A Case of Thrombocytopenia with MYH9 Gene Mutation Found in Siblings

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Myosin heavy chain 9 (MYH9) related diseases are autosomal dominant diseases characterized by macrothrombocytopenia and inclusion bodies in leukocyte, which can be accompanied by extra-hematologic symptoms such as sensorineural hearing loss, renal dysfunction, and cataract. They are often diagnosed incidentally in adulthood or misdiagnosed as idiopathic thrombocytopenic purpura (ITP), leading to unnecessary treatment with intravenous high-dose gamma-globulin, steroids, or splenectomy. Here, we report the case of a brother and sister confirmed to have a MYH9 gene mutation during follow-up. An 8-year-old boy was confirmed to have thrombocytopenia at birth and treated with intravenous gamma-globulin under suspicion of ITP or sepsis. He was discharged after showing an increase in platelet count. Subsequently, during outpatient workup, he exhibited thrombocytopenia, large platelets, and neutrophilic inclusion bodies. His 10-year-old sister also presented with the same findings. In 2021, DNA analysis revealed that they share a mutation (c.4270G > A, p. Asp1424Asn), a pathogenic variant associated with MYH9-related disorder.

Keywords: MYH9-related diseases; Macrothrombocytopenia; Non-muscle myosin heavy chain A; Case reports

INTRODUCTION

Myosin heavy chain 9 (MYH9)-related disease is caused by pathogenic variants in MYH9, which encodes a heavy chain of non-muscle myosin. Diseases associated with MYH9 gene mutation include the May-Hegglin anomaly, Sebastian, Fechtner, and Epstein syndrome [1]. While these were previously described as four distinct disorders, they are now considered together as the spectrum of MYH9-related disorders [2]. They are characterized by macrothrombocytopenia, the variable appearance of leukocyte inclusions, and other abnormalities, including sensorineural hearing loss, cataracts, and nephritis [3,4]. MYH9 gene mutation-related diseases are rare genetic diseases. The prevalence is estimated to be as high as 1 in 25,000, although only a few hundred kindreds have been described [5]. They are often asymptomatic and are often diagnosed incidentally in adulthood or misdiagnosed as idiopathic thrombocytopenic purpura (ITP) [6]. We report the case of siblings with chronic thrombocytopenia, confirmed to have MYH9 gene mutation of c.4270G > A (p. Asp1424Asn) during follow-up at Soonchunhyang University Cheonan Hospital from 2012 to the present.

In 2012, a male newborn who was born by vaginal delivery at 37 weeks of gestational age (birth weight: 3,380 g) was transferred to the neonatal intensive care unit (NICU) of Soonchunhyang University Cheonan Hospital on the day of birth, due to continuous grunting after birth. His maternal grandmother had thrombocytopenia and got a splenectomy in the past. Their uncle had history of hearing loss. His initial complete blood count (CBC) revealed thrombocytopenia, with a platelet count of 57,000/μL (normal range, 84–478 × 10^3/μL). Other laboratory findings showed elevated aspartate aminotransferase, which was 142 IU/L (normal range, 30–100 IU/L) and other findings were normal including white blood cell count (26,310/μL; normal range, 9.1–34 × 10^3/μL) and prothrombin time/activated partial thromboplastin time values. We suspected that the newborn could have ITP or sepsis due to thrombocytopenia and moaning signs. We initiated treatment with intravenous gamma-globulin (3.5 g/day, for 2 days) and antibiotics. After 10 days, his platelet count had recovered to 138,000/μL, and his overall condition showed improvement. Blood culture showed no growth of the pathogen. His hearing test results before dis-
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Charge were normal. Then he was discharged from the hospital. Twenty days post-discharge, the patient returned for a follow-up, and we checked his CBC to check his platelet level. His CBC showed platelet count 85,000/μL and other results were normal. Because the platelet count could be observed in ITP, the patient was sent home without treatment. When he returned to the hospital 1 month later, his CBC revealed an increased platelet count of 139,000/μL.

