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ORIGINAL ARTICLE

Cernunnos defect in an Iranian patient with T^- B^+ NK^+ severe combined immunodeficiency: A case report and review of the literature

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Abstract

Background: Defective Cernunnos gene in nonhomologous end-joining (NHEJ) pathway of the DNA repair is responsible for radiosensitive severe combined immunodeficiency (SCID). Herein, presented a new patient with Cernunnos deficiency and summarized the clinical, immunological, and molecular features of reported patients in the literature.

Case: The patient was a 6-month-old female born to consanguineous parents. She presented with long-lasting fever, diarrhea, poor feeding, and restlessness. She had suffered from recurrent fever of unknown origin and multiple episodes of oral candidiasis. In the physical examination, microcephaly, failure to thrive, oral candidiasis, pustular rash on fingers, and perianal ulcers, but no dysmorphic feature were observed. The immunologic workup revealed lymphopenia, neutropenia, normocytic anemia, low T- but normal B- and natural killer (NK)- cells, low immunoglobulin (Ig)G, and normal IgA, IgM, and IgE. The T-cell receptor excision circle (TREC) was low and the lymphocyte transformation test (LTT) was abnormal to mitogens and antigens. She was diagnosed with T^- B^+ NK^+ SCID and improved by intravenous immunoglobulin along with antimicrobials. A homozygous splice site variant, c.390 + 1G > T, at the intron 3 of the *NHEJ1*, was identified and the diagnosis of Cernunnos deficiency was established. However, while a candidate for hematopoietic stem cell transplantation, she developed sepsis and died at 11 months of age.

Conclusions: Cernunnos deficiency should be considered as a differential diagnosis in patients with microcephaly, growth retardation, recurrent infections, T-cell defects, and hypogammaglobulinemia. The normal B-cell level in the index patient is an unexpected finding in Cernunnos deficiency which requires further evaluation.

KEYWORDS
BCG, Cernunnos deficiency, inborn errors of immunity, NHEJ1, SCID, severe combined immunodeficiency

1 | INTRODUCTION

Cernunnos, which is encoded by *NHEJ1* gene (OMIM number: 611290) on chromosome 2q35, is involved in the nonhomologous end-joining (NHEJ) pathway of the DNA repair. Other components of the pathway include DNA ligase IV, XRCC4, Artemis, and DNA-PKcs (DNA-dependent protein kinase catalytic subunit), deficiency of which contribute to the development of well-described chromosomal instability syndromes (Slatter & Gennery, 2020). Cernunnos is involved in the junctional diversity of the antigen receptors and plays important role in DNA double-strand break repair and V(D)J recombination (Menon & Povirk, 2017).

In 2003, a patient (2BN patient) with severe combined immunodeficiency (SCID) phenotype, short stature, and increased radiosensitivity was identified. Her cells showed impaired V(D)J recombination and defects in rejoining DNA strand breaks, however, at the time she did not have defects in any of the known NHEJ factors (Dai et al., 2003). Two years later, Ahnesorg et al. (2006) used a yeast two-hybrid screen in 2BN patient's cells for XRCC4 interactors and identified a conserved 33 kDa protein with structural similarities to XRCC4, thus named it XRCC4-like factor or XLF. They showed that XLF directly interacts with XRCC4-Ligase IV complex in vitro and in vivo. They also produced XLF-complemented cells by introducing the wild-type XLF cDNA to 2BN cells and showed that they are far more susceptible to radiation exposure.

Another research team independently introduced five patients with similar features and defined Cernunnos gene defect through cDNA functional complementation cloning. These shared features included growth retardation, microcephaly, dysmorphic features, recurrent infections, and combined immunodeficiency (with low B and T cells but normal natural killer (NK) cells), hypogammaglobulinemia, and increased sensitivity of their fibroblast to gamma ionizing radiation (Buck et al., 2006).

In the latest International Union of Immunological Societies (IUIS) classification of human inborn errors of immunity (IEI), Cernunnos deficiency is categorized as $T^-B^-NK^+$ severe combined immunodeficiency (Bousfiha et al., 2020). According to the Iranian National Registry of Primary Immunodeficiencies (Abolhassani et al., 2018), CID/SCID compromises 12% of 3056 registered IEI patients and the lowest survival rate among different categories of IEI is observed in patients with a CID (mainly severe CID) in the first 5 years of life, which could have been prevented by earlier diagnosis and treatment.

Although most of the chromosomal instability syndromes have clinically indistinguishable shared features, introducing newly identified patients with novel pathogenic variants can help characterize each syndrome in a more precise way, prevent some of the iatrogenic complications such as radioactive-related damages, and reduce the diagnosis delay in similar patients, which itself has a considerable impact in therapeutic decision-making (such as early application of hematopoietic stem cell transplantation [HSCT]) and prognosis. In this viewpoint, we aim to present an Iranian patient with SCID phenotype, who was found to have defect in the *NHEJ1* gene, however, with unexpected immunologic profile. We also reviewed all patients with Cernunnos deficiency reported in the literature.

