Neurological features and computed tomography of the brain in children with ornithine carbamoyl transferase deficiency

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SUMMARY The clinical features and the computed tomographic appearances of the brain in seven children with ornithine carbamoyl transferase deficiency are described. Episodic vomiting and drowsiness, acute encephalopathy, failure to thrive and developmental retardation were common, but focal neurological symptoms and signs were also observed. The CT appearances were non-specific with generalised or focal changes. They were related to the severity, the duration and the age of onset of the hyperammonaemia. Since the CT changes may suggest conditions other than metabolic disease, the emergency investigation of a child with an encephalopathy should include the estimation of plasma ammonium and, if elevated, the appropriate investigations to establish the cause.

Acute encephalopathy in childhood may be caused by hyperammonaemia and one group of disorders that may be responsible are inborn errors of the urea cycle. These are potentially treatable conditions of which the commonest is ornithine carbamoyl transferase deficiency which has an X-linked mode of inheritance. The precise incidence is unknown, but from our recent experience and from that of others it is more common than has been recognised.

Most males with ornithine carbamoyl transferase deficiency have little enzyme activity and are severely affected. They present with an overwhelming illness in the neonatal period and most will die despite vigorous treatment. In girls the severity of the illness is very variable even within one kindred. The most severely affected present in the first year of life with persistent vomiting, developmental retardation and failure to thrive. During acute exacerbations neurological symptoms and signs such as headaches, irritability, ataxia, slurring of speech, alterations in consciousness and fits may predominate. The illness often has a rather characteristic fluctuating course with symptoms being aggravated by intercurrent infection or any stress that precipitates protein catabolism. Other patients have few symptoms but may still develop severe encephalopathy unexpectedly. Boys with some residual enzyme activity have been described with a presentation similar to that of females.

Plasma ammonium levels are variable depending on the age of the patient, the protein intake and the residual enzyme activity. In those with mild disease the plasma ammonium concentration may be normal. During severe encephalopathy the concentration usually, but not invariably, exceeds 300 µmol/l. In ornithine carbamoyl transferase deficiency there are no diagnostic abnormalities of the plasma amino acids, but in common with other urea cycle disorders the concentration of alanine and glutamine are often raised. As a result of the metabolic block there is an increased synthesis of pyrimidines and their precursors including orotic acid and the measurement of these compounds in the urine is a useful screening test for this disorder. Final confirmation of the diagnosis is made by measuring the ornithine carbamoyl transferase activity in liver or jejunal biopsy material. The most satisfactory currently available method for the detection of carriers is to measure orotic acid excretion in the urine after a standard protein load.

In this paper we describe seven patients with ornithine carbamoyl transferase deficiency who presented with an undiagnosed encephalopathy in whom we have observed considerable variation in the appearance of the computed tomographic (CT) scan of the brain.

Case 1

This girl, whose two brothers died of pulmonary haemorrhage in the neonatal period, was born normally at term. There were no neonatal problems, but she failed to thrive. At 9 months of age she had an episode of diarrhoea, vomiting and drowsiness which was thought to be due to encephalitis. She made a satisfactory recovery, but subsequently had many further attacks, during which she became drowsy, irritable and ataxic. Her developmen-
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Fig 1 Case 1 (a) plain CT. There is extensive symmetrical low density in the white matter of both cerebral hemispheres. (b) similar sections 1 month later. There has been considerable clearing of low density with slight enlargement of the lateral ventricles.

Tal progress had been normal up to the time of the first attack, but thereafter her development slowed. At two years and eight months she was referred to the Hospital for Sick Children. On examination she was small (height and weight less than the third percentile) and mentally retarded (approximately at an 18 month level), but otherwise the physical and neurological examination was unremarkable. Plasma ammonium, glutamine and alanine and urine orotic acid concentrations were elevated (table). CT on admission showed extensive bilateral symmetrical well defined low density of the white matter of the cerebral hemispheres, sparing the internal capsules (fig 1A). Since she has been treated she has had no further episodes of encephalopathy with hyperammonaemia. Repeat CT one month after the previous scan showed less extensive white matter low density. The lateral ventricles, though still normal in size, were slightly larger (fig 1B).

Comment Failure of thrive, retardation and vomiting with acute exacerbation is typical of ornithine carbamoyl transferase deficiency and the biochemical findings in the patient and her family were diagnostic. The CT appearances though not specific were consistent with a metabolic disorder. The history of episodic encephalopathy combined with her tolerance of marked hyperammonaemia suggests that the latter was longstanding and was responsible for the CT scan appearances.

