Case Report

Novel *ADAMTS13* mutation in a family with three recurrent neonatal deaths: a case report and literature review

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Background: Upshaw-Schulman syndrome (USS) is rare, autosomal recessive, hereditary thrombotic thrombocytopenic purpura (TTP) caused by variants in a disintegrin-like and metalloprotease with thrombospondin type 1 motif (*ADAMTS13*). USS has a heterogeneous clinical course, and most symptoms overlap with other diseases. Early diagnosis may have important implications for the patients. We found novel ADAMTS13 mutation and explored the clinical features and prognosis of newborn-onset USS to increase awareness of the disease.

Case Description: The same, non-consanguineous couple had three unexplained neonatal deaths. The symptoms of the three infants were mainly severe jaundice, anemia and thrombocytopenia after birth, which was consistent with the reported USS symptoms of neonates and died rapidly suddenly in the during rescue efforts. By using whole-exome sequencing (WES) for the study family, we found a novel heterozygous compound in *ADAMTS13* (c.1187 (exon10) G>A (p.C396Y)/c.1595 (exon14) G>T (p.C532F)) that was carried by the three newborns originating from father and mother respectively. We reviewed nine published studies of newborn-onset USS and compared our cases for clinical symptoms and laboratory testing. All nine published cases were diagnosed by ADAMTS13 activity; in seven cases gene mutation analysis was performed and eight cases were still alive at the time of publication.

Conclusions: The case has added clinicians' awareness of the diagnosis and treatment of USS. A novel rare mutation in *ADAMTS13* broadens the spectrum of genetic causes of this rare disorder and expands the phenotypic spectrum.

Keywords: *ADAMTS13*; neonatal death; thrombotic thrombocytopenic purpura; Upshaw-Schulman syndrome (USS); case report

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Introduction

Upshaw-Schulman syndrome (USS, OMIM#274150), known as congenital thrombotic thrombocytopenic purpura (TTP), is a rare autosomal recessive disorder caused by mutations of a disintegrin-like and metalloprotease with thrombospondin type 1 motif (*ADAMTS13*) (OMIM#604134) (1). TTP presents as hemolytic anemia, thrombocytopenia, microvascular thrombosis, and end-

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organ damage. Plasma exchange is the preferred treatment, and can reduce the fatality rate of TTP by >80%. The first case of hereditary TTP was described in an 8-year-old girl in 1960 by Schulman *et al.* (2). Upshaw described another child with a similar clinical manifestation in 1978 (3) and in 2004 Schiff *et al.* reported two children with delayed diagnosis (4). Previous studies have found that USS is caused by gene mutations in *ADAMTS13*, showing <10% of its activity (1) and currently, more than 150 gene mutations of *ADAMTS13* have been reported worldwide, including missense, nonsense, splice-site alterations, nucleotide deletions, and insertions. *ADAMTS13* is located on chromosome 9q34, is 37 kb in length and contains 29 exons. Mutations affect the entire ADAMTS13 protein, changing the secretion and activity of ADAMTS13 to varying degrees (5).

ADAMTS13 is a metalloproteinase and specifically cleaves a macroporous von-Willebrand Factor (VWF) multimer with thrombogenic effect. A homozygous or complex heterozygous mutation will inactivate *ADAMTS13*, which impairs the synthesis or secretion of disintegrin-like and metalloproteinases. When the plasma ADAMTS13 antigen or activity is decreased, uncleaved the supermolecular VWF multimer (UL-VWFM) accumulates in the blood, causing abnormal platelet aggregation and extensive microvascular thrombosis. Patients may present with some or all of thrombocytopenia, hemolytic anemia, nervous system abnormalities, renal insufficiency and fever (5). Here, we report three cases of neonatal deaths in the same family, each presenting with early jaundice, and thrombocytopenia. A novel heterozygous compound in *ADAMTS13* that originated from father and mother respectively expands the phenotypic spectrum and broadens the spectrum of genetic causes of this rare disorder. We present the following article in accordance with the CARE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-114/rc).

Case presentations

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients' parents for publication of this case report and accompanying images. Copies of the written consent are available for review by the editorial office of this journal.

