

## 3-phosphoglycerate dehydrogenase deficiency: a case report of a treatable cause of seizures

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Serine deficiency disorders are a new group of neurometabolic diseases resulting from a deficiency in one of the three enzymes in the biosynthetic pathway of L-serine. Deficiency of the enzyme 3-phosphoglycerate dehydrogenase (3-PGDH), which catalyzes the first step in the biosynthetic pathway, leads to congenital microcephaly, severe psychomotor retardation, and intractable seizures.

We report a 4½-year-old boy who presented with congenital microcephaly, psychomotor retardation, hypertonia, strabismus, and drug-resistant seizures due to 3-PGDH deficiency. His seizures responded to L-serine and glycine supplementation only.

This potentially treatable disease should be borne in mind in patients with congenital microcephaly, psychomotor retardation and seizures. A timely diagnosis based on the detection of low cerebrospinal fluid levels of L-serine and glycine is expected to further increase the success of L-serine and glycine supplementation in these patients.

**Key words:** L-serine deficiency syndromes, 3-phosphoglycerate dehydrogenase deficiency, congenital microcephaly, drug-resistant seizures, L-serine supplementation.

L-serine is a non-essential amino acid that may be derived from four possible sources: dietary intake, degradation of protein and phospholipids, biosynthesis from the glycolytic pathway intermediate 3-phosphoglycerate, or glycine. Since serine is required for both brain development and function, adequate serine supply to the central nervous system is necessary. This is not surprising when one considers its role in the synthesis of proteins, membrane lipids, and neuromodulators glycine and D-serine and its relation to the formation of some other compounds such as folates, cysteine, and methionine<sup>1</sup>. A significant amount of L-serine in the central nervous system must be supplied by de novo synthesis from glucose since the transport of serine across the blood-brain barrier is poor<sup>2</sup>.

In the biosynthetic pathway of L-serine, 3-phosphoglycerate is first converted into 3-phosphohydroxypyruvate by the catalytic

activity of 3-phosphoglycerate dehydrogenase (3-PGDH). L-serine is then synthesized via two consecutive reactions catalyzed by 3-phosphoserine aminotransferase (PSAT) and 3-phosphoserine phosphatase (PSP), respectively (Fig. 1)<sup>1,3</sup>. Serine deficiency disorders are a new group of neurometabolic diseases resulting from deficiency of one of these three enzymes<sup>3</sup>. Jaeken et al.<sup>4</sup> were the first to report disorders of L-serine synthesis due to 3-PGDH deficiency. 3-PGDH is characterized by congenital microcephaly, psychomotor retardation and seizures<sup>3,4</sup>.

Serine deficiency disorders can be treated successfully if treatment is begun before symptoms appear<sup>3,5</sup>. Hence, although rare, as evidenced by the small number of patients reported to date, recognition of the clinical phenotype is important<sup>3</sup>. We herein report a new case of 3-PGDH deficiency in order to

