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Multisystem inflammatory syndrome in children treated with intravenous immunoglobulin monotherapy: a single-center retrospective study

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Abstract

Background Multisystem inflammatory syndrome in children (MIS-C) is one of the complications of SARS-CoV-2 infection. This study aims to evaluate the clinical and laboratory characteristics, as well as treatment results, of MIS-C patients who received intravenous immunoglobulin (IVIG) monotherapy.

Methods This retrospective study included patients diagnosed with MIS-C. Demographic data, organ involvements at the admission, laboratory evaluations for diagnosis, treatment, and follow-up were recorded. We evaluated outcomes by the length of the intensive care unit stay, the total hospitalization period, complications, and mortality.

Results A total of 95 patients diagnosed with MIS-C were evaluated. The mean age was 118.8 (± 52.5) months. 76.8% of the patients had four or more organ systems involved. Seventy-nine patients (83%) were hospitalized in the pediatric intensive care unit (PICU) for a mean of 4.59 days. Seventy-seven (81%) patients received IVIG. A second dose of IVIG was administered to 66.3% of patients. All patients received vitamin D and C supplementation. Six patients who had cardiac involvement or cerebral infarction were treated with plasmapheresis. No patients received steroids. There was no mortality at the end of the follow-up.

Conclusions Favorable outcomes may be obtained with IVIG monotherapy in MIS-C patients. More clinical trials are needed to establish the role of supportive treatments like vitamin D and C in MIS-C management.

Keywords Intravenous immunoglobulin, Multisystem inflammatory syndrome in children (MIS-C), COVID-19, Pediatric intensive care unit, Children

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Background

On March 2020, the World Health Organization (WHO) declared a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) [1]. Early in the pandemic, many reports showed that the disease displayed a milder course in children compared to adults, with a mortality rate of less than 1% [2]. However, an unexpected clinical entity (multisystem inflammatory syndrome in children, MIS-C) emerged in children starting in April 2020. This hyperinflammatory condition shares similarities with Kawasaki Disease (KD) and occurred 4–6 weeks after exposure to the virus [3].

As the MIS-C cases increased, the WHO and health authorities from the US (Centers for Disease Control and Prevention, CDC) and Europe (Royal College of Paediatrics and Child Health, RCPCH) published case definitions and treatment protocols to guide the care of these patients [4–6]. The diagnosis of MIS-C primarily relies on exposure to SARS-CoV-2, involvement of systems, and markers of hyperinflammation. Importantly, since MIS-C shares clinical features with other infections, malignancies, and childhood rheumatic diseases, a thorough differential diagnosis is necessary.

We aimed to show that even though favorable outcomes of the combination of IVIG plus corticosteroids are reported, good outcomes can also be obtained with IVIG monotherapy early phase of the Covid pandemic in 2020–2021.

Methods

The study was conducted between May 2020 and March 2021. The center is a referral hospital with the region's only pediatric intensive care and infectious disease specialists, serving a population of approximately five million. We retrospectively evaluated patients with MIS-C who met the diagnostic criteria of the WHO, CDC, or RCPCH. These patients were either admitted to the center or transferred to our center on the day of diagnosis. Patients transferred to our hospital after treatment initiation were excluded from our analysis. All patients underwent SARS-CoV-2 nasopharyngeal PCR and serum antibody testing and were assessed for prior COVID-19 exposure. A pediatric cardiologist evaluated each patient. Cardiovascular involvement was determined by the presence of at least one of the following: vasoactive support requirement, ejection fraction (EF) < 55% on echocardiography, coronary artery dilatation (> 2.5 mm for the left coronary artery), pericarditis or pericardial effusion, elevated troponin or B-type natriuretic peptide (BNP) levels, cardiac arrhythmia, pulmonary edema due to left heart failure, or the need for cardiopulmonary resuscitation. Gastrointestinal involvement was determined by the presence of the following: stomachache, appendicitis, vomiting, diarrhea, and hepatomegaly. Lung involvement was determined by the presence of the following: pleural fluid drainage, pleural effusion, cough, difficulty of breathing, and tachypnea. Neurologic Involvement involvement was determined by the presence of the following: encephalopathy, headache, confusion, and lethargy. Hematological involvement was determined by the presence of the following: lymphopenia, thrombocytopenia, anemia, and elevated d-dimer. Kidney involvement was determined by the presence of the elevated creatinine and/or urea levels. We recorded demographic data, organ involvement at admission, and laboratory evaluations (for diagnosis, treatment, and follow-up). Outcomes included length of ICU stay, total hospitalization, complications, and mortality.

