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PIK3R1 mutation associated with primary immunodeficiency: a case of a 14-year-old male and review of the literature: case report

Abstract

We report a rare case of a 14-year-old boy diagnosed with Activated phosphoinositide 3-kinase delta syndrome Type 2 (APDS2). Based on a typical clinical presentation (Delayed teething, Prominent lymphadenopathy and recurrent characteristic infections started early in life and including multiple episodes of bilateral conjunctivitis, an extensive herpes skin infection in addition to recurrent upper sinopulmonary infections) along with suggestive laboratory immunological findings, and positive confirmatory genetic testing. After diagnosis, the patient was commenced on prophylactic antibiotics which resulted in a reduction in the frequency of his infections and hospitalizations. The targeted therapy of mTOR inhibition with Sirolimus and the possibility of hematopoietic stem cells transplantation are considered and discussed with the family, and he is on regular follow-up with the Allergy/Immunology team.

APDS is a rare but increasingly reported inborn error of immunity. Gain-of-function and loss-of-function mutations in phosphoinositide 3-kinase (PIK3CD (encoding $p110\delta$) and PIK3R1 (encoding $p85\alpha$, $p55\alpha$, *and* $p50\alpha$)) lead to APDS1 and APDS2, respectively.

Our aim in reporting our case is to allow room for more elaboration of the different genotypes and clinical presentations of both types of APDS, in which early and accurate diagnosis will subsequently help in the initiation of outcome-improving therapy.

Keywords: primary immunodeficiency, case report

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Background

The phosphatidylinositol 3–kinase (PI3K) signaling pathway is involved in a broad range of cellular processes, including growth, metabolism, differentiation, proliferation, motility, and survival. The $PI3K\delta$ enzyme complex is primarily present in the immune system and comprises a catalytic ($p110\delta$) and regulatory ($p85\alpha$) subunit. Dynamic regulation of $PI3K\delta$ activity is required to ensure normal function and differentiation of immune cells. (APDS) is among a growing number of newly defined primary immunodeficiency (PID) syndromes in which the causal mutations have been identified by next-generation sequencing. Gain-of-function and loss-of-function mutations in PIK3CD (encoding $P110\delta$) and PIK3R1 (encoding $p85\alpha$, $p55\alpha$, *and* $p50\alpha$) lead to APDS1 and APDS2, respectively.

Since 2013, around 285 cases with germline mutations in genes involved in the $PI3K\delta$ pathway (PIK3CD, PIK3R1, or phosphatase and tensin homolog [PTEN]) were reported to prove that both over activation and underactivation of $PI3K\delta$ lead to impaired and dysregulated immunity.

While conventional immunodeficiency therapies such as immunoglobulins replacement, antibiotic prophylaxis, and hematopoietic stem cell transplant can be used, some targeted therapies of mTOR inhibition with Sirolimus and selective $PI3K\delta$ inhibitors (e.g., Leniolisib) have been tested.

Case presentation

A 14-year-old Sudanese child was referred to Immunology/ Allergy team at KSAMC with a history of failure to thrive and recurrent infections after an initial workup were done in his home country Sudan.

He was born after a full-term uneventful pregnancy. He was born via elective Caesarean section as the mother had a previous history of two abortions. The mother of the patient is a 46-year-old family medicine physician who had difficulty in conceiving as she was diagnosed with the polycystic ovarian syndrome (POCS). She also has a history of total thyroidectomy on levothyroxine, Diabetes, and hypertension. The father is a 51-year-old healthy adult. Our index case has a 9-year-old younger brother who was treated for epilepsy and is currently off medications. There is no history of consanguinity.

Regarding family history, the patient's uncle has Autism, and a grandfather from the maternal side with a history of chronic renal failure. More than one of his cousins suffers from ataxia and multiple atopies, all from the maternal side as well.

Past medical history revealed a normal immediate postnatal period with a birth weight of 3.2 kilograms. He was admitted to the special care baby unit for several days due to the prolonged physiological jaundice required a phototherapy. At one month of age, he started to suffer from multiple episodes of bilateral conjunctivitis, excessive tearing, and eczematous skin rashes. His eczema was complicated by multiple skin infections. His conjunctivitis and Eczema both improved gradually by the age of 6 months.

