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Case Report

ORAI1 defect in a patient with disseminated CMV infection and severe hypotonia

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ABSTRACT

Background. A clinical presentation similar to severe combined immunodeficiency (SCID) with defective T cell activation but normal lymphocyte development occurs due to certain molecule defects including *ORAI1*- and *STIM1*.

Case. A four-month-old girl sufferd from fever, restlessness, diarrhea, and poor weight gain following the neonatal period. There was consanguinity and a positive family history. She had hypotonia and spontaneous opisthotonic posture. Refractory and extensive CMV infections were detected; immunological investigations revealed normal quantitative immunoglobulins and low numbers of CD3+, CD4+, and CD8+ cells. The next generation sequencing analysis revealed a mutation in the *ORAI1* gene.

Conclusions. The present patient's history of refractory and widespread CMV infections shows a clinically substantial reduction in resistance against opportunistic microorganisms. This case emphasizes the importance of considering STIM1 and ORAI1 defects in patients with SCID phenotype and neurologic involvement, such as hypotonia.

Key words: primary immunodeficiency diseases, CMV infection, ORAI1 deficiency.

Primary immunodeficiency diseases (PIDs) are inherited defects of the innate or adaptive arms of the immune system that lead to an increase in the incidence, frequency, or severity of infections, malignancies, and immune dysregulation.[1] The most severe form of primary immunodeficiency, needing immediate care, is severe combined immunodeficiency (SCID). T and B cell development/function are defective in SCID, and cellular and adaptive immune responses are impaired. In the early months of life, patients present with severe infections caused by viral, fungal, and bacterial agents.[2]

Despite normal lymphocyte development and number, a clinical presentation similar to SCID occurs due to certain molecule defects leading to compromised T cell activation. Calcium is a critical second messenger essential for lymphocyte and non-immune cell activation. Stromal interacting molecule (STIM) 1 and STIM2 found in the endoplasmic reticulum (ER) membrane and ORAI1 are the critical molecules in the development of Ca2+ channels (CRAC) which is a crucial step of signal transduction and lymphocyte activation. The amount of ER

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Ca2+ controls the CRAC channel. Its opening results in Ca2+ influx or store-operated Ca2+ entry (SOCE). SOCE is an essential Ca2+ signaling pathway in lymphocytes necessary for activating several Ca2+-dependent enzymes and transcription factors that regulate immune cell development, proliferation, and function.[3]

ORAI1- and STIM1-deficient patients have a clinical phenotype that is similar to SCID, with recurrent and chronic infections, autoimmunity, ectodermal dysplasia, aberrant enamel development, and muscular hypotonia.[4] In a review; congenital myopathy was observed in all patients with ORAI1 mutations. Generalized muscular hypotonia resulted in poor head control, delayed ambulation, and a positive Gower's sign.[5]

Here, we report an infant with a mutation in the *ORAI1* gene who presented with CMV infection and hypotonia.

Case Report

A four-month-old female patient presented with complaints of fever, restlessness, diarrhea, and poor weight gain after the neonatal period. Diarrhea was watery, non-bloody, and 8-10 times a day. There was parental consanguinity and a sibling death during infancy due to diarrhea. Physical examination revealed fever (38.8°C), irritability and cachexia. Weight and height were 4250 g (<3p) and 60 cm (10p), respectively. She had pale skin, cutis marmoratus on the legs, retrognathia, and a high-arched palate. She had axial hypotonia, no head control, and spontaneous opisthotonic posture. Object tracking was defective. Deep tendon reflexes were normoactive without clonus. During the evaluation for chronic diarrhea, we detected a high serum cytomegalovirus (CMV) viral load (316.000 copies/ml). Echocardiography showed left ventricular hypertrophy and myopericarditis. Upper endoscopy and colonoscopy showed a normal mucosal appearance the hematoxylin-eosin staining of the colonic mucosa revealed viral inclusion bodies in the lamina propria; and immunohistochemical studies showed CMV antigen positivity. We could not test CMV PCR from the colon tissue biopsy. Bone marrow aspiration was performed for prolonged fever and showed a high CMV viral load (398,471 copies/ml). Brain magnetic resonance imaging (MRI) showed mild inferior vermian hypoplasia, elongated midbrain, thin corpus callosum, and symmetric T2 hyperintensity along with restricted diffusion in the central tegmental tracts of the pons (Fig. 1).

