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Trigonocephaly and the Opitz C syndrome

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SUMMARY We present 12 cases of trigonocephaly of which six were associated with other malformations. On the basis of this experience we examine the diagnostic criteria for the presumed autosomal recessive trigonocephaly C syndrome.

The term trigonocephaly was coined by Welcker in 1862[1] on the basis of seven cases. It describes a congenital cranial anomaly in which a narrow pointed forehead, often associated with some biparietal widening, results in a skull which is triangular in shape when viewed from above. Partial or complete obliteration of the metopic suture is a characteristic feature. In their reviews Currarino and Silverman[2] in 1960 and Anderson *et al*[3] in 1962 noted that a number of early European authors had made reference to associated malformations, particularly of the forebrain. Their own cases, and those in published reports, could be divided broadly into a major group in which metopic synostosis was an isolated defect associated with only cosmetic problems, and a second group where major malformations and mental retardation were evident. Subsequent advances in cytogenetics have shown that aneuploidy can account for some of the cases in the latter group; trigonocephaly has been reported as a feature in 3q−, 7p−, 9p−, 11q−, and trisomy 13q.[4 5]

In 1969 Opitz *et al*[6] reported a brother and sister both of whom died in infancy from the effects of a multiple malformation syndrome which included trigonocephaly. The chromosomes appeared normal. Given the eponym C syndrome after the family name, it was reported as a new syndrome, possibly with recessive inheritance. Three further cases were reported in 1975.[7 8] In 1981 Antley *et al*[9] reviewed the experience of eight centres and found six further cases. In one of these the parents were second cousins, and in another the fetus in a subsequent pregnancy was considered to be affected and was terminated. These observations, and the equal sex ratio, led the authors to conclude that an autosomal recessive gene defect is the likely basis for this syndrome.

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We review twelve children with trigonocephaly seen at The Hospital for Sick Children, Great Ormond Street, six with multiple malformations of whom two have reached adulthood, and six with an isolated metopic craniostenosis. On this basis we examine the diagnostic criteria, prognosis, and risks of recurrence.

Methods of ascertainment

Cases 3, 4, 5, and 6 were identified among patients referred to the Genetics Clinic after the report in 1981 by Antley *et al.*[9]

Case 2 was ascertained as part of a research study of twins and triplets with heart defects. Examination of the notes made when this girl was an infant revealed that she had trigonocephaly with multiple malformations. It was also noted that the clinical features were very similar to another child who had recently been a patient at the hospital, case 1. Cases 1 and 2 were visited at home in order to assess their current clinical state.

Since 1959 patients referred to the Neurosurgical Unit with craniosynostosis have been recorded in a discrete index. Review of this revealed six cases of trigonocephaly among the 300 records, all of which were isolated anomalies.

Case reports (table 1)

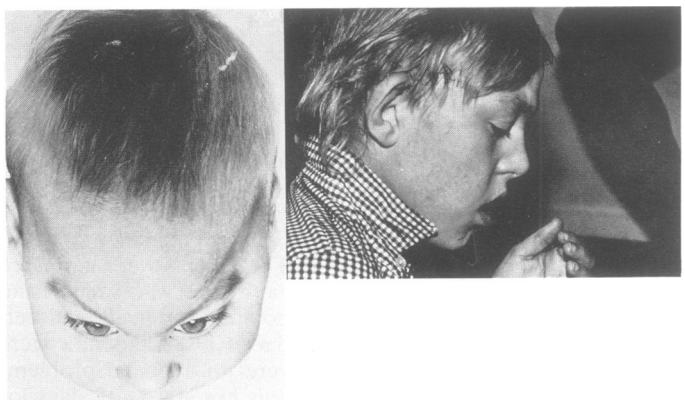
CASE 1

Case 1, a boy, was born on 30.4.63 at 39 weeks' gestation, weighing 2·835 kg. Pregnancy and delivery were uneventful. The parents were unrelated and there was one healthy sib. A small head circumference with a pointed forehead and left occipital prominence and a deep sacral dimple were noted at birth. There were no neonatal problems and he was referred to this hospital at 12 days for review of his cranial malformations (fig 1a).

