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Cervical vertebral fusion (Klippel-Feil) syndrome with consanguineous parents

Summary. We describe a female infant with the cervical vertebral fusion (Klippel-Feil) syndrome whom we recognized at birth because of her short neck, restriction of cervical movement, and low posterior hairline. X-ray examination showed anomalies of C1, and between C2-3 and C3-4; thus, we classified her as type II, with variable cervical fusion. At 24 months she was small and manifested hearing deficiency. The mother and father were consanguineous with five common ancestors four generations ago, which resulted in a coefficient of inbreeding equivalent to a second cousin relationship. The parents and grandparents were phenotypically normal, and the parents were radiologically normal. This form of the syndrome has previously been said to be autosomal dominant. Our conclusion of determination by a single autosomal recessive gene is evidence of genetic heterogeneity.

The syndrome which results from cervical vertebral anomalies (usually fusion), attributed to Klippel and to Feil, encompasses the appearance of a short neck, painless restriction of cervical movement, and a low posterior hairline, at least as it is generally recognized. Radiological criteria define three types, based in the main on the number of vertebral fusions. The second type has been further divided according to the specific vertebrae fused.

The aetiology of this congenital malformation

FIG. 1. Proposita at 24 months.

appeared to be monogenic in those instances where there were similarly affected members in successive generations or where sibs were affected. Sporadic cases presented the usual dilemma about cause except possibly where the parents were consanguineous, a finding supportive of a genetic origin. Genetic heterogeneity seems apparent not only with regard to the three types but also within type II.

This report describes a case of type II of the syndrome, which we recognized at birth, presents the pedigree which included five ancestors common to both parents, and suggests that the aetiology in this instance is a single autosomal recessive gene.

Case report

A white female infant was born to a 19-year-old woman and a 26-year-old man. She was the result of their first pregnancy which lasted approximately 36 weeks. Her birthweight was 1930 g, length 42 cm, head circumference 31 cm, and chest circumference 24 cm. She appeared to have a short neck, with her chin resting on the sternum anteriorly and the hairline reaching the level of the upper scapulae posteriorly. The central portion of her anterior chest was particularly prominent creating a depression just below the line of each shoulder. There were hemangiomas over the centre of the forehead and below the left naris. A systolic murmur, maximal at the base of the heart, appeared first at 5 days. Her appearance was somewhat like that of the XO syn-

drome, but analysis of nuclear chromatin was consistent with the presence of two X chromosomes.

Her course in the hospital was troubled first by diarrhoea and then by abdominal distension, and throughout the first 4 weeks by inadequate growth. She left the hospital at the age of 6 weeks weighing 2410 g.

Subsequently, she gained in weight consistently, but her height remained below normal. By 6 months, the cardiac murmur was barely audible. Her limitation in neck mobility, including flexion and extension as well as rotation, became increasingly apparent with motor development. She had recurrent infection of her ears, and the parents noticed that she did not respond normally to vocal stimuli. When tested at 17 months, she responded to speech presented through a speaker at levels between 60 and 70 decibels. However, she made no responses to simple questions at levels below 60 decibels, which was decidedly abnormal.

At 24 months she was below the 3rd centile for weight, height, and head circumference and in the 3rd to 10th centile for chest circumference. Her neck was short and broad (Fig. 1), and she managed to look to the side by rotating the upper portion of her trunk with her head. We considered her developmental level to be between 18 and 24 months in spite of some disability in fine motor functioning.

X-ray examination showed anomalous development of the first cervical vertebra which the radiologists stated would become more evident as ossification became more complete. There was also incomplete segmentation between C-2 and C-3 and between C-3 and C-4 (Fig. 2). At least one vertebral segment was missing from the cervical-thoracic area. There appeared to be two sets of cervical ribs which accentuated the shortening of the neck. There remained just 10 pairs of ribs attached to the thoracic vertebrae. The lumbosacral spine looked entirely normal.

The parents appeared to be normal phenotypically, though the height of the mother was 146 cm and of the father 172 cm. Each appeared to have a normal cervical spine radiologically. The family tended to shortness, the paternal grandfather was 172 cm, the paternal grandmother 156 cm, the maternal grandfather 172 cm, and the maternal grandmother 156 cm. All appeared to be normal.

Pedigree

Fig. 3 shows the ancestral pedigree, which is abbreviated to include only those ancestors involved in the consanguinity. By careful questioning we were reassured that there was no relative who was either identically or similarly affected. The only relatives whose phenotype might possibly be causally associated with that of the probanda seemed to be the parents, because of their shortness, but each was otherwise physically normal, and the upper spine of each was normal on x-ray examination.

