Pitfalls in counselling: the craniosynostoses

Romana Marini, Karen Temple, Lyn Chitty, Sally Genet, Michael Baraitser

Abstract

We describe three families to highlight the variability of expression and penetrance that can occur in the craniosynostoses. In two of the families, gene carriers were only identified in retrospect by looking at photographs of other family members. In the third family, identical twins were initially thought to be discordant for sagittal craniosynostosis until early skull x rays were examined and both were found to be affected. The dilemmas faced when counselling these families are discussed.

Variability of expression and penetrance is well known to occur in a number of dominantly inherited conditions including some of the craniosynostoses. This occurs particularly in Crouzon, Pfeiffer, and Saethre-Chotzen syndromes¹ and is a significant hazard in counselling. The main practical problem is the calculation of risks to further children after the birth of a child with one of these syndromes. In general, most geneticists would be aware of the need to examine both parents carefully and, as the sutures close in childhood, the usual procedure would be to examine the head shape, facial appearance, hands, and feet, and where possible look at childhood photographs. A value judgment can then be made as to whether each parent is a carrier or not. Unfortunately this might not be sufficient.

We report two instances to illustrate this point. In addition, we describe a third family where identical twins showed marked differences in the degree of expression of sagittal craniosynostosis and where mistakes would have been made in adulthood had

early skull x rays of these affected twins not been performed.

Case reports

FAMILY 1

The proband (fig 1), a female, was the first child of unrelated Caucasian parents aged 23 years (mother) and 26 years (father). At birth she was noted to have an asymmetrical face and skull with depression of the right forehead, and a skull x ray showed a right coronal synostosis. Examination at 9 months showed development to be proceeding normally. The head circumference was 44.1 cm (25th to 50th centile) and the anterior fontanelle was small. A prominent ear crus and mild left ptosis were noted. The rest of the examination was normal including hands and feet, hearing, and vision. A diagnosis of Saethre-Chotzen syndrome was made.

Figure 1 Father and daughter (family 1). The daughter has Saethre-Chotzen syndrome. Note the normal craniofacial appearance of the father.

Department of Endocrinology, Ospedale Pediatrico Bambino Gesù, Istituto di Ricerca Scientifica, Piazza S Onofrio 4, 00165 Roma, Italy.
R Marini

Clinical Genetics Unit, Hospitals for Sick Children, Great Ormond Street, London WC1N 3JH.
K Temple, L Chitty, S Genet, M Baraitser

Correspondence to Dr Baraitser, Department of Clinical Genetics, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.

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A CT scan at 9 months of age showed mildly enlarged ventricles and prominent cortical sulci. At 16 months of age the child underwent an operation for craniofacial reconstruction.

Her parents came to the genetic clinic seeking advice as to risks of recurrence in future pregnancies. The initial impression on careful inspection was that neither parent was a gene carrier. Head shape was normal in both parents as were the hands, feet, and ears. The family history, however, indicated that the father (fig 1) had an affected sister who had had an operation for bilateral coronal synostosis in the 1960s and this was confirmed by early photographs of the proband's aunt (fig 2) and operation notes. No information was available on the grandparents, but they were not thought to have had an unusual head shape.

FAMILY 2

The proband, a male, was the third child of unrelated Caucasian parents who were 35 years (mother) and 33 years (father) at the time of his birth. He had two healthy brothers. At birth he was noted to have a number of congenital anomalies including an unusual shaped skull, a preauricular skin tag on the left, a bifid uvula, an undescended right testis, and a penoscrotal hypospadias. Examination at 10 months of age showed marked turriccephaly and brachycephaly with prominent ridged coronal sutures, an enlarged anterior fontanelle, shallow orbits with hypoplastic supraorbital ridges, and proptosis which was more marked on the right. In addition he had a variable divergent squint. There were no abnormalities in his hands and feet and his motor development was normal. Skull x ray showed bilateral coronal synostosis.

He had several admissions to hospital for repair of

the hypospadias, right orchidopexy, and removal of the ear tag. At 2 years of age a mixed bilateral hearing loss was noted. At operation, he was found to have abnormal ossicles with short malleus handles bilaterally. He has been left with a moderate hearing loss, worse on the left than the right with a definite sensorineural component.

Figure 3 Mother and son (family 2). The son has bilateral coronal synostosis. Note the minimal proptosis but normal head shape in the mother.

Figure 2 Early photographs of the proband's paternal aunt (family 1) to show evidence of craniosynostosis. Note the prominent ear crus.

Figure 4 The proband's maternal grandparents (family 2). The grandfather has an unusual head shape and clearly is a gene carrier.

