Commentary

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Rylance and Moreland draw attention to the advantages of monitoring salivary anticonvulsant drug levels rather than blood levels in children. The non-invasive nature of this investigation, together with the fact that the salivary level reflects the free and pharmacologically-active concentration in plasma rather than the total concentration, make this method attractive. However, three difficulties arise which need stressing. Firstly, the measurement should be confined to phenytoin and carbamazepine because the salivary concentrations of the other antiepileptic drugs do not accurately reflect the free concentration. Secondly, the problem of oral contamination with liquid and chewable preparations is a real one, as Rylance and Moreland point out, and care has to be taken to ensure that the sampling is at least 5 hours after dosing. Thirdly, the concentration of the drugs in saliva is much lower than in plasma (one-tenth of the plasma concentration for phenytoin and one-quarter for carbamazepine). A substantial proportion of the levels encountered will therefore be around the limit of sensitivity of routine analytical techniques and the theoretical advantage of salivary levels may be more than offset by inaccuracy of measurement. Experience has shown[1] that the coefficient of variation of analyses increases with decreasing concentration and may become of such a magnitude that the result may become more misleading than helpful. Although it is possible to achieve greater accuracy (as Rylance and Moreland have done), standards in most routine laboratories currently fall short of those necessary for salivary sampling to be a satisfactory substitute for venepuncture.

Reference

[1] Griffiths A, Hebdige S, Perucca E, Richens A. Quality control in drug measurement. *Therapeutic Drug Monitoring* 1980; **2**: 51–9.

Early infantile variant of Krabbe globoid cell leucodystrophy with lung involvement

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SUMMARY An 8-week-old boy presented with a history of irritability, progressive feeding difficulty, generalised weakness, tachypnoea, and minor motor seizures. The clinical course was characterised by rapidly progressive respiratory failure, and neurological deterioration culminating in death at age 15 weeks. Electron microscopical examination and histological studies of the lung showed the presence of numerous intra-alveolar and a few interstitial macrophages. Enzyme studies and subsequent histopathological studies on brain confirmed the diagnosis of an unusual variant of Krabbe globoid cell leucodystrophy.

Krabbe globoid cell leucodystrophy (GLD) is a hereditary degenerative brain disease caused by lack of the enzyme, galactosylceramide β-galactosidase.[1] Typically it is characterised by the onset at between 4 and 8 months of progressive developmental retardation, failure to thrive, seizures, spasticity, and blindness, culminating in death by age 2–3 years. We report here an unusual, early-infantile variant of GLD in which primary lung involvement was prominent.

Case report

The patient was a boy, the fourth child born to apparently unrelated parents. The antenatal history and birth had been normal. Birthweight was 4170 g. From the first day of life, he showed pronounced irritability and twitchiness. By age 2–3 weeks he had progressive feeding difficulty and became increasingly inactive and drowsy. Weight gain ceased. Breathing became rapid and was punctuated by frequent sighing. Two weeks before admission, occasional brief right-sided seizures had been noted.

On admission to hospital at 8 weeks he weighed 4395 g; his length was 57 cm and head circumference 38 cm. He was afebrile, wasted, and drowsy, and

showed little spontaneous voluntary movement. He exhibited pronounced generalised muscle weakness and flaccidity. He had conjugate gaze, but followed poorly with his eyes. The pupils reacted sluggishly but equally to light. The fundi were normal. Deep tendon reflexes were absent. Touching the patient often precipitated sustained right-sided convulsive jerking movements spreading from the arm to involve the entire right side. Breathing was at a rate of 40–70 per minute with slight subcostal indrawing. Ausculation of the chest showed fine inspiratory rales throughout both lungs.

Initial laboratory studies showed moderate leucocytosis ($10{\cdot}0$–$14{\cdot}0 \times 10^9$/l) with marked unexplained eosinophilia (9–21%). A chest roentgenogram showed widespread increase in pulmonary markings interpreted as compatible with interstitial infiltration due to primary diffuse inflammatory lung disease (Fig. 1). Blood gas analyses showed mild compensated respiratory acidosis. Multiple serological studies on both the patient and his mother, and cultures of blood, urine, cerebrospinal fluid (CSF), bone marrow, and tracheal aspirates for bacterial and viral pathogens, chlamydia, and mycoplasma were all negative. Microscopical examination of the CSF on three occasions showed 2–4 leucocytes $\times 10^6$/l; the glucose concentration was normal, but the protein was slightly to moderately increased ($1{\cdot}02$–$3{\cdot}08$ g/l). The electroencephalogram showed diffuse abnormality in keeping with a metabolic encephalopathy.

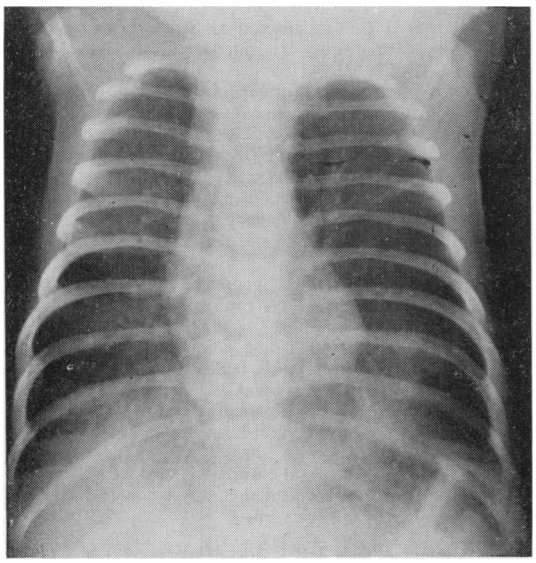

Fig. 1 *Chest roentgenogram showing pronounced hyperinflation and diffuse increase in the interstitial markings of both lungs.*

