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SHORT REPORT

Early-onset hyperargininaemia: A severe disorder?

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Summary Hyperargininaemia is a rare inborn error of metabolism due to a defect in the final step of the urea cycle. Infantile onset is the most common presentation with recurrent vomiting and psychomotor delay associated with spastic paraparesis; chronic hyperammonaemia is often overlooked. Neonatal and early-onset presentations are very uncommon and their clinical course not well-described. We report on a 3-week-old hyperargininaemic girl who presented with neurological deterioration associated with liver failure and 47-day ammonia intoxication before diagnosis could be made and treatment started. Despite appropriate but delayed treatment, our patient exhibited severe psychomotor delay at age 1 year.
Conclusion Early identification and management of this rare but potentially treatable affection is crucial as delayed management may result in poor neurological outcome.

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Abbreviations

EAA	essential amino acids
GAA	guanidinoacetate
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
UCD	urea cycle disorder

Introduction

Hyperargininaemia (OMIM #207800) is an autosomal recessively inherited metabolic disorder due to a defect in liver arginase 1 enzyme (EC 3.5.3.1). Arginase is involved in the final step of the urea cycle and catalyses the conversion of arginine to urea and ornithine (Ash 2004). In the majority of patients (infantile onset), episodes of irritability, poor feeding, recurrent vomiting and lethargy, sometimes progressing to coma with seizures, develop upon weaning or upon changing from formula to cow's milk. Following an initial period of normal development, progressive spastic paraparesis and mental deterioration occur at ages varying from 3 months to 4 years (De Deyn et al 1997; Scaglia and Lee 2006). Neonatal and early-onset presentations (before 3 months of age) are very rare. Although it has not been proven, this could be due partly to the

potential compensatory effect of arginase 2 isozyme activity, which could be enhanced several times by exposure to elevated levels of arginine (Crombez and Cederbaum 2005). Unlike other urea cycle disorders (UCDs), arginase deficiency does not commonly present with severe hyperammonaemia; however, prior to diagnosis, many infantile-onset patients show signs of chronic hyperammonaemia responsible for episodes of vomiting, clumsiness, ataxia, failure to thrive and protein avoidance. The potential neurotoxic role of arginine and its metabolites, the guanidino compounds, has been suggested (De Deyn et al 1997; Deignan et al 2008; Hiramatsu 2003) as an explanation for the peculiar neurological involvement described in these patients.

We present clinical, biochemical and neuroradiological data from the case study of a girl affected with early-onset hyperargininaemia.

Case report

A 3-week-old girl, the second child of non-consanguineous parents, was born after an uneventful pregnancy and a normal delivery. She was admitted to a primary care hospital because of respiratory distress that required transient ventilatory support. Two days later, she exhibited drowsiness and seizures. Initial laboratory studies revealed mild cytolysis (SGOT 70 IU/L, SGPT 45 IU/L, normal range <50 IU/L), liver failure (prothrombin time 25 s, normal range 12–15 s; factor V 30%) and hyperammonaemia (250 μmol/L, normal range <80 μmol/L). On day 44, a provisional diagnosis of arginase deficiency was made on the basis of marked elevation of plasma arginine levels (680 μmol/L, normal range <100 μmol/L) associated with orotic aciduria (200 mmol/mol creatinine, normal range <5 mmol/mol creatinine) and elevated guanidinoacetate (GAA) urinary excretion (880 mmol/mol creatinine, normal range <220) (Fig. 1). The diagnosis was further confirmed by a severe deficiency of arginase 1 activity in red blood cells (less than 1% of control value) and sequencing of *ARG1* gene, which revealed that the patient was homozygous for a previously reported pathogenic splicing mutation: IVS4−2A>G (Uchino et al 1995).

Soon after the diagnosis was suspected, the infant was first treated with a low-protein diet (natural protein 0.9 g/kg per day, with daily arginine intake approximately of 120 mg/day) for a 20-day period (day 47 to day 67; Fig. 1, red bar). After this period, clinical examination was normal; blood liver tests and coagulation were back to normal (data not shown), plasma ammonia and arginine levels, and urinary orotate and GAA excretions were within the normal range (Fig. 1).