A CT scan was performed at 7 years of age because of headaches and this showed normal sized ventricles and no other abnormalities. On review at 7 years 6 months of age he was well, with height, weight, and head circumference on the 3rd centile. Intellectual

development was within normal limits but he attended a school for the deaf.

His mother had minimal evidence of proptosis but a normal skull shape and normal hands and feet (fig 3). Without a family history an estimation of recurrence risks would have been difficult for this couple. The mother's family photograph album, however, clearly showed her father to be affected (fig 4) and an extended pedigree showed five generations of affected subjects.

FAMILY 3

The proband was one of twin boys born to healthy, unrelated, Caucasian parents. He had an older brother who is said to be normal. The twins were born by caesarean section at 32 weeks' gestation. At birth, the proband was noted to have an abnormal skull shape with a prominent ridge along the sagittal and the metopic suture lines. He also had shallow orbits. X rays showed fusion of the sagittal and metopic sutures. He underwent a successful craniectomy at the age of 3 months. His twin brother appeared normal. Both twins were seen in the genetics clinic when they were 5 years old. Development was normal and their parents were keen to know what the offspring risks would be for each twin. They had been told that the boys were identical twins after careful examination of the membranes at delivery. We have confirmed monozygosity by hybridising four single locus hypervariable DNA probes to Southern blots of the twins' DNA. In each case the twins had inherited the same band pattern from their parents. This could have occurred by chance with a probability of less than 1%. On examination, the proband's twin had a

Figure 5 Identical twins aged 5 years (family 3). Note the mild facial asymmetry in the proband (left) after early surgery. His twin brother has a normal craniofacial appearance (right).

Figure 6 Early photographs of the twins (family 3) to show the normal craniofacial appearance of the proband's brother (right) when compared to his obviously affected twin (left).

normal skull shape and the proband had some asymmetry, but otherwise they looked very similar (fig 5). Early photographs of the twins showed that the proband clearly had an abnormal skull shape but his brother appeared normal (fig 6). Fortunately, early skull x rays on the brother were available and these were reported as showing definite evidence of sagittal craniosynostosis as seen in his twin. We have subsequently counselled high risks to both twins' offspring.

Discussion

In the early 1930s the psychiatrists H Saethre and F Chotzen first described patients with craniosynostosis, facial asymmetry, ptosis of the eyelids, low frontal hairline, dystopia canthorum, brachydactyly, and partial soft tissue syndactyly. Since then it has been suggested that a prominent ear crus is an additional feature. The condition is inherited as an autosomal dominant trait with a high degree of penetrance although it is variable in its manifestation.¹ Few families have been described with features as minimal as those seen in the father of the proband in family 1. Carter *et al*² in 1982 suggested incomplete penetrance can occur because of the low proportion of affected sibs born to affected parents in his series and the high percentage of apparent new mutations in his series of affected probands.

Crouzon syndrome was first described by Crouzon in 1912. It is characterised by craniosynostosis, midfacial hypoplasia, proptosis secondary to shallow orbits, and a beak shaped nose. Inheritance follows an

autosomal dominant mode of transmission, expression is variable, but penetrance is said to be complete.³ Three sib pairs with normal parents have been described,⁴⁻⁶ although Cohen¹ dismissed the first two reports as not being Crouzon syndrome. Rollnick⁶ in her case report suggested that germinal mosaicism may be the explanation for apparently normal parents having two affected children. Although this is an obvious possibility, the minimal manifestations in the mother of the proband in family 2 do suggest that features may be very mild by adulthood.

Our third case stresses the difficulties that can arise in counselling families with craniosynostosis even when the diagnosis is strongly suggested (that is, in an identical twin of an obviously affected patient). The importance of early photographs in making the diagnosis of minimally affected gene carriers is well known and these cases underline the importance of taking skull x rays in such situations in childhood. On examination alone, the proband's twin brother in family 3 could well have been considered unaffected and counselled as such in adulthood. His affected brother would have been assumed to have either a non-genetic cause for his craniosynostosis or have a postzygotic new mutation. The presence of craniosynostosis in both boys makes it more likely that this is genetic, with high offspring risks for both boys.

Our first two families illustrate the importance of a careful family history in all counselling situations. They also confirm that caution is necessary before dismissing recurrence risks in sporadic cases of Saethre-Chotzen syndrome and Crouzon syndrome when parents appear normal. Not only is germinal

mosaicism a real possibility, as illustrated in other autosomal dominant conditions, but occasionally gene carriers can appear normal.

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