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Late onset ornithine carbamoyl transferase deficiency in males

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SUMMARY Six boys with ornithine carbamoyl transferase deficiency presenting in infancy or later childhood are described. There was wide variation in both the time of presentation and the symptoms, which may initially suggest a neurological, behavioural, or gastroenterological problem. Two patients died, as did two male siblings who were probably affected, but with early recognition of the hyperammonaemia the outlook is good.

Primary deficiency of ornithine carbamoyl transferase (EC 2.1.3.3) is the most common of the inherited disorders of the urea cycle. It has an X linked mode of inheritance and the hemizygous male usually develops severe hyperammonaemia in the neonatal period. The illness progresses rapidly with convulsions, coma, apnoea, and almost invariably death unless treated intensively.[1]

Although most of the affected males present in the neonatal period, a number have been reported who have presented later in infancy,[1] during childhood, or even in adult life. In some of these male patients the enzyme activity was reduced, which may explain the late onset,[2 3] while in others the deficiency appeared to be complete despite the late presentation.[4 5]

In this paper we describe six male patients with ornithine carbamoyl transferase deficiency who presented after the neonatal period. There was wide variation in the age of presentation and the symptoms. Certain aspects of two of the patients (cases 4 and 5) have been reported previously.[6]

Methods

Enzyme activity was measured in biopsy specimens—liver or jejunal mucosa—by the method of Nuzum and Snodgrass with modifications,[7] and urinary orotic acid by the method of Harris and Oberholzer.[8]

Case reports

The salient clinical features are summarised in table 1.

CASE 1

This boy was born by caesarean section for fetal distress and weighed 3800 g. During childhood his parents complained that he was a very difficult child, introverted with 'volcanic' tempers. At the age of 12 years he had an episode of confusion for which he was admitted to hospital, but no cause was found. Drug or solvent abuse was suspected. Subsequently he had three further episodes and during one of these he was noted to have a raised ammonia concentration. A protein load was clearly abnormal, but nothing further was done. At the age of 14 years he was admitted to hospital deeply unconscious. Four days before admission the patient had complained of feeling sleepy and the next day he was upset, demanding, and difficult. He then became confused and uncoordinated. The night before admission he had a high protein meal and the next morning he was found to be unrousable and limp. On admission he was unconscious with a paraparesis. The plasma ammonia concentration was 292 μmol/l. He was treated with intravenous sodium benzoate with a rapid fall in plasma ammonia (figure), however, he did not recover consciousness for three days. Urine orotic acid excretion was raised and his mother was found to be a carrier (table 2). Since then he has been treated with a low protein diet, arginine supplements, and sodium benzoate. He has remained generally well, although he has had further episodes of hyperammonaemia, particularly precipitated by energy restriction. At the age of 18 years he passed three 'A' levels at A grade and was accepted at medical school.

Table 1 *Summary of clinical features of late onset ornithine carbamoyl transferase deficiency*

Case No	*Symptoms before diagnosis*	*At diagnosis*		*Outcome*
		Age	*Symptoms and signs*	
1	From 12 years: episodes of confusion (?volcanic tempers')	14 years	Lethargy and confusion progressing to coma and paraparesis	Alive
2	At 17 months: one episode of vomiting and drowsiness, ataxia, 'visual problems' (see text)	24 months	Vomiting, drowsiness	Alive
3	Investigated prospectively because of brother (case 2)			Alive
4	Vomiting and drowsiness with infections: recent school progress poor	12 years	Vomiting, confused, 'could not see' progressing to variable conscious level	Dead
5	From 8 months: irritability, vomiting	12 months	Vomiting, coma	Dead
6	At 10 months: irritability, vomiting	11 months	Irritability, vomiting, and myoclonic jerks	Alive

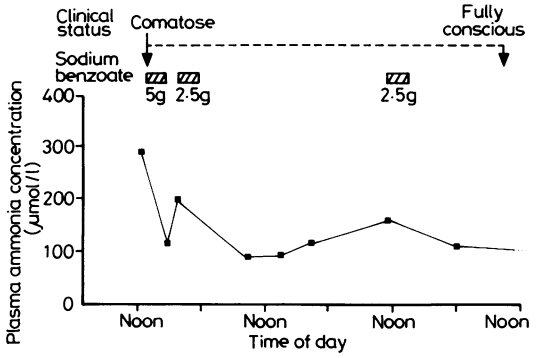

Figure *The course of plasma ammonia concentrations during an episode of encephalopathy treated with intravenous sodium benzoate in case 1.*

CASES 2 AND 3

Cases 2 and 3 are from the same family of four boys.

The first child in the family was born after a normal pregnancy and delivery. He was well until 16 months of age when he died after a short encephalopathic illness labelled as a 'cerebral degeneration'.

The second in the family (case 2) became ill for the first time at the age of 17 months when he was admitted to the hospital after two days of vomiting, drowsiness, ataxia, and visual problems (inability to focus on objects, dilatation of pupils, with little reaction to light or dark). He was treated with intravenous fluids and was back to normal within a week. At the age of 24 months he started intermittent vomiting every four to five days. During one episode he became drowsy and floppy. The plasma ammonia concentration was 330 μmol/l, with abnormal liver function, and raised urine orotic acid concentration. Ornithine carbamoyl transferase deficiency was confirmed by enzyme studies (table 2).

Table 2 *Biochemical features of late onset ornithine carbamoyl transferase deficiency*

Case No.	*Initial plasma ammonia concentration (μmol/l)*	*Orotic acid: creatinine ratio (μmol:mmol)**	*Enzyme activity*		*Mother's carrier status*	
			Ornithine carbamoyl transferase†	*Carbamoyl phosphate synthetase‡ (μmol/g/hour)*	*Family history*	*Loading test*
1	104	630	Not done	–	–	+
2	330	51	110	72	+	Not done
3	62	2·6	1·8 (jejunal mucosa)			
4	286	695	209	271	–	Refused
5	700	462	233	—	+	+
6	214	2800	372	195	–	+

Reference ranges—*orotic acid:creatinine ratio (μmol:mmol) at 2 weeks—10 years, 0·5–3·3 and >10 years, 0·4–1·2; †ornithine carbamoyl transferase activity, 2200–10 700 μmol/g/hour; and ‡carbamoyl phosphate synthetase activity, 76–515 μmol/g/hour.

He was treated with a low protein diet and he remained well up to the age of 6½ years when he developed abdominal pain and vomiting. He became drowsy, ataxic, and confused but he recovered after treatment with intravenous fluids and sodium benzoate. Although he does not keep consistently to the diet, he is now 9 years old, growing normally, and attends a normal school.

The other boy (case 3) is the fourth in the family. He was born after a normal pregnancy weighing 3600 g, and he had no perinatal problems. At the age of 1 month he was investigated for ornithine carbamoyl transferase deficiency because of his brother's history. Although the plasma amino acids and orotic:creatinine ratio were normal, plasma ammonia concentration was slightly raised and the ornithine carbamoyl transferase activity in jejunal mucosa was low (1·8 μmol citrulline/mg protein/hour (normal more that 51). He was well until the age of 13 months, when he developed bronchiolitis and became semicomatose. The ammonia concentrations rose to 147 μmol/l. He recovered quickly with intravenous fluids. He has had no further problems and is developing normally.

CASE 4 (case 5 in reference 6)
This boy, the only child in the family, was born by caesarean section after a failed trial of labour at 37 weeks' gestation; he weighed 2500 g. There were no neonatal problems. All his life he tended to vomit, particularly with infections, and occasionally he had been very drowsy during the episodes of vomiting but he always recovered spontaneously.

He became seriously ill for the first time at the age of 12 years when he was admitted with a two day history of vomiting, irritability, and deterioration of conscious level. He had not been doing well at school, however, and had recently been removed from his present school by his parents. For three days before his admission he had been vomiting but the parents were not particularly worried because of his history. On the third night he woke up from bed confused, incoherent, and said he could not see. He was admitted to a private nursing home and sedated with chlorpromazine, but then became more restless. He was admitted to the Hospital for Sick Children because of deteriorating conscious level. On examination he was drowsy and confused but rousable, screaming from time to time. He had no focal neurological signs. The plasma ammonium concentration was 286 μmol/l and the plasma glutamine and alanine were also raised. He was treated with intravenous fluids and later peritoneal dialysis. The plasma ammonia concentrations initially fell to 186 μmol/l, but 24 hours after admission he had a fit and his condition deteriorated rapidly. His ammonia rose to more that 2000 μmol/l and he died. Enzyme studies on a liver biopsy specimen were performed immediately after death and confirmed ornithine carbamoyl transferase deficiency (table 2). The family have refused further investigation.

CASE 5 (case 7 in reference 6)
This boy was born spontaneously but prematurely at 28 weeks' gestation; he weighed 1090 g. A brother had died of an encephalopathic illness aged 3 months. The patient was well until the age of 3 days when he started having apnoeic attacks. At the age of 24 days he developed Klebsiella pneumonia and meningitis with convulsions and soon after that necrotising enterocolitis. With intravenous feeding he recovered and was developing normally until the age of 8 months, when he became irritable and started vomiting. At the age of 12 months he was readmitted to hospital unconscious after severe vomiting. His condition deteriorated rapidly and he died. The plasma ammonia concentration was 700 μmol/l and the ornithine carbamoyl transferase activity of a specimen from needle biopsy taken immediately after death was reduced (table 2).

