GNE myopathy with thrombocytopenia: a case report and review of the literature

Joshua Rim, MD; Yuebing Li, MD, PhD
Department of Neurology, Neurological Institute, Cleveland Clinic, Cleveland, OH 44195, USA

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Case description

A 34-year-old man presented with bilateral leg weakness that had been slowly progressive for 3 years. At the initial visit, he reported bilateral foot drop, left being worse than right. He denied weakness in the upper extremities or sensory symptoms. Past medical history was unremarkable, and there was no family history of neuromuscular disorders. Neurologic exam revealed normal mentation, language and cranial nerve examination. Muscle strength exam revealed the following (Medical Research Council scale): shoulder abductors 4, elbow flexors 5, elbow extensors 5, finger abductors 3, deep finger flexors 4, hip flexors 3, knee extensors 4, knee flexors 3, dorsiflexors 2, and plantar flexors 2. Diffuse hyporeflexia was present. The remaining neurological examination was unremarkable.

Blood tests for electrolytes, thyroid, renal and liver function, and immunological evaluation were normal. Serum creatine kinase was elevated at 498 U/L (normal range: 51 to 298 U/L). Electrodiagnostic testing revealed the presence of short-duration and small-amplitude motor unit potentials and fibrillations/positive sharp wave discharges in the distal and proximal muscles of the left upper and lower extremities. Pulmonary function test and echocardiogram revealed normal findings. Genetic panel analysis of 98 myopathy-causative genes identified the following findings in the glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase (*GNE*) gene (NM.001128227): a nonsense c.1937C>G (p.Ser646Ter) and a missense c.304 A>T (p.Arg102Trp) mutation. The c.1937C>G mutation resulting in the creation of a stop codon was previously reported as being pathogenic for GNE myopathy.[1] Homozygous c.304 A>T mutation was previously detected in a 44-year-old female with GNE myopathy.[1] Parental analysis of our patient revealed that he was a compound heterozygote for these mutations, confirming the diagnosis of GNE myopathy.

During myopathy evaluation, patient was noted to have reduced platelet count of 91, 000 cells/μl (normal range: 150,000 to 400,000 cells/μl), leukocyte count of 2,700 cells/μl (normal range: 3,700 to 11,000 cells/μl) and neutrophil count of 1,200 cells/μl (normal range: 1,450 to 7,500 cells/μl). Peripheral blood smear showed normal blood cell morphology. A bone marrow aspiration showed no evidence of increased blasts or significant morphologic dysplasia. Ultrasound of abdomen revealed the presence of mild splenomegaly. A hematological evaluation did not reveal an etiology for his abnormal blood count. No prior excessive bleeding tendency or frequent infection was encountered.

Discussion

As a rare form of hereditary inclusion body myopathy, GNE myopathy is a slowly progressive adult-onset myopathy that preferentially affects the tibialis anterior muscle. Muscle histopathology typically reveals fiber atrophy with rimmed vacuoles in the absence of inflammation. In the literature, several reports described occurrence of thrombocytopenia in patients with *GNE* mutations.[2-8] In these patients, thrombocytopenia can be mild without clinically evident platelet dysfunction, similar to our patient.[2] However, thrombocytopenia can also be severe, occurring in early infancy, resulting easy bruising, epistaxis, menorrhagia, hemorrhage or hematoma.[4,7] Cases of requiring red blood cell and platelet transfusions were previously described.[7] On peripheral blood smear analysis, platelets tend to be abnormally large in GNE myopathy patients.[4,6-8]

Thrombocytopenia and myopathy due to *GNE* mutations may occur on the same individual or separately. Revel-Vilk et al. described 9 individuals with thrombocytopenia due to *GNE* mutations. In their report, 8 patients had no evidence of myopathy and the remaining patient had muscle weakness but muscle biopsy did not reveal typical findings of GNE myopathy.[7] A national database of GNE myopathy reported that 3 of 121(2.5%) Japanese patients with GNE myopathy reported thrombocytopenia.[3] Table 1 lists all reported patients with *GNE* mutations and thrombocytopenia. Among the 10 patients in Table 1, 5 were given diagnoses of idiopathic or immune-mediated thrombocytopenia, and 2 patients were found to have splenomegaly. In all patients, thrombocytopenia occurred earlier than myopathy or was found during the workup for myopathy.

