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Original Article

# Two new cases of serine deficiency disorders treated with L-serine

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ABSTRACT

*Objective and patients:* We report on two new cases of serine deficiency due respectively to 3-phosphoglycerate dehydrogenase (PHGDH) deficiency (Patient 1) and phosphoserine aminotransferase (PSAT1) deficiency (Patient 2), presenting with congenital microcephaly (<3rd centile at birth) and encephalopathy with spasticity. Patient 1 had also intractable seizures. A treatment with oral L-serine was started at age 4.5 years and 3 months respectively.

*Results:* Serine levels were low in plasma and CSF relative to the reference population, for which we confirm recently redefined intervals based on a larger number of samples. L-Serine treatment led in patient 1 to a significant reduction of seizures after one week of treatment and decrease of electroencephalographic abnormalities within one year. In patient 2 treatment with L-serine led to an improvement of spasticity. However for both patients, L-serine failed to improve substantially head circumference (HC) and neurocognitive development. In a couple related to patient's 2 family, dosage of serine was performed on fetal cord blood when the fetus presented severe microcephaly, showing reduced serine levels at 30 weeks of pregnancy.

*Conclusions:* L-Serine treatment in patients with 2 different serine synthesis defects, led to a significant reduction of seizures and an improvement of spasticity, but failed to improve substantially neurocognitive impairment. Therefore, CSF and plasma serine levels should

*Abbreviations:* PHGDH, 3-phosphoglycerate dehydrogenase; PSAT1, phosphoserine aminotransferase; HC, head circumference; CSF, cerebrospinal Fluid; 3-PSP, 3-phosphoserine phosphatase; EEG, electroencephalogram; IUGR, intrauterine growth retardation; MRI, magnetic resonance imaging.

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be measured in all cases of severe microcephaly at birth to screen for serine deficiency, as prompt treatment with L-serine may significantly impact the outcome of the disease. Reduced serine levels in fetal cord blood may also be diagnostic as early as 30 weeks of pregnancy.



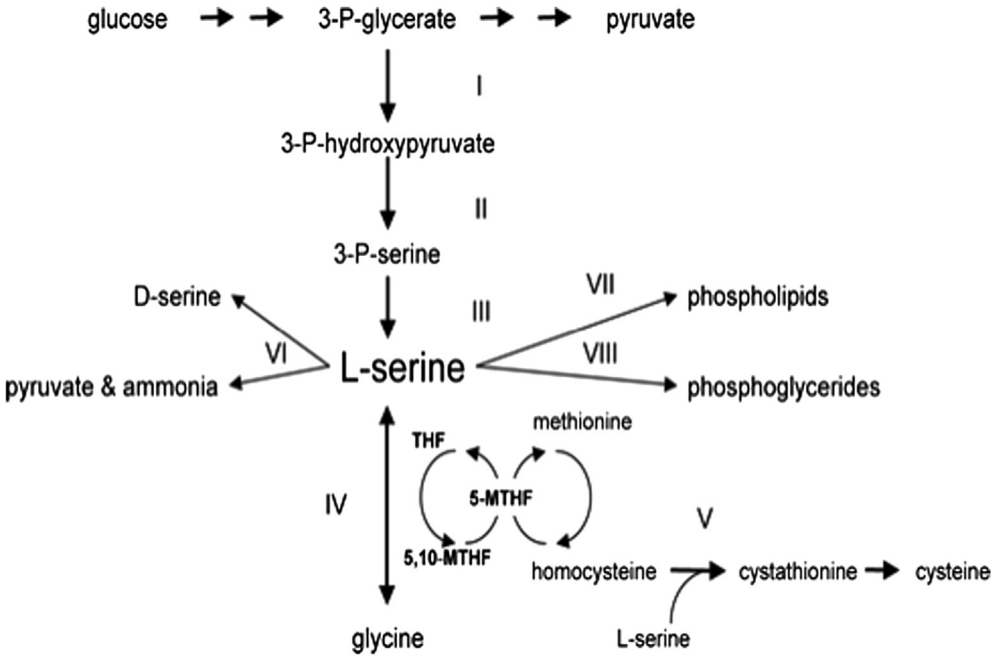
## 1. Introduction

Serine synthesis disorders are rare defects in the biosynthesis of the amino acid L-serine first described in 1996[1] (Fig. 1), involving PHGDH, the most frequent,[1–5] 3-phosphoserine phosphatase (3-PSP) reported in one patient,[3,6] and PSAT1 deficiency described in two siblings.[7] Mutations in the *SLC1A4* gene which codes the ASCT1 transporter of serine and other neutral amino acids have also been recently described.[8–10] Patients present with congenital microcephaly, severe psychomotor retardation with spastic tetraparesis and intractable seizures. Low concentrations of serine in plasma and CSF may orientate the diagnosis towards serine synthesis defects, which can be confirmed by enzymatic assays on cultured skin fibroblasts and/or by mutational analysis of the relevant genes. These disorders are potentially treatable by oral L-serine alone or combined with glycine with varying degrees of success.[4,11–13] Here we report on two additional patients, one with 3-PGDH and one with PSAT1 deficiency, and the first case of biochemical prenatal diagnosis from fetal cord blood.

## 2. Materials and methods

### 2.1. Patients

Patient 1, a boy, was born at 36 weeks of gestation with weight 2510 g (25th centile), length 44 cm (10th centile) and HC 30 cm (<3rd centile). Prenatal monitoring showed IUGR




I, 3-phosphoglycerate dehydrogenase; II, 3-phosphohydroxypyruvate aminotransferase;
III, 3-phosphoserine phosphatase; IV, serine hydroxymethyltransferases;
V, cystathionine β-synthase; VI, serine racemase;
VII, the synthesis of sphingolipids starts with the condensation
of L-serine and palmitoyl-CoA via serine palmitoyltransferase;
VIII, phosphatidylserine is derived from phosphatidylcholine
and phosphatidylethanolamine by the enzymes phosphatidylserine
synthase I and II.
THF, tetrahydrofolate; 5,10-MTHF, 5,10-
methylenetetrahydrofolate; 5-MTHF, 5-methyltetrahydrofolate

**Fig. 1 – Pathways of L-serine synthesis and utilization.**