2 | CASE REPORT

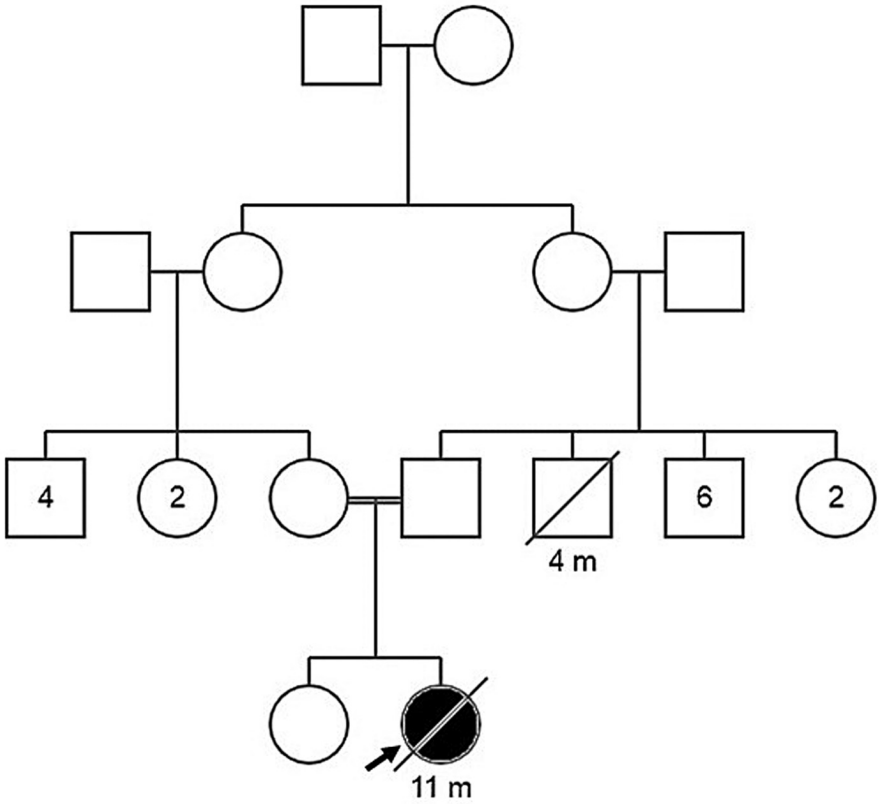
The patient was a 6-month-old female who was presented to our hospital with fever (for 2 weeks), diarrhea (for 5 days), poor feeding, and restlessness. She was born to consanguineous parents (first cousins). The family history was non-contributary and her 8-year-old brother was healthy (Figure 1).

The fever had been recurrent with unknown origin and she was hospitalized three times for fever workup. She had a history of urinary tract infection (UTI). She suffered from multiple episodes of oral candidiasis, controlled by Nystatin suspension.

On physical examination, the patient was toxic and febrile. She had microcephaly (head circumference: 36.5 cm, <3rd percentile) and failure to thrive (58 cm (−3.0 SD) height and 4.7 Kg (−3.7 SD) weight, <3rd percentile). No facial dysmorphism was observed. She had hoarseness and in the lung auscultation, rhonchi, and wheezing were noted. She had developed erythema and swelling at the site of the BCG vaccine injection, resolved after 10 days. Oral candidiasis, pustular rash on fingers, and multiple perianal punch out ulcers were found. No hepatosplenomegaly or lymphadenopathy was detected.

At this time the differential diagnoses included combined immunodeficiency, severe combined immunodeficiency, chronic granulomatous disease, congenital neutropenia, hemophagocytic lymphohistiocytosis,

FIGURE 1 The proband's Pedigree.



metabolic disorders, bacterial sepsis, and viral or fungal infections.

The chest x-ray and chest computed tomography (CT) scan were normal. In the head and neck CT scan mastoid opacification was reported. The echocardiography and abdominal ultrasound were also normal. Bronchoscopy evaluation, performed due to hoarseness, showed tracheomalacia in the lower one-third of the trachea. Bronchoalveolar lavage (BAL) culture and smear for bacteria and fungi were negative.

In the initial laboratory result, leukopenia (WBC: 1100 cell/μl), lymphopenia (ALC: 1089 cell/μl), neutropenia (ANC: 11 cell/μl), normocytic anemia (Hb: 7.5 g/dL), high inflammatory markers (ESR: 44 mm/hour, CRP: 153 mg/L) and lactate dehydrogenase (LDH: 444 IU/L), and abnormal liver enzymes (AST: 178 IU/L, ALT: 110 IU/L) were found. The blood culture was positive for gram positive cocci. The EBV and CMV viral load, HIV antibody (Ab), HBS antigen, HBS Ab, and HCV Ab were all negative. The COVID-19 polymerase chain reaction (PCR) test was negative. TORCH study and metabolic disorder workup were already performed in another center and yielded normal results. The bone marrow aspiration was hypocellular without any maturation arrest. In the immunologic workup, she had low T $CD3^+$ (141 cell/μl), low T $CD4^+$ (119 cell/μl), low T $CD8^+$ (22 cell/μl), normal B $CD19^+$ (555 cell/μl) and B $CD20^+$ (544 cell/μl), and normal NK $CD16^+CD56^+$ (272 cell/μl) cell counts. The immunologic profile revealed low IgG (83 mg/dL), while normal IgA (195 mg/dL), IgM (203 mg/dL), and IgE (0.2 IU/ml). The nitroblue tetrazolium (NBT) test was normal. The T-cell receptor excision circle (TREC) was low. The lymphocyte transformation test (LTT) was abnormal to mitogens and antigens (PHA: 1.5, BCG: 2, Candida: 1.5) (Supporting Information ESM_ 1).

She was placed on vancomycin (10 mg/kg/dose/QID) and meropenem (20 mg/kg/dose/TDS), voriconazole (30 mg/kg/BD), and G-CSF (10 mcg/kg/day due to persistent neutropenia). However, the fever persisted and the neutropenia was non-responsive to G-CSF.

She was diagnosed with T^- B^+ NK^+ severe combined immunodeficiency (SCID) and received intravenous immunoglobulin (IVIg) along with previously prescribed antimicrobials, which resulted in considerable clinical improvement. She was discharged with prophylactic treatment cotrimoxazole (10 mg/kg daily), voriconazole (5 mg/kg), acyclovir (15 mg/kg daily), isoniazid (25 mg daily), G-CSF (10 mcg/day), and monthly IVIg (3 gr/month).

