Short report

Familial lysinuric protein intolerance presenting as coma in two adult siblings

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SUMMARY Lysinuric protein intolerance (LPI) is an inborn error of metabolism which usually presents in infancy with failure to thrive and vomiting. Two patients are described who presented in adult life with hyperammonaemic coma due to LPI. Both had been underweight and had had intermittent gastrointestinal symptoms during childhood. They were of normal intellect and had maintained good health, until presentation in their thirties, by unconscious dietary protein avoidance. The diagnosis of LPI should be considered in patients who present with obscure relapsing coma associated with hyperammonaemia. Considerable clinical improvement may result from dietary protein restriction and citrulline supplementation.

Lysinuric protein intolerance (LPI) is an autosomal recessive disorder of dibasic amino acid transport which was first described by Perheentupa and Visa-korpi in 1965.¹ Renal tubular and intestinal transport of dibasic amino acids is deficient resulting in renal hyperdiaminoaciduria, especially lysinuria, and in subnormal plasma levels of arginine, ornithine and lysine.² In addition, urea cycle operation is defective and marked hyperammonaemia occurs after protein ingestion.³

More than half of the reported cases have come from Finland, where the incidence of the disease is estimated to be 1 in 60 000 to 80 000 live births.⁴ Cases have been reported from elsewhere including Ireland,⁵ Canada,⁶ and North America,⁷ but there have been no previous reports from Britain.

Typically the disorder presents in infancy with protein intolerance, manifested by feeding difficulties, vomiting, diarrhoea and poor growth. Post-prandial hyperammonaemia produces episodes of lethargy, convulsions or coma and patients consequently develop an aversion to protein-rich foods. Other features may include mental retardation, hepato-

splenomegaly, short stature, muscle weakness, lens opacities, hyperelastic skin, hyperextensible joints and osteoporosis.⁴ Initial presentation in adult life is uncommon and may be overlooked.^{8–11}

We describe two brothers who presented in their thirties with coma of obscure origin, due to this inborn error of metabolism.

Case reports

Case 1 The patient was a 36 year old Cumbrian man who was self employed in a fruit-transport business. He was transferred to the neurology department for investigation of relapsing coma. He had been unwell for several weeks with lassitude, anorexia, intermittent lower abdominal pain and weight loss of about 6.5 kg. On the day of admission to his local hospital he had begun to feel unwell a short time after eating chicken for lunch. During the afternoon he had developed abdominal pain and vomiting, and by evening had become confused and drowsy. His level of consciousness progressively deteriorated and he was referred to hospital in coma. During childhood he had always been regarded as underweight and malnourished. He had been hospitalised at the age of 7 years for investigation, but no definite cause had been established.

On admission to hospital he was unconscious but flexed all 4 limbs to painful stimuli. He was afebrile and there was no meningism. He was observed to have Kussmaul respiration, but no other general medical abnormalities were observed. There was generalised hyperreflexia without any other abnormal neurological signs. Initial laboratory investiga-

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tions, including CSF examination and toxicology screen, failed to reveal a cause for the coma and the patient was observed. Within a few hours his conscious level had improved though he remained confused and agitated. However, within 24 hours he again lapsed into unconsciousness and he was transferred to our unit for neurological assessment.

Examination at the time of transfer revealed that he was pale and thin and looked generally unwell. He was mildly confused, drowsy and unable to give a clear history. There was a degree of hyperventilation and mild splenic enlargement but no other abnormalities on general examination. On neurological examination he was noted to have slight dysarthria, hypertonicity of both lower limbs with 10 beats of clonus at the ankles, generalised hyperreflexia but flexor plantar responses.

