Under recognition of late onset ornithine transcarbamylase deficiency

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Abstract

Late onset ornithine transcarbamylase deficiency (McKusick 311250) is reported in four Finnish patients, two boys and two heterozygous girls. The subtle onset and course of ornithine transcarbamylase deficiency emphasises the need for plasma ammonia and amino acid measurements in clinical situations suggesting a disorder of this nature.

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Deficiency of the mitochondrial matrix enzyme transcarbamylase leads to the most common defect of the urea cycle resulting in a serious impairment of ammonia metabolism. The defect is inherited as an X linked trait. If untreated, symptoms include impairment of consciousness, vomiting, convulsion, coma, and death. In the past 15 years there have been numerous case reports of homozygous men with a fatal late onset course of the disease.^{1 2} Despite the growing number of cases the disorder is still under recognised, especially in boys.

Case reports

All children presented were born at term following an uneventful pregnancy. Table 1 presents clinical details for each case.

Patient 1 had a history of atopic disease with dietary restrictions to egg and cows milk which may have caused a delay in the onset of symptoms. After running into a wall he was admitted

to a paediatric surgical ward. Because of bouts of aggression and odd behaviour, encephalitis was suspected and the patient transferred to a paediatric intensive care unit. There his condition varied between weariness and almost normal. On day 9 he became unconscious, vomited, and was incontinent of faeces. His pupils became enlarged and non-responsive to light. Laboratory studies revealed hyperammonaemia, increased glutamine (1387 µmol/l), decreased citrulline (3 µmol/l), and increased urinary orotate (365.8 µmol/mmol creatinine). Despite emergency treatment he died on day 14 from massive cerebral oedema.

Symptoms in patient 2 appeared concomitantly with the birth of her sister and were misinterpreted as signs of jealousy. On laboratory examination the first urinary orotate was in the normal range and carbamoyl phosphate synthetase deficiency was suggested. A second analysis revealed high concentrations of orotate (1304 µmol/mmol creatinine).

Patient 3 was referred to hospital because the examiner could not obtain visual contact with the patient and a metabolic disorder was suspected. Her mother has recently given birth to another boy (patient 5) who is carrying the same mutation as patient 3 and was immediately started on a low protein diet, oral arginine, citrulline, and phenylbutyrate.

Patient 4 was formerly well but his parents revealed a long standing aversion to a diet rich in protein, and symptoms which had been interpreted as defiance. The child was admitted to a paediatric emergency room where a metabolic disorder was suspected, leading to measurements of plasma ammonia and amino acids.

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Table 1 Patient details

	Age at onset	Initial symptoms	Initial investigations	DNA analysis	Outcome
Patient 1 (male)	5 years	Running into a wall, nausea, vomiting	EEG with slow delta waves, CCT normal, Total blood count and C reactive protein normal, ALT slightly elevated, NH ₄ ⁺ initially not taken, later clearly elevated (400-906 µmol/l)	G>A exchange of the first base of codon 208 changing alanine to threonine. Typical for late onset disease in males ³	Died on day 14
Patient 2 (female)	3½ years	Attacks of absence, increasing signs of aggression, confusion, sleeplessness, atetotic movements of upper limbs	EEG with signs of general disturbance on both hemispheres, slight hyperammonaemia (123 µmol/l), ALT elevated (299 U/l), citrulline decreased (13 µmol/l), first urinary orotate was normal	Heterozygosity for an A>G mutation in codon 80 changing lysine into glutamic acid; not formerly described	Alive, development almost normal, disease under control
Patient 3 (male)	1 year 3 months	Increasing weariness, crying, restlessness, vomiting	CCT normal, ALT elevated (102 U/l), NH ₄ ⁺ fluctuating (67-218-146 µmol/l), citrulline decreased (<10 µmol/l), urinary orotate elevated (220 µmol/mmol creatinine)	Abnormal migration pattern at exon 8 with a deletion of a GAG triplet corresponding to codon 272 or 273 causing deletion of one adjacent glutamic acid residue. Formerly described for late onset ³	Alive, development almost normal, disease under control
Patient 4 (female)	4 years 8 months	Outbursts of rage and fury, clumsy walk, slurred speech, emotional lability	ALT elevated (64-119 U/l), NH ₄ ⁺ fluctuating (143-201-124 µmol/l), low citrulline (13 µmol/l), urinary orotate elevated (95 µmol/mmol creatinine)	Abnormal migration pattern in exon 3 with a CGA (Arg) to CAA (Gln) mutation of codon 92. One of the first mutations described ⁴	Alive, development normal, disease under control
[Patient 5] (male)	The patient is a brother of patient 3 and was therefore neonatally screened for ornithine transcarbamylase deficiency and revealed the same mutation as his brother (see patient 3). He was initially treated and yet had no episodes of hyperammonaemia. His development is normal				

CCT, cranial computed tomography.

Discussion

In all four patients onset of symptoms occurred after one month of age which is in concert with the definition of late onset disease. All had an initially slightly high alanine aminotransferase (ALT, see table 1). One patient died and this may have been preventable if a metabolic disorder had been suspected. DNA analysis revealed a mutation which seems to be very typical for late onset disease with a lethal outcome.³ Patients 2 and 4 were both heterozygous girls with milder symptoms, interpreted by their parents as jealousy or defiance. Patient 3 benefited from two facts which may have saved his life. Firstly he presented with symptoms at a relatively young age, which motivated his general practitioner to refer him to hospital care. Secondly he was admitted to a hospital located in an area with a relatively high incidence of metabolic disorders, which resulted in the immediate suspicion of a metabolic disease; plasma ammonia and amino acids were measured.

Recent research on the biochemical and molecular picture of ornithine transcarbamylase deficiency revealed a wide spectrum of genetic defects which results in different phenotypes.¹⁻⁶ Oppliger Leibundgut *et al*⁶ have shown that there may be poor correlation between residual enzyme activity in vitro and the clinical course of the disorder, which makes ornithine transcarbamylase deficiency unpredictable. Additionally, investigation of a large number of patients by Tuchman *et al*¹ has

shown that of all reported mutations which resulted in a late onset course, 50% occurred in boys. This matches with late onset cases in Finland diagnosed during the last 10 years, of which seven of the 14 new cases were men; the oldest one was diagnosed at the age of 18 years. The aim of our report is to remind clinicians that late onset ornithine transcarbamylase deficiency occurs at almost any age, half are boys, and unexplained symptoms such as rage, fury, confusion, or simply acting in an odd way should provoke paediatricians to measure plasma ammonia, amino acids, and transaminases.

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