INTERMITTENTLY PROGRESSIVE DYSKINETIC SYNDROME IN GLUTARIC ACIDURIA

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Kyllerman, M. and Steen, G.: *Intermittently progressive dyskinetic syndrome in glutaric aciduria.* Neuropädiatrie 8: 397—404 (1977). A case of glutaric aciduria, a recently discovered inborn error of tryptophan-lysine metabolism, is reported. Development was normal during the first year of life. Signs of dyskinesia and dystonia associated with developmental regression occurred twice during gastrointestinal disease. By two years of age, a dystonic syndrome with a severe motor and language disability had resulted.

Introduction

Glutaric acid is an intermediary in the degradation of tryptophan, lysine and hydroxylysine. A new inborn error of amino acid metabolism, glutaric aciduria, due to a defect of glutaryl-CoA dehydrogenase, was recently discovered (1,2). Two siblings, excreting large amounts of glutaric acid, together with small amounts of glutaconic and 3-hydroxyglutaric acids (3) were described. The clinical picture was characterized by intermittent metabolic acidosis, spasticity, athetosis, and mental retardation. Neurological deterioration seemed to occur at episodes, related to gastrointestinal infections. An oral load of lysine produced a striking increase in glutaric acid excretion, and protein restriction reduced this excretion. The first report has been followed by a brief description of another sibship (4).

In this report, we describe the fifth case of glutaric aciduria. The two-year old infant showed a peculiar combination of ordinary development during the first year, a stepwise regression of motor achievement, and the appearance of dyskinetic and dystonic signs, precipitated by gastrointestinal disease. Mental and emotional development appeared to be only slightly affected by two years of age.

Case reports

This 2-year old girl was the first child to healthy non-consanguineous parents. Pre-, peri- and postnatal periods were uneventful. Birth weight at term was 3090 grams. Head growth velocity and psychomotor development were keenly observed during the first year because of a macrocephaly.

Table I Acid-base balance in catabolic states with concomitant neurological deterioration

Blood	12 months	24 months
pH	7.32	7.31
Stand. bic. (mmol/l)	15.0	17.7
Base excess (mmol/l)	— 13	— 8
pCO$_2$ (kPa)	3.0	4.7
Oxygen saturation (%)	98	96

Between 4 and 7 months of age she had three attacks of sudden crying, apnoea and cyanosis, followed by loss of colour, hypotonus and fatigue. This occurred at the age when solid foods rich in protein were introduced into a diet previously based on a cow's milk formula. Pediatric examination by 8 months was inconclusive. A diagnosis of "affect fits" was ventured.

Twelve months old prior to falling ill she walked a few steps, showed fine finger opposition and could speak a few words. There were no abnormal movements. On the fourth day of a common cold she developed a temperature of 39.2° C, anorexia and a moderate diarrhoea. Three days later she started to vomit and showed a sudden general deterioration with tachypnoea, stiffness and minor convulsions. She was admitted to the local pediatric clinic and a glucose solution supplemented with sodium chloride and potassium chloride was administered parenterally. There was a compensated metabolic acidosis which was corrected on the fourth day of treatment (Table I).

During the first night at hospital she was irritable and had short generalized convulsions. On the second and third days she had three brief periods of apnoea and cyanosis with spontaneous recovery. A tentative diagnosis of encephalitis without meningeal signs was made.

Gross and fine motor performance deteriorated at the same time. She could barely manage to balance her head and could not roll over. A general muscular hypotonus and dyskinesia became obvious. She was given an adequate training programme at the regional habilitation center[1]) and in the following months regained some motor proficiency. By two years of age she sat balancing herself with falling reactions forwards and sidewards present, although somewhat inefficient. A general dyskinesia was evident with small jerking movements in trunk and proximal extremities when sitting, but not during sleep or when lying down. Fine motor performance was dyscoordinated. Her fingers showed athetotic postures. There was poor coordination of tongue movements and swallowing which interfered considerably with feeding. A visuomotor apraxia with difficulty to follow fast moving objects was partly compensated for by head turning. There was neither any strabismus nor gaze paralysis. She made modulated sounds but not words. The general muscle tone was subnormal and there were no signs of spasticity. Mental capacity as far as could be tested seemed quite ordinary for her age.