Laboratory investigations There was a mild normochromic, normocytic anaemia with a haemoglobin of 11.3 g/dl; the erythrocyte sedimentation rate and blood glucose were normal. Plasma urea was at the lower end of normal 2.8–3.3 mmol/l and the bicarbonate varied from 11 to 18 mmol/l; the sodium, potassium and creatinine were normal. Arterial pH varied from 7.28 to 7.51. The serum proteins were low, the total protein being 46 g/l (clinical reference range: 62–79) with an albumin level of 30 g/l (39–51). Plasma ammonia levels were considerably elevated on several occasions, with values up to 10 times the upper limit of normal. The remaining liver function tests and serum calcium were normal. There was no abnormal porphyrinuria. Electrocardiogram and chest radiograph were unremarkable; auto-antibodies were negative; the IgG level was low at 4.39 g/l (6–16) but the other immunoglobulins were normal. Plasma lactate, pyruvate and oxalate were normal as was the lactate/pyruvate ratio. Gastroduodenoscopy, jejunal biopsy and barium follow-through showed no abnormality. Ultrasound scan of the abdomen showed enlargement of the liver and spleen. Isotope liver scan showed good uptake in an enlarged liver. An initial electroencephalogram showed diffuse slow wave activity compatible with a metabolic encephalopathy. Eight days later the record was normal and alpha dominant. Estimation of 24 hour urinary amino acids showed an increased excretion of lysine of 4114 μ mol (0–590) and of ornithine 577 μ mol (0–44). The urinary arginine output was at the upper limit of normal, 58 μ mol/24 h (0–60). Plasma levels of these amino acids were low: lysine 52 μ mol/l (120–240); ornithine 16 μ mol/l (30–150); arginine was undetectable. An oral alanine challenge test, with 240 mmol of L-alanine, produced a rise in plasma ammonia from 24 μ mol/l to 235 μ mol/l (11–35). Citrulline supplementation of 1 gm four times daily prior to a second alanine load resulted in considerable amelioration of the hyperammonaemia (see figure).

After the diagnosis of lysinuric protein intolerance had been established a more detailed enquiry was made into the patient's dietary habits. He had lived on a farm all his life, but did not enjoy the same foods as the rest of the family. In particular he avoided lean meat, cheese, milk and eggs. If he ate appreciable amounts of protein he would feel nauseated and unwell for several hours afterwards. He particularly liked tomatoes and would consume several kilograms each week. Immediately prior to the onset of his presenting illness he had lost his fruit-transport business as the result of financial

Fig Plasma ammonia levels in case 1.

difficulties and no longer had such ready access to the large quantities of fruit and vegetables to which he was accustomed. No doubt this enforced modification of his dietary habits, resulting in greater consumption of protein, precipitated his presentation.

We were unable to elicit any family history of similar symptoms and on direct questioning his parents and 3 siblings were reported to be well.

The patient was advised to take 40 g of protein per day and was prescribed citrulline 1 gm with each meal. Within a few weeks he had gained 10 kilograms in weight and his haemoglobin and serum protein levels had improved to within the normal range. During 25 months of follow-up he had had no further episodes of nausea, abdominal pain or impairment of consciousness.

Case 2 The 32 year old brother of the first patient presented 9 months later. He was a farm worker and had been unwell for 3 weeks with intermittent nausea, anorexia and upper abdominal pain. On the evening of admission he had eaten fish and shortly afterwards became drowsy and ataxic. On arrival at hospital he was unconscious but flexed all four limbs to painful stimuli. There were 6 beats of clonus at both ankles and generally brisk reflexes, but no other abnormal physical signs. According to his mother the patient, as a child, had avoided eating eggs and meat. However, since leaving school he no longer avoided these. He had always been small and thin as a child, though less so than his older brother. At the age of 10 he had been admitted to hospital for several weeks with abdominal pain and nausea, for which no cause was established.

