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Glutaric Aciduria Type 1 and Nonaccidental Head Injury

ABBREVIATIONS. NAI, nonaccidental injury in childhood; GA1, glutaric aciduria type 1.

Subdural hemorrhage has been a recognized manifestation of nonaccidental injury in childhood (NAI) since 1860.[1] The presence of subdural collections, often with coexisting retinal hemorrhages, fractures, and multiple traumatic injury, greatly raise the clinical index of suspicion for child abuse.[2–5] The finding of subdural blood in an infant presents a difficult and important diagnostic challenge for pediatricians given the legal and social import of child abuse.

Glutaric aciduria type 1 (GA1) is a relatively rare inborn error of metabolism that presents in infancy with a range of neurological features. It is increasingly recognized that GA1 is associated with acute subdural hemorrhage and chronic subdural collections.[6–8]

We present a case of an infant with bilateral subdural hematoma in whom a diagnosis of NAI was initially made. Subsequent metabolic investigation of the child led to a diagnosis of GA1 with important therapeutic, social, and legal consequences.

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CASE REPORT

An 8-week-old white male infant was referred to this hospital by his general practitioner after a head injury. The history from the mother was that the infant was upstairs being carried by his 7-year-old brother who fell, dropping the infant against a wall. She was downstairs and was alerted by the infant's cry. The infant vomited and was noted to be drowsy. He was then taken immediately to the general practitioner's office.

The infant was born by spontaneous vaginal delivery at 38 weeks' gestation after a normal pregnancy. He was noted to be asymmetrically growth retarded with weight below the 10th percentile and head circumference on the 50th percentile. The infant was bottle-fed from birth, received the first diphtheria, tetanus, and pertussis-polio-*Haemophilus influenzae* type b vaccination, and was well until the day of presentation.

The family consisted of this infant and 2 older half-siblings, aged 4 and 7, who were well. All 3 children were from different nonconsanguineous partners. The mother was a 25-year-old, unemployed, and unsupported lone parent with learning difficulties who was known to social services.

On presentation the infant was noted to be well-grown, quiet, and pale, but alert. The head circumference was now over the 97th centile. The anterior fontanelle was large and full with splaying of the coronal sutures. There was some erythema over the right parietal region but no evidence of bruising or external injury. The systemic examination, including neurologic examination, was unremarkable.

A skull radiograph showed no fractures. Routine laboratory investigations including coagulation studies were within normal limits. A transcranial ultrasound scan revealed bilateral subdural collections. On the evening of admission the infant developed right-sided focal seizures that required treatment with phenobarbitone and phenytoin.

A computed tomography scan was performed (Fig 1). This showed bilateral frontal subdural collections larger on the right side, with some effacement of the cortical sulci. Additionally there was a fresh subdural hemorrhage high in the left parietal region. The ventricles were rather small in size. Diffuse low-density white matter changes in both hemispheres were also reported.

The infant underwent emergency drainage of blood-stained fluid from both subdural collections. He had no further seizures. A radiographic skeletal survey was conducted. It was reported that there was a fracture through the midshaft of the right radius and a metaphyseal fracture of the distal right radius with significant periosteal reactions. Formal ophthalmologic review revealed 1 pinpoint hemorrhage on the right fundus.

In view of the history and the pattern of clinical and radiologic findings, it was decided that the infant had probably been subjected to NAI. Child protection procedures were instituted. Police investigations resulted in a criminal charges being brought against the mother by the Crown Prosecution Service. The infant was discharged into interim foster care after 2 weeks in hospital at which point he was well and seizure-free.

When reviewed at 6 months of age the child was noted to have macrocephaly and global developmental delay, particularly in gross motor function. He had bilateral conductive hearing deficit with some sensorineural deficit. He showed marked left-sided preference. Urine organic acid analysis was performed and gas chromatography-mass spectrometry showed markedly elevated excretion of glutaric acid and 3-hydroxyglutaric acid, with glutaric acid concentration 1500 μmol/mmol creatinine.

