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Fatal cerebral edema associated with serine deficiency in CSF*

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Introduction

L-Serine is a non-essential amino acid which plays an important role in cellular proliferation, is a precursor of the neurotransmitters D-serine and glycine and is involved in one-carbon metabolism. L-Serine can be derived from different sources such as dietary intake, degradation of proteins and phospholipids and from glucose via the glycolytic intermediates 3-phosphoglycerate and 3-phosphohydroxypyruvate (1). Three enzymes are involved in serine biosynthesis, 3-phosphoglycerate dehydrogenase (3-PGDH), 3-phosphohydroxypyruvate aminotransferase; and phosphoserine phosphatase. Genetic 3-PGDH deficiency (2, 3) is associated with congenital microcephaly, severe psychomotor retardation and intractable seizures (4). The biochemical hallmark of this disorder is a significantly reduced concentration of L-serine and, to a variable degree, also glycine, in cerebrospinal fluid (CSF) and plasma (3). Here we describe two patients with severe encephalopathy associated with a viral infection and serine deficiency in plasma and CSF. In the medical histories asthma is the only notable clinical condition. Possible mechanisms for the extremely low serine concentrations in CSF will be discussed.

Patient 1

A 7-year old, normally developing girl was known with moderately severe asthma for which she used inhalation therapy. The day before her death, she presented with a mild febrile condition including malaise, headache and nausea. Medical examination did not show any abnormality. The morning before her death, her mother found her unresponsive in bed, probably following a seizure. At that time blood glucose, as measured by a bed-side apparatus, was 2.1 mmol/l.
In the emergency room, the patient had convulsions which responded to diazepam. Physical examination showed normal blood pressure, no hepatosplenomegaly, normal pupils and no signs of trauma or bleeding. Hypoglycemia or electrolyte disturbances were excluded. Liver enzymes and bilirubine were slightly elevated and blood ammonia was normal (15 µmol/l).
She regained consciousness during 1.5 hours but became progressively dyspnoeic and presented suddenly with an apnea and desaturation, decortication rigidity, bilateral fixed mydriatic pupils and deep coma. She was intubated. A brain CT-scan showed bilateral central herniation and cerebral edema. There were indisputable signs of brain death and she died within 24 hours after the first symptoms.
Amino acid analysis of both plasma and CSF revealed strongly decreased serine concentrations (table 1A-C) comparable to levels observed in patients with 3-PGDH deficiency (4). Enantiomer separation revealed D-serine to be 0.9 µmol/l (ref. 0.8-4.3 µmol/l) and L-serine of 4.0 µmol/l (ref. 17.2-44.0 µmol/l) with slightly elevated D-serine/total serine ratio of 18% in CSF (5). The concentrations of the other amino acids were normal or decreased according to a non-specific pattern (data not shown). A deficiency of 3-phosphoglycerate dehydrogenase was excluded in cultured fibroblasts (43 nmol/mg.min; normal 29.5±2.7 nmol/mg/min). Further metabolic screening revealed increased ketone bodies and lactate in urine, plasma and CSF (data not shown). The plasma acylcarnitine profile showed an elevated concentration of OH-C4-carnitine. A fatty acid oxidation defect was excluded. Brain microscopy showed bilateral necrosis in the cerebral tonsils which is compatible with central herniation. No signs of encephalitis or meningitis were found, but diffuse interstitial edema was obviously present. Postmortem microbiology sampling yielded a para-influenza type II virus in the lungs, probably explaining the fever-onset and asthmatic signs as presenting condition. The clinical picture reflects probably a toxic encephalopathy.

