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Dietary treatment of hyperlysinaemia

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SUMMARY We describe the lysine restricted, dietary management of three out of four siblings who were identified as having hyperlysinaemia. The diets, started in the neonatal period, were maintained for varying periods with unpredictable success. The propositus, who was not treated, was diagnosed at the age of 5 years, by which time he was already severely handicapped, presumably because of his metabolic disorder. Tentative recommendations are put forward for the management of this seemingly rare disorder. Mild chronic ammonia toxicity may be a factor in the pathogenesis of this condition.

The importance of hyperlysinaemia as a direct or indirect cause of neurological damage and mental retardation is open to dispute. Previous reports provide conflicting data,[1–5] and while not stating unequivocally that hyperlysinaemia is entirely benign more recent evidence, from a large review of 10 cases identified by neonatal screening programmes or family surveys, suggests that the relationship is coincidental.[6] It has also been stated that there is no evidence supporting the use of a low protein diet to reduce plasma lysine concentrations.

We report the dietary management, by lysine restriction, of three affected siblings in a Pakistani family, in which the propositus was found to have hyperlysinaemia during investigations for profound mental and physical handicap. The development of these children has been carefully monitored during periods on and off treatment.

Subjects and methods

The family tree is shown in fig 1. The parents are first cousins. The propositus, K, was born in Pakistan as were his two elder siblings, both of whom died in early infancy, the first of a chest infection and the second after recurrent convulsions. His birth was said to have been normal but from the age of 2 months he developed convulsions, although he does not seem to suffer from them now. He presented to us at the age of 5 years with severe mental and physical handicap, being unable to walk unsupported or talk and, on clinical examination, had a developmental age of 10 months. He was thin and underweight with no dysmorphic features. He had a moderate increase in adductor muscle tone and hyper-reflexia in both legs. His hearing was thought to be normal but he had poor vision. No possible cause for his retardation other than hyperlysinaemia was found on investigation. He was not treated with a diet and subsequently showed no clinical improvement (table 1). Unfortunately he developed bilateral massive retinal detachment, which was confirmed by pathological examination after enucleation of one eye because of a suspected but disproved tumour. Recently, computed tomography has shown low density changes in the white matter of the cerebrum suggestive of demyelination. There was also evidence of mild shrinkage of the cerebellum and brain stem.

Three of the remaining four younger siblings, all of whom were born in the United Kingdom, were shown by screening soon after birth to have hyperlysinaemia. Thereafter, they were treated with a lysine restricted diet in an effort to prevent neurological sequelae. Their developmental progress was very carefully monitored by one of us (NB), using

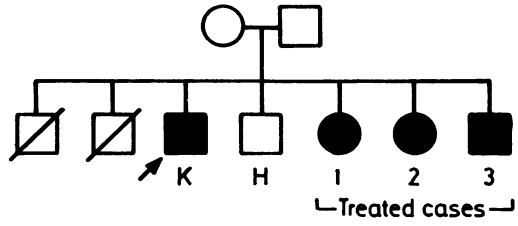

Fig 1 *Family pedigree. K is the propositus; his brother, H, had no evidence of hyperlysinaemia. The two older siblings died in early infancy.*

Table 1 *Griffiths's psychometric assessment of propositus and his affected siblings*

Case No	*Chronological age (months)*	*Griffiths's mental age (months)*	*Griffiths's intelligence quotient*
Propositus	126·0	9·5	30·0
Case 1	19·0	19·8	104·0
	21·0	21·5	102·0
	22·0	23·0	104·5
	24·0	24·1	100·4
Case 2	2·5	3·7	148·0
	7·5	9·5	125·0
	14·5	16·0	114·3
	17·0	17·9	105·3
	20·0	17·9	89·5
Case 3	5·0	5·0	100·0

the Griffiths's scale of mental development. This surveillance was continued after the low lysine diets were discontinued. The fourth child, H, was not shown to have evidence of hyperlysinaemia, after repeated plasma amino acid analyses up to the age of 7 months, and has subsequently made normal developmental progress.