By 7 months of age, the patient started to have a poor appetite and feeding refusal, so his growth parameters fell below the fifth centile. He failed to thrive despite regular nutritional reviews and interventions. There was also a history of delayed teething, but otherwise, the patient developed normally. The patient is fully immunized with no significant reactions to vaccines.

Our case has a prominent history of chronic cervical and inguinal lymphadenopathy and recurrent infections involving different body systems as follows:

Skin: There is a history of eczema early in life associated with two significant episodes of Impetigo. An extensive herpes skin infection was documented by age of 7 years.

Ears: History of recurrent suppurative otitis media (6-7 episodes) resulted in grommets placement for 6 months.

Nose and throat: He has allergic rhinitis and sinusitis on nasal steroids treatment. The patient has also a history of recurrent Tonsillitis requiring adenectomy twice at 10 months and 9 years old.

Oral cavity: Documented history of Mumps and history of gum abscess and severe dental caries.

Chest: There is no history of recurrent pneumonia.

Abdomen: Diagnosed with Hepatitis A at age of 8 years and he was treated surgically for an episode of appendicitis complicated by rupture and collection at age of 9 years.

Renal system: No history of recurrent UTIs, but there is a history of gross hematuria started by age of 5 years and reoccurred at 12 years old, last episode was associated with edema, proteinuria, and the patient planned for renal biopsy as a possible glomerulonephritis case.

Hematology: There is no history of sepsis/bacteremia. He has anemia with a baseline Hg of 9-10 (microcytic, hypochromic anemia of chronic disease), and other cell lines are within normal range. No history of blood product transfusions.

Regarding his allergies profile, the patient developed an anaphylactic reaction when he received IVIG later after his diagnosis was established. He had no history of allergies to other drugs or foods, but he has a history of contact dermatitis, one incident of extensive urticaria that responded well to antihistamines besides the previously mentioned eczema and allergic rhinitis.

On examination, there is no major dysmorphology noted apart from short stature, thick eyebrows, and broad nasal bridge. The patient has severe dental caries, dry skin, bilateral cervical and unilateral inguinal (Left) lymphadenopathy. The rest of the systemic examination was normal. No hepatosplenomegaly.

At age of 10 years, the patient was seen initially by an allergy/immunology service in his home country Hospital in Sudan as a case of failure to thrive with recurrent infections. His initial workup showed normal CBC, normal T cell counts but low B cells. IgA was less than 0.06 g/l, IgG2 0.37 g/l, while other immunoglobulins levels were normal. By measuring C. tetani toxin antibodies pre- and post-vaccination, the patient had no protective level. ANA, PCNA, and AMA-M2 autoantibodies were all weakly positive.

At this stage, an inborn error of immunity was suspected, and prophylactic antibiotics (Azithromycin, septrin, Augmentin) were commenced and alternated every 3 months which resulted in a reduction in the frequency of infections. The patient was also kept on Lisinopril to control his persistent proteinuria.

At age of 14 years old our patient was referred and seen by Allergy/Immunology team in KSAMC. Based on history and initial investigations, genetic testing was done, and a heterozygous pathogenic variant was identified in the PIK3R1 gene (Figure 1).

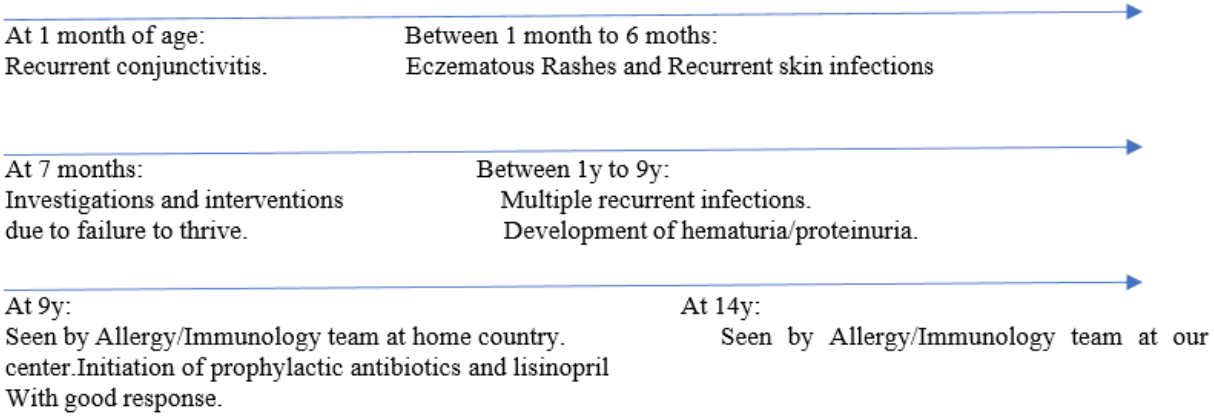

Figure 1 Timeline of historical and current medical history.