A tracheostomy was done and ventilatory assistance was begun one week after admission because of progressive respiratory failure. An open lung biopsy was done. The microscopical appearances of the tissue showed widespread distension of alveoli and alveolar ducts by numerous, large, macrophage-like cells with densely eosinophilic cytoplasm and large amber-coloured or brown cytoplasmic inclusions. The inclusions, which exhibited faint autofluorescence, were strongly periodic-acid Schiff-(PAS-) positive and stained with Sudan black. Stains for iron were negative. Although multinucleated macrophages were present, no typical globoid cells were found either at this or at the subsequent necropsy examination. There was no evidence of acute or granulomatous inflammatory reaction. Electron microscopical examination of the lung biopsy showed numerous macrophages containing large, amorphous, electron-dense, membrane-bound inclusions scattered within the cytoplasm (Fig. 2). No crystalloid, tubular inclusions, reported to be present in globoid cells in the brain in GLD,[2 3] were found in the tissue. No virus particles were seen.

Leucocyte arylsulfatase A, β-galactosidase, and β-hexosaminidase activities were all normal. Galactosylceramide β-galactosidase activity of peripheral blood leucocytes and of liver tissue subsequently obtained at necropsy was measured as described by Suzuki and Suzuki[4] with the use of radiolabelled galactosylceramide as substrate. Leucocyte enzyme activity in 36 control subjects of both sexes and all ages was $3{\cdot}67 \pm 0{\cdot}41$ nmol substrate hydrolysed/mg protein/h (mean ± SEM). The patient had no detectable enzyme activity; the activity in leucocytes from his mother was 1·47 nmol/mg protein/h. Liver homogenates showed a similar profound deficiency

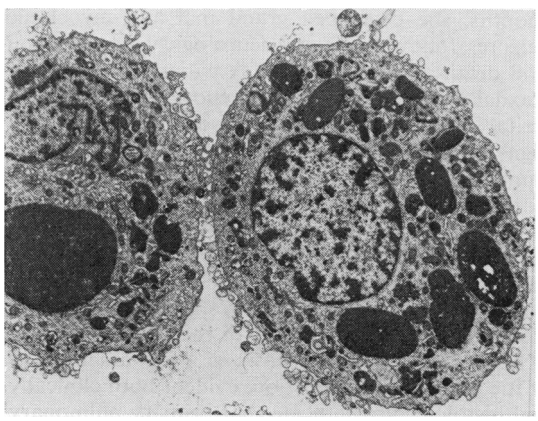

Fig. 2 *Electron micrograph of intra-alveolar macrophages showing membrane-bound, cytoplasmic inclusions, × 1500.*

of enzyme activity (patient, undetectable; control, 1·0 nmol/mg protein/h).

After a course characterised by progressive neurological deterioration, the infant died at age 15 weeks. At necropsy the brain and spinal cord showed gross and histopathological features typical of Krabbe GLD. The lungs were firm and had a fine granular appearance on cut section. The microscopical appearances were indistinguishable from those of the biopsy done at age 9 weeks.

Discussion

In most previously reported cases of Krabbe GLD, patients have developed normally for the first 3 to 5 months of life. Implacable crying and irritability are often the first signs of illness; seizures, hypertonicity, and developmental regression generally follow rapidly. The patient reported here, with histopathologically and biochemically confirmed Krabbe GLD, is noteworthy for two reasons: the very early onset of clinical signs of the disease, and the apparent primary involvement of lung. The earliest signs of unusual irritability dated from the first day of life; by 2–3 weeks he had developed significant feeding difficulty owing to generalised weakness and increasing drowsiness.

Other workers have described patients with GLD in whom signs of disease have been evident within the first few weeks of birth. One of the 6 patients described by Hagberg *et al.*[5] presented with a history of intractible vomiting dating from the first week of life; at age 2½ months he exhibited pronounced irritability and pathological variations in muscle tone, and he subsequently died aged 14½ months. Schochet *et al.*[6] described a patient who showed increased muscle tone, clenched fists, and persistent extension of all extremities from birth. At age 5 months, she developed grand mal and myoclonic seizures, followed by rapid neurological deterioration and death at age 9 months. A patient described by Laxdal and Hallgrimsson[7] is reported to have been irritable since birth and had never smiled, although signs comparable in severity to those exhibited by our patient at age 4–6 weeks did not become apparent until she was 3–4 months old.

Clinical and radiographic pulmonary findings were particularly prominent in our patient. In view of the nature and severity of associated neurological deficits in our patient, central respiratory depression almost certainly contributed to the rapid evolution of his disease. In addition however, the characteristics of the pulmonary infiltration, evident both clinically and histologically, indicate that primary pulmonary involvement very probably accelerated the course of the disease. The diffuse distribution of the pulmonary infiltrate, the absence of interstitial, acute, or granulomatous inflammatory reaction, and the persistence of the clinical and radiographic findings in the lungs despite tracheostomy and aggressive tracheobronchial toilet indicate that recurrent aspiration could not alone account for the pulmonary disease, although initially this possibility had to be considered in view of the evidence of pseudobulbar palsy.

While the cultures of lung and the histological and ultrastructural studies of tissue obtained at biopsy showed no evidence of infection or infestation, numerous intra-alveolar macrophages were identified containing PAS-positive intracellular structures. These were morphologically different from the multinucleated giant cells reported in the lungs of a 14-month-old infant with GLD by Hager and Oehlert,[8] and no typical globoid cells were found. Moreover, the ultrastructural features of the intracellular inclusions were different from those seen in various cellular elements of the brain in GLD.[2 3] We suggest that our patient, and possibly some other reported cases of Krabbe GLD, represents an unusual and rapidly progressive genetic variant of early onset of the disease.

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