

Miyozin Ağır Zincir 9 İlişkili Trombosit Bozukluğu: Zor Tani

Difficult Diagnosis of Myosin Heavy Chain 9 Related Platelet Disorder

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ÖZ

Myosin Heavy Chain 9 (MYH9) hatalı mutasyonları, trombosit disfonksiyonları, lökosit Döhle gövdeleri, değişken ölçüde sensorinöral sağırılık, katarakt ve glomerulopati ile karakterize edilmiştir.

Üçlü trombositopeni, sensörinöral işitme kaybı ve son dönem böbrek hastalığı (ESRD) olan kadın hasta sunulmuştur. 25 yaşında kadın hasta kronik trombositopeni ve üremik semptomlar ile başvurdu. Kronolojik olarak ITP, Bernard - Soulier ve Alport sendromu tanıları alan hastaya oral metilprednizolon, ardından intravenöz immünoglobulin (IVIG) ve azatioprin 300 mg / gün verildiği öğrenildi. Tanı tekrar değerlendirildi; kemik iliği biyopsisinde retikülün artışı ile megakaryosit sayısında artış izlendi. Odyogram, iki taraflı yüksek frekanslı bir sensorinöral işitme açığına ortaya çıkardı. Renal biyopside kronik glomerüloskleroz ile uyumlu özellikler saptandı. MYH9 gen NM_002473.5 p.R702C (c.2104CT) heterozigot mutasyon bulundu. MHY9 ilişkili Hastalık (MHY9RD) tanısı konulan hastaya 75 mg / gün eltrombopag ile tedavi verildi. Trombosit sayısı, 17 000 mm³'e yükseldikten sonra periton kateteri komplikasyonsuz yerleştirildi.

MHY9RD, ESRD ve ciddi işitme kaybı ile karakterize nadir bir sendromdur. Böbrek biyopsisi ve invazif girişimler öncesi eltrombopag tedavisi uygulanabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Trombosit disfonksiyonu, İşitme kaybı, Son dönem böbrek hastalığı, MHY9 ilişkili hastalıklar

ABSTRACT

Myosin Heavy Chain 9 (MYH9) missense mutations have been characterized by large platelets, leukocyte Döhle bodies, in variable extent sensorineural deafness, cataracts, and glomerulopathy.

A 25-year old female with triad of thrombocytopenia, sensorineural hearing loss and end stage renal disease (ESRD) presented with uremic symptoms with a history of chronic thrombocytopenia with since childhood. She was misdiagnosed with ITP, Bernard -Soulier and Alport syndrome chronologically. First she was treated oral methylprednisolone, then pulses of intravenous immunoglobulin (IVIG) and azathioprine 300 mg/day were tried with no response. The diagnosis was re-evaluated; bone marrow biopsy revealed increased number of megakaryocytes with decreased platelet budding, increased reticulin build-up. The audiogram revealed a profound high-frequency sensorineural hearing deficit bilaterally. Renal biopsy revealed features consistent with chronic glomerulosclerosis. MYH9 gen NM_002473.5 p.R702C (c.2104CT) heterozygous mutation was found. She has been diagnosed with MHY9 Related Disease (MHY9RD) and treated with eltrombopag 75 mg/day. After a successful increase to 17 000mm³ in platelet count, the peritoneal catheter was implanted successfully without complications.

MHY9RD is a rare syndrome that can end with ESRD and severe hearing loss. This rare diagnosis should be kept in mind and treatment modalities like renal biopsy should be done with Eltrombopag.

Keywords: Platelet disorder, Hearing Loss, End Stage Renal Disease, MHY9 related diseases

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INTRODUCTION

Myosin heavy chain 9 (MYH9)-related platelet disorders (MYH9RD), previously defined in four inherited syndromes (Epstein syndrome, Fechtner syndrome, Sebastian syndrome, May-Hegglin anomaly) are a group of inherited thrombocytopenias characterized with giant platelets and Döhle body-like inclusion bodies. MYH9RD is a rare disease with a prevalence of 1-9:1,000, 000 worldwide (1). Mild forms are discovered incidentally and severe forms are usually misdiagnosed. Thus the prevalence might be higher than actually observed (2).

The MYH9 gene (22q13.1) encodes the heavy chain of the isoform A of the non-muscle myosin of class II (myosin-9), a cytoskeletal contractile protein. Myosin-9 is found in most cell types and tissues. There are heterozygous pathogenic variants due to mutations in MYH9 gene. The clinical findings often get worse throughout life with late onset non-hematologic manifestations(3,4).

Presence and severity of spontaneous bleeding correlate with the degree of thrombocytopenia, but most affected individuals have no spontaneous bleeding (9) and fatal bleeding is rare. The late onset of MYH9RD related manifestations can develop anytime between infancy and adulthood. The overall annual rates per 100 affected persons are 1.71 for sensorineural hearing loss, 0.77 for nephropathy, and 0.57 for cataract (9). The mean age of onset for glomerulopathy is 27 (9). Seventy two percent of them are diagnosed before the age of 35. In most individuals, kidney damage progressively evolves to end stage renal disease (ESRD) starting with proteinuria and microhematuria. The overall annual rate for progression to ESRD is 6.79% (5).