Later, the genetic study using Whole Exome Sequencing showed a homozygous canonical splice site variant, c.390 + 1G > T, at the intron 3 of *NHEJ1* gene (NM_024782.3); based on the American College of Medical Genetics (ACMG) guidelines this variant can be classified as likely pathogenic and the diagnosis of Cernunnos deficiency was established (CADD score: 34). This variant has not been reported previously, but

TABLE 1 Summary of demographic, clinical, and molecular findings in Cernunnos deficiency

Pt	Sex	Country of origin	Parental Consanguinity	FH of IEIs, Early death, or miscarriage	AOD (month)	Infectious complications	Growth failure	Neurologic/learning disorders	Anomalies
1	F	USA	No	Yes	72	Immunodeficiency	Yes	None	–
2	–	France	No	No	168	Recurrent RTI, Invasive warts, Severe cholangitis	Yes	Microcephaly, Mental retardation	Urogenital and bone malformation, Facial dysmorphia
3	–	Turkey	Yes	Yes	24	Recurrent RTI and GI tract infections	Yes	Microcephaly	None
4*	M	Turkey	Yes	Yes	156	*Pneumocystis carinii* pneumonia, chronic Giardia lamblia enteritis, Salmonella and Campylobacter enteritis, molluscum contagiosum, and warts	Yes	Microcephaly	Facial dysmorphia, Bone malformation
5*	F	Turkey	Yes	Yes	24	Recurrent RTI	Yes	Microcephaly	Facial dysmorphia, Bone malformation
6	M	Italy	Yes	No	84	Recurrent RTI	Yes	Microcephaly	Facial dysmorphia
7	M	Spain	Yes	No	144	Recurrent RTI	No	Microcephaly, developmental delay	Facial dysmorphia
8*	M	Germany	No	Yes	72	Chronic diarrhea, Recurrent RTI, Adenoviral arthritis, UTI	Yes	Microcephaly	None
9*	M	Germany	No	Yes	24	Recurrent RTI	No	None	None
10	M	Malaysia	No	No	96	–	No	Microcephaly	Facial dysmorphia, Clinodactyly
11	M	Turkey	Yes	No	12	–	Yes	Microcephaly	None
12	F	Turkey	Yes	Yes	20	Recurrent RTI, Mucocutaneous candidiasis, purulent otitis, Diffuse molluscum contagiosum	Yes	Microcephaly	None
13	–	Poland	No	No	72	Recurrent RTI	Yes	Microcephaly, dd	None
14	M	Pakistan	Yes	No	24	Episodic diarrhea, vomiting and cough	Yes	Microcephaly, dd	None
15	M	Turkey	Yes	No	132	Recurrent RTI, UTI	Yes	Microcephaly, Febrile seizure, moderate dd	Microphthalmia, Blepharophimosis, posterior cleft palate, acral anomalies
16	F	Turkey	Yes	Yes	1	Diarrhea	Yes	Microcephaly	Facial dysmorphia
17	F	Turkey	Yes	Yes	9	Recurrent RTI, UTI, Otitis media, CMV pneumonia	Yes	Microcephaly	Facial dysmorphia

Cytopenia	Other Clinical features	Zygosity/variant type/ affected exon(s) or intron(s)	c. DNA change (NM_024782.3)	Treatments	Life status at the time of study	Ref
–	–	Homozygous/Frameshift dup/Exon 2	c.11dupT (p.E5Gfs*43)	BMT	Alive	Dai et al. (2003)
AIHA, ITP	Chromosomal abnormalities	Compound heterozygous/ Missenses; missense/ Exon 2; exon3	c.169C > G (p.R57G); c.367T > C (p.C123R)	IS, IGRT, Splenectomy	Deceased (18 y, Septic Shock)	Buck et al. (2006)
None	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	IGRT	Deceased (4 y, Septic Shock)	Buck et al. (2006)
AIHA, ITP	–	Homozygous/Indel/Intron 2	c.177 + 1_177 + 3delGTAinsTT	IGRT, AB prophylaxis	Alive	Buck et al. (2006)
None	–	Homozygous/Indel/Intron 2	c.177 + 1_177 + 3delGTAinsTT	IGRT, AB prophylaxis	Alive	Buck et al. (2006)
Bone marrow aplasia, Pancytopenia	Chromosomal abnormalities	Homozygous/Missense/ Exon 2	c.169C > G (p.R57G)	IGRT	Alive	Buck et al. (2006), Faraci et al. (2009)
None	–	Homozygous/Missense/ Exon 2	c.169C > G (p.R57G)	–	Alive	Dutrannoy et al. (2010)
Neutropenia	Hepatosplenomegaly, Abdominal lymphadenopathy	Compound heterozygous/ Frame shift dup; large deletion/Exon 4; exons 2 and 3	c.495dupA (p.D166Rfs*20); 1.9 kb deletion	IGRT	Alive	Dutrannoy et al. (2010), Meyer-Bahlburg et al. (2014)
None	None	Compound heterozygous/ Fame shift dup; large deletion/Exon 4; exons 2 and 3	c.495dupA (p.D166Rfs*20); 1.9 kb deletion	None	Alive	Dutrannoy et al. (2010)
Thrombocytopenia	Left hearing loss	Compound heterozygous/ Nonsense; large deletion/Exon 4; exons 1–3	c.526C > T (p. R176*); 6.9 kb deletion	IGRT, AB prophylaxis	Alive	Dutrannoy et al. (2010)
AIHA	dystrophy and mouth lesions	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	Blood transfusions, BMT	Deceased (1.5 y, Septic shock)	Dutrannoy et al. (2010)
None	Wheezing attacks, clubbing, bronchiolitis Obliterans, pulmonary HTN	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	IGRT, AB prophylaxis	Deceased (4.5 y, Unknown)	Turul et al. (2011)
None	–	Homozygous/Nonsense/ Exon 4	c.501C > A (p.Y167*)	–	Alive	Du et al. (2012)
None	–	Homozygous/Nonsense/ Exon 2	c.169C > T (p.R57*)	–	Alive	Du et al. (2012)
None	Bilateral VUR	Homozygous/Large deletion/Exons 2–5	ex 2–5 deletion	IGRT	Alive	Du et al. (2012), Verloes et al. (2001)
None	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT	Alive	Çağdaş et al. (2012)
Neutropenia, Coombs positive AIHA	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	Irradiated RBC transfusions, IGRT, IS, AB prophylaxis, BMT	Alive	Çağdaş et al. (2012)