The study was approved by the local ethics committee in Health Sciences University, Gazi Yasargil Training and Research Hospital (Decision No: 860, 7/2021).

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The Kolmogorov–Smirnov test assessed the normality of univariate data distributions. For comparing two independent groups with normally distributed variables, we employed the Independent-Samples T-test. The Mann–Whitney U test was used for non-normally distributed variables. Categorical variables were compared using the Fisher Exact test or Pearson Chi-Square test, depending on data characteristics. Numerical variables are presented as mean ± SD (standard deviation) and median in tables, while categorical variables are shown as data numbers (n (%)). A 95% confidence level was used, and a p-value less than 0.05 was considered statistically significant.

Results

A total of 95 patients who met CDC, RCPCH, and WHO case definitions for MIS-C were included in the study. Fifty-five (58%) were male. The mean age was 118.8 (± 52.5) months, with 50 patients (52%) younger than 10 years. SARS-CoV-2 IgG antibody positivity was found in 94 patients (98.9%). Only one patient (1.1%) had a positive nasopharyngeal PCR test. Sixty-seven patients (70.1%) reported contact history with a confirmed COVID-19 case. The mean duration of symptoms before hospital admission was 5.6 (± 1.9) days. Seventy-nine (83.2%) patients had no previously known diseases. The majority (76.8%) had involvement of four or more organ systems. Seventy-nine patients (83%) were admitted to the PICU for a mean of 4.59 days. The remaining 16 were hospitalized directly in normal wards (Table 1). The mean PICU length of stay was 4.59 (± 2.7) days, with

Table 1 Demographic data, clinical characteristics, and outcome of the patients at the admission

	n (%)	Mean (STD)
Age (Months)		118.8 (52.5)
Gender, Male	55 (58)	
Body Mass Index		18.5 (12.3)
Duration of symptoms before admission[a]		5.6 (1.9)
Duration of fever		5.6 (2.2)
Underlying disease	16 (16.8)	
Contact with a patient with COVID-19	67 (70.1)	
COVID-19 PCR positive	1 (1.1)	
Antibody positive	94 (98.9)	
Number of System Involvement		
2	15 (15.8)	
3	7 (7.4)	
≥ 4	73 (76.8)	
Patients hospitalized in PICU	79 (83)	
Outcome		
Length of stay in PICU[a]		4.59 (2.7)
Duration of total hospital stay[a]		9.1 (5.2)
Mortality	None	

PICU Pediatric Intensive Care Unit

[a] Days

a mean total hospital stay of 9.1 (± 5.2) days. There were no deaths during the follow-up period.

Table 2 outlines the specific systems involved. All patients presented with fever at admission, lasting an average of 5.6 (± 2.4) days. Additional symptoms included myalgia in 72 patients (75.7%), skin rashes in 56 (58.9%), conjunctivitis in 56 (58.9%), and sore throat in 34 (36.8%). Fifty-two patients (54.7%) had mucosal changes, 50 (52.6%) had cervical or abdominal lymphadenopathies, and 28 (29.4%) had hand and foot edema. Gastrointestinal involvement was most common (98.9%). Notably, all six appendicitis cases occurred in patients under 10 years old, while hepatic involvement was more prevalent in those older than 10 ($p=0.028$). Cardiovascular involvement was observed in 76 patients (80%). No arrhythmia was seen in patients older than 10 years of age. Coronary involvement was found in five patients (5.2%), with no difference between age groups. Valvular pathologies were detected in 49 patients (52.6%). None had cardiac sequelae at discharge. Lymphopenia was more common in patients over 10 years old ($p=0.015$). 41 patients had pulmonary findings, with no age-related statistical difference. Kidney involvement was found in 39 patients (41.1%), significantly higher in those over 10 years old.

