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Case Report

De Novo MYH9-Related Macrothrombocytopenia in a Toddler: Insights From Platelet Mass Index

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Abstract

Aims/Background: Myosin heavy chain 9-related disease (MYH9-RD) is a rare inherited disorder characterised by macrothrombocytopenia, often misdiagnosed as immune thrombocytopenia (ITP). Early identification is crucial to prevent unnecessary treatments and to ensure appropriate monitoring. The present case aims to highlight the diagnostic challenges and clinical management of MYH9-RD in a toddler, emphasising the importance of early genetic testing. **Case Presentation**: We discuss a 13.5-month-old girl with macrothrombocytopenia lacking Döhle bodies, who initially received intravenous immunoglobulin (IVIg) and corticosteroids without any response. Within two months, whole-exome sequencing identified a pathogenic *MYH9* mutation (c.287C>T; p.Ser96Leu). **Results**: One year later, the patient remains clinically stable without significant bleeding. The occurrence of petechial rash exhibited a more pronounced correlation with platelet mass index (PMI) values compared to platelet count (PLT), underscoring its significance in clinical evaluation. **Conclusion**: MYH9-RD should be considered in cases of IVIg-resistant thrombocytopenia accompanied by macrothrombocytes. Timely genetic testing can facilitate accurate diagnosis and may help avoid unnecessary procedures, while routine renal and auditory monitoring is important for managing the S96L variant.

Keywords: MYH9; blood platelets; thrombocytopenia; case report; platelet mass index; Epstein syndrome

1. Introduction

Myosin heavy chain 9-related disease (MYH9-RD) is an umbrella term for disorders characterized by *MYH9* mutations and macrothrombocytopenia (i.e., low platelet count (PLT) with giant platelets), which can be accompanied by non-syndromic and progressive sensorineural hearing loss, presenile cataracts, elevation of liver enzymes, or progressive nephropathy often leading to end-stage renal disease. Epstein syndrome, Fechtner syndrome (Alport-like syndrome with macrothrombocytopenia), May-Hegglin anomaly, and Sebastian syndrome are pathologic entities comprising the MYH9-RD spectrum. The *MYH9* gene encodes a conventional non-muscle myosin (myosin IIA; located in 22q12.3) involved in several essential functions such as cytokinesis, cell motility, and cell shape maintenance [1].

We hereby report the diagnostic challenges of a young female toddler who presented with macrothrombocytopenia and a petechial rash, diagnosed with MHY9-RD two months after admission. One year after the diagnosis, the child remains well without any bleeding events and is undergoing regular monitoring of her renal and auditory functions.

2. Case Report

Following the Declaration of Helsinki, and adhering to the CARE guidelines (**Supplementary Table 1**) (https://www.equator-network.org/reporting-guidelines/care/; accessed on 10 April 2025), we hereby report a well-appearing 13.5-month-old girl admitted to our department following the results of a routine check-up that revealed thrombocytopenia with a PLT count of 11 $\times$ 10^9/L (normal range: 150–450 $\times$ 10^9/L), a mean platelet volume (MPV) of 12.3 fL (normal range: 7.5–10 fL), a plateletcrit (PCT) of 0.014% (normal range: 0.15–0.35%), a platelet distribution width (PDW) of 14.6% (normal range: 12–17.5%), and a platelet mass index (PMI) of 135.3 fL $\times$ 10^9/L (defined as the product of PLT multiplied by MPV; inferred normal range: 1125–4500 fL $\times$ 10^9/L). History was negative for febrile illness, indications of infection, trauma, recent vaccination (last vaccination was 1.5 months ago), or medication. Family history was also negative for thrombocytopenia. Physical examination revealed only sparse petechiae on the face and right forearm and minor bruises around the knees, previously attributed to the toddler's first steps. The review of the peripheral blood smear confirmed the presence of large platelets and ruled out microangiopathy. No leukocyte or red blood cell defect was detected, and the direct anti-globulin test returned negative. Coagulation and PLT function tests were within normal range. Im-

munoglobulins at baseline were also normal, and screening for chronic and acute infections was negative.