Patient 2

A 4-year-old girl with normal mental development was suffering from asthma for which she used medication. She had a normal height, but had severe malnutrition (weight< 2-SD) due to feeding difficulties related to behavioral problems. Because of sleep disturbances the patient had been on treatment with alimemazine (an anti-histaminic sedative agent) for four months. Two days before her death (in the evening, day 1), she presented with fever (39-40 °C) without other particularities. The next morning (day 2) she was found in bed with tonic clonic seizures. The seizures were resistant to multiple anticonvulsine drugs. There were no signs of respiratory or circulatory failure. On admis-

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sion, serum glucose was 4.0 mmol/l with CSF glucose 1.0 mmol/l; serum electrolytes were normal as well as blood ammonia (15 µmol/l). There were no signs of a bacterial CNS infection in CSF, there was no pleocytosis and bacterial and viral cultures remained negative; later nasal cultures however showed an adenovirus V. Blood CRP was > 300 mg/ml.

Physical examination showed a very ill girl with coma scores E1, M4, V1. Intubation and cardial support were effective for some hours but then a rapid deterioration was seen with an isoelectric EEG pattern and absent stem reflexes. After a repeated isoelectric EEG the next day supportive treatment was discontinued. No postmortem examination was performed.

Metabolic investigations in plasma and CSF taken at day 2 showed particularly low plasma and CSF serine concentrations. The concentrations of the other amino acids were normal or decreased according to a non-specific pattern (data not shown). Unfortunately, no fibroblasts were available for the analysis of 3-PGDH activity. Plasma lactate and 3-hydroxybutyrate were clearly increased as well as CSF lactate (data not shown). Urine organic acid analysis showed a moderate ketonuria as well as a marginally elevated lactate excretion.

Discussion

Here we present two young female patients with extremely low serine concentrations in CSF and plasma comparable to 3-PGDH deficient patients without clinical features suggestive for a serine biosynthesis defect. Both patients showed a rapidly progressive toxic encephalopathy and brain edema causing death within 24 hours after the first symptoms.

Acute toxic encephalopathy has been described in young children (2-3 years of age) without a notable medical history with cerebral edema and fatal brain stem compression as the major cause of death. Possible triggers include infections by several bacteria as well as viruses. Our patients suffered from parainfluenza virus type II (patient 1) and a nasal adenovirus 5 (patient 2), respectively. Both viruses have been associated with an (acute) encephalopathy (6).

The pathogenesis of acute toxic encephalopathy has not been elucidated. Toxins leading to either endothelial cell damage with disruption of the blood-brain barrier or directly affecting cells leading to cytotoxic edema might play a role (7). A relation between acute encephalopathy and low CSF serine concentration has never been reported.

Both our patients had an overnight (fasting) period before serious neurological symptoms occurred. Low plasma concentrations of (essential) amino acids and increased ketone bodies in urine and plasma reflected this fasting state. In addition, plasma alanine concentrations of 72 µM and 181 µM made a gluconeogenesis defect unlikely. In cases of fasting in combination with fever/illness, a cerebral hypoglycemic state could trigger formation of ketone bodies as an alternative source of energy for the brain. In patient 1, we confirmed an increased concentration of 3-OH-butyrate in CSF. In patient 2, the low CSF glucose concentration relative to the plasma concentration might suggest a GLUT-1 transporter defect (MIM# 606777) despite absence of clinical symptoms of this genetic defect (8); CSF glucose concentration, however, normalized upon glucose bolus.

In addition to ketone bodies, L-serine is a potential energy source under certain conditions in cerebral tissue. L-serine does not easily cross the blood-brain barrier and glial cells contain the enzymes of the complete serine synthesis and degradation pathways. Serine racemase, present in different regions of the brain, can synthesize D-serine, as well as pyruvate, from L-serine (9). The formed pyruvate may act as a local, emergency energy substrate (10). In both patients with a clear cerebral emergency situation L-serine might have been used as an alternative energy source. The relatively high percentage of D-serine (18% of total serine, ref.: 3-16%) (5) supports this possibility.

