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

patients, UROS is defective only in a small number of myelodysplastic cells resulting from a somatic mutation in either *UROS* or *GATA1*. In that scenario, the number of clones carrying the pathogenic variant might be too low to be detected by standard molecular methods but sufficient to cause clinical and biochemical symptoms consistent with CEP.

Case presentation: The patient is a 52-year-old woman with a complicated past medical history who presented to a tertiary medical center with blistering lesions that started 2 years ago. Her past medical history is remarkable for type 2 diabetes, hypertension, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, and peripheral vascular disease.

She was diagnosed with CEP at her local clinic but had not had any medical interventions done locally. Over the years, her clinical condition deteriorated progressively where now she had multiple areas of ulceration and blistering with hypopigmented scarring in sun-exposed areas, particularly on her face and scalp, deep routed ulcers in her hands and arm, and reddish discoloration of her urine. In the preceding months, she had also developed worsening pancytopenia needing blood transfusion. A bone marrow biopsy showed erythroid hyperplasia with dyspoietic changes confined to the erythroid lineage and hypercellularity but no morphological evidence of malignancy. Molecular DNA analysis detected pathogenic variants in the genes *BCOR* and *TET2*, both associated with myelodysplastic syndrome and acute myeloid leukemia. Based on these findings, the patient was diagnosed with low-risk myelodysplastic syndrome.

Porphyrin analysis showed elevated levels of uro- and coproporphyrins in urine, type I porphyrin isomers in feces, and slightly increased total porphyrin in erythrocytes—a biochemical profile consistent with CEP. However, next-generation sequencing of 11 genes associated with porphyria did not detect any pathogenic variants, and the measured UROS activity in erythrocytes was within the normal range.

Conclusion: The case presented here is, to our knowledge, the first female patient reported with a late-onset CEP-like phenotype associated with myelodysplastic syndrome. This demonstrates the value of biochemical investigation and clinical examination in cases where DNA analysis proves inconclusive.

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eP019

Case presentation: Dual diagnosis of LCHAD deficiency and type 1 diabetes mellitus and complexities of management

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Background: Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase (LCHAD) Deficiency (OMIM # 609016) is an autosomal recessive of mitochondrial fatty acid β-oxidation caused by biallelic pathogenic variants in the *HADHA* gene. In this condition, fasting or catabolism, in the absence of adequate caloric intake, can result in hypoglycemia. Hypoglycemia leads to the utilization of free fatty acids, which then enter the mitochondria via the carnitine cycle. In individuals with a fully functional LCHAD enzyme, the hydroxy form of free fatty acids is oxidized to acetyl-CoA, which is then used to produce ketones; this process can compensate for the energy needs not satisfied by glucose. LCHAD Deficiency prevents adequate production of ketones and results in the accumulation of fatty acid intermediates that inhibit gluconeogenesis. The build-up of fatty acid intermediates is toxic. Features in untreated patients may include severe hypoketotic hypoglycemia, lethargy, liver dysfunction, hepatomegaly, metabolic acidosis, clotting abnormalities, hyperammonemia, cardiomyopathy, and sudden death. Treatment for LCHAD Deficiency includes avoidance of fasting, a diet limited in long chain fatty acids, and medium-chain triglyceride supplementation.

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disorder that results in the destruction of pancreatic beta cells, which produce insulin. Insulin regulates the metabolism of carbohydrates, fats, and protein by promoting the absorption of glucose from the blood into liver, fat, and skeletal muscle cells. Treatment for T1DM includes exogenous insulin, diet, and exercise. Good glycemic control is required to reduce the risk of long-term sequelae of chronic hyperglycemia. One risk of strict glycemic control is the development of hypoglycemia.

The presence of both LCHAD Deficiency and T1DM in a single patient has not been reported to date.

Case presentation: We report our experience of management of a 10-year-old female with both LCHAD Deficiency and T1DM. She was diagnosed via newborn screening and managed at a different center until 6 years of age when she moved and transitioned care to our institution. Genetic testing revealed compound heterozygous variants in *HADHA* (NM_000182.4: c.[955 G>A];[c.499_501delACAinsCC]). She was treated in the standard fashion with avoidance of fasting, dietary management, and medium-chain triglyceride supplementation. She has struggled with compliance to her treatment regimen, particularly regarding the use of medium-chain triglyceride supplementation given the combination of taste, side effects and burden of supplementation.

At 9 years of age, she presented to her primary care physician's office with a several-week history of fatigue, abdominal pain, decreased appetite, and weight loss. Point of care blood glucose level was found to be 631. She was sent to the emergency department, where labs were remarkable for pH of 7.36 with a normal anion gap, HbA1c of 13.8, glucose and 20 ketones present in the urine, and significantly elevated glutamic acid decarboxylase antibody. She was admitted for stabilization and initiation of an insulin regimen for her new diagnosis of T1DM. Genetics was consulted in the hospital and recommended close monitoring of blood glucose levels, both in the hospital and upon discharge, given the risks associated with hypoglycemia in both conditions. Given the concern for hypoglycemia, a continuous glucose monitoring device was recommended, and continuous glucose monitoring was initiated after discharge from the hospital.

Her diet has been closely managed with assistance of both a metabolic dietician and diabetic dietician and requires close monitoring of both fat and carbohydrate intake. She and her family have struggled with compliance secondary to her many dietary restrictions and the complexity of management. She has not had any further hospitalizations since her diagnosis of T1DM.

Conclusion: Rare cases of T1DM in the setting of other fatty acid oxidation disorders (MCAD and VLCAD Deficiency) have been reported, but T1DM has not been reported in the setting of LCHAD Deficiency. To our knowledge, this is the first reported case of a patient diagnosed with both LCHAD Deficiency and T1DM. This case highlights the difficulty of managing these two coexisting conditions, as tight glycemic control in T1DM is necessary to prevent sequelae of hyperglycemia but comes with the risk of inducing hypoglycemia, which can result in a life-threatening metabolic crisis secondary to LCHAD Deficiency.

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