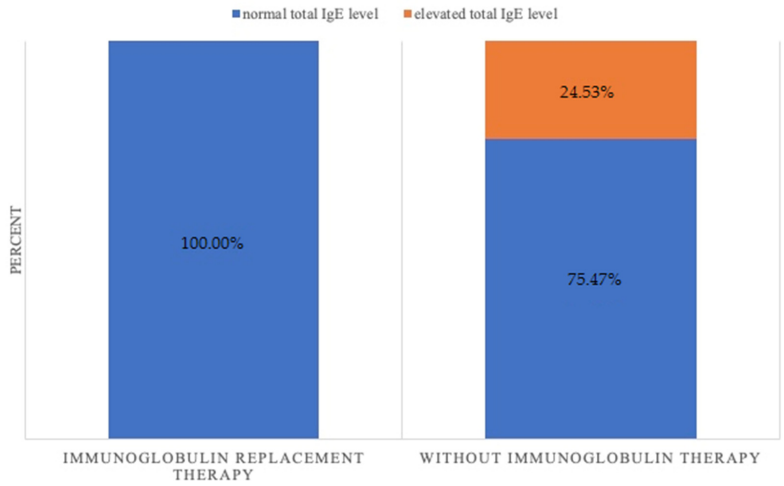


Figure 3. Total IgE level in relation to immunoglobulin replacement therapy ($p = 0.04$).

3.3. Blood Eosinophilia

Increased counts of eosinophils were observed in the blood of 15.28% ($n = 11$) of the 72 patients included in the study. Eosinophilia was slightly more often observed in females ($n = 5$; 19.23% of all females) than in males ($n = 6$; 13.04% of all males), but the difference was not statistically significant ($p = 0.48$). The counts of eosinophils did not correlate with sIgE presence ($p = 0.74$), clinical symptoms of allergy (Tables S3 and S5; $p = 0.62$), skin eczema ($p = 0.85$), recurrent respiratory tract infections ($p = 0.29$), or total IgE level ($p = 0.66$).

3.4. Clinical Manifestations

Of the 72 patients included in the study, 18.06% were previously diagnosed by a trained allergist/pulmonologist with asthma, 20.84% with AR, 23.61% with FA, and 25% with AD; urticaria occurred in 2.78% of the patients, AC in 1.39%, and drug-induced anaphylaxis in 1.39% (Table S5). Previous diagnoses were obtained from the patients' medical records.

4. Discussion

IgE plays a key role in the pathogenesis of allergic diseases, especially in mast cell/basophil activation, as well as in antigen/allergen presentation. The level of total IgE was considered in early studies as a marker to identify allergic subjects, but it became evident that total IgE levels cannot confirm an allergy status in a patient [14,15].

Performing serological diagnostics in patients with PID presents some challenges. For example, in patients with a common variable immunodeficiency (CVID), who show extremely low levels of IgE, traditional methods of sIgE measurement may provide false-negative results. In such conditions, sensitization should be confirmed using other methods, for example, bronchial provocation tests with allergens, etc. [16]. In a study conducted by Lawrence et al., an undetectable IgE level appeared in 75.6% (95% CI, 65.6–85.7%) of patients with CVID, and allergen sIgE was not detectable in 96.5% of patients with CVID [17]. Three patients with CVID participated in our study, and sIgE (but not total IgE) correlated with clinical symptoms of allergy (Table 2). However, it is worth adding that the sIgE level was between 0.35 and 0.70 kU/L in these patients, and the correlation was not confirmed by an oral food challenge.

According to some studies, the cut-off level of 0.35 kUa/L for allergen-specific IgE might be insufficient to predict clinical reactivity [18–22]. For example, in the study by

Garcia-Ara et al., it was shown that different cut-off points for specific IgE levels for milk and casein, which indicated clinical reactivity, were found at different ages. The specific IgE levels that were predictors of clinical reactivity (positive predictive value $\geq$ 90%), grew as the age of the infants increased: 1.5, 6, and 14 kUA/L for milk for patients in the age ranges of 13–18 and 19–24 months and in the third year, respectively [18]. However, it is worth noticing that this study was not conducted among children with PID. The application of the predictive values of a diagnostic test changes with the disease prevalence, and consequently, these values are not valid for populations with a different prevalence [18]. In our study, an sIgE concentration between 0.35 kU/L and 3.5 kU/L was detected among 27.78% (n = 20) of the patients with PID, while 22.22% (n = 16) of the study group had an sIgE level above 3.5 kU/L. Nevertheless, we are aware that the utility of, especially, food-specific IgE concentrations in predicting symptomatic food allergies in the context of IEI patients may be questionable, and further studies including, e.g., oral food challenges are needed. Defining the cut-off values for specific IgE among patients with immunodeficiency would be helpful in clinical practice.

Allergy tests, both skin testing and in vitro sIgE tests, must always be interpreted in the context of the patient's specific clinical history, because a "positive" test does not always entail clinical allergy [23–25]. The definitive diagnosis of an IgE-mediated allergy requires the detection of specific IgE and knowledge of the history of allergy on exposure to that allergen [15]. It is not uncommon to find allergen-specific IgE in the serum of people who do not report allergic symptoms [26].

The likelihood that a positive sIgE test result will correlate with clinical symptoms is influenced by the degree of positivity, the type of allergen, and the patient's clinical history. Venom- and food-specific IgE have been reported in up to 25% and 60% of the general population, respectively [26–28]. In food-allergic subjects, the test sensitivity can be improved by using higher cutoffs, which, however, are food-specific. The predictive values also vary with age. Younger children and infants show symptoms while presenting lower sIgE levels compared with older children [18]. Patients with higher sIgE levels are more likely to develop symptoms upon exposure to an allergen than patients with lower sIgE levels. However, strongly positive tests do not necessarily predict the severity of allergic symptoms (anaphylaxis) [29]. Regrettably, the threshold levels have not been determined for most allergens.

An elevated level IgE is often associated with a number of PIDs, such as hyper IgE syndrome, WAS, Netherton syndrome, IPEX syndrome, Omenn syndrome [30]. One phenotype of complete DiGeorge syndrome has oligoclonal T cell expansion with elevated IgE levels. The pathophysiological role of increased IgE in these disorders is unclear. However, patients with these disorders were not included in this study. Children with hypogammaglobulinemia (n = 20) involving one or more main classes of immunoglobulins as well as patients with IgG subclass deficiency (n = 20) constituted the majority of the study group. The prevalence of sIgE and clinical symptoms of allergy varied between the types of PID (Table 2), affecting 50% (sIgE presence) and 61.11% (self-reported allergy symptoms) of the patients in the study group, respectively.

In the USIDNET study, the prevalence of FA as well as AD in PID patients from the USA was found to be lower than in the general population (FA, 2.5%; AD, 10.7%). However, the authors indicated that FA was more commonly reported in patients with specific PIDs, compared to what would be expected in the general population, i.e., in the presence of combined immunodeficiencies (33.3%), sIgAD (25%), CD40 ligand deficiency (7.7%), primary hypogammaglobulinemia (7.1%), hyper IgE syndrome (6.3%) [11]. AD was most commonly reported in patients with a deficiency of the nuclear factor κB essential modulator (62.5%), WAS (41.5%), combined immunodeficiency (33.3%), selective IgM deficiency (33.3%), and hyper IgE syndrome (25%) [11].

Although the problem of the coexistence of allergy and PID diseases has been a subject of investigation in a number of studies, the results are largely inconsistent. While in an Iranian study involving patients with sIgAD, atopic eczema was observed in 52%

of the patients [12], in Brazil, it affected only 2.38% of the patients [31], and in a study conducted in Sweden, a statistically significant correlation between AD and sIgAD was not observed [13]. In a study conducted by Dadkhah et al., 20% of Iranian patients with hypogammaglobulinemia additionally suffered from asthma, 22% of patients were diagnosed with AR, and 9% with AD [32]. A study from Kuwait confirmed that 19% of PID patients suffered from AD [33]. A 2020 study conducted in a Polish city in patients with Ab deficiencies revealed that the total level of IgE was elevated in 21% of the patients, and sIgE against inhalant allergens was found in 21% of the patients. The most common clinical manifestations included asthma (66.7% patients), AD (22.8%), and AR (12.3%) [34]. In our study, a comparable, elevated total IgE level (23.53%; Table 2) was observed in patients with PAD. The presence of sIgE was much more common (47.06%) in our patients with PAD, but it is worth mentioning that in our study, we used a larger test kit with more allergens, and different laboratory methods were applied in both studies (ImmunoCAP vs. Polycheck).

In the group of patients with PID, differences with regard to the place of residence and an increased prevalence of allergy in patients residing in urban areas were observed, which mirrors the results of epidemiological studies involving the general population [35]. This is definitely an interesting observation, and more studies concerning the impact of environmental factors on the prevalence of serum sIgE and the progress of allergy in this particular group of patients are needed.

The fact that the values of the total IgE level were normal in PID patients undergoing IRT is an interesting observation that is confirmed by some other studies [36,37]. Durandy et al. treated a cohort of children with recurrent infections with low doses of Ig and observed that in several allergic patients from this group, in whom serum IgE concentrations were high, the serum levels of IgE were normalized after 3 to 4 months of Ig therapy [38]. A study conducted by Jee et al. in patients with AD and an elevated total IgE concentration demonstrated that intravenous immune globulin (IVIg) therapy (2 g/kg/month) had an impact on IgE levels: the levels declined during IVIg treatment but returned to their initial values 6 months after treatment [37]. Noh et al. investigated 41 children given a single dose of IVIg and observed that in 40% of the subjects there was a significant improvement associated with a decrease in serum IgE [39]. This effect may be associated with the immunomodulatory effect of IVIg or stem from a downregulation of the factors driving IgE production [39,40]. The impact of substitutional doses of immunoglobulins on total IgE and specific IgE in PID patients in a long-time perspective requires further research and should involve a larger study group. However, it is worth noticing that few patients in the Ig replacement therapy group (e.g., with X-linked agammaglobulinemia, CVID) might have a deficiency of other antibody classes, including IgE; however, there were also patients with other conditions, such as IgG subclass deficiency/Nijmegen breakage syndrome/ataxia–telangiectasia, in that group (IRT+).

Another point to be addressed regards patients with reported symptoms of allergy without positive ($\geq$0.35 kU/L) sIgE (n = 10). Two patients from that group were receiving Ig replacement therapy at a stable dose during the entire study, two had an sIgE concentration between 0.15 kU/L and 0.35 kU/L against cat dander, and another two against birch pollen with airway allergic symptoms. The possibility of non-IgE-mediated mechanisms remains to be investigated.

The main limitations of this study was the use of a single method for confirming patients' sensitization, without provocation tests and assessment of asthma phenotypes. These issues will be addressed in follow-up studies.

In IEI, an abnormally functioning immune system often does not protect the organism from infections and permits abnormal and excessive hypersensitivity reactions. The development of allergies in IEI is caused by the disruption of the complex balance between effector and regulatory cells in the immune system [6]. The potential mechanisms leading to such dysregulation include failure of central thymic tolerance, imbalance between effector and regulatory T-cell functions, failure in the production of counter-regulating interferon-

gamma (IFN-γ) [6,41]. Possible differences in microbial colonization and infection patterns are additional factors of interest.

5. Conclusions

This study revealed that the prevalence of allergic diseases and atopy in the pediatric population with IEI is high. PID patients should be carefully monitored with regard to their risk of allergy. The study showed that serum sIgE and total IgE together might be a plausible diagnostic tool for these patients. However, for patients with IRT, the assessment of total IgE is not useful in the context of allergy. Further, more detailed studies including patients with increased levels of sIgE are needed.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/children9040466/s1, Table S1: Patients' baseline characteristics according to PID classification. Table S2: Characteristics of patients during immunoglobulin replacement therapy (n = 19). Table S3: Characteristics of patients with positive ($\geq$0.35 kU/L) sIgE against allergens. Table S4: Number of patients with the maximum sIgE concentration against allergens. Table S5: Manifestation of allergy in patients with PID, expressed as previously diagnosed asthma, food allergy, allergic conjunctivitis, atopic dermatitis, allergic rhinitis, or urticaria.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Wroclaw Medical University (protocol code 333/2020; date of approval 30 June 2020).

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Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

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Abbreviations

A	asthma
Ab	antibody(ies)
AC	allergic conjunctivitis
AD	atopic dermatitis
AR	allergic rhinitis
A-T	ataxia–telangiectasia
BSA	bovine serum albumin
CVID	common variable immunodeficiency
FA	food allergy

HSCT	hematopoietic stem cell transplantation
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IEI	inborn errors of immunity
IFN-γ	interferon-gamma
IgE/G/A/M	immunoglobulin(s) class E/G/A/M
IPEX syndrome	immunodysregulation, polyendocrinopathy, enteropathy X-linked syndrome
IRT	immunoglobulin replacement therapy
IUIS	International Union of Immunodeficiency Societies
n	number
NBS	Nijmegen breakage syndrome
NHANES	The National Health and Nutrition Examination Survey
PAD	predominantly antibody deficiencies
PID	primary immunodeficiency
PRKDC	Protein Kinase, DNA-Activated, Catalytic Subunit
sIgE	allergen-specific immunoglobulin class E
sIgAD	selective IgA deficiency
SCID	severe combined immunodeficiency
SPT	skin prick test
U	urticaria
USIDNET	US Immunodeficiency Network
WAS	Wiskott–Aldrich syndrome
X-linked	gene is located in the X chromosome

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Assessment of autoantibodies in paediatric population with primary immunodeficiencies: a pilot study

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Assessment of autoantibodies in paediatric population with primary immunodeficiencies: a pilot study

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Abstract

Background The correlation between primary immunodeficiencies (PIDs) and autoimmunity shows ethnic and geographical diversity. The aim of our study was to accumulate more data in paediatric PID population.

Methods 58 children aged 1–17 and with PID (study group) and 14 age-matched immunocompetent individuals (control group) were included in the study. Serum levels of 17 different specific IgG antibodies against autoantigens were measured by means of a quantitative enzyme immunoassay. Immunoglobulin levels were analysed in relation to a detailed medical examination.

Results Autoantibodies against one or more antigens were detected in the sera of 24.14% (n = 14) subjects in the study group. The most frequent were anti-thyroid peroxidase (anti-TPO) antibodies (n = 8; 13.8%). Anti-TPO antibody levels were elevated more often in PID patients with a positive family history of autoimmune diseases (p = 0.04). The screening for anti-deamidated gliadin peptide (DGP) and anti-tissue transglutaminase (tTG) antibodies in our series allowed identifying two previously undiagnosed cases of coeliac disease in PID patients. There was no statistically significant difference between the study and the control group in terms of the autoantibodies prevalence.

Conclusions This study provides data on the prevalence of autoantibodies in paediatric population diagnosed with PID. Selected autoantibodies (i.e. anti-tTG, anti-DGP) might be useful for the screening of PID to avoid the delay of diagnosis of an autoimmune disease.

Keywords Autoantibody, Autoimmunity, Coeliac disease, Immune dysregulation, Inborn errors of immunity, Primary immunodeficiency

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Background

Inborn errors of immunity (IEI) are a heterogeneous group of inherited diseases caused by monogenic germline mutations and result in the loss or gain of the function of the encoded protein. Individually, most IEI occur rarely, but collectively they are more common than is generally believed [1, 2]. The description of clinical phenotypes is constantly updated in the growing field of primary immunodeficiencies (PIDs) [1, 3–5]. The 55 novel gene defects reported in the last IEI update bring the total number of IEI to 485. In practice, IEI are associated

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with increased susceptibility to infectious diseases (especially severe, atypical, and/or recurrent infections). The diversity of autoimmune, autoinflammatory, allergic and/or malignant phenotypes is also associated with IEI [1].