Intravenous immunoglobulin (IVIg) was initially administered as per immune thrombocytopenia (ITP). Two days later, after no significant response in PLT count, prednisolone was administered, adhering to the respective childhood ITP recommendations [2]. New petechiae were halted at this phase, and corticosteroids were discontinued when the next-generation sequencing (NGS) results set the diagnosis, and medication was deemed redundant.

Whole-exome sequencing (WES) was performed using the Twist Human Core EF Multiplex Complete Kit (Twist Bioscience, San Francisco, CA, USA) and the NextSeq 500 System (Illumina, Inc., San Diego, CA, USA). Bioinformatic analysis was conducted using the SOPHiA DDM™ platform (Sophia Genetics SA, Boston, MA, USA). WES revealed a *de novo* pathogenic c.287C>T (p.Ser96Leu) variant in *MYH9* (heterozygous; NM_002473.6; GRCh37/hg19: chr22:36744995 (rs121913657); registered in ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/variation/14083/; accessed on 10 April 2025). This variant leads practically to a missense mutation, which is pathogenic for macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss. The *in silico* analysis of the defect was conducted using Genomnis software (https://hsf.genomnis.com/; accessed on 10 April 2025; Human Splicing Finder Professional), the Human Splicing Finder Matrix, and the MaxEnt algorithm. The predicted impact of this variant suggests the alteration of auxiliary sequences chaperoned by a significant alteration of the Exonic Splicing Enhancer (ESE)/Exonic Splicing Silencer (ESS) motifs ratio (i.e., the balance between ESEs and ESSs), indicating a high likelihood for the exon to be skipped, potentially leading to alternative isoforms or aberrant splicing (Fig. 1).

Regarding the patient's follow-up period, the median PLT count was 10 $\times$ 10^9/L (interquartile range [IQR] 5; range: 6–18 $\times$ 10^9/L), the mean MPV was 11 fL (standard deviation [SD] 0.9; range: 8.8–12.8 fL), and the mean PMI was 115.9 fL $\times$ 10^9/L (SD 37.4; range: 60.6–187.2 fL $\times$ 10^9/L). Median PCT was 0.011% (IQR 0.006; range: 0.007–0.019%), and median PDW was 19.1% (IQR 4; range: 14.6–21.8%). IBM SPSS Statistics version 29.0.2.0 (IBM Corp., Armonk, NY, USA) was employed for the statistical analyses. PMI was significantly lower in follow-up visits where new petechiae were recorded than in follow-up visits without a new rash (73.5 vs. 123.5 fL $\times$ 10^9/L; $p < 0.001$), and PMI values <85 fL $\times$ 10^9/L predicted petechial rash occurrence (Fig. 2). PMI performed better than PLT count in predicting the manifestation of new petechiae. Binary logistic regression using the forward conditional method identified PMI as the first among five indices added to the model. Subsequently, PLT and PCT were included, indicating their potential to predict the outcome, while MPV and PDW yielded non-significant results. In the backwards logistic regression (LR) method, PMI remained in the model when all other indices were excluded, signifying it as the strongest predictor of a new petechial rash. The "Enter" method confirmed the prediction of new petechiae by PMI, PCT, and PLT ($p = 0.005$, 0.006, and 0.007, respectively), with PMI showing the highest Exp(β) (5.759) and Nagelkerke R^2 (0.689), demonstrating superior explanatory power for the model (explaining more variance in the outcome compared to 0.672 and 0.600 for PLT and PCT, respectively). The binary logistic regression results are available in **Supplementary Table 2**, along with the correlation coefficients of new petechiae with all five PLT indices in **Supplementary Table 3**. The Receiver Operating Characteristic (ROC) Curve revealed that PMI values below 85 fL $\times$ 10^9/L can effectively predict the occurrence of petechial rash (Area Under the Curve [AUC] 0.95; sensitivity 92.9%; specificity 100%; $p < 0.001$). Apart from petechiae, no clinically significant bleeding events were observed during the follow-up period.

