Congenital anal anomalies in two families with the Opitz G syndrome

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SUMMARY Five children from two families presented to a regional neonatal surgical unit between 1959 and 1984 with congenital anal anomalies and other malformations resulting from an autosomal dominant inherited condition, the Opitz G syndrome. This and other Mendelian causes of congenital anal malformations are briefly discussed in view of their importance for genetic counselling.

The frequency of imperforate anus among the newborn of North America in one study was 2.4 per 10 000 births.¹ In 42% of these cases the anomaly was isolated and in the remainder it occurred in association with other malformations. Cases with isolated imperforate anus are usually sporadic and the empiric recurrence risk is less than 1%,² but there are reports of familial cases of isolated anal anomalies (McKusick³ Catalogue Nos 10710, 20750, 30180). Imperforate anus with other malformations has several possible causes, including chromosome imbalance, single gene defects, various teratogens, and unknown factors.⁴ Single gene defects are important in view of the high recurrence risk, but as they are rare and often variable in presentation, the diagnosis may be overlooked. In this report we describe two families in which a rare autosomal dominant congenital malformation syndrome, the Opitz G syndrome, was present. Over a period of 25 years five subjects from these two families presented in the newborn period to a regional paediatric surgical unit with malformations which required surgical treatment.

Case reports

FAMILY 1

The pedigree is shown in fig 1. The proband (IV.2) was the second child of unrelated Scottish parents. He was born in 1984 at 36 weeks' gestation by elective Caesarean section for polyhydramnios and raised maternal blood pressure. The birth weight

(2.36 kg) was on the 10th centile, while the head circumference (OFC 33 cm) and the length (48 cm) were close to the 50th centile. He had an imperforate anus which was treated by anoplasty, hypertelorism, a high arched palate, and positional talipes calcaneovalgus deformity (fig 2). Postoperatively he had frequent cyanotic attacks and was unable to swallow his secretions. All subsequent attempts at oral feeding resulted in choking and aspiration of fluid into the lungs. Repeated barium studies showed pharyngeal incoordination with regurgitation into the nasopharynx and aspiration into the trachea. He remained in hospital from birth and needed to be entirely tube fed during the first year occasionally requiring nasopharyngeal suction when secretions were excessive. At one year of age his length, weight, and OFC were just below the 10th centile. He had hypertelorism and significant developmental delay with overall function estimated to

FIG 1 Pedigree of family 1.

FIG 2 The proband, family 1. Note hypertelorism and the feeding tube.

be at an eight month level. Chromosome analysis showed a normal 46,XY male karyotype. At 14 months of age the proband was found apnoeic in his cot at home and attempts at resuscitation were unsuccessful. Full necropsy revealed no internal malformations or evidence of aspiration, but there were mild inflammatory changes in the bronchi.

The proband's mother had no history of swallowing problems, hoarseness, or constipation. She attended a normal school but required some remedial teaching. Her only physical signs were hypertelorism (inner canthal, outer canthal, and interpupillary distances were above the 90th centile) and an anteriorly placed anus. The proband's sister also has hypertelorism but is otherwise normal. Two half sibs of the proband's mother (III.6 and III.7) were reported to have died in the newborn period after undergoing surgery for imperforate anus, but hospital records could not be traced to verify this. Another relative of the proband (III.3) had congenital anal stenosis treated by an anal stretch procedure at six weeks of age in 1959. He also had hypertelorism and glandular hypospadias (fig 3); he attended a normal school and is employed as a non-skilled manual worker. This man's son (IV.3) was born with hypertelorism and a low type of imperforate anus which was repaired by anoplasty. He subsequently had recurrent choking and cyanotic attacks on attempting oral feeds which resolved by six weeks of age. At five years, his height was on the

25th centile and development within normal limits; his only abnormal physical sign is hypertelorism.

FAMILY 2

The two affected boys were half sibs born of the same mother but with different fathers. The elder presented at birth in 1961 with hypertelorism, a cleft lip and alveolar margin, an umbilical hernia, and glandular hypospadias (fig 4). He had initial feeding

FIG 3 Congenital anal stenosis (note the perianal skin tag) and hypospadias in III.3, family 1.

FIG 4 The first born affected boy in family 2. Note hypertelorism and repaired cleft lip.

difficulties but these resolved after repair of the cleft at three months. Subsequent development has been entirely normal. His half brother, born in 1983, had hypertelorism, posteriorly rotated ears, an umbilical hernia, and hypospadias (fig 5). He also had a low type of imperforate anus and a cardiac murmur thought to indicate a small VSD. In infancy he was described as a sickly baby and tended to vomit after most feeds. He sat at nine months, walked at 16 months, and knew six words at 18 months. At this

age his weight and OFC were on the 3rd centile and his height on the 10th centile. Chromosome analysis showed a normal 46,XY male karyotype.

The mother of both boys gave no history of feeding difficulties in infancy or of constipation. She is of normal intelligence and does not have hypertelorism. There was no other family history of note.