The correlation between PIDs and autoimmunity has been extensively analysed [6–12]. In the past, PIDs and autoimmune diseases (AD) were considered independent, or even polar opposites [7, 8]. Nowadays, PIDs are regarded as unprecedented models connecting defined monogenic defects with clinical manifestations of incorrect immune regulation and a clinical picture characterised by infectious complications and autoimmunity [5, 6, 13]. The pathogenic process leading to the autoimmunity is complex and includes disturbed B cell differentiation and germ-center reactions, altered T cell central or peripheral tolerance, uncontrolled lymphocyte proliferation and differentiation, disturbances in Treg/Th17 balance, dysfunctional complement and innate immune activation, and the defective clearance of the infectious agents [6, 11].

Scientific data suggests that autoimmunity may be associated with PIDs in a significant proportion of patients [14–18]. Autoimmune manifestations are observed frequently in patients with primary antibody deficiencies (PADs), but are also reported in individuals with combined immunodeficiency disorders (CIDs) [19]. Moreover, many PIDs are associated with defects in the frequency and function of T regulatory (Treg) cells, as well as with the production of autoantibodies (AA). The IUIS classification features an independent category named"diseases of immune dysregulation". A regulatory disorder can cause abnormal activation and expansion of immune cells, leading to autoimmunity, hyperinflammation and malignant proliferation [8]. Those might result in a bad prognosis in patients with immune dysregulation compared to those with only high susceptibility to infections [13, 14]. Due to the coexistence of autoimmunity and immunodeficiency in some cases, the treatment may be challenging and requires a personalised approach [18].

To this date, several studies have been conducted to analyse the frequency as well as the mechanisms of an AD in PIDs [14, 15]. Most of the published studies were concentrated on clinical presentation of AD. However, their interpretation is difficult due to ethnic and geographical diversity. More data is required for conclusive evidence. The occurrence of AA in paediatric PID patients has not been well established. Considering its poor prognosis and difficult treatment, a better understanding of the wide spectrum of immune dysregulation in IEI is required for precise and timely diagnosis, as well as disease monitoring and therapy. The aim of our study was to collect more data about the occurrence of AA in paediatric PID population.

Methods

The study was approved by the Bioethical Commission of Wrocław Medical University, Wrocław, Poland. Patients included in the study group remained under the care of the Clinical Immunology and Paediatric Department of the J. Gromkowski Provincial Hospital in Wrocław due to the previously diagnosed PIDs (by a trained immunologist, according to the IUIS classification and ICD-10). Age-matched immunocompetent individuals constituted the control group (Additional file 1: Table S1). The control group consisted of patients with occasional or mild recurrent infections (less than 8 per 12 months, often treated without antibiotics, mostly upper respiratory tract infections) diagnosed in the Department of Immunology and Paediatrics who did not show abnormalities in immunological tests and did not meet IUIS criteria for inborn errors of immunity (IEI).

Blood samples were collected between 2020 and 2021. All parents or legal guardians and patients over 16 years of age signed informed consent before participating in the research.

The control group numbered 14 subjects (n = 7 boys, n = 7 girls) whose age ranged from 1 year old up to 16 years old (median age = 7; mean age = 7). The study group included 58 subjects (n = 36 boys, n = 22 girls) aged 1–17 (median age = 7; mean age = 8). Patients with predominantly antibody deficiencies (PADs; n = 46; 79.31%) comprised the majority of the study group, followed by individuals diagnosed with CIDs associated with syndromic features (n = 5; 8.62%). The baseline characteristics of the patients are presented in Additional file 2: Table S2. During the study period, eight patients (13.79%) were undergoing immunoglobulin replacement therapy (IRT), one (1.67%) completed treatment with high doses of immunoglobulins (Ig) due to immune thrombocytopenia, while 49 (84.48%) did not receive IRT (IRT−). Individuals receiving IRT (IRT +) included patients with X-linked agammaglobulinemia (XLA; n = 1), common variable immunodeficiency (CVID; n = 3), IgG subclass and IgM deficiency (n = 1), IgG deficiency (n = 1), as well as ataxia-telangiectasia (A-T; n = 2). Doses of Ig were individualized and were within 0.2–0.8 g/kg. In all cases, substitution therapy had started before the inclusion in the current study. The blood samples were collected immediately before Ig infusion.

During the study, detailed medical history of the patients was collected, in particular place of residence (village, town, city), diagnosis of autoimmune disease, family history of autoimmune diseases, recurrent respiratory tract infections, PID complications, presence of hepato- and/or splenomegaly and/or lymphadenopathy, medications taken, diagnosis of allergic diseases,

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results of tests conducted before inclusion in the IRT (if available).

The following parameters were evaluated based on venous blood samples during the study period among the study group: (1) concentration of specific IgG antibodies against antigens: Ro/SS-A 52, La/SS-B, Scl-70, PM/Scl-100, Sm, PCNA, dsDNA, ribosomal P protein, CENP-B, AMA M2, MPO, PR3, TPO, TG, deamidated gliadin peptides (DGP), tissue transglutaminase (tTG), intrinsic factor (IF); (2) haemoglobin (Hgb) level; (3) white blood cell (WBC) count; (4) platelet count; (5) IgG and IgG subclass concentration; (6) anti-tTG IgA in part of the study group. Anti-tTG IgA and anti-DGP IgA together with total IgA were measured in the control group according to the guidelines for immunocompetent subjects [38].

Autoantibodies were measured by means of a quantitative enzyme immunoassay—the Polycheck ® test (Biocheck GmbH, Munster, Germany). The threshold for a positive result was ≥ 0.80 kU/L. According to the assay characteristics, the sensitivity of an assay was 96.4% and the specificity was 97%. The IgG concentration was evaluated using immunoturbidimetry, while IgG subclass levels by the nephelometric method. Immunoglobulin levels, Hgb level, WBC count and platelet count reference ranges depended on the age of the tested individual.

A statistical analysis of data was conducted based on a spreadsheet prepared in Microsoft Office Excel (Microsoft Corp. Washington, WA, USA) and Statistica v.13—Mann–Whitney U test for non-parametric quantitative data and Pearson's chi-squared test for qualitative data. The significance level was established at $\alpha = 0.05$. A p-value less than 0.05 was considered statistically significant.

Results

Prevalence of autoantibodies

Autoantibodies against one or more antigens from the used kit were detected in sera of 24.14% (n = 14) PID patients (Table 1). Most of patients had positive AA against one (n = 7) or two (n = 4) antigens. The majority of individuals with positive AA were boys (n = 9), however, there was no statistically significant difference in terms of gender (p = 0.844). There was no statistically significant difference between PID patients and healthy controls in case of antinuclear antibodies (ANA; p = 0.551) and anti-thyroid peroxidase (anti-TPO; p = 0.609).

Eight out of 58 patients (13.8%) had positive (≥ 0.80 kU/L) anti-TPO antibodies, which were the most frequently increased AA. None of these patients were previously diagnosed with Hashimoto's thyroiditis. Two out of eight patients with positive anti-TPO antibodies were undergoing immunoglobulin replacement therapy (IRT). The difference between patients receiving IRT and those who were not included in the treatment was statistically significant (p = 0.0009; Fig. 1). Anti-TPO antibodies were elevated more often in patients with a positive family history of AD, including Hashimoto's thyroiditis (n = 3; p = 0.044; Fig. 2). Two out of 10 subjects from the control group had positive anti-TPO, however the level of antibodies was low and clinically insignificant (< 1.00 kU/L).

Positive anti-deamidated gliadin peptide (anti-DGP) antibodies were detected in 6.9% (n = 4) of patients in the study group, two of them had also elevated anti-tissue transglutaminase (anti-tTG) IgG antibodies. Only one of the patients with antibodies specific to coeliac disease (CD) had been previously diagnosed with CD. Although none of the control group had positive anti-tTG and anti-DGP IgA antibodies, the difference between the study and the control group was not statistically significant (p = 0.312). 3.45% of those in the study group (n = 2) had positive anti-Sm antibodies and only one (1.72%) had anti-La/SS-B antibodies.

There was no significant difference between PAD patients and patients with other PIDs with regard to the presence of AA.

There was a significant correlation (p = 0.0009) between positive coeliac antibodies and IgG levels in the study group—patients with positive anti-DGP and/or anti-tTG IgG had normal (n = 3) or increased (n = 1) total IgG levels. A significant difference was observed with regard to IgG1 levels and presence of coeliac autoantibodies (p = 0.00009) as well.

Clinical manifestations

Among all 58 patients included in the study, only 8.62% (n = 5) had a previous diagnosis of autoimmune disease, including CD (n = 2), autoimmune thrombocytopenia (n = 2) and autoimmune neutropenia (AN; n = 1; Table 2). Most of them were girls (n = 3), but the difference between the sexes was not statistically significant (p = 0.113). Three patients were previously diagnosed with hypothyroidism. Among four patients with positive anti-DGP and/or anti-tTG, only one had been previously diagnosed with CD and IgG subclass deficiency, one was under immunological care due to AN and lymphocyte T deficiency with a history of pyogenic infections, two were complaining of chronic diarrhoea (one of them had selective IgA deficiency and the other IgM deficiency). CD was then confirmed by means of other serological tests (e.g. anti-endomysial antibodies IgA/IgG) and typical histopathological changes were found in duodenal mucosa in two out of three patients.

18.97% (n = 11) of patients with PIDs had hepatomegaly and/or splenomegaly and/or lymphadenopathy (considered as lymphoproliferation below) documented

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Table 1 Characteristics of PID patients with positive autoantibodies (> = 0.80 kU/l)

Patient no.	Age (years)	Type of PID	Reported clinical symptoms and signs	Detected autoantibodies	IgG (mg/dl)	IRT	Family history of autoimmune diseases	Diagnosis of autoimmune disease
1	17	PAD (selective IgA deficiency)	Hepatomegaly Splenomegaly	Anti-Sm = 67 kU/l Anti-SS-B = 0.92 kU/l	1386 [680–1530]	No	No	Not confirmed
2	13	PAD (selective IgA deficiency)	Chronic diarrhoea	Anti-DGP = 1.4 kU/l	1472 [518–1284]	No	Yes (coeliac disease)	CD—not confirmed with other tests
3	6	PAD (selective IgA deficiency)	Failure to thrive	Anti-TPO = 3.3 kU/l Anti-IF = 1.1	1296 [540–1822]	No	Yes (Hashimoto disease)	Not confirmed
4	6	PAD (selective IgA deficiency)	Failure to thrive	Anti-TPO = 4 kU/l Anti-TG = 0.53 kU/l	1376 [553–1631]	No	Yes (Hashimoto disease)	Not confirmed
5	8	PAD (IgM deficiency)	Chronic diarrhoea Hepatomegaly	Anti-DGP = 7.4 kU/l Anti-tTG = 1.1 kU/l Anti-tTG IgA = 140 AU/ml	823 [553–1631]	No	Yes (coeliac disease)	Confirmed CD
6	4	PAD (IgG subclass deficiency)	Chronic diarrhoea Failure to thrive Coeliac disease	Anti-DGP = 14 kU/l Anti-tTG = 1.1 kU/l Anti-tTG IgA = 1140 AU/ml	480 [468–1150]	No	No	CD (diagnosed before the study)
7	7	PAD (IgG subclass deficiency)	Hypothyroidism Coeliac disease	Anti-TPO = 10 kU/l	751 [553–1631]	No	Yes (psoriasis)	Under endocrinologist care
8	9	PAD (IgG subclass deficiency)	No	Anti-TPO = 3.4 kU/l	826 [540–1822]	No	Yes (Hashimoto disease)	Not confirmed
9	6	PAD (IgG subclass deficiency)	Failure to thrive	Anti-TPO = 1.3 kU/l	964 [553–1232]	No	No	Not confirmed
10	15	PAD (X-linked agammaglobulinemia)	No	Anti-TPO = 1.1 kU/l	872 [518–1284]	Yes	Yes	Not confirmed
11	11	Ataxia-telangiectasia	No	Anti-TPO = 0.92 kU/l	906 [553–1631]	Yes	No	Not confirmed
12	10	Lymphocyte T deficiency	Skin eczema	anti-Sm = 1.8 kU/l	939 [553–1631]	No	Unknown	Not confirmed
13	4	Phagocyte number and/or function deficiency	No	Anti-TPO = 6.2 kU/l Anti-TG = 1 kU/l	665 [468–1150]	No	Yes	Not confirmed
14	3	Other: lymphocyte T deficiency, chronic neutropenia	Papulovesicular eczema	Anti-DGP = 8.4 kU/l Anti-tTG IgA = 18.7 AU/ml	1098 [540–1822]	No	No	Confirmed CD

Anti-SS-B—anti Sjogren's Syndrome B; CD—coeliac disease; DGP—deamidated gliadin peptides; IF—intrinsic factor; Ig—immunoglobulin; IRT—immunoglobulin replacement therapy; No—number; PAD—predominantly antibody deficiency; PID—primary immunodeficiencies; Sm—Smith antigen; TG—thyroglobulin; TPO—thyroid peroxidase; tTG—tissue transglutaminase

in their medical history. It more often affected boys (n = 10) than girls (n = 1), and the difference between the sexes was statistically significant (p = 0.025). All patients with CVID who took part in the study (n = 3) had developed lymphoproliferation. In two of them, it proved to be the cause of immunological diagnostics (collaterally with recurrent respiratory tract infections).

Haematological findingss

Among 58 patients in the study group, haematological abnormalities were quite common in the course of the research. Decreased haemoglobin levels were found in 12.07% (n = 7) of patients, leukopenia in 25.86% (n = 15) and neutropenia in 22.41 (n = 13) (antineutrophil antibodies were detected in one case of chronic neutropenia). There were two cases of immune thrombocytopenia. No

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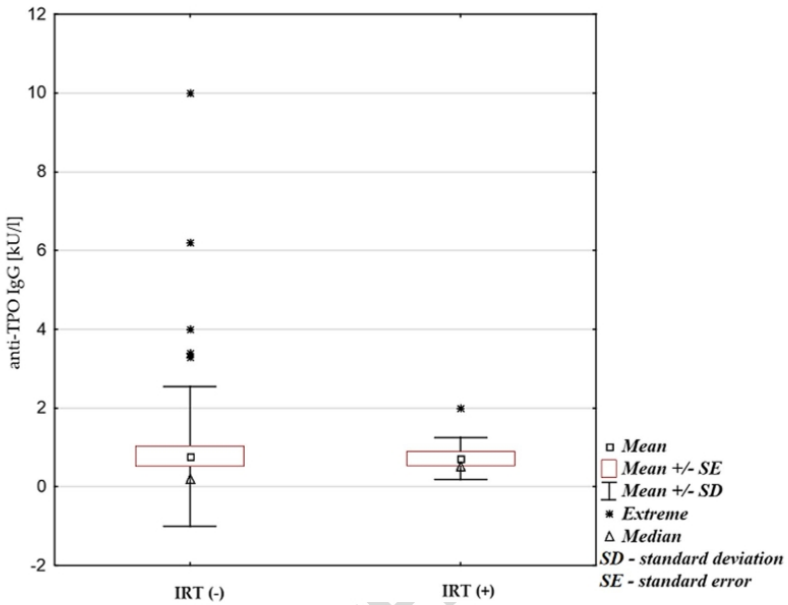

Fig.1 Anti-TPO antibodies level in patients undergoing (IRT+) and not undergoing (IRT −) immunoglobulin replacement therapy (IRT; p = 0.0009; Mann–Whitney U test for non-parametric quantitative data)

statistically significant difference was found between patients with positive or negative AA in the presence of leukopenia (p = 0.664), neutropenia (0.526) and anaemia (0.358). Such factors as gender, IRT, recurrent infections, positive family history of autoimmune diseases, lymphoproliferation did not correlate with the presence of anaemia, leukopenia or neutropenia.

Discussion

The coexistence of immunodeficiency and autoimmunity is an important research field because of the parallel hypoimmune and hyperimmune state one of each other [18, 20]. The main pathophysiologic mechanisms leading to the development of autoimmunity in PIDs are still under debate. Investigation of complex immune regulatory and signalling mechanisms coupled with the genetic analysis, reveals complex relationships between primary immunodeficiency syndromes and autoimmune diseases [12, 21].

It was demonstrated that in PID patients, either tolerance or ignorance may be affected by intense antigen load as a result of recurrent or persistent infections (by molecular mimicry and/or the presence of superantigens) and defects in antigen clearance, which make patients liable to dysregulated immune responses and autoimmune disorders [18]. Defective antigen clearance may result in end-organ deposition of immune complexes, cellular activation, chronic inflammation, and tissue destruction, as well as in the formation of anti-tissue antibodies [18]. In this study, the majority of patients (n = 38) had a history of recurrent infections (i.e. recurrent otitis media/sinusitis/pneumonia/abscesses), yet no statistically significant difference between patients with positive/negative autoantibodies and recurrent infections was found.

Autoimmunity is an easily recognised complication in PID patients, but data about its prevalence among paediatric individuals are limited. Most of the reported studies on the frequency of autoimmune and inflammatory manifestations in PID patients were conducted in adults. A recent French national study by Fischer et al. [14], which is the largest to date and includes all types of PID and autoimmune manifestations, was carried out in both paediatric and adult populations. One or more autoimmune and inflammatory complications were recorded in 26.2% of all subjects with a risk of onset throughout the patient's lifetime. The study highlighted the increased risk of developing inflammatory bowel disease and arthritis in PID children compared to the general population [14].

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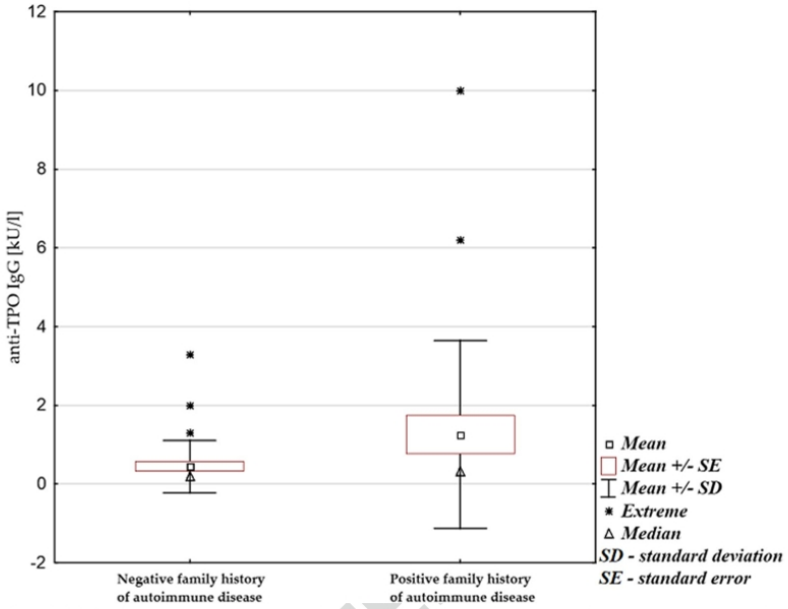

Fig. 2 Anti-TPO antibodies level in patients with a positive and negative family history of autoimmune diseases (p = 0.044; Mann–Whitney U test for non-parametric quantitative data)

Table 2 Prevalence of autoantibodies and previously diagnosed autoimmune diseases among recruited PID patients

Type of PID (n = 58)	Previous diagnosis of autoimmune disease	Presence of autoantibodies
Combined immunodeficiency with associated or syndromic features (CID; n = 5)	0.00% (n = 0)	20% (n = 1)
Predominantly antibody deficiency* (PAD; n = 46)	8.7% (n = 4)	21.74% (n = 10)
Congenital defects of phagocyte number, function or both (n = 3)	0.00% (n = 0)	33.33% (n = 1)
Complement deficiency (n = 2)	0.00% (n = 0)	0.00% (n = 0)
Others** (n = 2)	50.00% (n = 1)	100.00% (n = 2)

*PAD: CVID/IgG subclass deficiency/IgG subclass deficiency with IgA deficiency/IgG deficiency/IgG and IgA deficiency/IgM deficiency/IgM and IgG subclass deficiency/IgM and IgA deficiency/IgM, IgG and IgA deficiency/selective IgA deficiency/transient hypogammaglobulinemia of infancy/X-linked agammaglobulinemia

**Others: lymphocyte T deficiency/ lymphocyte T deficiency and autoimmune neutropenia

Ab—antibody; CID—combined immunodeficiency; CVID—common variable immunodeficiency; Ig—immunoglobulin; n —number; PAD—predominantly antibody deficiency; PID—primary immunodeficiencies

In a retrospective study by Kaplan et al. [22] conducted in Turkish children with PID, autoimmune and inflammatory manifestations were observed in 10.1% and the median age of autoimmunity initial time was 61.3 ± 53 months. In comparison to this study, most of the patients were male (55.4%). However, consanguinity was present in the case of 34.9%. The distribution of PID types associated with autoimmunity was different (phagocyte deficiencies—56%, CIDs—53%, immune dysregulation diseases—52%). The most common autoimmune manifestation was autoimmune thyroiditis. Our study group did not include individual diagnosed with documented Hashimoto's thyroiditis before the study, but three others had hypothyroidism. During the research, anti-TPO antibodies were the most frequently increased ones and statistically occurred more often in children with a positive family history of Hashimoto's thyroiditis. This group of patients was characterized by a larger risk

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of potential development of autoimmune thyroiditis and should be monitored in this regard. However, the presence of anti-TPO antibodies in a significant percent of the control group (20%) and the lack of statistical difference between groups challenges anti-TPO as a screening marker in an asymptomatic patients. Presented results should be considered with caution due to the small number of patients. Thereupon, further studies on representative groups are crucial.

In a study by Tahiat et al [23] carried out on Algerian patients diagnosed with PID aged 0.1–80, AA were found in 32.4% of PID patients and 15.8% of healthy controls ($p < 0.0005$). Anti-nuclear antibodies (ANA) (10.0%) and transglutaminase antibodies (TGA) (8.4%) occurred most frequently. Taking into account that our study group was smaller and consisted of children, ANA were found in 3.45% of patients and TGA in 5.17% (anti-DGP IgG in 6.9%). In Tahiat's study, almost one-third of patients with positive AA had no autoimmune manifestations, while in this one, 28.57% (4/14) of patients with positive AA were completely asymptomatic in the course of the research. The authors highlighted that positive results regarding AA should be interpreted with caution in patients diagnosed with PIDs due to their low positive predictive value.

It seems paradoxical that AA are produced against self-antigens in patients with CVID, who, at the same time, have low IgG levels and do not produce specific antibodies after vaccinations. In this study, none of the patients with CVID had positive AA. One individual with X-linked agammaglobulinemia had positive anti-TPO antibodies, but this result should be considered with caution since this particular patient was undergoing IRT. Patients with XLA are not expected to produce AA, yet the "leaky" production of autoantibodies and defects in central B-cell tolerance have been reported [24, 25]. The use of intravenous/subcutaneous immunoglobulin in regular therapy may interfere with immunologic tests for AA detection. However, in our study, a generally higher anti-TPO IgG concentration has been recorded in a group that did not undergo IRT.

It has been shown that patients with various PIDs may also develop intestinal inflammation as one of the leading symptoms. Furthermore, it has been demonstrated that individuals diagnosed with CD may have immunodeficiency (i.e. sIgAD; CVID) [18, 26]. Antibodies characteristic of CD were present in 6.9% (n = 4) of patients and only one had been previously diagnosed with this syndrome. The screening for anti-DGP and anti-tTG antibodies in the series identified two earlier undiagnosed CDs. In both cases, CD was confirmed by further testing. Moreover, one patient had sIgAD, a low (1.4 kU/l) level of anti-DGP IgG antibodies and a positive family history of CD, yet further tests did not confirm the diagnosis. Another patient with IgG subclass deficiency had been previously diagnosed with CD and stuck to a gluten-free diet and in this case, antibodies were not detected. Although there was no statistically significant difference between the study group and the control group in regard to coeliac antibodies, it is worth to consider screening for coeliac disease in PID patients. The lack of significant difference between groups probably arised from small number of cases in the control group.

The high prevalence of AD within IgAD and CVID cohorts together with a recent report on the increased prevalence of autoimmunity (10%) in their normoglobulinemic first-degree relatives indicate a role of a common genetic denominator in the induction of these diseases. Studies on the genetic linkage and HLA have demonstrated that IgAD and CVID share a major susceptibility locus in the DQ-DR haplotype on chromosome 6 [27–29]. In our study, 66.67% of patients with sIgAD had positive AA and most of them had a positive family history of AD. Based on the evidence concerning the concurrence of sIgAD and autoimmune disorders, it is worth considering screening patients with sIgAD for autoantibodies.

The IgG subclass deficiency causes susceptibility to infections, however, according to studies, it does not appear to be associated with AD until it co-occurs with IgA deficiency [27, 30, 31]. In our study, 21.05% (n = 4) of patients with isolated IgG subclass deficiency had positive AA and half of them had been previously diagnosed with an AD (coeliac disease in both cases).

The serological diagnosis of most AD is based on AA circulating in the serum and/or plasma and the presence of immune complex deposits containing AA and a complement [18]. Due to the hypogammaglobulinemic condition in individuals diagnosed with PADs and some types of CIDs, diagnostic tests based on antibodies may not be useful in these patients. Specific antibody deficiency (SAD) and CVID are obvious examples of PADs in which the production of AA is low or negative due to dysfunctions of the immune system [32, 33]. Despite a close relationship between the diagnosis of autoimmunity and AA, the results of some PID patients' tests are persistently negative for disease-specific autoantibodies. On the other hand, multiple studies show that positive AA are more common among PID patients rather than healthy controls [23].

In our study, we found a statistically significant difference between patients with positive and negative coeliac autoantibodies according to IgG level. Higher levels of IgG were observed among PID patients with positive AA. The difference in IgG levels in CVID patients was reported by Boileau et al. [34]—the authors observed a significantly higher IgG levels

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among CVID patients with autoimmune cytopenia. Other studies have shown that CVID patients with autoimmunity exhibit higher levels of IgM compared to non-autoimmune phenotypes [6, 35]. In this project, the correlation between IgG levels and the presence of autoantibodies should be interpreted in a broad context. Lower IgG levels and a greater percentage of IgG deficiency among patients with negative AA may constitute the cause of negative results of autoantibody tests. In our study, IgM levels did not correlate with the presence of autoantibodies.

Autoimmune diagnostics in patients undergoing IRT seems even more complicated as the use of Ig may interfere with some of the immunologic tests. Therefore, it may be helpful to use frozen serum for future testing if IRT has been initiated [36].

Early onset autoimmunity and autoimmunity that involves multiple organs (known as polyautoimmunity) or significant lymphoproliferation may be signs of an underlying IEI and suggest an immune dysregulation defect. Therefore the awareness of signs of AD and immune dysregulation among patients and clinicians is of the utmost importance. Clinical symptoms, as well as patient personal and family history are crucial in diagnostics and management of patients with IEI. The patients should be closely followed up, especially with regard to their immune status. Combined with genetic information or family history, the presence of elevated levels of autoantibodies may be highly predictive of the later onset of an autoimmune disorder and improve efforts at prevention in individuals at high risk of disease whenever possible. On the other hand, the presence of the AA in a patient does not guarantee a diagnosis of AD and the screening of variable AA might involve considerable cost. Furthermore, autoantibodies can be detected in otherwise healthy individuals and their production is not sufficient for clinical disease. However if the symptoms of an AD occur, especially among patients with already positive AA, an early and proper diagnosis may be helpful to avoid a diagnostic delay. The positive autoantibodies help to support the diagnosis. This is crucial, especially when the treatment requires balancing between increased susceptibility to infections and the additional suppression of the immune system [37].

A main limitation for definitive conclusions was small number of the study and the control group. Since the control group consisted of patients with occasional or mild recurrent infections who did not meet the IUIS criteria for IEI, the comparison between groups should be taken with caution.

Conclusions

Paediatric PID population requires more detailed assessment of the immune status because autoimmunity often develops at an early age. Selected autoantibodies (i.e. anti-tTG, anti-DGP) may be useful for the screening of PID to avoid a delay of the diagnosis of an autoimmune disease. Early and proper diagnosis can provide treatment options before serious organ damage occurs. Cost-effectiveness analysis should be considered along with the risk factors and clinical symptoms. AQ2

Abbreviations

AA	Autoantibody
AD	Autoimmune disease
AMA-M2	Anti-mitochondrial M2
AN	Autoimmune neutropenia
ANA	Antinuclear antibodies
Anti-Scl-70	Anti-topoisomerase I
A-T	Ataxia–telangiectasia
CD	Coeliac disease
CENP-B	Centromere protein B
CIDs	Combined immunodeficiency disorders
CVID	Common variable immunodeficiency
DGP	Deamidated gliadin peptides
dsDNA	Double-stranded DNA
Hgb	Haemoglobin
HLA	Human leukocyte antigen
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IEI	Inborn errors of immunity
IF	Intrinsic factor
IgE/G/A/M	Immunoglobulin(s) class E/G/A/M
IRT	Immunoglobulin replacement therapy
IUIS	International Union of Immunodeficiency Societies
MPO	Myeloperoxidase
n	Number
PAD	Predominantly antibody deficiencies
PCNA	Proliferating cell nuclear antigen
PIDs	Primary immunodeficiencies
PR3	Proteinase 3
SAD	Specific antibody deficiency
sIgAD	Selective IgA deficiency
SS-A	Sjogren's syndrome related antigen A
SS-B	Sjogren's syndrome type B antigen
Sm	Smith antigen
TPO	Thyroid peroxidase
TG	Thyroglobulin
tTG	Tissue transglutaminase
Treg	T regulatory cells
WBC	White blood cell
X-linked	Gene is located in the X chromosome
XLA	X-linked agammaglobulinemia

Supplementary Information

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Additional file 1.

Additional file 2.

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Author contributions
Conceptualization, K.P.-S., A.L.-U. and M.J.; Data curation, K.P.-S.; Formal analysis, K.P.-S.; Founding acquisition, K.P.-S. and M.J.; Investigation, K.P.-S. and M.Z.-W.; Methodology, K.P.-S., M.Z.-W. and M.J.; Project administration, K.P.-S.; Supervision, A.L.-U. and M.J.; Visualization, K.P.-S.; Writing—original draft, K.P.-S.; Writing—review & editing, A.L.-U. and M.J. All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with ICMJE criteria.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request. The raw de-identified data may be made available upon reasonable request from the corresponding authors.

Declarations

Ethics approval and consent to participate
The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Wroclaw Medical University (protocol code 333/2020; date of approval 30 June 2020). All subjects over 16 years of age gave their informed consent for inclusion before they participated in the study. The consent was obtained from the parent or legal gaurdians of all participants.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests in relation to this manuscript.

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Review

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Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation

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Abstract: Inborn errors of immunity (IEI), formerly known as primary immunodeficiency disorders (PIDs), are inherited disorders caused by damaging germline variants in single genes, which result in increased susceptibility to infections and in allergic, autoimmune, autoinflammatory, nonmalignant lymphoproliferative, and neoplastic conditions. Along with well-known warning signs of PID, attention should be paid to signs of immune dysregulation, which seem to be equally important to susceptibility to infection in defining IEI. The modern diagnostics of IEI offer a variety of approaches but with some problems. The aim of this review is to discuss the diagnostic challenges in IEI patients in the context of an immune dysregulation background.

Keywords: allergy; autoimmunity; autoimmune lymphoproliferative syndrome; inborn errors of immunity; lymphoproliferation; malignancy; primary immunodeficiency

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1. Introduction

Inborn errors of immunity (IEI), formerly known as primary immunodeficiency disorders (PIDs), are inherited disorders caused by damaging germline variants in single genes, resulting not only in increased susceptibility to infections but also in allergic, autoimmune, autoinflammatory, nonmalignant lymphoproliferative, and malignant manifestations. According to the most recent report by the International Union of Immunological Societies (IUIS), the identified IEI were classified in 10 tables with subtables segregating groups of disorders into overlapping phenotypes: (1) immunodeficiencies affecting cellular and humoral immunity (combined immunodeficiencies); (2) combined immunodeficiencies with associated or syndromic features; (3) predominantly antibody deficiencies; (4) diseases of immune dysregulation; (5) congenital defects of phagocyte number or function; (6) defects in intrinsic and innate immunity; (7) autoinflammatory diseases; (8) complement deficiencies; (9) bone marrow failure disorders; and (10) phenocopies of IEI. The 55 novel monogenic gene defects positioned in the last IEI update enhanced the total number of IEI to 485 [1,2].

