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SHORT REPORT

Post-mortem MRI reveals CPT2 deficiency after sudden infant death

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Abstract Inherited metabolic disorders are the cause of a small but significant number of sudden infant deaths in infants. We report on a boy who suddenly died at 10 months of age during an acute illness. Parents declined autopsy; nevertheless, they accepted a whole body MRI, which revealed hepatomegaly with steatosis. Acylcarnitine profile of a blood sample from neonatal Guthrie screening led to the diagnosis of type 2 carnitine palmitoyltransferase deficiency. To conclude, whole body MRI is useful in the investigation of some inherited metabolic causes of sudden infant death, which might prevent future deaths in the family. It is a good alternative when autopsy is refused.

Keywords Sudden infant death · Post-mortem MRI · CPT2 deficiency

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Introduction

Sudden infant death syndrome (SIDS) is now defined as the sudden unexpected death of an infant of less than 1 year of age, which remains unexplained after a thorough investigation including performance of a complete autopsy and review of the circumstances of death and the clinical history [7]. Despite declines in prevalence during the past two decades, SIDS continues to be the leading cause of death for infants aged between 1 month and 1 year in developed countries. Little progress has been made in identifying the cause(s) of this syndrome. On the other hand, at least 12 fatty acid oxidation (FAO) disorders are known to be responsible for sudden death, usually occurring after fasting, often associated with intercurrent illness [10]. Post-mortem diagnosis of FAO disorders might be difficult, and the prevalence of these disorders among SIDS is unknown. We report on a boy who suddenly died at 10 months of age on whom a type 2 carnitine palmitoyltransferase (CPT2) deficiency was diagnosed after SIDS.

Case report

We report on a 10-month-old male infant who was the first child of parents who were first cousins originating from an isolated village in Algeria. The mother was 30 years old. The

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pregnancy was uncomplicated, and prenatal ultrasound examinations were normal. The patient was born prematurely at 34 weeks of gestation by caesarean section because of a narrow pelvis. Growth parameters were normal at birth (weight=2,420 g, size=47 cm, head circumference=34 cm). He required conventional phototherapy for neonatal jaundice and a transient nutritional support by nasogastric tube. The patient was discharged from the hospital at 14 days. He was readmitted at 1 month of chronological age with a diagnosis of necrotizing enterocolitis, secondarily complicated with a duodenal stenosis operated successfully at 5 months of corrected age. At 10 months of corrected age, he developed gastroenteritis with diarrhoea, vomiting and fever. The parents were not worried when they put him to bed. The day after that, he was found lifeless in his cot lying on his back and then was transported to our SIDS reference centre. Clinical examination did not reveal an obvious cause of death. No hepatomegaly was noted at this stage. However, the abdomen hardened quickly after death, and liver size was difficult to appreciate. Serum titres for infections (procalcitonin, CRP and IL6), blood cell count and liver enzyme levels were in the normal range. Cerebrospinal fluid (CSF) analysis showed no pleocytosis, normal protein level but null glucose level. No bacteria could be isolated. The parents declined traditional autopsy but accepted a whole body post-mortem MRI. The liver was increased in size, with hypersignal in T1-weighted images suggesting steatosis (Fig. 1). An inborn error of metabolism was suspected. Although urinary organic acid chromatography was normal, a disorder of carnitine uptake or of long-chain fatty acid transport within mitochondria was suspected. This prompted us to study the acylcarnitine profile on a blood sample from neonatal Guthrie screening kept in the reference centre since the third day of life. Neonatal plasma acylcarnitine profile, performed using stable isotope dilution and electrospray tandem mass spectrometry, demonstrated elevation of long-chain species compared with short chain with ratio C16+C18:1/C2=1.56 (normal 0.03–0.15), C2=3 μmol/l (normal, 3–42 μmol/l), C16=3.28 μmol/l (normal, 0.25–9.7 μmol/l) and C18:1=2.97 μmol/l (normal, 0.25–5.0 μmol/l). Direct sequencing of the *CPT2* gene revealed a homozygous missense mutation (c.1883A>C; Y628S). Both parents were heterozygous for the mutation.

Discussion

Recognition of FAO disorders among SIDS cases is of prime importance, allowing genetic counselling, pre- and neonatal diagnosis and screening of siblings potentially at risk for life-threatening episodes of fasting intolerance. However, post-mortem screening of FAO disorders among SIDS is difficult. Post-mortem blood spot acylcarnitine profiles are usually not interpretable. As previously reported and as confirmed in the present study, the acylcarnitine profiles could be determined from blood spots on a Guthrie card collected at birth [6]. A familial history of other sudden unexpected death or description by the parents of lethargic episodes suggestive of hypoglycaemia may point towards a FAO disorder. The only symptom noted in our case was an atypical necrotizing enterocolitis diagnosed at 40 weeks' corrected gestational age. However, it is not a common presenting symptom of FAO disorders, and physicians were not suspicious because both hypoglycaemia and hepatomegaly were not observed at that time. The

