Pediatric Rheumatology

CASE REPORT

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Three cases of autoinflammatory disease with novel NLRC4 mutations, and the first mutation reported in the CARD domain of NLRC4 associated with autoinflammatory infantile enterocolitis (AIFEC)

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Abstract

Background Gain of function (GOF) mutations in NOD-like receptor family CARD-containing 4 protein (NLRC4) gene induce a wide spectrum of autoinflammatory phenotypes. Currently, we categorize them into four groups: familial cold autoinflammatory syndrome (FCAS)4, autoinflammatory infantile enterocolitis (AIFEC), NLRC4-macrophage associated syndrome (MAS), and neonatal-onset multisystem inflammatory disease (NOMID). The rarity and complexity of the disease necessitate the description of new cases and a reexamination of our understanding of the condition.

Case presentations We present three patients with NLRC4-GOF mutations and AIFEC phenotypes. The first patient is an infant girl with periodic fever, seizure, high inflammatory markers, and an episode of macrophage associated syndrome (MAS). History of recurrent fever episodes since childhood was reported in mother and maternal grandmother. A heterozygous mutation was found in CARD domain of NLRC4: c.A91C: p.Asn31His. The second patient is an adolescent boy with periodic fever, diarrhea, aphthous stomatitis, seizure, and central nervous system (CNS) vasculitis. A heterozygous mutation was found in NLRC4 gene: c.1202T > C. p. Val401Ala. The third patient is a child with chronic diarrhea and elevated inflammatory markers. We found a heterozygous mutation in NLRC4 gene: c.390delG: p.S132Afs*21. All mutations have been reported for the first time as NLRC4 mutations associated with autoinflammation. We introduced novel mutations in the CARD domain and between CARD and NBD domain in the first and third cases, respectively. All three children are under remission following treatment.

†Razieh Sangsari, Pejman Rohani and Vahid Ziaee contributed equally to this work.

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Conclusions NLRC4-GOF mutations can be associated with autoinflammation with diverse symptoms. Given the rarity of the disease and the possibility of new mutations being identified, the existence of a phenotype/genotype correlation has yet to be thoroughly investigated. The variety in manifestations and severity spectrum mandates a variety of treatments. Adalimumab has shown favorable outcomes in our AIFEC cases.

Keywords NLRC4, Familial cold autoinflammatory syndrome, FCAS4, Autoinflammatory infantile enterocolitis, AIFEC, NLRC4-macrophage associated syndrome, NLRC4-MAS

Background

Inflammasomes are large cytosolic multiprotein complexes that serve as the innate immunity system receptors. They are triggered and assembled in response to different forms of stress, such as infections, and activate caspase-1-mediated inflammatory responses. This leads to cleavage and secretion of proinflammatory cytokines interleukin (IL)-1β and IL-18, initiation of inflammatory cascades, and a form of cell death referred to as pyroptosis. The role of inflammasomes in autoimmunity and autoinflammation has been well studied, and today we believe they play a part in the pathogenesis of many other disorders as well, such as neurologic and metabolic diseases. Nucleotide-binding oligomerization domain (NOD), Leucine-rich Repeat and Pyrin domain containing (NLRP)1, NLRP3, NLRP6, NLRP7, NLRP12, NOD-like receptor (NLR)-family caspase activating and recruitment domain (CARD) domain-containing protein 4 (NLRC4), NLR Family Apoptosis Inhibitory Protein (NAIP), and absent in melanoma 2 (AIM2) are the main identified inflammasomes [1, 2].

The NLRC4 gene is located on chromosome 2p22.3 and is made of nine exons. It encodes a protein of 1024 amino acids. The NLRC4 protein has an N-terminal CARD a central nucleotide-binding domain (NBD), and a leucine-rich repeat (LRR) domain. The NBD consists of a helix domain 1 (HD1), a winged helix domain (WHD), and a HD2. This NBD-HD1-WHD-HD2 combination is referred to as the NOD or NACHT. The CARD domain interacts with itself and other CARD proteins to oligomerize, and the LRR domain is believed to be a regulatory domain since its removal results in a constitutionally active NLR protein [3, 4].

