So the total probability of pedigree Pe for possibility C is

\[
\left(\frac{1}{2}\right) \left(\frac{P}{4}\right) \left(\frac{P^3}{8}\right) \left(\frac{1}{4}\right) \left(\frac{P}{4}\right).
\]

The total probability of getting the pedigree of the family Pe is \(\frac{1}{2} (A + B + C)\).
The log likelihood for the family \(L \theta = \log_{10}\left(\frac{1}{2} (A + B + C)\right)\)
and the lod score \(Z \theta = L \theta - L(\frac{1}{2})\)
\[
= \log_{10}\left[\frac{pq^6 (q^2 + p) + p^3q^4 (pq + q) + p^4}{0.0742}\right]
\]
For various values of \(\theta\) these give lod scores as listed in the Table.

<table>
<thead>
<tr>
<th>(\theta)</th>
<th>For family Pe</th>
<th>Family I, Emery (1966)</th>
<th>Total lod score</th>
<th>Relative likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>-0.325</td>
<td>-0.442</td>
<td>-0.767</td>
<td>0.171</td>
</tr>
<tr>
<td>0.10</td>
<td>-0.179</td>
<td>-0.188</td>
<td>-0.357</td>
<td>0.429</td>
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<tr>
<td>0.15</td>
<td>-0.158</td>
<td>-0.062</td>
<td>-0.220</td>
<td>0.603</td>
</tr>
<tr>
<td>0.20</td>
<td>-0.182</td>
<td>0.010</td>
<td>-0.172</td>
<td>0.673</td>
</tr>
<tr>
<td>0.25</td>
<td>-0.220</td>
<td>0.051</td>
<td>-0.169</td>
<td>0.678</td>
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<tr>
<td>0.30</td>
<td>-0.249</td>
<td>0.070</td>
<td>-0.179</td>
<td>0.662</td>
</tr>
<tr>
<td>0.35</td>
<td>-0.246</td>
<td>0.073</td>
<td>-0.173</td>
<td>0.671</td>
</tr>
<tr>
<td>0.40</td>
<td>-0.201</td>
<td>0.061</td>
<td>-0.140</td>
<td>0.724</td>
</tr>
<tr>
<td>0.45</td>
<td>-0.114</td>
<td>0.037</td>
<td>-0.077</td>
<td>0.838</td>
</tr>
</tbody>
</table>

I am grateful to Dr Ruth Sanger, not only for doing the Xg(a +) blood groups, but also for her help and advice. I also want to thank Professor Emery for drawing my attention to family L and for letting me have his lod scores. The CK levels were done at the Area Laboratory at Taunton Hospital by courtesy of Dr. J. Harkness.

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The Surgery, Church's Square, Taunton, Somerset.

Reference


GM₁ gangliosidosis type 1 in twins

SUMMARY This report describes 7-month-old monozygotic twin female infants with GM₁ gangliosidosis type I. In addition to the usual clinical and biochemical abnormalities general-
ized intracutaneous telangiectasis were present in both infants.

Generalized gangliosidosis, an inborn error of metabolism secondary to deficiency of the enzyme B galactosidase (Okada and O'Brien, 1968), is biochemically characterized by the visceral accumulation of a keratin sulphate-like mucopolysaccharide (Suzuki, 1968) in addition to the neuronal and visceral accumulation of a monosialanganglioside GM₁ (ganglioside nomenclature of Svennerholm, 1964).

Clinically, two distinct phenotypes (type I and type II) of disease have been recognized, distinguished by age of onset and degree of visceral and skeletal involvement. Inheritance is autosomal recessive in pattern (Derry et al., 1968). In patients with type I disease neurological degeneration is progressive and despite good supportive therapy, survival past the age of 2 years is uncommon (O'Brien, 1969).

In type II disease the onset of neurological symptoms is later (7 to 16 months) and the coarsening of facial features, hepatosplenomegaly, and fundus changes characteristic of type I disease do not occur. Radiographic lesions, when present, are mild. Neurological degeneration is rapidly progressive with seizures occurring in approximately 50% of patients (Wolfe et al., 1970).

Definitive diagnosis is dependent on demonstration of a reduction in the enzyme B galactosidase in peripheral leucocytes or in cultured skin fibroblasts. The enzyme assay is effective in the identification of both homozygous and heterozygous gene carriers and, in addition, has been successfully used for the prenatal diagnosis of afflicted infants (Nadler and Gerbie, 1970).

The occurrence of generalized gangliosidosis in twins has yet to be reported though the disease is well established as a distinct clinical and biochemical entity and has been the subject of several comprehensive reviews (Okada and O'Brien, 1968; Wolfe et al., 1970). This communication describes the occurrence of the infantile form (type I) of this disease in monozygotic twins.

Case reports

Seven-month-old twin Caucasian female infants were referred for examination of hepatosplenomegaly and psychomotor retardation. They were products of a 38-week uncomplicated pregnancy with normal labour and delivery. Gross and microscopical examination of the placenta revealed two amniot and one chorion.

