Sensorineural Hearing Loss and Hypothyroidism in A Patient with Cernunnos Deficiency; A Case Report

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Abstract

Cernunnos deficiency is a rare radiosensitive form of severe combined immunodeficiency (SCID). Herein, we report a patient with recurrent infections, birdlike face, microcephaly, Failure to thrive (FTT), and hypogammaglobinemia accompanied by considerable and rare features of sensorineural hearing loss and hypothyroidism with a mutation in splicing site of the third intron of non-homologous end joining 1 (NHEJ1) gene. The mutation was associated with T-B-NK + in flowcytometry. Distinct clinical manifestation along with a rarely reported genetic site mutation was noticeable in the reported case. The clinicians should be sensitive enough to suspect SCID in any patient with recurrent infections, microcephaly, FTT, and hypogammaglobinemia. Also, it is highlightable that every case of SCID with microcephaly should prompt us to the SCIDs with genetic mutations sensitive to radiation and further investigations are mandatory in highly suspicious patients.

Highlights

- Every case of SCID with microcephaly should prompt us to the radiosensitive genetic mutations and further investigations are mandatory in highly suspicious patients.
- The patient had sensorineural hearing loss with impaired auditory brainstem response, hypothyroidism as well as classic presentations of microcephaly, bird-like face, FTT, and recurrent infection.
- Cernunnos deficiency can have wide range of clinical features with slightly different gene mutations. Our patient had a rarely reported genetic mutation in splicing site of the third intron of NHEJ1 gene.

1. Introduction

SCID (severe combined immunodeficiency) is a generic term for a group of immune system deficiencies. The cornerstone of SCID pathology, is defect in T lymphocyte development that can affect either their number or their function with subsequent effects on both B lymphocytes and natural killer (NK) cell populations.(1) Based on background mechanism, SCID subtypes can be classified as impairment of cytokine mediated signaling, defects in V(D)J recombination, impaired signaling through the pre-T cell receptor, increased lymphocyte apoptosis, defects in thymus embryogenesis, complete DiGeorge Anomaly, impaired calcium flux and other mechanisms. These mechanisms shape 4 main subgroups of SCID based on flowcytometric studies: T^- B^- NK^-, T^- B^- NK^+, T^- B^+ NK^- and T^- B^+ NK^+.(2)

Population T^- B^- NK^+ is a notable group in B cell-negative radiosensitive SCID and there are 5 cardinal genes that undergo mutation in this subgroup, result in SCID. All of these 5 genes encode components of the non-homologous DNA double-strand breaks end-joining system and are listed below:

- DNA cross link repair 1C (DCLRE1C) gene for Artemis protein (1).
- LIG4 gene for DNA ligase IV (3).

- X-Ray repair cross complementing 4 (XRCC4) gene that encodes protein repair which binds DNA ligase IV (4, 5).
- PRKDC gene for DNA protein kinase catalytic subunit (6).
- Non-homologous end joining 1 (NHEJ1) gene that encodes Cernunnos (6).

In this article we introduce a case of Cernunnos deficiency presented by microcephaly, mouth thrush, perforated otitis media, BCGosis and failure to thrive (FTT).

2. Case Presentation

An eight-months-old female infant was brought to emergency ward due to fever and vomiting with a history of oral thrush. The patient was the third child of a consanguineous parents. The older two siblings of the patient have expired; (the first one due to infection in neonatal period and the second one due to prematurity just few hours after birth). The patient has been vaccinated as the national instructions. Also, the history of moderate to severe eczema was notable. The physical examination revealed developmental delay, FTT, microcephaly (head circumference was 36 cm at 8-month age) and bird-like facial appearance. Bilateral otitis and purulent secretion from axillary lymphadenitis (after BCG vaccination, a routine protocol in Iran, since 2-months old) was also noted. The report of audiometry brainstem response (ABR) exhibited bilateral mild sensorineural hearing loss (SNHL) in the 2000 Hz to 4000 Hz frequency range.

A normal lumbar puncture with negative culture results, negative blood culture and negative urine culture were the primary laboratory findings. Chest-X ray showed an atrophic thymus with mild increase in broncho-vascular markings in both sides. The patient’s complete blood cell count (CBC) revealed lymphopenia with absolute lymphocytic count of 585 cell/μL. (Table.1) Bone marrow aspiration revealed increased myeloid series and maturation arrest while myeloid to erythroid ratio was normal.

