High prevalence of primary immune deficiencies in children with autoimmune disorders

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Abstract

Objective

Autoimmunity is a well-recognised manifestation of primary immunodeficiency disorders. However, the prevalence of primary immunodeficiency among children with autoimmune diseases is not well characterised. The objective of this retrospective study was to describe the prevalence of primary immunodeficiency disorders in a paediatric population with autoimmune diseases.

Patients and methods

We retrospectively analysed a cohort of patients investigated for diverse autoimmune conditions from June 1st 2005 to December 31st 2006 in the Rheumatology and Immunology service of a tertiary care paediatric hospital in Canada. The clinical data of patients were reported. Independently of their baseline characteristics, patients underwent a systematic immunologic workup, which was performed before treatment initiation.

Results

Thirty-three patients were included in this study. We identified 5 patients (15%) with a primary immunodeficiency disorder: common variable immunodeficiency (n=2), combined immunodeficiency (n=1) and complement component deficiency (n=2). Four other patients (12%) displayed decreased levels of immunoglobulins, B-cell lymphopenia and/or abnormal vaccinal response but did not fulfil the criteria of a defined primary immunodeficiency disorder at the time of the study. Importantly, none of these 9 patients had a particular familial history and none had a history of recurrent infections.

Conclusion

A significant proportion of patients presenting with an autoimmune condition have an underlying primary immunodeficiency disorder that may not be clinically obvious. Additional prospective investigations are needed to further define the role for routine immunologic testing in daily clinical rheumatologic practice.

Key words

Autoimmunity, primary immunodeficiency disorders, common variable immunodeficiency, combined immunodeficiency, complement component deficiency.

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Introduction

Although primary immunodeficiency disorders (PID) have traditionally been associated with recurrent infectious episodes, it is well recognised that entities such as autoimmune (AI), allergic and neoplastic disorders also belong to the PID spectrum. For more than three decades, numerous reports have confirmed that AI disorders are potential complications of PID. One association that often comes to mind is that of early complement component deficiencies and systemic lupus erythematosus (SLE) but virtually every type of PID can be complicated by AI manifestations. Various cohort studies of patients with common variable immunodeficiency (CVID) from different countries have shown that 22% to 50% will develop AI manifestations, the most frequent being idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AHA) (1-4). In addition, autoimmunity is the most prevalent disorder in selective IgA deficient individuals affecting up to 36% of them (5). In addition, autoimmunity may be the consequence of combined immunodeficiencies as reflected by the association of AI cytopenia in combined immunodeficiencies (CID) characterised by "leaky" defects in T cell development (6, 7). Autoimmune phenomenon also occur in some well-defined immunodeficiency syndromes as shown by the increased frequency of ITP and arthritis in DiGeorge syndrome and of AHA and vasculitis in Wiskott-Aldrich syndrome (8).

However, studies that specifically address the prevalence of PID in patients with AI disorders are sparse. To describe the prevalence of PID in a paediatric population with AI disorders, we performed a retrospective study in which the immune system of patients was systematically investigated in search of an immune deficiency.

Patients and methods

Patients

This retrospective study took place in the Immunology and Rheumatology division of CHU Sainte-Justine, a large tertiary care paediatric hospital in Canada. A chart review for every patient referred to the rheumatology clinic for diagnostic advice or therapeutic management of an AI condition between June 2005 and December 2006 was undertaken. Patients could have been referred from their family doctor, paediatrician or from any paediatric subspecialty. Only patients with well-recognised AI conditions, as listed in the NIH document entitled *Autoimmune Diseases Research Plan* were included in the study (9). Autoimmune neutropenia was also included despite its absence from the above-mentioned document.

Exclusion criteria

Patients specifically addressed to rule out an immunodeficiency disorder were excluded from this study, as were those with pre-existent immunosuppressive therapy, including corticosteroids, which could have biased the interpretation of

Table I. Baseline characteristics of patients*.