The diagnosis of GA1 was confirmed enzymologically by demonstrating absent glutaryl-CoA dehydrogenase activity in cultured fibroblasts. The child's glutaryl-CoA dehydrogenase activity was 0.01 μmol/h/g protein with a control range of 5.0 $\pm$ 1.6 μmol/h/g protein.[9] Two experts reviewed the radiographs and concluded that the supposed radial fracture was a nutrient artery; however, the periosteal reactions were confirmed and still caused concern that there had been inappropriate handling of the infant.

The infant was commenced on a reduced lysine/tryptophan diet with carnitine supplementation, and appropriate management of intercurrent illnesses. The child has had 4 hospital admissions to date with mild catabolic illnesses. He remains markedly globally delayed but has not yet developed any new neurologic features.

In light of the new diagnosis, Crown proceedings against the natural mother were temporarily suspended. A court hearing

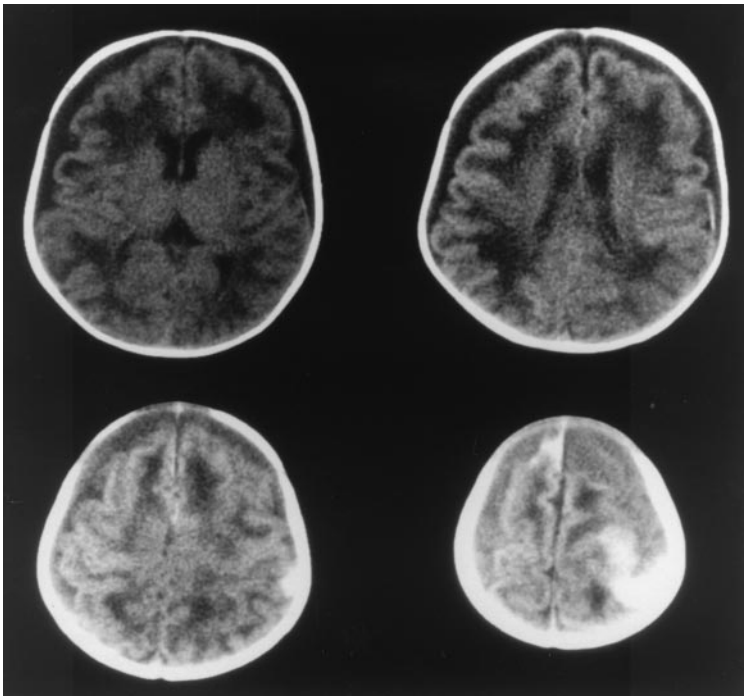

Fig 1. Axial computed tomography from the infant on the day of presentation. There are bilateral frontal subdural collections with some cortical effacement and a fresh high left parietal collection. Diffuse white matter signal attenuation is seen in both hemispheres.

raised doubts about the mother's ability to maintain a safe environment for the infant and the child remained in the care of social services with the hope that he would be adopted.

DISCUSSION

GA1 is an autosomal recessive disorder of lysine, hydroxylysine, and tryptophan catabolism caused by deficiency of mitochondrial glutaryl-CoA dehydrogenase, first described in 1975.[10] The population frequency has been estimated at 1 in 30 000 neonates in a Scandinavian study.[11] It is biochemically characterized by elevated urinary excretion of glutaric acid, 3-hydroxyglutaric acid, and glutarylcarnitine, reduced plasma carnitine, and reduced or absent glutaryl-CoA dehydrogenase activity in fibroblasts and leukocytes (11 for review). Molecular studies show that a wide variety of mutations in the human glutaryl-CoA dehydrogenase gene are responsible for causing the disease.[13]

Such allelic heterogeneity may underlie the wide phenotypic variations seen in this neurometabolic disorder. Unlike other organic acidemias, metabolic and lactic acidosis, hyperammonemia and hypoglycemia are rarely present. The 'typical' presentation is within the first 12 months of life of an acute metabolic encephalopathic crisis followed by loss of motor skills and development of a dystonic-dyskinetic movement disorder often with preservation of intellectual function. Orofacial dyskinesias with concomitant feeding difficulties are notable. A prominent clinical findings is of macrocephaly, often not present at birth, but rather an abnormal increase in head circumference during infancy. Retinal hemorrhages are found in 20% to 30% of patients.[12] Seizures are seen in 20% of children with GA1.[14]

Earlier presentations are with less florid neurological symptoms such as hypotonia, irritability, and mild encephalopathic episodes with few sequelae.