From day 67, sodium benzoate (250 mg/kg per day) was given to the patient. Finally, an essential amino acids mixture deprived of arginine (EAA) was added to the diet from day 94 in order to enhance anabolism and to supply sufficient intake of vitamin and trace elements. At 1 year of age, while the child was treated with protein-restricted diet (natural protein 1 g/kg per day, with arginine daily intake 300 mg/day, EAA mix-

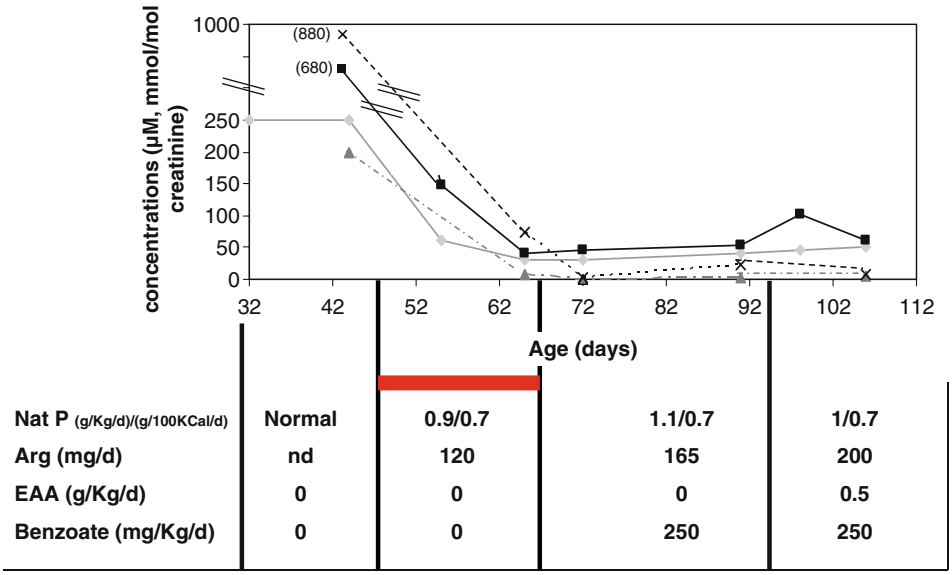

Fig. 1 Evolution of metabolic parameters: ×, urinary GAA excretion (mmol/mol creatinine), ■, plasma arginine(μmol/L), ♦, plasma ammonia level (μmol/L), ▲, urinary orotic acid excretion (mmol/mol creatinine). Nat P. amount of natural protein; nd, not determined; EAA, essential amino acids. Red bar indicates 20-day-period with arginine-restricted diet alone

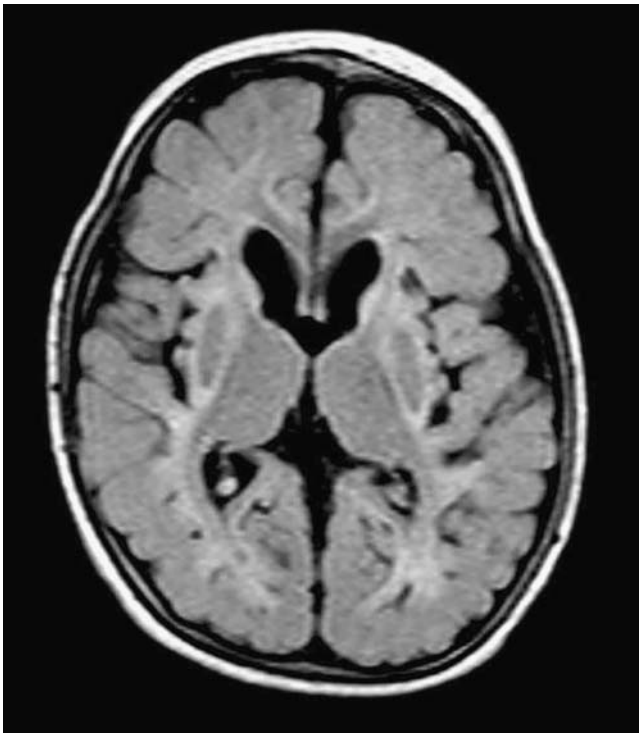

Fig. 2 Transverse FLAIR MRI (at the age of 13 months) showing cortical and subcortical atrophy with enlarged pericerebral spaces and ventricles, hyperintensity and shrinkage of lenticular nuclei and supratentorial white matter