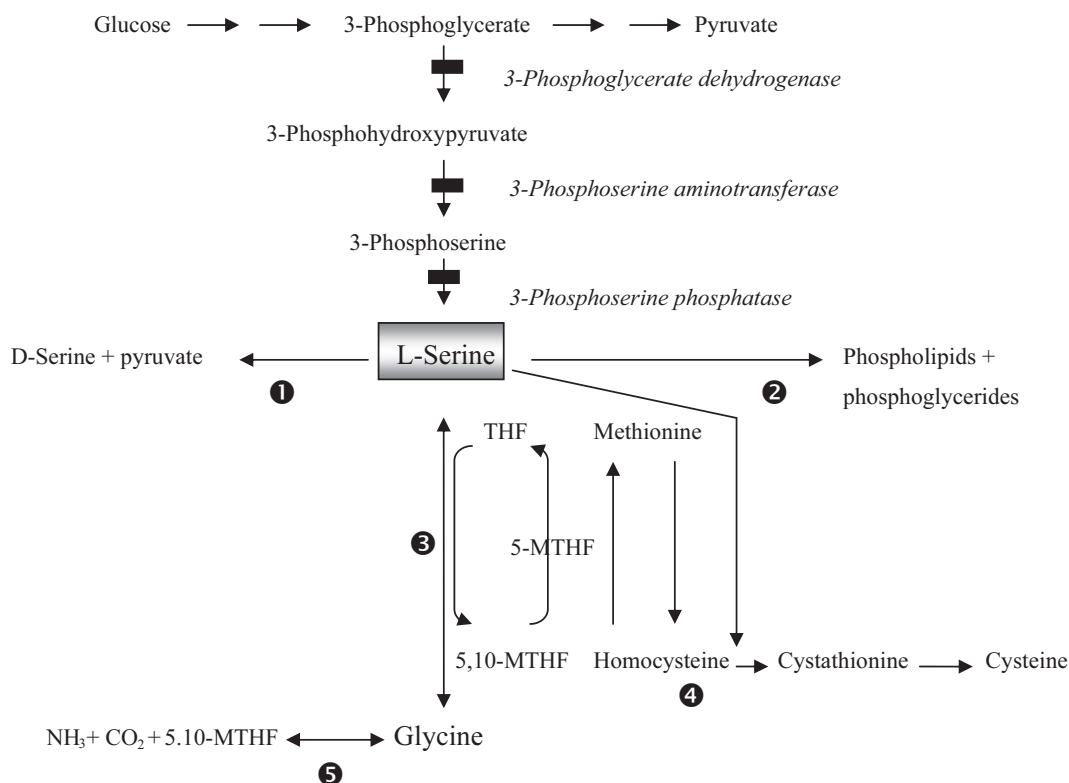


Fig. 1. L-serine biosynthesis and catabolism. THF: Tetrahydrofolate. 5-MTHF: 5-Methyl tetrahydrofolate. 5,10-MTHF: 5,10-Methylenetetrahydrofolate. ■ Enzyme blocks.

① Serine racemase. ② Synthesis of phospholipids and phosphoglycerides from cytidine diphosphodiacylglycerol and palmitoyl-coenzyme. ③ Serine hydroxymethyl transferases. ④ Cystathionine  $\beta$ -synthase. ⑤ Glycine cleavage system.

draw the clinicians' attention to this potentially treatable L-serine biosynthesis defect in patients presenting with congenital microcephaly, psychomotor retardation and seizures.

### Case Report

A nine-month-old boy was the first child of a healthy, consanguineous couple. He was born at term by cesarean section because of prolonged labor, with a birth weight of 2900 g. He was hospitalized for the first week of life due to meconium aspiration. When he was first admitted to the hospital at three months of age for the evaluation of early closure of his anterior fontanel, detected in the local health center when brought for routine immunization, microcephaly was noted (Fig. 2). On physical examination at the Pediatric Neurology Department of our hospital, his body weight was 6200 g (<3<sup>rd</sup> p),

length 62 cm (<3<sup>rd</sup> p), and head circumference 37 cm (<3<sup>rd</sup> p) at nine months of age. He was unable to recognize his mother, and had no head control, head banging and stereotypic movements in the extremities, strabismus, and peripheral hypertonia with increased deep tendon reflexes (Fig. 3).

During the follow-up period, he began to have seizures at 1½ years. Pyridoxine and folinic acid treatments were initiated with no effect. He was first placed on clonazepam alone, and levetiracetam (Keppra®) was added to his therapeutic regimen thereafter. His seizures were drug-resistant.

