Conclusion: This case illustrates the need for further biochemical studies in patients with high clinical suspicion for disease and non-diagnostic comprehensive genetic testing. Establishment of diagnosis has been life altering for our patient and his family, as they have appreciated developmental gains within days of initiating appropriate neurotransmitter replacement and tyrosine supplementation. Without this biochemical evaluation, our patient would have suffered natural disease progression. Our experience shows one should consider further biochemical evaluation in a child with severe hypotonia with negative molecular sequencing.

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ePO17

GNE gene variants associated with thrombocytopenia with or without GNE myopathy

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Introduction: GNE Myopathy is a rare, degenerative skeletal muscle disease, first presenting with anterior tibialis weakness then progressing proximally, relatively sparing the quadriceps. Symptoms usually develop in early adulthood (between 20-40 years) and include bilateral foot drop and rimmed vacuoles on muscle biopsy. Most patients become wheelchair dependent within a decade after onset. Upper limbs are usually involved around a decade later than the lower limbs. GNE myopathy is caused by biallelic variants in *GNE*, which encodes the rate limiting bifunctional enzyme in sialic acid synthesis, UDP-N-acetyl-glucosamine-2-epimerase/N-acetylmannosamine kinase (GNE), leading to decreased sialic acid production. Sialic acid is a negatively charged sugar, that serves as the terminal sugar of many N- and O-linked glycoproteins; it serves many functions in cell interactions and signaling. Recently, *GNE* variants have been associated with thrombocytopenia, with or without manifestations of myopathy. To investigate this phenomenon, we performed a literature review and analyzed data of patients in our GNE myopathy prospective natural history (NH) study.
Methods: Data were collected through a prospective NH study of individuals with GNE myopathy (NCT1417533). Patients are admitted to the NIH Clinical Center for investigations, including physical function tests, questionnaires, blood analysis (including a complete blood count at each visit), and cardiac and pulmonary function tests. Patient platelet data were compared to normal values. For the literature review, two authors performed a search of all reports including *GNE* and thrombocytopenia. Clinical manifestations as well as variants identified were compared to those of our cohort.
Results: We analyzed a total of 126 platelet counts obtained from 51 GNE myopathy patients (61% female), between 21 and 65 years of age at their baseline to our NH study, with at least one platelet count obtained during subsequent visits. The average platelet count for females was 251 X 10^9 cells/L (range 144–390) and 205 X 10^9 cells/L for males (range 103-300), which are within the normal range for our laboratory (173–369 and 161-347, respectively). However, these values are lower than the expected means of 271 for females ($p < 0.001$) or 254 for males ($p < 0.0001$), based upon our lab's normal ranges. A total of 8 individuals were below the normal range at some point, but above the pathologic thrombocytopenia cutoff (100). None presented signs of thrombocytopenia. The literature review yielded 25 patients with thrombocytopenia (17 without myopathy and 8 with myopathy) and biallelic *GNE* variants. The *GNE* variants in the 25 patients included 7 novel variants not reported in individuals with GNE myopathy and 11 variants previously associated with GNE myopathy. The novel variants were not localized to specific functional GNE domains but were scattered across the entire *GNE* gene and found in Chinese, European, Pakistani, Thai, and Palestinian Arab populations. None of our 51 NH study patients had any of the 18 *GNE* variants associated with thrombocytopenia.
Conclusion: Although there was no evident thrombocytopenia in our NH study cohort, the average platelet count was slightly lower than expected, suggesting a potential role of GNE in platelet survival. Previous studies indicate that sialic acid has a significant role in platelet function. Mice deficient in a sialyltransferase had decreased sialic acid and platelet survival times, leading to thrombocytopenia. Patients with GNE myopathy and thrombocytopenia had increased reticulated platelets, suggesting that pathogenic *GNE* variants may contribute to platelet surface hyposialylation, resulting in increased platelet clearance by the Ashwell-Morell receptor.
Patients with GNE-related thrombocytopenia should be followed for developing signs of GNE myopathy, since most reported individuals were likely too young to develop signs of GNE myopathy. The addition of *GNE* on gene panels for platelet disorder gene panels should also be promoted. GNE myopathy patients should also have their platelets assessed and monitored. To better characterize this phenomenon, we have expanded our NH study to include other (non-muscle) *GNE*-related clinical conditions and younger individuals.

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ePO18

Late-onset congenital erythropoietic porphyria associated with myeloid malignancy

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Background: Congenital erythropoietic porphyria (CEP, OMIM #263700) is a rare disorder of heme biosynthesis characterized biochemically by elevated excretion of type I porphyrin isomers in urine and feces. The disorder is caused by decreased uroporphyrinogen III synthase (UROS) activity, leading to an overproduction of the dead-end metabolites uro- and coproporphyrinogen I, primarily in the bone marrow, and the subsequent deposition of type I porphyrin isomers in tissues.
In most cases, the CEP results from homozygous or compound heterozygous pathogenic variants in the *UROS* gene. More rarely, it presents in males with specific variations of the X-linked transcription factor GATA1, which leads to decreased UROS expression in erythroid precursor cells. The clinical severity of CEP is variable and ranges from hydrops fetalis due to hemolytic anemia *in utero* to a mild adult-onset form with cutaneous manifestations only. Typically, however, the disorder presents soon after birth with cutaneous photosensitivity and hemolytic anemia.
A small number of patients have been reported in the literature with clinical and biochemical features of CEP without pathogenic variants in the *UROS* or *GATA1* genes and with normal UROS activity in erythrocytes. These patients were all males with myeloid malignancy who first presented with symptoms of cutaneous porphyria after the age of 50. The underlying cause of the CEP-like phenotype in these patients is unknown. It has been hypothesized that in those