At 4 weeks the child developed cyanotic episodes associated with stiffness and twitching which responded to anticonvulsive therapy. This was modified following recurrent fits at 6 months. Head circumference was noted to be progressing along the 3rd centile but development was clearly delayed. There was an internal strabismus. He had a grossly abnormal EEG and an air encephalogram indicated cerebral atrophy with deformity of the anterior horns of the lateral ventricle.

TABLE 1 *Clinical manifestations of five patients with trigonocephaly and multiple malformations compared on a similar format to those summarised by Antley et al.[9] (Italicised features have been added.)*

	Case no					*Summary*	
	1	*2*	*3*	*4*	*5*	*Previous*	*Present*
Sex	M	F	F	F	M	6F 5M	3F 2M
Trigonocephaly	+	+	+	+	+		
Neonatal OFC (centile)	3rd	3rd	3rd			5/9	3/3
Postnatal microcephaly	−	+	+	+	+	4/5	4/5
Cowlick	−	−	−	−	−	6/9	0/5
Apparently short neck	+	+	+	−	+	9/10	4/5
Hypoplastic nose with broad root and epicanthus	+	+	+	+	+	11/11	5/5
Anteverted nares	+	+	+	−	+		4/5
Characteristic palate		+	+	−	+	9/9	3/4
Long simple philtrum	+	+	+	+	+	9/10	5/5
Attached frenulum				+	−	4/5	1/2
Neonatal micrognathia	+	+	+	+		9/10	4/4
Ear: reduced cartilage		+		+	+	6/8	3/3
Ear: abnormal shape	+	+	+	−	+	8/10	4/5
Ear: low set and/or posteriorly rotated	−	+	−	+	+	10/10	3/5
Upward slanting palpebral fissures	+	+	+	+	+	9/10	5/5
Hypotelorism	−	+	+	+	+		4/5
Strabismus	+	+	+	+	−	8/11	4/5
Polysyndactyly	−	−	−	−	−	4/11	0/5
Bridged palmar or simian crease	+	+	−	−	−	6/9	2/5
Ulnar deviation of fingers	−	−	−	−	−	4/10	0/5
Clinodactyly	+	+	+	+	−		4/5
Short limbs	−	+		+	+	4/10	3/4
Varus or equinovalgus deformities	+	−	+	+	+	4/10	4/5
Contractures	−	+	−/	+	−	5/6	1/5
Dislocated/dysplastic joints	−	+	+	−	−	6/7	2/5
Cryptorchidism/prominent clitoris	+		−	−		8/11	1/3
Haemangiomas/naevi	−	+	+	−	−	8/9	2/5
Sacral dimple	+	−	−	−	−	4/4	1/5
Pectus	−	+	+	+	−	5/10	3/5
Cardiovascular defect	−	?+	+	−	−	8/11	2/5
Survival	Alive 20 y	Alive 19 y	Died 7 mth	Died 2½ y	Alive 10 mth	Died at early age 5/11	2/5



(a) (b)

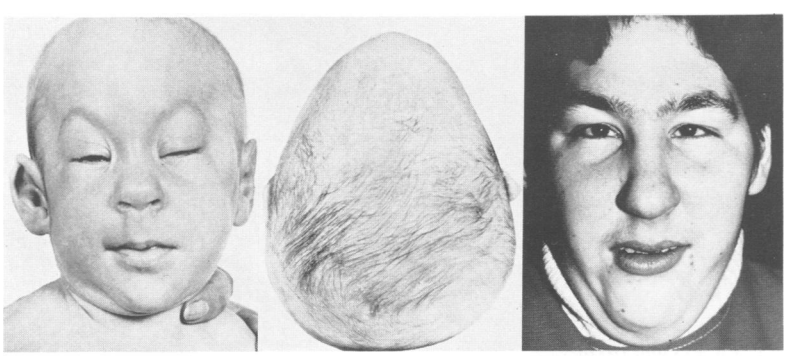
FIG 1 *Facial appearance of case 1 (a) in infancy and (b) at 19 years.*