	All patients (n=33)
Female sex	23 (70)
Caucasian	23 (70)
Consanguinity†	0
Repeated infections suggesting a PID‡	0
Familial history of AI diseases	14 (42)
Mean age at onset of AI disease°	9 ± 4
AI conditions	36
Connective tissue diseases¶	12 (33)
AI cytopenia	7 (19)
Vasculitis	5 (14)
Hashimoto's thyroiditis	4 (11)
Crohn's disease	3 (8)
AI hepatitis	2 (6)
Alopecia areata	1 (3)
Guillain-Barré syndrome	1 (3)
Ocular myasthenia gravis	1 (3)
Patients with 2 AI conditions•	3 (9)

*Data are presented as number (%) unless otherwise specified.
† Data unavailable for 2 patients.
‡ As described in reference 10.
° Age in years ± standard deviation.
¶ Types of connective tissue diseases: SLE (6), localised scleroderma (4), Sjogren's syndrome (1) and mixed connective tissue disease (1).
• All 3 patients had Hashimoto's thyroiditis combined with other AI disorders: Evans syndrome, mixed connective tissue disease and autoimmune hepatitis.
PID: primary immunodeficiency; AI: autoimmune.

the immunological workup. In addition, because an immune workup was not systematically performed in patients with juvenile idiopathic arthritis (JIA) as it was done for other types of AI diseases (for limiting cost), these patients were excluded from the study in order to avoid having a significant number of incomplete data.

Data collected

Demographic variables examined were age, sex and ethnicity. Age at onset and the type of AI diseases were noted. Comorbidities associated with PID were inquired: pattern of infections suggesting an immunodeficient state (10), allergic disorders (asthma, eczema, allergic rhinitis, food allergies) and neoplasia. Familial history of AI disorders and consanguinity were also noted.

Immunological investigations

An immunologic workup was done for all patients, as it was part of the initial investigations for patients with AI conditions in our department. Parameters measured were: T cells subpopulations (CD3, CD4, CD8), naive CD4 T cells (defined as CD45RA+CD31+ cells among CD4+ cells), B cells (CD19) and memory B cells (CD27+ cells among CD19+ cells), NK cells (CD56+CD3-), plasma levels of immunoglobulins (IgG, IgG2, IgA, IgM and IgE), vaccinal responses (antibody titers considered were those measured after a booster dose if the initial vaccinal response was abnormal), complement component levels (C3, C4, CH50 and specific complement component levels when CH50 was low). In addition, a dihydrorhodamine 123 oxidation test was performed to exclude a chronic granulomatosous disease in patients with Crohn's disease. The diagnosis of PID was established and classified according to the criteria of the Pan-American Group for Immunodeficiency and of the European Society for Immunodeficiencies (11, 12). Patients fulfilling criteria for possible instead of probable PID were classified in the undefined PID group.

Approval for the present study was obtained from the Bioethics Board of CHU Sainte-Justine.

Results

From June 2005 to December 2006, 39 patients were referred for advice concerning diagnosis or therapeutic management of AI conditions other than JIA. Five patients were excluded because their pre-existent immunosuppressive therapy could have biased the interpretation of the immunological workup. In addition, one patient's chart was not available for review. Thirty-three patients were thus included in this study. The majority were girls, Caucasian and had only one AI disease. Complete demographic data and type of AI diseases are detailed in Table I.

Out of the 33 patients, 24 (73%) had a normal immunological workup and 9 patients (27%) were found to have an abnormal immunological workup. Among these 9 patients, 5 (15% of the study population) had a well-defined PID (PID group: patients 1 to 5) and 4 (12 % of the study population) did not fulfil the criteria of a defined PID (undefined immunological abnormalities group: patients 6 to 9).

Of the 5 patients in the PID group, 1 had CID (patient 1), 2 had CVID (patients 2 and 3) and 2 had a complement component deficiency (patient 4 with C1q deficiency and patient 5 with partial C2 deficiency). The complete immunological workup of these 5 patients and their respective AI disease are shown in Table II. The immunological abnormalities

Table II. Immune workup of patients in the PID and undefined immunological abnormalities groups.

