A Serine Synthesis Defect Presenting With a Charcot-Marie-Tooth–Like Polyneuropathy

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Background: Serine synthesis defects, characterized by developmental delay and seizures, have been described in children.

Objective: To describe a case of serine synthesis defect due to 3-phosphoglycerate dehydrogenase deficiency in an adult with prominent chronic polyneuropathy.

Design: Case report.

Setting: Neurologic referral center.

Patient: A 31-year-old man with congenital cataracts, mild psychomotor retardation, slight cerebellar ataxia, and chronic axonal sensorimotor polyneuropathy.

Interventions: Electrophysiologic, metabolic, and genetic testing and treatment with oral L-serine.

Main Outcome Measures: Serine values in plasma and cerebrospinal fluid and clinical examination.

Results: Amino acid analysis showed low serine levels in plasma and cerebrospinal fluid, and genetic analysis revealed 2 heterozygous mutations in the PGDH gene. Treatment with high-dose serine resulted in normalization of plasma serine values and subjective functional improvement.

Conclusions: This case expands the phenotypic spectrum of 3-phosphoglycerate dehydrogenase deficiency. Plasma amino acid chromatography should be added to the list of investigations performed in patients with Charcot-Marie-Tooth–like polyneuropathy, especially if it is associated with psychomotor delay and congenital cataracts.


L-SERINE IS A NONESSENTIAL amino acid whose biosynthesis via the phosphorylated pathway is known to play an essential role in the central nervous system.1 Three enzymes are involved in this pathway: 3-phosphoglycerate dehydrogenase (3-PGDH), phosphoserine aminotransferase, and phosphoserine phosphatase (Figure 1). Serine synthesis defects caused by deficiencies in each of these 3 enzymes, most of which were caused by 3-PGDH deficiency, have been reported in children.2 Although 3-PGDH deficiency was first described 15 years ago,3 only a dozen cases have been reported to date, with 2 clinical forms described: an infantile form, characterized by severe encephalopathy with microcephaly and intractable epilepsy, and a juvenile form, with milder developmental delay and seizures.4 Herein, we report a novel presentation of 3-PGDH deficiency in an adult with prominent Charcot-Marie-Tooth–like polyneuropathy.

REPORT OF A CASE

A 31-year-old man was referred for the evaluation of atypical Charcot-Marie-Tooth–like polyneuropathy. The family history was unremarkable except for a maculopathy in the patient's brother. Pregnancy, delivery, and the perinatal period were normal. A congenital cataract was detected and treated at 3 months of age. He walked at age 16 months. The first walking difficulties appeared at age 8 years and slowly increased thereafter, but the patient could still walk without help. Progressive disability was noticed in the upper limbs from age 26 years onward, making writing and buttoning increasingly difficult. Clinical examination at age 30 years showed distal amyotrophy in the upper and lower limbs, with length-dependent symmetrical sensorimotor deficits. Motor deficit was severe distally in the lower limbs (Medical Research Council grade [of a possible 5]: 1 for the tibialis anterior, 0 for the extensor hallucis longus, 3 for the fibularis longus, and 3 for the tri-
Thes.5 Amino acid chromatography showed low serine levels born errors of metabolism causing peripheral neuropathy, a metabolic workup was performed to search for including monly responsible for Charcot-Marie-Tooth disease, included. No mutations were found in the genes most com-

Acquired causes of axonal polyneuropathies were ex-
gings from magnetic resonance spectroscopy were normal. Head circumference was 54 cm (third percentile). He had an asymptomatic multidirectional nystagmus. His gait was slightly ataxic due to a cerebellar syndrome. The Overall Neuropathy Limitations Scale score, measuring functional impairment, was 5 of a possible 12. The Mini-Mental State Examination score was 20 (of a possible 30), and the Frontal Assessment Battery score was 11 (of a possible 18).

Nerve conduction studies showed severe axonal sensorimotor polyneuropathy compatible with Charcot-Marie-Tooth disease type 2: absence of sensory nerve action potentials in the 4 limbs, absence of compound motor action potentials in the lower limbs, and reduced compound motor action potentials in the upper limbs, with preserved conduction velocities (Table). Needle electromyography revealed a 4-limb chronic neurogenic pattern with active denervation signs. Brain magnetic resonance imaging showed nonspecific T2-weighted hyperintensities, and findings from magnetic resonance spectroscopy were normal. Acquired causes of axonal polyneuropathies were excluded. No mutations were found in the genes most commonly responsible for Charcot-Marie-Tooth disease, including PMP22, P0, MFN2, GDAP1, and GJB1 (connexin 32).

Because of congenital cataracts and mild mental retardation, a metabolic workup was performed to search for inborn errors of metabolism causing peripheral neuropathies. Amino acid chromatography showed low serine levels in plasma (0.35 mg/dL [reference range, 0.66-2.26 mg/dL]) and in cerebrospinal fluid (CSF) (0.14 mg/dL [reference range, 0.21-0.43 mg/dL]). Glycine levels were also decreased in plasma (0.70 mg/dL [reference range, 0.94-2.62 mg/dL]) [to convert to micromoles per liter, multiply by 100]. Standard CSF investigations showed normal cellularity but a high protein concentration (0.11 mg/dL [to convert to grams per liter, multiply by 10]).

Sequencing of the PGDH gene revealed 2 compound heterozygous mutations: a novel mutation (c.1471C>T), predicted to change arginine at position 491 to tryptophan, and an already reported one (c.1273G>A), predicted to change valine at position 425 to methionine (Figure 2). Mutation analysis in the patient's parents confirmed that these mutations were inherited in an autosomal recessive manner. The newly described mutation was not found in 105 control participants, as determined by allele-specific polymerase chain reaction.