Case 1

A 39-week-gestation female infant was vaginally delivered 24 h after spontaneous rupture of membranes with a birth weight of 1,950 g, and Apgar score (6) 8/3/3 (1'/5'/10') on May 20, 2015. This was the first baby of the couple. The 24-year-old mother was diagnosed with gestational hypertension and gestational diabetes mellitus (GDM) during pregnancy and referred to the Prenatal Diagnosis Center of Jiangsu Province for the evaluation of intrauterine growth restriction (IUGR) noted on routine antenatal examination at 39 weeks. Following admission, increased cardiothoracic ratio, and myocardial thickening were noted. Genetic diagnosis was not performed because of premature rupture of membranes and irregular contractions. The newborn presented with jaundice, cyanosis and tachypnea immediately after delivery. Heart rate and blood oxygenation dropped sharply 4 min later. At that time, the baby was markedly icteric and had many petechial hemorrhages. Transcutaneous bilirubin (TCB) assay was 12.8 mg/dL. The liver was palpable 4 cm below the costal margin and the spleen was 1 cm. The newborn was resuscitated, but died of cardiac arrest. Cord blood hemoglobin (Hb) was 74 g/L, white blood cell (WBC) count was 44×10^9/L, red blood cell (RBC) count was 1.79×10^{12}/L, hematocrit (Hct) was 23.9%, and platelet count (Plt) was 44×10^9/L. A routine peripheral blood sample gave similar results. Lactate dehydrogenase (LDH) was 2,422 U/L, total bilirubin (TBIL) was 136.4 μmol/L, and direct bilirubin (DBIL) 15.4 μmol/L. Blood smear showed all stages of immature RBCs, abnormal RBCs and mature RBCs that were uneven in size (*Table 1*). The couple was consulted but refused genetic testing and autopsy partially for financial reasons, but donated the placenta and corpse to the hospital. There were no obvious abnormalities on placental pathologic examination.

Case 2

One year later, a second female infant was born at 37^{+3} weeks' gestation by oxytocin induction due to mild preeclampsia, with a birth weight of 3,240 g and Apgar score of 9/10/10 (1'/5'/10') on December 1, 2016. Maternal blood pressure during pregnancy was unstable and fetal ultrasound showed separation (11 mm) of the left renal pelvis. Prenatal diagnosis had again not been accepted because of they had no family history. The mother had irregular antenatal examinations at a local hospital and was

Table 1 Comparison of the clinical features of the three cases in this study and those in the literature

Features	Case 1	Case 2	Case 3	Lehmberg *et al.* 2017 (7)		Jubinskey *et al.*, 2003 (8)	Sharma *et al.*, 2016 (9)	Sudour *et al.*, 2007 (10)	Tanabe *et al.*, 2012 (11)		Tsujii *et al.*, 2016 (12)	Liu and Wang, 2019 (13)
Maternal												
Gestational complications	PIH, GDM	PIH	PIH	–	–	–	–	–	ND	ND	ND	ND
Prenatal ultrasound	Increased cardiothoracic ratio, myocardial thickening, IUGR	Left renal pelvis separation (11 mm)	–	–	–	–	–	–	ND	ND	ND	ND
Infant												
Gestational age (weeks)	39	37^{+3}	39^{+3}	40	33	Full-term	38	40.5	37^{+6}	40^{+2}	39	ND
Sex	F	F	F	M	M	F	F	M	M	F	F	M
Birth weight (g)	1,950	3,240	3,600	4,180	2,395	3,870	2,800	4,160	2,750	3,018	3,470	ND
Apgar score	8/3/3	9/10/10	9/10/10	7/7/7	9/10/10	ND	8/9/9	9/10	ND	ND	ND	ND
Onset age	Immediately	12 h	Immediately	1 d	3 d	4 h	40 h	6 h	11 h	27 h	6 h	2 d
Death age	1 h	30 h	7 h	Alive	Alive	Alive	42 h	Alive	Alive	Alive	Alive	Alive
Symptoms												
Fever	–	–	–	ND	+	+	+	–	ND	ND	ND	ND
Tachypneic &Cyanotic	+	+	+	ND	ND	+	+	–	ND	+	ND	ND
Jaundice	+	+	+	+	+	+	+	+	+	+	+	+
Bruising& petechia	+	+	+	+	ND	–	+	+	+	ND	+	ND
Hepatosplenomegaly	+	Liver	Liver	ND	ND	–	–	–	ND	ND	ND	ND
Hematuria	–	–	–	+	ND	+	+	+	ND	ND	+	ND
Laboratory tests												
WBC ($\times10^9$/L)	85.4	25.5	12.8	ND	ND	30	ND	29	ND	ND	27	9
Hb (g/L)	103	108	193	60	67	ND	63	11	ND	ND	139	69
Plt ($\times10^9$/L)	51	146	20	27	21	84	28	38	7	10	3	28
Coombs test	ND	ND	ND	(–)	(–)	(–)	ND	ND	(+)	(–)	ND	(–)
Blood type	ND	AB (+)	AB (+)	ND	ND	A (+)	ND	ND	B (+)	AB (+)	ND	ND
TBIL (μmol/L)	136.4*	433.8	125.6	316	410	ND	ND	ND	ND	405.3	432.6	515.8
IBIL (μmol/L)	121	410.85	110.9	ND	ND	ND	376.2	325	ND	ND	425.8	496.8