ture 0.5 g/kg per day), she had normal growth and nutritional status. Plasma ammonia value was 50 μmol/L; arginine plasma level was 90 μmol/L (normal range <100 μmol/L); branched-chain amino acids plasma levels were in the normal range; urinary orotic acid was 10 mmol/mol creatinine (normal range <5); and GAA urinary excretion was 90 mmol/mol creatinine (normal range <220). At that age, GAA levels in CSF were within the normal range (data not shown). Despite these satisfactory biological results, our patient developed severe psychomotor delay with moderate pyramidal signs and acquired microcephaly. Brain MRI performed at 2 (data not shown) and 13 months of age (Fig. 2) revealed severe cortical atrophy with extensive white-matter lesions and lenticular atrophy.

Discussion

Hyperargininaemia is the rarest cause of primary hyperammonaemia. Symptomatic neonatal presentations are uncommon with only three reported cases. Two of them presented with neurological deterioration, one of them including cholestasis (Jordá et al 1986), leading to early death at 7 weeks (Jordá et al 1986) and 2 days of age (Picker et al 2003) respectively. One case of isolated hepatic presentation has been described in a neonate with a cholestatic cirrhotic liver who was mentally normal at 2 years of age (Braga et al 1997).

Neonatal familial screening was performed in three asymptomatic neonates. These exhibited elevated plasma arginine levels and were therefore treated from birth. One of them is presently over 35 years old and has remained totally asymptomatic (Crombez and Cederbaum 2005; De Deyn et al 1997; Snyderman et al 1979); the two others were reported to be normal children over 4 years of age (De Deyn et al 1997). One patient was diagnosed prenatally and was therefore treated from birth with a favourable outcome at 18 months of age (De Deyn et al 1997).

Only two patients who were less than 3 months of age at diagnosis have been mentioned (De Deyn et al 1997). Our patient has shown early neurological deterioration with hyperammonaemia and liver failure. Despite appropriate but delayed therapy started from day 47 with prompt normalization of ammonia, arginine and guanidino compounds levels in body fluids (Fig. 1), she has developed an early and severe encephalopathy. Three main mechanisms responsible for this poor neurological outcome can be discussed: chronic hyperammonaemia, arginine and guanidino compound intoxication, or both. Comparing neuroimaging findings in our patient with those reported in other neonatal UCD defects (Takanashi et al 2003), it appears that our patient may have suffered mainly from chronic hyperammonaemia. Conversely, progressive spastic paraparesis described in infantile-onset patients may be secondary to arginine and guanidino compound intoxication (De Deyn et al 1997). Only the three neonatal patients who were screened and the one prenatally diagnosed have remained asymptomatic. They may have escaped from both neonatal hyperammonaemia and chronic arginine and guanidino compound neurotoxicity.

In inherited disorders of essential amino acid catabolism., i.e. phenylketonuria (PKU) and maple syrup urine disease (MSUD), minimal phenylalanine and leucine requirements are respectively covered with an average natural protein intake of 0.7 g/100 kcal per day, which is approximately half of the protein intake of a breast-fed neonate (Janas and Picciano 1986; Ogier de Baulny et al 2003). By analogy with this approach, our patient was treated with a similar protein intake in order to approximately cover the minimal protein daily requirement. In contrast to reports in the literature (Marescau et al 1990), with this diet our patient had normal growth, no malnutrition, no signs

of arginine deficiency, and normalized all the biochemical parameters.

In conclusion, this report exemplifies that hyperargininaemia, if not identified early, may cause symptomatic hyperammonaemia in the neonatal period and requires early management as usually recommended in all UCD defects. In addition to ammonia control, arginine and its guanidino metabolites must be lowered because of their neuropathogenic role. Early identification and treatment of this potentially treatable inborn error of metabolism may result in a better outcome.

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