Physical examination showed small, hypoactive
female infants with macrocephaly and coarse facial features (Fig.). Length and weight were below the third centile and head circumference was at the seventy-fifth centile. Facial abnormalities included frontal bossing, periorbital oedema, depressed nasal bridge, increased distance between the nose and upper lip, and alveolar ridge hyperplasia; the infants also had horizontal nystagmus, poor pupillary responses to light, clear corneas, and bilateral cherry red spots. Their liver and spleen were enlarged. Both had limitation of motion at their hip joints and non-pitting oedema over their tibiae, wrists, and ankles; generalized fine intracutaneous telangiectasias, hypotonia, pronounced head lag, persistence of primitive reflexes, and an inability to roll over.

Skeletal x-ray films showed J-shaped sella, spatulate ribs, widened, wedge-shaped metacarpals, widened humeral diaphyses, with cortical rarefaction, and beaking of L1 vertebrae in both infants.

Vacuolization of peripheral lymphocytes and bone marrow histiocytes was noted. Limited studies of the ABO, Rh, MNS, and Kell systems were consistent with monozygotic twinning. Beta-galactosidase activity in cultured skin fibroblasts was below 10% of normal.

Discussion

The infantile form (type I) of generalized gangliosidosis is characterized by coarse facial features, gingival ridge hyperplasia, oedema, hepatosplenomegaly, progressive CNS degeneration, skeletal, and neurological abnormalities. The features of the syndrome are usually evident at birth or early in the neonatal period (O'Brien, 1969). Other abnormalities include vacuolization of peripheral lymphocytes and marrow histiocytes, foamy mononuclear cells in the urinary sediment, and pronounced reduction of β-galactosidase activity in leucocytes and fibroblasts. The skeletal changes are usually apparent by 6 months of age (Landing et al., 1964).

The infants described in this report represent, to our knowledge, the first report of this disease in presumed monozygotic twins. Both infants showed the facial, neurological, visceral, radiological, and enzymatic abnormalities previously described. In addition, both infants had generalized intracutaneous telangiectasias not previously described in this syndrome.

We thank Dr Henry L. Nadler for the beta-galactosidase assay and his advice.

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2The views expressed here are those of the authors and do not necessarily reflect the United States Air Force or The Department of Defense.
References


Reproductive ability of an adult female with Silver-Russell syndrome

SUMMARY An adult female with typical features of Silver-Russell dwarfism gave birth to a viable infant. Despite the abnormalities in sexual development that may be associated with the Silver-Russell syndrome, fertility is not necessarily impaired, at least in females.

The growth and development of children with the Silver-Russell syndrome have been studied (Silver, 1964; Tanner et al., 1975). There is, however, virtually no information available about adult patients with this syndrome. It is known that both male and female Silver-Russell dwarfs develop secondary sexual characteristics (Rimoin, 1969; McDowell and Sproles, 1973) but fertility of these patients has not been described previously.

Case report

The patient is a Puerto Rican female, born when her father and mother were 24 years of age. She was the second of 3 children; the 2 sisters were normal and over 152 cm tall. A paternal aunt and a paternal uncle are short in comparison to other family members. The patient’s mother is 157 cm tall and her father is 175 cm tall. During the patient’s gestation her mother gained only 4535 g though she was delivered at term. Birthweight was only 1871 g. During infancy the patient had severe feeding difficulties and exhibited poor weight gain and excessive sweating. A grand mal seizure occurred at 1 month of age, at which time a doctor diagnosed hydrocephalus. At 3 months, asymmetry of the extremities (smaller on the right) and congenital dislocation of both hips were noted. The anterior fontanelle was large up to age 18 months.

Motor development was slow, with poor head control until 8 months of age, and walking began at 2 years. Language development was normal, however, and the patient’s intelligence remains above average.

Evaluation at another hospital in New York City at age 9 years revealed a height of 99 cm (50th centile for 3½ years) and weight of 11·8 kg (50th centile for 2½ years). The diminished size of the right upper and lower extremities was noted. The development of sexual characteristics was described as early, but the exact age was not recalled. Menarche occurred at age 11 years in the patient, and at ages 13 years and 15 years in her younger and older sisters, respectively. Bone age was less than 6 years at 9 years chronologically, and was 8 years at 11 years, 8 months of age.

The patient married a paternal first cousin, and at 26 years of age gave birth to a son after a 7-month gestation. Delivery was uneventful, and the infant’s birthweight was 1927 g. The son had bilateral cleft lip and palate, normal intelligence, and stature slightly below the third centile, but did not have features of Silver-Russell syndrome.

At the time of this investigation, the patient was 32 years old, her height was 131 cm and weight 25 kg. She had microcephaly with a head circumference of 48·5 cm. The face is triangular with mild micrognathia and turned down corners of the mouth (Fig. 1). The palate was slightly high arched, and the teeth were crowded. The left pinna was simple and larger than the right. The hairline was normal for a female. The neck was not webbed, and the chest configuration was normal and symmetrical. Breast development was normal. The abdomen appeared protuberant because of a lordotic posture. There was female distribution of pubic hair. The trunk and extremities were asymmetrical (Fig. 2). The right and left upper extremities measured 50·5 cm and 53·25 cm, respectively from the acromion to the tip of the 5th finger; there was a 2 cm leg length discrepancy, the left larger than the right, and the maximal calf circumference was 24·25 cm on the left and 21·75 cm on the right. There was a limitation of hip abduction to 30° bilaterally. The feet showed partial syndactyly

1Supported by a grant from the National Institutes of Health (GM 191000).