Table 3 summarizes patients' laboratory findings. All patients had elevated C-reactive protein (CRP) levels. Eighty-three patients had elevated sedimentation rate,

Table 2 System involvement of the patients

	N (%)	1–120 moa[a]	> 120 moa[a]	*P*
Clinical features		50	45	
Fever	95 (100)	50 (100)	45 (100)	
Myalgia	72 (75.7)	37 (74)	35 (77.7)	0.668[p]
Cutaneous Involvement	56 (58.9)	32 (64)	24 (53.3)	0.291[p]
Conjunctivitis	56 (58.9)	32 (64)	24 (53.3)	0.291[p]
Sore Throat	34 (36.8)	21 (42)	13 (28.8)	0.183[p]
Mucosal Involvement	52 (54.7)	33 (66)	19 (42.2)	0.020[p]
Lymphadenopathy	50 (52.6)	29 (58)	21 (46.6)	0.269[p]
Hand and Foot edema	28 (29.4)	19 (38)	9 (20)	0.055
Kidney Involvement	39 (41.1)	14 (28)	25 (55.5)	0.006[p]
Elevated Creatinine Levels	18 (18.9)	5 (10)	13 (28.8)	0.019[p]
Elevated Urea Levels	38 (40)	14 (28)	24 (53.3)	0.012[p]
GIS Involvement	94 (98.9)	50 (10)	44 (97.7)	0.289[p]
Stomachache	74 (77.8)	38 (76)	36 (80)	0.639[p]
Appendicitis	6 (6.3)	6 (12)	0 (0)	0.028[fe]
Vomiting	39 (41)	19 (38)	20 (44.4)	0.524[p]
Diarrhea	42 (44)	21 (42)	21 (46.6)	0.647[p]
Hepatomegaly	21 (22.1)	10 (20)	11 (24.4)	0.602[p]
Hepatic Involvement	41 (43.1)	15 (30)	26 (57.7)	0.006[p]
Mesentery Lymph Node	12 (12.6)	8 (16)	8 (17.7)	0.354[fe]
CVS Involvement	76 (80)	40 (80)	36 (80)	1.00[p]
Pericardial Effusion	8 (8.4)	5 (10)	3 (6.6)	0.718[fe]
Coronary Involvement	5 (5.2)	3 (6)	2 (4.44)	1.00[fe]
Arrhythmia	4 (4.2)	0 (0)	4 (8.8)	0.047[fe]
EF < %55	4 (4.2)	1 (2)	3 (6.6)	0.341[fe]
Elevated ProBNP	73 (76.8)	39 (78)	34 (75.5)	0.786[p]
Elevated Troponin	34 (35.7)	13 (26)	21 (46.6)	0.034[p]
Elevated CK-MB	16 (16.8)	8 (16)	8 (17.7)	0.813[p]
Lung Involvement	41 (43.1)	19 (38)	22 (48.8)	0.285[p]
Pleural fluid drainage	2 (2.1)	0 (0)	2 (4.4)	0.222[fe]
Pleural effusion	36 (37.8)	16 (32)	20 (44.4)	0.212[p]
Cough	9 (9.4)	2 (4)	7 (15.5)	0.080[fe]
Difficulty of Breathing	11 (11.5)	3 (6)	8 (17.7)	0.108[fe]
Tachypnea	8 (8.4)	3 (6)	5 (11.1)	0.470[fe]
Neurologic Involvement	39 (41.1)	16 (32)	23 (51.1)	0.059[p]
Encephalopathy	7 (7.3)	4 (8)	3 (6.6)	1.00[fe]
Headache	37 (39)	14 (28)	23 (51.1)	0.021[p]
Confusion	8 (8.4)	5 (10)	3 (6.6)	0.718[fe]
Lethargy	9 (9.4)	4 (8)	5 (11.1)	0.731[fe]
Hematological Involvement	68 (71.5)	34 (68)	34 (75.5)	0.415[p]
Lymphopenia	62 (65.2)	27 (54)	35 (77.7)	0.015[p]
Thrombocytopenia	16 (16.8)	12 (24)	5 (11.1)	0.102[p]
Anemia	12 (12.6)	9 (18)	13 (28.8)	0.127[fe]
Elevated D-dimer	92 (96.8)	49 (98)	43 (95.5)	0.289[p]

