

Rapidly progressive glucocorticoid-resistant childhood-primary angiitis of the central nervous system positive for HLA-B51 and A26: a case report

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ABSTRACT

Primary angiitis of the central nervous system (PACNS) is a rare inflammatory vasculitis localised to the central nervous system. Treatment of severe PACNS often includes glucocorticoids and cyclophosphamide; however, some cases exhibit resistance to glucocorticoids, leading to severe neurological sequelae. In this case report, a 14-year-old female patient presented with fever, headache, and short-term memory loss. Her blood test results showed no significant abnormalities. HLA-B51 and A26 were both positive. Cerebrospinal fluid examination showed no elevated interleukin-6. Brain magnetic resonance imaging with fluid-attenuated inversion recovery sequences demonstrated hyperintense signals in the bilateral basal ganglia, left thalamus, and insula. Contrast-enhanced T1-weighted imaging showed peripheral enhancement of the lesions. Given the possibility of a demyelinating disorder, glucocorticoids were administered. However, the patient remained febrile, and magnetic resonance imaging (MRI) revealed disease progression. To differentiate infectious and malignant diseases, a biopsy of the left thalamic lesion was performed. Histopathological examination revealed coexisting lymphocytic and granulocytic vasculitis affecting small arteries and arterioles. Based on the clinical course and laboratory results, the patient was diagnosed with PACNS. Despite intravenous immunoglobulin, intravenous cyclophosphamide, and rituximab, the patient became comatose, and the brain MRI worsened. Following infliximab, clinical symptoms and brain MRI improved. The clinical course suggests that infliximab was effective for this patient with glucocorticoid-resistant PACNS. As potential associations have been previously reported between HLA-B51/A26 and vasculitis in Behçet disease, our case may suggest a pathophysiological link between vascular-BD and a subset of PACNS, which may also explain the good clinical response to infliximab. Further research is warranted to address this hypothesis.

KEYWORDS HLA-A26; HLA-B51; infliximab; primary angiitis of the central nervous system; magnetic resonance imaging

Introduction

Primary angiitis of the central nervous system (PACNS) is a rare inflammatory vasculitis affecting the central nervous system (CNS) [1]. It is essential to distinguish PACNS from other vasculitides, infectious, demyelinating, and malignant diseases. A definitive diagnosis may require histopathological diagnosis *via* brain biopsy, which is a highly invasive procedure [2, 3]. Treatment of severe PACNS often includes the administration of glucocorticoids and cyclophosphamide; however, some patients exhibit resistance to glucocorticoids, leading to severe neurological sequelae [2, 3]. Here, we present a paediatric case of rapidly progressive, glucocorticoid-resistant PACNS positive for HLA-B51 and A26, which improved following treatment with infliximabs (IFX).

Case presentation

A 14-year-old female patient presented with fever, headache, and short-term memory loss. The patient had no significant perinatal or medical history and exhibited no symptoms suggestive of Behçet disease (BD). The patient's mother reported a history of recurrent genital ulcers. Physical examination revealed no abnormalities. Blood test results showed no significant abnormalities. Human leukocyte antigens (HLA) B51 and A26 were positive (Table 1). Cerebrospinal fluid (CSF) analysis revealed no specific abnormalities, including normal interleukin-6 (IL-6) levels (Table 1). Brain magnetic resonance imaging (MRI) with fluid-attenuated inversion recovery (FLAIR) sequences demonstrated hyperintense signals in the bilateral basal ganglia, left thalamus, and insula (Figure 1A). T1-weighted images (T1WI) showed

Table 1. Laboratory data of the patient.