Review at the age of 19 years revealed a severely retarded boy in residential care. His height was 134 cm (below the 3rd centile) and his head circumference had reached 51 cm. It was reported that following correction of bilateral equinovarus deformity at the age of 8 years he had become able to walk but continued to prefer bottom shuffling. He vocalised but had no speech. He helped with his own dressing and was able to feed himself. His trigonocephaly was still evident (fig 1b), as was a prominent nuchal ridge with a small bony lump 1·5 cm in diameter on the left side of the occiput. There was mild synophrys and upward slanting palpabral fissures, but relatively normal eye placement with an outer canthal distance of 8 cm, interpupillary distance of 6·5 cm, and inner canthal distance of 3 cm. The nasal bridge had developed well causing the epicanthic folds to disappear. The philtrum was well defined but short (1·5 cm) with a nose length of 4·5 cm. His ears were long, normally inserted, and probably of simple form but were grossly swollen owing to head banging. The mouth was wide and the palate was highly arched. His neck was short and his nipples widely spaced. His hands were short with bilateral single palmar creases together with tapering fingers and clinodactyly of both fifth fingers. The big toes were short and the other toes were crowded. Puberty was delayed with only one testis palpable, a prepubertal penis and scrotum, and sparse pubic and facial hair. He was judged to be severely mentally retarded. Chromosome analysis with G banding gave a normal karyotype.

CASE 2

Case 2, a girl, was born at 34 weeks' gestation, the second of triplets. Birth weight was 1·332 kg and her male co-triplets weighed 2·239 kg and 2·041 kg. Her parents are of European origin and unrelated. The co-triplets and the paternal half sister have remained healthy. The abnormal skull shape was evident from birth. Early weight gain was poor mainly due to feeding difficulty. At 5 months her weight had risen to only 2·353 kg. On referral striking trigonocephaly, a small anterior fontanelle, increased biparietal diameter, and prominent occiput were noted (fig 2a, b). She had clinical features of a ventricular septal defect. At 6 months she was able to smile but unable to hold up her head. An EEG showed definite abnormality with asymmetry between the two hemispheres most marked in the frontal and temporal regions. There was relative poverty of activity over the left side. She began to walk at 2 years 3 months, 9 months later than her sibs, and began to feed herself at the age of 3 years. At this stage, in addition to global retardation, she was noted to have persistence of the metopic ridge, yellow teeth, and a high palate.

Review at the age of 19 years revealed a moderately to severely retarded girl unable to dress herself and having very little recognisable speech. She continued to live with her parents with whom she had good social interaction and who reported her to be able to understand simple instructions. Her head circumference remained small at 46·5 cm but the trigonocephaly was much less striking. There was mild synophrys and somewhat close set eyes (inner canthal distance 3·2 cm, interpupillary distance 6 cm, outer canthal distance 8·75 cm). She had a long nose of 5·65 cm and a short philtrum of 1·6 cm (fig 2c). She was able to hear normally but had minor anomalies of helix folding. A broad anterior alveolar ridge was noted with crowded and rather carous teeth. She was 125 cm tall (below the 3rd centile) with a stooping posture. She had lax finger joints but limited extension of the elbows. Short broad thumbs, long big toes, and poor circulation in the extremities were noted. The strawberry naevi had faded and she had apparently normal pubertal development with good breast development. Her cardiac murmur had become insignificant. Chromosome analysis with G banding revealed a normal 46,XX karyotype.