TABLE 1 (Continued)

Pt	Sex	Country of origin	Parental Consanguinity	FH of IEIs, Early death, or miscarriage	AOD (month)	Infectious complications	Growth failure	Neurologic/learning disorders	Anomalies
18	F	Turkey	Yes	Yes	36	Recurrent perianal abscess	Yes	Microcephaly,	Facial dysmorphia, polydactyly
19	M	Turkey	Yes	Yes	7	Oral thrush, Recurrent RTI, chronic diarrhea, fungal abscess	Yes	Microcephaly, Focal convulsion	Facial dysmorphia
20	F	Turkey	Yes	No	42	RTI, diarrhea	Yes	Microcephaly	Facial dysmorphia
21	–	Netherlands	–	–	48	Recurrent RTI	Yes	Microcephaly	–
22	–	Netherlands	–	–	1.5	Diarrhea	Yes	Microcephaly	–
23	–	Netherlands	–	–	15	UTI, RTI	Yes	Microcephaly	–
24	–	Netherlands	–	–	120	RTI	Yes	Microcephaly	–
25	–	Netherlands	–	–	96	–	Yes	Microcephaly	–
26	–	Netherlands	–	–	11	Recurrent fungal RTI	Yes	Microcephaly	–
27	–	Netherlands	–	–	96	Recurrent RTI	Yes	Microcephaly	–
28	–	Netherlands	–	–	108	RTI, Diarrhea	Yes	Microcephaly	–
29	–	Netherlands	–	–	12	BCGitis, Otitis	Yes	Microcephaly	–
30	M	Spain	Yes	No	48	RTI	Yes	None	None
31*	M	Saudi Arabia	Yes	Yes	180	Chest infections, Bronchiectasis, Hepatitis B	Yes	Microcephaly, Neurological manifestations (Hyperreflexia), dd	Facial dysmorphia, Radial deviation of little fingers
32*	F	Saudi Arabia	Yes	Yes	2	Chest infections, Bronchiectasis, Hepatitis B	Yes	Microcephaly, muscle spasms, mouth pulling to one side, progressive ataxia, worsening proximal muscle weakness, and inability to walk without assistance, dd	Facial dysmorphia
33*	M	Saudi Arabia	Yes	Yes	12	Recurrent otitis media, Hepatitis B	Yes	Microcephaly, Neurological manifestation, dd	Facial dysmorphia
34	F	Iran	Yes	Yes	36	BCG adenitis, Mastoiditis, Otitis media, UTI, Oral candidiasis, Pansinusitis	Yes	Microcephaly	None
35	M	Pakistan	–	–	256	No	Yes	Microcephaly	Skeletal anomalies (clinodactyly)
36	F	Spain	No	No	4.5	–	Yes	Microcephaly	None

Cytopenia	Other Clinical features	Zygosity/variant type/ affected exon(s) or intron(s)	c. DNA change (NM_024782.3)	Treatments	Life status at the time of study	Ref
Pancytopenia, Neutropenia	Spontaneous chromosomal breakages	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	IGRT, BMT (candidate)	Alive	Cipe et al. (2014)
Pancytopenia, Neutropenia	NHL	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	Anti-epileptic, Chemotherapy (RTX and MTX), IGRT, AB prophylaxis	Alive	Patiroglu et al. (2015)
Pancytopenia	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	IGRT, AB prophylaxis	Alive	Akar et al., 2016)
–	–	Homozygous/Nonsense/ Exon 4	c.501C > A (p.Y167*)	BMT	Alive	Speert et al. (2016)
–	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT	Alive	Speert et al. (2016)
–	Autoimmunity	Homozygous/Nonsense/ Exon 2	c.169C > T (p.R57*)	BMT	Alive	Speert et al. (2016)
–	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT	Alive	Speert et al. (2016)
–	–	Homozygous/Frameshift dup/Exon 3	c.324dupG (p.R109Afs*3)	BMT (candidate)	Alive	Speert et al. (2016)
–	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT (candidate)	Alive	Speert et al. (2016)
–	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT (candidate)	Alive	Speert et al. (2016)
–	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT	Alive	Speert et al. (2016)
–	Autoimmunity	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT	Alive	Speert et al. (2016)
Bone marrow aplasia, Pancytopenia	Short telomere	Homozygous/Nonsense/ Exon 2	c.169C > T (p.R57*)	IGRT, Blood transfusion, BMT	Deceased (8 y, Severe complications after HSCT)	Carrillo et al. (2017)
Pancytopenia	–	Homozygous/Canonical splice site/Intron 3	c.390 + 1G > C	IGRT, AB prophylaxis	Alive	Sheikh et al. (2017)
Pancytopenia	–	Homozygous/Canonical splice site/Intron 3	c.390 + 1G > C	IGRT, AB prophylaxis	Deceased (20 y, Septic shock)	Sheikh et al. (2017)
Pancytopenia	Allergic to IVIg	Homozygous/Canonical splice site/Intron 3	c.390 + 1G > C	No IGRT due to anaphylaxis	Alive	Sheikh et al. (2017)
Autoimmune anemia and thrombocytopenia	Neonatal hypothyroidism, Splenomegaly, Lymphadenopathy	Homozygous/Nonsense/ Exon 5	c.526C > T (p.R176*)	Levothyroxine, AB prophylaxis, IGRT, BMT	Alive	Yazdani et al. (2017)
Mild pancytopenia	MDS (Initially monosomy 7, replaced by del (20))	Homozygous/Missense/ Exon 3	c.236T > C (p.L79P)	–	Alive	Kager et al. (2018)
None	–	Homozygous/Nonsense/ Exon 2	c.169C > T (p.R57*)	BMT	Alive	Recio et al. (2018)