[p] Pearson chi square test

[fe] Fischer exact test

[a] Months of age

Table 3 Laboratory evaluation at the admission

Parameters (normal range)	Patients with abnormal results n (%)	Mean	Std. Deviation
Complete blood count			
Leukocyte count, /mm^3	47 (49.4)	10,655.0	6200.9
Lymphocyte count, /mm^3	54 (56.8)	1117.4	822.9
Neutrophile count, /mm^3	49 (51.5)	9082.7	5727.1
Platelet count, /mm^3	16 (16.8)	191,557.9	110,071.6
Inflammatory markers			
CRP (0-5 mg/dL)	95 (100)	170.6	76.5
Procalcitonin (0–1 pg/ml)	95 (100)	17.2	27.8
Sedimentation (0–20 mm/h)	83 (98.9)	59.1	28.9
Ferritin (13–150 µg/L)	81 (85.2)	1120.4	1827.3
IL-6 (0–5.9 pg/ml)	37 (39.3)	91.8	245.2
ProBNP (10–500 pg/ml)	43 (54.2)	6911.5	10,770.2
LDH, IU/L	39 (41.05)	447.9	1345.6
D-dimer, µgFEU/mL	94 (98.9)	2143.4	2666.1
Fibrinogen, mg/dL	46 (48.9)	418.6	192.1
Hematological work-up			
APTT	6 (6.3)	29.1	4.5
INR	54 (56.8)	1.4	0.3
Cardiac markers			
Troponin (0–0.3 ng/ml)	36 (37.8)	0.7	2.1
CK-MB (0–2.88 µg/L)	17 (17.8)	4.9	14
Basic metabolic panel			
Urea, mg/dl	41 (43.2)	59.0	95.9
Creatinine, mg/dL	18 (18.9)	1.0	1.2
ALT, IU/L	20 (21.05)	99.9	402.3
AST IU/L	42 (44.2)	126.9	493.8
Albumin, g/L	60 (63.1)	25.2	4.6
Vitamin D (< 20 ng/ml)	75 (78)	14.0	19

80 had elevated procalcitonin, 92 had elevated ferritin, and 37 had elevated IL-6. Pro-Brain Natriuretic Peptide (BNP) was positive in 80 patients (84.2%), making it the most common pathological cardiac value. Additionally, 75 patients (78%) had low serum vitamin D levels.

Seventy-seven patients (81%) received IVIG at 2 g/kg (maximum dose 100 g/day) using a 12-h infusion protocol (Table 4). Due to persistently high inflammatory markers and unresponsiveness to the initial dose, 66.3% of patients received a second IVIG dose. High-dose aspirin was administered to 81% of patients. After fever resolution, 65.3% continued anticoagulation with low-dose aspirin. Elevated D-dimer levels were found in 79 patients (83.2%), who received daily enoxaparin at 100 mg/kg. Fifty-seven patients (60%) received a lower dose of enoxaparin, either as a continuation of anticoagulation or as initial treatment. All patients received vitamin D and C supplementation. Six patients with cardiac involvement or cerebral infarction underwent plasmapheresis. Continuous venovenous hemodiafiltration was required for one patient with medically unresponsive renal failure. Twenty-three patients (24%) needed inotropic support for a mean duration of 2.88 (± 1.62) days. No patients received steroids.

Discussion

We evaluated the clinical characteristics of MIS-C patients, none of whom received corticosteroid treatment or specific immunotherapies. Our findings suggest that IVIG combined with vitamin D and C supplementation leads to favorable outcomes. Since the identification of MIS-C, treatment has focused on immunomodulation, antiplatelet/anticoagulation, and supportive care. Primary immunomodulatory approaches include IVIG, corticosteroids, and targeted neutralization of inflammatory cytokines [7]. Further research is needed to fully evaluate the outcomes of these immunomodulatory treatments.

