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Beneficial Effects of L-Serine and Glycine in the Management of Seizures in 3-Phosphoglycerate Dehydrogenase Deficiency

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3-Phosphoglycerate dehydrogenase (3-PGDH) deficiency is an inborn error of serine biosynthesis. Patients are affected with congenital microcephaly, psychomotor retardation, and intractable seizures. The effects of oral treatment with amino acids were investigated in 2 siblings. L-Serine up to 500 mg/kg/day was not sufficient for seizure control. Addition of glycine 200 mg/kg/day resulted in complete disappearance of seizures. Electroencephalographic abnormalities gradually resolved after 6 months. We conclude that 3-PGDH can be treated effectively by a combination of L-serine and glycine.

de Koning TJ, Duran M, Dorland L, Gooskens R, Van Schaftingen E, Jaeken J, Blau N, Berger R, Poll-The BT. Beneficial effects of L-serine and glycine in the management of seizures in 3-phosphoglycerate dehydrogenase deficiency. Ann Neurol 1998;44:261–265

3-Phosphoglycerate dehydrogenase (3-PGDH) deficiency is a rare inborn error of serine biosynthesis characterized by congenital microcephaly, seizures, and severe psychomotor retardation. The disorder was only recently described by Jaeken and co-workers.[1] Biochemical abnormalities in this disorder are found in the fasted state and consist of low concentrations of the amino acids serine and glycine in plasma and cerebrospinal fluid (CSF). The defect affects the conversion of 3-phosphoglycerate to 3-phosphohydroxypyruvate, the first step in the serine biosynthesis pathway (Fig). In

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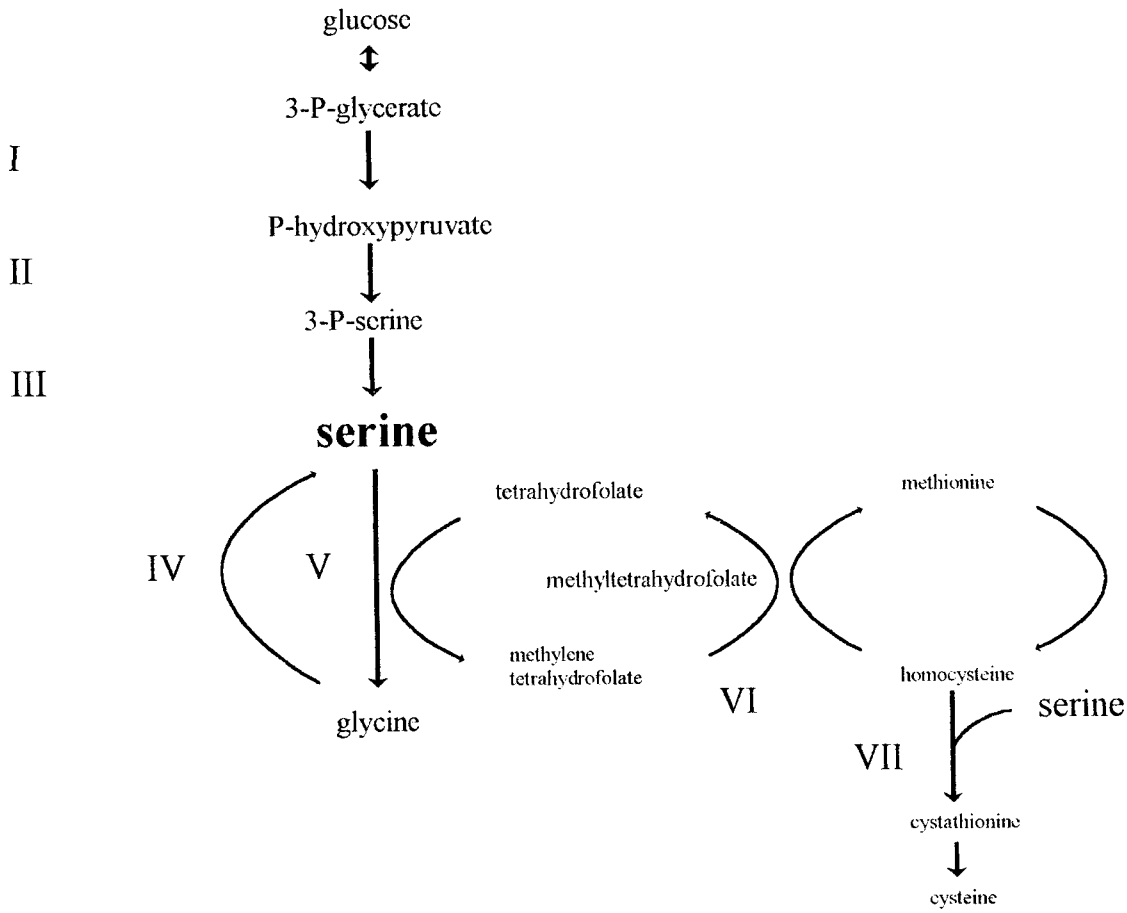