The diagnosis of hyperlysinaemia in the propositus was made after detailed biochemical studies that have been reported by Gray *et al.*[7] Plasma lysine concentration was greatly raised and was shown by in vitro studies in fibroblasts to be caused by a deficiency of lysine oxidation.[7]

In this study fasting plasma lysine concentrations were monitored in the affected siblings by the methods reported above. At the same time plasma ammonia concentrations were also monitored by a standard enzymatic method based on the reductive amination of α-ketoglutarate using glutamate dehydrogenase and reduced nicotinamide adenine dinucleotide.

The low lysine diets were constructed by following the principles used in the management of other amino acid disorders. A lysine free amino acid mix (Scientific Hospital Supplies) was used to provide the equivalent of 3 g of protein/kg of body weight/day, during the first year of life. Lysine was provided in the form of small measured amounts of standard formula baby milk. Initially 88 mg of lysine/kg of body weight/day was permitted, this being the lower limit of theoretical requirement for a normal infant. Energy requirements were ensured by the addition of glucose polymers and fat emulsion. This mixture was supplemented with vitamins (three Ketovite tablets and 5 ml Ketovite liquid per day, Paines and Byrne), minerals, and trace elements (Aminogran Mineral Mix, Allen and Hanbury).

As lysine occurs in all proteins, the provision of a weaning diet presented difficulties. All protein rich baby foods and solids were avoided and the bulk of protein requirements continued to be provided by the lysine free amino acid mix. To this were added controlled amounts of low protein foods such as rice and potatoes, which contain known amounts of lysine.[8] Foods containing very small amounts of protein such as fruit were allowed freely. Energy intake was maintained by the addition of low protein bread and biscuits. In the latter half of the first year of life and thereafter, in an effort to promote tighter control of plasma lysine concentrations, it was found possible to reduce the dietary intake of lysine to as little as 40 mg/kg of body weight/day.

Results

CASE 1

This girl was born at term after an uneventful pregnancy and delivery. She was diagnosed at the age of 4 days and a low protein diet from 2 weeks of age, followed by a low lysine diet from 7 weeks of age started. Variations in the low lysine diet and corresponding plasma lysine concentrations are shown in fig 2. Mean ammonia concentrations compared with cases 2 and 3 are shown in table 2. Her diet was formally stopped at the age of 22 months after the birth of her younger sister (case 2). The subsequent rise in plasma lysine concentrations to seven to eight times the normal range confirmed that, to a certain degree, the low lysine diet had been adhered to at home.

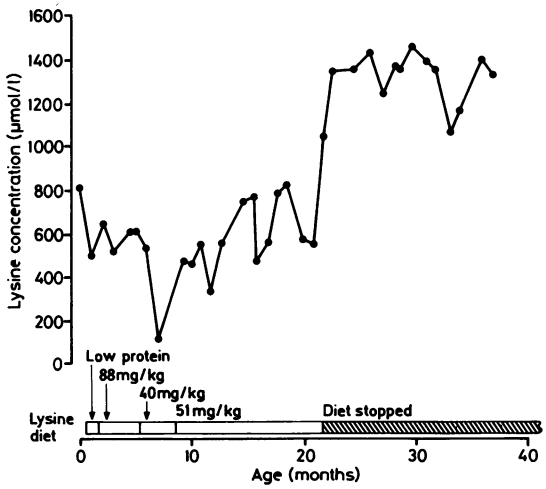

Fig 2 *Case 1: diet and monthly plasma lysine concentrations (normal range at >4 months of age, 45–150 μmol/l).*

Table 2 *Mean plasma ammonia concentrations in the three affected siblings*

Case No	*Mean (SD) ammonia concentration (μmol/l)*	*No of estimations*
1	52·9 (21·9)	81
2	70·3 (52·1)	48
3	63·7 (15·0)	11

Her developmental progress as measured on the Griffiths's scale has been and remains satisfactory (table 1). Her performance on items requiring speech was below average—this was mainly due to her language difficulties experienced as a result of being reared in a mixed language environment. Her growth has been normal, with height and weight on the 50th centile. A computed tomogram at the age of 3 years and 4 months showed no abnormality. She remains well after being on a normal diet for 20 months.

