Eur J Pediatr (1990) 149:634–636

European Journal of
Pediatrics

Late-onset form of partial N-acetylglutamate synthetase deficiency

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Received August 29, 1989 / Accepted November 17, 1989

Abstract. A 13-month-old female presented with neurological deterioration of 1 month duration and hyperammonaemia. N-acetylglutamate synthetase activity in the liver was reduced to 33% of the control. A male cousin and a female sister had died following a similar clinical course. This is the first report of late-onset N-acetylglutamate synthetase deficiency. An autosomal-recessive mode of inheritance is suggested.

Key words: Hyperammonaemia – N-acetylglutamate synthetase deficiency

Introduction

In the first step of the urea cycle, the formation of carbamoylphosphate (CP) requires N-acetylglutamate (NAG) as an activator of carbamoylphosphate synthetase (CPS). NAG is synthesized by N-acetylglutamate synthetase (NAGS) from glutamate and acetyl-CoA. This enzyme therefore, plays an important role in ammonia detoxification and its complete deficiency leads to neonatal hyperammonaemia as has been reported in two patients [2, 3].

We describe the third case of NAGS deficiency. This patient like her two siblings, presented around her 1st birthday and deteriorated rapidly with a fatal outcome. Residual enzyme activity combined with a low protein intake were probably the main reasons for this late onset.

Case reports

Patient IV-5 (Fig. 1) was a female of Moslem origin. Her parents are first cousins and she was their third child. She was referred to us at the age of 13 months for evaluation of recent neurological deterioration. She was born following an uneventful pregnancy and her birth weight was 3.4 kg. She was exclusively breast fed for 11 months, when cow's milk, fruit and chicken were introduced. At 1 year, she could crawl, sit up, and stand with support. At that time she had a short febrile illness after which she was noted to fall down frequently and had difficulty in reaching for objects. Her spontaneous activity decreased markedly and she became less alert and responsive. Convulsions or significant episodes of vomiting were not reported.

On admission, she was in stage II coma. Tachycardia (132/min) and shallow breathing (16/min) were noted. The head circumference was 43.2 cm, the weight was 7 kg – both at the 3rd percentile. Severe muscular hypotonia, easily elicited deep tendon reflexes, pendulous patellar reflexes, bilateral facial palsy and mild liver enlargement were found.

Laboratory investigations disclosed a haemoglobin concentration of 10.4 g%, mean corpuscular volume of 70, WBC of 16,400/mm^3 with a normal differential count and thrombocytes – 992,000/mm^3. Blood pH was 7.36, PCO_2 – 35 mm Hg, and HCO_3 – 20 meq/l. Liver transaminases were slightly elevated but the alkaline phosphatase, lactate dehydrogenase, prothrombin time and bilirubin were all within the normal range. Blood ammonia level was 81 μmol/l (normal ≤ 40 μmol/l).

On EEG diffuse slow delta activity with triphasic waves were recorded. Brain computed tomography showed generalized cortical atrophy and slight ventricular dilatation with no overt signs of increased intracranial pressure.

Treatment with intravenous glucose, carnitine and vitamin B_6 improved the patient's alertness within a few hours. Her spontaneous activity increased but severe ataxia was then observed. Oral feeding with a protein content of 0.5 g/kg per day was followed by

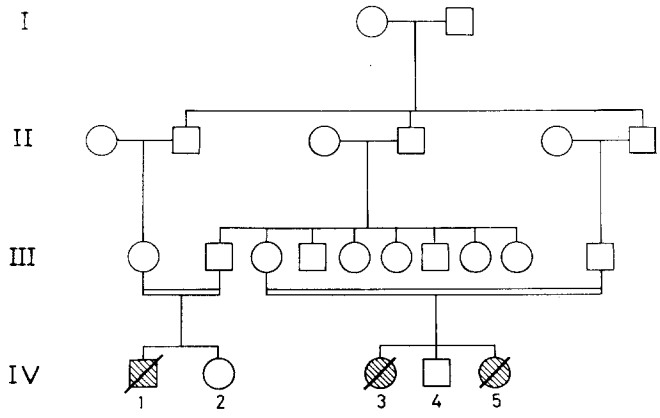

Fig. 1. The family pedigree

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Abbreviations: CP = carbamoylphosphate; CPS = carbamoylphosphate synthetase; NAG = N-acetylglutamate; NAGS = N-acetylglutamate synthethase; OTC = ornithine transcarbamoylase

recurrent vomiting and hyperammonaemia (241 μmol/l). Intravenous sodium benzoate and arginine, oral neomycin and lactulose, were initiated.

