ORIGINAL ARTICLE

Neurological outcome of patients with ornithine carbamoyltransferase deficiency

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Background: Ornithine carbamoyltransferase (OCT) deficiency is the commonest of the inherited urea cycle disorders.
Aims: To determine the long term neurological and cognitive outcome of continuously treated surviving patients.
Methods: Twenty eight surviving children (five boys) with OCT deficiency who had been treated continuously with a low protein diet and alternative pathway therapy were identified. Those aged 5–16 years had a detailed neurological examination and psychometric testing.
Results: Four presented in the neonatal period and four were treated prospectively following antenatal diagnosis. Median (range) age at diagnosis for the later onset group was 19 (2–144) months; median time between onset of symptoms and diagnosis was 10 (2–48) months. Nine children had had less than three episodes of hyperammonaemic encephalopathy, the others more. Seven had focal abnormalities on neurological examination; 14 had global cognitive impairment; four had a normal IQ but specific learning difficulties. Sixteen underwent neuroimaging which was normal in three, showed focal abnormalities of the cerebral hemispheres in six, and global cerebral atrophy in seven.
Conclusion: Eighteen of 28 surviving children with OCT deficiency had disabling neurological complications. Plasma ammonia at diagnosis was the only factor that predicted this outcome. While most neurological complications could be attributed to hyperammonaemic encephalopathy, other mechanisms may also contribute to the neurological abnormalities.

Ornithine carbamoyltransferase (OCT) deficiency is the most common urea cycle disorder.[1] The gene encoding OCT is located on Xp2.1; the enzyme is expressed in the liver and the gut, but the major complications are neurological.

Affected hemizygous males usually present in the neonatal period with severe hyperammonaemic encephalopathy that is often fatal despite vigorous treatment. As a result of lyonisation the clinical phenotype in heterozygote females is variable, even within one kindred. The most severely affected females present in the first year of life, some in the neonatal period, with persistent vomiting, developmental delay, and failure to thrive. During acute exacerbations neurological symptoms such as headaches, irritability, ataxia, and alterations in consciousness predominate. The illness has a characteristic fluctuating course with symptoms being aggravated by intercurrent infection or any other stress factor that precipitates protein catabolism. Some patients have few symptoms but may still develop severe encephalopathy unexpectedly.[2 3] Affected males who have residual enzyme activity usually present later in life in a similar way to the females.[4]

Biochemically, OCT deficiency impairs synthesis of citrulline, arginine, and urea which leads to accumulation of nitrogen as ammonium, alanine, and glutamine and the diversion of carbamoyl phosphate into pyrimidine synthesis via orotic acid (fig 1[1]). The principles of treatment of OCT deficiency are dietary protein restriction, arginine supplementation, and the diversion of nitrogen excretion via alternate pathways.

Relatively little is known about the long term neurological and cognitive outcome of continuously treated OCT deficiency. Boys with neonatal onset of the disorder do badly, with a poor cognitive outcome and a high frequency of neurological complications.[5] Girls also have a poor outcome, with cognitive disability reported in 20–40%.[6] Here we report the long term neurological and cognitive outcome of continuously treated surviving patients managed at one centre.

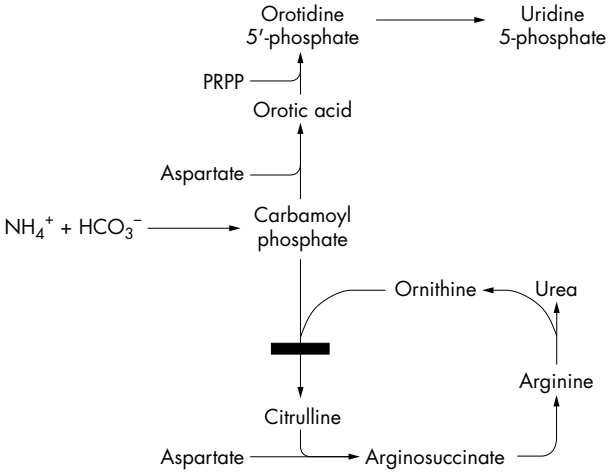

Figure 1 The urea cycle and the uridine synthesis pathways. PRPP, phosphoribosyl pyrophosphate. Solid block shows the site of the missing enzyme in OCT deficiency.