TABLE 1 (Continued)

Pt	Sex	Country of origin	Parental Consanguinity	FH of IEIs, Early death, or miscarriage	AOD (month)	Infectious complications	Growth failure	Neurologic/learning disorders	Anomalies
37	F	Spain	No	No	94	RTI	Yes	Microcephaly	Facial dysmorphia
38	F	Iran	Yes	Yes	30	Axillary lymphadenitis following BCG	Yes	Microcephaly, dd	–
39	F	Turkey	Yes	Yes	18	–	Yes	dd	–
40	F	Turkey	Yes	Yes	66	–	Yes	dd	–
41	M	Oman	Yes	Yes	3	Klebsiella pneumonia sepsis	Yes	Microcephaly	Facial dysmorphia, Ectopic kidney with normal function
42	M	India	–	–	204	–	–	–	–
43	–	Italy	–	–	108	–	–	–	Facial dysmorphia
44*	–	Italy	–	Yes	144	–	–	–	Facial dysmorphia
45*	–	Italy	–	Yes	180	–	–	–	Facial dysmorphia
46	M	India	–	–	10	Recurrent gastroenteritis, Pneumonia, CMV infection	–	–	–
47	M	India	–	–	11	Skin pustule and abscess, Oral thrush	–	–	–
48	F	Iran	Yes	Yes	2	Oral thrush, BCGitis, Bilateral otitis	Yes	Microcephaly, dd, bilateral mild sensorineural hearing loss	No
49	F	Iran	Yes	No	6	Oral candidiasis, Diarrhea, UTI, BCGitis, mastoiditis	Yes	Microcephaly	None

Abbreviations: AB; antibiotic, AIHA; autoimmune hemolytic anemia, AOD; age of diagnosis, BCG; bacillus Calmette–Guerin, BMF; bone marrow failure, BMT; bone marrow transplant, CMV; cytomegalovirus, dd; developmental delay, FH; family history, FTT; failure to thrive, GI; gastrointestinal, HTN; hypertension, IEI; inborn error of immunity, IGRT; immunoglobulin replacement therapy, IS; immunosuppressive, ITP; immune thrombocytopenic purpura, IVIg; intravenous immunoglobulin, MDS; Myelodysplastic syndrome, MTX; methotrexate, NHL; non-Hodgkin lymphoma, RTI; respiratory tract infection, RTX; rituximab, UTI; urinary tract infection,

* Siblings.

Sheikh et al. (Sheikh et al., 2017) have reported another nucleotide change (c.390 + 1G > C) at the same position in a Saudi Arabian family with three affected siblings. They showed that this change results in two aberrantly spliced mRNA isoforms, both causing in-frame deletions at the RNA level (skipping full length of exon 3 containing 71 amino acids and skipping of 69 bp at the end of exon 3 including 23 amino acids). They did not find any protein expression using immunoblotting. Considering their results, we can confer that our detected variant would have a similar effect and act as a loss of function variant.

Our patient mildly improved and was candidate for the HSCT. However, in the meanwhile, her clinical condition deteriorated and she unfortunately died at 11 months of age due to sepsis.

3 | DISCUSSION

NHEJ pathway, in which Cernunnos (XLF) is a core player, is active throughout the cell cycle (particularly in G1) and mediates ligation of broken DNA double strands without any need of homologous template. Moreover, NHEJ functions in the generation of T-cell receptor and immunoglobulin repertoire, making it a ubiquitous pathway in DNA repair and immune system. Therefore, loss of function mutations in genes involved in NHEJ lead to

Cytopenia	Other Clinical features	Zygosity/variant type/ affected exon(s) or intron(s)	c. DNA change (NM_024782.3)	Treatments	Life status at the time of study	Ref
ITP	–	Homozygous/Nonsense/ Exon 2	c.169C > T (p.R57*)	BMT	Alive	Recio et al. (2018)
AIHA	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	IS	Alive	Esmaeilzadeh et al. (2019)
–	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT	Alive	Firtina et al. (2020)
–	–	Homozygous/Nonsense/ Exon 5	c.532C > T (p.R178*)	BMT	Alive	Firtina et al. (2020)
AIHA, G6PD def.	Supraventricular tachycardia	Homozygous/Missense/ Exon 3	c.367 T > C (p.C123R)	Blood transfusion, AB, IS, adenosine and cardioversion, IGRT	Deceased	Al-Marhoobi et al. (2020)
–	AML	Homozygous/Canonical splice site/Intron 4	c.530-2A > T	–	–	Arunachalam et al. (2021)
Aplastic anemia (BMF)	–	Homozygous/Missense/ Exon 2	c.169C > G (p.R57G)	BMT	Alive	Miano et al. (2021)
Aplastic anemia (BMF)	–	Homozygous/Missense/ Exon 4	c.506A > T (p.E169V)	BMT	Alive	Miano et al. (2021)
Aplastic anemia (BMF)	–	Homozygous/Missense/ Exon 4	c.506A > T (p.E169V)	BMT	Alive	Miano et al. (2021)
AIHA	–	Homozygous/Frameshift/ del/Exon 5	c.544_545delGA (p.E182Tfs*3)	IS	–	Vignesh et al. (2020)
–	Generalized erythematous macular rash	Homozygous/Frameshift/ del/Exon 3	c.221_222delGT (p.C74Sfs*4)	–	–	Vignesh et al. (2020)
No	Eczema, thymus atrophy, hypothyroidism	Homozygous/Canonical splice site/Intron 3	c.390 + 1G > T	Levothyroxine, AB prophylaxis, IGRT, BMT (candidate)	Alive	Farsi et al. (2021)
Bicytopenia	Tracheomalacia, perianal ulcers, pustular rash on fingers	Homozygous/Canonical splice site/Intron 3	c.390 + 1G > T	IGRT, AB prophylaxis, BMT (candidate)	Deceased (11 months, Septic shock)	This report, 2022

CID or SCID in both human and mice with often shared clinical phenotypes (Menon & Povirk, 2017; Sharma et al., 2020).