In the context of MIS-C, given the recent virus exposure and inapparent active infection, in early commentaries, the hyperinflammatory state in MIS-C was thought

Table 4 Treatment modalities of the patients

Treatment	N (%)
Vitamin C (1 g/day)	95 (100)
Vitamin D (2000 U/day)	95 (100)
IVIG treatment	77 (81.1)
A second dose of IVIG	63 (66.3)
ASA (dose: 60 mg/kg/day)	77 (81.1)
ASA (dose: 3 mg/kg/day)	62 (65.3)
Enoxaparin (dose 50 mg/kg)	57 (60)
Enoxaparin (dose 100 mg/kg)	79 (83.2)
Plasmapheresis	6 (6.5)
Inotropic support	23 (24.2)
Adrenaline	12 (12.6)
Noradrenaline	16 (16.8)
Milrinone	2 (2.1)
Dopamine	2 (2.1)
Mechanical Ventilation	3 (3.2)
Hemodialysis	1 (1.1)
IL-1 Inhibitor (Anakinra)	0
Glucocorticoids	0

to be associated with a post-infectious phenomena [8]. Clinically, MIS-C presents with elevated inflammatory markers and multi-system involvement [9]. Potential mechanisms of cardiac injury include direct viral invasion of myocytes, a delayed inflammatory response, and hypotension-induced myocardial ischemia [10].

An early analysis revealed a unique sequence motif within the SARS-CoV-2 spike protein, absent in other coronaviruses [11]. This motif shares similarities with bacterial superantigens, which can trigger a pathway leading to toxic shock syndrome. Its resemblance to Staphylococcal enterotoxin B may cause the excessive release of pro-inflammatory cytokines from T cells and antigen-presenting cells [11, 12]. This cytokine storm mechanism could explain the multi-organ damage seen in MIS-C. Given IVIG's demonstrated high affinity for Staphylococcal enterotoxin B [13], it has the potential to be an effective treatment option for MIS-C.

In the present study, we treated 81% of the patients with IVIG with a quite favorable outcome. In COVID-19-associated myocarditis IVIG displayed substantial benefit [14]. Using KD management strategies, IVIG is recommended as an initial immunomodulation with aspirin in intensive care unit recommendations [15]. Conflicting evidence exists regarding IVIG's role in milder MIS-C cases [16]. Villacis-Nunez et al. found that IVIG plus corticosteroids led to longer hospitalizations compared to corticosteroids alone. They suggest initial corticosteroid monotherapy, offering advantages like shorter treatment duration and similar efficacy. However, early MIS-C case reports documented IVIG failures [17, 18], and 18% of patients required a second IVIG dose [19]. Controlled studies are needed to clarify which patient groups benefit most from various immunomodulatory approaches. In our study, 66% of patients received a second IVIG dose, and we observed no significant side effects, such as hemolytic anemia or volume overload. Due to its anti-inflammatory activity at high doses and anti-platelet activity at low doses, aspirin is one of the mainstays of KD treatment. Acute phase dosages vary, with some experts recommending up to 100 mg/kg/day and others 30-50 mg/kg/day [20, 21]. Given the clinical similarities between MIS-C and KD, early on, aspirin was chosen for its anti-platelet effect. In our study, we initiated high-dose aspirin for patients without contraindications. Most studies has suggested treatment protocols such as intravenous immunoglobulin, corticosteroids, anti-cytokine and immunomodulatory agents. Current research suggested that the combination of IVIG plus corticosteroids is more effective with favorable outcomes. Patients with refractory disease or cardiac involvement also received second-line treatment with anti-cytokine and immunomodulatory agents. in accordance with the American College of Rheumatology and the National Institute of Health recommendations [22].

We hypothesize that these high doses, in conjunction with IVIG, may have helped control the hyperinflammatory state without the need for steroids.