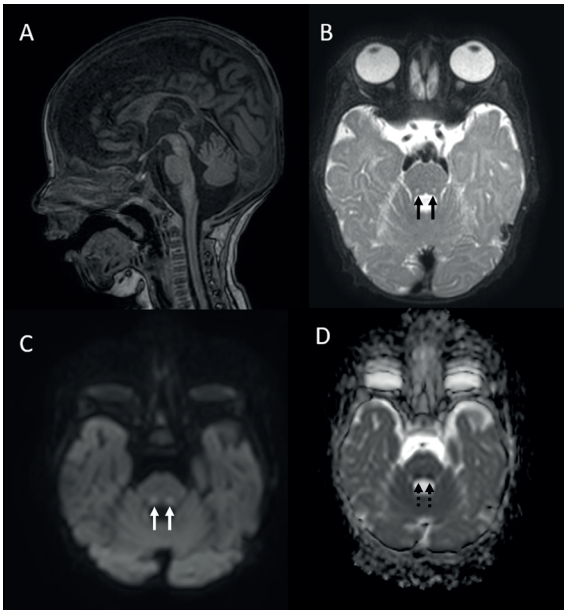

Fig. 1. Brain MRI of the patient at 4 months-old. Sagittal T1-weighted (W) image (A) shows mild inferior vermian hypoplasia, elongated midbrain and thin corpus callosum. Axial T2-W image (B) shows bilateral T2 hyperintensity of central tegmental tracts in the pons (arrows) and diffusion restriction as demonstrated by hyperintensity on trace diffusion (C) and low ADC values on ADC map (D).

Regarding PID, immunological investigations revealed normal quantitative immunoglobulins and low numbers of CD3+, CD4+, and CD8+ cells (Table I). Since she had low levels of serum uric acid levels and T cell counts, we analyzed the purine nucleoside phosphorylase (PNP) enzyme activity, and it was normal.

Table I. Immunological evaluation of the patient

Parameters	On admission	Reference values
Complete blood count		
Hemoglobin (g/dl)	8.0	9.5-13.5
WBC (/mm^3)	6,600	6,700-14,000
ANC (/mm^3)	1,540	1,000-7,000
ALC (/mm^3)	4,000	3,900-9,000
AEC (/mm^3)	80	100-1,000
Trombocytes (/mm^3)	382,000	150,000-450,000
Immunoglobulins (mg/dl)		
IgA	93.9	13.5-72
IgG	1,320	294-1,165
IgM	47.9	33-154
Total IgE (IU/L)	2.88	0-65
Anti HBs (mIU/ml)	173.64	
Lymphocyte subpopulations (% and absolute counts /mm^3)		
CD3+	38%	51-77
	1,406	2,500-5,600
CD3+CD4+	28%	35-56
	1,036	1,800-4,000
CD3+CD8+	11%	12-23
	407	590-1,600
CD16+56+	10%	3-14
	370	170-830
CD19+	50%	11-41
	1,850	430-3,000
CD45RA	82%	
CD45RO	17%	
TCR $\alpha\beta$	35%	
TCR $\gamma\delta$	2%	
Lymphocyte activation test		
CD3	36%	59.1-80.7
CD4	25%	
CD25	30%	86.9-99.8
CD69	21%	61.2-91.8
CD3+CD25+	28%	52.4-93.7
CD4+CD25+	19%	
CD3+CD69+	17%	47.9-84.8
CD4+CD69+	12%	

AEC: absolute eosinophil count, ALC: absolute lymphocyte count, ANC: absolute neutrophil count, Ig: immunoglobulin, WBC: white blood cell.

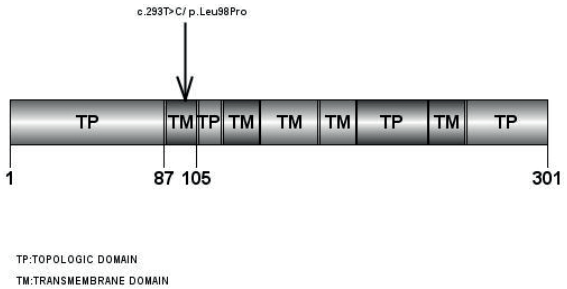

Fig. 2. Representation of the ORAI1 gene and the patient's mutation.

The patient had low lymphocyte activation and proliferation test results compared to the control, therefore she was diagnosed with combined immunodeficiency. Subsequently, we started her monthly immunoglobulin replacement therapy and gave gancyclovir and CMV hyper immunoglobulin therapies for CMV infection. Despite treatment, serum CMV copy number increased (1,373,511 copies/ml). The patient died at the age of five months owing to aspiration pneumonia.

After her death, we detected a homozygous mutation in the *ORAI1* gene (c.293T>C/p.Leu98Pro) by the next-generation sequencing PID panel analysis (Fig. 2). The Sanger sequencing and family segregation of the genetic defect confirmed the variant and we provided genetic counseling to the family.

An informed consent was received from the family for the manuscript.

Discussion

We here describe an infant who presented with a combined immunodeficiency phenotype with hypotonia and disseminated CMV infection. This case highlights STIM1 and ORAI1 defects in patients with SCID phenotype and neurologic involvement, such as hypotonia.