Table 1 (*continued*)

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Features	Case 1	Case 2	Case 3	Lehmberg *et al.* 2017 (8)		Jubinskey *et al.*, 2003 (9)	Sharma *et al.*, 2016 (10)	Sudour *et al.*, 2007 (11)	Tanabe *et al.*, 2012 (12)		Tsujii *et al.*, 2016 (13)	Liu and Wang, 2019 (14)
DBIL (μmol/L)	15.4*	22.95	14.7	ND	ND	17	ND	ND	ND	ND	6.8	19
LDH (U/L)	2,422*	2,897	1,909	5,553	656	ND	3,200	ND	ND	ND	ND	3,453
APTT (s)	ND	96.2	69.5	ND	ND	ND	ND	ND	ND	ND	45	ND
PT (s)	ND	27.9	15.3	ND	ND	ND	ND	ND	ND	ND	ND	ND
Peripheral blood smear	All stages of immature RBCs, abnormal RBCs and mature RBCs are obviously uneven in size	ND	ND	Massive increase of schistocytes	ND	RBC fragments	Fragmented RBCs, giant platelets and inadequate platelets	Massive increase of schistocytes	ND	ND	Schistocytes	RBC fragments
Genetic analysis	c.1187 (exon10) G>A (p.C396Y)/ c.1595 (exon14) G>T (p.C532F)	c.1187 (exon10) G>A (p.C396Y)/ c.1595 (exon14) G>T (p.C532F)	c.1187 (exon10) G>A (p.C396Y)/ c.1595 (exon14) G>T (p.C532F)	c.2104 (exon 17) G > C (p. Gly702Arg)/c. 2281 (exon 19) G>A (p.Gly761Ser)	delEx15 + 16/c.3655C >T (p. Arg1219Trp)	ND	c 2203 G4T-p. Glu735X	ND	p.R398C (c.1192 C>T, exon 10)/ p.Q723K (c.2167 C>A, exon 18)	p.Q449X (c.1345 C>T, exon 12)	c.41510G>A/ c.824+13C>T/ c.2017A>T (p.I673F)	c.330+1G>A/ p.G1079G
ADAMTS13 activity (%)	ND	ND	ND	Undetectable	4	10	<1	0.5	0.5	0.5	<0.5	<5
ADAMTS13 activity of parents (%)	ND	ND	ND	ND	ND	Partially deficient	ND	62/54	46/30	50/44	42/43	ND
Treatment												
Respiratory support	+	+	+	–	–	–	+	–	–	–	–	–
Phototherapy	–	+	+	+	+	+	+	+	+	–	–	–
Antibiotic	–	–	+	+	+	+	–	+	–	+	+	–
Transfusion FFP	–	+	+	+	+	–	–	+	+	+	+	+
Transfusion platelet	–	–	+	+	+	+	+	+	–	+	–	+
Transfusion RBCs	–	+	+	–	–	–	–	+	–	–	–	+
Exchange transfusion	–	–	–	–	–	–	–	–	+	+	–	–