PATIENTS AND METHODS

All surviving children with OCT deficiency diagnosed and managed at one centre since 1977 were identified. Patients who were seen for review alone and those living abroad were not included. The diagnosis was suspected by finding hyperammonaemia, reduced plasma concentrations of citrulline and arginine, and increased urinary excretion of orotic acid. The diagnosis was confirmed by measurement of hepatic OCT activity or, more recently, by mutation analysis. All had

Abbreviations: OCT, ornithine carbamoyltransferase

Table 1 Cognitive and neurological outcome of OCT deficiency

	Neurological outcome			
Cognitive outcome	Normal	Abnormal neuroimaging, no focal signs	Abnormal neuroimaging, focal signs	Total
Normal	8	2	0	10 (6)
Specific LD	2	0	2	4 (4)
Moderate LD	3	2	3	8 (7)
Severe LD	2	2	2	6 (6)
Total	15 (11)	6 (5)	7 (7)	28 (23)

The neurological findings (columns) are subdivided into groups: normal where there was neither neuroimaging abnormality nor focal neurological signs; abnormal neuroimaging but no focal neurological signs; and abnormal imaging with focal neurological signs.
The cognitive outcome (rows) was also subdivided into groups: normal where IQ was >70; specific learning difficulties where IQ was >70 but specific difficulties were found; and moderate and severe global learning difficulties (LD). Figures in brackets show the number of girls.

been continuously treated with dietary protein restriction, supplementation with arginine, and alternate pathway therapy utilising sodium benzoate and sodium phenylbutyrate. The aim of treatment was to maintain plasma glutamine concentration at less than 1000 μM with normal growth. Those aged between 5 and 16 years were seen for a neurological examination and cognitive assessment; others had their case notes reviewed.

Cognitive assessment was based on the WISC-III.[7] If the cognitive profile on the WISC-III was uneven or when there was a history of difficulties at school and the measured IQ was normal, further tests of attainment (WORD, WOND),[8 9] memory,[10] and executive function (Stroop, Wisconsin card sort, and Chicago word fluency)[11–13] were administered. Children were classified as having moderate (IQ 50–70), severe (IQ <50), and specific learning difficulties.

Hyperammonaemic encephalopathy was defined as an episode of impaired consciousness with a plasma ammonia concentration greater than 100 μM.

Factors that might affect the outcome of OCT were determined from the history and case note review. Continuous data were transformed to normalise distributions. For univariate analyses, categorical data were compared using Fisher's exact test and groups were compared using Student's *t* test. The multivariate analysis used logistic regression.

RESULTS

Twenty eight children (five boys, 23 girls) with OCT deficiency were assessed. Four presented in the neonatal period (three girls) and four were treated prospectively from birth after prenatal diagnosis (three girls). Twenty children had later onset disease (three boys and 17 girls). Median age at diagnosis for the later onset group was 19 (range 2–144) months; median time between onset of symptoms and diagnosis was 10 (range 2–48) months. In the entire later onset group, the diagnosis was established following one or more episodes of hyperammonaemic encephalopathy. In the prospectively treated children, two (one girl) had no episodes of hyperammonaemic encephalopathy. Overall, nine children had three or less episodes of hyperammonaemic encephalopathy, the others more than three.

Table 1 presents the neurological outcome of OCT deficiency. Eighteen children (64%; 17 girls) had learning difficulties with or without a focal neurological abnormality. Seven (25%; all girls) had residual focal abnormalities on neurological examination: two had spastic quadriparesis, four mixed dystonic/spastic hemiplegia, and one spastic diplegia. Fourteen (50%; 13 girls) had global cognitive impairment (moderate in eight and severe in six). Four (14%; all girls) had a normal IQ but specific learning difficulties (dyslexia in two, deficits in executive function in two). Sixteen underwent neuroimaging (either computed tomography or magnetic resonance imaging of the brain) which was normal in three, showed focal abnormalities of the cerebral hemispheres in six, and global cerebral atrophy in seven. Eight of the 20 children with late onset (outside the neonatal period) OCT deficiency were neurologically and cognitively normal. Three of the four prospectively treated children were normal; the other girl, who had not had an episode of hyperammonaemic encephalopathy, had a specific deficit in executive function.