Investigations

(Table 1) (Table 2).

Table 1 Initial Workup

Investigation	Result	Ref. range
IgA	Less than 0.06 g/l	
IgM	1.93 g/l	0.31-1.79
IgE	1.9 IU/ml	Up to 200
IgG	13.5 g/l	6.9-15
IgG2	0.37 g/l	0.68-1.55
T cells	1945	1000-2200
B cells	148	110-570
NK cells	423	70-480
C. tetani toxin antibodies (pre- and post- vaccination)	Less than 0.05, no protection	

Table 2 Genetic Study

Sequence variants							
Gene	**Variant coordinates**	**Amino acid**	**SNP identifier**	**Zygosity**	**In silico parameters**	**Allele frequencies**	**Type and classification**
PIK3R1	NM_181523.2: c.1425+1G<C		rs587777709	heterozygous	PolyPhen: N/A Align-GVDG: N/A SIFT: N/A Mutation Taster: Disease causing Conservation_nl: high Conservation_aa: N/A 2/2 likely splice effect	gnomAD: - ESP: - 1000 G: - CentoMD: -	Splicing Pathogenic (class 1)

Variant interpretation:

PIK3R1, c.1425+1G<C.

The PIK3R1, c.1425+1G<C is predicted to disrupt the highly conserved donor splice site. According to HGMD professional 2020.3, this variant has previously been described as disease-causing for ypogammaglobulinemia and recurrent infections by Deau et al., 2014 (PMID: 25133428), Lucas et al., 2014 (PMID: 25488983), Kuhlen et al., 2016 (PIMD: 26529633). ClinVar lists this variant as pathogenic (clinical testing, Variation ID: 156009). It is classified as pathogenic (class 1) according to the recommendations of CENTOGENE and ACGM.

Pathogenic variant in the PIK3R1 gene is associated with immunodeficiency type 36(IMD36), an autosomal dominant disorder. Clinical features include primary immunodeficiency, recurrent respiratory infections, recurrent bacterial infections, chronic viral infections, hypogammaglobulinemia, decreased memory B cells, and decreased naive CD4+ and CD8+ T cells. Onset is in early childhood (OMIM: 616005).

Treatment: A diagnosis of Activated $PI3K\delta$ syndrome (APDS) type 2 was confirmed. Later, the patient was commenced on regular IVIG transfusion, mTOR inhibitor (Sirolimus) beside continuation of prophylactic antibiotics. Our index case has a history of anaphylaxis while IVIG transfusion which explained by an undetectable IgA level and the presence of an IgA antibody. Low IgA content IVIG product was used to overcome these issues alongside with premedication before each IVIG transfusion.

A referral and frequent follow ups with clinical dietitian clinic were arranged to ensure better and steady weight gain which help decreasing the rate of infections and improve the quality of life of our patient.

As IVIG transfusions and starting of Sirolimus was commenced as long-term therapy for antibody deficiency, the decision of HSCT is considered and discussed with the family as the only definitive therapy.

Outcome and follow-up: Since commencing of periodic IVIG transfusions and Sirolimus, a decrease in the frequency of infections was noted. Weight gaining, energy and school performance of the patient also improved over the subsequent months after the diagnosis and initiation of the management.

Discussion

The phosphatidylinositol 3 kinase (PI3K) family includes signal-transducing lipid kinases that phosphorylate the 3-hydroxyl group of phosphoinositide of cell membranes. Since their discovery in 1985, an array of different classes and isoforms of PI3K family members have been reported, which differ in their expression pattern, substrate specificity, and the mechanisms regulating their activation. Class, I PI3Ks is heterodimers consisting of a catalytic and a regulatory subunit. They are further divided into two subclasses, IA $(PI3K\alpha, PI3K\beta, PI3K\delta)$ and IB $(PI3K\gamma)$.[1] The $PI3K\delta$ enzyme complex is primarily present in the immune system and comprises a catalytic ($p110\delta$) and regulatory ($p85\alpha$) subunit. Dynamic regulation of $PI3K\delta$ activity is required to ensure normal function and differentiation of immune cells.[2] Gain-of-function and loss-of-function mutations in PIK3CD (encoding $P110\delta$) and PIK3R1 (encoding $p85\alpha$, $p55\alpha$, *and* $p50\alpha$) lead to APDS1 and APDS2, respectively.[3]

