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Case report

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome in two siblings; same mutation but different clinical manifestations at onset

Short title: Different clinical findings of IPEX syndrome

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What is already known on this topic?

Though enteropathy, endocrinopathy and skin manifestations are considered the classic triad IPEX syndrome, it is clinically characterized by a wide spectrum of severe autoimmune diseases. The absence of the classic clinical triad of the disease may have led to a delay in diagnosis of IPEX syndrome.

What this study adds?

IPEX syndrome can present different clinical presentation in siblings despite having the same mutation of FOXP3 gene. IPEX syndrome should be suspected in any male infant not only who had classical triad but also who had only one main disorder related to IPEX syndrome like infantile diabetes.

Abbreviations

AHA: Autoimmune hemolytic anemia

FOXP3: Forkhead box protein 3

HbA1c: Hemoglobin A1c

HSCT: Hematopoietic stem cell transplantation

IPEX: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked

Abstract

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is an early onset systemic autoimmune genetic disorder caused by mutation of the *forkhead box protein 3 (FOXP3)* gene. Enteropathy, endocrinopathy and skin manifestations are considered the classic triad of IPEX syndrome. However, the patients with IPEX syndrome display a variety of phenotypes including life threatening multi-organ autoimmunity.

Here, we present the case of two siblings with IPEX syndrome with the same hemizygous mutation, but with different types of symptomology at onset of the disease.

Keywords: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; neonatal diabetes; renal disease

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Introduction

Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is an early onset systemic autoimmune genetic disorder caused by mutation of the *forkhead box protein 3 (FOXP3)* gene. FOXP3 is located in the short arm of the X chromosome (Xp11.3-q13.3). The FOXP3 gene regulates production and function of the FOXP3 protein which is essential for the regulatory function of T regulatory (T_{reg}) cells (1,2). T_{reg} suppresses several functions of neighboring T effector (T_{eff}) cells. Treg cell dysfunction is the main cause of immune dysfunction including severe enteropathy, type 1 diabetes, and dermatitis in IPEX syndrome. However, persistent autoreactive B cells and autoreactive T_H17 cell expansion contribute to autoimmune disorder in this syndrome (1-3). Recurrent infections, hemolytic anemia and cytopenia, autoimmune thyroiditis, and other autoimmune disorders like hepatitis and nephritis are additional manifestations of IPEX syndrome (3).

IPEX syndrome is clinically characterized by a wide spectrum of severe autoimmune diseases, but the patients with IPEX syndrome commonly present with early onset intractable diarrhea within the first weeks of life. If not treated, most patients die within the first two years of life because of the consequences of the autoimmune manifestations, sepsis, and complications from failure to thrive (2). Nevertheless, there are some reported patients with longer life. The type and severity of symptoms and the onset of the IPEX syndrome may differ from one patient to another, causing diagnostic delays (3-7).

Here, we present the case of two siblings with IPEX syndrome with the same hemizygous mutation, but with different types of symptomology at onset; one with dermatitis, type 1 diabetes mellitus and autoimmune hemolytic anemia (AHA) while the other with dermatitis, enteritis, and glomerulonephritis. Verbal and written parental informed consents were obtained for both siblings.

Cases

Patient 1

A 5-month old male infant referred for evaluation for hyperglycemia. His past history and medical records revealed a two-weeks of hospitalization at 3-month of age with bronchopneumonia that was treated with antibiotics, and hyperglycemia with normal hemoglobin A1c (HbA1c) and C-peptide levels that was controlled by insulin within three days. According to his family history

our patient was the fourth child of nonconsanguineous healthy parents and had two healthy elder sisters and one elder brother (patient 2) with diagnoses of mesangial proliferative glomerulonephritis, and suspected (but could not definitively diagnosed) immune deficiency due to having malnutrition, chronic diarrhea, dermatitis, elevated total IgE levels and recurrent severe respiratory tract infections.

Physical examination at admission revealed a pale infant with eczematous lesions of the neck and scalp. His weight and height were at 50. percentile (7.3 kg and 66.5 cm, respectively). The findings of the rest of his physical examination were unremarkable.

Main clinical and laboratory findings at admission are shown on Table. Presence of an elevated reticulocyte count (4.49 %), a positive result of a direct Coombs test, and peripheral blood smear showing hemolysis, suggested the diagnosis of AHA. Serum chemical analyses showed an elevated serum glucose with normal blood gas analysis. Urine analysis was normal except glucosuria. His HbA1c was slightly elevated with reduced and normal fasting and postprandial C-peptide levels (0.68 ng/m/L and 1.86 ng/mL, respectively, range 0.9-7.1 ng/mL). Anti-islet cell (ICA) and anti-insulin antibodies were normal whereas anti-glutamic acid decarboxylase (GADA) was elevated. He was diagnosed as diabetes mellitus and insulin treatment was started.