Laboratory investigations including complete routine blood count, liver and kidney function tests, TORCH serology, maternal blood phenylalanine level, urine sulfite test, serum biotinidase activity, tandem-mass spectrometry, plasma and urine amino acids, and urine



Fig. 2. A picture of the patient showing microcephaly and strabismus.

organic acid analysis revealed no abnormalities with the exception of low cerebrospinal fluid (CSF) concentrations of serine ( $10.4 \mu\text{mol/L}$ , N:  $24\text{--}105 \mu\text{mol/L}$ ) and glycine ( $0.8 \mu\text{mol/L}$ , N:  $3\text{--}23 \mu\text{mol/L}$ ). Upon detection of low CSF levels of glycine and serine, 3-PGDH activity was measured subsequently in his cultured skin fibroblasts (kindly performed by Tom J. de Koning, Utrecht, The Netherlands) and found to be very low ( $7 \text{ nmol/min.mg protein}$ , N:  $32 \pm 3$ ).



Fig. 3. Spastic diplegia in the lower extremities of the patient.

EEG showed a hypsarrhythmia pattern with an epileptiform activity predominantly originating from the left hemisphere. A delayed latency in the right eye on electroretinogram, bilaterally delayed P1 latencies on visual evoked potential testing, and low amplitudes of the IV<sup>th</sup> and V<sup>th</sup> waves on brainstem auditory evoked potential testing were detected. On magnetic resonance imaging (MRI) of the brain, there was a diffuse and remarkable hypomyelination of the cerebral white matter with blurred lateral ventricular walls and thin corpus callosum (Figs. 4a-e).

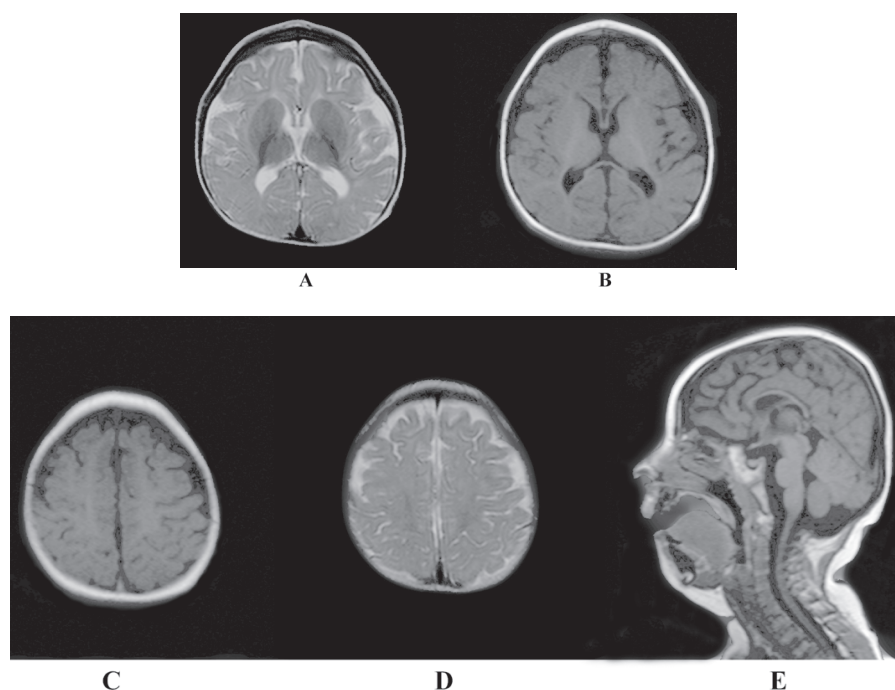


Fig. 4. Axial T1-weighted spin-echo (SE)(TR/TE; 500/15 ms)(A, B) and T2-weighted turbo SE (TR/TE; 3800/90 ms) images (C, D) show diffuse hypomyelination at the age of 18 months. Thin corpus callosum is seen on sagittal T1-weighted image (E).

His IQ was found to be at the level of a nine-month-old infant when tested at 2½ years using Bayley Scales of Infant Development.

