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SCIENTIFIC LETTER

Usefulness of a specialised primary immunodeficiencies clinic☆

Utilidad de una consulta especializada en inmunodeficiencias primarias

Dear Editor:

Primary immunodeficiencies (PIDs) are diseases said to be ''rare''. Although their individual prevalence is low, each year new genes are found that are associated with immunodeficiency. At present, there are 340 known defects, when in 2000 fewer than 100 had been identified.[1] These diseases may be more prevalent than previously thought. It is estimated that 1 in 2000 individuals has a PID,[1,2] a prevalence that is higher than that of leukaemia in the United States.[2]

Primary immunodeficiencies may have onset with recurrent infections in childhood, although at times they manifest as autoinflammation or autoimmunity.[1,3] These less typical presentations may result in delay diagnosis, when early identification has an impact on outcomes, prevents morbidity and reduces mortality in PIDs requiring stem cell transplantation.[3]

In 2012, a specialised clinic was created within our department for follow-up of patients with confirmed PID and screening of patients with suspected PID. From its inception to 2017, the clinic has provided care for 135 children, 57% of who were referred in the past 2 years and 41% in 2017.

Of this total, 57% of patients have PID confirmed by the Department of Immunology of our hospital (77/135) and 15% are still under evaluation (21/135), while PID was ruled out in the remaining 27% (37/135). Of the children referred from other hospitals, 78% had a PID (25/32), as did 50% of children referred from other departments in our hospital (39/79) and 42% of children referred from primary care (8/19) ($P = .009$). The reason for referral was severe/recurrent infections in 51% (69/135), diagnosis of PID in 22% (30/135), lymphopaenia or hypogammaglobulinaemia in 19% (26/135), family history of PID in 6% (8/135) and delayed separation of the umbilical cord in 1.4% (2/135). Before referral, 20% were receiving antibiotic prophylaxis or immunoglobulin replacement therapy (28/135).

Table 1 summarises the diagnosed PIDs, and Fig. 1 the characteristics of the patients. A history of consanguinity was present in 9% of patients (6/71). All children with symptomatic infection by cytomegalovirus ($n = 6$) had a PID.

Of all patients with PID, 34% required admission at the time of the first visit (26/75) compared to 11% of patients ultimately found to be healthy (4/37) ($P = .006$). Of the children with PID referred from a different hospital, 68% (17/25) were admitted at the time of the first visit, as were 18% (7/39) of those referred from another department in our hospital and 12% (1/8) of patients referred from primary care ($P = .0001$).

Fifty-seven percent of children with PID required immunoglobulin replacement therapy (42/74) and 41% antibiotic prophylaxis (31/75), while 36% underwent or require stem cell transplantation (28/77). The mortality in our study was of 13% (10/77).

Each passing day, we learn of additional genetic abnormalities associated with PIDs. These diseases carry a high morbidity and mortality, especially in cases of delayed diagnosis. Recurrent infection is a frequent reason for consultation and determining which patients require an immunologic evaluation is challenging. A history of consanguinity is a risk factor that should alert clinicians of the possibility of a PID. A recent case series of children with a history of recurrent infection found that 21% had a PID,[4] a high prevalence that could be explained by the large proportion of consanguinity (38%).

However, infection is not always the initial presentation. In recent years, the classic signs used to detect PIDs have been questioned,[5] as they cannot be used to identify patients with PID due to immune dysregulation, who have onset with autoimmunity or inflammation. Fischer et al. have reported that children with PID have a risk that is 830, 80 and 40 times greater of haemolytic anaemia, inflammatory bowel disease and rheumatoid arthritis, respectively, compared to the general paediatric population.[6]

The data suggest that failure to thrive, symptomatic cytomegalovirus infection and a family history of PID are relevant warning signs.[3–5] Patients with more severe disease, referred from hospitals or requiring admission are also at higher risk.

We have recently observed an increase in the referral of patients, many with well-founded diagnostic suspicion and more than half with a final diagnosis of PID. This is due to the increasing number of cases diagnosed in the Department of Immunology of our hospital and the growing awareness of referring physicians of the existence of this specialised clinic.

Referred patients get appointments in a paediatrics clinic that does not have a waitlist. When the reason for referral is recurrent infection or suspected PID, patients are managed

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Table 1 Diagnosis in patients with PID managed in our clinic according to the most recent classification of the International Union of Immunological Societies.

Diagnosed PID	Patients
1. Combined IDs	50% (39/77)
SCID	
Adenosine deaminase deficiency	4
γc deficiency	4
RAG2 deficiency	2
CD3δ deficiency	2
DCLRE1C (Artemis) deficiency	1
RAG1 deficiency	1
SCID without molecular confirmation	2
Non-severe CID	
MHC class II deficiency	4
CD40 ligand deficiency	1
CID with associated or syndromic features	
Ataxia-telangiectasia	4
DiGeorge syndrome	4
Kabuki syndrome	2
Dyskeratosis congenita	2
Wiskott-Aldrich syndrome	2
Cartilage hair hypoplasia	1
Immunodeficiency with multiple intestinal atresias (TTC7A)	1
Calcium channel defects (ORAI-1)	1
Autosomal dominant hyper-IgE syndrome (STAT3)	1
2. Predominantly antibody deficiencies	34% (26/77)
X-linked agammaglobulinaemia	8
Selective IgA deficiency	8
Common variable immunodeficiency disorder	7
Specific antibody response absence	2
Subclass deficiency	1
3. Diseases of immune dysregulation	4% (3/77)
ALPS-caspase 10	2
CTLA-4 deficiency	1
4. Congenital defects of phagocyte number or function	6% (5/77)
Chronic granulomatous disease	5
5. Defects in innate immunity	1% (1/77)
IL-12 receptor β deficiency	1
6. Complement deficiency	4% (3/77)
CD46 deficiency	3

Source: Adapted from Picard et al.[1]
CID, combined immunodeficiency; SCID, severe combined immunodeficiency.