Case 2
This girl was normal up to the age of 3 months when she began to have unexplained episodes of vomiting, drowsiness and abdominal pain. In one of these at the age of 5 years she lost consciousness and recovered spontaneously, but she had several further milder episodes. At the age of 7 she was admitted to hospital deeply comatose with fixed dilated pupils, papilloedema and decerebrate rigidity. CT showed diffuse low density in both cerebral hemispheres without abnormal enhancement (fig 2).
developed a left hemiparesis. CT scan showed symmetrical low density of the white matter involving only the periventricular region on the left side, but extending to the cortex on the right side (fig 3) with slightly abnormal enhancement peripherally in the right fronto-parietal region. Lumbar CSF and serological studies for virus infection were normal. When referred to the Hospital for Sick Children she was small, irritable and had a left hemiparesis. Her plasma ammonium was elevated (table) and investigations confirmed the presence of ornithine carbamoyl transferase deficiency. On treatment she has thrived and regained lost skills with resolution of all her focal neurological features. 

Comment The early history is typical of hyperammonaemia. The first scan at a time when she was not acutely ill, showed diffuse low density consistent with a metabolic disorder, but the second showed focal changes which are unusual in this condition.

Case 4

This girl was 14 days postmature following a pregnancy complicated by persistent hyperemesis. She weighed 2.6 kg and was apparently normal until 3 weeks of age when she became drowsy with occasional twitching of the lower limbs, culminating at 7 weeks in a series of focal convulsions. At 2 months when examined at the Hospital for Sick Children, she was a floppy, unresponsive baby with poor head control, brisk reflexes and bilateral ankle clonus. CT scan (fig 4A) showed extensive low density throughout the grey and white matter of both hemispheres without abnormal enhancement. There was atrophy of the basal ganglia and brain stem with enlargement of the ventricular system and basal cisterns. She had mild hyperammonaemia (36 to 133 μmol per litre) and a lactacidosis. No abnormal organic acids were detected in her urine and investigations for congenital infections were negative. By 6 months of age she had made no developmental progress. The plasma ammonium and urine orotic acid were raised (table) and ornithine carbamoyl transferase deficiency was confirmed by assay of enzyme activity in a liver biopsy. CT (fig 4B) showed increase in the diffuse atrophy which spared the cerebellum. At necropsy at 13 months the brain was

![Fig 2 Case 2 (a, b) CT after intravenous contrast injection. There is extensive symmetrical low density in both cerebral hemispheres. The lateral and 3rd ventricles are small.](https://example.com/image)

<table>
<thead>
<tr>
<th>Patient (age when ammonium first measured)</th>
<th>Sex</th>
<th>Initial plasma ammonium (μmol/l)</th>
<th>Orotic acid/creatinine ratio (μmol/mmol)</th>
<th>Liver enzymes (μmol/g/l)</th>
<th>Mother carrier status</th>
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<td>1 (2y 8m) F</td>
<td>520</td>
<td>615+</td>
<td>ND</td>
<td>OCT 385</td>
<td>+</td>
</tr>
<tr>
<td>2 (7y) F</td>
<td>414</td>
<td>600</td>
<td>CPS 176</td>
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<tr>
<td>3 (10m) F</td>
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<td>103+</td>
<td>CPS 343</td>
<td>?</td>
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<td>4 (10w) F</td>
<td>1st admission 36</td>
<td>13-9</td>
<td>CPS 154</td>
<td>+</td>
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<tr>
<td>5 (12y) M</td>
<td>2nd admission 275</td>
<td>23</td>
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<td>6 (9m) M</td>
<td>286</td>
<td>3-1</td>
<td>CPS 181</td>
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<tr>
<td>7 (12m) M</td>
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<td>CPS 209</td>
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<td>8 (13m) M</td>
<td>Maximum 2500+</td>
<td>695</td>
<td>CPS 271</td>
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<td></td>
<td>OCT 1244</td>
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<tr>
<td>10 (1yr) M</td>
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<td></td>
<td>OCT 233</td>
<td></td>
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<tr>
<td>11 (1yr) M</td>
<td></td>
<td></td>
<td>ASA Lyase 199</td>
<td></td>
<td></td>
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</tbody>
</table>

ND = not done
+ = carrier status proven by protein load.
? = normal response to protein load—carrier status uncertain.
* = full details in Levin et al.10
† = other pyrimidines, uridine and uracil visible in chromatogram

Reference values

| Plasma ammonium < 40 μmol/l | 2wk-1yr (1-0-3-2) |
| Urine orotic acid/creatinine ratio (μmol/mmol) (Harris and Oberholzer 1980) | 1-10yr (0-5-3-3) |
| Liver enzymes (μmol/g/h) | 10-yr (0-4-1-2) |

Enzyme activities

OCT = ornithine carbamoyl transferase > 4000 μmol/g/h
CPS = carbamoyl phosphate synthetase 70-550 μmol/g/h
ASA lyase = argininosuccinate lyase 54-188 μmol/g/h (values for specimens taken immediately post mortem)
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grossly shrunken with extensive destruction and cystic change (fig 4C). The neuropathology will be reported in detail elsewhere. (Harding B, Leonard JV, Erdohazi M, in preparation.)