The COVID-19 pandemic had an impact on various fields of medicine. In the context of clinical immunology and IEI, it has uncovered several new IEI [1]. Each time, the appearance of new pathogens is a potential challenge for the general population and also healthcare systems because of the lack of significant pre-existing immune memory. Similarly, in the case of pathogens learned about so far, patients with specific germline genetic variants (causing known and unknown IEI) may be more exposed to severe disease than the general population. Research on the COVID-19 pandemic course led to the detection of genes and mechanisms necessary for anti-SARS-CoV-2 immunity. About 2–3% of cases of severe SARS-CoV2 infection resulted from germline LOF/LOE variants in the

type 1 IFN signaling pathway: *TLR3*, *UNC93B1*, *TICAM1*, *TBK1*, *IRF3*, *IRF7*, *IFNAR1*, and *IFNAR2* [1]. According to Asano et al., X-linked recessive TLR7 deficiency is a highly penetrant genetic etiology of severe COVID-19 among 1.8% of males below the age of 60 years [3].

The defects of the number or the function of immune system elements determine the clinical presentation of an IEI. Family history, as well as personal and clinical data, are considered a core element of patient initial management. Extensive anamnesis and clinical evaluation are the main tools for a suspected diagnosis of IEI [4]. The early diagnosis of IEI can be life-saving but remains challenging due to the low prevalence of these pathologies. This can result in the delay of diagnosis and consequently in a worse prognosis [5].

Disease manifestation appearance (i.e., Nijmegen breakage syndrome (NBS), Shwachman-Diamond syndrome, and DiGeorge syndrome), as well as subject growth during both in utero life and later, may suggest the diagnosis of IEI and provide an important diagnostic clue [6]. Severe and/or recurrent infections, consanguinity, or an unexplained death in one's family are well-known signs of IEI; however, more attention should be paid to signs of immune dysregulation. Immune dysregulation is defined as a breakdown or malfunction of molecular control of immune system processes, and it is used to characterize an array of autoimmune and inflammatory conditions [7]. According to IUIS classification, there are 10 IEI categories based on their underlying molecular defect. One of them is called 'diseases of immune dysregulation'. Moreover, it has been established that other patients with humoral, cellular, or innate immune system deficiencies are also at risk of autoimmune or inflammatory conditions [8]. Currently, signs of immune dysregulation are of great importance in defining IEI, as well as an increased tendency to infection.

The modern diagnostics of IEI include various diagnostic measures, such as a simple blood count with particular attention paid to the total absolute lymphocyte count, the serum immunoglobulin levels, and the complete sequencing of the exome or genome [9]. However, during the clinical evaluation of a patient with suspected or confirmed IEI, we should be aware of the possible problems and finer points that may restrict diagnosis in patients with IEI. The aim of this review is to summarize these diagnostic challenges, in particular, in the context of immune dysregulation in IEI patients.

2. Allergic Disease

Allergy develops on account of disturbed function of the immune system. The immune system depends on a complex balance of activation, to defend against invasive, foreign pathogens, and control, to differentiate between self and foreign matter. Allergic reactions are exaggerated immune responses against specific allergens [10,11]. The comorbidity of IEI and allergy appears because of the impairment of the immune system, leading to infectious susceptibility; however, it is still able to trigger an allergic response [8]. The mechanisms underlying the relationship between atopy and immunodeficiency are better recognized, thanks to the discovery and characterization of genetic variants, often showing "a new face of old disorders" [8]. Several studies indicated the potential mechanisms leading to such dysregulation, which include the failure of central thymic tolerance, an imbalance between the effector and regulatory T-cell function, a failure in the production of counter regulating interferon-gamma (IFN-γ), disturbed cytokine production, and possible differences in microbial colonization and infection patterns [8,12,13].

Thanks to growing interest in the coexistence of allergy and IEI, the topic has been investigated in a number of studies. However, the results are still inconsistent. For example, in one Iranian study atopic dermatitis (AD) was present in 52% of patients with selective IgA deficiency (sIgAD) [14], while among Brazilian patients with sIgAD, AD was found in 2.3% [8,15]. In the USIDENT study, AD was most commonly reported in patients with a deficiency of the nuclear factor κB (NFkB) essential modulator (62.5%), the Wiskott–Aldrich syndrome (WAS: 41.5%), combined immunodeficiency (CID: 33.3%), selective IgM deficiency (33.3%), and autosomal-dominant hyper-IgE syndrome (AD-HIES; 25%) [8,16]. A cohort study of patients with early onset severe combined immunodefi-

ciency due to adenosine deaminase deficiency (ADA-SCID) demonstrated that atopy was present in 56% of the patients, including mild AD in 11.1%. Severe AD was not a common feature [17]. A possible explanation of the diverse results are ethnic and geographical diversity and differences in methodological approaches.

Potential diagnostic difficulties may start even at the beginning in diagnosing IEI. An underlying, sometimes severe immune deficiency can manifest as common allergic symptoms, and IEI may masquerade allergic atopic patients [10]. In clinical practice, there are few warning signs of an underlying IEI among atopic phenotypes, and these include severe atopic disease, usually with a poor response to standard therapies, early-onset of the disease, a positive family history for IEI and/or severe familial atopy, and immunological abnormalities [11].

The standard screening tests for antibody deficiency include the measurement of immunoglobulin, IgG, IgA, and IgM levels in serum and the interpretation according to age-related reference values [18]. The routine measurement of serum IgE is not obligatory in the management of patients with suspected antibody deficiency and a history of recurrent infections. Previously, the level of total IgE was considered as a marker to catch allergic patients, but because it is nonspecific, it cannot confirm the allergy status of a patient [19,20]. Non-immunodeficient patients have variable IgE concentrations associated with atopic disease such as allergic rhinitis (AR), asthma, food allergy (FA), and AD, as well as other conditions, including parasitic disease [21]. However, in the context of PID, IgE measurement plays a role, especially in patients with concomitant eczema. Elevated IgE is common in a number of IEI, such as HIES, WAS, Netherton syndrome, immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome, and Omenn syndrome [22]. One phenotype of complete DiGeorge syndrome, which is known as atypical complete DiGeorge syndrome, has oligoclonal T cell expansion with elevated IgE levels with concomitant generalized rash and lymphadenopathy [23]. The pathophysiological role of increased IgE in these disorders was not clearly characterized; however, there are few hypotheses [13]. Increased IgE production is associated not only with well-defined genetic syndromes but also with humoral, cellular, innate, and combined immunodeficiency disorders [5]. However, a high IgE (>180 IU/mL) is very rare in common variable immunodeficiency (CVID) (0.3% of patients) [21].

There are particular PIDs associated with atopy, especially eczema and elevated serum IgE, which can be confirmed by genetic tests and the identification of specific mutations. Mutations in the *WAS* gene on the X chromosome, which encodes the WAS protein (WASP), are a cause of Wiskott–Aldrich syndrome, characterized by recurrent infections, thrombocytopenia with small platelets, and eczema [8]. The mechanism for atopy in WAS is not fully described; however, impairment of regulatory T-cell (Treg) function is a possible contributor [8,24–26]. In total, 33% of patients with WAS and 20% of patients with X-linked thrombocytopenia (XLT) had positive food allergen-specific IgE (sIgE), in a study conducted by Lexmond et al. [8,27]. Food sensitization was generally detected with greater sensitivity using sIgE testing than by skin prick testing (SPT).

A dominant-negative heterozygous mutation in signal transduction and the activator of transcription 3 (STAT3) leads to autosomal-dominant hyper-IgE syndrome (AD-HIES), previously known as Job syndrome, with characteristic features such as chronic eczema, recurrent staphylococcal skin infections, pneumonia, increased serum IgE, and eosinophilia [10]. Skin findings distinguishing it from AD include a distinctive thickened texture of the facial skin, retroauricular fissures, and severe folliculitis of the axillae and groin [5]. Serum IgE levels are often >2000 IU/mL, and eosinophilia levels are often >700 cells/mL (eosinophilia does not correlate with the elevation in IgE), but patients usually do not suffer from symptomatic allergic disease such as AR, FA, or anaphylaxis [10,28]. Disturbances in the inflammatory process, and associated immune regulatory defects, are present. In clinical practice, a lower limit of 2000 IU/mL is often considered as a cutoff for AD-HIES. However, patients with HIES with lower IgE levels and STAT3 pathogenic variants have been reported [29]. Moreover, the serum IgE level does not correlate with

the severity and activity of the disease, and paradoxically patients with STAT3 loss-of-function (LOF) mutations are rather protected from severe allergic reactions. A potential explanation of this protection is disturbed mast cell degranulation, as well as vascular reaction to histamine caused by the STAT3 mutation itself [8,30–32]. SPT results and clinical symptoms of allergy are consistent with the specific IgE (sIgE) results in AD-HIES. Both skin and blood test results are comparable between patients with AD-HIES and healthy controls [32]. Defective neutrophil chemotaxis has been described among AD-HIES patients, and variable specific antibody production is seen [5,33]. Patients may require immunoglobulin replacement.

At the end of 20th century, the National Institutes of Health HIES scoring system was originally presented where a score of 30 has a sensitivity of 87.5 percent and a specificity of 80.6 percent [34]. It is noteworthy that some patients (e.g., some young children), may not meet the scoring criteria. Thereupon, in cases of positive family history of HIES and some distinctive features, according to experts, molecular screening should still be performed even if the score is below 30. Other diagnostic guidelines takes into account five cardinal clinical features (recurrent pneumonia, newborn rash, pathologic bone fractures, characteristic facies, and high palate) with total IgE level and Th17 cell count [35]. Molecular genetic testing is crucial to establish the diagnosis of the AD-HIES.

Autosomal-recessive-HIES (AR-HIES) is characterized by highly elevated serum levels of IgE, eczema, recurrent staphylococcal abscesses, and hypereosinophilia. In contrast to AD-HIES, where patients are usually free from allergic manifestations, 50% to 70% of patients with AR-HIES suffer from severe allergies, i.e., eczema, anaphylaxis to food, and environmental allergies, and 30% have asthma [10,32]. Pulmonary disease is usually asthma-related as compared with AD-HIES, with pneumatocele and lung damage due to prior infections [10].

Some patients with DOCK8 or TYK2 deficiency were previously classified as AR-HIES with harmful allergic symptoms [36]. Now, we better recognize the differences in the clinical features. DOCK8 deficiency is a combined immunodeficiency characterized by allergic inflammation, severe atopy, high IgE, susceptibility towards cutaneous viral infections, and malignancy [37]. TYK2 deficiency is also a combined immunodeficiency with recurrent skin viral infections, while eczema and elevated IgE are variably found. A study conducted by Boos et al. revealed that total serum IgE levels similarly increased in STAT3-HIES, DOCK8 deficiency, and AD patients. The ratio of aeroallergen-specific IgE to total IgE was the highest in AD, whereas patients with DOCK8 deficiency showed the highest specific serum IgE against food allergens. Th2-cell numbers were significantly increased in DOCK8 deficiency and AD patients compared to STAT3-HIES patients and controls. The study showed that hyper-IgE syndromes and atopic dermatitis patients showed a different sensitization pattern of serum IgE corresponding to the allergic disease manifestations and Th-cell subset data, suggesting a key role of DOCK8 in the development of FA [32]. Moreover, according to Wilkie et al., defective Treg function may contribute to the increased skin inflammation and the eczema in DOCK8 deficient patients [38]. IEI with elevated IgE are summarized in Table 1.

Table 1. Inborn errors of immunity with elevated IgE.

Disease	IUIS Classification	Inheritance	Mutation	Characteristics	Immunological Features
Hyper IgE syndrome (HIES)	Combined immunodeficiencies with associated syndromic features	AD LOF	*STAT3*	Infectious disease and immunological manifestations (skin abscesses, recurrent sinopulmonary infections, bacterial infections, pulmonary aspergillus, Pneumocystis jirovecii, and chronic mucocutaneous candidiasis) Craniofacial, dental, musculoskeletal, neurological, and vascular abnormalities	Eosinophilia ↑ IgE ↓-specific antibody production Intermittent chemotactic defectsImpaired inflammatory cytokine production Reduced or absent Th17 cells Defective Th17 cell production of IL-17 Decreased IFN-γ production upon stimulation Decreased $CD8^+$ memory T cellsDiminished delayed-type hypersensitivity and lymphoproliferative responses to antigenic stimulation
ZNF341 deficiency (phenocopy of AD-HIES)	Combined immunodeficiencies with associated syndromic features	AR	*ZNF341*	Mild facial dysmorphism Early onset eczema Recurrent bacterial infections (respiratory, skin infections) Lung abscesses and pneumatoceles Musculoskeletal abnormalities Retention of primary teeth	↑ IgE- and IgG ↓-specific antibody production ↓ memory B cells excess of Th2 cells ↓ Th17 and NK cells
Loeys–Dietz syndrome (TGFBR deficiency)	Combined immunodeficiencies with associated syndromic features	AD	*TGFBR1TGFBR2*	Recurrent respiratory infections Eczema Food allergy Musculoskeletal abnormalities Retention of primary teeth Vascular abnormalities	↑ IgE
PGM3 deficiency (hyperimmunoglobulin E-like syndrome with glycosylation defects)	Combined immunodeficiencies with associated syndromic features	AR	*PGM3*	Impaired immunity (recurrent respiratory tract infections, abscesses) Severe atopy, asthma, eczema, and food allergy Autoimmunity Neurocognitive impairment Skeletal dysplasia	Neutropenia T and B cell lymphopenia Eosinophilia ↑ IgE levels N/↑ IgG and IgA Progressive bone marrow failure
Comel–Netherton syndrome	Combined immunodeficiencies with associated syndromic features	AR	*SPINK5*	Congenital ichthyosis Bamboo hair Recurrent bacterial infections Atopy Failure to thrive	↑ IgE and IgA ↓ switched and non-switched B cells
CARD11 deficiency	Combined immunodeficiencies with associated syndromic features	AD LOF	*CARD11*	Severe atopic dermatitis Food allergy Molluscum contagiosum infection Recurrent respiratory infections Lymphoma Various phenotypes from SCID to combined immunodeficiency, associated with atopy and elevated IgE levels or isolated severe atopy	↑ IgE Poor specific antibody production Impaired activation of both NF-kB and mTORC1 pathways N/↓ B cell numbers Defective T-cell activation and proliferation Skewing toward Th2
ERBIN deficiency	Combined immunodeficiencies with associated syndromic features	AD	*ERBB2IP*	Recurrent respiratory infections Susceptibility to S.aureus Eczema Atopy Joint hypermobility, sometimes vascular abnormalities	↑ IgE ↑ circulating Treg

Table 1. *Cont.*

Disease	IUIS Classification	Inheritance	Mutation	Characteristics	Immunological Features
IL6R deficiency	Combined immunodeficiencies with associated syndromic features	AR	*IL6R*	Immunodeficiency (recurrent pyogenic infections, cold abscesses) Atopy Abnormal inflammatory responses	High circulating IL-6 levels Normal/↓ serum IgM, IgG, and IgA Very ↑ IgE ↓-specific antibody productionReduced switched memory B
Interleukin 6 signal transducer (IL6ST) deficiency	Combined immunodeficiencies with associated syndromic features	AR	*IL6ST*	Recurrent infections Boils Eczema Bronchiectasis Pulmonary abscesses Skeletal abnormalities (scoliosis, bone fractures, and craniosynostosis) Retention of primary teeth	Eosinophilia ↑ IgE, Specific antibody production variably affected Impaired B cell memory and acute-phase response ↓ Th17 cells
DOCK8 deficiency	Immunodeficiencies affecting cellular and humoral immunity	AR	*DOCK8*	Recurrent viral and bacterial infections Cutaneous infections (staphylococcal, viral, and fungal) Severe atopy Often multiple severe allergies to food and environmental allergens Hepatic disorders Early-onset malignancy	Eosinophilia ↓ T cell numbers (with normal CD4/CD8 ratio) and variably decreased or normal B- and NK-cell numbers ↓ production of TNFα and IFNγ ↓ numbers of Th17 T cells ↑ Th 2 ↑ IL-4 and IL-13 Few Treg with poor function ↓ IgM levels and variable IgA and IgG levels ↑ IgE Poor antibody responses
TYK2 deficiency	Defects in intrinsic and innate immunity	AR	*TYK2*	Susceptibility to intracellular bacteria (mycobacteria, Salmonella) and viruses Eczema	Impaired cellular responses to IL-10, IL-12, and IL-23 and type I IFNs
Omenn syndrome (OS)	Immunodeficiencies affecting cellular and humoral immunity (usually a $T\text{-}B\text{-}NK^+$ SCID)	AR	various	Erythroderma Alopecia Aplasia/hypoplasia of the eyebrow Desquamation of skin Dry skin Edema Chronic diarrhea Failure to thrive Hepatosplenomegaly Lymphadenopathy Pneumonia Sometimes anemia, autoimmunity, hypothyroidism, and lymphoma	Eosinophilia ↑ IgE Abnormal secretion of IL-4 and IL-5 from activated T cells Exaggerated Th2 response Absence of B cells in the circulation
Wiscott–Aldrich syndrome (WAS)	Combined immunodeficiencies with associated syndromic features	XL	*WAS*	Recurrent bacterial and viral infections Bloody diarrhea Eczema Thrombocytopenia with small platelets ↑ risk of malignancy Autoimmune diseases IgA nephropathy	Eosinophilia Often ↑ IgE and IgA ↓ IgM ↓ antibody responses to polysaccharides Progressive ↓ in T cells numbers Abnormal lymphocyte responses to anti-CD3

The presence of sIgE (≥0.35 kU/L) against BSA in 33.33% (n = 24) of patients with PID was an interesting finding. In most of these cases (n = 20; 83.33%), it correlated with clinical symptoms of milk allergy at the time of the study or in the past. sIgE against BSA showed low values (<0.7 kU/L; n = 12). A higher concentration of sIgE against BSA was observed in patients without Ig replacement therapy than in patients receiving Ig substitution therapy, and the difference between these two groups was statistically significant (p = 0.03; Figure 1).

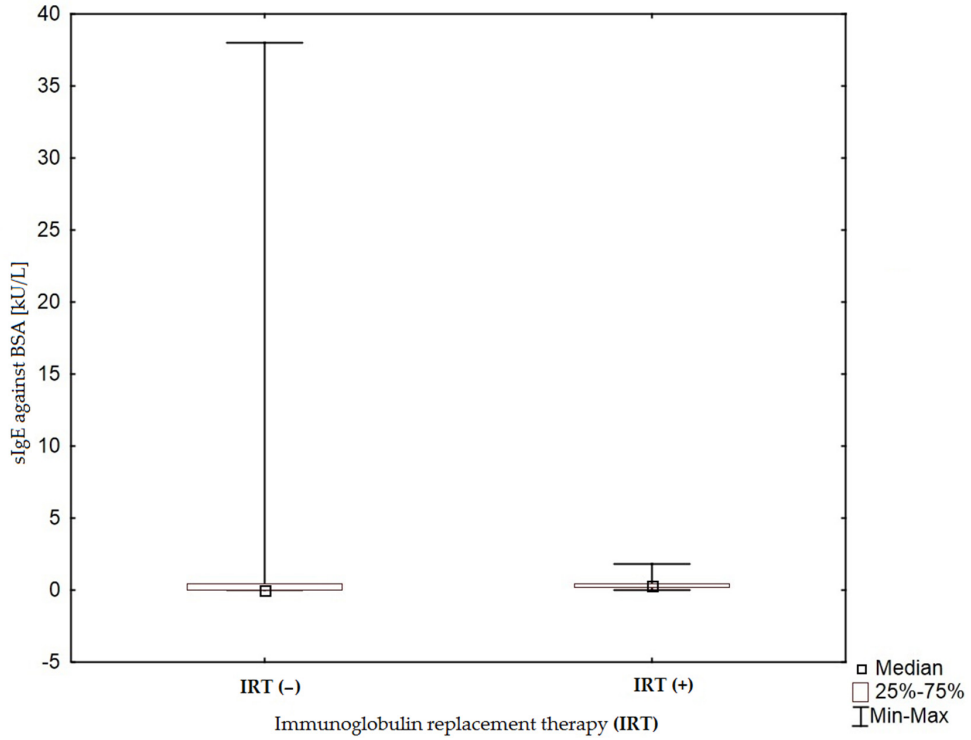

Figure 1. Concentration of sIgE against BSA (bovine serum albumin) in PID patients during immunoglobulin replacement therapy (IRT+) and not receiving IRT (IRT−) (p = 0.03).

Twenty-one (29.17%) patients showed chronic or recurrent skin eczema, and the majority of them (n = 16) had a significantly increased sIgE level (p = 0.003).

There was no significant correlation between the prevalence of recurrent respiratory tract infections and the serum sIgE level (p = 0.55).

The levels of sIgE against inhalant allergens correlated with an elevated total IgE (p = 0.0002). However, no correlation with blood eosinophilia (p = 0.85), recurrent respiratory tract infections (p = 0.23), family history of allergic diseases (p = 0.99) was observed. There was no significant difference between males and females (p = 0.39).

The levels of sIgE against food allergens did not correlate with eosinophilia (p = 0.31), total IgE (p = 0.14), weight deficiency (p = 0.87), height deficiency (p = 0.65), positive family history of allergy (p = 0.53). There was no effect of the treatment with antihistamine medications (p = 0.54).

Although 72.22% (n = 26) of the patients with increased sIgE were males, the difference between the sexes was not significant (p = 0.14). In addition, there was no significant difference between different groups of PID (Table 2).

On the other hand, low levels of IgE interest immunologists. Selective IgE deficiency (defined as a significant decrease in the levels of IgE (<2.5 IU/mL) in patients whose other immunoglobulin levels, including IgG, IgG subclasses, and IgA levels, are normal) has not been included in international classification systems for IEI [1]. Low serum levels of IgE can be associated with some well-defined IEI: common variable immunodeficiency (CVID), IgG subclass deficiencies, sIgAD, ataxia-telangiectasia (A-T), and agammaglobulinemia [39–41]. According to studies, an undetectable serum IgE (<2 IU/mL) occurs in only 3.3% of the general population [21]. In contrast, Lawrence et al. found that an undetectable IgE occurs in 75.6% of patients with CVID [21]. Another finding was a significant correlation between serum IgE with serum IgG, suggesting that lower IgE occurs in patients with more severe hypogammaglobulinemia. Moreover, false-negative results may appear using traditional methods of sIgE measurement, and allergen sIgE was not detectable in 96.5% of patients with CVID. Many patients with CVID report symptoms of rhinitis, wheeze, or adverse reactions to antibiotics, but it is difficult to detect allergic sensitization among them, especially using SPT or serum sIgE [41–43]. In these cases, sensitization should be confirmed using different methods, for example, an oral provocation challenge, and bronchial provocation tests with allergens [41]. The interpretation of food-specific IgE values and their usefulness in predicting symptomatic food allergies in the context of IEI patients is a potential field for further studies.

While diagnostics among PID patients during Ig replacement therapy (IRT) are often challenging, in the context of allergy, studies suggest that current Ig products are not a significant source of IgE [21].

3. Autoimmunity

There is also a high degree of overlap between autoimmune diseases and IEI in the context of genetic linkages and causes [44]. The molecular mechanisms responsible for the immune dysregulation in patients with IEI still are not fully recognized [45]. The usage of genetic analysis and a better understanding of the involved immune regulatory and signaling mechanisms is revealing the complex relationships between IEI syndromes and autoimmune diseases [44]. In the past, IEI and autoimmune diseases were considered as opposites; now, we know that genetic mutations may affect multiple immune cells and molecules, and in consequence IEI does not exclude autoimmunity. Furthermore, autoimmune diseases often coexist with some IEI [46].

The potential mechanisms associated with the pathogenesis of autoimmunity include impaired B cell differentiation and germ-center reactions, altered T cell central or peripheral tolerance, uncontrolled lymphocyte proliferation and differentiation, disturbances in Treg/Th17 balance, dysfunctional complement and innate immune activation, and the defective clearance of the infectious agents [45,46].

A French national study by Fischer et al. includes all types of IEI and autoimmune manifestations. The study demonstrated that autoimmunity is a significant component of clinical presentation of all types of IEI: one or more autoimmune and inflammatory manifestations were noted in 26.2% of 2183 retrospectively screened IEI patients, with a risk of onset throughout the patient's lifetime. The risk of autoimmune cytopenia (AIC) was at least 120 times higher than in the general population; among children the risk of inflammatory bowel disease (IBD) was 80 times higher, while the risk of arthritis was 40 times higher. The risk of other autoimmune complications was approximately 10 times higher. Autoimmune manifestations occurred in patients with all types of IEI; however, patients with T-cell defects or CVID had, statistically speaking, the highest risk for autoimmunity [47].

The signs and symptoms of most rheumatic diseases are classified in international American College of Rheumatology (ACR) or European League Against Rheumatism (EULAR) criteria. The management of autoimmunity in patients with IEI is often challenging because immune dysregulation, as well as permanent inflammation, may influence the diagnostic process. Moreover, when assessing a patient with IEI for possible autoimmunity, it is important to consider a broad differential diagnosis, because infectious diseases, adverse

effects of medications, and malignancies can mimic autoimmune processes. Thereupon, a complete diagnostic process is not effortless and requires a history, a complete physical examination, wide laboratory testing, imaging, and even pathological investigations [48]. Clinicians must be aware of the characteristic clinical features of autoimmune diseases among IEI patients. These include polyautoimmunity, which is defined as the presence of more than one autoimmune disease in a single patient and early onset autoimmunity (the presence of autoimmune disease at any age that is earlier than usual) [46]. Some IEI are associated with specific autoimmune diseases, and the awareness of these patterns also allows clinicians to monitor patients more effectively.

During evaluation of a patient with IEI and suspected autoimmunity, some laboratory tests are needed. This includes a complete blood count with differential, acute phase reactants, autoantibodies, serologies, flow cytometry, cytokine analysis, levels of complement, human leukocyte antigen (HLA) typing, and comprehensive endocrine and/or metabolic panels [48].

On the other hand, laboratory tests may help to catch patients with IEI among heterogenous group of patients with already diagnosed autoimmunity. Immune phenotyping and immunoglobulin (Ig) levels are indispensable. The ratio of naïve and memory T cells (CD45RA/CD45RO) may differentiate patients with late-onset or profound combined immunodeficiency disorders [49–52].

In addition, specific subsets of T and B cells have been linked to IEI with autoimmunity. These include the expansion of TCRαβ $CD4^{-}CD8^{-}$ (double-negative) T cells in autoimmune lymphoproliferative syndrome (ALPS), $CD19^{hi}21^{lo}$ B cells in CVID with autoimmunity, an abnormal count of Treg in Tregopathies, Th17 cells in STAT1 GOF patients, and expanding follicular helper T cells (Tfh) in CTLA4 and LRBA deficiency. Changes in these subsets may also predict the progression of autoimmune complications or a response to therapy [52,53].

Primary antibody deficiencies (PADs) are the most common inherited IEI in humans, with recurrent infections as a predominant presenting complaint. However, various types of PADs are also associated with inflammatory disorders, granulomatous lesions, lymphoproliferative diseases, and cancer. Several studies have reported that PAD patients are predisposed to autoimmune complications [47,54].

X-linked agammaglobulinemia (XLA), also known as Bruton agammaglobulinemia, is the prototype antibody deficiency [55]. Function-loss mutations in Bruton's tyrosine kinase (BTK) lead to a block in B-cell maturation, a near total absence of B cells in the periphery, and severe reductions in serum immunoglobulins. Surprisingly, most patients with XLA have a small number of B cells, or "leaky B cells", in the peripheral blood [54,56]. Patients with XLA are rather at a low risk of autoimmune or inflammatory diseases compared with other IEI patients, but several studies suggest that some XLA patients show symptoms with similar diagnostic features to rheumatoid arthritis (RA), IBD, alopecia, enteropathy, autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura (ITP), neutropenia, and Kawasaki disease [54,57–59]. These patients are not expected to produce autoantibodies; however, surprisingly, the "leaky" production of autoantibodies and defects in B-cell central tolerance has been reported [54,60,61].

Autoimmune diseases occur in 20–30% of CVID patients. The most reportable are autoimmune cytopenias such as ITP, AIHA, and Evans syndrome; however, organ-specific and systemic autoimmune diseases are also described [45,62–64].

It is worth mentioning that it is not uncommon that autoimmune complications are the first or the only clinical manifestation of CVID during diagnostics [54,65].

A cohort study on CVID patients with immune cytopenia showed higher levels of serum immunoglobulin, CD19hi B cells, and T CD4 effector T cells, accompanied by reduced naïve T cells [45,66]. Moreover, according to several studies, Treg frequency and their functional characteristics are disturbed in CVID patients [54,67–69], which may result in elevated levels of activated T cells; autoimmunity; and chronic inflammation. Defects in Tregs are also correlated with the expansion of CD21low B cells in CVID patients with

autoimmunity [70–72]. In a study by Boileau et al., the serum IgG level in CVID patients with autoimmunity (cytopenia and others) was greater than in CVID patients without autoimmunity [66]. Other studies revealed that CVID patients with autoimmunity have higher levels of IgM compared with non-autoimmune phenotypes [73,74]. On the other hand, markedly depressed serum immunoglobulin levels have been reported in patients with RA, Sjogren's syndrome (SS), and systemic lupus erythematosus (SLE), prompting suspicion of IEI [75,76].

Autoantibodies circulating in the serum and/or plasma, as well as the immune complex deposits containing autoantibodies and complement, are essential diagnostic tools in most autoimmune diseases. In patients with hypogammaglobulinemia (i.e., CVID, XLA etc.) and some types of CIDs, diagnostic tests that are based on antibodies may be not useful and provide false-negative results. For example, the diagnosis of definite autoimmune hepatitis (AIH) in CVID patients is definitely challenging. According to the European Association for the Study of the Liver (EASL), both histologic evidence of moderate to severe interface hepatitis and the positivity of the typical autoantibodies are required to make an AIH diagnosis [77,78]. It is not surprising that CVID patients generally may not have autoantibodies, even in the case of noticeable autoimmune complications.

However, in a study by Tahiat et al. among 299 IEI patients with a dominance of PAD (27.8%) and CID (26.1%), autoantibodies were found in 32.4% of all IEI patients, compared with 15.8% of healthy subjects. Anti-nuclear antibodies (ANA) (10.0%), transglutaminase antibody (TGA) (8.4%), RBC antibodies (6.7%), anti-smooth muscle antibody (ASMA) (5.4%), and ASCA (5.0%) were the most common autoantibodies. The authors have concluded that considering the association of some autoimmune diseases with certain PIDs, screening for corresponding autoantibodies would be recommended. However, due to the low positive predictive value of the autoantibodies, the results should be interpreted with caution in patients with IEI [79].

Oppositely, the production of specific antibodies may by impaired even when the level of main classes of immunoglobulins is normal in specific antibody deficiency (SAD). Consequently, most autoantibodies are not found in these patients [48,80,81]. In sIgAD, as well as in CVID with IgA deficiency, it is obvious that there is a lack of antibodies in this immunoglobulin class (for example, tissue transglutaminase IgA–tTg IgA). On the other hand, among patients during IRT, exogenous Ig may interfere with some of the special immunologic tests. That is why it is worth considering if some screening tests such as autoantibodies should be performed before the therapy is being initiated or the serum should be frozen for future testing [48].