CASE 2

This girl also had an unremarkable perinatal history. She was diagnosed and started on a low lysine diet at 2 weeks of age. Variations in the diet and plasma lysine concentrations are shown in fig 3. Despite plasma lysine concentrations four times the normal range, formal psychometric assessment at 17 months of age confirmed the clinical impression of normality (table 1) and so the diet was stopped on a trial basis. After three months off the diet, however, there was evidence of deterioration of locomotor skills, lack of progress in cognitive skills (table 1), and clinical assessment showed signs of an early spastic diplegia. The diet was recommenced which resulted in a 75% drop in plasma lysine concentrations. A computed tomogram showed evidence of a patchy demyelination of the pons. Resumption of the diet has not yet resulted in her regaining her lost locomotor skills.

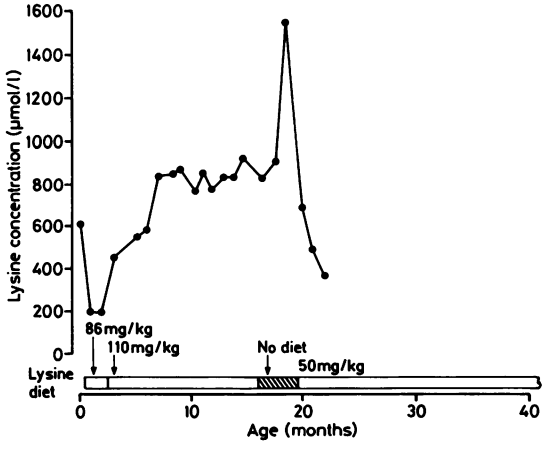

Fig 3 *Case 2: diet and monthly plasma lysine concentrations (normal range at >4 months of age, 45–150 μmol/l).*

So far there appears to have been no deleterious effect on her intellectual development. Although the Griffiths's intelligence quotient scores in table 1 show a steady decline over the five assessments, this decline was wholly accounted for by language difficulties up to the age of 17 months when the diet was discontinued. Her scores on the hearing and speech subtest showed a similar pattern to her sister (case 1). The final Griffiths's score reported was severely affected by loss of locomotor skills. She made fewer gains than on previous occasions on the cognitive subtests but her performance remained within the normal range. Her growth has been unaffected with height and weight increasing steadily along the 25th centile.

CASE 3

This boy was also diagnosed as having hyperlysinaemia at 5 days of age after a normal, term delivery. Since being on a low lysine diet from 1 week of age, developmental assessment at 5 months of age shows him to be within the normal range. His plasma lysine concentrations have also climbed to nearly four times normal. Recently his lysine intake was reduced from 88 to 45 mg/kg of body weight/day after the discovery of low density areas on computed tomography; this suggests the possibility of some pontine atrophy. Thus far he has no neurological signs and in particular his muscle tone and tendon reflexes are normal.

Discussion

Doubt exists as to whether persistent hyperlysinaemia can itself produce adverse neurological or physical effects.[1–5] Nevertheless, because of the possible causal relation between the hyperlysinaemia and neurological abnormalities in the index case K, we have closely and continuously monitored the progress of the other three affected children.