The second episode of gastrointestinal disease occurred by two years of age.

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Table II

Birth	Development	Symptoms	Signs
1 mo		normal neonatal period	
4 mo	starts to crawl grasps for objects	occasional fits of crying, apnoea, cyanosis and stiffness followed by loss of colour, sweating, limpness and fatigue	
6 mo	turns over		
8 mo	sits unassisted		
12 mo	walks with support takes a few steps on her own masters a few words		
	Regression motor 2—3 mo level mental ordinary no speech	Vomiting and diarrhoea for several days. Apnoic attacks and fits of stiffness No contact	Ketonuria and fully compensated metabolic acidosis. *Dyskinesia (choreo-athetosis)* *Hypotonus*
	Slow improvement motor 7—8 mo level mental ordinary modulated sounds		*slow improvement of Dyskinesia*
24 mo	*New regression* motor 6—8 week level mental ordinary? no spontaneous sounds	Second episode of vomiting and diarrhoea convulsion, somnolent, shifting general muscle tension	Ketonuria and fully compensated metabolic acidosis *Dystonia* *Hypotonus increased* *Dyskinesia (Athetosis)*

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After several days of a slight diarrhoea with anorexia she had a generalized convulsion and became extremely tired and limp. A metabolic acidosis of the same degree as before was found (Table I). After a couple of days an almost complete loss of the achieved motor function was evident. At the same time dystonic signs appeared. The arms were held in a decerebrate posture maximally pronated and stretched behind the back with the fists closed. This was an intermittent, involuntary dystonic position triggered by intentional effort or simply by leaning forward. During prone or supine rest and sleep she was quite immobile and hypotonic. There were still no signs of spasticity. She was constantly fretful and did not show quite the same interest in objects and persons as before. Psychological evaluation (same observer) did not reveal any significant loss of mental capacity. Opthalmological examination was normal.

Further investigations following the second relapse resulted in diagnosis. A diet low in protein, tryptophan and lysine was introduced. Results of treatment will be reported later.

Laboratory investigations

Several EEGs during and between the bouts of disease were normal. ECHO-encephalography showed normal ventricle size and midline structures. There were neither acanthocytes nor vacuolated lymphocytes found in the blood smear. A lipoprotein electrophoresis showed a normal pattern, and serum cholesterol and triglycerides were within the normal range. The plasma amino acids were normal, as well as the serum proteins separated by agarose gel electrophoresis. The levels of copper, ceruloplasmin and uric acid in serum were all within normal ranges. Serum aspartate aminotransferase and alanine aminotransferase were increased to 1.10 and 1.15 µcat/l (reference value < 0.7). Alkaline phosphatase, thymol turbidity and direct reacting bilirubin values were normal. Serum urea was 3.0 mmol/l (reference value 3—10 mmol/l) and urine protein electophoresis pattern was normal. Tests for urine acetoacetate and acetone were negative in non-catabolic phase, but strongly positive in the two bouts of metabolic acidosis heralding neurological symptoms. Urinary glucose was negative at the same time. Total protein of cerebrospinal fluid was 79 g/l (reference value 50—75 g/l). The cerebrospinal fluid protein electrophoresis showed an increase of alpha- and gammaglobulins as in barrier damage.