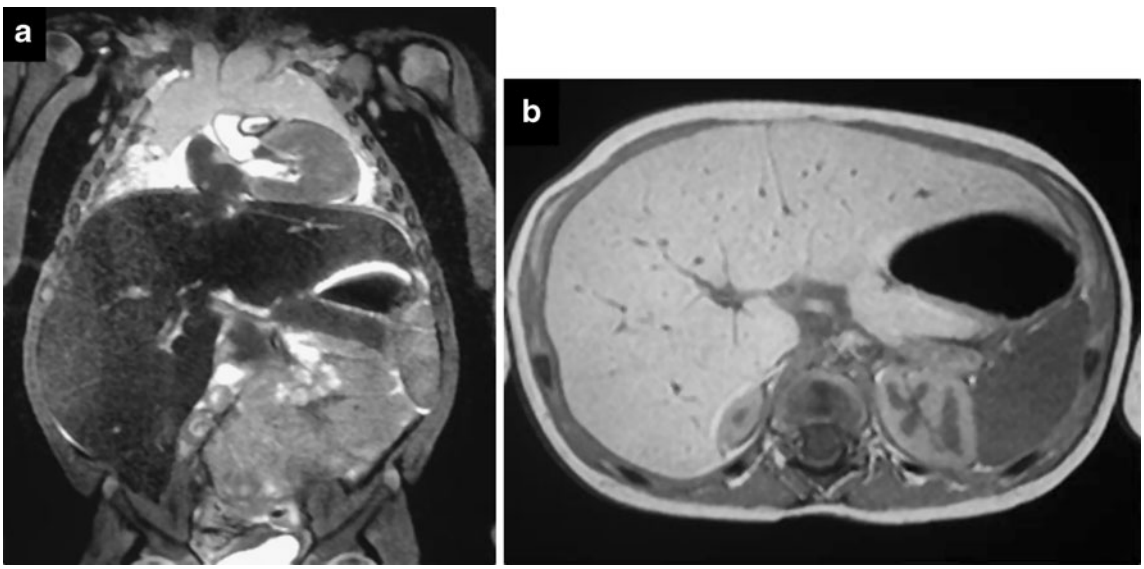

Fig. 1 Total body post-mortem MRI. **a** Coronal T2-weighted sequence. Marked liver hyposignal compared with the spleen signal. **b** Axial T1-weighted sequence. Hepatomegaly with homogeneous hypersignal compared with the spleen signal

normal size of the liver noted in previous physical examinations before death is in accordance with the well-known observation that hepatomegaly occurs only during acute attack in FAO disorders. Severe hypoglycaemia can be difficult to prove as the cause of death. Blood glucose concentrations cannot be determined due to the rapid post-mortem breakdown of metabolism [8]. Interestingly, when the CSF is analysed in the first hours following the death as in the case reported, low glucose level could reflect severe pre-mortem hypoglycaemia. A urine test, negative or inappropriately low for ketones in FAO disorders, could be useful. Autopsy could contribute to the post-mortem diagnosis of FAO disorders by the simultaneous measurement of C8–C20 fatty acids, glucose, lactate and other metabolites of liver homogenate [3]. However, liver histology is not performed in all cases of SIDS.

In this report, post-mortem MRI was a key determinant in the diagnostic procedure and led to the diagnosis of CPT2 deficiency. Autopsies following SIDS are important for excluding an unnatural cause of death and identifying potential familial conditions, which may allow prevention of future deaths in the family. The cause of 30–50% of unexpected infant death is now determined by autopsies [13]. However, in our experience and in the literature, about 40% of parents refuse the autopsy due to religious or personal reasons. Thus, we propose non-invasive autopsy by whole-body MRI for these patients. Indeed, a few studies have even reported the value of MRI as an alternative to autopsy in post-mortem examinations among adults, foetuses and neonates [1, 4, 11, 12]. However, no study comparing the results of autopsies and post-mortem MRI in SIDS has been published yet. Although maceration can influence the quality of post-mortem MRI, images were usually of good quality (Fig. 1). MRI can detect 55–70% of the malformations that autopsy can detect in foetuses and neonates [1, 4, 12]. The rate of detection of central nervous system malformations is good. No study has focused on post-mortem liver MRI. In our observation, the marked liver T1 hypersignal and T2 hyposignal compared with the spleen signal suggested steatosis. Only the liver biopsy could have confirmed this hypothesis, but the parents refused. Aetiologies of liver steatosis in young children are mainly metabolic disorders [5]. Consequently, the consanguinity, the context of death during an acute event (gastroenteritis) and liver post-mortem MRI findings suggested a FAO disorder. Post-mortem MRI has some limitations. Although cardiac anomalies are an important cause of SIDS, the reported sensitivity of their detection by MRI is low [1]. Cardiomyopathy is observed in 25% of patients with a FAO disorder and in about half of severe infantile patients with *CPT2* deficiency [9]. Cardiac MRI was considered to be normal in our patient, but we cannot completely exclude cardiomyopathy.

To conclude, this case demonstrates the importance of MRI in the post-mortem screening of inborn errors of metabolism such as FAO disorders in SIDS cases. Among FAO disorders, only *MCAD* deficiency has been extensively studied in SIDS cases [2]. In a study by Boles et al., 313 SIDS cases were subjected to biochemical screening [3]. Fourteen of these matched with biochemical profiles seen in FAO disorders, but only two had a *MCAD* mutation. These findings emphasise the importance of investigating other FAO disorders such as CPT2 deficiency in cases of SIDS.

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