(a) (b) (c)

FIG 2 *Case 2. (a) Facial appearance at 5 months. (b) Skull shape at 5 months. (c) Facial appearance at 19 years.*

CASE 3

This female child was born to healthy non-consanguineous parents. Amniocentesis had been carried out following the finding of a raised serum alphafetoprotein. Amniotic fluid alphafetoprotein and chromosome analysis were normal, though a reduced biparietal diameter was noted. Birth weight was 3·325 kg with a head circumference of 31·5 cm and length of 46·5 cm. An abnormal facies, a trigonocephalic skull, and a large pigmented hairy naevus over the left forearm were noted at birth (fig 3a). Comment was made on the prominent metopic suture on referral at 3 weeks (fig 3b). There were major feeding problems due to a poor suck reflex and little evidence of developmental progress. Seizures were suspected but an EEG was normal. At 3 weeks heart failure with cardiomegaly led to the discovery of a severe congenital mitral stenosis, which caused her death at 7 months of age.

At necropsy her weight had reached 5·45 kg with a crown-heel length of 63 cm and crown-rump length of 42 cm. Head circumference was 38·5 cm with a biparietal diameter of 9·3 cm. The brain weighed 570 g and was normal on external examination. The mitral valve cusps were noted to be thickened and nodular with very short chordae tendinae extending to the tips of grossly hypertrophied papillary muscles. The other valves were normal. The foramen ovale was patent and the right coronary ostium was ectopic, arising 1 cm above the aortic cusps.

CASE 4

This female was the first born of unrelated parents. The family history was negative. The pregnancy had been uneventful and the birth in February 1980 followed a normal labour and delivery. Trigonocephaly with a prominent metopic suture and an impalpable anterior fontanelle were noted. An unusual clenched hand posture prompted chromosome analysis, but this was normal. When followed up at 2 months, the child was noted to have difficulty swallowing though sucking reflex was normal. The head circumference was 36 cm and her general awareness was noted to be poor. There were flexion deformities of the fingers, limited abduction of the hips, and limited extension of the elbows, with metatarsus varus deformity at the left ankle.

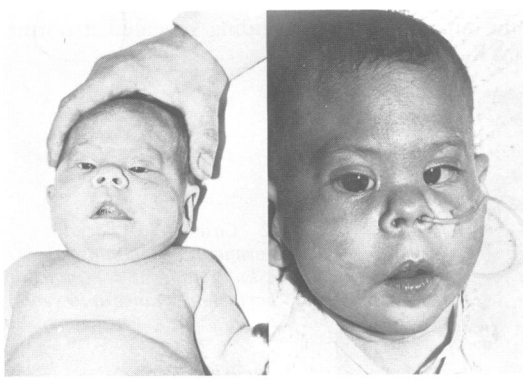
She was referred for diagnosis at 21 months of age at which time a marked delay in psychomotor development was evident. She was unable to sit and paid little attention to her surroundings. There was still obvious trigonocephaly (fig 4), large soft pinnae, and broad alveolar ridges. Necropsy following death at 2½ years revealed a brain with polymicrogyria, absent corpus callosum, olivary dysplasia, cerebellar heterotopias, and paucity of central white matter and descending tracts.

The mother's second pregnancy resulted, in February 1981, in the birth of a male child following a normal delivery. He was noted to have multiple congenital abnormalities with arthrogryposis, rocker-bottom feet, and single palmar creases. His facial appearance was noted to be very similar to that of his sister. He died at the age of 2 days from respiratory distress syndrome. A limited necropsy revealed a poorly formed gyral pattern.

The mother gave birth to two healthy daughters in 1982 and 1983.