Organic acids in urine

The urinary content of organic acids was examined by gas chromatography-mass spectrometry, principally as described before (5). The acids were extracted with ethyl acetate, oxo groups were reacted with methoxylamine hydrochloride, and other functional groups with trimethylsilyl reagent (5). The gas chromatogram (see Fig. 1) revealed a very large abnormal peak (peak 3) with a mass spectrum identical with that of derivatized glutaric acid (Sigma Chem Comp., St. Louis, Mo.,
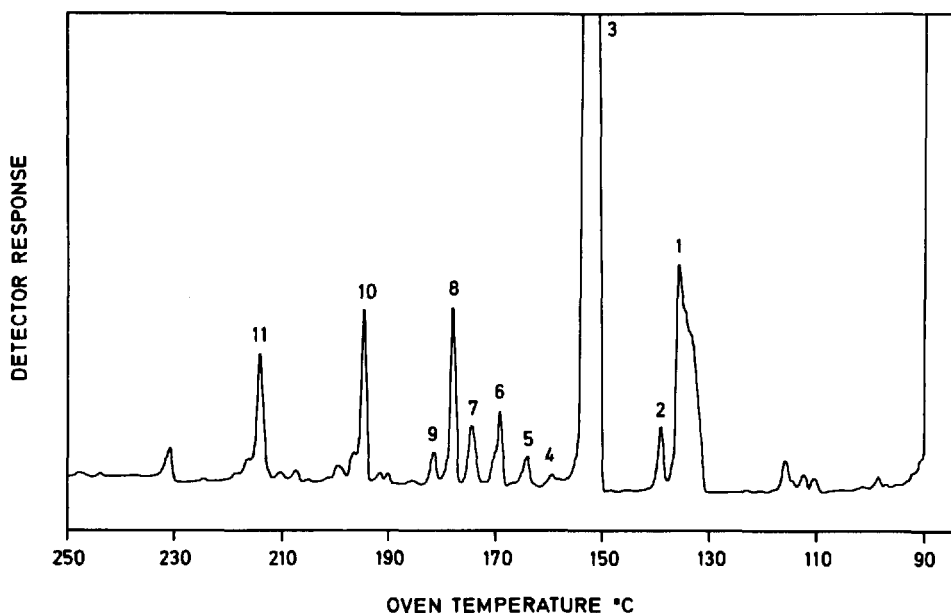
Fig. 1 Gas chromatography of trimethylsilyl derivatives of organic acids from the urine of the present case. Oxo groups were derivatized with methoxylamine before trimethylsilylation. The gas chromatograph was equipped with a packed 2-m glass column with 3%0 OV-17 on 100—120 mesh Gas Chrom Q. Temperature was programmed at a rate of 4° C per min. The peaks were identified as follows:

1. urea + phosphoric acid, 2. succinic acid, 3. glutaric acid, 4. glutaconic acid, 5. adipic acid, 6. 3-hydroxyglutaric acid, 7. internal standard (2-methyl-3-hydroxybenzoic acid), 8. 2-oxoglutaric acid, 9. p-hydoxyphenyl-acetic acid, 10. citric acid, 11. hippuric acid

USA). Glutaconic acid (peak 4) and 3-hydroxyglutaric acid (peak 6) were identified by their mass spectra, using a reference catalogue of mass spectra (6). The other components of Fig. 1 are considered normal, although the 2-oxo-glutaric acid peak is seldom of this size. Quantitative estimation of glutaric acid was made by gas chromatography with a standard curve prepared by additions of glutaric acid to normal urine. The values of Table III are thus corrected for extraction efficiency and detector response.

The urinary concentration of glutaric acid ranged from 31—56 mmol/l, or 4.4—11.8 mol/mol creatinine. The excretion of glutaric acid is thus of the same order of magnitude as reported for the first two cases (1). Healthy subjects never excrete more than traces of this acid, that is less than 0.02 mol/mol creatinine. After dietary treatment had been started (low intake of protein, lysine and tryptophan), glutaric acid excretion decreased rapidly to 1.5—4.2 mmol/, or 0.06—1.1 mol/mol crea-tinine.

