J. Inher. Metab. Dis. 19 (1996) 223–226

Short Communication – SSIEM Award

3-Phosphoglycerate dehydrogenase deficiency and 3-phosphoserine phosphatase deficiency: Inborn errors of serine biosynthesis

J. JAEKEN[1]*, M. DETHEUX[2], L. VAN MALDERGEM[3], J. P. FRIJNS[4], P. ALLIET[5], M. FOULON[6], H. CARCHON[1] and E. VAN SCHAFTINGEN[2]

Departments of [1]Paediatrics and [4]Genetics, University of Leuven; [2]Laboratory of Physiological Chemistry, Institute of Cellular and Molecular Pathology, Brussels; [3]Institute of Morphology, Loverval; [5]Virga Jesse Hospital, Hasselt; [6]Civic Hospital, Charlerloi, Belgium

**Correspondence: University Hospital Gasthuisberg, Department of Pediatrics, Centre for Metabolic Diseases, Herestraat 49, B-3000 Leuven, Belgium*

Aminoacidopathies are as a rule catabolic defects (Scriver et al 1995). We have discovered two defects in an amino acid synthesis pathway, namely that of serine (Figure 1). One is 3-phosphoglycerate dehydrogenase (EC 1.1.1.95) deficiency found in two brothers with a severe encephalopathy of prenatal onset and very low serine levels in the cerebrospinal fluid. The other is 3-phosphoserine phosphatase (EC 3.1.3.3) deficiency detected as a (compound?) heterozygous state in a boy with Williams syndrome, providing evidence that the 3-phosphoserine phosphatase locus is close to the elastin locus on chromosome 7q11.23.

CASE REPORTS

Patients A and B were brothers from a Turkish family. The parents were first cousins. The younger brother (patient A) was born after a normal term pregnancy with weight 2130 g (3rd centile (P_3) = 2600 g), length 43 cm (P_3 = 47 cm), and head circumference 29 cm (P_3 = 33 cm). At the age of 3.5 months he was admitted for investigation of bilateral cataract and feeding difficulties. He showed a severe growth and psychomotor retardation and hypogonadism, and was hypertonic and hyperexcitable. At 1 year he developed epilepsy. Plasma amino acid analysis revealed low fasting concentrations of serine (29 and 55 μmol/L, range for age 70–187) and low to normal fasting concentrations of glycine (77 and 97 μmol/L, normal 80–341). In CSF, serine was severely decreased (6 μmol/L, normal 35–80), and glycine was also decreased but less severely (2.8 μmol/L, normal 3.6–9). Oral treatment with serine significantly increased CSF serine in a dose-dependent way: the CSF serine was 15 μmol/L after 1 week at 100 mg/kg per day (in three divided doses) and 20 μmol/L after 1 week at 200 mg/kg per day. Under the latter dose the convulsions stopped after 1 week. Magnetic resonance imaging of the brain showed cortical and

subcortical hypotrophy as well as evidence of dysmyelination. The older brother (patient B) showed a similar clinical picture but no cataracts. At 7 years, weight was 13 kg (P_3 = 18 kg), length 104 cm (P_3 = 110 cm) and head circumference 42.2 cm (P_3 = 49 cm). Psychomotor development was nearly absent. In plasma serine was normal 2 h after feeding, whereas in CSF serine was decreased (8 μmol/L, normal 20–40) and glycine was low normal (3 μmol/L, normal 3–7).

Patient C, a Belgian boy, was born after 37 weeks pregnancy, with birth weight 1760 g, length 42.5 cm and head circumference 30 cm. He had early feeding difficulties associated with gastro-oesophageal reflux and oesophagitis. On the other hand, he had a special facies suggestive of Williams syndrome: puffy eyelids, broad forehead, bitemporal narrowness, wide mouth, full cheeks and micrognathia. Psychomotor development was slow (12 months at the age of 22 months). Testes volume was normal. Fluorescent *in situ* hybridization using the elastin Williams syndrome chromosome region (WSCR) probe revealed the presence of a submicroscopic 7q11.23 deletion in all 10 examined lymphocytes. Plasma amino acid analysis revealed decreased to low normal fasting serine levels (53–80 μmol/L, normal range for age 70–187). CSF serine was decreased (18 μmol/L at 1 year, control range 27–57). Plasma and CSF phosphoserine and glycine levels were normal. Under treatment with serine at 200 mg/kg per day (in three divided doses) fasting CSF serine level was 23 μmol/L (control range 27–57) before the morning serine dose, while with 300 mg/kg per day a low normal value of 29 μmol/L was obtained. During this treatment a slight catch-up of head growth was noted.

METHODS AND RESULTS

Enzymes of the serine biosynthesis pathway were assayed in fibroblasts and lymphoblasts as described elsewhere (Jaeken et al, in press).

In patients A and B, the activity of 3-phosphoglycerate dehydrogenase in fibroblasts was 22% and 13% of the mean control value, respectively (6.6 and 3.7 mU/mg protein; controls (n = 15; mean ± SD) 29.5 ± 2.6). Activities of 3-phosphoserine aminotransferase and of 3-phosphoserine phosphatase were normal.

In patient C, 3-phosphoserine phosphatase activity amounted to only about 26% of the mean control value both in fibroblasts (0.43 mU/mg protein; controls (n = 11; mean ± SD) 1.67 ± 0.18), and in lymphoblasts (0.36 mU/mg protein; controls (n = 11; mean ± SD) 1.34 ± 0.09), whereas the activities of 3-phosphoglycerate dehydrogenase and of 3-phosphoserine aminotransferase were normal.

