J. Inher. Metab. Dis. 19 (1996) 153–156

Short Communication

Progressive generalized brain atrophy and infantile spasms associated with cytochrome *c* oxidase deficiency

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Severe neonatal acidosis has been described in association with inborn errors of the enzymes involved in oxidative phosphorylation and the pyruvate dehydrogenase complex. The patients develop irritability, feeding difficulties, hypotonia and respiratory insufficiency within hours or days after birth. The clinical course is rapidly progressive and most patients die within a few days owing to uncontrollable lactic acidosis. Possible presenting signs and symptoms are nonspecific; differential diagnosis with more common neonatal problems such as sepsis, intracranial haemorrhage and meningitis can thus be difficult.

Cytochrome *c* oxidase (COX; EC 1.9.3.1) or complex IV, the last component of the respiratory chain, catalyses the transfer of electrons from cytochrome *c* to molecular oxygen. Fatal neonatal lactic acidosis in association with COX deficiency was first described by Trijbels et al (1983), but a benign form of complex IV deficiency in which severe neonatal onset is followed by spontaneous improvement with increasing activity of the enzyme has also been demonstrated (DiMauro et al 1983, 1994). We report a patient with COX deficiency who developed lactic acidosis (lactate in plasma 28 mmol/L, normal values <2; pyruvate in plasma 0.28 mmol/L, normal values <0.08) at the age of 1 day. Despite appropriate medication to reduce the lactate and pyruvate concentrations, the patient developed signs of severe encephalopathy almost 6 weeks after normalization of these concentrations.

CASE REPORT

A boy, second child of non-consanguineous parents, was born after a term pregnancy and normal delivery (birth weight 3460 g, length 49.5 cm, head circumference 36 cm). It was

the third pregnancy of the mother: the first ended at 19 weeks with death *in utero* of twins; the second ended at term with the birth of a healthy boy. The patient was admitted to the pediatric ward of the local hospital at the age of 1 day for evaluation of his feeding difficulties and tachypnoea. Laboratory investigations revealed severe metabolic acidosis with a pH of 7.02, a base excess of −24.8 mmol/L, and elevated lactate and pyruvate as mentioned above.

The patient was removed to the children's intensive care unit of the Academic Medical Centre and treated by peritoneal dialysis, vitamins in high doses, and carnitine until the lactate and pyruvate concentrations were normalized after 12 days. Ultrasonography of the brain was performed at ages 9 days, 14 days and 4 months. These images showed progressive (sub)cortical atrophy as evidenced by separation of the hemispheres and progressive sulcal widening. Midsagittal images likewise suggested progressive atrophy of the vermis, but sequential images were not distinct enough to differentiate between prenatal-onset hypoplasia or postnatal atrophy in the case of the cerebellum. MRI at the age of 4 months showed extreme cerebral and cerebellar atrophy or hypoplasia, while myelination was nearly normal for age both in the supra- and infratentorial parts (Figure 1).

In the following months the patient was hospitalized several times because of increasing myoclonic seizures, feeding difficulties and progressive retardation. During this period, appropriate medication was used to maintain the lactate and pyruvate concentrations in plasma at normal levels. However, the clinical condition of the patient is at present (at the age of 25 months) very severe with epileptic insults, feeding problems, dystrophy and hypotonia. His head circumference is now only 42.5 cm, which is significantly smaller than that of age-matched controls.

BIOCHEMICAL STUDIES

The lactate-to-pyruvate ratios in cultured fibroblasts after incubation with glucose, and the ATP production (Wanders et al 1993), were normal. The activities of enzymes involved in oxidative phosphorylation showed no abnormalities, except for the activity of complex IV. In fibroblasts (COX 0.22 k/min per mg protein; controls 0.45–0.62), lymphoblasts (COX 0.38 k/min per mg protein, controls 0.68–0.98) and liver (COX 8.3 mU/mg protein; controls 13.9–108) complex IV showed about a 2-fold reduction in enzymatic activity; in muscle the reduction was more severe (COX 8 k/min per g wet weight at the age of 9 days; controls 45–161; and COX 10 k/min per g wet weight at the age of 8 months; controls 68–437).