Serine treatment was introduced at 120 mg/kg/d in 3 divided doses. After 1 month, this treatment resulted in normalization of plasma serine values to 1.08 mg/dL and plasma glycine values to 1.61 mg/dL. The treatment was well tolerated, and the patient reported subjective improvement. The dose was then reduced to 80 mg/kg/d in 2 divided doses. Serine and glycine levels were maintained in the low-normal range in blood (serine: 0.90 mg/dL; glycine: 1.00 mg/dL), but serine levels were slightly below the reference range in CSF (serine: 0.19 mg/dL; glycine: 0.05 mg/dL). After 3 months of treatment (120 mg/kg/d for 1 month and 80 mg/kg/d for 2 months), the patient felt better, could walk longer and faster, and was less clumsy. For example, walking time from work was reduced from 20 to 13 minutes, and he broke fewer plates at his workplace in a school canteen. This subjective improvement was also noticed by the family and was sustained during the following 9 months (last follow-up). Clinically, no objective significant changes were noted: the Medical Research Council and Overall Neuropathy Limitations Scale scores were the same, as were sensory examination findings. Only the Mini-Mental State Examination score seemed to have improved a bit, to 23 (of a possible 30). Findings from electromyographic analysis were unchanged after 1 and 4 months of treatment.

The 31-year-old patient described herein presented with an overall milder and phenotypically different form of serine synthesis defect secondary to 3-PGDH defi-

Figure 1. The phosphorylated l-serine biosynthesis pathway. 3-PGDH indicates 3-phosphoglycerate dehydrogenase; PSAT, phosphoserine aminotransferase; PSPH, phosphoserine phosphatase; and SHMT, serine hydroxymethyltransferase.
ciency. He was a compound heterozygote for a known severe mutation and for a novel, and possibly milder, one. This observation expands the clinical phenotype of 3-PGDH deficiency. Two autosomal recessive forms of PGDH deficiency have been described until now that differ mostly by their degree of severity. The most frequently reported infantile form is associated with congenital microcephaly, severe psychomotor retardation, and intractable seizures and is sometimes associated with cataracts, nystagmus, spastic tetraparesis, hypogonadism, and irritability. In those patients, brain magnetic resonance imaging shows hypomyelination or white matter attenuation. Recently, a milder form has been reported in 2 siblings with absence seizures of juvenile onset, mild developmental delay, and behavioral disturbances. No peripheral neuropathy was noticed in any of these patients; however, only a dozen patients have been described, from which it is difficult to delineate a full clinical spectrum.

Figure 2. Mutational analysis of the patient and his parents. Two heterozygous mutations, c.1273G>A (p.Val425Met) in exon 11 (inherited from the father) and c.1471C>T (p.Arg491Trp) in exon 12 (inherited from the mother), were found in the PGDH gene.
Strong arguments support that the present patient's clinical symptoms, including neuropathy, are caused by a serine synthesis defect: (1) A case of serine deficiency associated with peripheral neuropathy has been previously reported\(^8\) in a 15-year-old girl who had decreased plasma and CSF serine levels. Oral treatment with serine, 400 mg/kg/d, was said to have improved her axonal polyneuropathy. Hyperactivity of serine hydroxymethyltransferase was suggested to be the cause in her case, but no molecular diagnosis was made.\(^9\) (2) The mild developmental delay and congenital cataracts observed in the present patient have been previously described in 3-PGDH deficiency.\(^3,4\) (3) Although we cannot exclude a placebo effect, sustained subjective improvement was reported by the patient and his family after treatment with oral serine and normalization of the blood serine concentration.

This case would then be one of the few pharmacologically treatable forms of Charcot-Marie-Tooth disease to be reported. A possible hereditary corticosteroid-responsive form was reported\(^10\) in 1982 but was never confirmed. Another potentially treatable form would be that of Charcot-Marie-Tooth disease type 2 caused by the TRPV4 mutation, in which treatment with calcium channel inhibitors could theoretically be beneficial.\(^11\) Furthermore, several inborn errors of metabolism potentially revealed by chronic peripheral neuropathy might be amenable to treatments, including cerebrotendinous xanthomatosis, pyruvate dehydrogenase deficiency, and Refsum disease.\(^5\)

In the infantile form, treatment with serine, 500 to 700 mg/kg/d, and glycine, 200 to 300 mg/kg/d, resulted in lowered seizure frequency and increased white matter volume on magnetic resonance imaging but no or poor progression of psychomotor development.\(^12,13\) In the juvenile form, treatment with serine, 100 to 150 mg/kg/d, resulted in control of seizures and correction of behavioral abnormalities.\(^4\) In the present patient, an even lower dosage of 80 mg/kg/d resulted in normalization of plasma serine levels, but the CSF serine concentration remained slightly decreased, indicating that 120 mg/kg/d should be the best dosage. Although the patient reported subjective improvement of his condition, the treatment effect was not spectacular, with Medical Research Council and Overall Neuropathy Limitations Scale scores remaining stable. It is assumed that severe axonal loss resulting from a long-lasting untreated neuropathy is irreversible. Previous studies\(^12,13\) of patients with 3-PGDH deficiency disorder showed that clinical improvement was limited in patients treated after the onset of symptoms, whereas 1 patient treated before birth remained asymptomatic at age 5 years. This finding emphasizes the importance of early diagnosis and treatment in serine deficiency disorders, before irreversible neurologic damage occurs.

Considering the vast clinical spectrum of 3-PGDH deficiency, this disorder probably remains underdiagnosed. Since the condition is potentially treatable, plasma amino acid chromatography should be added to the list of investigations performed in patients with Charcot-Marie-Tooth-like polyneuropathy, especially if it is associated with psychomotor delay and congenital cataracts.