Based on decreased absolute CD3 and CD4 (less than 300 /μmol) and impaired lymphocyte transformation test (LTT) to PHA SCID was diagnosed (Table 2.). Therefore, the patient received intravenous immune globulin (IVIG) and was discharged with prophylactic antiviral (Acyclovir) and anti-PCP (prophylaxis for pneumocystis pneumonia, Cotrimoxazole) medications.

Table 1
Laboratory findings

Laboratory findings	8-month	15-month	18-month	Unit	Normal range
Hb	10.4	11.7	8.2	gr/dl	13–17
Plt	288000	212000	14000	cell/ml	150000–450000
WBC	3900	4100	2300	cell/μl	4000–11000
ANC	3120	1640	1219	cell/μl	Birth: 2700–14400 2-weeks: 1500–5400 4-weeks: 1500–5400 2-6-month: 1000–5000 6-12-month: 1000–85000 1-6-year: 1000–8500 6-12-year: 1000–8000
ALC	585	1968	460	cell/μl	Birth: 2000–8000 2-weeks: 2800–9100 4-weeks: 2800–9100 2-6-month: 4000–10000 6-12-month: 4000–12000 1-6-year: 1500–9500 6-12-year: 1500–7000
IgG level (ELISA)	115	501	-	mg/dl	< 1 month: 700–1600 1-3-month: 250–750 4-6-month: 180–800 7- 24-month: 300–1000 3-5-year: 500–1300 6-9-year: 600–1300 10-13-year: 700–1400

WBC, white blood count; Hb, hemoglobin; PLT, platelet; ANC, absolute neutrophil count; ALC, absolute lymphocyte count.

Laboratory findings	8-month	15-month	18-month	Unit	Normal range
IgA level (ELISA)	23		-	mg/dl	< 1 month: 7–94 1-2-month: 10–131 1-2-year: 19–220 4-5-year: 48–345 6-7-year: 41–297 11-13-year: 44–395
IgM level (ELISA)	85		-	mg/dl	< 1 month: 10–30 1-3-month: 10–70 4-12-month: 20–100 1-2-year: 40–140 3-5-year: 40–180 6-13-year: 40–150
IgE level (ELISA)	2	0.5	-	IU/mL	< 1 year: Up to 10 1-5-year: Up to 68 6-15-year: Up to 68
CD3	333.45 (57%)	-	-	cell/µl (%)	35–78%
CD4/CD8	8.1	-	-	cell/µl (%)	1–3
CD4	286.65 (49%)	-	-	cell/µl (%)	22–62%
CD8	35.1 (6%)	-	-	cell/µl (%)	12–36%
CD16	93.6 (16%)	-	-	cell/µl (%)	4–30%

WBC, white blood count; Hb, hemoglobin; PLT, platelet; ANC, absolute neutrophil count; ALC, absolute lymphocyte count.

Laboratory findings	8-month	15-month	18-month	Unit	Normal range
CD19	23.4 (4%)	-	-	cell/µl (%)	3–14%
CD20	23.4 (4%)	-	-	cell/µl (%)	3–15%
CD56	70.2 (12%)	-	-	cell/µl (%)	4–30%

WBC, white blood count; Hb, hemoglobin; PLT, platelet; ANC, absolute neutrophil count; ALC, absolute lymphocyte count.

Table 2
The LTT test result

Antigen	Patient's response	Normal range
PHA	1.4	≥ 3
BCG	1.3	≥ 2.5
Candida	1	≥ 2.5

PHA, phytohemagglutinin, BCG, Bacillus Calmette-Guerin

About 16 days later the patient re-hospitalized for another episode of bilateral purulent otitis media. Assessment of cytomegalovirus (CMV) viral load and other viral markers such as IgM and IgG levels of Toxoplasma and human immunodeficiency virus (HIV) were negative. Three months later, while receiving prophylactic antiviral and antibiotics, another hospitalization required due to atypical respiratory tract infection.

At 18 month another hospital admission for oral intolerance and oral thrush was documented. Previous hospitalization for fever and poor feeding was also notable at 17-month. The CBC showed thrombocytopenia that considered as a sign of sepsis and was managed by wide spectrum antibiotics, and transfusion of packed cell, FFP and Platelets.

Genetic analysis with whole exome sequencing (WES) detected homozygous canonical splice site variant in NHEJ1 gene in intron 3 (variant c.390 + 1G > T) that could be consider a likely pathogenic variant which has not been reported previously for the pathogenicity. The mutation was in consistence with the

phenotype of the patient (SCID with microcephaly, growth retardation and sensitivity to ionizing radiation).