One year later, the patient is generally well without bleeding incidents and is regularly monitored, including kidney function and hearing acuity, according to published relevant schedules.

3. Discussion

MYH9-RD is a rare genetic disorder with a reported prevalence of 1–9/1,000,000 (https://www.orpha.net/en/disease/detail/182050; accessed on 10 April 2025). Recent studies, however, suggest a significantly elevated prevalence rate of approximately 1 in 20,000. This discrepancy is attributed to advancements in the molecular characterisation of thrombocytopenia cases [3]. Notably, MYH9-RD is commonly misdiagnosed as immune thrombocytopenia in over 90% of cases, even in individuals with markedly elevated MPV [4]. Promptly identifying the pathogenic *MYH9* variant can provide valuable insights into our patient's clinical course and prevent unnecessary treatments [5–7].

The localisation pattern of neutrophil MYH9 provides critical insights for documenting Döhle inclusions. In the present case, neutrophil inclusions were not observed, which aligns with the localisation pattern associated with the S96L mutant [8]. The clinical course of known mutations (such as S96L) can be predicted based on published genotype-phenotype correlations [9]. In this case, although not present, hearing loss and nephritis are anticipated (each with up to a 75% chance), while cataracts are not expected; therefore, the corresponding follow-up schedule was approved. Despite the high penetrance of S96L, the variation in the age of onset of nephritis and hearing loss among the affected patients depends on epigenetic modifications, environmental influences, and genetic epistasis. Therefore, longitudinal monitoring is necessary to detect any future changes [8,9]. PLT counts may exhibit a slight increase after treatment with prednisolone; however, the presence of giant PLTs in this case, along with the initial lack of re-