Treatment was begun with serine (500 mg/kg/day, qid) alone at 16 months and in combination with glycine (150 mg/kg/day, qid) later at age 20 months. The clinical effect of serine and glycine supplementation was limited, with only a marginal improvement in seizure control and responsiveness. He is currently 4½ years old and has a severe mental and motor developmental delay.

### Discussion

Disorders of amino acid catabolism such as phenylketonuria and non-ketotic hyperglycinemia are among the most frequent inborn errors of metabolism in humans, and have been recognized for many years. There is accumulation of characteristic metabolites in front of the enzyme block in these aminoacidopathies. More recently, biosynthesis disorders were reported as human disease. In contrast with the disorders of amino acid catabolism, these patients were identified because of very low concentrations of serine and glycine in plasma and CSF<sup>1</sup>. Three disorders of serine biosynthesis have been reported so far: 3-PGDH deficiency<sup>4</sup>, 3-PSAT deficiency<sup>2</sup>, and 3-PSP deficiency<sup>6</sup>.

3-phosphoserine aminotransferase (PSAT) deficiency has been identified in two siblings who showed low concentrations of serine and glycine in plasma and CSF. Clinically, the index patient presented with intractable seizures, acquired microcephaly, hypertonia, and psychomotor retardation and died at seven months of age despite supplementation with serine and glycine. The younger sibling received treatment from birth, which led to a normal outcome at three years of age<sup>2</sup>. 3-PSP deficiency has only been reported in a single patient. This boy also suffered from Williams syndrome<sup>6</sup>. A girl with serine deficiency with a progressive polyneuropathy combined with ichthyosis, growth retardation and delayed puberty has also been reported. The activities of the three L-serine biosynthetic enzymes were normal in her cultured skin fibroblasts, and the basic defect remains to be resolved in this patient<sup>7</sup>.

3-phosphoglycerate dehydrogenase-deficient patients exhibit serious neurological symptoms, such as congenital microcephaly, severe

psychomotor retardation and seizures. Patients were born with congenital microcephaly. Severe psychomotor retardation develops in the first months of life, and this is followed by the onset of seizures at six months to one year<sup>2,3</sup>. The presented case came to the clinicians' attention with microcephaly at three months of age. Severe developmental delay was noted in the course of the disease. At 1½ years of age, he began experiencing intractable seizures, as has been the case in the patients reported in the literature<sup>2</sup>. Among the other neurological abnormalities were hyperexcitability, generalized hypertonia, spastic quadriplegia, and nystagmus. In some others, adducted thumbs, cataract, hypogonadism, and megaloblastic anemia were present as additional clinical features<sup>3</sup>. Of these, our patient had generalized hypertonia, spastic diplegia and strabismus.

Recently, a juvenile and much milder phenotype of 3-PGDH deficiency was reported in two children with normal early developmental milestones and subsequent moderate developmental delay, with atypical absence seizures developing at school age<sup>8</sup>. Microcephaly was not present, nor were there pyramidal signs. The patients were diagnosed in their teens, with one of the patients displaying severe behavioral abnormalities and mood disturbances at that time. Cranial MRI in both children revealed no abnormalities and no hypomyelination. The patients had atypical absence seizures with the accompanying EEG abnormalities. Additional patients need to be reported to determine whether these absence seizures are specific for the juvenile phenotype, but the fact that multiple seizure patterns were observed in the infantile phenotype makes this less likely.

These two children expand the clinical phenotype of 3-PGDH deficiency towards a very mild seizure disorder with moderate developmental delay, meaning that many children with mild developmental delay and seizures are potential candidates for amino acid testing for 3-PGDH deficiency.

The presence of severe neurological symptoms in the presented case and in those previously reported infantile cases illustrate the importance of the serine biosynthesis pathway for brain development and function<sup>1,2</sup>. The mechanisms by which serine deficiency leads to pathological consequences, however, are not known.