	Sex	Age~	AI conditions	IgG°	IgG2*	IgA†	IgM‡	T cells (10^6/L)	Naïve CD4+ T cells¥ (10^6/L)	Memory B cells•	Vaccine response			PID
											MMR	Hib	DT	
1	M	15	Pancytopenia	N	0.58	<0.10	N	N	2%	3%	a	a	a	CID
2	M	15	Hashimoto's thyroiditis	4.15	N	0.43	N	N	N	N	N	N/A	d	CVID
3	F	15	ITP	3.77	0.60	<0.10	N	N	13%	5%	N/A	↓	a	CVID
4	M	9	SLE	N	N	N	N	N	N/A	N/A	N/A	N/A	N/A	C1q deficit
5	F	16	SLE	N	N/A	N	N	N	N	N	N/A	N/A	N/A	Partial C2 deficit
6	F	15	Crohn's disease	6.20	N/A	N	0.30	N	N	5%	N	N/A	a	Possible CVID
7	M	14	Alopecia areata	N	N	<0.10	0.23	N	N	6%	N	N	d	Possible CVID
8	F	14	CPA	N	N	N	N	N	N	3%	N	N	N	-
9	F	9	LSc	N	N	N	N	N	N	4%	N	N/A	N	-

Values that are abnormal are quantified with the lowest abnormal value shown.

~Age in years at initial immunological investigation; °IgG normal range between 9 and 16 years old: 6,89 - 16,42 g/L; *IgG2 normal range between 9 and 16 years old: 1,99 - 5,27 g/L; †IgA normal range between 9 and 16 years old: 0,65 - 4,02 g/L; ‡IgM normal range between 9 and 16 years old: 0,56 - 1,84 g/L; ¥Defined as CD31+CD45RA+/CD4+ cells; normal range between 9 and 16 years old: 30-70%; •Defined as CD27+ cells among CD19+ cells; normal value >10%.

AI: autoimmune; MMR: measle, mumps, rubella vaccine; Hib: haemophilus influenza b vaccine; DT: diphteria tetanos vaccine; PID: primary immunodeficiency disorder; M: male; F: female; N: normal; a: absent vaccinal response; N/A: not available; d: dissociated vaccinal response; ↓: decrease; CID: combined immunodeficiency; CVID: common variable immunodeficiency; ITP: idiopathic thrombocytopenic purpura; SLE: systemic lupus erythematosus; CPA: cutaneous polyarteritis nodosa; LSc: localised scleroderma.

found in patient 1, 2 and 3 were persistent over an observation period ranging from 2.5 to 4 years. Patient 4 had undetectable level of C1q confirmed on 2 occasions. Similarly, patient 5 had low levels of C2 confirmed on 2 occasions. Patient 1 underwent testing of the common cytokine receptor gamma-chain gene that was normal. Notably, no patient had more than one AI disease or a history of repeated infections.

Among patients in the undefined immunological abnormalities group, 2 had decreased levels of immunoglobulins (IgG and IgM in patient 6, and IgA and IgM in patient 7) and decreased memory B cells associated with an abnormal vaccinal response, thus fulfilling the criteria for possible CVID (patients 6 and 7) (11). The other 2 patients had an isolated diminution of memory B cells (patients 8 and 9). The details of their immunological workup are also displayed in Table II. All patients in the undefined immunological abnormalities group showed persistent abnormal immune workups over an observation period ranging from 1 to 4.5 years.

As shown in Table III, the age of onset of autoimmunity was similar between the normal immune workup and PID groups, and patients with multiple AI diseases were only recovered in the normal immune workup group.

Table III. Comparison of patient characteristics between groups*.