Haematology		Coagulation		Immunology		Cerebrospinal fluid	
White blood cell	5 100 / μ l	PT-INR	1.13	IgG	1096 mg/dl	Cell count	0
Neutrophil	42 %	APTT	34.6 sec	IgA	192.1 mg/dl	Glucose	60 mg/dl
Lymphocyte	51 %	Fibrinogen	292 mg/dl	IgM	93.4 mg/dl	Protein	34.7 mg/dl
Red blood cell	433 $\times 10^4$ / μ l	FDP	<2.0 μ g/dl	ANA	40	IgG index	0.61
Haemoglobin	13.4 g/dl	D-dimer	<0.3 μ g/dl	MPO-ANCA	<1.0 U/ml	MBP	156 pg/ml
Platelet	16 $\times 10^4$ / μ l			PR3-ANCA	<1.0 U/ml	OB	negative
		<u>Infection</u>		sIL-2R	259.7 U/ml	MOG-Ab	negative
Biochemistry		CMV IgM	negative	CD3	68 %	HSV IgM	negative
AST	16 IU/l	CMV IgG	negative	CD4/8	0.72	HSV IgG	negative
ALT	10 IU/l	VCA IgM	<10	CD19	16.5 %	HSV RT-PCR	negative
LD	162 IU/l	VCA IgG	40	CD56	17.8 %	VZV IgM	negative
Albumin	4.4 g/dl	EBNA IgG	40	Anti-AQP4-Ab	negative	VZV IgG	negative
Urea nitrogen	13.3 mg/dl	VZV IgM	negative	Anti-MOG-Ab	negative	VZV RT-PCR	negative
Creatinine	0.69 mg/dl	VZV IgG	7.3(+)			IL-6	4 pg/ml
Creatinine kinase	92 IU/l	HSV IgM	negative	<u>HLA Class I</u>			
Ferritin	63.8 ng/ml	HSV IgG	negative	A2	A26		
CRP	0.02 mg/dl	HIV IgG	negative	B39	B51		
ESR	15 mm/h	T-SPOT.TB	negative	Cw7	Cw14		

ACE, angiotensin converting enzyme; ALT, alanine aminotransferase; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; APTT, activated partial thromboplastin time; AQP4-Ab, aquaporin4 antibody; AST, aspartate aminotransferase; CD, cluster of differentiation; CMV, cytomegalovirus; CRP, C-reactive protein; EBNA, Epstein-Barr virus nuclear antigen; ESR, erythrocyte sedimentation rate; FDP, fibrinogen/fibrin degradation products; HIV, human immunodeficiency virus; HLA: human leukocyte antigen; HSV, herpes simplex virus; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; IL, interleukin; INR, international normalised time; LD, lactate dehydrogenase; MBP, myelin basic protein; MOG-Ab, myelin oligodendrocyte glycoprotein antibody; MPO, myeloperoxidase; OB, oligoclonal band; PR3, protein 3; PT, prothrombin time; RT-PCR, real-time polymerase chain reaction; sIL-2R, soluble interleukin-2 receptor; VCA, virus capsid antigen; VZV, varicella zoster virus.

hyperintense foci within these lesions, which are consistent with haemorrhage (Figure 1B). Contrast-enhanced T1-weighted subtraction images (CE-T1WSI) showed peripheral enhancement of the lesions (Figure 1C). Magnetic resonance angiography revealed no abnormalities. Ophthalmologic examination revealed that the patient did not have uveitis.

Given the possibility of a demyelinating disorder, two courses of methylprednisolone pulse therapy were administered (Figure 2). However, the patient remained febrile, and a follow-up MRI revealed disease progression. Oligoclonal bands and anti-myelin oligodendrocyte glycoprotein antibodies in both serum and CSF showed negative results. As the glucocorticoid response was also poor, we considered it was unlikely that the patient had a demyelinating disorder. To differentiate the case from infectious diseases and malignant diseases such as malignant lymphoma, a biopsy of the left thalamic lesion was performed. Histopathological examination revealed coexisting lymphocytic and granulocytic vasculitis affecting small arteries and arterioles, accompanied by patchy necrosis (Figure 3). Multiple real-time polymerase chain reaction tests (161 types of viruses, 73 types of bacteria, 25 types of fungi, and five types of protozoa) and next-generation sequencers revealed no pathogens [4–6]. Ultrasound and computed tomography scans showed no findings suggesting vasculitis in any area other than in the CNS. Although HLA-B51 and A26 were positive, there were no major symptoms suggestive of BD. Furthermore, there was no increase in CSF IL-6, an indicator for neuro-Behçet's disease (neuro-BD); therefore, the diagnosis of neuro-BD was not made. Based on the clinical course and these laboratory findings, the possibility of infectious diseases, demyelinating diseases, or malignant diseases was low, and no findings of vasculitis outside the central nervous system were observed. Therefore, the patient was diagnosed with small-vessel PACNS.