In order to explore the relation between neurological and cognitive outcome, these were each divided into two groups: normal and abnormal. After constructing a 2×2 table, a significant association of focal neurological signs with learning difficulties was found (Fisher's exact test $p = 0.03$); indeed, no child with focal neurological signs had a normal cognitive outcome. In order to explore clinical determinants of outcome, two further outcome groups were defined: normal and abnormal (children with focal neurological signs, learning difficulties, or both). In a univariate analysis, no significant differences were found between the two outcome groups for age at diagnosis (geometric mean difference between the outcome groups 1.4 months, $p = 0.58$), delay between onset of symptoms and diagnosis (geometric mean difference 1.2 months, $p = 0.97$), and the proportion with more than three episodes of hyperammonaemic encephalopathy ($p = 0.13$). Significant differences were found for plasma ammonia concentration at diagnosis (geometric mean difference between the outcome groups 0.43 μM, $p = 0.017$) and urine orotate excretion at diagnosis (geometric mean difference 0.071 mmol/mol creatinine, $p = 0.049$). When plasma ammonia concentration and urinary orotate excretion were entered as covariates into a backward stepwise logistic regression model, only plasma ammonia concentration at diagnosis was a significant predictor of outcome ($p = 0.047$).

DISCUSSION

In this series, over 60% of surviving children with OCT deficiency, treated continuously with dietary protein restriction, arginine, and alternate pathway therapy, had disabling neurological complications. This is a higher prevalence than previous series,[6 14 15] except for those patients that present in the neonatal period.[5] We found a high prevalence of specific learning deficits in OCT deficiency. This may account for the higher incidence of neurological complications, because specific learning difficulties may only become apparent in older children and may be overlooked if the IQ is found to be normal. Suspicion of specific learning deficits may be raised by unevenness of the subtest profile on IQ testing, but diagnosis requires further testing of attainments and higher cognitive function. The prevalence of specific learning difficulties in the normal child population is 6%,[16] which is less than half the prevalence found here. Furthermore, clinical experience suggests that specific deficits in executive function are very rare except in the context of specific disorders such as traumatic brain injury. This suggests that specific learning difficulties are a complication of OCT deficiency. Like others,[17]

we found that prospectively treated children had a better outcome. However, one prospectively treated girl had developed disabling symptoms (such as an inability to structure her day) of a deficit in executive function in early adolescence.

Overall, 25% of this series of children surviving OCT deficiency had one or more focal neurological deficits. The presentation of OCT deficiency as stroke like episodes is well recognised,[2 18–22] although such a high prevalence of residual focal defects has not previously been described.

The neurological complications of OCT deficiency may be caused by the accumulation of glutamine, causing cerebral oedema during an episode of hyperammonaemic encephalopathy.[1] However, there are several lines of evidence which suggest that this might not be the sole mechanism. We found here that whether a child had more than three episodes of hyperammonaemic encephalopathy or not was not a significant predictor of outcome. Furthermore, of the two prospectively treated children who had never had hyperammonaemic encephalopathy, one child developed specific difficulties with executive function that localised to the left orbitofrontal lobe. Six children with more than three episodes of hyperammonaemic encephalopathy had a normal outcome. We have previously shown that glutamine accumulates in each cerebral hemisphere to a comparable degree during hyperammonaemic encephalopathy, but that oedema was confined to a single cerebral hemisphere.[21] We have also found that parents recognise subtle signs of metabolic disturbance (for example, irritability without acute illness) in their children with OCT. This improves rapidly with an increase in their medication,[23] and is unlikely to be caused by cerebral oedema. Lastly, we found that plasma ammonia concentration at presentation predicted outcome, confirming a previous finding.[15] Ammonia is known to have many different effects on the brain that are not mutually exclusive,[24] and more subtle effects than glutamine accumulation with cerebral oedema might be responsible for some of the neurological symptoms.

In conclusion, 60% of surviving, continuously treated children with OCT deficiency had disabling neurological complications. While hyperammonaemic encephalopathy can cause structural brain damage, it is possible that more subtle effects of hyperammonaemia may also contribute to the neurological complications. Early diagnosis and treatment of OCT deficiency remains important.

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