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Table III The urinary excretion of glutaric acid in the present case

Date of sampling	Glutaric acid excretion		
	mmol/l	mol/mol creatinine	mmol/24 hrs
10/2—11/2	55.7	11.8	11.7
14/2—15/2	31.1	7.1	8.4
16/2	33.0	5.5	—
17/2	43.9	5.2	—
18/2	35.6	4.4	—
28/2	Start of diet with low tryptophan-lysine content*		
2/3	1.5	0.06	—
7/3	4.2	1.1	—
9/3	3.0	0.18	—
27/3—28/3	3.4	0.31	0.22
17/4—18/4	5.3	0.48	0.50
Reference value		<0.02	

* The diet contained protein 0.9 g/kg, lysine 40 mg/kg and tryptophan 20 mg/kg. The time period 10/2—18/4 corresponds to an age of 25—27 months

The 24-hour excretion was about 10 mmol before treatment and about 0.2—0.5 mmol during treatment.

Discussion

The presented case of glutaric aciduria was, by two years for age, characterized by extrapyramidal neurological signs in the absence of spasticity or significant mental retardation. In the previously reported first sibship (1), there was dystonia and athetosis, while mental capacity seemed to be less affected than motor performance. One of the children, who seemed more severely damaged, also had signs of spasticity. The other sibship with massive glutaric aciduria and neurologic disturbances has not been clinically described (4). Our patient showed an intermittent neurological deterioration with athetosis at one year of age with a moderate handicap, and then by two years of age a severely incapacitating dystonia. If the process would be allowed to continue, one may expect a more extensive loss of cerebral function, with the appearance of pyramidal tract symptoms and mental retardation. The present as well as the two first cases showed an initial period of normal psychomotor development, interrupted by episodes of gastrointestinal disease and sudden deterioration.

Concerning the pathogenesis of the neurologic dysfunction, the pathological metabolites might have produced a continuous toxic effect, but this appears to have been of minor importance, since there was an initial period of ordinary development and a catch-up between the two periods of regression. The sudden appearance of new clinical symptoms and signs would favour an

intermittent toxic action, due to very high levels of metabolites during catabolic episodes, perhaps in combination with other factors such as acidosis and hypoglycemia.

It has been shown that glutaric acid and related metabolites are inhibitors of brain glutamate decarboxylase, and this may explain the extrapyramidal symptoms (7). If this inhibition as such is responsible for the major part of neurologic dysfunction, then one would expect a rapid improvement on an elimination diet. A restriction of protein, lysine and tryptophan for six weeks produced a striking reduction of glutaric acid excretion (see table III), but did not normalize the neurological picture, although there was a definite reduction of irritability and hypertonus. The lack of major effects is probaly due to an irreversible neuronal damage during the two attacks of deterioration. A moderate elevation of cerebrospinal protein, and an electrophoresis pattern of barrier damage may support this opinion.

Glutaric acid has been reported to be highly nephrotoxic in rabbits (8). So far, there is no elevation of serum urea and no evidence of glomerular or tubular protein leakage in our case. On the other hand, there was an increase in aminotransferase acitivity in serum, probably related to a toxic effect on the liver. The aminotransferase activity was rapidly normalized during treatment.

Two possible ways of treatment are obvious. Intense treatment during acute catabolic episodes seems to be of the utmost importance. Gluconeogenesis from amino acids must be reduced, by parenteral glucose administration. Metabolic acidosis should also be corrected. Small intermittent doses of insulin and possibly also somatotrophin may also be attempted to reduce amino acid catabolism. The long-term effect of continuous dietary elimination therapy remains to be evaluated.

Addendum

After submission of this paper for publication, *Gregersen* et al. (9) have further described clinical and laboratory findings in the previously reported two brothers. *Goodman* et al. (10) have reported on a subtotal putamen and marginal caudate sclerosis found at autopsy in one of their cases. *Brandt* (11) has recently reported on the sixth diagnosed case in a six year old choreo-athetotic Danish girl of normal intelligence.

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