Gain of function (GOF) mutations in the NLRC4 gene induce a wide spectrum of autoinflammatory phenotypes. Currently, we categorize them into four groups: familial cold autoinflammatory syndrome (FCAS)4, autoinflammatory infantile enterocolitis (AIFEC), NLRC4-macrophage associated syndrome (MAS), and neonatal-onset multisystem inflammatory disease (NOMID) [5]. Patients in AIFEC and MAS groups present with severe symptoms necessitating treatment with immunosuppressives and biologics and have high mortality [6–8]. On the other hand, FCAS4 patients present with milder symptoms, including urticarial rash and arthritis, their symptoms are usually induced by exposure to cold, and most of them do not require treatment [9]. NOMID phenotype has been reported very rarely [10]. There are still debates on the possibility of a genotype-phenotype correlation [5, 11].

The rarity and complexity of the disease necessitate the description of new cases and a reexamination of our understanding of the condition. In this report, we present three cases with novel NLRC4 mutations, one of the first to be reported in the CARD domain.

Case presentations

First patient

Our patient was a girl born prematurely from a mother who had a positive COVID test during the third trimester. She was admitted with hydrops fetalis, hepatosplenomegaly, and cholestasis post-natal, and was treated with suspected sepsis for one month. She was admitted again at the age of two months due to protracted fever and diarrhea. The stool exam was normal, but the stool calprotectin level was over 2000 μg/g. Laboratory evaluations found mildly elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Metabolic screening yielded normal results. After finding thrombocytopenia and elevated C-reactive protein (CRP), estimated sedimentation rate (ESR), D-Dimer, ferritin, and COVID immunoglobulin (Ig)M and IgG levels, she was diagnosed and treated with the impression of Multisystem Inflammatory Syndrome in Neonates (MIS-N) with methylprednisolone. She was discharged in good condition and had no major complaints for one year except for occasional episodes of fever. Follow-up laboratory evaluations found mildly elevated AST and ALT, and elevated ESR, CRP, and stool calprotectin levels. The parents were related, and the older sibling was healthy. The mother and maternal grandmother expressed a history of periodic fevers in their childhood.

The patient experienced a few episodes of fever afterward. When she was 12 months, the whole exome sequencing (WES) found a heterozygous mutation in NLRC4: p.Asn31His, reported as a variant of unknown significance (VUS) (Table 1). To our knowledge, this mutation has not been reported before. Sanger sequencing confirmed the mutation, and the mother was found to carry a heterozygous mutation (Fig. 1). Adalimumab (biosimilar CinnoRA) was prescribed for three months (one third of the 40 mg vial every two weeks) in addition

Table 1 Characteristics of our patients with gain of function NLRC4 mutation

Patients	1	2	3
NLRC4 Mutation	NM_001199138:exon3: c.A91C: p.Asn31His	NM_001199139:exon4: c.1202T > C. p. Val401Ala.	NM_001199138:exon4: c.390delG: p.Ser132Alafs*21
Age of onset	2 months	2 years	Birth
Age of diagnosis	12 months	14 years	2 years
Current age/ last follow-up	21 months	16 years	3 years
Fever	Yes	Yes	No
GI	Diarrhea	Bloody Diarrhea	Diarrhea
Neurologic	Seizure	Seizure. Beading and irregularity in MCA	No
Skin	No	No	No
Oral Aphthous	No	Yes	No
Elevated ESR/CRP	Yes	Yes	Yes
Phenotype	AIFEC	AIFEC	AIFEC
Treatment	Methylprednisolone in attack. Adalimumab afterwards.	Cyclophosphamide and prednisolone in attack. Colchicine and adalimumab afterwards.	Prednisolone, azathioprine
Outcome	Discontinuation of symptoms	Discontinuation of symptoms	Discontinuation of symptoms

GI: gastrointestinal; ESR: estimated sedimentation rate; CRP: C-reactive protein; AIFEC: autoinflammatory infantile enterocolitis; MCA: middle cerebral artery

to prednisolone (0.5 mg/kg/day). At the age of fifteen months, she was admitted again with a brief episode of seizure, in the form of jerky movements of her right hand and staring, following an episode of fever and diarrhea. Electroencephalography (EEG) did not find any epileptic discharge. Bilateral ventriculomegaly was found in brain sonography. She was discharged with a prescription for phenobarbital and continuation of adalimumab with the same dose.