In this case, we reported the clinical manifestations and management of a patient with heterozygous MYH9 R702 mutation.

Case Report

A 25-year old female patient with triad of thrombocytopenia, sensorineural hearing loss and chronic kidney disease (CKD) stage V treated with

peritoneal dialysis with MYH9RD heterozygous pattern is presented. She had a history of chronic thrombocytopenia ($< 30\ 000/\text{mm}^3$), recurrent epistaxis, gum bleeding, anemia and petechia since she was 5 years old and menorrhagia for the last 10 years with the initial diagnosis of ITP. She has no findings of cataract on eye examination.

She was given oral methylprednisolone 60 mg/day and pulses of intravenous immunoglobulin (IVIG) because of steroid unresponsiveness. With no response again; azathioprine 300 mg/day was given. Diagnosis of ITP was re-evaluated and bone marrow biopsy was done, relieving megakaryocytes with ultrastructural abnormalities and reticulin build-up. Bernard -Soulier syndrome was excluded. An audiogram was done at the age of 22 because of progressive hearing loss revealing bilateral high-frequency sensorineural hearing deficit. Genetic analysis showed an heterozygous mutation in MYH9 gene: NM_002473.5 p.R702C (c.2104C>T). She developed nephrotic syndrome; with a proteinuria of 1.6 gr-3.5 gr/day and renal function loss. Kidney biopsy done at the age of 24 and was reported as Alport syndrome with global sclerosis and fibrotic crescents in glomeruli, tubular atrophy with lymphocytic infiltration compatible with chronic glomerulosclerosis.

The patient is almost deaf and has a creatinine clearance below 10 ml/min and a platelet count below 10 000/mm³. She has been treated with Eltrombopag achieving an increase in platelets up to 17 000/mm³. As for the renal replacement therapy she has been doing peritoneal dialysis so far.

DISCUSSION

The exact mechanism of renal damage in MYH9RD is not fully understood but few available reports (6-8) suggest that focal segmental glomerulosclerosis (FSGS) preceded by a mild mesangial proliferation and expansion, with focal GBM thickening.

NMMHCIIA protein is commonly expressed in podocytes and mesangial cells(9). The protein distribution in MYH9RD is altered. Defective NMMHCIIA protein which is a major component of the actin myosin contractile apparatus in the podocyte foot process, might disrupt the glomerular

filtration barrier by altering the podocyte cytoskeleton (9,10).

Since renal biopsy is mostly avoided in Epstein-Fechtner syndrome, only three reports on renal pathological findings are available in the literature (6-8). Epstein et al. described the renal morphology in a 13-year-old patient with Epstein syndrome (6). Genetic mutation of MYH9 R702C was identified by Heath et al.(4) in this patient. Moxey-Mims et al. (7) performed renal biopsy twice in an African-American female with Fechtner's syndrome. But the type of MYH9 mutation in this patient was not identified in the article. The first biopsy revealed proliferation of mesangial cells and matrix with GBM alterations, such as effacement, thickening, and splitting. The second biopsy of the this patient demonstrated global sclerotic changes in 75% of glomeruli (7). Moxey-Mims et al.(7) concluded that these renal changes are similar to those in Alport syndrome. Ghiggeri et al.(8) performed renal biopsy in Fechtner syndrome patients with D1424H mutation, and electron microscopy showed focal and segmental effacement of podocytes and loss of the interpodocyte slit diaphragm. The histopathological changes reported so far are not unique and might be observed in various types of glomerulonephritis. However every histopathological finding in these patients is important for the differential diagnosis of this rare syndrome especially from Alport syndrome. Dysfunction of NMMHC-IIA molecule in podocytes causes alterations in GBM in Epstein syndrome with MYH9 mutation.

With this case, we reported that a patient with MYH9 gene: NM_002473.5 p.R702C (c.2104C>T) heterozygous mutation show deterioration of renal function with progressive hearing disability. Several mutations including S96L, R702C, R702H, R1165C, and D1424 have been associated with the development of nephritis (4,9,10). There are non-syndromic sensorineural hearing loss syndromes that are not associated with platelet defects. A single NM_002473.5c.2114G>A (p.Arg705His) pathogenic variant in two unrelated families (11,12) and four families with the p.Arg705 His pathogenic variant with macrothrombocytopenia and neutrophil MYH9 aggregates along with sensorineural hearing loss were reported (13,14). Heath et al. (4) and

Dong et al.(9) described the development of nephritis in patients with R702 mutations. It was reported by Dong et al.(9) and Miyazaki et al.(15) that there were families with heterozygous mutations of MYH9 gene and established clinical course with related disorders.

In conclusion, progressive deterioration of renal function in patients with heterozygous MYH9 R702 mutation might be expected. Due to its rarity, a high index of suspicion is of prime importance to diagnose these patients in order to prevent misdiagnosis and overtreatment.

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