Some IEI patients are constantly negative for disease-specific autoantibodies, and in the case of clinical suspicion of autoimmune disease, other diagnostic methods should be considered. Medical imaging is often a part of the clinical evaluation of patients with suspected autoimmune disorder. In the case of IEI patients, some difficulties may appear at this point too. In particular types of IEI there is a problem with radiosensitivity, which limits the use of medical radiation for the diagnosis of autoimmunity [82–84]. Genetic instability, defective DNA repair, and a predisposition to malignancy are associated with specific types of IEI. A-T and NBS are well-defined IEI connected with defective DNA repair [85], where patients might be sensitive to radiation. X-ray exposure should be limited to diagnostic purposes only when it is medically necessary because patients should be protected from unnecessary medical techniques that incorporate radiation. Substitution with magnetic resonance imaging (MRI) or ultrasound is desirable [48].

Histopathological examination is sometimes crucial and clinically indicated in a diagnostic process. Diagnostic challenges may occur here as well. In IEI patients, as an effect of immunoglobulins and immune cells deficiency, affected tissue can have a different histological appearance in comparison to healthy individuals [48,78,86–88].

Since autoimmune cytopenia (AIC) is a common finding in IEI patients, Westermann-Clark et al. evaluated 154 pediatric patients with AIC in the context of IEI. Splenomegaly, short stature, and recurrent or chronic infections were common clinical features among

patients with AIC and IEI. IEI patients were more likely to have AIHA or Evans syndrome than AIC-only patients. Patients with both IEI and AIC more often had low CD3 and CD8 cells; low IgA and IgG levels; and a higher prevalence of autoantibodies to red blood cells, platelets, or neutrophils. AIC diagnosis preceded IEI diagnosis by 3 years on average, except among those with partial DiGeorge syndrome [89]. The early detection of patients with comorbid IEI and AIC may improve treatment outcomes.

The main molecular defects and common autoimmune complications among IEI are summarized in Table 2.

Table 2. Common autoimmune presentation in inborn errors of immunity (IEI).

IUIS Classification	Disease	Main Molecular Defect	Common Autoimmune Disease
Immunodeficiencies affecting cellular and humoral immunity	ICOS deficiency	ICOS	Arthritis, SLE, MS, and enteropathy
Combined immunodeficiencies with associated syndromic features	22q11 deletion syndrome (DiGeorge syndrome)	Large deletion typically in chromosome 22	AIC, AIT, and arthritis
	Wiskott–Aldrich syndrome	WAS	AIC, IBD, GN, arthritis, and vasculitis
Predominantly antibody deficiencies	X-linked agammaglobulinemia	Btk	RA, JIA, IBD, AIC, AIT, PND, KD, DM, T1D, SD, and alopecia
	CVID	Various	AIC (ITP, AIHA, AN), RA, JIA, SLE, IBD, AIT, PA, SS, and vitiligo
	Selective IgA deficiency	Unknown	AIC (ITP, AIHA), IBD, CD, PV, MG, SLE, RA, JIA, T1D, and AIT
	P110 delta deficiency	PIK3CD	IBD, AIC
	Hyper IgM syndrome	CD40, CD40L	AIT, IBD, RA, JIA, AIHA, and AGN
Diseases of immune dysregulation	LRBA deficiency	LRBA	AIC (AIHA, ITP, AN), IBD, RA, and JIA
	APECED	AIRE	T1D, AD, AIT, hypoparathyroidism, enteropathy, adrenal corticotropic hormone insufficiency, growth hormone insufficiency, vitiligo, alopecia, autoimmune hepatitis, and ovarian/testicular failure
	IPEX	FOXP3	IBD, AIC, AIT, vitiligo, alopecia, hepatitis, and early onset diabetes
	CTLA4 haploinsufficiency	CTLA4	IBD, AIC, SLE, and arthritis
	XIAP deficiency	XIAP	IBD, AIC, and hepatitis
	Early onset inflammatory bowel disease syndromes	various	IBD, arthritis
	STAT3 GOF	STAT3	IBD, AIC, hepatitis, and early-onset T1D
	ALPS	various	AIC, GN, endocrinopathies, and SLE
Congenital defects of phagocyte number, function, or both	Chronic granulomatous disease	CYBB	IBD, AIC, AIT, JIA, GN, SLE, APLA, and autoimmune pulmonary disease
Defects in innate immunity	STAT1 deficiency	STAT1 GOF	AIC, AIT, T1D, and SLE
Autoinflammatory disorders	Type 1 interferonopathies	various	SLE, AIC, and vasculopathy
Complement deficiencies	Complement deficiencies	various	SLE, vasculitis

Abbreviations: AD—Addison's disease; AIC—autoimmune cytopenia; AIHA—autoimmune hemolytic anemia; AIT—autoimmune thyroid disease; AN—autoimmune neutropenia; ALPS—autoimmune lymphoproliferative syndrome; APECED—autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; APLA—antiphospholipid antibodies; CD—celiac disease; CVID—common variable immunodeficiency; GN—glomerulonephritis; GOF—gain-of-function; IBD—inflammatory bowel disease; IUIS—International Union of Immunological Societies; JIA—juvenile idiopathic arthritis; IPEX—immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome; ITP—immune thrombocytopenia; MS – multiple sclerosis; RA—rheumatoid arthritis; SLE—systemic lupus erythematosus; and T1D—type 1 diabetes.

4. Non-Malignant Lymphoproliferation

Ranging from reactive polyclonal hyperplasia (associated with immune disorders) to true monoclonal disease (malignant process), lymphoproliferative disorders (LPDs)

constitute a heterogeneous group of diseases in clinical and genetic terms. LPDs occur when the physiological control of proliferation of both T and B cells collapses. Disturbances in this control may occur in many conditions where immunity is compromised. This creates difficulties (both in the clinical assessment of the patient and in the identification of pathogenic mechanisms) to differentiate LPDs [90]. They are observed in patients with immunodeficiency or immune dysregulation syndromes such as CVID, SCID, WAS, A-T, Chediak-Higashi syndrome (CHS), and X-linked lymphoproliferative disorders [91]. Additionally, splenomegaly and/or generalized lymphadenopathy are described in disorders such as CD27 deficiency, CD70, ITK deficiency, and XLP type 1. Autoimmune disorders, hypersensitivity reactions, and viral infections, including human immunodeficiency virus (HIV) infection, are also prone to developing lymphoproliferative disorders. Lymphoproliferation as well as lymphomas (both Hodgkin's and non-Hodgkin's lymphomas) are often associated with Epstein–Barr virus (EBV) infection. Moreover, both lymphadenopathy and splenomegaly can be caused by nonspecific infections, in CVID but also in almost any other PID, and they are not always primarily associated with immune dysregulation [92]. Transplant patients, as well as those taking immunosuppressants such as cyclosporine, sirolimus, and tacrolimus, are also at risk of developing benign LPDs [93].

Autoimmune lymphoproliferative syndrome (ALPS) is an example of a disease resulting from impaired apoptosis of lymphocytes, mostly as a consequence of abnormalities associated with programmed cell death mediated by Fas. Fas is a transmembrane receptor located on the cell surface and is one of the tumor necrosis factor receptors (TNFR). It is responsible for the induction of apoptosis, which is triggered after binding with the appropriate ligand (FasL). When the *FAS* gene is mutated, there are defects in the external pathway of programmed cell death [94]. Clinically, patients develop chronic lymphoproliferation and an increased number of T cells, which are referred to as "double negative T cells" (DNT) with $CD4^{-}/CD8^{-}$, $CD3^{+}$, and $TCR\alpha\beta^{+}$ phenotype [95].

ALPS usually presents in infancy or early childhood (the median age is 31–36 months), most often in the form of nonmalignant lymphoid expansion with lymphadenopathy, splenomegaly, and/or hepatomegaly and AIC, including hemolytic anemia and thrombocytopenia. In a minority of patients, clinical symptoms may appear later in life (18 to 35 years). In a French cohort, patients with later disease onset often presented autoimmune manifestations rather than LPD [96,97]. Patients often do not present symptoms that would suggest an infectious or neoplastic etiology. Most patients have an increased number of T and B lymphocytes, as well as polyclonal hypergammaglobulinemia. Hypogammaglobulinaemia, often not associated with increased susceptibility to infections, may occur in approximately 10% of cases. Autoimmunity is a common feature of ALPS and can be the first ALPS manifestation; however, it is not always present at the time of diagnosis. Autoantibodies are detected in up to 80% of patients, most often anticardiolipin antibodies or direct Coombs' antibodies, but only half of them actually have an autoimmune disease, usually AIHA, ITP, or autoimmune neutropenia (AIN). A pledge of hemolysis during examination of blood smears, as well as the detection of autoantibodies and a degree of reticulocytosis, are helpful in distinguishing AIC from the effects of coexistent hypersplenism. Another helpful diagnostic tip is that AIC often manifests clinically. Autoantibodies typically have high affinity and are IgG-derived, in contrast to naturally occurring autoantibodies of the same specificity that are low-affinity and IgM-derived. Autoimmune diseases that affect other systems than the haematopoietic system can also occur but are much rarer [98]. Regardless of the time since the disease onset, symptoms such as lymphadenopathy and/or splenomegaly will ultimately be seen in 100% of ALPS patients and are required for diagnosis. The areas most commonly affected by lymphadenopathy are the neck, mediastinum, armpits, groin, and pelvis, although virtually any lymph node can become enlarged. Lymphoproliferation tends to subside over time, and by the age of 20, as much as 66% of patients achieve complete remission, while the rest of the patients experience a significant improvement. Infections are sporadic but can also occur as a result of neutropenia and/or nasopharyngeal obstruction due to lymphadenopathy [99]. Moreover, patients with ALPS

are characterized by an increased risk of cancer (estimated at 10–20%); the most common forms of cancer are Hodgkin's lymphoma and non-Hodgkin's lymphoma [100].

Lymphoma can develop at any age in ALPS–FAS but is rare as a presenting feature. Distinguishing a benign node from a questionable node is a diagnostic challenge because of the frequent concomitant presence of benign/typical lymphadenopathy and splenomegaly seen with ALPS. Important clues for lymphoma are classic alarm symptoms (B symptoms), including fever, night sweats, itching, and weight loss. Positron emission tomography (PET)-based imaging may be helpful for distinguishing "good" from "bad" nodes on the basis of the presumed higher metabolic activity of malignant lymphoid tissue [101]. The nonmalignant lymphadenopathy fluctuates, and PET scan results fluctuate similarly. Lymphoma nodes more often are continuously chemically active ("hot"). Lymphoma typically originates in the B cell lineage, but T cell lymphomas have also occurred.

The required criteria for the diagnosis of ALPS include chronic lymphoproliferation lasting more than 6 months with the exclusion of neoplastic and infectious lymphoproliferation. In isolated lymphadenopathy, they must involve two distinct nodal regions. The second of the required criteria includes elevated counts of double negative T cells in peripheral blood that exceed 1.5% of the total number of lymphocytes or 2.5% in the case of T lymphocytes [102]. In addition, the diagnostics include genetic, biochemical (increased concentration of vitamin B12/IL-10/IL-18/sFASL/FAS), and histopathological tests.

5. Neoplastic Manifestations

Along with a predisposition to severe and recurrent infections and autoimmunity, neoplasms form a triad that identifies the most common symptoms in a variety of IEI. Despite this, there is a lack of systematic data on the cancer risk and type of neoplasms seen in most IEI. The development of malignant neoplasms most often occurs in patients with CVID, and in patients with defects in genes regulating DNA repair, cell cycle, apoptosis, or bone marrow maturation. Available population cohort studies suggest that the increased risk of developing cancer is limited to specific and rare forms of IEI and is mainly due to an increased risk of developing lymphoma [103–106]. The highest risk of lymphomas was reported in NBS (49%), X-linked lymphoproliferative syndrome (XLP; 24–30%), A-T (15–19%), ALPS (7–15%), and the mentioned CVID (1.8–8.2%) [96,103,107,108]. Among CVID patients, there is a 7- to 10-fold increase in gastric cancer incidence, which is related to the lack of secretory IgA [109,110]. In patients with CVID, extra-nodal non-Hodgkin's B-cell lymphomas and mucosa-associated lymphomas are the most common [111]. Unlike most IEI, lymphomas in CVID are more common in people in the 4th to 7th decade of life and are usually EBV-negative [111,112]. In a study by Ludvigsson et al., individuals with IgA deficiency were at a moderately increased risk of cancer, with excess risks of gastrointestinal cancer. Children with IgA deficiency were at no increased risk of cancer, but the statistical power was limited in subanalyses [113].

Common high-grade DNA strand repair defects with chromosomal instability are seen in the A-T. Ruptures of dsDNA cause a high percentage of malignant tumors, chromosome instability, and abnormal rearrangements of V (D) J genes; a recombination of class switches and/or somatic hypermutations (the *ATM* gene in A-T, the *NBN* gene in NBS, the *DCLRE1C* gene in severe combined deficiency immunodeficiency with sensitivity to ionizing radiation and Omenn syndrome, the *LIG4* gene in the LIG4 syndrome, and the *LIG1* gene in DNA ligase 1 deficiency) cause complex immunodeficiencies and malignant neoplasms, most often lymphomas [114,115]. Patients with Bloom's syndrome (*BLM* gene) age prematurely and are susceptible to non-Hodgkin's lymphoma (NHL). Patients with Schimke syndrome (*SMARCAL1* gene) show chromosomal instability and an increased risk of malignant neoplasm, including NHL and osteosarcoma [116,117].

Malignancies associated with impaired telomere maintenance are observed in genetically heterogeneous congenital dyskeratosis and its clinically severe variant of Hoyeraal Hreidarsson syndrome, NBS and A-T. Disorders of telomerase lead to the defective function of rapidly dividing cells and increased susceptibility to hematological and solid tumors [114].

IEI, which inherently affect hematopoiesis, make it susceptible to malignant neoplasms. In Fanconi anemia, a genetically heterogeneous disorder, pancytopenia, hematologic malignancies, solid tumors, and clinical immunodeficiency phenotypes are observed. Mutations of the *WAS* gene coding for the WASP disrupt the connection between GTPases and the actin cytoskeleton, thus disrupting the regulation of signaling in hematopoietic cells. Myelodysplasia, leukemias, and lymphomas in patients with WAS are seen more frequently [107,114,118]. The deficiency of the hematologic transcription factor GATA2 leads to phenotypically variable immunodeficiency, primary alveolar proteinosis, Emberger syndrome with lymphedema and/or a predisposition to myelodysplastic syndrome, acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), and EBV lymphoma [119]. The risk of leukemia is increased with some severe congenital neutropenia (ELANE, HAX1, and WASP) but not increased with the *ELANE* mutation that causes cyclic neutropenia. An increased risk of leukemia has not been reported in other PIDs associated with neutropenia [120]. Mutations in the *CD40L* gene cause X-linked immunodeficiency with hyperimmunoglobulin M. In the case of CD40L and CD40 ligand deficiencies, a Cryptosporidium biliary tract infection may lead to sclerosing cholangitis, cirrhosis, and an increased risk of hepatocellular carcinoma and biliary tract cancer [121–123].

Almost 20% of all human malignancies are associated with chronic infections with such pathogens as HBV, HCV, HPV, EBV, HHV8/KSHV, HTLV-I, HIV-1, HIV-2, JCV, Merkel cell carcinoma (MCV), Helicobacter pylori, schistosomes, or hepatic flukes [124,125]. Additionally, in IEI patients, chronic infections are often associated with malignancies. They were mostly described in connection with EBV, HPV, and HHV8 infections [107,126–128]. HPV can cause cancer of the cervix, vagina, vulva, anus, and penis, as well as squamous cell carcinoma of the oral cavity. Patients with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome are particularly prone to HPV infection, resulting in numerous warts, condylomata acuminate, and subsequent severe papillomatosis and malignant transformation of the lesions [128].