Second patient

The patient was a 15-year-old boy, born to unrelated parents. Except for a history of childhood aphthous stomatitis in the father, there was no significant family history, and the older brother was healthy. The patient complained of periodic fevers and episodes of bloody stools from the age of two years. There were no complaints before that age. The episodes of aphthous stomatitis accompanying fever started when he was five years old. He had one episode of febrile seizure when he was six, and one episode of seizure without fever when he was 10. At the age of 11, he was admitted with headache and vomiting. Laboratory evaluations found elevated inflammatory markers. Magnetic resonance angiography (MRA) showed some irregular caliber narrowing and beading of the distal parts of the left middle cerebral artery (MCA). Colonoscopy was in favor of inflammatory bowel disease (IBD). In addition to colchicine 1 mg/day and prednisolone 0.5 mg/kg/day, cyclophosphamide was prescribed monthly for 11 months with the impression of neuro-Behcet's. Since the follow-up MRA showed total recovery, cyclophosphamide therapy was stopped. He had no complaints for two years until he was referred with back pain. Following bone densitometry, osteopenia was diagnosed, and zoledronic acid was prescribed every six months. At the age of 14, WES results were prepared and a heterozygous mutation was found in the NLRC4 gene: p. Val401Ala, reported as VUS (Table 1). To our knowledge, this mutation has not been reported before. The parents did not consent for their own genetic study. In light of the WES findings, adalimumab (biosimilar CinnoRA) was prescribed 40 mg every two weeks, and colchicine and prednisolone were continued. The patient has been symptom-free in the past two years, and he is being treated with adalimumab 40 mg every two weeks and colchicine 1 mg daily.

Third patient

The patient was an 18-month-old boy admitted with chronic diarrhea. There was a history of recurrent episodes of diarrhea from the neonatal period. No other abnormal history was mentioned. He was born from consanguineous parents and had a healthy older sister. He had a cousin who had passed away following a prolonged episode of diarrhea. Upon physical exam, no abnormality could be found except for a low weight for age.

Laboratory evaluations found normal leukocyte and thrombocyte counts, elevated ESR and CRP, normal stool exam, and a calprotectin level of 1384 μg/g. Flow-cytometry and immunoglobulin levels were normal. Celiac screening yielded normal results. Colonoscopy was in favor of IBD, and the biopsy showed focal active colitis with focal excess eosinophilic infiltration in lamina propria. WES revealed a heterozygous mutation in NLRC4 gene::p.S132Afs*21, reported as likely pathogenic (Table 1). To our knowledge, this mutation has not been reported before. The parents did not consent for their own genetic study. The patient has been treated with