Having infantile diabetes mellitus, dermatitis and AHA, and an elder brother with suspected immune deficiency, IPEX syndrome was considered and then established genetically by FOXP3 whole gene sequence analysis that revealed a hemizygous p.250K.del (c.748_750delAAG) mutation. His mother was found heterozygous for the same mutation. The same mutation has been reported in two cases with IPEX syndrome so far (7,8).

At the age of 1 year the patient underwent a successful hematopoietic HLA-matched sibling donor stem cell transplantation (HSCT) with significant improvement in his general course. Dermatitis, and AHA completely resolved at 14 months of age. However, after 3 months insulin-free period, hyperglycemia recurred and a course of insulin treatment had to be restarted. At the last follow-up at the age of 4.6 years, the patient was in good clinical condition with normal growth and HbA1c has been maintained at <8 % with insulin (0.8 IU/kg/day). There are also no accompanying endocrine diseases except diabetes mellitus.

Patient 2

He was elder brother of Patient 1 and the 3rd child of the parents. At the age of 7 months, he was diagnosed eczematous dermatitis due to skin lesions localized on the neck and trunk. He developed intractable diarrhea and albuminuria when he was around one year old. After that, he was hospitalized several times in different medical centers due to recurrent pneumonia with eczematous skin lesions or albuminuria diagnosed as mesangial proliferative glomerulonephritis by renal biopsy at the age of 18 months. Immunoglobulin E level was as high as 1368 U/ml, other immunoglobulins were normal (Table). Afterwards, he was suspected to have an immune deficiency as he had malnutrition, chronic diarrhea, dermatitis, elevated total immunoglobulin E levels and recurrent severe respiratory tract infections but this could not be definitively diagnosed. His CD4 and CD8 T lymphocyte counts, NK cells and CD19 B lymphocyte counts were within normal limits. Isohemagglutinins could not be determined since his blood group was AB. He had a positive response againts hepatitis B vaccine, however pneumococcal vaccine response could not be determined as the testing was not available. The patient had lifelong problems with mesangial proliferative glomerulonephritis requiring immunosuppression with steroids, After we diagnosed his younger brother (Patient 1) as IPEX syndrome, we thought the same diagnosis for Patient 2 and confirmed it by showing the same mutation (hemizygous p.250delK (c.748_750delAAG) in exon 6 of FOXP3 gene when he was 3.5 years old. The patient died of candida sepsis following severe pneumonia at the age of 4 years. No evidence of diabetes mellitus and other endocrine disease was detected in that patient during his lifetime.

Discussion

Enteropathy, endocrinopathy and skin manifestations are considered the classic triad of IPEX syndrome (2,4,5). However, the patients with IPEX syndrome display a variety of phenotypes including life threatening multi-organ autoimmunity. We report here on two siblings of IPEX syndrome, which presented different clinical presentation in the infantile period despite having the same mutation of FOXP3 gene. In addition to dermatitis and immune deficiency findings with recurrent infections, one of the siblings

had diabetes mellitus and AHA without enteropathy and the other had mesangial proliferative glomerulonephritis with enteropathy in the first year of the life.

Autoimmune enteropathy is the most common manifestation of IPEX syndrome which present within the early weeks of life with intractable diarrhea. Patient 1 had never experienced chronic diarrhea to that day, but Patient 2 had intractable diarrhea around the age of one.

It was reported that the frequency of autoimmune endocrinopathies was 65% which most commonly include type 1 diabetes and hypothyroidism or hyperthyroidism among IPEX patients (3,5). On the other hand, it has been suggested that some of the infantile diabetes cases of unknown etiology might be mild form of IPEX syndrome (9). Bae et al. (10) reported an IPEX patient who presented diabetes at 11 months of age but the diagnosis of IPEX was made 10 years later. Therefore, the diagnosis of IPEX should be kept in mind in the male patients who diagnosed of diabetes in infancy, even though they had no other features of IPEX syndrome at initial.