On postoperative day one, the patient developed a high fever and experienced drowsiness. An additional

course of methylprednisolone pulse therapy, intravenous immunoglobulin (400 mg/kg/day for 5 days), and intravenous cyclophosphamide (IVCY) (15 mg/kg/dose) was administered. One week later, the patient developed a persistent high-grade fever that progressed to a coma, accompanied by worsening brain MRI findings. Rituximab (RTX) (375 mg/m²/dose) was added to the treatment regimen, and IVCY and RTX were each administered twice. However, the patient's symptoms did not improve, and the patient had seizures. Brain MRI continued to deteriorate (Figure 1D–F). Contrast-enhanced MR angiography and venography showed no abnormal findings. IVCY was discontinued due to haemorrhagic cystitis, despite the use of mesna and a large amount of fluid. IFX was administered in consideration of possible neuro-Behçet disease (NBD), given the presence of HLA-B51 and HLA-A26. The day after IFX administration, the patient's fever became higher. In response, IFX was administered only once, and RTX was administered a total of four times. Three weeks after the first IFX (following the fourth RTX administration), the fever subsided, and brain MRI findings showed a slight tendency towards improvement. It was difficult to determine whether the effects of IVCY or RTX were delayed or whether this improvement was due to the effect of IFX, which was administered only once. Therefore, IFX administration was not resumed after the 4th time RTX was completed, and the progression of fever and MRI findings were monitored to determine which drug was most effective. The patient had been afebrile for 9 days, but had recurrent fever and re-exacerbation on MRI findings. Considering the possibility that this was due to the effect of IFX administered only once, IFX (5 mg/kg/time, 4-week interval) was restarted. The patient's fever subsided 3 weeks after resuming IFX, and brain MRI findings also showed a tendency towards improvement. Subsequently, colchicine and mycophenolate mofetil were added as maintenance therapy. Following this intervention, the patient's level of consciousness and brain MRI findings