Comment During the first admission the blood ammonia was not markedly elevated despite receiving a normal protein intake (2.5 kg per day) and she was thought to have a congenital lactic acidosis or alternatively a congenital infection. However, an excess of orotic acid was present in the urine and ornithine carbamoyl transferase deficiency was confirmed. The lactic acidosis was shown to be secondary to the fits and excessive muscle activity. The CT appearances already present at 10 weeks indicated extensive symmetrical brain damage and since the hyperammonaemia was apparently mild and the symptoms slight it seems probable that the changes in the brain were initiated in utero. Mother was shown to be a carrier with a low protein intake because of marked protein intolerance. She had had severe hyperamnios throughout pregnancy.

Case 5
This 12-year-old boy was admitted with a two day history of vomiting, irritability and deterioration in the level of consciousness. He had had episodes of vomiting and drowsiness during childhood illnesses from which he recovered spontaneously and his subsequent development was normal. On admission he was drowsy and confused without localising signs. The plasma ammonium, glutamine and alanine levels were elevated and enzyme studies on liver biopsy material confirmed ornithine carbamoyl transferase deficiency (table). CT was normal. During the first 24 hours the plasma ammonium fell from 286 to 186 μmol/l but his neurological condition deteriorated and then, despite the intensive treatment, the plasma ammonium rose rapidly and he died.

Comment Though this patient had developed normally and had few symptoms prior to the terminal illness the bouts of drowsiness and vomiting are suggestive of a urea cycle disorder. Even patients with apparently mild disease may develop severe encephalopathy and plasma ammonium levels are not a reliable prognostic guide.

Case 6
This boy's early clinical course has been previously reported. Following an episode of coma treated at the age of 6 months the diagnosis of ornithine carbamoyl transferase deficiency had been confirmed. On a low protein diet he thrived but his developmental progress was poor. At the age of 6 years his developmental quotient on several scales was between 40 and 60 and he remained severely retarded. At the age of 5 years he started having grand mal fits and during the next 8 years he had several hospital admissions for treatment of encephalopathy precipitated by infections. At the age of 13 he was admitted drowsy with ataxia and mild left hemiparesis. CT showed moderate cerebral atrophy and bilateral extracerebral fluid collections (fig 5A) which gradually resolved over 9 months with clinical improvement (fig 5B). At the age of 14½ years he died after an episode of protracted vomiting.

Comment This boy's early course is typical of hyperammonaemia, but the cause of his intellectual deterioration without obvious illness between the age of 2 and 5 years is unclear. Episodic hyperammonaemia could have been responsible for the cerebral damage that was manifest as cerebral atrophy and this predisposed to the development of subdural effusions.

Case 7
This boy was born spontaneously at 28 weeks gestation weighing 1.09 kg and was well until the 3rd day when he started having apnoeic attacks which did not need assisted ventilation. At the age of 24 days he developed Klebsiella pneumonia and meningitis with convulsions which were difficult to control. Necrotising enterocolitis requiring intravenous feeding followed after which oral feeds were reintroduced (SMA Wyeth). On this he began to thrive and made normal developmental progress until the age of 8 months when he became irritable and started vomiting. At the age of 7 months he was admitted for investigation of a suspected gastro-intestinal disorder. At the age of 1 year he was readmitted unconscious after more vomiting and a small haematoma. He had a left hemiplegia and his neurological condition rapidly deteriorated. CT showed slightly enlarged lateral ventricles, a normal fourth ventricle, but the third ventricle could not be seen. No intracranial subarachnoid spaces were seen. There was reduced density of the supratentorial grey and white matter and in the brain stem, but the cerebellar hemispheres were normal (fig 6). The plasma ammonium was 700 μmol/l and despite treatment it rose to 1464 μmol/l before death. The hepatic ornithine carbamoyl transferase deficiency activity of needle biopsy taken immediately after death was reduced (table). At necropsy there was diffuse brain swelling with transventorial and tonsillar herniation. Subsequent investigation revealed that the maternal grandmother, mother and sister were carriers and the

Fig 3 Case 3 Plain CT. There is extensive low density in the right frontal and parietal lobes and in the deep white matter in the left frontal lobe.
Fig 4  Case 4 (a) aged 2 months, plain scan. There is extensive symmetrical low density throughout both hemispheres sparing most of the central grey matter which appears unusually dense by comparison. The brain stem is atrophic. There is enlargement of the lateral ventricles and basal cisterns (b) aged 6 months, enhanced scan. There has been increase in the degree of diffuse cerebral atrophy (c) coronal slices of fixed brain. Lower figure showing surface of occipital poles with grossly shrunken gyri alternating with widened cystic ones. Upper figure shows the cross section of the shrunken and cystic gyri, enlarged posterior horns and lack of demarcation between grey and white matter except on the inferior medial surfaces.
ventricles can be explained by obstruction to the third ventricle causing biventricular hydrocephalus, but there could also have been cerebral atrophy that was only partly masked by the brain swelling.