We reviewed the literature published from 2003 to date on a series of 49 patients with autosomal recessive hypomorphic mutations in *NHEJ1* including the present case report. The literature search and evaluation were performed using "NHEJ1", "nonhomologous end-joining factor 1", "XLF', "XRCC4-like factor", and "Cernunnos" keywords. In addition, reference lists of major reviews and case series were manually searched for additional studies. Table 1 summarizes demographic, clinical, and molecular findings of reported patients.

The most common clinical manifestations are growth failure (n = 40, 81.6%), infectious disorders (n = 38%, 77.6%), and microcephaly (n = 38%, 77.6%) (Figure 2). Other less frequent manifestations included cytopenia (n = 24%, 48.9%), facial dysmorphism (n = 20%, 40.8%), neurologic/learning disorder (microcephaly, developmental delay, and seizures) (n = 14%, 28.6%), skeletal anomalies (mainly acral malformations) (n = 8%, 16.3%), organomegaly (n = 3%, 6.1%), and malignancy (n = 3%, 6.1%).

Infectious disorders mostly included respiratory tract infections (n = 27%, 55.1%) and diarrhea (n = 11%, 22.5%), followed by ear-nose-throat disorders (n = 7%, 14.3%),

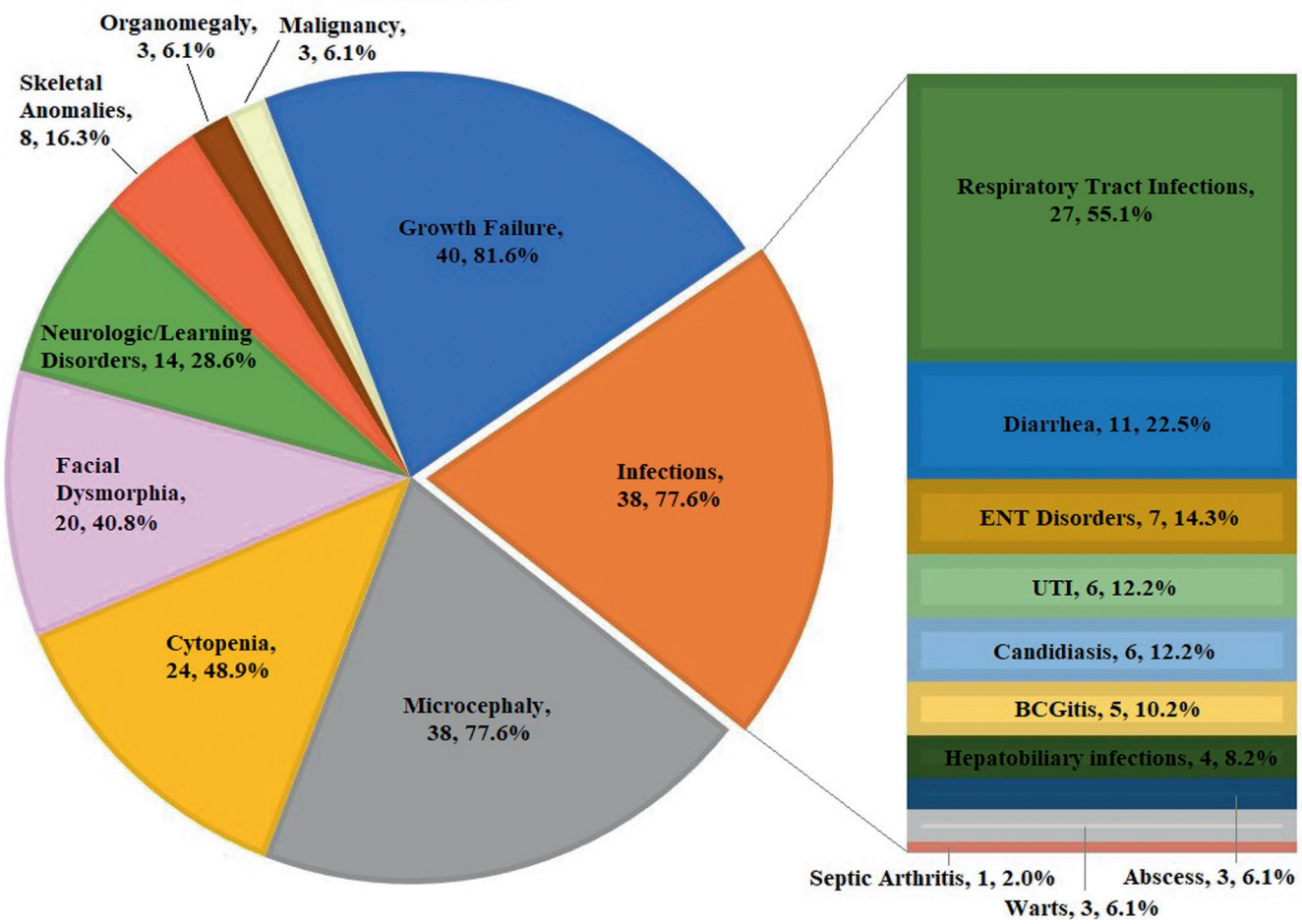


FIGURE 2 The spectrum of clinical manifestations among 49 patients with Cernunnos deficiency. The most common clinical manifestations are growth failure, microcephaly, and infectious disorders. RTI; respiratory tract infection, UTI; urinary tract infection, ENT; ear-nose-throat, BCG; bacillus Calmette–Guerin.

