Letters to the Editors

Hyper-IgD syndrome in a patient with IgA immunodeficiency

Sirs,

A 9-year-old Greek girl, presented with a three-day history of myalgias, fever up to 40^0 C and erythematous cutaneous plaques. Family history was unremarkable. From her past medical history, she had recurrent infections (pneumonia, staphylococcus dermatitis, tonsillitis), transient knee monoarthritis and selective IgA immunodeficiency which was revealed five years ago during investigation for febrile cervical lymphadenopathy.

Physical examination showed warm, erythematous plaques on her upper and lower extremities. Blood tests revealed neutrophilic leukocytosis, normochromic, normocytic anaemia and elevated acute phase reactants (Table I). Repeated blood, throat and urine cultures as well as the antibodies against Mycoplasma pneumoniae, Adenovirus and Epstein-Barr were all negative. Chest x-ray, abdominal ultrasound and angiotensin-converting enzyme (ACE) were normal. Antinuclear and anti-neutrophil cytoplasmic antibodies were not detected and C3 and C4 serum levels were within normal limits. Polyclonal hypergammaglobulinaemia was noticed and measurement of serum immunoglobulins showed elevated IgD levels: 880 IU/ml (normal value: <100 IU/ml) and very low IgA levels: 6 mg/dl (normal value: 34-305mg/dl). Peripheral blood genetic analysis revealed two heterozygous mutations, p.G376S and p.V377I, on exon 11 of the Mevalonate Kinase (MVK) gene, which confirmed the diagnosis of hyper-IgD syndrome (HIDS). Spontaneous recovery was noticed awaiting laboratory results. Next flare was treated with Canakinumab, with very good response. Clinical symptomatology subsided and inflammation markers returned to normal (Table I). One year later, the child is symptoms-free.

HIDS is an autosomal-recessive inherited autoinflammatory condition, caused by mutations in the mevalonate kinase (MVK) gene, which lead to decreased activity of this enzyme (1). MVK participates in the synthesis of cholesterol and non-sterol isoprenoids (2). Its deficiency leads to a shortage of isoprenoids participating in geranylgeranylation of proteins (3), inactivating thus RhoA GTPase and subsequently contributing to activation of pyrin inflammasome. This, in turn, primes overproduction of IL-1b which appears to be a key player in the pathogenesis and clinical expression of HIDS (4, 5). It is still unclear, if the accumulated substrate of mevalonate acid (MVK) contributes to inflammatory response (1).

HIDS usually presents in early childhood with recurrent episodes of fever lasting 3–7 days (6). Common clinical manifestations include gastrointestinal symptomatology, arthritis, lymphadenopathy, liver and spleen enlargement. Skin involvement is present in more than half of the patients. The most common forms are maculopapular and urticarial rash while purpuric rash and erythema nodosum – as in our case-have also been reported (6). Laboratory features include leukocytosis and elevated acute-phase reactants. Mevalonic acid may be detected in urine during febrile episodes (2).

Table I. Selection of laboratory parameters measured at the time of diagnosis and 1 month after treatment with Canakinumab.

Parameter	At the time of diagnosis	After treatment with Canakinumab
White blood cells (mm^3)	14.200	4.950
Neutrophils (%)	84%	51%
Haemoglobin (gr/dl)	9.1	11.9
Platelets (mm^3)	324.000	207.000
ESR (mm/hr)	128	27
CRP (mg/dl)	190,0	6,9
IgD (IU/ml)*	880	NM
IgA (mg/dl)¶	6	NM
SAA (mg/dl)§	787	6
Ferritin (ng/ml)#	183	13

ESR: erythrocyte sedimentation rate. CRP: C-reactive protein, IgD: Immunoglobulin D, IgA: Immunoglobulin A, SAA: serum amyloid A, NM: not measured. *normal values: <100 IU/ml, ¶normal values: 34–305 mg/dl, §normal values: <6.4 mg/dl, #normal values 12–73 ng/ml.

Treatment could be challenging. Non-steroidal anti-inflammatories and disease modifying antirheumatic drugs have been used with limited success. Steroids given early at attack onset seem to be beneficial. Biologic treatment with anti-IL-1 regimes (Anakinra, Canakinumab) and Etanercept, appears to be the most effective, while Tocilizumab has also been used (7).

Serum IgD levels are elevated in about 80% of the patients (6), while IgA is also increased in more than half of HIDS patients (6). Interestingly, our patient had selective IgA deficiency. The latter has a range of clinical manifestations, like allergies, gastrointestinal disorders and recurrent sinopulmonary infections, as in our case, but most patients are asymptomatic (8). Its pathogenesis is largely unclear, however there seems to be an impaired ability for B cells to be switched to IgA secreting plasmacytes. Aberrancies in T cells and in various cytokines as well as several mutations associated with sIgA immunodeficiency have been also described (9). sIgA immunodeficiency has been associated with a variety of autoimmune diseases (10) but it has not been described in patients with autoinflammatory syndromes.

In conclusion, we describe the first patient with HIDS combined with sIgA deficiency, highlighting that these are not mutually-exclusive diagnoses.

Aknowledgements

We would like to thank Prof. Haralampos M. Moutsopoulos for critically reviewing our manuscript and for his continuous mentorship, guidance, inspiration, and support.

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Competing interests: none declared.

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