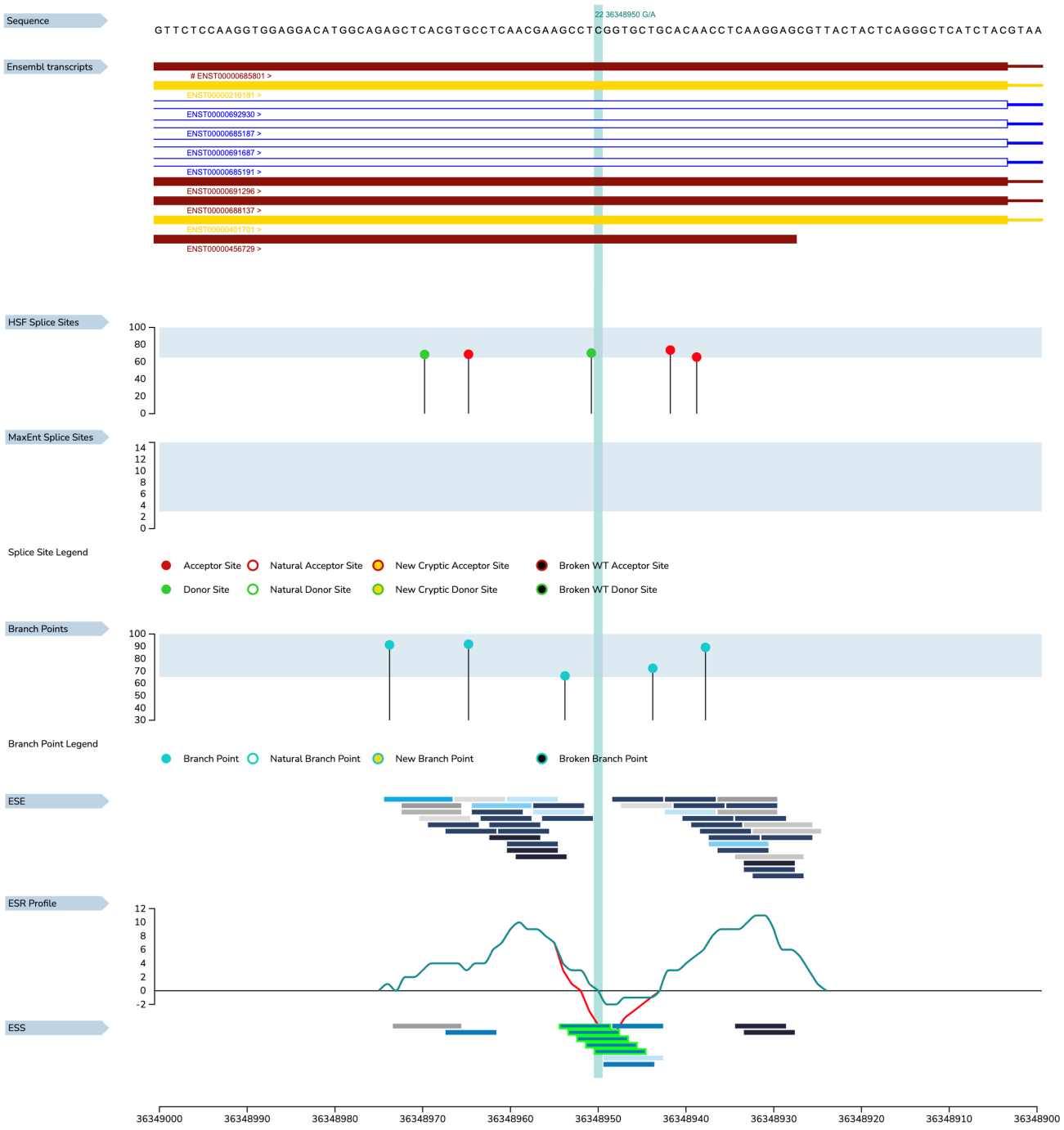

Fig. 1. The predicted impact of myosin heavy chain (*MYH9*) c.287C>T (p.Ser96Leu). ESE, Exonic Splicing Enhancers; ESR, exonic splicing regulatory elements; ESS, Exonic Splicing Silencers; HSF, Human Splicing Finder; WT, wild-type.

sponse to IVIg administration, prompted the investigation using WES when the coagulation and PLT function tests yielded negative results. Notably, a mean PLT diameter of >3.74 µm is diagnostic for MYH9-RD and can effectively discriminate ITP cases (>91%) [1,10]. During the peripheral blood smear review (dried and stained), it is helpful to note that the typical diameters of red blood cells and lymphocytes span from 6.2 to 8.2 µm and 6 to 15 µm, respectively [11]. One year after the patient's admission, the peripheral blood smear offers a detailed insight into the disease (Fig. 3). The use of PMI over PLT for assessing bleeding risk and the need for transfusions has been previously documented [12,13]. The prevalence of sporadic cases resulting from *de novo* mutations, along with the incomplete penetrance of these variants, complicates the determination of inheritance patterns [14]. Therefore, evaluating parental genotypes is recommended for family planning and follow-up assessments.