UTI ($n = 6\%$, 12.2%), candidiasis ($n = 6\%$, 12.2%), bacillus Calmette–Guerin (BCG) lymphadenitis ($n = 5\%$, 10.2%), hepatobiliary disorders (Hepatitis B and cholangitis) ($n = 4\%$, 8.2%), and less commonly warts ($n = 3\%$, 6.1%), abscesses ($n = 3\%$, 6.1%), and septic arthritis ($n = 1\%$, 2.0%).

A summary of immunologic characteristics in reported patients is illustrated in Figure 3 and Supporting Information ESM_2. Most patients had lymphopenia (32 of 39%, 82.1%), low T $CD3^+$ cells (31 of 38%, 81.6%), low T $CD4^+$ cells (23 of 27%, 85.2%), low T $CD8^+$ cells (20 of 27, 74.1%), low B cells (36 of 38%, 94.7%), but normal NK cells (20 of 30%, 67%). In addition, seven of 30 (23.3%) patients had elevated NK levels. The LTT was had suboptimal results in 16 out 18 (88.9%) patients. The majority of patients exhibited low IgG (27 of 35%, 77.2%) and low IgA (28 of 34, 82.0%), while the number of patients with low (15 of 32%, 46.9%) and normal (13 of 32%, 40.6%) IgM was rather equal. The interesting finding in our patient was T^- B^+ NK^+ flowcytometry pattern, which is not commonly expected in Cernunnos deficiency. Another patient with the similar immunologic phenotype was also an Iranian patient with BCG lymphadenitis, neonatal hypothyroidism, variable infections (mastoiditis, otitis media, candidiasis, and complicated UTI), failure to thrive (FTT), microcephaly, organomegaly, and cytopenia. She had normal $CD19^+$ B-cell population, but different affected XLF domain (Yazdani et al., 2017). These observations may be explained by ethnic/genetic background of these two patients.

As depicted in Figure 4, 20 different causative variants have been reported in patients affected by Cernunnos deficiency. XLF consists of a globular head domain, interacting with XRCC4, a coiled-coil stalk domain, and interacting with another XLF to form homodimer. The protein also has a C-terminal region that mediate its binding to DNA and also binding to Ku protein (a recruiting hub for multiple NHEJ factors) through a highly conserved Ku-binding motif (KBM).

All the variants have been located in globular head and coiled-coil stalk domains, more than half of them clustered in just 16 amino acids (166 to 182) of stalk domain. Nonsense variants are the most common point mutations

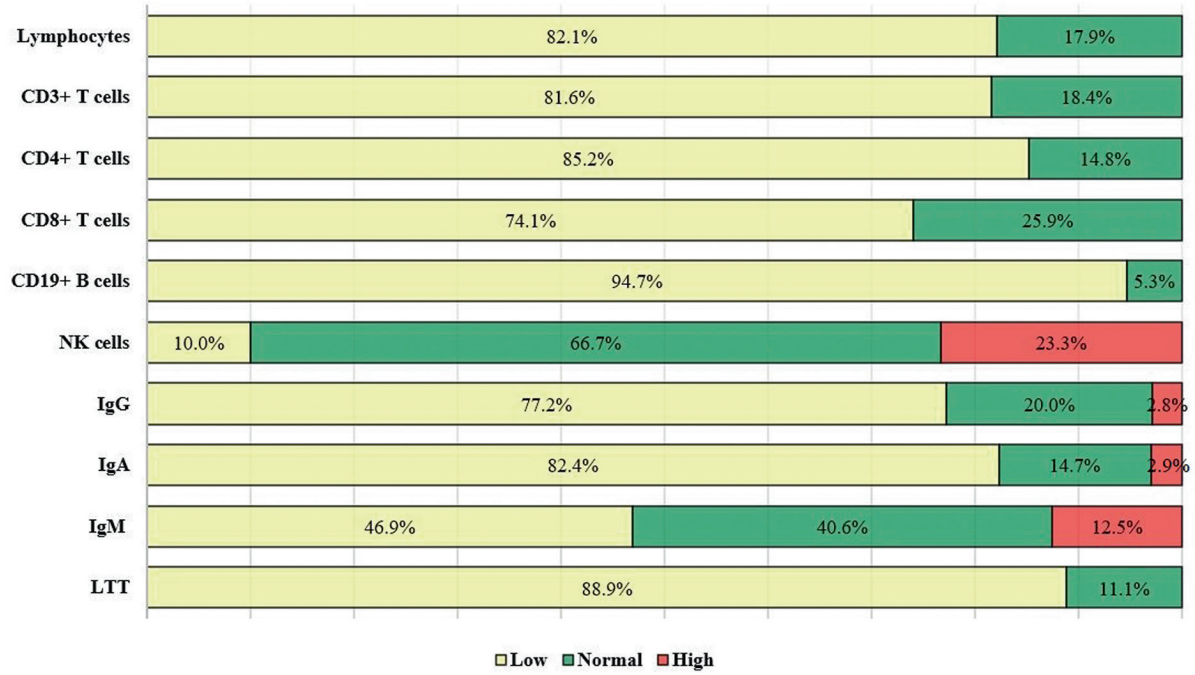


FIGURE 3 Immunological phenotype of patients with Cernunnos deficiency. The majority of patients represented lymphopenia, low T cells and its subset, low B cells, and normal natural killer (NK) cells. In addition, abnormal lymphocyte transformation test (LTT) and low serum IgG and IgA were reported in most of the reported patients, while the number of patients with low and normal IgM was rather equal.

