An infant with multiple congenital abnormalities and biochemical findings suggesting a variant of galactosialidosis

B Say, F A Hommes, S A Malik, N J Carpenter

Abstract

A female newborn probably with a variant form of galactosialidosis is described. The patient, in addition to the common findings seen in early infantile forms of classical galactosialidosis, displayed an unusual combination of congenital malformations including complex cyanotic congenital heart disease with dextrocardia and situs inversus.

Galactosialidosis is a well established genetic disorder with several clinical types, such as early and late infantile forms, as well as a juvenile/adult form. The biochemical studies in these patients show a combined deficiency of β -galactosidase and neuraminidase. In the early infantile form, the clinical picture consists of oedema, ascites, skeletal dysplasia, and ocular findings including cherry red spots.¹

We present a newborn infant with biochemical findings resembling galactosialidosis who also had an unusual combination of congenital malformations including complex cyanotic congenital heart disease with dextrocardia and situs inversus.

Case report

A Caucasian female infant was born at 33 weeks of gestation to an unrelated 27 year old gravida 2 para 0 mother and 28 year old father. The family history showed that a sib of this infant born at 24 weeks of gestation had died at 24 hours of age. However, no biochemical or necropsy studies were carried out. Apgar scores for our patient were 5 and 7 at one and five minutes, respectively. She was intubated and placed on mechanical ventilation for poor respiratory effort and persistent cyanosis. Her birth weight was 2170 g (10th centile), length 45 cm (90th centile), and head circumference 28 cm (10th centile). She had moderate respiratory distress and a harsh pansystolic grade III/VI murmur. There was shortening of the fourth fingers bilaterally. The rest of the physical examination was within normal limits with the exception of marked generalised hypotonia.

The infant had multiple investigations for extremely raised WBC count ($54\,800/\text{mm}^3$) and C-reactive protein. She was maintained on total parenteral nutrition throughout the hospital course and some oral feedings as tolerated. A random urine specimen was negative for mucopolysaccharides. She developed mild

cholestatic jaundice with conjugated bilirubin of 5.6 mg/dl late during her stay in hospital. Her eye examinations were initially normal but the last examination before death showed marked oedema of the eyelids. The corneae and lenses were clear and the discs and macular regions were normal. At 35 days of age, she developed claw-like hands and generalised oedema which did not respond to diuretics.

The infant's condition deteriorated gradually with increasing hypotonia and generalised oedema. She developed renal failure, massive ascites, and marked acidosis. Cardiac function and blood pressure remained stable until the day before death when blood pressure started dropping. She died at 78 days of age. Permission for necropsy was denied.

A chest radiograph on admission showed dextrocardia, complete situs inversus, and normal looking lungs. An echocardiogram indicated a functioning univentricular heart of left ventricular type, a single AV inlet, two semilunar valves at the same level, and patent ductus arteriosus. Cardiac catheterisation confirmed these anomalies. EEG and head sonograms were normal. A CT scan of the head at 47 days of age was consistent with microcephaly with a small calvarium in relationship to the face. Skeletal survey done at 43 days of age showed diffuse periosteal reaction and new bone formation in the shafts of all long bones (figure). All through her hospital stay she continued to be dependent on a ventilator.

Cytogenetic studies by Giemsa-trypsin banding of prometaphase chromosomes from lymphocytes showed a normal 46,XX karyotype. The karyotypes of the parents were also normal. Biochemical studies included thin layer chromatography for oligosaccharides which showed an abnormal pattern similar but not completely identical to that observed in neuraminidase deficiency.² Excretion of unbound sialic acid was 1.52 mmol/g creatinine (normal 0.90 ± 0.35) and of total sialic acid was 5.02 mmol/g creatinine (normal 1.86 ± 1.05).³ The activity of β -galactosidase, determined twice in skin fibroblasts was 57 and 142 nmol/h/mg protein (normal 186 to 546). The neuraminidase activity in fibroblasts was 20 nmol/h/mg protein (normal 25 to 63).⁴ The enzyme activities in the parents were as follows: β -galactosidase, 194 in the father and 80 in the mother; neuraminidase, 13 in the father and 89 in the mother. Clearly, the biochemical findings in this infant did not fit with those seen in patients with classical early onset galactosialidosis. We postulate that she probably has a variant form of this disorder.

H Allen Chapman
Research Institute of
Medical Genetics,
Children's Medical
Center, Tulsa, OK
74135, USA.

B Say
N J Carpenter

Biochemical Genetics
Laboratory, Medical
College of Georgia
and Gracewood State
School and Hospital,
Gracewood, GA 30812,
USA.
F A Hommes

Eastern Oklahoma
Perinatal Center, St
Francis Hospital, 6161
S Yale, Tulsa, OK
74136, USA.
S A Malik

Correspondence to Dr Say.
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Radiograph of the arm at 6 weeks of age showing diffuse periosteal reaction involving the shafts of the long bones.

Discussion

The common clinical manifestations of infantile galactosialidosis mainly result from generalised sphingolipid storage and consequently mimic those seen in GM1 gangliosidosis. These include hypotonia, hepatosplenomegaly, dysostosis multiplex, frequently with significant periosteal new bone formation, and progressive neuromotor degeneration with or without retinal cherry spots.¹ The patients may also display macrocephaly with coarse facial features, generalised oedema, and

ascites.⁵ Routine screening tests for inborn errors of metabolism usually give normal results, therefore delaying the diagnosis. Testing for vacuolated lymphocytes for screening purposes appears to be useful. A definitive diagnosis, however, requires oligosaccharide chromatography followed by the appropriate enzyme studies. Galactosialidosis can be diagnosed by showing a deficiency of the lysosomal β -galactosidase and neuraminidase or by assay of lysosomal carboxypeptidase activity obligatory for the maturation of the protective protein precursor, which in turn is necessary for the formation of a stable multienzyme complex containing the β -galactosidase and neuraminidase.⁶

The patient presented here displayed several congenital malformations which, as far as we could find, have not been reported previously in patients with classical galactosialidosis. However, our patient did not seem to be a clear cut case of this entity and may represent a variant form of it, associated with major congenital malformations. On the other hand, the malformations observed may represent coincidental findings. Finally, it is also possible that both the biochemical and organic pathology recorded are the result of a submicroscopic chromosome abnormality.

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