Fig. Pathways of serine biosynthesis and the interrelation of the serine/glycine interconversion with the transsulfuration pathway of methionine to cysteine. I = 3-Phosphoglycerate dehydrogenase; II = 3-phosphohydroxypyruvate aminotransferase; III = 3-phosphoserine phosphatase; IV = glycine cleavage system and serine hydroxymethyltransferase; V = serine hydroxymethyltransferase; VI = methylenetetrahydrofolate reductase; VII = cystathionine synthase.

this pathway, serine is converted into glycine, within the same reaction as the formation of methylenetetrahydrofolate. Methylenetetrahydrofolate is reduced to methyltetrahydrofolate, which is a methyl donor for the remethylation of homocysteine to methionine.

In an earlier report, amelioration of seizures was reported with oral serine supplementation, and this observation makes 3-PGDH a potentially treatable disorder.[1] In the present report 2 siblings with 3-PGDH deficiency were investigated. Both patients were treated with L-serine and glycine supplementation and were monitored regularly over a period of 12 months for clinical and biochemical effects. Our data indicate that the seizures and biochemical abnormalities in 3-PGDH deficiency can be treated effectively with high doses of amino acids. L-Serine supplementation was insufficient for seizure control, but the addition of glycine to the treatment resulted in complete disappearance of seizures and epileptic abnormalities on electroencephalogram (EEG).

Patients and Methods

Patient Histories

The 2 siblings were born to consanguineous Turkish parents. The mother had asymptomatic 3-methylglutaconic aciduria.

PATIENT 1. This 7-year-old boy was born microcephalic with a head circumference of 32 cm (below the third centile) with normal weight and height. Generalized tonic–clonic seizures started when he was 12 months of age and psychomotor retardation was evident at that time. At the age of 7 years, he presented with profound psychomotor retardation, spastic tetraplegia, and a "seesaw"-type nystagmus. He had 10 to 50 seizures per day, consisting of tonic and atonic seizures, as well as absences. He was treated without success with clonazepam and sodium valproate. EEG showed multifocal epileptiform discharges with poor background activity. Magnetic resonance imaging (MRI) of the brain revealed cortical atrophy, asymmetric ventricles, and hypomyelination. Laboratory investigations showed megaloblastic anemia (hemoglobin, 5.5 mmol/L; normal, 7.4–8.5 mmol/L; mean corpuscular volume, 95 fl; normal, 77–90 fl) and thrombo-

cytopenia (thrombocytes, 100 × 10^9/L; normal, 150–400 10^9/L). Amino acid analysis in the fasted state showed very low concentrations for serine and glycine in plasma and CSF and a low concentration of methyltetrahydrofolate in CSF (Table 1). All other amino acids including total homocysteine and methionine were normal in plasma, CSF, and urine. 3-PGDH activity in cultured skin fibroblasts was deficient, with 3.9 mU/mg of protein (normal, 29.5 ± 2.6).

PATIENT 2. Patient 2 is the younger brother of Patient 1. At birth, his head circumference was 32 cm (below the third centile) with normal weight and height. Psychomotor retardation was evident at 6 months. Seizures started at the age of 13 months. Examination at the age of 5 years revealed pronounced psychomotor retardation, a pendular-type nystagmus, pale optic disks, and severe spastic tetraplegia. Seizures were unsuccessfully treated with clonazepam, sodium valproate, and clobazam. EEG showed severe multifocal epileptic abnormalities with almost no background activity. MRI of his brain revealed hypomyelination and cortical atrophy very similar to that of his brother. Laboratory tests showed a megaloblastic anemia (hemoglobin, 6.2 mmol/L; mean corpuscular volume, 98 fl). Serine and glycine concentrations in the fasted state were low in plasma and CSF as was methyltetrahydrofolate in the CSF (see Table 1). All other amino acids including total homocysteine and methionine were normal. 3-PGDH activity in cultured skin fibroblasts was 1.7 mU/mg of protein. The parents were found to have normal 3-PGDH activity in skin fibroblasts, that is, 23.2 and 27.9 mU/mg of protein in the father and mother, respectively.

Treatment Protocol

In Patient 2, treatment was initiated with L-serine 100 mg/kg/day orally. Both siblings were subsequently treated with L-serine up to 500 mg/kg/day. Because of persistent seizures, glycine 200 mg/kg/day was added to the treatment. The amino acids were given orally in six divided doses. Dosages were adjusted every 2 to 4 weeks. The antiepileptic medications were maintained during treatment. EEGs were performed before the treatment and after 1, 2, 4, 12, 26, and 52 weeks. The parents kept daily records of seizure frequency and duration. Serine, glycine, and methyltetrahydrofolate were monitored regularly. Routine laboratory tests were performed frequently to detect possible side effects. Informed consent was obtained from the parents and the study was approved by the hospital's ethics committee.

Amino Acid and Folate Analysis

Quantitative analyses of amino acids in plasma and CSF were performed by a Biotronik LC 7000 analyzer (Biotronik AG, Maintal, Germany) by standard procedures.[2,3] Methylenetetrahydrofolate could not be analyzed, so the reduced form, methyltetrahydrofolate, was investigated in the CSF. This was determined by high-performance liquid chromatography (HPLC; Waters), using a reversed-phase ODS1 column (250 × 4.6 mm) with amperometric detection (flow, 1.2 ml/min; mobile phase, 50 mM sodium acetate, pH 4.6, 25 mg EDTA/L).

Results

Plasma and CSF amino acid concentrations before and during treatment, and methyltetrahydrofolate values in CSF, are listed in Table 2.

In Patient 2, treatment with L-serine 100 mg/kg/day had neither clinical nor biochemical effects. L-Serine 200 mg/kg/day in both patients also had no effect on the seizure frequency. Only L-serine 500 mg/kg/day resulted in some improvement of behavior and seizure control, and the hematological abnormalities disap-

Table 1. Biochemical Findings in Plasma and Cerebrospinal Fluid, in Patients 1 and 2 with 3-Phosphoglycerate Dehydrogenase Deficiency, Before and During Treatment

	Treatment (mg/kg/day)		Plasma[a] (μmol/L)		CSF[a] (μmol/L)		CSF[a] CH_3THF (nmol/L)
	L-Serine	Glycine	L-Serine	Glycine	L-Serine	Glycine	
Patient 1	—	—	49	186	6	1	24
	200	—	62	173	20	6	33
	500	—	74	210	18	5	55
	500	200	105	330	29	7	71
Patient 2	—	—	64	174	8	4	5
	100	—	28	129	8	4	0
	200	—	54	203	13	2	15
	500	—	86	258	29	3	32
	500	200	161	413	25	6	65
Control values[b]			127 ± 27	232 ± 36	38 ± 2	7 ± 2	41–117

Except for serine in CSF, amino acid concentrations and methyltetrahydrofolate concentrations reach the reference ranges at the end of treatment. Reference values in the fasted state: plasma serine, 127 ± 27 μmol/L; plasma glycine, 232 ± 36 μmol/L; CSF serine, 38 ± 2 μmol/L; CSF glycine, 7 ± 2 μmol/L.

[a]Concentrations in the fasted state.
[b]Mean ± SD, or range.

CSF = cerebrospinal fluid; CH_3THF = methyltetrahydrofolate.

Table 2. Main Clinical Characteristics of Patients with 3-Phosphoglycerate Dehydrogenase Deficiency

	Jaeken et al Study[a]		Present Report	
	Patient 1	Patient 2	Patient 1	Patient 2
Age at diagnosis (yr)	1	7	7	5
Age at onset of seizures (yr)	1	0.16	1	1
Intrauterine growth retardation	+	NM	−	−
Postnatal growth retardation	+	+	−	−
Congenital microcephaly	+	NM	+	+
Adducted thumbs	+	+	−	−
Hypogonadism	+	+	−	−
Cataract	+	−	−	−
Nystagmus	−	−	+	+
Psychomotor retardation	+	+	+	+
Spastic tetraplegia	−	+	+	+
Megaloblastic anemia	NM	NM	+	+
Thrombocytopenia	NM	NM	+	−
MRI of the brain	Atrophy; dysmyelination	Atrophy; dysmyelination	Atrophy; hypomyelination	Atrophy; hypomyelination

[a]Jaeken and colleagues.[1]

NM = not mentioned; + = present; − = not present; MRI = magnetic resonance imaging.

peared. After adding glycine 200 mg/kg/day to the treatment, clinically manifest seizures disappeared completely within 2 weeks. The patients became more alert and cheerful and demonstrated less self-destructive behavior and showed improvement of feeding problems. The multifocal epileptic EEG abnormalities gradually resolved after 6 months of treatment in both siblings. Fasted plasma serine and glycine concentrations became normal during therapy. In CSF, glycine concentrations and methyltetrahydrofolate values became normal whereas serine values remained just below normal. During the 12 months of follow-up, no adverse effects were documented.