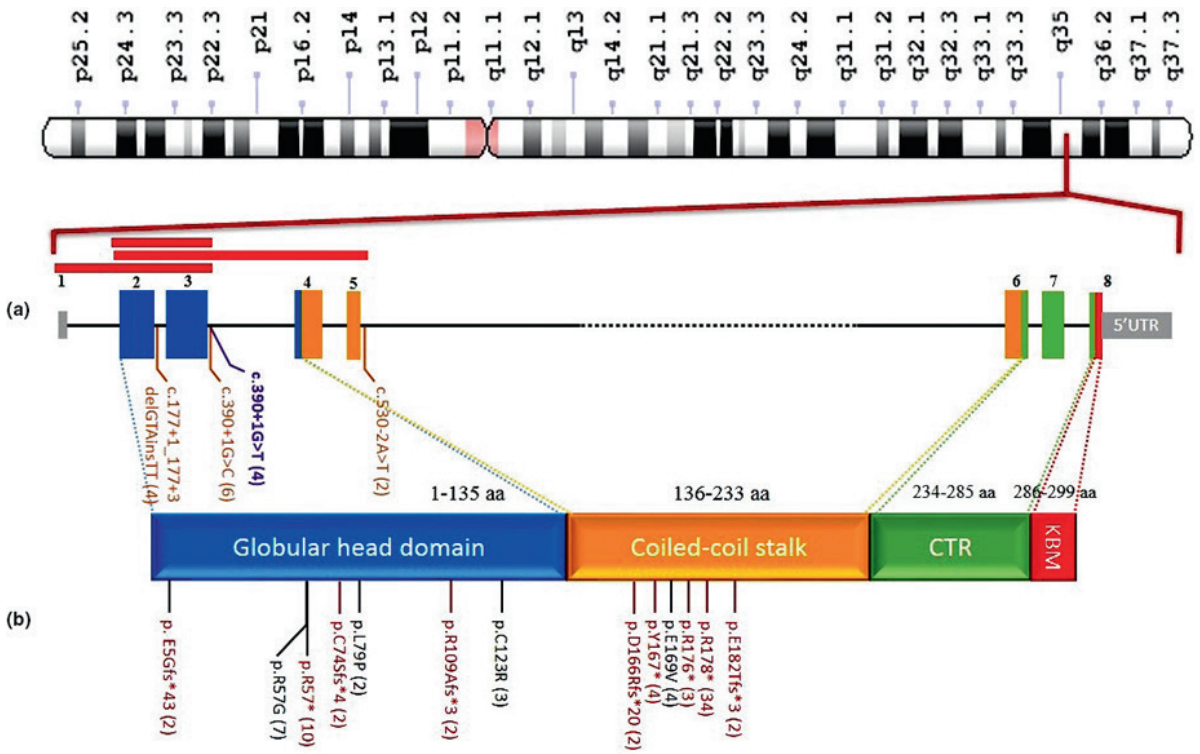


FIGURE 4 Spectrum of mutations in functional regions of XLF. (a) Schematic representation of *NHEJ1* exons (the size of exons is displayed on their scale, but the scales for introns and untranslated regions have not been regarded) and functional region of XLF protein [amino acids numbers corresponding to globular head (blue) and coiled-coil stalk (orange) domains are from Menon and Povirk (2017) and for Ku-binding motif (KBM) is from Frit et al. (2019); CTR: C-terminal region. (b) Reported variants. Missense variants are shown in black, frameshift and nonsense in red, splicing variant in brown and the proband's variant in purple. Red boxes on top of exons show reported large deletions. Numbers in parentheses show allele count of each variant.

(52%), followed by missense and splicing (16.4%), frameshift variants (10.2%), and large deletion (5.1%). There is no clear correlation regarding type/location of the mutation and clinical presentations/severity in the patients. As illustrated in Table 1, the three siblings reported by Sheikh et al. have similar symptoms, but our patient with the same affected nucleotide had different symptoms with no dysmorphic features or neurological presentation, but having skin manifestation.

In patients with SCID, including Cernunnos deficiency, HSCT is associated with favorable outcomes and provide long-term immune reconstitution. In this review, 17 out of 19 patients (89.5%) who received HSCT survived. Six other patients were planned for HSCT, one of whom (this report) had died while waiting for a matched donor. Finding an appropriate donor can be a general obstacle, yet patients with Cernunnos deficiency have some limitations regarding conditioning regimen. In other words, the co-administration of chemotherapy and radiotherapy can be harmful due to the varying degrees of radiosensitivity observed in these patients (Haddad & Hoenig, 2019; Slatter & Gennery, 2020). Recently, Slack et al. in a cohort of patients with DNA double-strand break repair disorders, reported 77 patients with DNA ligase IV deficiency, Cernunnos deficiency, or Nijmegen breakage syndrome, of whom 73 patients had received conditioning regimen, 69% were survived and the survival rate was notably higher among those with RIC regimen ($p = 0.006$) (Slack et al., 2018). Further specific studies are required to ascertain the role of HSCT in the survival of Cernunnos deficient patients. Besides, studies on $XLF^{-/-}$ mice have shown that the slope of B-cell loss in bone marrow and spleen increases and stem cell differentiation deteriorates with aging, affecting all hematopoietic lineages (Roch et al., 2019). Therefore, timely diagnosis of Cernunnos deficiency and taking measurements for early transplantation remarkably affect patients' morbidity and mortality.

In conclusion, Cernunnos deficiency should be considered as a differential diagnosis in patients with microcephaly, growth retardation, recurrent infections, T-cell defects, and hypogammaglobulinemia. Normal B-cells should not rule out the diagnosis, as patients may display T^{-} B^{+} NK^{+} phenotype.

AUTHOR CONTRIBUTIONS

M. Jamee and Z. Chavoshzadeh contributed to the conceptualization, data curation, and supervision of the study; M. Jamee wrote the original draft; Z. Chvoshzadeh, N. Khakbazan Fard, Sh. Fallah, M. Fallahi, B. Sh. Shamsian, and S. Sharafian diagnosed and managed the patient when she was alive; Z. Golchehre performed genetic analyses and draw Figure 4. All authors read and approved the final manuscript.

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CONSENT

Informed consent was obtained from the parents of the patients prior to inclusion in the study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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