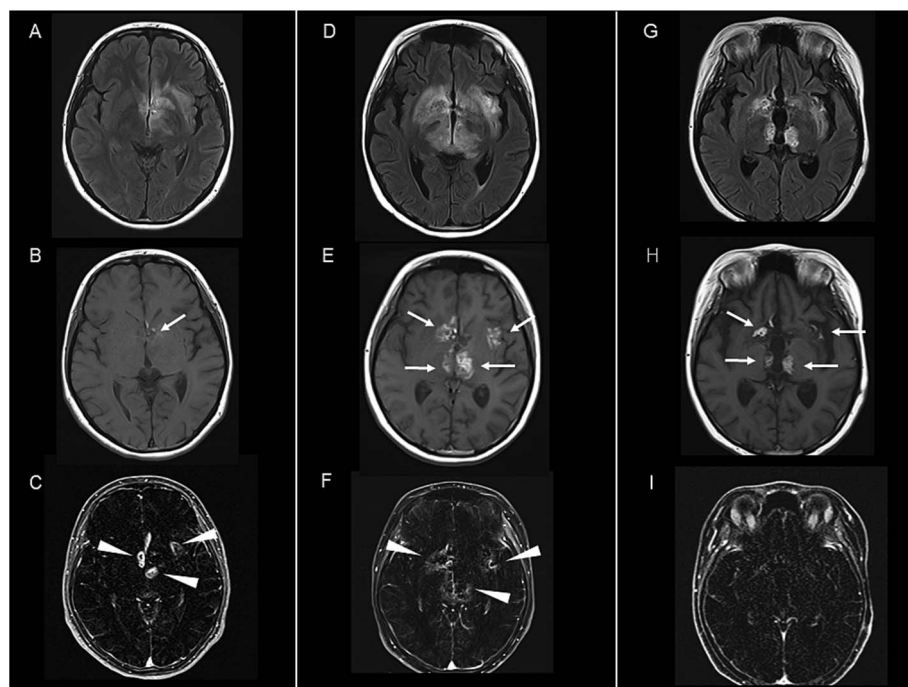


Figure 1. Brain magnetic resonance imaging. (A)–(C) At the initial presentation. (D)–(F) Following the administration of glucocorticoids, intravenous immunoglobulins, intravenous cyclophosphamide, and rituximab. (G)–(I) Ten months after infliximab initiation. (A), (D), (G) Fluid-attenuated inversion recovery (FLAIR) image. (B), (E), (H) T1-weighted image (T1WI). (C), (F), (I) Contrast-enhanced T1-weighted subtraction image (CE-T1WSI). (A) FLAIR image shows high signal intensities in the bilateral basal ganglia, left thalamus, and insula. (B) T1WI shows hyperintense foci in the left putamen (arrows), suggestive of haemorrhage. (C) CE-T1WSI shows peripheral enhancement (arrowheads) of the lesions. (D–F) FLAIR image (D) shows lesion enlargement and the appearance of a lesion in the right thalamus. T1WI (E) shows an enlargement of intralesional haemorrhage (arrows). CE-T1WSI (F) shows persistent peripheral enhancement (arrowheads) of the lesions. (G–I) FLAIR image (G) shows a reduction in lesion size. T1WI shows residual hyperintensity (arrows), suggestive of coagulate necrosis. CE-T1WSI shows resolution (H and I).

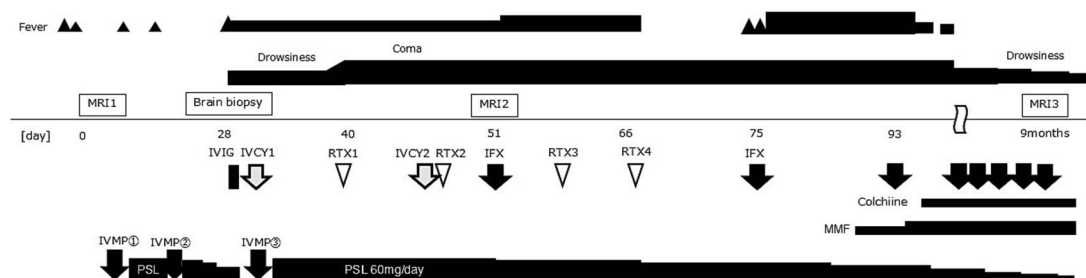


Figure 2. Clinical course after admission. The upper bars represent the patient's symptoms of fever and state of consciousness. The lower bars represent each treatment. IFX, infliximab; IVCY, intravenous cyclophosphamide; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; MMF, mycophenolate mofetil; MRI, magnetic resonance imaging; PSL, prednisolone; RTX, rituximab.

gradually improved (Figure 1G–I). CE-T1WSI revealed the resolution of the previously observed peripheral enhancement, which suggested subsiding vascular activity (Figure 1F). At 1-year follow-up, the patient remains bedridden but is able to respond to 'yes or no' questions, move her arms and legs according to instructions, and take small amounts of liquids by mouth.

Discussion

There are no specific laboratory findings for the diagnosis of PACNS. Thus, it is essential to rule out other diseases, such as infectious, demyelinating, and malignant diseases. Brain biopsy, although invasive, is useful in diagnosing PACNS. Infectious diseases can also cause vasculitis of the CNS; notably, varicella zoster virus (VZV) vasculopathy is a disease that must be differentiated from PACNS [7, 8]. To

differentiate PACNS from VZV vasculopathy, the current literature emphasises CSF antibody more than cerebrospinal fluid PCR [7]. In the present case, the patient had been vaccinated against chickenpox, had no history of chickenpox, and had negative PCR results on CSF and brain biopsy specimens, as well as negative CSF antibodies. These findings suggest that VZV vasculopathy is not present. For many other infectious diseases, comprehensive pathogen analysis was performed using brain biopsy specimens, but no pathogens were detected. Based on these findings, the possibility of infectious diseases was excluded.