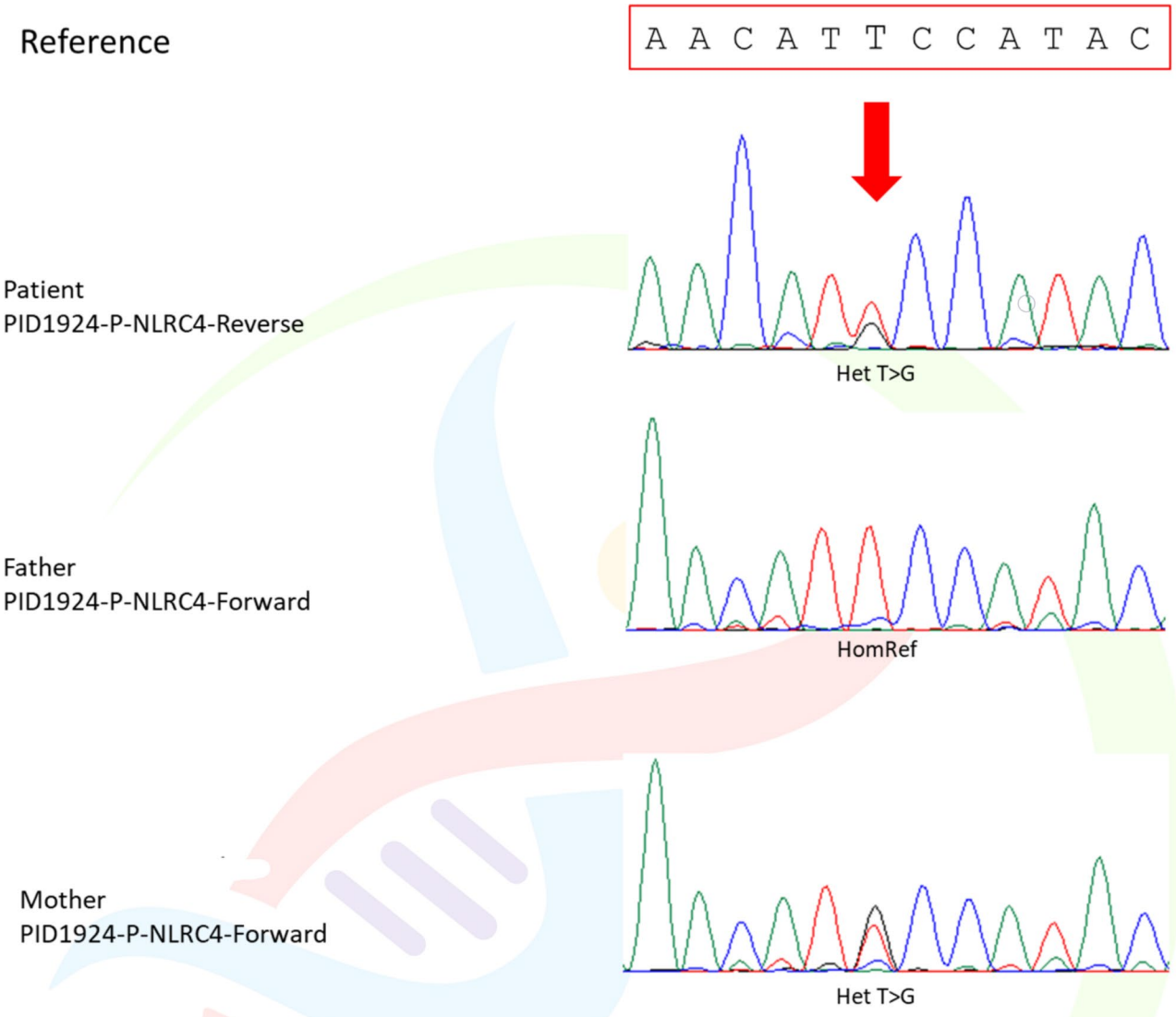

Fig. 1 Genetic analysis of the first patient with NLRC4 mutation

prednisolone 0.5 mg/kg/day and azathioprine 2 mg/kg/day in the previous year. He has had normal defecation and has gained weight favorably.

Patients' characteristics are summarized in Table 1.

Discussion

Disorders associated with GOF mutations of NLRC4 are categorized into four groups: AIFEC, MAS, NOMID, and FCAS4. AIFEC is a chronic inflammatory disease presented with episodes of extreme acuity. Severe diarrhea which can start from the neonatal period is characteristic of AIFEC. MAS-like attacks can lead to intensive care unit (ICU) admission and death. Apart from the attacks, AIFEC is a chronic inflammatory disease. The patients display moderately elevated acute phase reactants and highly elevated serum IL-18 concentrations between flares and present various signs and symptoms such as those of the skin, hepatic, and nervous system [8, 12, 13]. All of our patients seem to fall into this category. The first patient was primarily diagnosed with MISN; however, the occurrence of the second attack, the history of recurrent fever in the mother and grandmother, and ultimately the WES results are very much compatible with NLRC4 inflammasomopathy and AIFEC. In light of the new findings, the first attack is now understood to be a MAS-like attack. Recent studies have found new associations with NLRC4 mutation, such as monogenic lupus [14].