Decreased synthesis of serine-derived compounds such as membrane lipids (phospholipids or ceramides) or the neuromodulators glycine and D-serine might play a role here. Isomerization of L-serine by serine racemase to D-serine was shown to be decreased in the CSF of children with 3-PGDH deficiency<sup>9</sup>. Alternatively, lack of L-serine might lead to deficiency of 1-carbon groups that are essential for purine and pyrimidine metabolism<sup>2</sup>.

Electroencephalograms in patients with 3-PGDH showed a pattern of hypsarrhythmia or severe multifocal epileptic abnormalities with poor background activity<sup>3</sup>. On EEG tracings of the presented case, a generalized hypsarrhythmia and foci of seizure activity were detected. Different patterns of clinical seizures were observed in 3-PGDH-deficient patients<sup>3</sup>. Our patient had seizures of generalized tonic clonic type.

As demonstrated in our patient, attenuation of white matter volume and hypomyelination on MRI studies have been reported in 3-PGDH deficiency<sup>10</sup>.

3-phosphoglycerate dehydrogenase deficiency is characterized biochemically by reduced plasma and CSF L-serine concentrations after an overnight fast. Plasma glycine concentrations were reported to range between 128-190  $\mu\text{mol/L}$ , serine between 28-64  $\mu\text{mol/L}$ , glycine concentrations in CSF between 1-4  $\mu\text{mol/L}$ , and serine concentration between 6-8  $\mu\text{mol/L}$  in previously reported 3-PGDH-deficient patients. Urine amino acid analysis has no diagnostic value. 3-PGDH deficiency can be confirmed in cultured skin fibroblasts<sup>3</sup>. Low CSF levels of serine and glycine in our patient led us to suspect a serine deficiency disorder in the present case. Detection of low activity of 3-PGDH in cultured skin fibroblasts subsequently confirmed the diagnosis of 3-PGDH deficiency.

3-phosphoglycerate dehydrogenase deficiency is an autosomal recessive disorder and the 3-PGDH gene is located on chromosome 1q12. In the past, only missense mutations in the C-terminal region of the gene have been identified, suggesting that only very mild mutations are compatible with life<sup>11</sup>. However, in contrast with this hypothesis, mutations throughout the gene have been reported recently<sup>12</sup>. The presented case had p. V261M, c. 781G>A mutation. Prenatal

diagnosis is possible by mutation analysis only and not by enzymatic assay because of a lack of data on enzyme activity in chorionic villi and amniocytes<sup>3</sup>. Molecular data in our patient could be used if prenatal diagnosis is to be made in a subsequent pregnancy.

Oral supplementation of the deficient amino acids has been proven to be very effective in the treatment of seizures. The seizures usually respond to oral treatment with high dosages of L-serine alone or in combination with glycine. Amelioration of the convulsions in these patients by pharmacological supplementation of L-serine gives further evidence to the causal relationship between reduced L-serine concentrations and seizures. Treatment should start with L-serine at a dose of 400-600 mg/kg/day in four to six doses; in most of the cases, the dose of L-serine is around 600 mg/kg/day. If seizures are not controlled, glycine can be added to the treatment at a dose of 200-300 mg/kg/day<sup>3,5</sup>. We started treating our case with L-serine alone at a dose of 500 mg/kg/day and then added glycine at a dose of 150 mg/kg/day. This therapeutic regimen helped with the control of seizures but showed no beneficial effect on the developmental delay. The biochemical abnormalities normalize during treatment with amino acids, although in some patients serine levels remain just below the normal range<sup>5</sup>. We could not measure CSF serine and glycine concentrations again to assess the efficiency of L-serine treatment along with glycine since the parents denied a repeat lumbar puncture. CSF levels of D-serine could not be measured for the same reason.