Finally, the patient referred for bone marrow transplantation, received prophylactic antibiotics and antifungal and IVIG regularly. Pre-operative endocrinology consult revealed hypothyroidism with TSH = 7.2, T4 = 8.3 which was normalized receiving Levothyroxine.

3. Discussion

Repeated admissions with atypical infections lead to clinical suspicion of immunodeficiency and decreased CD3 and CD4, as well as impaired LTT results, suggested SCID. Microcephaly, developmental delay and FTT guided us to specific subtypes of SCID associated with these symptoms such as Cernunnos deficiency and radio-sensitive genetic mutations. Combination of microcephaly, recurrent infections with opportunistic and atypical microorganism while receiving prophylactic antibiotics, FTT, lymphopenia, decreased IgA, IgE and IgG levels, T^- B^- NK^+ flow cytometry and impaired LTT in the patient were all clues to immunodeficiency. As implied in introduction, mutations in DCLRE1C gene, LIG4 gene, XRCC4 gene, PRKDC gene and NHEJ1 gene are associated with T^- B^- NK^+ subgroup of SCID (1, 3, 4, 6). Mutation in NHEJ1 gene causes Cernunnos deficiency which results in pre-T cell receptor defect by impairment of VDJ recombination pathway. Microcephaly and growth retardation are common clinical features of DNA ligase IV and Cernunnos/XLF deficiency and are not reported in Artemis and PRKDC defects.(7) Recio et al. reported that not only mutations in Cernunnos gene show variable clinical features but also the immunological profile would vary (5). Mild to severe T-cell lymphopenia was para clinically investigated in patients with NHEJ1 mutations in which the CD4 + and/or CD8 + number would be impaired (5). The genetic mutation in our case was in splicing site of NHEJ third intron detected by WES. It is of great importance as it is a novel mutation, not previously reported, compatible with patient's phenotype.

The most common clinical manifestations of Cernunnos deficiency are growth retardation, microcephaly, recurrent opportunistic infections, radio-sensitivity, dysmorphic faces (bird-like) and developmental delay that were all compatible with our case (2, 8). To the best of our knowledge, there is no reported evidence for the sensorineural hearing loss in patients with cernunnos immunodeficiency.

Concurrent lymphopenia, with decreased IgA, IgE, IgG levels and normal IgM level dedicated an impaired V(D)J recombination.(7) Normal IgM level is justifiable by antibody production activity of remnant B cells and Cernunnos might play a role in class switch recombination (CSR), in addition to V(D)J recombination in the literature.(9) Yazdani et al. reported that 14.8% of Cernunnos deficiency cases have normal or increased levels of some immunoglobulin subtypes.(8)

Another interesting finding that should be highlighted in the case is hypothyroidism that has been less reported in Cernunnos deficient patients (8).

This case is the second reported Iranian case of Cernunnos deficiency. The first case, reported by Yazdani et al. was a 3-year-old girl presented by BCGosis, oral thrush, recurrent infections, FTT, microcephaly and lymphopenia, with normal B cell count, IgA, and IgM concentration but decreased IgG levels (8).

There are not so many therapeutic strategies for Cernunnos deficiency and hematopoietic stem cell transplantation (HSCT) is the only present curative treatment with promising results and expected survival rates of 90%.(10) HSCT can be conducted by HLA identical related or unrelated donor.(10, 11) In the absence of proper HSCT most of Cernunnos deficiency cases only survive the first years of life and after then will expire due to septic shock.(8)

In case of concurrent autoimmune manifestations steroids are often useful for managing the patient's signs and symptoms but definitive treatment is again HSCT.(12)

Ultimately in any patient with recurrent infections, birdlike face, microcephaly, FTT and hypogammaglobinemia SCIDs with radiosensitive genetic mutations such as Cernunnos-XLF and ligase IV mutations should be suspected strongly.

Declarations

Competing Interests: The authors declare that they have no competing interests.

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Ethical issues: The informed consent and permission for the use of patient's clinical data has been provided and the patient's parent approved it in Persian which is available in her medical records in our hospital.

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Authors' contributions: Collected patient data – YF, MH, MK, ZC, SE. Drafted the manuscript and searched the literature – YF, MH, GE, BSS, RMG. Reviewed and edited the manuscript – all authors. All authors read and approved the final manuscript.

Consent for publication: the patient consent in Persian has been obtained from the patients' parent and is available in her clinical medical records.

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