Potential protective roles of vitamins, especially vitamin D, have been discussed in the context of COVID-19 [23, 24]. However, studies examining the relationship between vitamin D deficiency and ICU admission, pulmonary complications, hospitalization, and inflammation have yielded inconsistent results. This inconsistency is likely due to the heterogeneity of study populations. Recent research suggests a modest overall protective effect of vitamin D in preventing respiratory infections in children, with the most significant benefit seen in those younger than 12 months [25]. Vitamin D has been considered for MIS-C due to its direct antiviral effects [26] and its influence on both innate and adaptive immune systems [27]. Prior to COVID-19, studies suggested that low 25(OH)D levels in Kawasaki Disease might contribute to the development and severity of coronary arterial lesions [28]. Berthelot JM et al. reviewed the role of the STING (stimulator of interferon genes) pathway in Kawasaki-like disease, noting that its activation is associated with interferon overproduction and worse outcomes in arterial aneurysms [29]. Vitamin D has been proposed to limit this hyperimmune response, potentially lessening the damaging effects of pro-inflammatory cytokines in Kawasaki Disease. The same hypothesis applies to MIS-C, and sequential vitamin D measurements during

the disease may provide insights into its severity and progression [30]. In our study, 78% of patients had vitamin D levels below 20 ng/ml, and all patients received 2000 IU/day vitamin D supplementation during their hospital stay. This serves as preliminary data supporting the need for vitamin D supplementation in MIS-C patients. We also administered vitamin C during hospitalization; however, there's insufficient data supporting its use in COVID-19 [31]. Proposed benefits of vitamin C include its antioxidant and free radical scavenging effects, which could activate anti-inflammatory mechanisms, modulate cellular immunity and vascular integrity, and serve as a cofactor in catecholamine production [32]. Controlled trials are still needed to definitively establish the effects of vitamin C in MIS-C and COVID-19.

Our analysis revealed that renal involvement was significantly higher in patients older than 10 years. This aligns with the findings of Yilmaz Ciftdogan et al., who observed more acute kidney injury in Turkish patients over 12 years old [33]. In contrast, cardiac involvement did not differ significantly between age groups, a finding consistent with other research [32]. In this study, the patients with cardiac involvement had elevated inflammatory and cardiac biomarkers in line with previous reports [34, 35]. Additionally, we did observe a significantly higher frequency of arrhythmia in children older than 10 years. Jain et al. similarly reported that older patients were more likely to present with shock [36]. Interestingly, case reports of MIS-C with appendicitis have become more common as the number of cases increases globally [36]. Out of 42 cases presenting with acute abdomen (in both COVID-19 and MIS-C patients), Yock-Corrales A et al. found 34 cases involved intraoperative diagnosis of acute appendicitis, while 4 were MIS-C diagnoses not requiring surgery [37].

Our study has several limitations. Firstly, its retrospective design makes it difficult to assess the specific impact of vitamin supplementation on outcomes. Secondly, we were unable to track vitamin levels over time, limiting our analysis. Finally, the relatively small patient sample size prevented a meaningful comparison between patients who received IVIG treatment and those who did not.

The most important strength of this study was that it was conducted in the the rather early phase of the Covid 19 pandemic in 2020–2021.

Conclusions

A standardized, ideal treatment for MIS-C has not yet been established due to a lack of controlled trials. Current treatment primarily relies on supportive and immunomodulatory therapies. Favorable outcomes may be obtained with IVIG monotherapy, while the effectiveness of supportive treatments like vitamin D and C requires further clinical investigation.

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Authors' contributions
Murat Kangin: Conception and design of the study, Acquisition of data, Literature research, writing manuscript, Final approval of the version to be submitted; Asuman Akar: Conception and design of the study, Acquisition of data, Analysis and interpretation of data; Mehmet Nur Talay: Acquisition of data, Analysis and interpretation of data; Ozlem Gul: Data collection and processing, Conception and design of the study, Acquisition of data; Muhammed Tas: Conception and design of the study, Acquisition of data, Analysis and interpretation of data; Ayten Semdinoglu: Conception and design of the study, Acquisition of data, Analysis and interpretation of data, Caner Alparslan: Conception and design of the study, Acquisition of data, Analysis and interpretation of data; Sevgen Tanir Basaranoglu: Analysis and interpretation of data, writing manuscript, critical review. Nurhayat Yakut: Analysis and interpretation of data, writing manuscript, critical review. All authors read and approved the final manuscript. All authors meet the ICMJE authorship criteria.

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
The study was approved by the local ethics committee in Health Sciences University, Gazi Yasargil Training and Research Hospital (Decision No: 860, 7/2021).

Consent for publication
Written consent to publish was obtained from the patients and parents.

Competing interests
There are no conflicts of interest.

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