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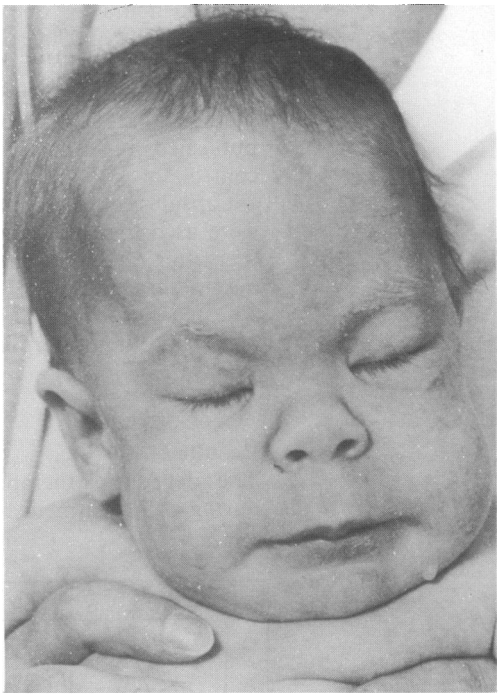
Sialic acid storage disease

P D Cameron, V Dubowitz, G T N Besley, A H Fensom

Abstract

A baby girl with coarse facial features, hepatosplenomegaly, and developmental delay had raised free sialic acid concentrations in her urine and cultured fibroblasts. She died aged 13 months. Sialic acid is an important constituent of many glycoproteins and glycolipids; impaired release from the lysosome may be the underlying biochemical defect.

Disorders of sialic acid metabolism fall into four categories. Raised concentrations of bound sialic acid are found in conditions associated with neuraminidase deficiency.[1] No enzyme deficiency has been shown in three other categories where raised concentrations of free sialic acid are found: Salla disease, sialuria, and severe infantile sialic acid storage disease. Salla disease, named after an area in northern Finland, comprises progessive psychomotor retardation with lysosomal storage in patients reaching adult life.[2] Two cases of sialuria have been described where only sialic acid in the urine was raised. These patients had coarse facies, hepatosplenomegaly, a mild clinical course, and no lysosomal storage.[3] This case report concerns the fourth category: severe infantile sialic acid storage disease.



Dysmorphic features showing coarse facies, wispy hair and eyebrows, and telangiectasias.

Case report

The baby girl was the second child of healthy unrelated white parents; her brother, aged 2 years, was normal. Pregnancy was complicated by premature labour at 32 weeks' gestation; breech presentation necessitated a caesarean section. Birth weight and head circumference were both below the third centile. Resuscitation with intubation was required for five minutes. Initial problems included transient tachypnoea and episodes of cardiac failure with dusky spells and hepatomegaly. Chest radiographs showed cardiomegaly and pulmonary plethora. Transfusion was required for anaemia.

Dysmorphic features comprised hypertelorism, prominent epicanthic folds, strikingly fluffy eyebrows, a long philtrum, and a high arched palate (figure). Facial features were generally coarse. She had short stubby fingers and a square set thumb. Her skin was pale with wispy orange hair.

Diuretics and fluid restriction controlled her cardiac failure and she was discharged home at 8 weeks. She was readmitted at 11, 13, and 16 weeks with chest infections and cardiac failure. Hepatosplenomegaly and telangiectasias had become prominent. She developed a need for supplemental oxygen, and weight gain remained poor. By 5 months she had rarely smiled, she remained hypotonic, visual following was poor, and auditory response was absent.

Laboratory investigations at 5 months included measurement of blood concentrations of urea, electrolytes, and haemoglobin, liver function, blood and urine amino acids, urine mucopolysaccharides, and lactate. Chromosome analysis, iron studies, thyroid function tests, and lysosomal enzyme activities were also performed. All studies gave normal results. Skeletal survey, cranial ultrasound, and nitrogen washout tests were also normal. Chest radiography showed fine hazy shadowing in the lung fields and cardiomegaly. Ophthalmic examination showed an intermittent divergent strabis-

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Sialic acid concentrations in urine and cultured fibroblasts

	Patient	*Controls*	
		Mean	*Range*
Urine (μmol/mmol creatinine)			
Free	994	93, 78	
Bound	109	71, 52	
Fibroblasts (nmol/mg protein)			
Free	25	2·6	1·5–6·7 (n=9)
Bound	17	8·6	6·5–10·7 (n=5)

Sialic acid concentrations were measured by the thiobarbituric acid method[4] before and after hydrolysis.

mus and a pale retina. Blood smears showed vacuolated lymphocytes, monocytes, and neutrophils. A bone marrow specimen also showed vacuolated cells and an excess of eosinophils. The free sialic acid concentration of cultured fibroblasts and urine was raised (table), and a diagnosis of severe infantile sialic acid storage disease was made.

Subsequent clinical progress was poor. She remained extremely hypotonic and was socially unresponsive. Oxygen requirement persisted, and she eventually died with bronchopneumonia at 13 months. Permission for necropsy was refused.

Discussion

Stevenson *et al* described two unrelated cases of severe infantile sialic acid storage disease and reviewed five other cases in 1983.[4] The main features he identified were coarse facies, growth delay, appreciable mental retardation, hepatosplenomegaly, recurrent pneumonias, and in five, evidence of lysosomal storage with raised free sialic acid in cells and urine. The infant reported here displayed all these features, and she also showed a more pronounced respiratory impairment. Cardiac failure was also prominent, suggesting either a storage disorder of the myocardium, or a response to the respiratory problems. The presence of multiple widespread telangiectasias, presumably related to liver disease, is also a new finding.

The exact role of sialic acid in cellular function is unclear, but it is known to be an important constituent of many glycolipids and glycoproteins. It has been suggested that the underlying defect is impaired transport of free sialic acid across the lysosomal membranes, but the precise defect has yet to be identified.[5] Antenatal diagnosis is available by assaying free sialic acid in amniotic fluid or by chorionic villus biopsy.[6] Severe infantile sialic acid storage disease should be considered in a child presenting with coarse facial features, growth and developmental delay, hepatosplenomegaly, and evidence of abnormal storage in cells.

We are grateful to Dr AW Boon for allowing us to report his patient.

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Acute liver failure induced by carbamazepine

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Abstract

Two children developed acute liver failure while taking carbamazepine. Clinical and laboratory findings suggested an immunoallergic reaction, but only one child improved on steroids. Determination of liver function during the first few weeks of treatment and early detection of signs of idiosyncrasy may prevent this rare but severe complication.

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Since 1970, 14·5 million adults and children are estimated to have taken carbamazepine. Unwanted effects mainly or exclusively affecting the liver have been reported in 499 instances, but often other causes of liver damage were not excluded. In about half of these cases alteration in the results of liver function tests was the only abnormality reported (Ciba-Geigy, personal communication). There have been 17 deaths from liver disease, five in children,[1 2] but in only one of these was carbamazepine the sole hepatotoxin. We describe two children receiving carbamazepine who developed life threatening liver disease.

Case reports

CASE 1

A girl aged 11·6 years developed a severe maculopapular rash, intermittent fever, arthralgia, cough, anaemia, anorexia, diarrhoea, and vomiting four weeks after starting carbamazepine (16 mg/kg/24 hours) for focal epilepsy. Her medical history was negative. Carbamazepine was stopped, the blood concentration being 32 μmol/l (therapeutic range: 16–50 μmol/l). Two weeks later she developed jaundice. On admission, six days later, she was pale and jaundiced, with a generalised exfoliative rash, periorbital oedema, generalised lymphadenopathy, and stomatitis. Firm liver and spleen