In a recent systemic review, published in 2019 a comprehensive search limited to the English language was performed using PubMed, Web of Science, and Scopus databases. A total of 243 APDS patients were identified from 55 articles. For all patients, demographic, clinical, immunologic, and molecular data were collected. The median age of diagnosis was 12.0 (6.5–21.5) years with a median diagnostic delay of 7.0 (3.4–14.0) years. Overall, 179 APDS1 and 64 APDS2 patients were identified. The most common clinical manifestations were respiratory tract infections (pneumonia (43.6%), otitis media (28.8%), and sinusitis (25.9%)), lymph proliferation (70.4%), autoimmunity (28%), enteropathy (26.7%), failure to thrive (20.6%), and malignancy (12.8%). respiratory tract infections (65%) were the most common first presentation in APDS patients followed by organomegaly (15.8%). Among patients with an established primary diagnosis (n = 39), most patients were diagnosed initially with hyper-IgM (HIGM) syndrome (n = 11, 28.2%) or lymphoma (n = 8, 20.5%). Bronchiectasis was the most common structural complication in 28.4% of patients (4).

Sinusitis was significantly more common in APDS1, while pneumonia and eye infection were more frequently reported in APDS2 patients. Benign lymphoid proliferations including reactive hyperplasia and lymphadenitis in the gastrointestinal and respiratory tract were reported in 60 (24.7%) patients and more frequently in APDS1 patients. Tonsillar hypertrophy was observed in 21 (8.6%) patients with a predominant representation of APDS2 patients. See Table 3 for a detailed comparison between the common manifestations in both APDS types.[4]

Another study was done by Jeffrey I. Cohen from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, United States revealed that EBV viremia was detected in 46 and 22% of patients with mutations in PIK3CD and PIK3R1, respectively, and CMV viremia was detected in 20 and 21% of patients with mutations in PIK3CD and PIK3R1, respectively.[5]

Immunologic profiling in the previously mentioned 2019 systemic review showed decreased B cells in 74.8% and CD4+ T cells in 64.8% of APDS patients. Adjusted to the age-matched normal ranges, low IgG, IgA serum levels, and raised IgM levels were observed in 102 (57.6%), 98 (57.3%), and 107 (60.5%) patients, respectively, and 78 patients (48.1%) showed a hyper IgM (HIGM) phenotype. This HIGM immunophenotype was more prevalent in the APDS2 group when compared to the APDS1 group (63% vs. 40.7%, $p < 0.001$). Overall, 15.4% showed normal IgG, IgA, and IgM levels; 4.3% had selective IgA deficiency; 15.4% hypogammaglobulinemia; and 16.6% IgG subclass deficiency.[4] Considering the types of infections and because both B cells and T cells are affected in these patients, APDS should be characterized as a combined immunodeficiency.

Table 3 Clinical features in patients with APDS both types one and two by Mahnaz Jamee et al systemic review, 2019[4]