CASE 6
This boy was born after a normal pregnancy and delivery; he weighed 3200 g. There were no neonatal problems, but he did not feed well. He became ill for the first time at the age of 10 months when he was admitted to hospital with persistent vomiting and irritability. On examination there were no specific clinical signs. The only abnormal biochemical investigation was a slight rise in plasma aminotransferase activities. The ammonia concentration was not measured. Minor immunological abnormalities were detected and a diagnosis of food allergy made. One month after being admitted to the hospital he again became ill with episodes of lethargy, vomiting, irritability, and myoclonic jerks. His plasma ammonia concentration was raised (214 μmol/l) with abnormal liver function. Urine orotic acid after a protein load was raised suggesting ornithine carbamoyl transferase deficiency, which was confirmed by enzyme studies (table 2). A computed tomogram showed cerebral oedema. He was treated with a low protein diet, and has since done well on a normal diet with sodium benzoate.

Discussion

Ornithine carbamoyl transferase deficiency is X linked and most of the males are born with no detectable residual enzyme activity. They develop a severe illness in the neonatal period and unless intensively treated will die in the early months of

life. Females have a much more variable presentation ranging from severe disease in infancy to those who remain asymptomatic. Males with mild disease have generally been considered to be rare and in a recent review only 18 cases were documented.[1] Ten further males have been described since then,[9–15] and a number of others are incompletely reported. Most of the patients have presented in infancy with anorexia, vomiting, irritability, failure to thrive, and episodic encephalography. However, some patients have not presented until adult life.[16 17] Sixteen out of the 28 patients died. We have described a further six patients with symptoms presenting as late as 12 years of age and it is likely that two other boys in these families, both of whom died, were also affected (siblings of cases 2 and 3 and 5).

The initial symptoms of hyperammonaemia are varied and may be subtle, including confusion, irritability, or behavioural problems. These may be misdiagnosed as psychiatric problems, drug abuse, and food allergy. Two patients complained of visual disturbances. Alternatively, the main symptom may be vomiting, particularly at times of metabolic stress such as infections so that a gastrointestinal disorder may be suspected. This presentation is common in infancy, combined with poor developmental progress. Routine biochemical investigation often shows raised plasma aminotransferase activities suggesting 'hepatitis'.

The mainstay of day to day treatment is a low protein diet, although patients with late onset ornithine carbamoyl transferase deficiency may need only modest protein restriction (1·5–2·2 g/kg/day). Some will even be able to tolerate a normal diet. Other patients may prefer to eat a normal diet and to take sodium benzoate rather than be confined in what they eat. This compound is used to form an alternative pathway to urea for nitrogen excretion.[18] It is conjugated in the liver with glycine to form hippuric acid, which is rapidly excreted in the urine, thereby removing excess nitrogen. Given orally it is an effective and well tolerated drug for reducing plasma ammonia concentrations. The dose should not routinely exceed 250 mg/kg per day without monitoring plasma concentrations.[19]

Arginine is normally synthesised within the urea cycle and is not an essential amino acid. In ornithine carbamoyl transferase deficiency, however, because of the metabolic block it may become essential or semiessential in the more severely affected patients. Some with the late onset forms of ornithine carbamoyl transferase deficiency may require additional arginine supplements during periods of rapid growth or when the plasma arginine concentrations are very low (less than 30 μmol/l).[19]

Although the patients with late onset ornithine carbamoyl transferase deficiency may remain well for long periods, there is always a risk that hyperammonaemia may progress to more serious neurological problems such as coma and focal signs such as paraplegia and hemiplegia. Computed tomography may show focal hypodense areas.[6] Once a child has reached this stage, unless the diagnosis is made rapidly and the correct treatment instituted, the outlook is poor. Nevertheless, with early and effective treatment with sodium benzoate, as in case 1, the outlook can be excellent. The usual dose in these circumstances is 250 mg/kg given over four hours and followed by the same dose in the next 20 hours.[19]

The factors that precipitate an attack are not always understood and there may be long intervals between hyperammonaemic episodes. Although infection is a common precipitating factor, not all infections cause problems, the response being unpredictable. It is particularly difficult to explain why the boy in case 5 did not develop severe hyperammonaemia in the neonatal period when he had a severe infection. Energy restriction was a contributing factor in the episodes of hyperammonaemia of case 1 accelerating protein catabolism and hence hyperammonaemia.

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September 1988: we have diagnosed an additional case in a boy aged 6 months who had repeated episodes of screaming, irritability, and drowsiness lasting several days.