EBV in patients with IEI may cause chronic EBV viremia, hemophagocytic lymphohistiocytosis (HLH), dysgammaglobulinemia, atypical EBV-associated lymphoproliferative disorders (polymorphic B-cell hyperplasia, plasmocytic hyperplasia), and EBV-associated lymphomas [105,129,130]. In the rare heterogeneous KID syndrome (keratitis, ichthyosis, and deafness), mainly caused by mutations in the connexin 26 (*GJB2*) gene, 15% of patients develop squamous cell carcinoma, often in sun-exposed areas [131,132].

The estimated risk for developing cancer in patients with IEI ranges from 4 to 25 percent [133]. Furthermore, the diagnosis of the malignancy, both clinical and histological, can be challenging in the presence of non-malignant lymphoproliferation or bone marrow abnormalities. These states, as well as concomitant infections or complex co-morbidities, all can mimic a developing malignancy clinically, radiologically, and even histopathologically. Due to the statistically higher risk of the above-mentioned types of neoplasms, patients with IEI should undergo periodic age-appropriate screening tests, just like healthy people. However, the guidelines in this regard may differ depending on the IEI type and national or international recommendations. Patients with epidermodysplasia verruciformis (EV) should undergo regular dermatological check-ups due to an increased risk of skin cancer. Patients with A-T and their female family members with heterozygous mutant *ATM* should start the screening for breast cancer earlier than the general population, and this age depends on the type of the mutation in the *ATM* gene [134,135].

It is also worth mentioning that both NHL and Hodgkin lymphoma are diagnosed at younger ages in patients with IEI, and NHL is more common in males with IEI [136,137]. In patients with suspected lymphoma, medical management is the same as in immunocompetent patients; however, diagnostic difficulties may appear. Diagnostic tests useful in cancer screening include uric acid, lactate dehydrogenase (LDH), and erythrocyte sedimentation rate (ESR). Even histopathology, which is a gold standard of diagnosing malignancy, can be challenging in patients with IEI, particularly during the investigation of possible lymphoid malignancy.

If clinically indicated, a surgical biopsy providing sufficient material for the assessment of tissue architecture and ancillary diagnostic techniques is a better diagnostic option than needle core biopsy. Histological diagnosis may be difficult even when appropriate, high-quality material is gained [137,138]. For example, non-malignant lymphoproliferative lesions may precede, as well as co-exist with, lymphoid malignancies. Often, diagnostic boundaries between non-neoplastic and neoplastic lesions are ill-defined and difficult to apply. Lymphocyte clonality assessed by molecular techniques may help during diagnostics, but these alone cannot provide diagnostic certainty, and clonal B-cell and T-cell proliferations falling short of malignancy are not uncommon in IEI [138,139].

Patients with specific immunodeficiencies, including A-T, NBS, and CVID, should be informed about the increased risk of neoplasia associated with increased sensitivity to ionizing radiation. Before performing tests or therapy with the use of radiation, they should consult this fact with the attending immunologist. On the other hand, medical personnel should consider the benefit–risk ratio in terms of interventions with the use of ionizing radiation in the context of the underlying disease, taking into account the need to perform the examination, and the possibility of replacing the examination with radiation with alternative techniques without the use of ionizing radiation.

Advances in the diagnosis and treatment of patients with IEI contributed to a significant extension of the life of those patients who previously had no chance to live to adulthood. Patients with IEI require multidisciplinary care; therefore, physicians of various specialties should be aware of the increased tendency to develop neoplasms in these patients. Patients should be thoroughly informed about the alarm symptoms of malignant neoplasms, especially lymphoma. Cancer in a patient with IEI is more often extensive or disseminated at the time of diagnosis, which is associated with a worse prognosis. Patients with IEI are more likely to develop NHL with B-cell origin, with high histologic grades and extranodal involvement, especially in the gastrointestinal tract or central nervous system. Early diagnosis can provide better treatment options before serious organ damage occurs.

The most prevalent types of malignancies among IEI patients have been summarized in Table 3.

Table 3. Most common types of cancer among patients with IEI.

Disease	IUIS Classification	Type of Malignancy
SCID	Immunodeficiencies affecting cellular and humoral immunity (Ia)	Lymphoma
ITK deficiency	Immunodeficiencies affecting cellular and humoral immunity (Ib)	EBV-associated lymphoproliferation Lymphoma
IKAROS deficiency (CD154)	Immunodeficiencies affecting cellular and humoral immunity (Ib)	T-ALL
DOCK8 deficiency	Immunodeficiencies affecting cellular and humoral immunity (Ib)	Vulvar, facial, and anal squamous cell dysplasia and carcinomas;T cell lymphoma-leukemiaBurkitt lymphomaNHL
STK4 deficiency	Immunodeficiencies affecting cellular and humoral immunity (Ib)	Lymphoma
RHOH deficiency	Immunodeficiencies affecting cellular and humoral immunity (Ib)	Lymphoma
OX40 deficiency	Immunodeficiencies affecting cellular and humoral immunity (Ib)	Kaposi sarcoma
CD40/CD40L deficiency	Immunodeficiencies affecting cellular and humoral immunity (Ib)	Hepatocarcinoma Cholangiocarcinoma Peripheral neuroectodermal tumors of the gastrointestinal tract and the pancreas Lymphoma

Table 3. *Cont.*

Disease	IUIS Classification	Type of Malignancy
Wiskott–Aldrich syndrome	Combined immunodeficiency of T and B cell with associated or syndromic features	Lymphoma EBV-related B-cell lymphoma Leukemia Cerebellar astrocytoma Kaposi sarcoma Smooth muscle tumors
Ataxia-telangiectasia	Combined immunodeficiency of T and B cell with associated or syndromic features	Leukemia Lymphoma Breast cancer Gastrointestinal malignancies (possible)
Nijmegen breakage syndrome	Combined immunodeficiency of T and B cell with associated or syndromic features	Lymphoma Acute leukemia Solid tumors
Bloom syndrome	Combined immunodeficiency of T and B cell with associated or syndromic features	Leukemia Lymphoma
PMS2 deficiency	Combined immunodeficiency of T and B cell with associated or syndromic features	Lymphoma Colorectal carcinoma Brain tumors
MCM4 deficiency	Combined immunodeficiency of T and B cell with associated or syndromic features	B cells lymphoma
Ligase I deficiency	Combined immunodeficiency of T and B cell with associated or syndromic features	Lymphoma
Cartilage-hair hypoplasia	Combined immunodeficiency of T and B cell with associated or syndromic features	Lymphoma Leukemia Squamous cell carcinoma Basal cell carcinoma
Schimke syndrome	Combined immunodeficiency of T and B cell with associated or syndromic features	Osteosarcoma NHL
Autosomal dominant hyper-IgE syndrome (AD-HIES)	Combined immunodeficiency of T and B cell with associated or syndromic features	NHL
CID with early-onset asthma, eczema and food allergies, autoimmunity ID with atopic dermatitis (CARD11)	Combined immunodeficiency of T and B cell with associated or syndromic features	Lymphoma
X-linked agammaglobulinemia	Predominantly antibody deficiencies	Lymphoreticular malignancies Gastric and colorectal adenocarcinoma Squamous cell carcinoma of the lung
Common variable immunodeficiency (CVID)	Predominantly antibody deficiencies	Lymphoma Thymus cancer Gastric cancer
Selective IgA deficiency	Predominantly antibody deficiencies	Gastrointestinal cancer
X-linked lymphoproliferative disease (XLP1)	Diseases of immune dysregulation	Lymphoma
CD27 deficiency	Diseases of immune dysregulation	Lymphoma
RASGRP1 deficiency	Diseases of immune dysregulation	EBV-associated lymphoma
CD70 deficiency	Diseases of immune dysregulation	Hodgkin lymphoma
CTPS1 deficiency	Diseases of immune dysregulation	B-cell NH lymphoma
CD137 deficiency	Diseases of immune dysregulation	B-cell lymphoma

Table 3. *Cont.*

Disease	IUIS Classification	Type of Malignancy
XL magnesium EBV and neoplasia (XMEN)	Diseases of immune dysregulation	Lymphoma
ALPS–FAS	Diseases of immune dysregulation	Lymphoma
Severe congenital neutropenia	Congenital defects of phagocyte number, function, or both	MDS/leukemia
HAX1 deficiency	Congenital defects of phagocyte number, function, or both	MDS/leukemia
Shwachman-Diamond syndrome	Congenital defects of phagocyte number, function, or both	Leukemia
GATA2 deficiency	Congenital defects of phagocyte number, function, or both	AML/CMML
WHIM syndrome	Defects in intrinsic and innate immunity	HPV-related cancers Lymphoma
Epidermodysplasia verruciformis	Defects in intrinsic and innate immunity	Squamous cell carcinoma

Abbreviations: AML—acute myelogenous leukemia; CMML—chronic myelomonocytic leukemia; EBV—Epstein–Barr virus; HPV—human papillomavirus; MDS—myelodysplastic syndrome; NHL—non-Hodgkin lymphoma; and T-ALL—T-cell acute lymphoblastic leukemia.

6. Diseases of Immune Dysregulation

Diseases of immune dysregulation are a separate and independent category of IEI in IUIS classification [1]. This category includes i.a. familial hemophagocytic lymphohistiocytosis (FHL syndromes), FHL syndromes with hypopigmentation, regulatory T cell defects, autoimmunity with or without lymphoproliferation, immune dysregulation with colitis, ALPS, and a susceptibility to EBV and lymphoproliferative conditions. This category is often the most difficult to define clinically and to diagnose without extensive sequencing since there is a significant phenotypic overlap between different genetic causes, the evolution of features over time, and phenotypic heterogeneity. On the other hand, these diseases have improved our understanding of the pathways that drive autoimmunity in IEI.

Early-onset autoimmunity, autoimmunity that involves multiple organs, a strong family history of autoimmunity, autoimmunity in combination with susceptibility to infection, or significant lymphoproliferation all suggest an immune dysregulation defect.

Diseases of immune dysregulation, according to IUIS classification, are summarized in Table S1.

Over the years, the wide application of whole-exome sequencing/whole-genome sequencing has significantly promoted the discovery and further study of new IEI and its number has doubled from 2009 to 2019 [1,140]. It is worth mentioning that the number of cases for any particular IEI is usually few, and because of that, a large-scale study of IEI can hardly be conducted [140]. Furthermore, there are several difficulties in identifying IEI connected with immune dysregulation. There are still countries where genetic tests are not widespread and freely available, mostly because of their costs. Moreover, in some patients more than one mutation is present, which makes it even more difficult to find [140,141]. In addition, phenotypes of the same mutation vary between patients, ranging from mild or uncharacteristic symptoms to even life-threatening manifestations [140,142,143]. In conclusion, patients with immune dysregulation should be examined scrupulously, and genetic diagnostics should be conducted in cases when it is necessary and possible [140]. Early and proper diagnosis seems crucial when we consider IEI patients. In cases of IEI patients with immune dysregulation, it is even more important.

The treatment is often challenging and sometimes requires balancing between increased susceptibility to infection and the additional suppression of the immune system [144]. Not so long ago, treatment options for IEI patients remained limited. They included the intensive treatment of infections; IRT; and bone marrow transplant in some cases. IRT has been a

standard, often live-saving treatment for IEI that has affected antibody production for the past four decades. Both intravenous (IVIg) and subcutaneous (SCIg) immunoglobulins are often suitable for lifelong therapy. High-dose IVIg, together with corticosteroids, is a standard therapy for ITP [144]. A significant increase in the field of clinical immunology, including molecular biology techniques, gene therapy, or the use of immune modulators, allowed the development of modern and precise therapies [145]. Equally, having better knowledge of IEI pathophysiology enables the implementation of targeted therapy. IEI is an excellent example of disease where such "precision medicine" can be applied. Precision medicine is an approach based on advances in genetic research and data analysis. It offers breakthroughs in the treatment of the disease and has the potential to overturn traditional methods of practicing medicine.

Such medicines (new or repurposed) modify intracellular pathways whose function is disturbed because of specific genetic defect [144]. Thanks to precision medicine, the treatment can selectively influence a specific cell function instead of affecting the entire immune system. Moreover, the adverse side effects that affect other tissues are possible to avoid.

Although the term "precision medicine" is relatively new, it has been part of healthcare for many years. For example, a person who needs a blood transfusion does not receive blood from a randomly selected donor; instead, the donor's blood group is matched to that of the recipient to reduce the risk of complications. Precision medicine is already used in the treatment of diabetes and cancer. It is especially useful in cases of breast, lung, skin, colon, prostate, and pancreatic cancer. Its other promising applications include cardiology, signs of aging, rare childhood diseases, cystic fibrosis, and HIV.

In the context of immunedysregulation, the usage of small molecules and biologics effectively helps with reversing the clinical manifestations of immunedysregulation and hyperinflammation. Knowledge about the genetic etiology of activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS) allowed one to explore PI3Kδ inhibition as a precision medicine [146,147]. Leniolisib, a small-molecule, selective PI3Kδ inhibitor, causes the dose-dependent suppression of PI3Kδ pathway hyperactivation. Clinical trials are currently underway to establish the safety and efficacy of selective PI3K δ inhibitors as a possible therapeutic option in patients with APDS. One is related to the oral administration of leniolisib (NCT02435173), the other to the inhaled administration of nemiralisib (NCT02593539). So far, the 12-week dose escalation of leniolisib has been shown to be safe and effective in reducing lymphadenopathy, splenomegaly, and cytopenia [144,147].

7. Conclusions

IEI is a group of rare diseases that can be camouflaged or not considered because of the predominant clinical features of atopy, autoimmunity, or lymphoproliferation. Consequently, some patients will remain undiagnosed. This risk impairs their quality of life, morbidity, and mortality, especially when exposed to agents reducing the immune competence. An underlying IEI should be particularly considered, especially in severe cases of atopic disease with concomitant signs of autoimmunity and unusual, recurrent or severe infections, so appropriate treatment regimens can be initiated and inappropriate immune suppression avoided.

In terms of the scientific evidence, it is still debatable whether allergy and cancer should be considered as risk factors or rather the consequences of the underlying IEI. Autoimmunity, as well as malignancy, worsen the IEI patients' prognosis. Another important issue in IEI is their exact pathogenesis, as well as the gene–phenotype relationship. The recent advances in genetics also revolutionized the field of IEI. Until now, the increased use of new sequencing techniques allowed for the identification of different monogenic causes of IEI. They enabled the better understanding of genotype–phenotype correlations and consequently led to better therapeutic strategies targeting the immune dysregulation in IEI [45]. The unmet needs include the unified nomenclature; the pathophysiological

mechanisms assessment, for example, the lymphoma' genesis in IEI patients; and better, more personalized treatment strategies [148].

Novel diagnostic approaches, as well as evidence-based treatment guidelines that consider the underlying immunodeficiency rather than using extrapolation from non-IEI settings, are necessary. The recommendations for validated screening of cohorts at risk of allergy, autoimmunity, and malignancy are of the utmost importance.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11144220/s1, Table S1: Diseases of immune dysregulation according to IUIS classification. Accessed on 8 July 2022.

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Załączniki

Zgoda Komisji Bioetycznej na realizację projektu

KOMISJA BIOETYCZNA
przy
Uniwersytecie Medycznym
we Wrocławiu
ul. Pasteura 1; 50-367 WROCŁAW

OPINIA KOMISJI BIOETYCZNEJ Nr KB – 333/2020

Komisja Bioetyczna przy Uniwersytecie Medycznym we Wrocławiu, powołana zarządzeniem Rektora Uniwersytetu Medycznego we Wrocławiu nr 133/XV R/2017 z dnia 21 grudnia 2017 r. oraz działająca w trybie przewidzianym rozporządzeniem Ministra Zdrowia i Opieki Społecznej z dnia 11 maja 1999 r. (Dz.U. nr 47, poz. 480) na podstawie ustawy o zawodzie lekarza z dnia 5 grudnia 1996 r. (Dz.U. nr 28 z 1997 r. poz. 152 z późniejszymi zmianami) w składzie:

prof. dr hab. Jacek Daroszewski (choroby wewnętrzne, endokrynologia, diabetologia)
prof. dr hab. Krzysztof Grabowski (chirurgia)
dr Henryk Kaczkowski (chirurgia szczękowa, chirurgia stomatologiczna)
mgr Irena Knabel-Krzyszowska (farmacja)
prof. dr hab. Jerzy Liebhart (choroby wewnętrzne, alergologia)
ks. dr hab. Piotr Mrzygłód, prof. nadzw. (duchowny)
mgr Luiza Müller (prawo)
dr hab. Sławomir Sidorowicz (psychiatria)
prof. dr hab. Leszek Szenborn, (pediatria, choroby zakaźne)
Danuta Tarkowska (pielęgniarstwo)
prof. dr hab. Anna Wiela-Hojeńska (farmakologia kliniczna)
dr hab. Andrzej Wojnar, prof. nadzw. (histopatologia, dermatologia) przedstawiciel Dolnośląskiej Izby Lekarskiej)
dr hab. Jacek Zieliński (filozofia)

pod przewodnictwem
prof. dr hab. Jana Kornafela (ginekologia i położnictwo, onkologia)

Przestrzegając w działalności zasad Good Clinical Practice oraz zasad Deklaracji Helsińskiej, po zapoznaniu się z projektem badawczym pt.