Early treatment improved the patients' prognosis with regard to their psychomotor development as evidenced by successful treatment of a prenatally diagnosed case with supplementation of the mother with L-serine starting from 27 weeks of gestation. Treatment was continued on the second day of life and at the age of three years, the girl demonstrates normal psychomotor development<sup>3,5,13</sup>. The normal outcome in the younger sibling with 3-PSAT deficiency in whom L-serine supplementation was initiated shortly after birth also emphasizes the importance of early diagnosis in serine deficiency disorders<sup>2</sup>. The relatively late diagnosis in the present case might lead to poor outcome with respect to psychomotor retardation and seizures.

For many inborn errors of metabolism, plasma and urine are used for initial investigations, but this is not the case for L-serine biosynthesis defects, since urine is not informative and plasma can only be of diagnostic value when tested after an overnight fast. Traditionally, the biochemical diagnosis of inborn errors is based on the detection of elevated concentrations of respective metabolites, so the detection of low values of amino acids in CSF and plasma may easily be overlooked. In fact, low metabolite concentrations are equally as important as elevated levels. All these reasons explain why many of the patients remain undiagnosed and thus the frequency of such disorders seems to be rare. It is clear from the discussions above that careful evaluation of amino acid concentrations in body fluids in patients with disorders of the central nervous system is of utmost importance. Correct diagnosis made in the index case will provide the opportunity to administer very early and effective treatment to the subsequent affected siblings in these families.

#### REFERENCES

1. de Koning TJ, Snell K, Duran M, Berger R, Poll-The BT, Surtees R. L-serine in disease and development. *Biochem J* 2003; 371: 653-661.
2. Hart CE, Race V, Achouri Y, et al. Phosphoserine aminotransferase deficiency: a novel disorder of the serine biosynthesis pathway. *Am J Hum Genet* 2007; 80: 931-937.
3. de Koning TJ, Klomp LW. Serine-deficiency syndromes. *Curr Opin Neurol* 2004; 17: 197-204.
4. Jaeken J, Detheux M, Maldergem V, Foulon M, Carchon H, van Schaftingen E. 3-phosphoglycerate dehydrogenase deficiency: an inborn error of serine biosynthesis. *Arch Dis Child* 1996; 74: 542-545.
5. de Koning TJ. Treatment with amino acids in serine deficiency disorders. *J Inher Metab Dis* 2006; 29: 347-351.
6. Jaeken J, Detheux M, Fryns JP, et al. Phosphoserine phosphatase deficiency in a patient with Williams syndrome. *J Med Genet* 1997; 34: 594-596.
7. Catsman-Berrevoets CE, de Klerk JB, Huijman JG, Duran M. Inborn error of serine biosynthesis, a new phenotype [abstract]. *Eur J Paediat Neurol* 1997; 1: A43.
8. Tabatabaie L, Klomp LW, Rubio-Gozalbo ME, et al. Expanding the clinical spectrum of 3-phosphoglycerate dehydrogenase deficiency. (Submitted 2009).
9. Fuchs SA, Dorland L, de Sain-van der Velden MG, et al. D-serine in the developing human central nervous system. *Ann Neurol* 2006; 60: 476-480.
10. de Koning TJ, Jaeken J, Pineda M, Van Maldergem L, Poll-The BT, van der Knaap MS. Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. *Neuropediatrics* 2000; 31: 287-292.
11. Klomp LW, de Koning TJ, Malingre HE, et al. Molecular characterization of 3-phosphoglycerate dehydrogenase deficiency – a neurometabolic disorder associated with reduced L-serine biosynthesis. *Am J Hum Genet* 2000; 67: 1389-1399.
12. Tabatabaie L, de Koning TJ, Geboers AJ, van den Berg IE, Berger R, Klomp LW. Novel mutations in 3-phosphoglycerate dehydrogenase (PHGDH) are distributed throughout the protein and result in altered enzyme kinetics. *Hum Mutat* 2009; 30: 749-756.
13. de Koning TJ, Klomp WJ, van Oppen AC, et al. Prenatal and early postnatal treatment in 3-phosphoglycerate dehydrogenase deficiency. *Lancet* 2004; 364: 2221-2222.