A phenotype/genotype correlation for NLRC4 mutations has been suggested by Wang et al. It has been implied that the patients with mutations in the WHD domain presented with mild inflammatory symptoms of FCAS4, while those with mutations in the NBD and HD1 domains presented severe inflammation, AIFEC, and MAS [5]. On the other hand, Bardet et al. argue

that NLRC4 GOF shows a poor phenotype/genotype correlation and mutations in NBD have been found in both severe and mild phenotypes [11]. Regarding our experience, our third patient had a mutation placed between CARD and NBD domain (exon 4), which has been reported for the first time. Our second patient had a mutation in HD1 domain, which is compatible with the hypothesis that mutations in the HD1 are associated with AIFEC phenotype. Remarkably, our first patient's mutation is in the CARD domain, and to our knowledge, this is the first mutation found in the CARD domain of NLRC4 associated with autoinflammation (Fig. 2).

Interestingly enough, somatic NLRC4 mosaicism can also be associated with autoinflammatory manifestations. Lonescu et al. introduced an adult female patient with recurrent episodes of fever, myalgia, arthralgia, diffuse abdominal pain, diarrhea, and systemic inflammation starting from the age of 47 years and responding to anti-IL-1 treatment. Postzygotic p.Ser171Phe NLRC4 variant was found in unfractionated blood [15]. Moreover, Wang et al. also reported a 69-year-old woman with recurrent rash and fever, and a skin biopsy in favor of vasculitis. They identified a somatic mutation in NLRC4 (p.His443Gln) with the highest mosaicism ratio in the patient's monocytes. The patient responded well to anti-IL-6 treatment [16]. Both of these patients had elevated levels of serum IL-18. Kawasaki et al. introduced the first case of NLRC4 mutation with a presentation of NOMID. The patient was a male infant with a recurrent erythematous rash on the oral circumference, palm, and foot, growth restriction, sensorineural deafness, and brain atrophy. They found a heterozygous NLRC4 mutation, p. Thr177Ala, as a specific mutation in diseased induced pluripotent stem cells (iPSC) clones [10].

The variety in manifestations and severity spectrum mandates a variety of treatments. Most of the FCAS4 patients have been well controlled with non-steroid anti-inflammatory drugs (NSAIDs). Steroids, colchicine, and rarely anakinra have also been used in these patients depending on the severity of manifestations [5, 17]. Attacks of AIFEC and MAS have been treated with immunosuppressives and biologics, sometimes ineffectively and leading to death [8, 13, 18]. Our first and second patients had life-threatening flares of disease. We managed the first patient's attack with methylprednisolone, and the second patient with prednisolone and cyclophosphamide due to CNS vasculitis. Afterward, we controlled their disease with adalimumab, and fortunately, they have not experienced any attacks since then (for 11 months and two years, respectively). Our third patient has not experienced a MAS-like attack, but he had been undergoing chronic diarrhea with high inflammatory markers. These manifestations have been controlled with prednisolone and azathioprine.

NLRC4 mutation is associated with increased levels of IL-1B and IL-18. The importance of IL-18 in the diagnosis of the disease has been well elucidated [7, 8]. Therefore, addressing IL-18 in treatment would be beneficial. Dramatic efficacy was found using recombinant IL-18 binding protein (BP) in one critically ill neonatal AIFEC patient whose disease was refractory to corticosteroids, cyclosporine, IL-1 inhibition, TNF-inhibition and integrin-inhibition [7]. This experience raises hope for curing severe cases of NLRC4 mutation inflammasomopathy. A clinical trial is being conducted on the efficacy, safety, and tolerability of MAS825, a bispecific IL-1β/IL-18 monoclonal antibody, in patients with monogenic IL-18-driven autoinflammatory diseases, including NLRC4-GOF [19]. However, serum analysis of IL-18 and treatment with the recombinant IL-18BP are not practical in resource-limited settings. This is also a limitation of our study. Recently, Bracaglia et al. reported the favorable outcome of a fecal microbiota transplant (FMT) in a patient with NLRC4 mutation with recurrent MAS attacks and persistent diarrhea. The patient had fever, enterocolitis, and recurrent HLH from the age of one month which were only partially controlled with immunomodulatory treatments, including high-dose glucocorticoids, cyclosporine, and high-dose anakinra. He developed multi-drug-resistant sepsis and recurrent