Consequently, the blood ammonia level decreased to 102 μmol/l. Nevertheless, she developed fever and diarrhoea and went into a deep coma. Inappropriate secretion of antidiuretic hormone was manifested by hyponatraemia (116 meq/l) and hypokalaemia (2.5 meq/l), together with natriuria (67 meq/l), kaliuria (22 meq/l) and oliguria. Fluid restriction and intravenous administration of hypertonic NaCl solution corrected the electrolyte disturbances but the patient remained in coma. Recurrent apnoeic episodes preceeded her death on the 10th day.

Her elder sister (patient IV-3) developed normally until 11 months of age when a similar neurological deterioration was first observed. She was never seen by any medical agency and died at home at the age of 13 months.

Her cousin (patient IV-1), was well until the age of 15 months. He then gradually lost the ability to walk or stand, was noted to have a squint and his consciousness deteriorated. When 18 months old he was admitted to another hospital where bilateral facial palsy, left abducens palsy and blurred consciousness were noted. Brain CT scan disclosed an arachnoid cyst in the fourth ventricle with no signs of increased intracranial pressure. His blood count was normal except for an elevated thrombocyte count (668,000/mm^3). Blood pH and ammonia levels were never determined. The cyst was removed operatively, however, he remained deeply comatose and died on the 3rd postoperative day.

Methods

NAGS activity in liver was determined according to Colombo et al. [6]. Liver homogenates, 1–10 and 1–300, respectively, prepared with the buffer described by Pearson and Brien [8], were used for CPS and ornithine transcarbamoylase (OTC) determination. CPS activity was determined according to Brown and Cohen [4] and OTC activity according to Campbell et al. [5].

Urinary organic acids were quantitated by gas chromatography and mass spectrometry. Ion-exchange chromatography was used for the quantitation of urinary orotate [1]. Amino acids were determined using automated ion-exchange chromatography (Biotronic LC 7000, Munich, FRG) with norvaline as an internal standard. Medium chain fatty acids in serum were determined according to Dionisi Vici et al. [7].

Results

The plasma amino acid levels are presented in Table 1. Notably, glutamine, alanine, proline, arginine and lysine levels were increased whereas citrulline was undetectable.

Urinary amino acid analysis detected normal levels of most acids. The excretion of glutamine, alanine, serine and glycine were above normal.

Organic acid analysis revealed a normal profile. Neither dicarboxylic acids nor suberylglycine could be detected. In serum, the concentration of octanoic acid was 4.1 μmol/l (normal range 1.2–3.5), of decanoic acid 5.7 μmol/l (1.3–8.2) and of dodecanoic acid 15.5 μmol/l (2.5–28). The orotic acid excretion was 3.60 mmol/mmol creatinine (normal range 0.19–3.85 mmol/mmol creatinine).

The liver cells contained many small and large fatty droplets. The mitochondria were small and dark. The matrix was electron dense and there was a reduced number of cristae. In addition, an increased number of microbodies and collagen fibres were seen between the cells.