DISCUSSION

Patients A and B had decreased concentrations of serine and of glycine in the cerebrospinal fluid and to some extent also in the blood, associated with a similar, severe neurological syndrome. This suggested a defect in the serine *de novo* biosynthetic pathway (Snell 1983), which was confirmed by finding, in fibroblasts of the two patients, a markedly decreased activity of phosphoglycerate dehydrogenase, the first step in this pathway (Figure 1). It is unlikely that 3-phosphoglycerate dehydrogenase deficiency results in significant accumulation of 3-phosphoglycerate, as this metabolite can be readily utilized by glycolysis. Therefore, the deficiency of brain serine seems to be the main

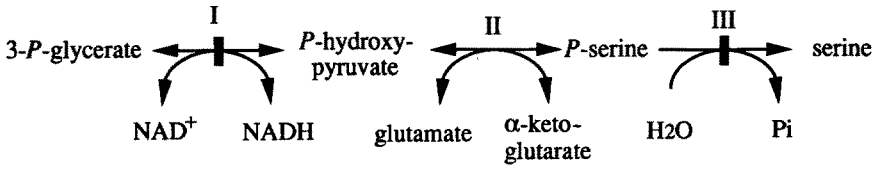

Figure 1 The pathway of *de novo* serine biosynthesis: I, 3-phosphoglycerate dehydrogenase; II, 3-phosphoserine aminotransferase; III, 3-phosphoserine phosphatase. Vertical bar under I denotes enzymatic defect in patients A and B; vertical bar under III indicates that in patient C

determinant of disease. Serine plays a major role in a number of different biosynthetic reactions, particularly in the synthesis of such important brain constituents as proteins, glycine, cysteine, serine phospholipids, sphingomyelins and cerebrosides. The fact that treatment by serine caused some improvement in the symptomatology indicates that the serine deficiency is at least partly responsible for the clinical picture in these patients. Different explanations can be provided for the fact that there is still a residual 3-phosphoglycerate dehydrogenase activity of about 20% with apparently normal kinetic properties. One possibility is that the defect resulted in the formation of a protein with decreased stability or with decreased V_{max} or even in a totally inactive enzyme. In the latter case the residual activity would have to be explained by the presence of a different isozyme. If the deficient enzyme is the only one to be expressed in brain, this organ would then be largely dependent on the serine supply from the blood. It has been stated that brain is dependent upon its own L-serine biosynthesis, because there is a limited transport of L-serine through the blood–brain barrier owing to competition with many other amino acids at the level of the neutral amino acid carrier (Smith et al 1987).

Patient C also had a decrease of serine concentrations in his body fluids but less pronounced than in patients A and B. A different defect was found in the synthesis of serine, namely in 3-phosphoserine phosphatase, the third and rate-limiting step in this pathway (Figure 1). On the other hand, the clinical picture was suggestive of Williams syndrome. This diagnosis was substantiated by finding a deletion in the elastin gene region of chromosome 7 (7q11.23) (Ewart et al 1993). The association of Williams syndrome and 3-phosphoserine phosphatase deficiency in the same patient suggests a relationship between them, the most probable being that the 3-phosphoserine phosphatase gene is closely linked to the elastin gene and therefore involved in the deletion. The enzyme had previously been assigned to chromosome 7, but the precise location remained uncertain (Koch et al 1983; Novelli and Dallapicola 1988). Thus patient C shows evidence for hemizygosity at the elastin locus (Williams syndrome), as well as for (compound?) heterozygosity for 3-phosphoserine phosphatase deficiency.

These defects of serine biosynthesis have not previously been reported. They are unusual among the aminoacidopathies, of which the large majority are catabolic defects (Scriver et al 1995).

ACKNOWLEDGEMENTS

We thank Mrs G. Berghenouse for competent technical help. This work was supported by the National Fund for Scientific Research (grants 3.0115.94 and 3.4596.92), by the Actions

de Recherche Concertées, and by the Belgian Federal Service for Scientific, Technical and Cultural Affairs. E.V.S. is Directeur de Recherche of the National Fund for Scientific Research.

REFERENCES

Ewart AK, Morris CA, Atkinson D, et al (1993) Hemizygosity at the elastin locus in a developmental disorder, Williams syndrome. *Nature Genet* **5**: 11–16.

Jaeken J, Detheux M, Van Maldergem L, Foulon M, Carchon H, Van Schaftingen E (in press). 3-Phosphoglycerate dehydrogenase deficiency: an inborn error of serine biosynthesis. *Arch Dis Child.*

Koch G, Eddy RL, Haley LL, Byers MG, McAvoy M, Shows TB (1983) Assignment of the human phosphoserine phosphatase gene (PSP) to the pter → q22 region of chromosome 7. *Cytogenet Cell Genet* **35**: 67–69.

Novelli G, Dallapicola B (1988) Gene dosage studies regionally assign the phosphoserine phosphatase gene to 7p15.1 or 2. *Ann Génét* **31**: 195–196.

Scriver CR, Beaudet AL, Sly WS, Valle D (1995) Amino acids. In Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease.* New York: McGraw-Hill, 1015–1368.

Smith QR, Momma S, Aoyagi M, Rapoport SI (1987) Kinetics of neutral amino acid transport across the blood–brain barrier. *J Neurochem* **49**: 1651–1658.

Snell K (1983) Enzymes of serine metabolism in normal, developing and neoplastic rat tissues. *Adv Enzym Regul* **22**: 325–400.