It has been suggested that up to one-third of IPEX patients had renal disease (2). Autoimmunity and long-term usage of nephrotoxic drugs are the main causes of renal disease in these patients. Renal involvement in IPEX syndrome can manifest as tubulointerstitial damage or glomerulopathy presenting as nephrotic syndrome (2,10-12). The mutation detected in the present family has been previously reported in a five-year old boy with IPEX syndrome with minimal change disease (7). Importantly, Patient 2, presented with a different clinical course from Patient 1 including mesangial proliferative glomerulonephritis, beside dermatitis, enteropathy, and hyperimmunoglobulin E, and he died at 4 years of age related to severe infection. Genotype and phenotype relation were evaluated in a large IPEX cohort, but found no unequivocal correlation (5). Our patients support strongly that there is no genotype-phenotype correlation in IPEX patients especially in the first years of the disease. Patient 1 had no clinical and laboratory findings of renal disease before and after HSCT. However, Park et al. (11) reviewed the possible genotype-phenotype correlations and suggested that enteropathic presentations, eczema, autoimmune hemolytic anemia and food allergy were associated with better survival, while thrombocytopenia, septic shock and mutations affecting the repressor domain, intron 7 or poly A sequence were associated with increased risk of death. As the number of reported cases increases, genotype-phenotype correlations will become clearer and its importance in predicting the disease course will become better in the future.

The heterogeneous clinical features of patients with IPEX syndrome can cause difficulties in early diagnosis. The reason for clinical diversity even in patients with the same mutaition in IPEX syndrome is controversial. Environmental factors have been suggested as a cause in this situation however, this could not be the case at least for our patients since they shared the similar environmental factors. It is of interest whether clinical diversity in IPEX syndrome could be related to the disease onset since the patients were not followed for many years and the actual natural course of the disease and progression is unknown. Also, management of IPEX syndrome may have an important role on the natural course of the disease. That is to say, a renal disease and/or enteritis could be developed in Patient 1 if HSCT was not performed, and Patient 2 might have developed T1D and/or AHA if he hadn't died. Therefore, we wanted to draw attention to the initial findings in terms of early diagnosis and treatment. The absence of the classic clinical triad of the disease may have led to a delay in diagnosis of IPEX syndrome in our older patient who had not endocrinopathy. Therefore, we highlight that it should be suspected in a male infant not only who had classical triad but also who had only one main disorder related to IPEX syndrome like infantile diabetes and molecular analysis should be considered to avoid delayed diagnosis.

In the family history of the Patient 1, the clinical picture of his older brother helped to make an early diagnosis of IPEX syndrome, although the patient did also not have the classic clinical triad. In this context, we would like to underline that family history should be taken with caution to avoid misdiagnosis regarding IPEX syndrome.

Author Disclosure Statement

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Authorship Contribution

Gülay Karagüzel made the diagnosis of IPEX syndrome, then all authors contributed to the treatment and follow-up of the patients. The manuscript was written by Gülay Karagüzel and Fazıl Orhan.

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Table: The clinical and laboratuary features of our patients and the reported patients who had the same mutation.

	Patient 1 At Diagnosis	**Patient 2 At onset / Diagnosis**	***Hashimura**[7]	***Wildin**[8]
Age at first admission	3-month	7-month	2-month	2-month
Age at diagnosis of IPEX	5-month	42-month	5-year	9-year
Consanguinity	-	-	NA	NA
Family history of the findings	+	+	+	+
Eczematous skin rash	+	+	+	+
Hepatosplenomegaly	-	+	NA	+
Reccurrent pneumonia	+	+	-	NA
Chronic diarrhea	-	+	-	+
Hemoglobin (gr/dl)	7.1	9.9 / 11.4	7.8	NA
White blood cell (mm^3)	8700	13100 / 7300	NA	NA
Eosinophilia (%)	8.4	3.7 / 10.3	NA	NA
Absolut neutrophil count (mm^3)	3300	5700 / 3700	NA	NA
Absolut lymphocyte count (mm^3)	3700	5800 / 2700	NA	NA
Direct Coombs test	+	/ NA	NA	NA
Serum albumin (gr/dL)	4.0	2.3	NA	NA
Serum glukoz (mg/dL)	400	91 / 82	373	NA
Immunoglobulin G (mg/dL)	856	762 / 652	NA	NA
Immunoglobulin M (mg/dL)	102	113/101	NA	NA
Immunoglobulin A (mg/dL)	30.8	85.6 / 43.8	NA	NA
Immunoglobulin E (IU/mL)	1538	1368 / 1042	1141	NA
Diabetes-related antibodies	+	NA / NA	NA	NA
Diabetes mellitus	+	-	+	+
AHA	+	-	+	-
Renal disease	-	+	+	-**
Hypothyroidism	-	-	-	-
Trombocytopenia	-	-	-	+
Other	-	-	-	Arthritis
FOXP3 mutation c.748_750delAAG, p.250K.del	+	+	+	+

NA: Not available; AHA: Autoimmune hemolytic anemia

*Reference 7 (Hashimura T, et al, Pediatr Nephrol 2009); Reference 8 (Wildin RS, et al, J Med Genet 2002)

**Reported progressive renal insufficiency secondary to long-term therapy with nephrotoxic drugs