The patient carried the BD-associated risk alleles HLA-B51 and A26. HLA-B51 is reportedly associated with severe organ manifestations, including vascular-BD and neuro-BD [9–12]. Nakajima *et al.* reported that 6.8% of BD cases showed HLA-B51/A26 double positivity, and these patients frequently had ocular and/or gastrointestinal lesions, both of which are

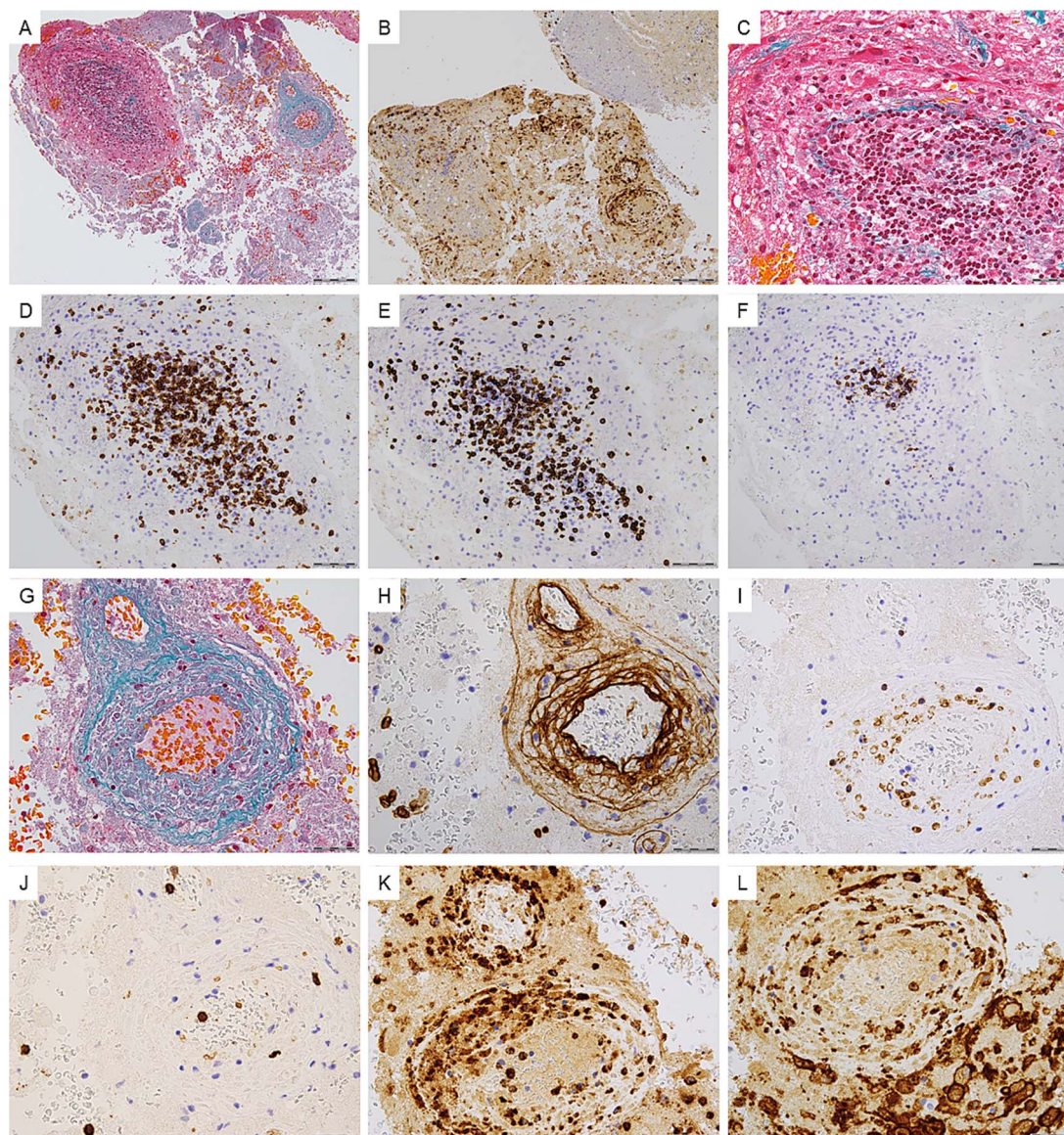


Figure 3. Pathological examination of the left thalamic lesion. (A) El-mas staining reveals a vasculopathic lesion with patchy necrosis within the grey matter. (B) MPO-positive granulocytes and monocytes infiltrate the necrotic regions. (C) El-mas staining shows mononuclear cell infiltration extending from Virchow–Robin spaces into viable brain parenchyma exhibiting astrogliosis. These perivascular mononuclear cells comprise lymphocytes, mature plasma cells, and macrophages without forming lymphoid follicle-like structures. (D)–(F) immunohistochemistry shows a predominance of CD5- and CD8-positive T lymphocytes (D, E), with relatively few CD20-positive B-lymphocytes (F). (G)–(L) necrotic changes are evident in small arteries and arterioles. El-mas (G) and type IV collagen staining (H) reveal loss of inner and outer elastic laminae and smooth muscle layers, with preservation of basement membrane meshwork. B-lymphocytes (I, CD79a), large granular T-lymphocytes (J, CD8), polymorphonuclear leucocytes (B and K, MPO), and M2 macrophages (L, CD163) infiltrate within the necrotic vascular wall. The pathological examination revealed vasculitis and associated microinfarct lesions. No evidence of malignancy was detected. Abbreviations: El-mas, Elastic–Masson; MPO, myeloperoxidase. Scale bar = 200 micrometres (A, B), 100 micrometres (D, E, F), and 50 micrometres (C, G, H, I, J, K, H).

considered primarily small vasculitis [13]. Given that genetic risk factors can be shared by different diseases with similar underlying pathophysiology, HLA-B51/A26 double positivity in our case indicates a pathogenic mechanism that is similar to vascular-BD. Since the efficacy of TNF inhibitors in treating vasculitis in BD has been established, the effectiveness of infliximab further supports a shared pathophysiology in our case and raises the possibility that the presence of risk alleles HLA-B51 and/or A26 may predict a therapeutic response of PACNS to TNF inhibitors. The significance of HLA in vasculitis localised in the central nervous system is yet to be investigated. There have been reports of neuro-BD cases in