	Normal immune workup (n=24) n (%)	PID (n=5) n (%)	Undefined immunological abnormalities (n=4) n (%)
Female sex	18 (75)	2 (40)	3 (75)
Caucasian	15 (63)	5 (100)	3 (75)
Familial history of AI diseases	10 (42)	2 (40)	2 (50)
Repeated infections suggesting a PID†	0	0	0
Allergic disorders	11 (46)	3 (60)	1 (25)
Mean age at onset of AI disease (years)‡	8 ± 5	8 ± 4	11 ± 2
AI conditions	27	5	4
Connective tissue diseases	9 (33)	2 (40)	1 (25)
AI cytopenia	5 (19)	2 (40)	0
Vasculitis	4 (15)	0	1 (25)
Hashimoto's thyroiditis	3 (11)	1 (20)	0
Crohn's disease	2 (7)	0	1 (25)
AI hepatitis	2 (7)	0	0
Alopecia areata	0	0	1 (25)
Guillain-Barré syndrome	1 (4)	0	0
Ocular myasthenia gravis	1 (4)	0	0
Patients with 2 AI conditions	3 (13)	0	0

*Data are presented as number (%) unless otherwise specified; †As defined by the Jeffrey Modell Foundation; ‡ Age in years ± standard deviation.
PID: primary immunodeficiency; AI: autoimmune.

Discussion

By systematically exploring the immune system of a cohort of paediatric patients with various AI conditions**,** we found a PID in a significant proportion (15%) of them. Moreover, when patients with undefined immunologic abnormalities were added, 27% of the AI cohort displayed an underlying dysimmunity. In the literature, other authors have shown that PID, including IgA deficiency, are more prevalent in patients with AI disorders. Liblau *et al*. reported that up to 4.6% of SLE and up to 4.3% of JIA patients were IgA deficient which is 10 to 20 times higher than the prevalence reported in the general population (5). Nevertheless, the immunological abnormalities that we found in our cohort are much more severe than an isolated IgA deficiency. It is noticeable that none of patients with well-defined PID or with abnormalities in their immunological workup had a positive infectious history. These findings emphasise the fact that autoimmunity may be the only manifestation of a PID and that the absence of a positive infectious history is not sufficient to exclude a PID.

Our findings are in agreement with previous studies as they show that humoral deficiencies are the most common PID linked to AI manifestations (8). Indeed, apart from the 2 patients with complement component deficiency, the remaining patients in the PID group and all of our undefined immunologic abnormalities patients had a dysfunctional humoral system that was expressed by low levels of one or more immunoglobulin isotypes and/or diminished memory B cells. Only one patient (patient 1) had a combined immunodeficiency. The mechanisms by which humoral deficiencies lead to autoimmunity are still not completely understood. A review by Brandt *et al*. has proposed different hypotheses including the effect of persistent antigen exposure, sharing of certain HLA alleles and the presence of variant of TNF and MBL alleles (13). Cytokine dysregulation and breakdown in central and peripheral tolerance induction and maintenance are other likely mechanisms that may induce autoimmunity in CVID patients (4). Of interest is the fact that all 4 patients with undefined PID displayed a significant diminution of their memory B cells. It has been suggested that among patients with CVID, those with absent or diminished switched memory B cells are at risk of subsequently developing an AI disorder (14).

Autoimmunity is also considered a hallmark of T cell deficiencies, and AI cytopenia are common in CID characterised by "leaky" defects in T cell development (6, 7, 15). Recently, authors have explored the link between autoimmunity and severe combined immunodeficiency and have outlined the role of defective central and peripheral tolerance in the expansion of a population of self-reactive T cells and, subsequently, the development of autoimmunity (6). The role of AIRE and FoxP3 in T cell homeostasis has also been addressed (6).

In our study, complement component deficiencies accounted for 40% of PID found. As is traditionally seen, early rather than terminal complement effectors were involved in the 2 patients who were both afflicted with SLE. Of note, patient 5 was diagnosed with partial C2 deficiency for which the etiopathogenic