Discussion

The 2 patients with 3-PGDH deficiency described in the current report showed a similar clinical phenotype as the patients reported by Jaeken and colleagues.[1] Congenital microcephaly, severe psychomotor retardation, and intractable seizures predominated the clinical phenotype. Megaloblastic anemia and thrombocytopenia have not been reported previously. An overview of clinical symptoms in patients with 3-PGDH deficiency reported thus far is summarized in Table 2. The relatively late onset of seizures in both siblings was remarkable; apparently there was no immediate toxic effect of the metabolic abnormalities in the neonatal period. The mother of our patients was noted to excrete 3-methylglutaconic acid. Mild maternal 3-methylglutaconic aciduria has been reported in association with congenital microcephaly in offspring but has also been detected in normal pregnancy.[4,5] Therefore, a causal relationship with the symptoms in our patients remains uncertain.

In our 2 siblings, L-serine 200 mg/kg/day was not sufficient to decrease the seizure frequency, in contrast to the patients in the report by Jaeken and colleagues.[1] Only after increasing the L-serine to 500 mg/kg/day, and adding glycine to the treatment, did the clinical seizures and epileptic abnormalities on EEG disappear in our patients. The clear anticonvulsant effect of glycine being added to the treatment was difficult to relate to amino acid concentrations. Only the plasma concentrations of serine and glycine (ie, not the CSF concentrations) increased considerably by the addition of glycine. The patients reported by Jaeken and associates[1] were lost to follow-up, so that it is not known whether the response to L-serine treatment with 200 mg/kg/day was consistent. A possible explanation of the higher need for amino acids in our patients might be the somewhat lower residual activity of 3-PGDH (ie, 6% and 13%) compared with the 13% and 22% reported by Jaeken and colleagues.[1] High doses of L-serine and glycine are probably needed for the transportation of considerable amounts of amino acid over the blood–brain barrier. All neutral amino acids are transported by the same neutral amino acid carrier and are therefore in competition with each other.[6] However, with high plasma concentrations and limited capacity for transport over the blood–brain barrier, amino acids are probably lost in urine. Our patients, indeed, had a high excretion of serine and glycine during treatment (data not shown). It was remarkable that both siblings showed no homocystinuria or hyperhomocysteinemia, given the very low concentrations of methyltetrahydrofolate in CSF. Neurological abnormalities were reported in methyltetrahydrofolate deficiency but were different than those found in our patients.[7,8]

The clinical features of patients with 3-PGDH deficiency and the response to treatment with amino acid supplementation indicate important functions of serine and glycine in brain metabolism. Little is known about the function of serine in human brain metabolism, but data from in vitro studies indicate important functions.[9,10] Glycine is known for its neurotransmitter functions.[11,12] It is therefore not surprising that severe neurological impairment is present in patients with deficiencies of both serine and glycine. The importance of diagnosing serine biosynthesis defects in patients with congenital microcephaly and seizures was recently reported.[13]

In conclusion, our results indicate beneficial effects of amino acid supplementation with both L-serine and glycine in the treatment of 3-PGDH deficiency.

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Familial Spinocerebellar Ataxia with Cerebellar Atrophy, Peripheral Neuropathy, and Elevated Level of Serum Creatine Kinase, γ-Globulin, and α-Fetoprotein

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Here, we report a familial spinocerebellar ataxia (FSCA), which has clinical features similar to Friedreich's ataxia, an ataxia with isolated vitamin E deficiency, and ataxia telangiectasia. However, the serum levels of creatine kinase, γ-globulin, and α-fetoprotein were elevated, and biochemical and genetic analyses ruled out diagnosis of these three ataxias as well as other FSCAs. Thus, this family is thought to have a new type of FSCA.

Watanabe M, Sugai Y, Concannon P, Koenig M, Schmitt M, Sato M, Shizuka M, Mizushima K, Ikeda Y, Tomidokoro Y, Okamoto K, Shoji M. Familial spinocerebellar ataxia with cerebellar atrophy, peripheral neuropathy, and elevated level of serum creatine kinase, γ-globulin, and α-fetoprotein. Ann Neurol 1998;44:265–269

Familial spinocerebellar ataxias (FSCAs) consist of genetically heterogenous subgroups. Friedreich's ataxia (FA), ataxia with isolated vitamin E deficiency (AVED), and ataxia telangiectasia (AT) are representative diseases with an autosomal recessive trait. The genes responsible for these FSCAs were recently cloned.[1–7] Here, we present a new type of FSCA that

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