**Discussion**

The appearances of the CT scans of the seven patients vary considerably but we suggest that they can be explained in terms of the duration and severity of the hyperammonaemia and the age of the patient.

Three patients were scanned during an episode of acute and fatal encephalopathy. Two patients (cases 2 and 7) being comatose at the time they were scanned. In one (case 2) CT demonstrated brain swelling with small ventricles and diffuse low density of the white matter. In the other (case 7) there was slight dilatation of the lateral ventricles but the third ventricle could not be seen. This child died the same day as the scan and brain swelling with tonsillar herniation was confirmed at necropsy. The changes are most likely to be due to acute hyperammonaemia causing cerebral oedema which is known to be present in such circumstances. The third patient (case 5) had an apparently normal scan, possibly because he was scanned before oedema developed. Two patients (cases 1 and 3) were scanned at a time when, although not well, they had no acute neurological disturbance. Both had previous episodes of encephalopathy and had high plasma ammonium concentrations on admission. From the clinical history we suspect that the plasma ammonium had been elevated for several months. In one child (case 1) the low density changes demonstrated in the white matter were at least partly reversible following treatment with a low protein diet. The other patient (case 3) developed a hemiparesis and subsequent CT scan showed a corresponding unilateral extension of the low density changes. Hemiparesis has been reported but the aetiology of this complication is not known. Vascular changes have not been noted at necropsy and angiography has not been described.

With more prolonged survival hyperammonaemia may cause cerebral atrophy. Case 6 was diagnosed at the age of 9 months and despite several attacks of acute encephalopathy he survived until the age of 14½ years. CT at the age of 13 years, undertaken because of increasing ataxia, showed marked cerebral atrophy and bilateral extracerebral collections of fluid. These could have been caused by mild trauma in the presence of cerebral atrophy that made him more vulnerable although an association with the hyperammonaemia cannot be discounted. This complication has been noted previously in a patient with citrullinaemia. An alternative explanation for the normal appearances of the scan of case 5 is that cerebral oedema was masked by atrophic changes likely to be present in a child of 12 years with this disorder. In Case 4 symptoms started at the age of 3 weeks and by

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**Fig 5** Case 6 (a) Aged 13 years. There is a high density extracerebral collection over the right cerebral hemisphere with a low density component posteriorly. There is a small low density subdural effusion over the posterior convexity of the left hemisphere. There is moderately severe cerebral atrophy. (b) Aged 13 years 9 months. There has been considerable resolution of the extracerebral collections but the cerebral atrophy is more marked.

**Fig 6** Case 7 Aged 1 yr. The lateral ventricles are slightly enlarged, but the 3rd ventricle and subarachnoid spaces are not visible. There is diffuse low density throughout the brain substance.

brother had died of an encephalopathic illness aged 3 months.

**Comment** The early course of this boy's illness was masked by prematurity and infection and characteristic symptoms did not start until the age of 8 months. CT showed the brain swelling which was present at necropsy. The dilatation of the lateral
the age of 10 weeks there was diffuse symmetrical cystic changes which became more extensive during the next 4 months. The necropsy confirmed the severe nature of the brain damage which was similar to that previously reported. We suggest that changes of this severity could not have developed solely post-natally and probably the mother was hyperammonaemic during her pregnancy despite her low protein intake and that this may have been responsible for a prenatal insult.

We conclude that acute severe hyperammonaemia may cause cerebral oedema, but over longer periods of time chronic elevation of plasma ammonia leads to changes in the grey and white matter of the brain that is not necessarily symmetrical. This will eventually cause cerebral atrophy. The immature brain may be particularly vulnerable to the toxic effects of ammonia as it is to other toxic agents.

Acute encephalopathy in childhood may be caused by a wide variety of agents including infections, vascular disorders, cerebral tumours, drug intoxication and poisoning, as well as many metabolic disorders. Hyperammonaemia is just one cause, but as is demonstrated in the clinical histories, it is still underdiagnosed. We would emphasise the importance of measuring the plasma ammonium in all children with an acute encephalopathy even if the scan demonstrates a focal lesion. If the ammonium concentration is raised it is still necessary to identify the cause.

The differential diagnosis includes not only disorders of the urea cycle but Reye's syndrome, inborn errors of amino acid, organic acid and of carnitine metabolism, sodium valproate therapy and even urinary tract infections. Regardless of the cause once a child has symptoms due to acute hyperammonaemia urgent treatment is indicated to reduce plasma ammonium concentrations and to prevent or control cerebral oedema.

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References

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