Parameters	Total	APDS1	APDS2	P-value
Pneumonia %	106 (43.6)	66 (36.9)	40 (62.5)	>0.001 *
Otitis %	70 (28.8)	53 (29.6)	17 (26.6)	0.644
Sinusitis %	63 (25.9)	53 (29.6)	10 (15.6)	0.028 *
Meningitis %	6 (2.5)	6 (3.4)	0	0.345
Diarrhea %	39 (16)	27 (15.1)	12 (18.8)	0.493
Bronchiectasis %	69 (28.4)	61 (34.1)	8 (12.5)	0.001 *
Abscess %	13 (5.3)	12 (6.7)	1 (1.6)	0.193
Septicemia %	13 (5.3)	10 (5.6)	3 (4.7)	1
Fungal Infection %	21 (8.6)	17 (9.5)	4 (6.3)	0.427
Enteropathy %	65 (26.7)	51 (28.5)	14 (21.9)	0.305
Arthritis %	4 (1.6)	3 (1.7)	1 (1.6)	1
Autoimmunity %	69 (28.4)	56 (31.3)	13 (20.3)	0.095
Lymphadenopathy %	149 (61.3)	100 (55.9)	49 (76.6)	0.004 *
Splenomegaly %	115 (47.3)	90 (50.3)	25 (39.1)	0.123
Hepatomegaly %	70 (28.8)	62 (34.6)	8 (12.5)	0.001 *
Failure to Thieve %	50 (20.6)	17 (9.5)	33 (51.6)	>0.001 *
Endocrinopathies %	13 (5.3)	11 (6.1)	2 (3.1)	0.523
Granulomatous lesions %	4 (1.6)	3 (1.7)	1 (1.6)	1
Malignancy %	31 (12.8)	19 (10.6)	12 (18.8)	0.094
Allergy and asthma %	15 (6.2)	14 (7.8)	1 (1.6)	0.125
Eye infection %	26 (10.7)	13 (7.3)	13 (20.3)	0.004 *
Neurologic abnormality %	34 (14)	17 (9.5)	17 (26.6)	0.001 *
ENT problems %	86 (35.7)	62 (34.8)	24 (38.1)	0.642
Hepatobiliary disorders %	17 (7)	13 (7.3)	4 (6.3)	1
Orthopedic abnormalities %	15 (6.2)	8 (4.5)	7 (10.9)	0.075
Dental problem %	10 (4.1)	7 (3.9)	3 (4.7)	0.726
BCGosis %	4 (1.6)	2 (1.1)	2 (3.1)	0.284

*P-value is statistically significant >0.05

Similar most common presentations (recurrent infection, lymphoproliferation, and autoimmunity) and immunoglobulins profiles (Hypogammaglobulinemia, Agammaglobulinemia, selective IgA deficiency, or hyper-IgM) were found in an Iranian Cohort of fifteen paediatric patients with APDS were studied and published in 2021.[33]

As in our case, Autosomal dominant mutations within splice acceptor and donor sites of exon 11 of the PIK3R1 gene lead to APDS2. In a Cohort study done by Elodie Elkaim et al., records of 36 patients with genetically diagnosed APDS2 were collected and reviewed. All presented with early-onset recurrent ear, nose, and throat (ENT) or bronchopulmonary infections (median onset, 1.7 years of age; range, the first month of life to 10 years of age). Chronic conjunctivitis was reported in 7 patients. Invasive bacterial infections were rare, being reported only in 2 cases. Of 17 patients who received BCG vaccination, 2 (P21 and P26) presented with persistent local skin lesions at the vaccination site. Persistent detection of the virus was reported in 36% of patients, with cytomegalovirus (CMV) and EBV the most common. Varicella-zoster virus, Hepatitis Viruses B and C, Measles, poxvirus, and papilloma virus infections were also reported. Except for chronic Giardia intestinalis in 1 patient and ocular toxoplasmosis in another, no other parasitic infections were reported. Chronic cutaneomucosal candidiasis was observed in 3 patients.[6]

Thirty-two (89%) of 36 patients had persistent (>6 months) benign lymphoproliferation either as chronic lymphadenopathy, splenomegaly, or ENT or gut infiltration. Ten (28%) patients had malignant diseases at a median age of onset of 23 years (range, 6–40 years). Six (17%) patients had autoimmune complications inform of Cytopenia (most common), insulin-dependent diabetes, arthritis, eczema, and autoimmune hepatitis.[6]

The majority of patients presented with decreased serum IgG and IgA levels before the onset of immunoglobulin replacement therapy (87%). Increased IgM levels were observed in most (58%) but not all patients.[6]

During the last decade, Cases of APDS2 keep reported in the literature[7–17] with very heterogenous clinical phenotypes as shown in this case report of four members of the same family (parents and 2 siblings). While the youngest child presented early in life with marked lymphoproliferation and died later due to EBV-induced diffuse large B cell lymphoma complications, the other sibling and parents had a milder course with recurrent sinopulmonary infections and mild adenotonsillar hypertrophies. All four patients had the same genetic mutation of the PIK3R1 gene.[14] Congenital infections are also reported, as shown in this case report describing disseminated and congenital toxoplasmosis in a mother and child who share a pathogenic mutation in PIK3R1.[32]