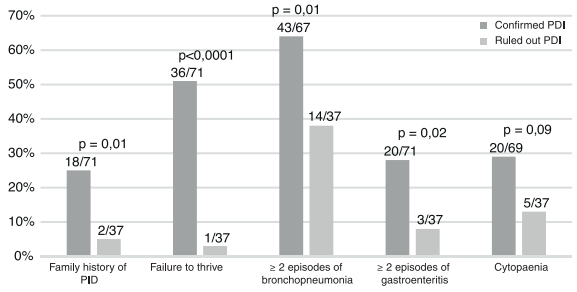

Figure 1 Personal and family history in children in who PID was confirmed and ruled out.

by paediatric specialists and a team of clinical immunologists.

There are limitations to our findings. Due to the retrospective nature of the analysis, there were incomplete data, as some variables were not documented in the records of some of the patients. Since the study was not multicentric, it contributes a particular perspective of the patients managed in a hospital with specific characteristics. Nevertheless, our findings reflect the increasing need for this type of clinic as a resource for paediatricians, so early and appropriate care can be offered to these children, thus reducing the associated morbidity.

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Cold urticaria and coeliac disease in a paediatric patient☆

Urticaria por frío y enfermedad celiaca en paciente pediátrico

Dear Editor:

Cold urticaria (CU) is a chronic form of urticaria that may be associated with various systemic disorders. Coeliac disease (CD) is also commonly associated with other disorders, usually of the immune system.

To date, there have been several descriptions of the association between CD and chronic idiopathic urticaria in children,[1] but we only found 1 case in the reviewed literature with diagnosis of CD in a patient with a previous history of CU where the cutaneous manifestations improved after excluding gluten from the diet.[2]

Given the current scarcity in the literature of data on the association between these two conditions, we considered that the description of this case of diagnosis of CD in the context of CU would be of interest.

The patient was a boy aged 5 years assessed due to episodes of urticaria in areas of the body exposed to environmental coldness with onset 2 months prior, manifesting with nasal itching in the absence of other mucosal, cutaneous, respiratory or gastrointestinal symptoms, and improving on returning to warmer settings. The episodes occurred in the absence of previous exercise, intake of drugs or intercurrent infection. The patient did not experience symptoms after bathing in the sea or a pool. The personal and family histories were unremarkable except for a history of rhinitis, hay fever and penicillin allergy in the mother.

The patient had a positive ice cube challenge and received a diagnosis of CU. Further tests included a complete blood count and chemistry panel, measurement of basal tryptase, C-reactive protein, thyroid-stimulating hormone, free thyroxine, anti-thyroid stimulating immunoglobulin and total IgE, total complement test (C3, C4 and C1 inhibitor) and determination of immunoglobulins, antinuclear antibodies, rheumatoid factor and cryoglobulins, all with normal results. The salient findings were serum levels of deamidated antigliadin (DMG) IgG antibodies of 7.3 AU/mL, anti-transglutaminase antibodies (ATA) IgA 11.6 AU/mL and anti-thyroid peroxidase (anti-TPO) antibodies of 63 IU/mL. The patient was instructed to take measures to avoid the cold and to maintain his usual diet without restrictions.

Three months later the patient remained free of gastrointestinal or systemic manifestations and occasionally exhibited very mild facial urticaria after exposure to cold. Laboratory tests revealed levels of DMG IgG of 58 AU/mL, ATA IgA of 66 AU/mL, ATA IgA greater than 200 AU/mL, with a positive result for detection of anti-endomysial antibodies (EMA) (titre of 1:160) and molecular detection of HLADQ2 (DQA1*05 B1*02) suggestive of sensitivity to gluten. The thyroid function was normal, with a negative result for anti-TSI and a level of anti-TPO of 54 IU/mL.

The patient received a diagnosis of CD and was prescribed a gluten-free diet, after which he exhibited a progressive decrease in the antibody levels, reaching normal values at 10 months, with improvement of cutaneous symptoms.

Cold urticaria is the fourth most frequent cause of chronic urticaria, with an estimated incidence of 0.05%. It can develop at any age, with a higher prevalence between ages 18 and 25 years and a predominance of the female sex (2:1). The diagnosis is based on a compatible history with development of symptoms on exposure to cold stimuli (environment, oral intake, contact) and a positive ice cube challenge. It can be inherited or acquired, and primary or secondary to systemic disorders (such as cryoglobulinemia, vasculitis, infection, hypothyroidism or blood disorders).[3]

Coeliac disease mainly affects individuals with a genetic predisposition (HLA DQ2/DQ8) and is frequently associated with other immune disorders, such as chronic idiopathic urticaria, diabetes type 1 or autoimmune thyroiditis, among others. In the case presented here, the diagnosis of CD was made based on the ESPGHAN5 criteria (presence of

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