Investigations The haemoglobin was 11.9 g/dl with normal indices. The plasma urea was low at 1.5 mmol/l; the creatinine and electrolytes were normal. The alkaline phosphatase was above the 75th centile for his age-group at 123 u/l; the serum proteins were low: total protein 51 g/l (reference range: 62–79), albumin 27 g/l (39–51). The plasma ammonia level 24 hours after the onset of the drowsiness was 138 μ mol/l (11–35), falling over the next 48 hours to 39 μ mol/l. The initial electroencephalogram showed diffuse slowing compatible with a generalised cortical disturbance. Six days later there was marked improvement, the only abnormality being a marginally slow dominant rhythm. Ultrasound scan of the abdomen and isotope liver scan showed moderate hepatosplenomegaly. Liver biopsy showed enlargement of hepatocytes, most marked in acinar zones 1 and 2. Cell membranes were thickened and there was a tendency towards a mosaic pattern without sinusoidal compression. There was no excess accumulation of lipid or glycogen and no iron deposition or cholestasis. Upper gastrointestinal endoscopy was normal. The 24 hour urinary lysine excretion at 5861 μ mol was 10 times the upper limit of normal, while the levels of ornithine 83 μ mol (0–44) and arginine 90 μ mol (0–60) were mildly increased. The plasma lysine level was subnormal at 99 μ mol/l (120–240), the other plasma amino acids were within the normal reference range.

The patient was advised to take up 40 gm per day of protein and was given citrulline supplementation 1 gm four times daily. He has remained well during 15 months of follow-up.

Discussion

The neurological dysfunction in lysinuric protein intolerance is related to the postprandial hyperammonaemia although the precise cause of the high plasma ammonia levels remains uncertain. Despite the fact that no abnormality of urea cycle enzymes has been identified in LPI,³ the rate of urea production is impaired. It has been suggested that this may be due to a lack of ornithine in the liver cell.¹² Simell found evidence of impaired uptake of diamino acids into hepatocytes and decreased metabolic clearance rates of arginine and ornithine from plasma.¹³ Subsequent in vitro studies revealed defective uptake of the non-metabolised analogue homoarginine by liver slices.¹⁴ Rajantie, Simell and Perheentupa showed that the concentrations of diamino acids and citrulline in the liver of patients with LPI were normal or increased.¹⁵ They put forward the hypothesis that in the affected hepatocytes a transport defect located in the basolateral cell membrane and in the mitochondrial membrane causes diamino acids to accumulate in cytoplasm since both the exit from the cell and transport into the mitochondria are impaired. However, since ornithine is necessary for the synthesis of urea, intramitochondrial depletion interrupts the urea cycle and results in hyperammonaemia.

Citrulline, which is metabolised to arginine and

ornithine, is absorbed by a mechanism which is unaffected in LPI. When administered therapeutically it appears to result in improved urea cycle function and amelioration of the postprandial rise of plasma ammonia.

Reports of LPI presenting for the first time in adult life are rare. Although one of the 19 patients in the series of Rajantie *et al* had reached the age of 22 years when diagnosed,⁹ other reported cases have been no older than their late teens.^{10,11} Kekomaki and colleagues described an 18 year old who became unwell after changes in his diet had been enforced by his family.⁸ This patient developed recurrent attacks of stupor and suffered intellectual damage before the diagnosis was made.

Our cases have some unusual features. Although both had had problems in childhood which, with the benefit of hindsight, were attributable to LPI, they had reached their thirties uneventfully before the condition had become clinically apparent. Clearly they had both managed to keep themselves in relatively good health by unconsciously avoiding dietary protein. It has been suggested that the prevalence of the condition may be higher than the small number of reported cases appears to indicate.¹⁶ Our experience lends some support to this view, suggesting that individuals may be unaware of the condition, considering their unusual diet to be nothing more than a food-fad. The diagnosis of LPI should certainly be considered in patients presenting with recurrent coma of obscure origin. The plasma ammonia level should be checked and a dietary history obtained in all such patients. It is important that the disorder is recognised because dietary protein restriction, perhaps with citrulline supplementation, can bring about considerable clinical improvement.

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