Undiagnosed, the disorder progresses to development of cerebral atrophy with pyramidal tract signs and mental retardation. Anorexia, insomnia, hyperthermia, and hyperhidrosis are common symptoms. Approximately 25% of children, however, present with subacute motor delay, insidious development of dystonia (often diagnosed as cerebral palsy), and mental retardation; encephalopathic episodes in this group are absent or milder.[14,15] There are reports of completely asymptomatic children with GA1.[8]

Therapy is directed at dietary manipulation. A reduced lysine/tryptophan diet, carnitine and riboflavin supplementation, and aggressive management of catabolic states including episodes of fever or vomiting are said to modify the progress of the disease.[12,18] This dietary control needs to be instituted early or in presymptomatic patients, although clear benefits of low protein diets beyond the age of 4 years are still to be shown.[12,15]

Neuroradiologic findings in GA1 are increasingly well-documented.[6–8,16–20] Consistent findings are of macrocephaly and frontotemporal cerebral atrophy with widening of the Sylvian fissures. Transient subependymal pseudocysts, diffuse white matter signal attenuation, and basal ganglia changes affecting the caudate nucleus are also well-described. The presence of acute and chronic subdural collections in GA1 was initially thought to be a rare association, but some large series report that 20% to 30% of patients with GA1 will have subdural collections.[14] The pathogenesis of subdural hemorrhage remains unclear but it is thought to arise from stretching of bridging veins attributable to cerebral atrophy—increased fragility leads to bleeds with minimal trauma. Alternatively, hemorrhage may occur from the outer membrane of a subdural effusion.[6,21]

The clinical features of subdural collections of different ages, retinal hemorrhages, and nonspecific symptoms in the absence of a history of adequate

trauma may lead clinicians to suspect NAI in a child with undiagnosed GA1.[15,23]

In our case, GA1 was diagnosed later because urine was sent for metabolic screen, requested because of macrocephaly and neurodevelopmental delay at follow-up. The diagnosis of GA1 provided 1 explanation for the subdural collections found in this infant. The expert review of the radiographic skeletal survey showing the presumed radial fracture to be a nutrient artery further weakened the evidence for NAI.

The periosteal reactions seen on radiograph remain unexplained. This, together with the atypical presentation with early seizures and marked neurodevelopmental sequelae in the absence of an encephalopathic episode, continues to raise the possibility of NAI. Children with neurometabolic disorders are at increased risk of NAI injury; heightened awareness of child protection issues should not end once a diagnosis of GA1 has been made.[23]

In the context of the general pediatric population subdural hemorrhages in infancy are common. A recently reported incidence is of nearly 21/100 000 children per year.[22] Subdural hemorrhages are associated with poor outcomes and nonspecific presentation, and more than four fifths of cases are highly suggestive of abuse with evidence of coexisting injury or a history of previous child abuse within the family.

It has been suggested that multidisciplinary social assessment, expert ophthalmoscopy, radiographic skeletal survey supplemented by either a bone scan or repeat survey, coagulation screening, and neuroradiologic investigations should be mandatory in the investigations of infants with subdural hemorrhage.[22,24,25]

We propose that screening for GA1 should be added to these investigations. Urine organic analysis, glutarylcarnitine measurement on blood spots, and plasma total and free carnitine estimations, followed by confirmatory enzymology, have been recently suggested as the best screen.[23]

The devastating social and legal consequences for a family facing a charge of child abuse place the onus on the attending pediatrician of meticulous exclusion of alternative diagnoses to NAI. It is additionally important to diagnose a potentially modifiable albeit rare metabolic disorder.

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Carbamazepine Overdose Recognized by a Tricyclic Antidepressant Assay

ABSTRACT. Altered mental status in an adolescent presents a diagnostic challenge, and the clinician depends on clinical evaluation and laboratory studies to determine therapy and prognosis. We report the case of

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