After 10 months from birth, he was admitted to our hospital for pneumonia treatment. His initial platelet count was 79,000/μL, which increased to 88,000/μL after 2 days of admission, and further to 114,000/μL after 6 days of admission. As the platelet count did not warrant treatment for ITP, we opted for observation. Our primary focus was on treating the pneumonia with antibiotics and conservative therapy. We recommended follow-up care for further monitoring. At the age of 2 years, the patient returned to hospital for follow-up, and his CBC revealed a platelet count of 117,000/μL. Although he had persistent thrombocytopenia, it was not severe. Consequently, we opted for yearly follow-up without treatment. At the age of 6 years, his peripheral blood smear (PB) morphology did not reveal any abnormalities other than thrombocytopenia (94,000/μL). However, at the age of 7 years, his CBC showed a platelet count of 89,000/μL, and giant platelets and neutrophilic inclusion body were observed in PB morphology. At the age of 9 years, his CBC revealed platelet count 57,000/μL and same findings were observed again. Autoantibody tests showed presence of antinuclear antibody with a homogeneous pattern. He did not show any other symptoms except for thrombocytopenia.

In 2014, a 3-year-old girl, the sister of the patient described above, was admitted to our hospital for treatment of fever, rash, and thrombocytopenia. Her initial platelet count was 35,000/μL (normal range, 150–400 × 10^3/μL) and other laboratory findings were normal. Because this platelet count needed not to be treated, we decided to just have observation and the platelet count was recovered to 72,000/μL after 3 days. However, she showed a platelet count between 50,000/μL and 100,000/μL on follow-up from 2014 to 2021. When she was 7 years old, her PB morphology did not show abnormalities and her platelet count was 72,000/μL. But, when she was 8 years old, we found giant platelets and neutrophilic inclusion body in her PB morphology like her brother. Like her brother, she did not show any other symptoms except for thrombocytopenia. At the age of 10 years old, mutational analysis was conducted, revealing a heterozygous mutation in the known MYH9 gene, specifically c.4270G>A (p. Asp1424Asn), identical to her brother’s mutation. Since their thrombocytopenia was not severe, and no additional symptoms associated with MYH9-related disease were observed, we recommended regular outpatient visits every 2–3 years during their recent follow-up in 2023.

The patient’s caregiver provided written informed consent for the publication of clinical details and images.

**DISCUSSION**

MYH9-related disorders result from mutations in MYH9 gene, which is located on chromosome 22q12-13, encoding for the heavy chain A of class II non-muscle myosin (NMMHC-IIA), a cytoskeletal contractile protein [6]. NMMHC-IIA proteins, which are expressed in many cells, including the platelets, leukocytes, kidneys, and cochleae, eye are associated with cell motility, cell phagocytosis, cell adhesion, cytokinesis, and cell architecture and develop.
development [6]. Therefore, the mutation of MYH9 gene may cause thrombocytopenia, renal injury, hearing loss, and cataracts. In Japan, a 3-year-old girl had been receiving follow-up care for thrombocytopenia and neonatal cataracts which were diagnosed at birth, and she was confirmed to have MYH9 gene mutation [7]. Also, there was a case of a 14-year-old boy with MYH9 gene mutation who had thrombocytopenia and nephrotic proteinuria, eventually received kidney transplantation [8].

In this study, we reported siblings who showed persistent thrombocytopenia and finally diagnosed as MYH9 gene related disorder. As far as we know, the patients in this case report were the first case of MYH9 gene mutation found in siblings in South Korea. MYH9 gene mutation is associated with development of cataracts, sensorineural hearing loss, and glomerulosclerosis, but MYH9 related disorders are very rare diseases, other organ involvements such as the ear, eye, kidneys, and liver were not recognized initially and they may be misdiagnosed as ITP and inappropriately managed with immunoglobulin, steroid, anti-D, and splenectomy [6,7]. In this case, the siblings did not exhibit any other symptoms except for thrombocytopenia, leading to a delayed diagnosis. Therefore, in patients with severe thrombocytopenia, history-taking to determine if there is family history of thrombocytopenia, and examination of the PB morphology for giant platelets and inclusion bodies in the leukocytes are necessary to confirm the presence of MYH9 gene mutations [6]. We report this case for emphasizing the importance of confirming MYH9 gene mutations, even in cases where there are no extra-hematologic symptoms, particularly when there is a family history of thrombocytopenia.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES