

## **Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome: a rare cause of food allergy and enteropathy**

### **Background:**

This case report discusses the clinical course and diagnostic pathways of an infant with an extremely rare condition termed IPEX syndrome (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked).<sup>1</sup> This is the first reported case of IPEX syndrome in South Africa.

### **Case Presentation**

#### *Clinical Course in the first 4 months of life*

Patient CZ, a firstborn male of Caucasian ethnicity, was born prematurely at 32 week's gestation to non-consanguineous parents. He initially exhibited symptoms of a transient hyperinsulinaemia, with macrosomia and hypoglycaemia. These symptoms settled after a few weeks, and normoglycaemia ensued. However, from the time of introduction of enteral feeds, he began having severe diarrhoea, even whilst receiving breast milk exclusively. A spiral of intractable diarrhoea, severe reflux, discomfort and failure to thrive followed, intertwined with recurrent episodes of sepsis which caused significant setbacks. The diarrhoea was predominantly secretory in nature, with episodes of bloody diarrhoea during some of his deteriorations. The little boy had ongoing severe diarrhoea with intake of expressed breast milk (even with strict maternal exclusion diet), soya as well as extensively hydrolysed formula. He was eventually started on an amino acid formula which he tolerated in small amounts.

The patient was furthermore noted to have a diffuse eczematous rash and mildly dystrophic finger nails. He had 3 episodes of unexplained transient diffuse urticarial rash which responded to antihistamine therapy.

In view of the intractable diarrhoea, an upper GIT endoscopy and colonoscopy were performed at 5 and 9 week's age respectively. Biopsy results were reported as follows:

- Oesophagus: Features consistent with reflux oesophagitis
- Gastric antrum: moderate chronic inflammation, increased eosinophils
- Duodenum: Lymphocytic duodenitis with villous atrophy
- Colon: features of chronic inflammation with numerous eosinophils in lamina propria

In the interim, he required prolonged bouts of parenteral nutrition through a central line in order to sustain growth. This was associated with further episode of sepsis, associated with significant relapse in diarrhoea and hypoalbuminaemia. *Klebsiella* species were grown on 2 blood cultures; several other febrile episodes had negative cultures. Each septic episode led to general deterioration, increased diarrhoea, feed intolerance and bone marrow suppression. He required several transfusions of packed red cells as well as platelets.

A total serum IgE level at 4 month's age was found to be extremely high >5000 kU/L, with normal IgG, A and M levels.

#### *Months 4-6*

As the aetiology of his enteropathy and recurrent sepsis remained unclear, and in view of the gut eosinophilia and extremely high IgE level, the patient was transferred to Vincent Pallotti hospital for an allergology assessment at the age of 4 months. On arrival he exhibited signs of malabsorption

with hypoalbuminaemia and growth faltering, and was also noted to have eczema and hepatosplenomegaly. He had patches of skin hyperpigmentation. He was noted to be persistently lymphopaenic, and rapidly became anaemic and thrombocytopaenic with each intercurrent septic episode. Moreover, he had haematuria (which became macroscopic during septic episodes) and persistent proteinuria, associated with a high blood pressure. Liver function tests were persistently deranged. His specific IgE levels to cow's milk protein came back high at 63.6 kU/L (casein 46.8 kU/L), IgE levels to several other foods (egg, wheat, soya, peanut, maize, coconut) were elevated to a lesser degree, with specific IgE levels ranging between 0.8 and 1.32 kU/L.

The picture was one of "leaky gut syndrome" syndrome with poor gut barrier function, leading to infection and allergy. However, there also seemed to be unexplained endocrinological and immunological issues, not typical of a straightforward eosinophilic enterocolitis. A decision was made to start with methylprednisolone treatment, despite its immunosuppressive effects, in hope of reducing the gut inflammation; the rationale being that with ongoing gut leakiness the vicious spiral of malnutrition and sepsis would continue. The response to steroids was excellent and rapid, with normalising stools and tolerance to good amounts of amino acid formula within 2 weeks.

Further immunological testing was performed, showing *positive auto-antibodies* as follows:

- Anti-goblet cell IgG
- Anti-thrombocyte IgG
- Direct coombs tests positivity
- Anti-acinar cell antibody
- Anti-smooth muscle antibodies

He was negative to anti-enterocyte antibody, anti-islet cell antibody, anti-Liver,Kidney,Muscle and anti-mitochondrial antibody, ANA, Rheumatoid factor, and anti-thyroid antibodies. Thyroid function tests were normal and he remained normoglycaemic. Random serum cortisol levels were normal.

T cell immunophenotyping showed generally reduced T cell subsets (reduced CD4, CD8 and CD45) but normal B cell levels. CD4+CD25+CD127lo cells (a screening test for Regulatory T cells) were slightly reduced at 4.27% in comparison to control of 5.94%.

The combination of enteropathy, features of autoimmunity, eczema and recurrent sepsis in the context of food allergies and high IgE prompted a suspicion of IPEX or IPEX-like syndrome. DNA analysis for this condition was not available in South Africa, hence was performed at Exeter University in the United Kingdom. A mutation in the FOXP3 gene sequence was found with a missense mutation on Exon 12, c1157G>A with a resultant malfunctioning protein p.Arg386His. This particular mutation had been recognised before in a patient with IPEX syndrome.<sup>2</sup> The DNA sequence, in conjunction with the clinical scenario, confirmed a diagnosis of IPEX syndrome.

In consultation with a team of experts from Seattle University in the USA, the patient received 3 infusions of Rituximab (a chimeric monoclonal antibody against the protein CD20) at weekly intervals to effect B cell depletion, in view of the multiple autoantibodies. He was also commenced on tacrolimus, maintaining levels at 5-7 µg/L. Oral steroids were slowly weaned. No immunisations were given but he is currently on 3-4 weekly infusions of intravenous immunoglobulin. All parameters improved rapidly, including feed tolerance, growth, markers of nutrition, haematopoietic parameters and frequency of septic episodes. The patient is now 6 months old, being cared for lovingly at home, doing extremely well on amino acid formula (which he drinks avidly!), tacrolimus, minimal steroids and vitamin support. He is currently being prepared and matched for a bone marrow transplant.

## **Discussion: IPEX syndrome**

### *Aetiology and Pathogenesis*

IPEX syndrome stands for “immune dysregulation, polyendocrinopathy, enteropathy, X-linked” syndrome. The central pathogenesis of IPEX is T regulatory cell dysfunction as a result of mutations in the FOXP3 gene.<sup>3</sup> FOXP3 is a member of a family of transcription factors called the forkhead box P family, which are fundamental for the normal differentiation of T regulatory cells. The T regulatory cell is involved in immunosuppressive activities essential to acquiring and maintaining immune tolerance.<sup>4</sup> Quantitative or functional deficiency of T regulatory cells leads to dysregulation of immune homeostasis, leading to lack of “tolerance” as manifest by autoimmune disease and allergic inflammation.

Cases of IPEX syndrome have been described sporadically throughout the world,<sup>2,5</sup> but there are fewer than 200 published cases worldwide. It is probably underdiagnosed and underreported. This is the first recognised case of IPEX syndrome in South Africa.

Patients with IPEX syndrome usually present in infancy, though certain less severe phenotypes may present later in life.<sup>5,6</sup> It is an X-linked disorder, however mutations can be familial or sporadic. A thorough family history is important, especially of severe enteropathy or early unexplained demise in male infants of maternal family members. In this particular case, the maternal grandmother had 3 unexplained male infant stillbirths, hence genetic mutations in maternal female family members are currently being explored. Female carriers are asymptomatic.

### *Clinical Features*

The classical presentation of IPEX syndrome is the typical triad of:<sup>1</sup>

- Severe chronic refractory diarrhoea secondary to autoimmune enteropathy
- Dermatitis
- Autoimmune endocrinopathy (usually type I diabetes; sometimes thyroiditis)

usually in association with a markedly elevated IgE level.

However, the presentation may vary, and in the case described above, the typical endocrinopathies are not present.

Other associations are:

- Severe food allergies, usually IgE-mediated<sup>7</sup>
- Immune-mediated cytopenias
- Exaggerated response and increased susceptibility to infection
- Nephritis<sup>8</sup>
- Hepatitis
- Hepatosplenomegaly

All of the above features were exhibited to varying degrees by our patient in the case report, and improved dramatically on immunosuppressive therapy.

Typical disease flares with acute worsening of diarrhoea, dermatitis, cytopenias or glucose control may occur in response to infections, vaccinations and introduction of new dietary proteins. These flares, as manifest in the above case, can cause significant setbacks and morbidity.

### *Diagnosis:*

An accumulation of “clues” is necessary to work towards the diagnosis, as follows:<sup>9</sup>

- GIT endoscopy (findings are non-specific and include villous atrophy, especially in the small intestine, mixed cellular infiltrate, and sometimes crypt hyperplasia or abscesses.)
- Screening for autoantibodies (gut, thyroid, pancreas, blood cell lines)
- Regulatory T cell immunophenotyping
- Immunoglobulin levels (especially IgE)
- Screening for diabetes, hypoadrenalism and thyroid dysfunction
- Screening for food allergies
- Definitive diagnosis by gene analysis for FOXP3 mutations. FOXP3 mutations were first identified in the year 2000,<sup>10</sup> and several mutations have been identified to date.<sup>2</sup>

### *Management:*

#### **Acute management includes:**<sup>9</sup>

1. Supportive management of nutrition (may require TPN, usually require at least an extensively hydrolysed formula or amino acid formula), hydration, hypoalbuminaemia
2. Prompt and aggressive treatment of intercurrent infections
3. Blood products if needed for cytopaenias.
4. Management of endocrinopathies
5. Isolation to prevent nosocomial infections

#### **Chronic management includes:**

1. *Immune suppression:* induction therapy with high dose corticosteroids leads to rapid improvement in symptoms. Some centres are choosing to go straight for steroid-sparing immunosuppressants (personal communication-Troy Torgerson). Induction with a B cell depleting monoclonal antibody (Rituximab) is also sometimes used, as in this case.
2. *Steroid sparing agents:* tacrolimus, cyclosporine A and sirolimus have all been used as monotherapy or in conjunction with steroids.<sup>11</sup>
3. Identifying and avoiding *dietary allergens*; and optimising nutrition
4. *Avoiding vaccinations;* instead providing immune support with 3-4 weekly intravenous immunoglobulins

#### **Definitive management: Haematopoetic Cell Transplantation (HCT)**

IPEX syndrome carries a poor prognosis without effective immunosuppression and intensive supportive treatment. Haematopoetic stem cell transplantation offers the only potential cure.<sup>12</sup> It seems the earlier the HCT is performed, the greater the potential for cure before long term end organ damage has occurred. Moreover, the “healthier” and less compromised the patient is at the time of HCT, the better the results.<sup>5</sup>

### *Conclusion:*

IPEX syndrome is an extremely rare immunological disorder with multisystem involvement stemming from genetic mutations in the FOXP3 gene. It is an example of how immune dysregulation can lead to autoimmunity and allergic manifestations in combination. Cases are likely underreported, and a

high index of suspicion is need to pursue the diagnosis. However, the earlier the diagnosis is made and therapy instituted, the better the long term prognosis.

## References

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Photograph showing acute urticarial rash in the patient in conjunction with background eczema (kindly provided by the baby's parents).