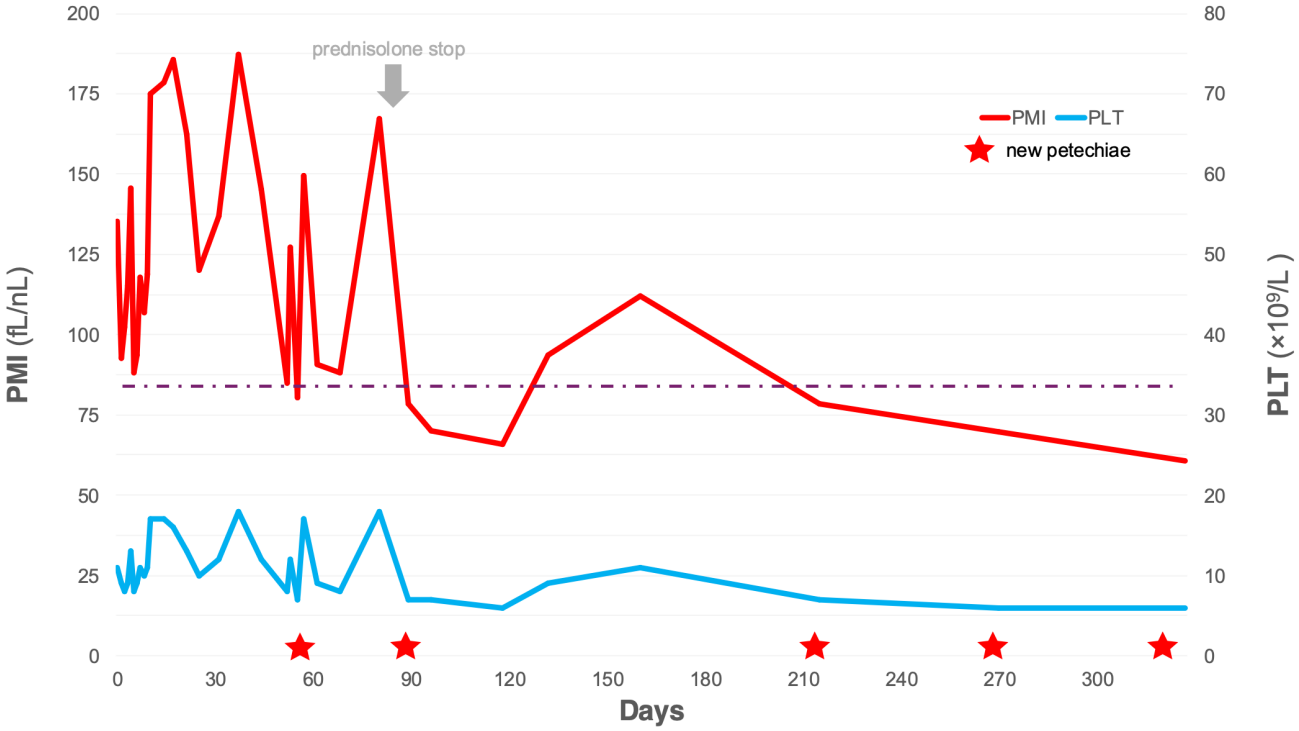

Fig. 2. PMI drops below 85 fL $\times$ 10^9/L (dashed line) and PLT counts $<$7.5 $\times$ 10^9/L associated with the manifestation of new petechiae (stars). PMI, platelet mass index; PLT, platelet count.