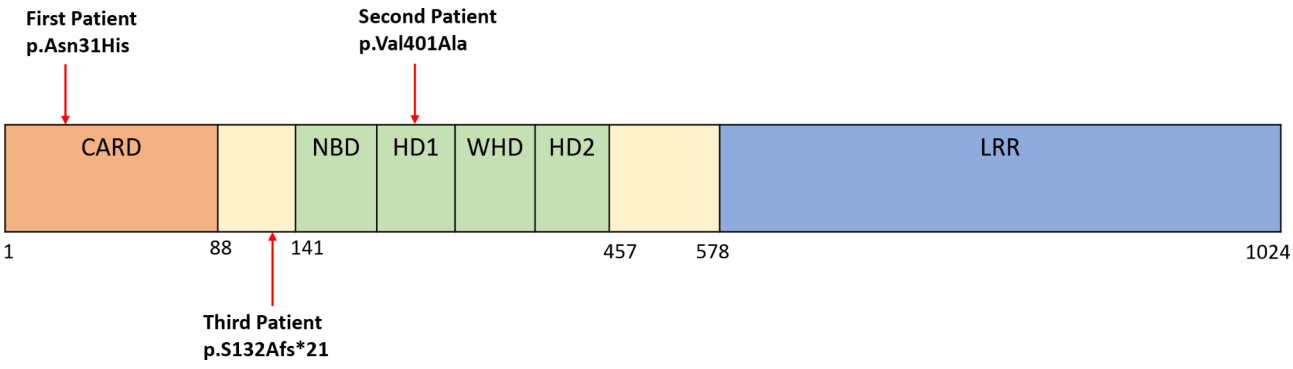

Fig. 2 NLRC4 protein showing our reported mutations

intestinal obstructions. Finally, FMT was tried. With Anakinra and prednisolone being continued, the patient's symptoms have not recurred in the past two years. IL-18 levels have remained high but decreased from more than 500,000 to 50,000 pg/ml [20].

Conclusion

NLRC4-GOF mutations can be associated with an autoinflammatory disease with diverse symptoms. Given the rarity of the disease and the possibility of new mutations being identified, the existence of a phenotype/genotype correlation has yet to be thoroughly investigated. The variety in manifestations and severity spectrum mandates a variety of treatments. Adalimumab has shown favorable outcomes in our AIFEC cases.

Abbreviations

IL	Interleukin
NOD	Nucleotide-binding oligomerization domain
NLRP	Leucine rich Repeat and Pyrin domain containing
NLR	NOD-like receptor
CARD	Caspase activating and recruitment domain
NLRC	NLR family CARD domain-containing protein
NAIP	NLR Family Apoptosis Inhibitory Protein
AIM	Absent in melanoma
NBD	Nucleotide binding domain
LRR	Leucine-rich repeat
HD	Helix domain
WHD	Winged helix domain
GOF	Gain of function
FCAS	Familial cold autoinflammatory syndrome
AIFEC	Autoinflammatory infantile enterocolitis
MAS	Macrophage activation syndrome
NOMID	Neonatal-onset multisystem inflammatory disease
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
HPLC	High-performance liquid chromatography
Ig	Immunoglobulin
CRP	C-reactive protein
ESR	Estimated sedimentation rate
MIS-N	Multisystem inflammatory syndrome in neonates
WES	Whole exome sequencing
VUS	Variant of unknown significance
EEG	Electroencephalography
MRA	Magnetic resonance angiography
MCA	Middle cerebral artery
IBD	Inflammatory bowel disease
GI	Gastrointestinal
ICU	Intensive care unit
iPSC	Induced pluripotent stem cells
NSAID	Non-steroid anti-inflammatory drugs

Acknowledgements
Not applicable.

Author contributions
KA, MA, KM, RS, MS, FS, PR, and VZ gathered the patients' data. MS and NM provided the genetic discussion of the patients. KA, VZ, PR, and RS analyzed the data. KA wrote the manuscript. All the authors reviewed and approved the manuscript.

Funding
No funding was donated to this research.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The ethical committee of Tehran University of Medical Sciences approved this study. Consent was obtained from the parents of patients for participating their children in this report of the patients.

Consent for publication
Consent was obtained from the parents of patients for publishing this report of the patients.

Competing interests
There are no competing interests to declare.

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Received: 3 June 2024 / Accepted: 26 August 2024
Published online: 18 October 2024

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