DISCUSSION

The initial hyperlactataemia of the patient with high lactate-to-pyruvate ratios in plasma (patient 100; controls <20) suggested an inborn error of oxidative phosphorylation. Biochemical studies showed that a generalized deficiency of complex IV was the most likely cause. The clinical presentation of respiratory-chain disorders is extremely variable. However, deficiency of complex IV and structural abnormalities of the brain are frequent observations in mitochondrial encephalomyopathies (DiMauro 1994; Nijtmans et al 1995). In the patient described, structural and functional abnormalities of the brain became evident after the initial lactic acidosis had been corrected by treatment. Hypoxia and severe

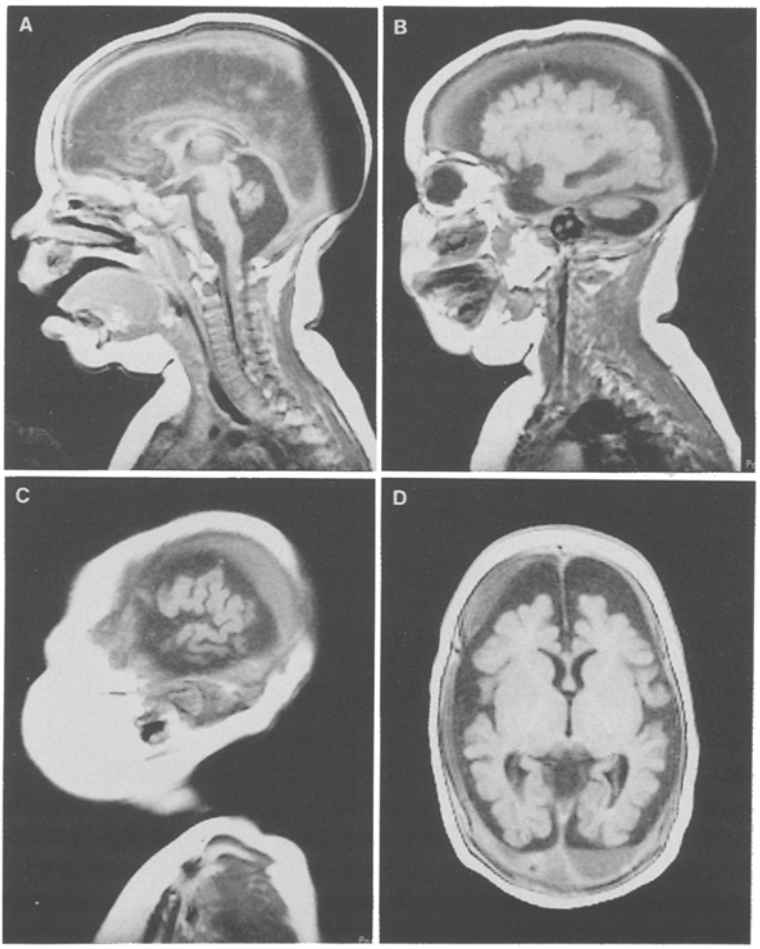

Figure 1 MRI of the brain at age 4 months: (A–C) sagittal; T1-weighted images; (D) transverse axial image. (A) Severe hypoplasia or atrophy of the cerebellar vermis and a relatively undeveloped pons. (B) Severe hypoplasia or atrophy of cerebellar hemisphere. (C) Lateral view of the insula, showing severe atrophy of the perisylvian cortex. Subdural haematomas, possibly due to cerebral shrinkage and overstretched bridging veins are evident in images (B), (C) and (D)

acidosis in the neonate often result in periventricular leukomalacia (PVL), usually evident within a month after the perinatal insult. In exogenous accidents to the perinatal brain the cerebellum is usually well preserved (Barth 1993). In the present patient, PVL was absent while myelination had progressed around the lateral ventricles, the anterior and posterior capsular limbs and the thalamus. A remarkable (sub)cortical atrophy of the cerebral hemispheres was present and the cerebellum was affected by severe atrophy of both the vermis and the cerebellar hemispheres. The abnormalities found on neuroimaging reflect a progressive brain disorder, rather than the sequelae to the brain of perinatal injury. MRI findings typical of Leigh syndrome, another presentation of COX deficiency (Arts et al

1987; DiMauro et al 1994) were not found in this patient. The present findings therefore reflect a rare type of early-onset progressive encephalopathy associated with COX deficiency.

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