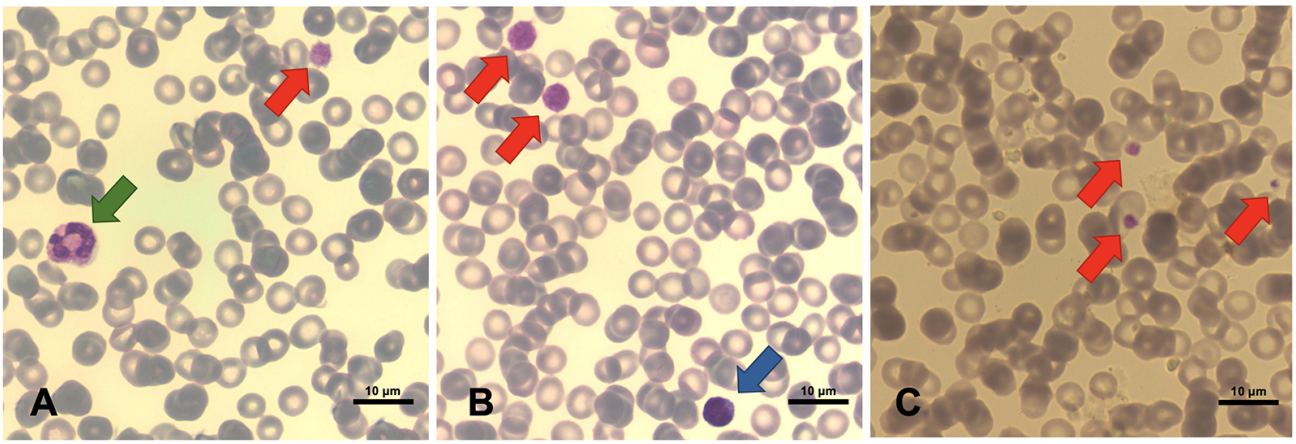

Fig. 3. The patient's latest peripheral blood smear (magnification: 100$\times$). (A) A giant PLT (red arrow) and a neutrophil without inclusions (green arrow). (B) A lymphocyte (blue arrow) and two additional giant PLTs (red arrows). Comparative image from admission (C) shows smaller and less distinct PLTs (red arrows) than those observed in subsequent smears.

No clinical practice guidelines for MYH9-RD have been published. Annual hematologic evaluations are recommended, and immediate medical attention is essential for each bleeding episode. Hemostatic challenges (menorrhagia, surgery, delivery, and other invasive procedures) require careful planning. Screening with an audiogram every three years (with immediate reporting of any worsening of hearing function) and for nephropathy every 6–12 months (depending on the variant) is also recommended. Aside from supportive care, no specific therapy exists to alleviate the systemic effects of the mutated *MYH9*. However, some patients have undergone long-term treatment with a thrombopoietin receptor agonist (TPO-RA) and achieved positive outcomes regarding thrombocytopenia [15]. The efficacy and safety of long-term TPO-RA administration for treating MYH9-RD have yet to be determined. A watch-and-wait strategy was chosen for our patient, involving regular follow-up assessments, with interventions considered only occasionally in the event of hemostatic challenges.

Our findings indicate that prednisolone may increase PLT counts, yet it does not prevent the occurrence of new petechiae. Furthermore, PMI may serve as a useful predictor of bleeding episodes. The strength of this case lies in the early identification of the *MYH9* mutation using WES, which directed appropriate clinical management and averted unnecessary treatments. However, a limitation of the study is the short follow-up period of one year, which may not adequately capture the long-term progression of nephropathy or hearing loss, both of which are part of the expected phenotype associated with S96L mutations. Additionally, all limitations relevant to case reports apply here as well.

4. Conclusion

The present case reinforces the importance of considering MYH9-RD in the differential diagnosis of thrombocytopenia with large platelets. Early genetic testing is crucial for an accurate diagnosis and appropriate management, preventing unnecessary treatments and enabling tailored follow-up strategies. Additionally, PMI may be a valuable tool in assessing bleeding risk and an accessory to the established PLT count.

Key Points

- Large PLTs with a mean diameter exceeding 3.74 µm (larger than half of a red blood cell in a blood smear) suggest MYH9-RD, making ITP a less likely diagnosis.
- Failure of IVIg treatment in the presence of giant PLTs should trigger *MYH9* molecular testing.
- Prompt diagnosis of MYH9-RD can alleviate the psychological and financial burden on patients while also avoiding unnecessary treatment.
- A low PMI (below 85 fL $\times$ 10^9/L) was more sensitive in predicting the occurrence of a petechial rash than the PLT count.
- The published genotype-phenotype correlations offer insights into each patient's prognosis.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

IP & ES: conceptualization; IK & IP: methodology; IP, MS, NK & ES: validation; IP, MS & NK: investigation; IK, NK & ES: resources; IK: writing - original draft preparation; IP, MS, NK & ES: writing - review and editing; IK: visualization; IP, NK and ES: supervision; IP, NK and ES: project administration. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Written informed consent was obtained from the patient's parents. The research was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/BJHM50376.

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