Thrombocytopenia in *GNE* myopathy is likely secondary to shortened platelet lifetime rather than ineffective thrombopoiesis. The *GNE* enzyme is responsible

for intracellular sialic acid synthesis. Sialic acid residues are important for platelet longevity, and proper aggregation and adhesion. Without proper sialylation of the cell wall, platelets cannot aggregate properly and are cleared more rapidly from the peripheral circulation.[7]

In our patient, mild leukopenia and neutropenia were observed, together with thrombocytopenia. Such a presentation has not been described previously in individuals with *GNE* mutations. We are unsure whether the occurrence of leukopenia and neutropenia is secondary to splenomegaly in our patient. As the *GNE* enzyme is expressed within all cells of the hematopoietic lineage, it is possible that the mutation may also result in leukopenia and neutropenia.

In patients who are highly suspected of having an inherited myopathy, a finding of unexplained thrombocytopenia, including a prior history of idiopathic thrombocytopenia, should bring GNE myopathy to the forefront of differential diagnosis.

Abbreviation

GNE : UDP-N-acetyl)-2-epimerase/
N-acetylmannosamine kinase

Corresponding author:
Yuebing Li, MD, PhD, Neuromuscular Center,
Cleveland Clinic Foundation, 9500 Euclid Avenue,
Cleveland, Ohio 44195
Telephone: (216) 445-9525
Fax: (216) 445-4653
liy@ccf.org

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Table 1. Cases of GNE myopathy with thrombocytopenia

Source	No. of patients	Mutation	Onset age of myopathy	Onset age of thrombocytopenia	Hematology workup
Zhen (2014)	2	p.Tyr217His and p.Asp546Glnfs*2 for both	Indiv 1: 25 years Indiv 2: 24 years	Indiv 1: 29 years Indiv 2: 26 years	Platelet count of 36,000 cells/µl for indiv 1, and 45,000 cells/µl for indiv 2. Megakaryocytes in the bone marrow increased for both subjects.
Mori-Yushimura (2014)	3	Indiv 1: p.Arg420X and p.Val572Leu Indiv 2: p.383insT and p.Val572Leu Indiv 3: p.Arg8X and P.Val572Leu	NA	NA	Platelet count of 9,500 cells/µl for indiv 1, 10,300 cells/µl for indiv 2 and 7,100 cells /µl for invid 3. All three were diagnosed as with idiopathic thrombocytopenia.
Izumi (2014)	2	p.Val603Leu and p.Gly739Ser for both	Indiv 1: adolescence Indiv 2: 18 years	Indiv 1: neonate Indiv 2: 2 years	Platelet count of 1,700-16,200 cells/µl for indiv 1, and 1,100-9,000 cells/µl for indiv 2. Bone marrow megakaryocytes increased for indiv 1 and normal for indiv 2. Splenomegaly for indiv 2.
Behnam (2014)	1	p.Cys612Gly	28 years	unclear	History of immune hrombocytopenic purpura
Paul (2020)	1	p.Leu634Phe and p.Arg42Gln	Twenties years	4 years	Platelet count of 71,000 cells/µl, and bone marrow showed increased megakaryocytes and abnormal platelet morphology. Diagnosed with idiopathic thrombocytopenia.
Our patient	1	p.Ser646X and p.Arg102Trp	31 years	Detected during myopathy evaluation	Platelet count of 91, 000 cells/µl, leukocyte count of 2,700 cells/µl and neutrophil count of 1200 cells/µl. Bone marrow exam normal. Splenomegaly present.

Abbreviations: GNE, UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase; indiv, individual