*, Umbilical cord blood. All data based on first sampling and symptoms after birth. PIH, pregnancy induced hypertension; d, days of age; F, female; h, hours of age; M, male; ND, not described or not done; Hb, hemoglobin; WBC, white blood cell; RBC, red blood cell; Hct, hematocrit; Plt, platelet count; LDH, lactate dehydrogenase; TBIL, total bilirubin; DBIL, direct bilirubin; FFP, fresh frozen plasma; +, symptom positive or treatment given; –, symptom negative or treatment not given.

referred to us because of abnormal fetal umbilical artery blood flow with bloody show in the third trimester. In the 12th hour of life, the newborn developed jaundice (TCB 18.5 mg/dL) and was transferred to the neonatal intensive care unit (NICU). Initial laboratory tests revealed pH 6.95, PCO_2 52.2 mmHg, PO_2 52.0 mmHg, and base excess (BE)–18.8 mmol/L. There was abnormal coagulation (Prothrombin time (PT) 27.9 s, Activated Partial Thromboplastin Time (APTT) 96.2 s, Fibrinogen (Fbg) 1.2 g/L, Thrombin time (TT) 24.9 s, D-dimer(D-D) 9,190 ng/mL, Fibrinogen degradation product (FDP) 103.9 ug/mL), high TBIL but acceptable routine blood values (*Table 1*). The physical examination revealed jaundice, petechiae and tachypnea. The liver was palpable 3.5 cm below the costal margin and the spleen was just palpable. Ultrasound examination detected a patent ductus arteriosus (PDA), and an atrial septal defect. Lungsand abdomen were normal on X-ray. After admission, the newborn was given ventilator-assisted respiratory support to correct the acidosis, as well as hemostasis interventions, infusion of RBCs, and fresh frozen plasma (FFP), and other symptomatic supportive treatments. Repeat routine blood review showed obvious changes (Hb 30 g/L, WBC 15.0×10^9/L, RBC 0.95×10^{12}/L, Hct 9.9% and Plt 255×10^9/L). At 30 h after birth, the infant deteriorated rapidly and died. The couple again refused genetic testing and autopsy but donated the placenta. No abnormalities showed on placental pathologic examination.

Case 3

On June 18, 2019, a third female infant was born at 39^{+3} weeks' gestation with a birth weight of 3.6 kg, normal Apgar scores of 9/10/10 at 1, 5 and 10 min of life and referred to the NICU immediately after birth because of the previous two unexplained neonatal deaths. This pregnancy had been complicated with preeclampsia and the mother still refused to undergo amniocentesis and genetic diagnosis. Both the prenatal fetal ultrasound and chromosome karyotyping of the couple were normal. Within 1 h of admission to the NICU, the newborn developed shortness of breath, bruising, loose bleeding point in the face and hypoglycemia. She was started on hood oxygen, hemostasis, and rehydration support therapy. At age of 5 h, the newborn showed an increase in oxygen requirement with an increase in breathing effort and due to impending respiratory failure, she was intubated for mechanical ventilation. At that point in time, the newborn was noted to have purple lips, cold limb tips, whole body skin bleeding spots and ecchymoses; her vital signs were unstable. Intensive phototherapy was started, with supplemental oxygen to improve microcirculation and component blood transfusion preparation. The newborn rapidly deteriorated after birth and was resuscitated but soon died of respiratory cardiac arrest. Blood gas analysis showed pH 7.33, PCO_2 46.7 mmHg, PO_2 44mmHg, BE –2.1 mmol/L, and SO_2 76.4%. The laboratory tests showed remarkably low Plt and abnormal coagulation (*Table 1*). Echocardiography revealed PDA, patent foramen ovale and pulmonary hypertension (64 mmHg). Autopsy was not accepted. No obvious abnormalities were found in placental pathology.

Genetic testing was finally conducted with the permission of the couple. Whole-exome sequencing (WES) of case 3 and the parents' whole blood samples were sent to the Beijing Full Spectrum Medical Laboratory for testing. The *ADAMTS13* c.1187 (exon10) G>A (p.C396Y)/c.1595 (exon14) G>T (p.C532F) complex heterozygous variation was detected in the three newborns (*Figure 1*). According to the 2012 American Society for Genetic Genetics (ACMG) variation classification criteria (14), the c.1187G>A (p.C396Y) variation is defined as having "Uncertain significance". This mutation has not been reported in either the previous literature or the large population sequencing databases. It is a rare mutation; the father of the newborns carried the variation; The variation of c.1595G>T (p.C532F) was also defined as "Uncertain significance", and not reported in the previous literature and large population sequencing databases. It is a rare mutation that the mother carried. The family was consistent with an autosomal recessive pathogenesis. The parents provided informed consent for the placenta to be donated to the hospital and for samples to enter the biological specimen bank. After receiving the genetic results of case 3, we submitted the placental tissues of case 1 and case 2 to Prenatal Diagnosis Center for genetic analysis (*Figure 1*). After learning the results for the three babies, we requested the parents to test plasma enzyme activity, but they did not consent.

Discussion

This study focused on a family case of three neonatal deaths. Gene detection confirmed that the three consecutive infants had the same compound gene mutations, which originated from their father and mother respectively, and led to the higher lethality compared with other reported cases. To our knowledge, this is a newly discovered gene mutation, which may add a new phenotype to this disease spectrum. Three

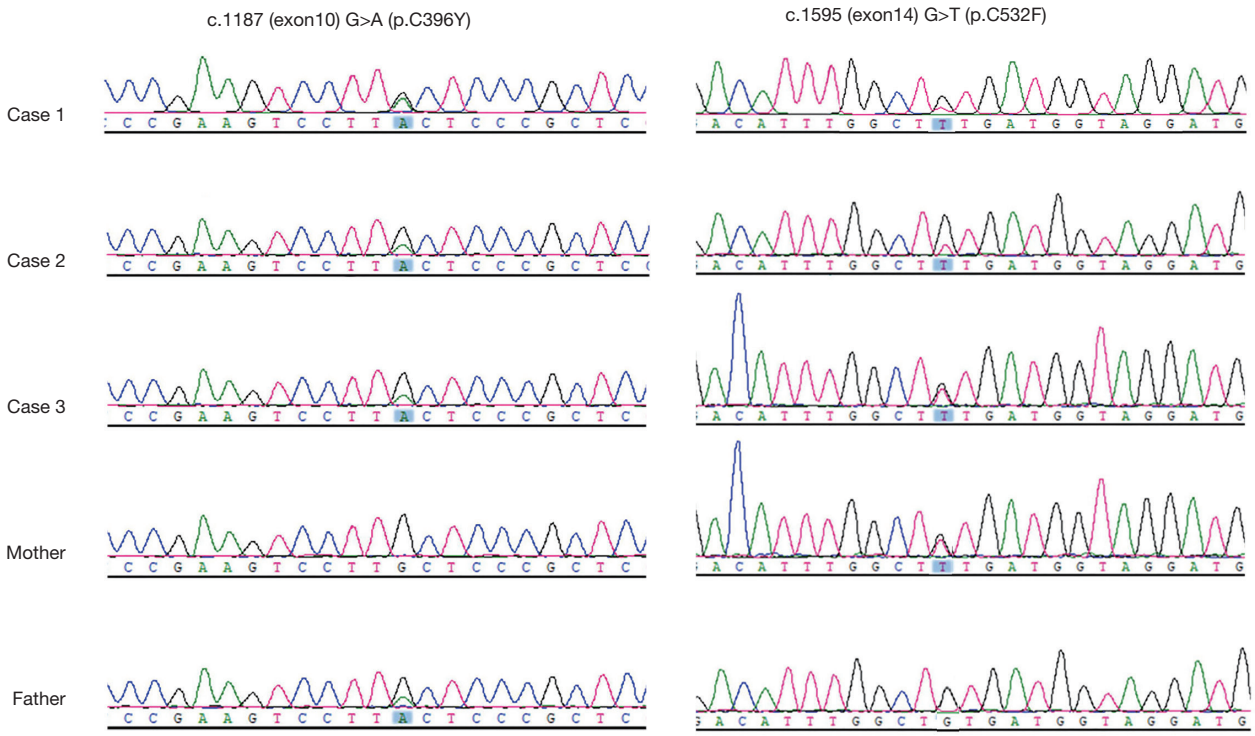

Figure 1 Sanger sequencing showing the mutation in the *ADAMTS13* gene.

infants showed severe symptoms at birth and died suddenly during rescue efforts.

The symptoms of the three infants were mainly severe jaundice, anemia and thrombocytopenia after birth, which was consistent with the reported USS symptoms of neonates. The diagnosis was supported by the genetic results. We reviewed nine published studies of newborn-onset patients (all were diagnosed by ADAMTS13 activity, in seven cases gene mutation analysis was performed) and compared them with our three cases for clinical symptoms and laboratory testing (*Table 1*) (7-13). In our literature review, all infants showed jaundice and thrombocytopenia after birth to varying degrees, accompanied by other different symptoms (e.g., fever and hematuria) (7,8). In all nine cases in the literature, only one case died (9). In that case there was a family history of neonatal death and the neonate showed dyspnea after disease onset, followed by a rapid deterioration, as was the case in this study.

Researchers have suggested that USS shows mild or no clinical symptoms in childhood, and its onset is considered to be caused by various factors (e.g., pregnancy, upregulated cytokine expression during severe infection and excessive drinking) (15). In a 10-year Japanese study, 37 patients had no history of neonatal onset, and of them 29 (79%) had a history of thrombocytopenia in childhood [misdiagnosed as idiopathic thrombocytopenic purpura (ITP)], and only 16 (43%) had undergone exchange transfusion for jaundice (16). The three infants in this study had early onset and they all had dyspnea and jaundice immediately after birth; infusion with fresh plasma during treatment did not significantly help the condition of the latter two infants, which was inconsistent with previous reports (7,10). Additionally, according to the study (16), of 15 cases of USS pregnancies, in 8 cases the infants were stillborn or died shortly after birth. It is believed that the lack of ADAMTS13 enzyme activity in the maternal plasma is harmful to both the mother and fetus. Among the nine cases we reviewed, enzyme activity was detected in the parents of five surviving cases:in one case there was mild deficiency of enzyme activity in the parents (8), and the other four cases were in the normal range (10-12). We speculate that the mother of the three neonates in this studyhas notably lower enzyme activity than normal, but this cannot be confirmed without analysis of plasma enzyme activity. The parent's consenting to WES of the third baby gave us some clues to the puzzle of continuous onset (17).

Based on the time of onset, USS is divided into earlyand lateonset, and onset in the neonatal period is classified as early (18). Mutations in the N-terminal domain (signal peptide-spacer) are closely related to more severe phenotypes (e.g., earlier onset), and some mutations seem to result in more severe phenotypes (18). The compound mutations in this study were in the domains of thrombospondin 1 (TSP1) and cysteine-rich (Cys-rich) of *ADAMTS13*, both of which are located in the N-terminal domain, and are a functional part of the cleavage of VWF polymer (19). Therefore, it is reasonable to suspect that the new mutation we have reported is the cause of earlier onset and low plasma enzyme activity but we do not have evidence from plasma enzyme activity or VWF polymer analysis to support our view.

Plasma transfusion and exchange is considered to be the first choice for USS treatment, and it has remarkable treatment effects in the acute phase. It supplements plasma enzyme activity and removes the adverse factors that lead to vascular endothelial cell injury and platelet aggregation (20). However, long-term transfusion of blood products increases the infection risk and causes great economic burden, accompanied by an unclear long-term influence on severely affected children with neonatal onset. Recent animal experiments have provided new methods for USS treatment, including *ADAMT13* recombinant and gene therapy (5). However, it has not been applied in humans and has an unknown effect. The couple was advised to use preimplantation genetic diagnosis to prevent the mutated gene being passed on to the next child.

In summary, the incidence of USS rate is low, and it has diverse clinical manifestations, which make early diagnosis difficult. Gene detection can assist, but later treatment remains complex, and the long-term complications are unclear. Improving the understanding of this disease is the key to saving infant patients' lives. For those with a clear family history, prenatal embryo selection might be the best option.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tp.amegroups.com/article/view/10.21037/tp-22-114/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-22-114/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patients' parents for publication of this case report and accompanying images. Copies of the written consent are available for review by the editorial office of this journal.

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