In order to study the role of L-serine in energy metabolism in the hypoglycemic brain we analyzed CSF of 4 patients diagnosed with a GLUT-1 deficiency. No changes in amino acids in CSF from these patients were observed (results not published). From this observation we conclude that a chronic low CSF glucose

Table 1. Summary of CSF and plasma amino acids in the two patients dying from brain stem compression after acute cerebral edema

Amino acid		Measurement			Reference values		
		CSF (µmol/l)	Plasma	Ratio	CSF (µmol/l)	Plasma	Ratio
Serine	Pat 1	8	31	0.258	19-38	95-166	0.276±0.053
	Pat 2	7	33	0.242			
Serine (3-PGDH def)*		6-8	28-64				
Glycine	Pat 1	5	107	0.047	0.7-15	139-317	<0.0400
	Pat 2	6	185	0.032			
Glycine (3-PGDH def)*		1-4	128-190				
Threonine	Pat 1	17	61	0.279	22-47	49-183	0.291±0.053
	Pat 2	11	29	0.379			
Alanine	Pat 1	14	72	0.194	8-42	153-560	0.112±0.028
	Pat 2	37	181	0.204			

* derived from (4)

concentration, as present in GLUT-1 deficient patients, does not explain the low CSF serine concentration.

An alternative explanation for the low CSF serine concentration is a decreased production of serine from glucose due to an acute hypoglycemic state. The low concentration of plasma L-serine, as observed in our patients, is in line with this idea. In general, fasting patients show mildly decreased plasma and CSF serine concentrations (dr. Ries Duran, personal communication) which are however not as low as those observed in our patients. These observations indicate that it is probably the extreme local energy deficit which might contribute to a low cerebral serine concentration.

In addition to hypoglycemia, an increased NADH/NAD^+ ratio as seen in anoxia might be considered as a cause of inhibition of serine synthesis. However, we observed increased concentrations of CSF L-serine (3-fold) and glycine (10-fold) in patients suffering from asphyxia patients as compared to controls (data not published).

In summary, we observed low serine concentrations in two patients who died from a cerebral edema with brainstem compression. The low serine concentrations were not the cause of an inherited disorder of metabolism but probably reflected a pathophysiological state of the brain in which L-serine was utilized either for the production of pyruvate via serine racemase or production of L-serine failed because of a lack of glucose.

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References

1. Koning TJ de, Snell K, Duran M, Berger R. L-serine in disease and development. Biochem J 2003; 371: 653-661.
2. Jaeken J, Detheux M, Van Maldergem L, Foulon M. 3-Phosphoglycerate dehydrogenase deficiency: an inborn error of serine biosynthesis. Arch Dis Child 1996; 74: 542-545.
3. Koning TJ de, Jaeken J, Pineda M, van Maldergem L. Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. Neuropediatrics 2000; 31: 287-292.
4. Koning TJ de, Klomp LW. Serine-deficiency syndromes. Curr Opin Neurol 2004; 17(2): 197-204.
5. Fuchs SA, Dorland L, Sain-van der Velden MG de, Hendriks M. D-serine in the developing human central nervous system. Ann Neurol 2006; 60: 476-480.
6. Hata M, Ito M, Kiyosawa S, Kimpara Y. A fatal case of encephalopathy possibly associated with human metapneumovirus infection. Jpn J Infect Dis 2007; 60(5): 328-329.
7. Kimelberg HK. Current concepts of brain edema. Review of laboratory investigations. J Neurosurg 1995; 83: 1051-1059.
8. Wang D, Pascual JM, Yang H, Engelstad K. Glut-1 deficiency syndrome: clinical, genetic, and therapeutic aspects. Ann Neurol 2005; 57: 111-118.
9. Miranda J de, Panizzutti R, Foltyn VN, Wolosker H. Cofactors of serine racemase that physiologically stimulate the synthesis of the N-methyl-D-aspartate (NMDA) receptor coagonist -serine. Proc Natl Acad Sci USA 2002; 99: 14527–14542.
10. Wu S, Barger SW, Sims TJ. Schwann cell and epineural fibroblast expression of serine racemase. Brain Res 2004; 1020: 161-166.