Table 1. Plasma amino acids of patient IV-5

	Control range (μM/l)	Patient
Taurine	20– 90	86
Threonine	30–130	70
Serine	25–170	79
Glutamic acid	25–250	92
Glutamine	60–470	549
Proline	50–190	220
Glycine	60–310	200
Alanine	100–310	477
Citrulline	10– 30	ND
Valine	60–260	93
Methionine	5– 30	10
Isoleucine	25– 95	23
Leucine	45–155	44
Tyrosine	10–120	68
Phenylalanine	20– 70	74
Ornithine	10–110	45
Lysine	45–145	175
Histidine	25–110	34
Arginine	10– 65	117

ND = not detected

Table 2. Enzymatic activities in liver tissue of patient IV-5

	Control range	Patient
CPS[a]	0.7– 2.1	0.7
OTC[b]	9.5– 33.3	20.7
NAGS[b]	144 –320	47.9

[a] Values are given in μmol/h per mg protein
[b] Values are given in nmol/min per g protein

The activity of CPS and OTC in liver homogenate was within the normal range (Table 2). The activity of arginine activated NAGS was reduced to 33% of the control.

Discussion

The patient presented with a neurological deterioration of a few weeks duration characterized by ataxia, gradual reduction of spontaneous activity, apathy and depression of consciousness. These symptoms are rather common in the late-onset form of most enzymatic defects of the urea cycle. In the present patient, the hyperammonaemia, the increased levels of plasma glutamine, alanine, proline and lysine and the undetectable levels of plasma citrulline, the absence of organic aciduria, and the normal orotic acid level, have all been suggestive of either CPS deficiency or NAGS deficiency. The lack of dicarboxylic aciduria and suberylglycine and the normal pattern of medium chain fatty acids in serum, rule out

medium chain acyl-CoA dehydrogenase deficiency, often contributing to a sudden infant death in infancy.

NAGS is a mitochondrial enzyme catalysing the formation of NAG from acetyl-CoA and glutamate. Since NAG is an activator of CPS, its deficiency results in underproduction of CP, simulating a deficiency of CPS itself. Enzymatic studies in liver tissue are required in order to distinguish these two defects.

NAGS activity in the liver of the present patient was reduced to 33% of the lower normal level. The finding of normal activities of CPS and OTC in the same specimen was indicative of its well-preserved state. The reduced activity of NAGS, a fairly stable enzyme, has therefore been interpreted as a true partial NAGS deficiency. Patients IV-1 and IV-3, who presented at the same age and exhibited a similar clinical course, probably suffered from the same enzymatic defect. These data indicate that NAGS deficiency is inherited in an autosomal-recessive mode.

Hitherto, two patients with NAGS deficiency have been reported [2, 3]. Both presented in the neonatal period and their hepatic NAGS activity was 2%–3% of the control [3]. In the present report the clinical onset in all three siblings was around the 1st birthday, probably due to a residual enzymatic activity. The deterioration seems to be precipitated by the introduction of high protein diet and accelerated, in the case of patient IV-5, by the febrile illness and the resultant catabolic state.

The unremmitting, downhill course of patient IV-5 is rather distinctive. It does neither resemble the episodic nature of late-onset CPS deficiency, OTC deficiency and argininosuccinic aciduria, nor the gradual development of psychomotor retardation and spastic diplegia which is typical of argininaemia. Furthermore, its relationship to the hyperammonaemia is unclear. The blood ammonia level on admission was only marginally elevated, and was thereafter easily controlled by sodium benzoate and arginine.

The liver pathology in patient IV-5 consisted mainly of fatty infiltration and mitochondrial changes, accompanied by moderate fibrosis. The possibility of a primary respiratory chain defect is unlikely in view of the normal serum pH and the lack of lactic aciduria. The non-specific pathological findings in our case differ from those reported in another NAGS deficiency case [9], where abundance of glycogen particles and cytoplasmic deposits of albumin were the most prominent abnormalities. Due to the discrepancy in residual enzymatic activities, it seems that no conclusions can be drawn from these differences.

The thrombocyte count was markedly elevated in patients IV-5 and IV-1. No haematological data have been reported in the other NAGS deficiency cases. At present it is unknown whether this finding is specifically related to the enzymatic defect or is purely co-incidental. Report of the thrombocyte count in future cases should clarify this issue.

In summary, partial NAGS deficiency can result in late-onset neurological disease. The diagnosis should be suspected in hyperammonaemic patients with the above amino and organic acid profiles. Confirmation of the defect requires enzymatic studies in liver tissue. It is suggested that the disease is inherited in an autosomal-recessive mode.

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