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POSTER ABSTRACTS

311.DISORDERS OF PLATELET NUMBER OR FUNCTION: CLINICAL AND EPIDEMIOLOGICAL

Clinical and Genetic Characteristics of 30 Patients Misdiagnosed As Having ITP with Non-Muscle Myosin Heavy Chain 9-Related Disease (MYH9-RD): A Retrospective Analysis in China

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Introduction : Non-muscle myosin heavy chain 9-related diseases (MYH9-RD) are rare autosomal dominant platelet (PLT) disorders presenting as nonsyndromic forms characterized by macrothrombocytopenia with giant PLTs and leukocyte inclusion bodies or as syndromic forms combining these hematological features with deafness, nephropathy, or cataracts. Owing to its low incidence and similar clinical manifestations, it is easily misdiagnosed as immune thrombocytopenia (ITP), leading to inappropriate treatment. To improve the diagnosis of this rare thrombocytopenic disease and minimize the misdiagnosis rate, we retrospectively analyzed the clinical, treatment, and genetic characteristics of patients with MYH9-RD who were initially misdiagnosed with ITP and compared the differences between pediatric and adult patients.

Methods: Patients from various sites in China were enrolled. The inclusion criteria were macrothrombocytopenia on peripheral blood smear, MYH9 gene mutation detected by next-generation sequencing or whole exon sequencing and verified by Sanger sequencing, and absence of other acquired thrombocytopenia diseases. We collected basic information, clinical manifestations, and laboratory test results via medical records and telephone interviews.

Results: Of the 30 patients, 17 were male, 13 were female, 14 were children, and 16 were adults. There was no significant difference in the mean PLT count ($\times 10^9$/L) at the time of diagnosis between children and adults (50.5 vs. 33.4, P=0.188). However, the median duration of misdiagnosis was significantly shorter in children (0.1 y vs. 9 y, P=0.000) (Table 1). Overall, 5 patients showed no signs of bleeding, while 25 presented with bleeding manifestations: 11 with skin bleeding spots and ecchymosis, 15 with epistaxis, 6 with gingival bleeding, and 3 with increased menstrual volume. Moreover, 21 patients showed no non-hematological manifestations, while 9 presented with non-hematological manifestations, which occurred exclusively in adult patients. Among the latter, 6 patients had nephropathy (2 underwent renal transplantation, and 2 underwent regular dialysis), 5 had hearing impairment (4 underwent high-frequency hearing impairment, and 1 received a cochlear implant due to deafness), and 1 had a congenital cataract. All patients received first- or second-line treatment for ITP. The most common treatment in children was immunoglobulins (12/14), followed by steroids (5/14) and traditional Chinese medicine (2/14). No children received >3 types of treatment, 4 children received >1, and 6 adult patients received >3. The highest number of treatment type for a single patient was up to 7. The median duration of ITP treatment was 1.5 y for adults and 0.1 y for children (P=0.002).

All patients presented heterozygous missense mutations in MYH9; 17/30 were spontaneous mutations, 7/30 were familial mutations (involving 6 paternal and 1 maternal origin), and 6/30 cases had an unknown inherited type. Fourteen cases were located in the N-terminal globular head region, and 16 cases were located in the C-terminal tail domain (Figure 1). Two novel mutations (not recorded in the Global Variome database), p. G1517V and p. K1674Q, were identified.

In 2 adult patients with p.R702C mutations, proteinuria occurred in adolescence, followed by chronic renal failure (CRF), end-stage renal failure, and hearing loss. The 3 children with p.R702C mutation were aged <4 years and exhibited no non-hematological symptoms. Three of the 5 adults with p.E1841K mutations had CRF and underwent kidney transplantation.

Conclusion s : Compared with pediatric patients, adult patients are more likely to be misdiagnosed with ITP, receive more types of inappropriate treatment for a longer period of time, and have more common non-hematological manifestations. To improve diagnostic accuracy and reduce the misdiagnosis rate for patients with thrombocytopenia, especially those with a poor response to ITP treatments, attention should be paid to mean PLT volume, family history, and genetic screening. Consistent with previous reports, patients with the p.R702C mutation showed early-stage kidney injury and hearing loss. The

incidence of spontaneous mutations (56.7%) was significantly higher than previously reported (25-35%). The genetic characteristics of MYH9-RD and genotype-phenotype relationships in China require further clarification.

Disclosures No relevant conflicts of interest to declare.