link with SLE is not yet proven (16).
Selective IgA deficiency was not detected in our cohort of patients, which may seem surprising since this is the most common form of PID (1 in 600 individuals) (8). Possible explanations could be that our cohort of patients was too small. In addition, it could result from the exclusion of JIA patients, in which selective IgA deficiency is known to be prevalent (5).
The specific types of AI diseases in our cohort of PID patients, except for a Hashimoto's thyroiditis in a patient with CVID, were in accordance with the usual associations found in the literature. Indeed, CVID patients have a 22–50% incidence of autoimmunity that most frequently takes the form of arthritis, inflammatory bowel disease-like colitis or other visceral granulomatous diseases and immune cytopenia (2-4, 8). The latter AI manifestation is also frequently associated with T cells deficiency or CID (6, 7, 15).
The consequences of identifying a PID are broad and extend beyond simple recognition of the disease. First, it allows establishing intravenous immunoglobulins (IVIG) replacement therapy and antibioprophylaxis, if indicated. In our cohort of PID patients, those who were diagnosed with CVID and CID were started on monthly IVIG therapy, in accordance with current practice guidelines (17). None of these patients had a history of recurrent infections but they all displayed an abnormal or absent vaccinal response and a low levels of at least 2 subtypes of immunoglobulins. These findings were felt to be significant, putting these patients at risk of ultimately developing infectious complications that could have been preventable with IVIG replacement therapy. Although no prospective studies have shown that IVIG replacement therapy in patients with humoral immunodeficiencies exerts an influence on the course of the AI disease or prevents the occurrence of some of the complications and associated conditions, these potential benefits were considered when the decisions of starting IVIG were made in our patients. One mechanism by which replacement doses of IVIG could prevent AI manifestations could be by preventing persistence of certain infectious agents (18). A recent report showed that the majority of patients with CVID developed hematologic AI disease before being supplemented with IVIG replacement therapy, suggesting that the latter treatment diminishes the occurrence of these conditions (19). Interestingly, the AI conditions of patients 1, 2, 6 and 7 improved while receiving IVIG replacement therapy. No improvement was noted for patient 3. In addition, the choice of immunosuppressive agents will require careful selection (20), keeping in mind the type of defective immune mechanism. Proceeding to a systematic immune workup screening in patients with AI disorders would also enable clinicians to identify patients with overt dysimmunity, some of whom being in the early stage of an evolving PID. Immune surveillance could therefore allow earlier targeted diagnosis. A recent study done in 32 children with CVID showed that delayed diagnosis of the immunodeficient state led to serious complications as 28% of patients had significant growth retardation (with height below the third percentile) and 16% of them had delayed development. Moreover, 13% of their cohort developed a neoplasia during the follow-up period (21). In accordance, the patients in our study with an altered immune profile who did not fulfil the criteria of a defined PID will need close follow up and repeated testing as they may evolve into an overt PID.
Our study has several limitations. First, the high proportion of patients found with an underlying immune disorder may be explained in part by a selection bias. The study took place in a tertiary care paediatric reference centre and consequently, we may have selected a baseline cohort of patients with more complex AI diseases who were at heightened risk of having an underlying PID. Secondly, some of the subspecialists may manage initially some of the AI conditions and refer the patients to our division only for recurrences or resistant disease or if an underlying systemic AI disease is suspected (AI cytopenia managed initially by the haematologist). As stated above, these cases may be more at risk of having an underlying immune dysfunction. In addition, by excluding JIA patients, which represent an important number of individuals, our baseline population of patients was smaller and hence it could have overestimated the percentage of PID. In addition, the present study do not allow one to associate certain types of PID with specific AI diseases, as our cohort of patient was too small to permit derivation of generalities.
Our findings must be considered exploratory as they come from a small retrospective cohort of children with various AI conditions, coming from a single centre and short-term experience, and would need to be validated in a prospective fashion and on a larger scale. Nevertheless, despite these limitations, our hypothesis is that PID is under diagnosed and by systematically exploring patients with AI diseases, a higher proportion of abnormal immune workup may be found.
In summary, a significant proportion of paediatric patients evaluated for an AI condition were found to have an underlying PID. Additionally, an altered immune profile not fulfilling the diagnosis criteria of a PID was present in a sizeable proportion of patients. For the vast majority of these patients, the only clinical manifestation of the immunodeficient status was autoimmunity. The results of our study emphasise the close relationship between autoimmunity and PID. Larger scale prospective multicentric trials are needed to confirm our findings. Studies specifically addressing the impact of systematic screening in search of a PID in patients with AI diseases are also awaited.

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