Interpretation of our recorded plasma lysine concentrations is very difficult because of considerable variation in values, almost all of which are very much above the range for normal children. Case 1 appears to show beyond doubt that exceedingly high concentrations up 1500 μmol/l can be tolerated with no apparent ill effect for a year or more. It might, however, be relevant that this child was only exposed to these persistently high concentrations after the process of brain myelination was com-

pleted at about the age of 2 years. It must also be remembered that the deterioration of motor skills and the appearance of abnormal physical signs in case 2 occurred only after she had been exposed to such high concentrations at the earlier age of 15 months—that is, theoretically before brain myelination had been completed (fig 3). These observations must also be compared with our experience of case 3. He already showed some suggestion of demyelination at the age of 7 months, even though his plasma lysine concentrations did not exceed 1000 μmol/l.

It has been suggested that neurological impairment might be produced by exposure to long term, low level ammonia intoxication.[7] In the propositus, although there was no postprandial increase in ammonia concentrations, raised concentrations of about 80 μmol/l were recorded before and after eating (normal less than 47 μmol/l). Standardised fasting ammonia concentrations have therefore been recorded in the other three affected children. Our data (table 2) suggest that ammonia concentrations may be of significance as both cases 2 and 3 have higher mean plasma ammonia concentrations than the unaffected case 1. The difference between cases 1 and 2 is significant ($t=2{\cdot}19$, $p<0{\cdot}025$). The distribution of mean plasma ammonia concentrations certainly appears to follow the pattern of clinical and developmental observations in a more understandable manner.

It is impossible with our limited and variable data to identify a critical ammonia concentration but it may be pertinent to note that case 1 has only had values of plasma ammonia of 100 μmol/l or more recorded on four occasions, all of which occurred after the age of 21 months, whereas case 2 has encountered such concentrations on seven occasions all of which were in her first 14 months of life. Thus far case 3 has only had one concentration of 100 μmol/l, which occurred at age 6 months. Regression analyses have shown no direct relationship between coincidental plasma lysine and ammonia concentration in these children ($r=0{\cdot}28$, $n=75$ for case 1 and $r=-0{\cdot}15$, $n=41$ for case 2). Also, neither blood concentration has appeared to be particularly raised during intercurrent illnesses, including upper respiratory tract infections and diarrhoeal illness. On four occasions, case 2 has had plasma ammonia concentrations greater than 150 μmol/l and on one occasion, a value of 320 μmmol/l was recorded. On none of these occasions did she appear to be particularly unwell.

The cause of the hyperammonaemia may be secondary to the competitive inhibition of arginase by high concentrations of lysine, thus interfering with ammonia elimination through the Krebs urea cycle.[9] This was the suggested explanation for the one documented case of periodic hyperlysinaemia associated with hyperammonaemia reported by Colombo *et al*,[10] but this explanation has been challenged by results from in vitro studies.[11] The lack of clinical or biochemical evidence of hyperammonaemia in other reported patients with persistent hyperlysinaemia is difficult to interpret. Most of these patients were not handicapped or if they were, had no ammonia studies done.[1–6] Certainly our cases would appear to be different from that of Colombo *et al* in that the hyperlysinaemia is persistent despite dietary measures and not associated with profound episodes of vomiting and coma when ammonia concentrations are raised. Instead, our cases appear to represent an intermediate situation between the two previously described types of hyperlysinaemia.

We have concern about compliance at home with the relatively complex low lysine diet. Planned and unplanned admissions to hospital and the employment of a 'linkworker' for the family who regularly visits the home, however, have not led to very significant changes in plasma lysine concentrations. It is also of note that when these children have been deliberately taken off their diets their plasma lysine concentrations have risen considerably.

It is extremely difficult to come to any firm conclusions about the management of young children with this disorder but in view of the severe developmental and physical problems of the index case and the possible developing problems in two of the other three affected children, some form of effective treatment must be sought. Our experience so far would tend to indicate that treatment with a low lysine diet may well be worthwhile and that plasma lysine concentrations are probably best kept well below 1000 μmol/l in the first 2 years of life. Also during the same period plasma ammonia concentrations should be monitored and if possible kept below 100 μmol/l and probably much lower. Unfortunately, in our experience, the plasma ammonia concentration does not seem to respond to dietary manipulation as well as plasma lysine concentrations.

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