Discussion

The features described in each of these families are consistent with the diagnosis of the G syndrome. This is a multiple congenital abnormality syndrome, first delineated by Opitz *et al*⁵ in 1969, which is inherited as an autosomal dominant trait.⁶⁻⁸ Males are generally more severely affected than females. This is supported by the presentation of our families and the occurrence of male to male transmission in family 1. On the basis of over 30 published cases, the cardinal features are hypertelorism, hypospadias, and swallowing defects. This latter problem may be due to oesophageal incoordination or a laryngeal cleft. Less common features are clefts of the lip and palate, abnormal bifurcation of the trachea, tracheo-oesophageal fistula, pulmonary hypoplasia, imperforate anus, and cardiac and renal defects. Mild mental retardation is a variable feature. Occasionally the more serious abnormalities cause death in the neonatal period. In general, middle ear structures are particularly vulnerable to malformation and an affected subject may have any combination of malformations or, like the mother of the affected boys in family 2, apparently none at all. Gynaecological and radiological examination of apparently asymptomatic females at risk of carrying the gene may rarely reveal occult genital, tracheo-bronchial, or pulmonary anomalies which indicate an affected subject.⁷

There is an excess of stillbirths and miscarriages in families with the G syndrome. Polyhydramnios was noted before delivery of the proband in family 1; this was probably due to defective fetal swallowing. Another rare in utero manifestation of the G syndrome is non-immune fetal hydrops and this was successfully treated in one case by thoracocentesis and intravenous transfusion of albumin carried out at fetoscopy.⁹

Several other syndromes may have an anorectal malformation as one feature (table). Some of these conditions carry a high recurrence risk and are recognised by their striking associated features, while other syndromes, based on a few reported cases, are incompletely delineated. Our experience with these two families underlines the importance of obtaining an extended pedigree while being alert to the possibility of variable expression of a single gene.

FIG 5 Second born affected boy in family 2. Note hypertelorism, posteriorly rotated ears, and the feeding tube.

TABLE Syndromes which may include an anal malformation.

Name	Features	McKusick catalogue No. ³	Inheritance
BBB syndrome†	Hypertelorism, hypospadias	31360	AD
G syndrome†	Hypertelorism, hypospadias, swallowing defects	30710	AD
Townes-Brocks syndrome	Hand, foot, and ear anomalies	10748*	AD
Rieger syndrome	Ocular anterior chamber anomalies, hypodontia	18050*	AD
Schinzel syndrome	Ulnar ray defects, delayed puberty, obesity	18145	AD
Cryptophthalmos syndrome	Palate, ear, renal, laryngeal, genital, digital, and eye malformations	21900*	AR
Kaufman-McKusick syndrome	Congenital heart disease, polydactyly, hydrometrocolpos	23670*	AR
Johanson-Blizzard syndrome	Hypoplastic nasal alae, exocrine pancreatic insufficiency, deafness, hypothyroidism	24380*	AR
FG syndrome	Macrocephaly, hypotonia, mental retardation, characteristic facies	30545*	XL
VATER association	Vertebral, anal, tracheo-oesophageal, renal and radial limb defects	19235	Sporadic
PIV syndrome	Polydactyly, vertebral anomalies	17410	Sporadic
Thanatophoric dysplasia	Micromelia, platyspondyly, early death	18760	Sporadic
Jarcho-Levin syndrome	Rib and vertebral defects, respiratory failure in infancy	27730*	AR
Christian skeletal dysplasia	Mental retardation, skeletal dysplasia, abducens palsy	30962	XL
Ivic syndrome	Radial defects, strabismus, thrombocytopenia, deafness	14775*	AD
Hall-Pallister syndrome	Hypothalamic hamartoblastoma, hypopituitarism, postaxial polydactyly	14651	Sporadic
Meckel syndrome	Encephalocele, polydactyly, cystic kidneys	24900*	AR
Saldino-Noonan syndrome	Short ribs, short limbs, postaxial polydactyly, visceral abnormalities, lethality	26353*	AR
Cat eye syndrome	Ocular coloboma, ear and renal anomalies, occasional mental retardation	11547	Chromosomal imbalance
Anosacral defect	Anterior sacral meningocele	20550	AR
Presacral teratoma	Sacral dysgenesis	31280 17645*	XLD AD

*Mode of inheritance accepted by McKusick.
 †Although listed in the sex linked catalogue, autosomal dominant inheritance is now accepted.
 AD, AR, XL: autosomal dominant, autosomal recessive, X linked inheritance.

defect as a cause of congenital malformations in second and third degree relatives.

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References

¹ Myriantopoulos NC, Chung CS. Congenital malformations in singletons: epidemiologic survey. *Birth Defects* 1974;**X**:1-58.
² Stephens FD, Smith ED. *Ano-rectal malformations in children*. Chicago: Year Book Medical Publishers, 1971:170-1.
³ McKusick VA. *Mendelian inheritance in man*. 6th ed. Baltimore: Johns Hopkins University Press, 1983.

⁴ Pinsky L. The syndromology of anorectal malformation (atresia, stenosis, ectopia). *Am J Med Genet* 1978;**1**:461-74.
⁵ Opitz JM, Frias JL, Gutenberger JE, Pellett JR. The G syndrome of multiple congenital anomalies. *Birth Defects* 1969;**V**(2):95-101.
⁶ Little JR, Opitz JM. The G syndrome. *Am J Dis Child* 1971;**121**:505-7.
⁷ Funderburk SJ, Stewart R. The G and BBB syndromes: case presentations, genetics and nosology. *Am J Med Genet* 1978;**2**:131-44.
⁸ Farndon PA, Donnai D. Male to male transmission of the G syndrome. *Clin Genet* 1983;**24**:446-8.
⁹ Patton MA, Baraitser M, Nickolaides K, Rodeck CH, Gamsu H. Prenatal treatment of fetal hydrops associated with the hypertelorism-dysphagia syndrome (Opitz G syndrome). *Prenatal Diagnosis* 1986;**6**:109-15.

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