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Short Communication

Partial *N*-Acetylglutamate Synthetase Deficiency: A New Case with Uncontrollable Movement Disorders

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N-Acetylglutamate synthetase (NAGS, EC 2.3.1.1), the deficiency of which (McKusick 23735) in humans has only previously been reported three times (Bachmann et al 1981, 1988; Elpeleg et al 1990), is a mitochondrial enzyme that normally catalyses the synthesis of *N*-acetylglutamate (NAG), an obligate activator of carbamoyl phosphate synthetase (CPS), which initiates the first step of urea synthesis from ammonia.

We report here a new patient with a very severe neurological presentation characterized by uncontrollable movements, development delay, visual impairment, failure to thrive and hyperammonaemia precipitated by the introduction of high-protein diet or febrile illness.

METHODS

Amino acids were determined using automated ion-exchange chromatography. Urinary organic acids were quantitated by gas chromatography and mass spectrometry. High-performance liquid chromatography (HPLC) was used for the quantitation of urinary orotate (Ferrari et al 1989). Biogenic amines were determined by electrochemical detection on HPLC. NAGS activity in liver was determined by Colombo according to his method (Colombo et al 1982).

CASE REPORT

S.E. is the first child of unrelated parents, born at term following an uneventful pregnancy; she was breast-fed for 2 months and then received milk formula, which led to the first symptoms, and she was admitted to a local hospital. The baby showed frequent episodes of vomiting and lethargy attributed to a presumed 'cow's milk intolerance'. Routine laboratory findings were within normal limits, except for a hyperammonaemia of 269 μmol/L. She was referred to our hospital at 5 months

of age for evaluation of progressive neurological deterioration and metabolic investigation.

On admission the weight was 6.120 kg and the head circumference was 40 cm – both at the 3rd centile. On neurological examination she had continuous generalized involuntary movements (uncontrollable head and body shakes) that made feeding quite difficult; she was hypotonic; the tendon reflexes were absent and extensor plantar responses were present. No obvious physical abnormalities were noted. EEG and EMG were normal; CT scan revealed a generalized cortical atrophy. In T_2 weighted image, brain magnetic resonance imaging (MRI) showed increased signal intensity in the centrum semiovale and initial cortical atrophy. BAEP demonstrated an increased latency through the auditory pathway. VEP were within normal limit but ERG was low.

Routine biochemistry was normal except for plasma ammonia, which was elevated (285 μmol/L). Metabolic studies revealed a high plasma concentration of alanine (682 μmol/L) and glutamine (755 μmol/L) and low concentration of citrulline (6 μmol/L); organic acids and plasma carnitine level were normal; orotic acid excretion was low (0.05 μmol/mmol creatinine; normal 0.32–3.74). Therefore, a primary organic aciduria as well as a secondary hyperammonaemia due to acyl-CoA dehydrogenase or carnitine deficiency was ruled out.

Since orotic acid excretion was repeatedly at the lower limit of the reference range, this supported a possible block of mitochondrial urea-cycle enzymes and a liver biopsy was performed. CPS activity was found to be normal (0.95 μmol h^{-1} (mg protein)$^{-1}$) while NAGS was reduced to 40% of the control (55 nmol min^{-1} (g protein)$^{-1}$; normal 144–320).

Restriction of protein intake with adequate caloric supply, sodium benzoate and arginine normalized plasma ammonia, lactate and amino acid levels. Only on one occasion, during an upper respiratory infection, did the plasma ammonia rise to 285 μmol/L. At 2 years of age, the child is profoundly mentally retarded and cortically blind. The involuntary movements and hypertonia progressively decreased. A repeated MRI showed a marked cortical atrophy and increased hyperintensity of signal lesions in the deep white matter and centrum semiovale (Figure 1).

DISCUSSION

This report of the second patient with a partial NAGS deficiency (Elpeleg et al 1990) shows a different clinical presentation of this disorder. Our patient presented with vomiting and severe neurological deterioration characterized by hypotonia, undetectable tendon reflexes but extensor plantar responses, visual impairment and persistent generalized involuntary movements (uncontrollable head and body shakes) so severe that feeding was quite difficult. The hyperammonaemia, the absence of organic aciduria, the normal carnitine levels and the undetectable orotic acid were all suggestive of CPS or NAGS deficiencies.

Enzymatic studies in liver tissue distinguished these two disorders and allowed the diagnosis of a partial deficiency. The finding of normal activities of CPS in the same specimen was indicative of a well-preserved sample. The reduced activity of NAGS, a fairly stable enzyme, has therefore been interpreted as true partial NAGS deficiency.

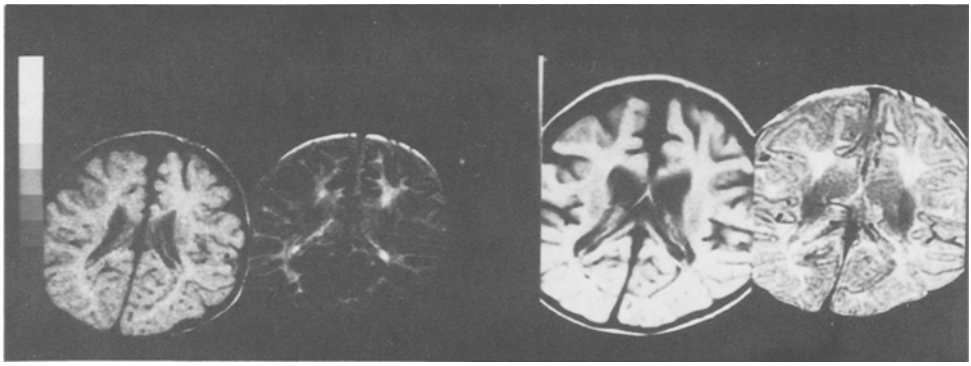

Figure 1 Magnetic resonance scans (TR 400 ms; TE 14 ms) at 5 months of age (on the left) and at 2 years of age (on the right) show a progressive cortical atrophy and a further increase of the signal intensity in the centrum semiovale (T_2-weighted spin echo image)

Our management consisted mainly of a protein-restricted diet with adequate caloric supply, sodium benzoate and arginine. It allowed control of the blood ammonia and gradually decreased generalized movements. These satisfactory results prevented the use of carbamyl glutatmate in this disease as used in the index patient (Schubiger et al 1991).

The two previous patients with NAGS deficiency reported in literature (Bachmann et al 1981, 1988) presented in the neonatal period with non-specific neurological signs. In the present report the clinical onset occurred after 2 months of life and with a characteristic picture. Behavioural alterations have been reported in older children with hyperammonaemia and in sparse-fur mice related to alterations in neurotransmitter systems (Batshaw et al 1990). Recently tryptophan and 5-hydroxyindoleacetic acid were measured in the patient's CSF and found to be marginally elevated (5.2 μmol/L and 295 nmol/L, respectively) despite the plasma ammonia level amounting to 85 μmol/L.

The question remains open whether isoenzymes of NAGS exist with perhaps other functions of *N*-acetylation in brain.

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