„Ocena występowania autoprzeciwciał oraz swoistych przeciwciał klasy IgE u pacjentów z pierwotnymi niedoborami odporności"

zgłoszonym przez **lek. Karolinę Pieniawską- Śmiech** doktorantkę w Katedrze i Zakładzie Immunologii Uniwersytetu Medycznego we Wrocławiu oraz złożonymi wraz z wnioskiem dokumentami, w tajnym głosowaniu postanowiła **wyrazić zgodę** na przeprowadzenie badania w Oddziale Immunologii Klinicznej i Pediatrii Wojewódzkiego Szpitala Specjalistycznego im. J. Gromkowskiego we Wrocławiu oraz Katedrze i Zakładzie Immunologii Klinicznej UMW pod nadzorem prof. dr hab. Marka Jutela **pod warunkiem zachowania anonimowości uzyskanych danych**.

Uwaga: Badanie to zostało objęte ubezpieczeniem odpowiedzialności cywilnej Uniwersytetu Medycznego we Wrocławiu z tytułu prowadzonej działalności.

Pouczenie: W ciągu 14 dni od otrzymania decyzji wnioskodawcy przysługuje prawo odwołania do Komisji Odwoławczej za pośrednictwem Komisji Bioetycznej UM we Wrocławiu.

Opinia powyższa dotyczy projektu badawczego dla młodych naukowców.

Numer rejestrowy CWN UMW: STM.A020.20.063

Wrocław, dnia 30 czerwca 2020 r.

Uniwersytet Medyczny we Wrocławiu
KOMISJA BIOETYCZNA
...niczego
prof. dr hab. Jan Kornafel

Oświadczenia współautorów

Karolina Pieniawska-Śmiech

Wrocław, 24 / 05 / 2023

Lek. Karolina Pieniawska-Śmiech
Katedra i Zakład Immunologii Klinicznej
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OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracach:

1. Pieniawska-Śmiech K, Lewandowicz-Uszyńska A, Zemelka-Wiacek M, Jutel M. Serum Allergen-Specific IgE among Pediatric Patients with Primary Immunodeficiency. *Children*. 2022; 9(4):466. https://doi.org/10.3390/children9040466
2. Pieniawska-Śmiech K, Pasternak G, Lewandowicz-Uszyńska A, Jutel M. Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation. *Journal of Clinical Medicine*. 2022; 11(14):4220. https://doi.org/10.3390/jcm11144220
3. Pieniawska-Śmiech K, Lewandowicz-Uszyńska A, Zemelka-Wiacek M, Jutel M. Assessment of autoantibodies in paediatric population with primary immunodeficiencies: a pilot study. BMC Immunology. 2023. DOI : 10.1186/s12865-023-00543-6 – praca przyjęta do druku.

mój udział polegał na: współpracy przy tworzeniu koncepcji i metodologii; pozyskaniu finansowania badań; rekrutacji badanych, pozyskiwaniu danych, analizie i interpretacji wyników prac; pisaniu i edycji manuskryptów

Uniwersytet Medyczny we Wrocławiu
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Uniwersytet Medyczny we Wrocławiu
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OŚWIADCZENIE WSPÓŁAUTORA

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1. Pieniawska-Śmiech K, Lewandowicz-Uszyńska A, Zemelka-Wiacek M, Jutel M. Serum Allergen-Specific IgE among Pediatric Patients with Primary Immunodeficiency. *Children*. 2022; 9(4):466. https://doi.org/10.3390/children9040466
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3. Pieniawska-Śmiech K, Lewandowicz-Uszyńska A, Zemelka-Wiacek M, Jutel M. Assessment of autoantibodies in paediatric population with primary immunodeficiencies: a pilot study. BMC Immunology. 2023. DOI : 10.1186/s12865-023-00543-6 – praca przyjęta do druku.

mój udział polegał na: współtworzeniu koncepcji, metodologii, analizie i interpretacji wyników prac; nadzorze merytorycznym; krytycznej ocenie i korekcie manuscryptów oraz ich ostatecznej akceptacji

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Wrocław, 24.05.2023

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracach:

1. Pieniawska-Śmiech K, Lewandowicz-Uszyńska A, Zemelka-Wiacek M, Jutel M. Serum Allergen-Specific IgE among Pediatric Patients with Primary Immunodeficiency. *Children*. 2022; 9(4):466. https://doi.org/10.3390/children9040466
2. Pieniawska-Śmiech K, Lewandowicz-Uszyńska A, Zemelka-Wiacek M, Jutel M. Assessment of autoantibodies in paediatric population with primary immunodeficiencies: a pilot study. BMC Immunology. 2023. DOI : 10.1186/s12865-023-00543-6 – praca przyjęta do druku.

mój udział polegał na: wykonywaniu badań laboratoryjnych (oznaczanie ilościowe sIgE oraz autoprzeciwciał metodą Polycheck), opracowywanie metodologii badań, krytycznej ocenie manuskryptów

Podpis

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Dr n.med. Gerard Pasternak

Wrocław, 22 / 05 / 2023

Dr n.med. Gerard Pasternak
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Uniwersytet Medyczny we Wrocławiu

OŚWIADCZENIE WSPÓŁAUTORA

Oświadczam, że w pracach:

1. Pieniawska-Śmiech K, Pasternak G, Lewandowicz-Uszyńska A, Jutel M. Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation. *Journal of Clinical Medicine*. 2022; 11(14):4220. https://doi.org/10.3390/jcm11144220

mój udział polegał na: zbieraniu danych literaturowych, tworzeniu manuskryptu.

Uniwersytet Medyczny we Wrocławiu
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IMMUNOLOGII I REUMATOLOGII
WIEKU ROZWOJOWEGO
adiunkt dydaktyczny
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Nota biograficzna doktoranta

Urodzona 11.05.1992 w Dębnie. Ukończyła studia na Wydziale Lekarskim z wyróżnieniem w 2017 roku uzyskując tytuł lekarza. Następnie odbywała staż podyplomowy w 4 Wojskowym Szpitalu Klinicznym z Polikliniką we Wrocławiu. W październiku 2018 roku rozpoczęła studia doktoranckie w Katedrze i Zakładzie Immunologii Klinicznej; od 2018 roku prowadziła zajęcia dydaktyczne zarówno w macierzystym zakładzie (immunologia kliniczna), jak i w III Katedrze i Klinice Pediatrii, Immunologii i Reumatologii Wieku Rozwojowego (propedeutyka pediatrii). W 2020 r. otrzymała dofinansowanie w ramach projektu Młodzi Naukowcy pt. „Ocena występowania autoprzeciwciał oraz swoistych przeciwciał klasy IgE u pacjentów z pierwotnymi niedoborami odporności". Od 2020 roku pracuje na Oddziale Immunologii Klinicznej i Pediatrii, na co dzień zajmując się diagnostyką i leczeniem pacjentów z pierwotnymi niedoborami odporności (PNO) oraz realizując szkolenie specjalizacyjne z pediatrii w trybie rezydentury. Jest autorką i współautorką kilku prac oryginalnych publikowanych w indeksowanych czasopismach, m.in. Frontiers in Immunology, BMC Immunology, Journal of Clinical Medicine, Children, Vaccines, Molecular Genetics & Genomic Medicine, Psychiatria Polska. Jej zainteresowania badawcze skupiają się na temacie zaburzeń regulacji immunologicznej, autoimmunizacji, chorób alergicznych u pacjentów z PNO.

Członek Polskiego Towarzystwa Pediatrycznego, w tym Komisji Rewizyjnej Dolnośląskiego Oddziału Polskiego Towarzystwa Pediatrycznego

Wykaz dotychczasowych osiągnięć doktoranta

Publikacje

- Autorka **10** publikacji, w tym **9** w indeksowanych czasopismach z IF.
  Sumaryczne wartości IF=**37,383**; MNiSW/KBN = **923**.
  Cytowania według bazy Web of Science= **24**; H-index = **4**

  Spośród publikacji z IF w **6/9** jestem autorem pierwszym i/lub korespondencyjnym.
- Autorstwo/współautorstwo **3** doniesień zjazdowych na konferencjach polskich oraz zagranicznych.

Projekty badawcze

- „Wpływ krioterapii ogólnoustrojowej na samopoczucie pacjentów z łuszczycą stawową oraz pacjentów z zaburzeniami nastroju" (Pbmn-167) – 2015-2016 r.
- „Funkcje poznawcze a ekspozycja na skrajnie niskie temperatury" (ST-842) – 2015-2016 r.
- „Ocena występowania autoprzeciwciał oraz swoistych przeciwciał klasy IgE u pacjentów z pierwotnymi niedoborami odporności" (STM.A020.20.063) – 2020-2022 r.

Działalność w towarzystwach naukowych

- 2022 – obecnie – członek Komisji Rewizyjnej Dolnośląskiego Oddziału Polskiego Towarzystwa Pediatrycznego

Liczba opublikowanych prac – 10:

1. **Pieniawska-Śmiech, K**., Bar, K., Babicki, M., Śmiech, K., & Lewandowicz-Uszyńska, A. (2020). Assessment of weight and height of patients with primary immunodeficiency disorders and group of children with recurrent respiratory tract infections. *BMC immunology*, *21*(1), 42.
2. **Pieniawska-Śmiech, K**., Kuraszewicz, A., Sado, J., Śmiech, K., & Lewandowicz-Uszyńska, A. (2021). Assessment of COVID-19 Incidence and the Ability to Synthesise Anti-SARS-CoV-2 Antibodies of Paediatric Patients with Primary Immunodeficiency. *Journal of clinical medicine*, *10*(21), 5111.
3. **Pieniawska-Śmiech, K.,** Lewandowicz-Uszyńska, A., Zemelka-Wiacek, M., & Jutel, M. (2022). Serum Allergen-Specific IgE among Pediatric Patients with Primary Immunodeficiency. *Children (Basel, Switzerland)*, *9*(4), 466.

4. **Pieniawska-Śmiech, K.,** Pasternak, G., Lewandowicz-Uszyńska, A., & Jutel, M. (2022). Diagnostic Challenges in Patients with Inborn Errors of Immunity with Different Manifestations of Immune Dysregulation. *Journal of clinical medicine*, *11*(14), 4220.

5. Rymaszewska, J., Urbanska, K., Szcześniak, D., Pawłowski, T., **Pieniawska-Śmiech, K**., Kokot, I., Pawlik-Sobecka, L., Płaczkowska, S., Zabłocka, A., & Stańczykiewicz, B. (2019). Whole-body cryotherapy - promising add-on treatment of depressive disorders. Krioterapia ogólnoustrojowa – obiecująca forma potencjalizacji leczenia zaburzeń depresyjnych. *Psychiatria polska*, *53*(5), 1053–1067.

6. Biela, M., Rydzanicz, M., Szymanska, K., **Pieniawska-Smiech, K**., Lewandowicz-Uszynska, A., Chruszcz, J., Benben, L., Kuzior-Plawiak, M., Szyld, P., Jakubiak, A., Szenborn, L., Ploski, R., & Smigiel, R. (2021). Variants of ATP1A3 in residue 756 cause a separate phenotype of relapsing encephalopathy with cerebellar ataxia (RECA)-Report of two cases and literature review. *Molecular genetics & genomic medicine*, *9*(9), e1772.

7. Kołtan, S., Ziętkiewicz, M., Grześk, E., Becht, R., Berdej-Szczot, E., Cienkusz, M., Ewertowska, M., Heropolitańska-Pliszka, E., Krysiak, N., Lewandowicz-Uszyńska, A., Mach-Tomalska, M., Matyja-Bednarczyk, A., Milchert, M., Napiórkowska-Baran, K., **Pieniawska-Śmiech, K.,** Pituch-Noworolska, A., Renke, J., Roliński, J., Rywczak, I., Stelmach-Gołdyś, A., … Pac, M. (2022). COVID-19 in unvaccinated patients with inborn errors of immunity-polish experience. *Frontiers in immunology*, *13*, 953700.

8. **Pieniawska K**, Śmiech K, Bar K, Pawlas K. Zawód przed zawodem - czy wypalenie może objawiać się już na studiach? Badanie populacji polskich studentów medycyny. *Medycyna Środowiskowa -Environmental Medicine*. 2017;20:22–31.

9. Pasternak G, **Pieniawska-Śmiech K**, Walkowiak M, Sado J, Pytel A, Jasińska P, Kierbiedź-Guzik N, Bolaczek P, Fleischer-Stępniewska K, Babicki M, Pentoś K, Lewandowicz-Uszyńska A. (2023). Before and After: Attitude and Adverse Effects Induced by the First and Second Doses of mRNA BNT162b2 Vaccine among Healthcare Professionals in the First Weeks after Their Introduction in Poland. *Vaccines*, 11(5):883.

10. **Pieniawska-Śmiech, K.,** Lewandowicz-Uszyńska, A., Zemelka-Wiacek, M., & Jutel, M. (2023). Assessment of autoantibodies in paediatric population with primary immunodeficiencies: a pilot study. BMC Immunology. DOI: 10.1186/s12865-023-00543-6

Liczba doniesień zjazdowych – 3

1. Biela, M., Rydzanicz, M., Szymańska, K., **Pieniawska-Śmiech, K**., Lewandowicz-Uszyńska, A., Chruszcz, J., Szenborn, L., Jakubiak, A., Płoski, R., & Śmigiel, R. (2022). Mutations of ATP1A3 in residue 756 cause a new phenotype, case report and literature review. *European Journal of Human Genetics*, *30*, 308–309 poz.P10.009.A.
2. Rymaszewska, J., Szcześniak, D., Trypka, E., Urbańska, K., Stańczykiewicz, B., **Pieniawska, K.,** Ubysz, J., & Zabłocka, A. (2017). Krioterapia ogólnoustrojowa a funkcje poznawcze u osób z zaburzeniami pamięci - wyniki wstępne. *Current Problems of Psychiatry*, 22.
3. Pawlik-Sobecka, L., Płaczkowska, S., Kokot, I., **Pieniawska, K**., Stańczykiewicz, B., Szcześniak, D., Urbańska, K., & Zabłocka, A. (2016). Wholebody cryotherapy as a novel supplementary treatment of memory deficits. W (Red.), *World Psychiatric Association International Congress „Psychiatry: integrative care for the community". Cape Town, South Africa, 18-22 November 2016. Accepted oral and poster abstracts, symposia and workshops NS - Neuroscience [online]* (s. 47–48 poz.670).

Rozdział w monografii

1. Pieniawska-Śmiech, K., Prościak, M., Lewicka, P., & Lewandowicz-Uszyńska, A. (2017). Choroba Kawasaki - problem ogólnopediatryczny. W I. Pirogowicz, B. Iwańczak, & A. Lewandowicz-Uszyńska (red.), *Dziecko - jego zdrowie i jego środowisko : objawy alarmowe w pediatrii z perspektywy gastroenterologa, ginekologa i immunologa klinicznego* (s. 90–98). Wrocławskie Wydawnictwo Naukowe Atla 2.