With four transmembrane domains, ORAI1 functions as a plasma membrane protein. Various types of human tissues and cells express ORAI1[5] required for the growth and function of skeletal muscle, eccrine sweat gland function, and tooth enamel calcification.[6] ORAI1 gene mutations have been associated with combined immunodeficiency and myopathy, as well as recurring severe infections caused by viral, bacterial, mycobacterial, and fungal pathogens, resulting in pneumonia, meningitis, enteritis, and sepsis.[4]

Our patient presented with heart, bowel, and bone marrow involvement of CMV infection. As gancyclovir, we administered CMV hyper immunoglobulin therapy to the patient. Although CMV infection in healthy children and adults is usually mild or asymptomatic, immunocompromised individuals are at risk of more severe disease including pneumonia, hepatitis, neutropenia, thrombocytopenia and enterocolitis.[7] Hematochezia and diarrhea are the most common symptoms of gastrointestinal invasive CMV (GI-CMV) infection.[8] Wetwittayakhlang et al.[9] reported that the presenting symptoms of GI-CMV may differ in immunocompromised and immunocompetent patients. Besides the typical finding of GI-CMV, gastrointestinal bleeding is less frequent in immunocompromised patients, although the disease was more extensive in that study. GI-CMV can be diagnosed with cytopathologic changes (owl-eye appearance) demonstrated by hematoxylin-eosin staining or CMV antigen identified by immunohistochemistry. Mucosal punched-out ulcers are the most prominent finding in endoscopic evaluation. However, relatively milder mucosal manifestations such as diffuse or focal erythema and edema are more common in immunocompromised patients.[9] Our patient with non-bloody diarrhea showed no endoscopic mucosal abnormality but positive histopathological findings of CMV colitis. Hence, tissue biopsy is required to exclude GI-CMV in immunocompromised patients.

Central nervous system (CNS) manifestations of cytomegalovirus (CMV) infection include meningitis, retinitis, encephalitis, and myeloradiculitis. These unusual manifestations occur almost exclusively among severely immunocompromised patients.[10] There was

no evidence of CMV infection on brain MRI in the present patient. However, central nervous system involvement is common in patients with PIDs and may be due to several factors, including infections and autoimmunity, and a direct result of defective genes. Neurologic involvement may occur as an initial manifestation of some of these conditions and may account for morbidity and mortality of affected patients.[11] To our knowledge, brain MRI findings of patients with ORAI1 deficiency are not present in the literature. Central hypotonia detected in our patient may be related to the structural abnormalities in brain MRI.

Myopathy in ORAI1- and STIM1-deficient patients becomes apparent soon after birth as global, nonprogressive muscular hypotonia with reduced muscle strength and endurance like in the presented patient. Peripheral hypotonia is the expected clinical finding in patients with ORAI1 deficiency due to myopathy, initial manifestations are insufficient head control and a general reduction in muscle tone.[12] We do not have a muscle biopsy to comment on the presence of such muscle involvement in our patient, clinical findings suggested central hypotonia. Myasthenia-induced recurrent respiratory tract infection is a poor prognostic factor in severe patients.[13] Our patient had a swallowing disorder related to hypotonia resulting in aspiration pneumonia and death.

Hemophagocytic lymphohistiocytosis (HLH) may be seen in ORAI1 deficiency due to a failure in lymphocyte cytotoxicity.[14] Our patient had anemia and recurrent fever but did not fulfill the criteria for HLH. Four ORAI1 deficiency patients, all having enamel hypoplasia, hypocalcified amelogenesis imperfecta, anhidrosis, and ectodermal dysplasia, were reported, and three novel biallelic mutations were detected in these four patients.[15] Recurring fever in our patient might be attributed to anhydrosis or recurrent infections.

In patients with *ORAI1* defect, as in our patient, lymphocyte count may be appropriate according to age-matched levels, as in the present patient. Immunoglobulin levels are generally variable. However, T cell proliferation is insufficient in response to mitogen and antigens. Although we start anti-microbial and immunoglobulin replacement therapy for patients with ORAI1 deficiency to prevent infections, hematopoietic stem cell transplantation (HSCT) is the only curative therapy.[16] Unfortunately, compatible family donor identified for HSCT was lacking, and the patient died while unrelated donor screening was ongoing.

In conclusion, refractory and disseminated CMV infections imply a substantial decline in defense against opportunistic microorganisms. Even though supportive treatments temporarily improve clinical symptoms, they are insufficient to prevent disease progression. The current case demonstrates the critical significance of evaluating ORAI1 deficiency in individuals with combined immunodeficiency and severe infantile hypotonia. In PIDs, the clinical history and physical examination results are the essential signals that guide patients to the diagnosis. Neonatal screening for PIDs may help the early diagnosis of these patients.

Ethical approval

Informed consent was obtained from the family for the publication of the case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: KD, SE, HNB; data collection: KD, SE, HNB, MO; analysis and interpretation of results: SE, DY, KKO, HHG, IE, DC, IT; draft manuscript preparation: KD, SE, DY, HHG, KKO. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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