which CNS lesions precede the typical symptoms of BD, such as genital ulcers and oral aphthous ulcers [14, 15]; hence, a similar pathogenesis cannot be excluded for the present case. However, BD is a systemic vasculitis syndrome, and clinical symptoms other than neurological symptoms are important for diagnosis. Inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate are elevated in blood tests of patients with BD, and cerebrospinal fluid IL-6 is elevated in neuro-BD [16], but neither of these was the case here. There are no specific histopathological findings between PACNS and neuro-BD, and the differences between them remain unclear. BD cannot be ruled out because the

classification criteria are not met; however, under the current classification criteria for BD [17, 18], the patient could not be diagnosed with neuro-BD. Based on the clinical course and laboratory findings mentioned above, the patient was instead diagnosed with PACNS at this time.

Glucocorticoids are commonly used as initial treatment, but glucocorticoid-resistant PACNS has been reported occasionally [2, 3]. High-dose glucocorticoids and cyclophosphamide are the recommended treatments for severe PACNS [2, 3]. However, although cyclophosphamide is effective in preventing relapse, its effectiveness as a remission-induction therapy remains limited [19]. Biological agents that have been previously reported for the treatment of PACNS include RTX, TNF inhibitors, and tocilizumab. RTX is commonly used as an adjunctive biological therapy in 22 cases of glucocorticoid-resistant or glucocorticoid-dependent PACNS [20–26]. TNF- α inhibitors, such as IFX and etanercept, have been employed in five cases [27–29], and tocilizumab has been used in four cases [30, 31]. However, data on these additional treatments in glucocorticoid-resistant PACNS remain limited. In the present case, the fever subsided, neuroimaging findings improved, and neurological symptoms gradually resolved after initiating IFX. Although spontaneous improvement or delayed effects of cyclophosphamide and RTX could not be excluded, the clinical course suggests that IFX was effective for this patient with glucocorticoid-resistant PACNS.

In conclusion, the present case highlights that PACNS may not be accompanied by abnormal blood examination findings, such as inflammation markers. This case supports IFX as a viable treatment option for glucocorticoid-resistant PACNS.

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Conflict of interest

M. Shimizu has received a speaker's fee from Novartis. Other authors have nothing to declare.

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Data availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Not applicable.

Patient consent

Written informed consent was obtained from the patient's parents for the publication of this case report.

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