Table 1 Clinical Characteristics of MYH9-RD Patients

Characteristic	Total (n=30)	Children (n=14)	Adults (n=16)	*P* value*
Sex, n (%)				
Female	13 (43.3)	4 (28.6)	9 (56.3))	
Male	17 (56.7)	10 (71.4)	7 (43.7)	
Median Age, year	16 (3.6-27.3)	3.4 (1.9-7.0)	26.5 (23.3-33.0)	
Mean platelet count by cell counter at the time of diagnosis,×10⁹/L	41.0±27.6	50.5±32.4	33.4±20.5	0.188
Mean platelet volume at the time of diagnosis, fL	15.7±1.3	15.5±1.1	15.68±1.3	0.294
Median age at the time of misdiagnosis as ITP, year	1.7 (0.3-17.5)	0.3 (0-0.7)	16.5 (3.4-20.0)	
Median duration of misdiagnosis, year	2.5 (0.1-9.8)	0.1 (0.1-0.6)	9 (5.5-16.0)	0.000
WHO bleeding scale, n (%)				
Grade 0	5 (16.7)	3 (21.4)	2 (12.5)	
Grade 1	15 (50.0)	9 (64.3)	6 (37.5)	
Grade 2	10 (33.3)	2 (14.3)	8 (50.0)	
Proteinuric nephropathy,‡ n (%)				
Yes	6 (20)	0 (0)	6 (37.5)	0.019
No	24 (80)	14 (100)	10 (62.5)	
Sensorineural hearing loss,§ n (%)				
Yes	5 (16.7)	0 (0)	5 (31.3)	0.045
No	25 (83.3)	14 (100)	11 (68.7)	
Cataract, n (%)				
Yes	1 (3.3)	0 (0)	1 (6.3)	0.314
No	29 (96.7)	14 (100)	15 (93.7)	
Types of treatment, n (%)				
≤3	24 (80)	14 (100)	10 (62.5)	0.019
>3	6 (20)	0 (0)	6 (37.5)	
Therapeutic method, n (%)				
Corticosteroids	17 (56.7)	5 (35.7)	12 (75)	
Immunoglobulin	19 (63.3)	12 (85.7)	7 (43.7)	
Traditional Chinese medicine	13 (43.3)	2 (14.3)	11 (68.8)	
rhTPO	6 (20)	0 (0)	6 (37.5)	
ELT	5 (16.7)	0 (0)	5 (31.3)	
AVA	3 (10)	0 (0)	3 (18.8)	
CsA	3 (10)	0 (0)	3 (18.8)	
Rituximab	1 (3.3)	0 (0)	1 (6.3)	
Splenectomy	1 (3.3)	0 (0)	1 (6.3)	
Median duration of ITP treatment, year	0.5 (0.1-2.6)	0.1 (0.1-0.6)	1.5 (0.4-8.5)	0.002

*Comparison between Children and Adults

‡Including proteinuria (24 hours of proteinuria of 0.5 g or more), chronic renal failure; end stage of renal failure and renal transplantation

§As determined by audiometric examination. Including high-frequency hearing impairment, deaf and cochlear implant

rhTPO recombinant thrombopoietin; ELT eltrombopag; AVA avatrombopag; CsA cyclosporine

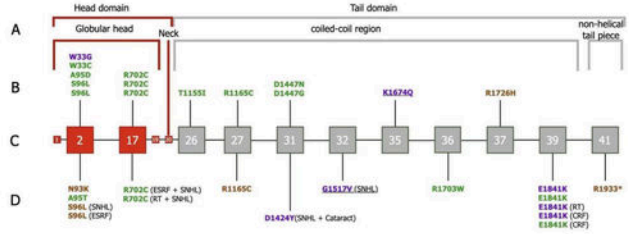

Figure 1. MYH9 Genetic Variants in 30 Patients. (A) Genomic structure of the *MYH9* gene, consisting of the N-terminal head domain encompassing the motor (globular head, encoded by exons 1–19 of MYH9) and the neck (exon 20) domains, as well as the C-terminal tail domain. The tail domain includes the long coiled-coil region (exons 21–40) and the short non-helical tailpiece (exon 41). (B) Distribution of mutations in pediatric patients categorized by exons. (C) Exons identified to be affected. The head domain is shown in red, while the tail domain is shown in gray. (D) Distribution of mutations in adult patients categorized by exons.

Purple indicates familial mutations, green indicates spontaneous mutations, and brown represents unknown inherited type. Underlined text indicates novel variants that were identified; one in pediatric patients and one in adult patients.

CRF chronic renal failure; **ESRF** end stage of renal failure; **RT** renal transplantation; **SNHL** sensorineural hearing loss

Figure 1

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