Chronic digital vasculitis,[17] short stature and failure to thrive,[11,12,14] microcephaly,[10] and other minor facial dysmorphology[14] were reported as associated findings with APDS2. Another rare but significant clinical phenotype that can be associated with mutations in the PIK3R1 gene is Short Syndrome (short stature, hyperextensibility, hernias, ocular depression [deeply set eyes], Rieger anomaly, teething delay, partial lipodystrophy, insulin resistance, and facial dysmorphic signs).[18–26] In a limited number of cases, patients can present with the two clinical phenotypes of PIK3R1 gene mutations APDS2 and SHORT syndrome.[27] Based on all previously mentioned findings we recommend that patients with mutations in the PIK3R1 gene should be seen by both clinical immunologists and clinical geneticists.

While conventional immunodeficiency therapies such as immunoglobulin replacement, antibiotic prophylaxis, and hematopoietic stem cell transplant can be used, other targeted therapies of mTOR inhibition with Sirolimus and selective $PI3K\delta$ inhibitors (e.g., Leniolisib) have been tested.[28] In the best traditions of drug repurposing, Valencic et al,[29] report the use of theophylline for the treatment of an 11-year-old girl with APDS, who was heterozygous for the mutation $56\ c.1425\beta 1G > A$ in PIK3R1. They report that a search of the literature showed that theophylline, a common drug used for the treatment of pulmonary obstruction, inhibits the action of $PI3K\delta$ at concentrations in the therapeutic range for the medication for asthma and apneas. Treatment with theophylline in this patient resulted in amelioration of her symptoms, a striking reduction in the

frequency of sinopulmonary infections, and substantial improvement in scholastic performance.

HSCT is still the definitive therapy for patients with APDS. In an international case series study of the clinical outcomes of patients with APDS 1/2 undergoing HCT. Fifty-seven patients with APDS who received HCT (43 with PIK3CD, 14 with PIK3R1 mutations) were included. Unrelated donors were the most frequent donor source (62%). Matched sibling donors (MSDs) were used in 11% of HCTs. With a median follow-up of 2.3 years, 2-year overall, and graft failure-free survival probabilities were 86% and 68%, respectively, and did not differ significantly by APDS1 versus APDS2, donor type, or conditioning intensity. The 2-year cumulative incidence of graft failure following first HCT was 17% overall but 42% if mammalian target of rapamycin inhibitor(s) (mTORi) were used in the first year post-HCT, compared with 9% without mTORi. Similarly, 2-year cumulative incidence of unplanned donor cell infusion was overall 28%, but 65% in the context of mTORi receipt and 23% without. Phenotype reversal occurred in 96% of evaluable patients, of whom 17% had mixed chimerism. Vulnerability to renal complications continued post-HCT, adding new insights into potential non-immunologic roles of phosphoinositide 3-kinase not correctable through HCT.[30]

A disease-specific registry collecting prospective and long-term follow-up data of patients with APDS was established by the United States Immunodeficiency Network (USENET)[31] and the European Society for Immunodeficiency. By reporting our case of APDS2, we aim to add to these accumulative efforts and allow room for more elaboration of the different genotypes and phenotypes of this rare syndrome which will help in accurate diagnosis and then initiation of outcome-improving therapy.

Learning points and conclusion

- A high index of suspicion is required to diagnose APDS; frontline clinicians should consider the diagnosis in any child with early-onset lymphadenopathy and recurrent infections including bilateral conjunctivitis, chronic viral infection in addition to recurrent upper Sino pulmonary infections. Other associated findings could be delayed teething and short stature.

- Genetic testing is readily available these days and will help to establish the diagnosis and steer the management.

- Early diagnosis and intervention are associated with a better outcome in form of decreasing the rate of infections and hospitalization.

- Different treatment modalities can be used in the management of APDS cases, while conventional immunodeficiency therapies such as immunoglobulin replacement, antibiotic prophylaxis, and hematopoietic stem cell transplant can be used; other targeted therapies of mTOR inhibition with Sirolimus and selective PI3Kδ inhibitors (e.g., Leniolisib) have been tested.

Patient perspective: According to the family, an earlier diagnosis and initiation of the IVIG would have helped and relieved a lot of psychosocial and financial burdens on the child and parents. Their main motivation to participate in this publication work is to contribute to raising awareness about the disease and to spare the rest of the families a lot of suffering.

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Conflicts of interest

The author declares no conflicts of interest.

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