The mother and father of the infant were consanguineous with altogether five common ancestors four generations ago. They were related as third cousins through I.1 and I.2, their common great-great grand-

FIG. 2. Cervical vertebrae of propoita at 15 months showing incomplete segmentation between C-2 and C-3, between C-3 and C-4, and one missing segment from the cervical-thoracic area.

parents, which contributed $\frac{1}{2 \times 3 \times 6}$ or 0.0039 to the coefficient of inbreeding (F) in the propoita. They were related as second cousins, once removed, through I.4 and I.5, great grandparents of the father of the propoita but great-great grandparents of her mother, which contributed $\frac{1}{1 \times 2 \times 8}$ or 0.0078 to the coefficient of inbreeding in the propoita. They were also related as half second

cousins, once removed through I.3, again the great grandparent of the father and the great-great grandparent of the mother. The sex of this ancestor could not be determined, and all we learned was that II.4 and III.3 were related as half brothers. The contribution of I.3 to the coefficient of inbreeding was $\frac{1}{2} \times \frac{1}{1 \times 2 \times 8}$ or 0.0039. By summation, the total $F = \frac{4}{2 \times 3 \times 6}$ or 0.0156, which is equivalent to that of a second cousin relationship.

The meaning of a coefficient of inbreeding of 0.0156 is that we can expect that at 1.56% of the loci there is homozygosity of two genes which share a common origin, or, alternatively, that at any particular locus we randomly select, there is a 1.56% chance of homozygosity by genes which were derived from the same gene.

Comment

Classification. Morphological criteria define three types of the cervical vertebral fusion syndrome according to the number and site of the fused segments. Type I is an extensive malformation in which several adjacent vertebrae are fused into an immovable unit or block. Type II encompasses the fewest defects, and the expression ranges from a diminished interspace or incomplete segmentation to complete fusion of two vertebrae. In type III, fusion of the lower dorsal or lumbar spines coexists with cervical fusions of either types I or II.

Type II is subdivided according to the site of the fusions: (1) C2-3 fusion may be manifest only as narrowing of the interspace or an anomalous atlanto-occipital joint, but more severe cases may include actual atlanto-occipital fusion, possibly basilar impression, or eight cervical vertebrae; (2) C5-6 may be fused or their interspace narrowed; and (3) variable cervical fusion includes instances

FIG. 3. Pedigree of the kindred.

where the vertebral defects do not fall into either of the preceding categories.

Whereas type I patients are obviously abnormal because of their appearance—that is a short neck, the limitation of rotation, and a low hairline—type III patients are not necessarily recognizable for their anomalies. Because of their normal appearance, type II patients are usually not recognized until the complications caused by their malformation are investigated or their anomaly is discovered incidentally (Gunderson *et al*, 1967; Poznanski, 1974).

Our patient represented a problem in classification, for her abnormal appearance was like that of a type I patient, but her cervical anomalies were like those in type II with variable fusion. Because she did not have blocked vertebrae but because of her anomalies in at least three sites—C1, C2–3, and C3–4—we considered her defects most likely to be classed as type II with variable fusion.

Hearing deficiency. Deafness has been said to be the second most common anomaly associated with the syndrome (Palant and Carter, 1972; Stark and Borton, 1973; McLay and Maran, 1969). There is histological and x-ray evidence that the structure of the inner ear is abnormal (Palant and Carter, 1972). Because there was no other deafness in the family and also because our patient seemed less severely affected than often occurs in the hereditary forms of deafness (Fraser, 1964), we concluded that her hearing deficiency was most probably associated with the syndrome and not independently determined.

Genetic determination and mode of inheritance. The patient appeared in the pedigree as a sporadic occurrence of her congenital malformations. Because there was no suspicion of any environmental agent, we concluded that genetic determination was probable. After rejection of the possibility of a phenocopy—an environmentally caused mimic of a genetically determined disorder—there remained three considerations: spontaneous mutation, reduced penetrance, and recessive homozygosity. The normality of the cervical vertebrae of the parents plus the phenotypic normality of the parents and the grandparents argued against the likelihood of reduced penetrance. Parental consanguinity favoured an interpretation of determination by a single autosomal recessive gene. The probability of spontaneous mutation can be further considered when there are more progeny.

The implication of the consanguinity to an understanding of the aetiology of this instance of the cervical vertebral fusion syndrome is the same as that

when there are consanguineous parents of any offspring who has a rare disorder, namely, that the disorder is genetically determined, probably by a recessive gene, which most likely came to be homozygous in the proposita as a result of descent from an ancestor common to both parents. Of course, this does not mean that one or both genes could not have arisen independently.

Gunderson *et al* (1967) suggested that type II with variable cervical fusion is caused by a single dominant gene with considerable variation in both penetrance and expression. If our case fits into type II with variable cervical fusion and if our conclusion of a single recessive gene is correct, then there is evidence of genetic heterogeneity for this clinical class, there apparently being both a dominant and a recessive gene producing the phenotype.

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Pterygium syndrome

Summary. The pterygium syndrome consists of webbing of the neck, the antecubital fossae and the popliteal regions together with flexion deformities of the limb joints and anomalies of the vertebrae. A family, three offspring of which appear to be affected with the same disorder, is presented. All three are female; there is also a normal female child of the same union.