CASE 5

Case 5, a male, was the first child of first cousin Muslim parents. The pregnancy was uneventful and the child was born at term following a normal delivery weighing 2·7 kg. When seen at 10 months,



(a) (b)

FIG 3 *Facial appearance of case 3 at (a) 3 weeks and (b) at 6 months. Note the prominent metopic ridge.*

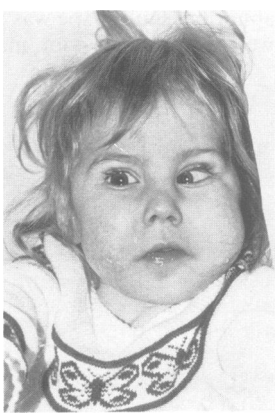


FIG 4 *Facial appearance of case 4 at 21 months.*

developmental delay and multiple congenital anomalies were evident. His weight and length were both just below the 3rd centile. The trigonocephalic skull was asymmetrical and the fontanelles appeared to be closed (fig 5). Despite lack of gross motor development he would grasp objects and smile at his mother. Chromosome analysis revealed a normal male karyotype. Ultrasound examination at 7 months had revealed a small brain.

Trigonocephaly with multiple malformations and chromosome anomaly

CASE 6

This male child was born in August 1980 at 37 weeks' gestation by lower segment Caesarian section and weighed 3·17 kg. Subsequent development was slow and there were major feeding difficulties due to poor sucking. He had two febrile convulsions during the first year. He smiled at 10 months but was unable to sit at 16 months when referred for further assessment. At this stage his head circumference was 44·7 cm and weight was 7·8 kg, both well below the 3rd centile, but his length was 77·5 cm which was on the 10th centile. He was noted to have several dysmorphic features (fig 6).

Skeletal survey revealed very retarded carpal centres and a generalised osteoporosis with undermodelling of the long bones. CT scan showed dilation of the lateral and third ventricles, absence of the cerebellar vermis, and a large fluid containing cavity in the posterior fossa. The basal cisterns were enlarged and there was prominence of the sylvian fissures, interhemispheric fissure, and cortical sulci. The picture was interpreted as being a variant of Dandy-Walker syndrome with cerebral atrophy. The chromosomes had been examined in a regional unit and had been reported to be normal. A diagnosis of trigonocephaly C syndrome was suggested. However, a second chromosome sample had been sent to our own laboratory where the preparation revealed a terminal deletion from the long arm of chromosome 3, with a breakpoint at 3q27 (46,XY,del(3)(pter→q27:)).

The child died at the age of 26 months and necropsy revealed a brain weight of 880 g with small cerebellar hemispheres and dilated ventricles. There was an acute pericarditis which had contributed to death.

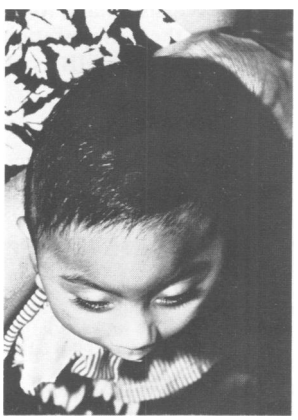


FIG 5 *Appearance of case 5 at 10 months.*

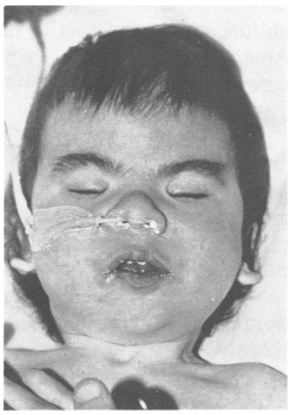


FIG 6 *Facial appearance of case 6 at 16 months.*

Isolated trigonocephaly

With the exception of one case of congenital deafness and one child of normal intellect with

TABLE 2 *Clinical features of six cases of simple trigonocephaly referred to the Neurosurgical Unit for assessment.*

	Case No					
	7	*8*	*9*	*10*	*11*	*12*
Sex	M	M	F	M	M	F
Birth weight (kg)	2·30	3·75		3·25	3·20	2·80
Early development	N	N	N	N	N	N
Late development		N	N	B		
Operation	–	–	+	–	+	+
Dysmorphic features						
Hypotelorism	–	+	+	+	+	+
Hypoplastic nose	+	–	+	–	–	–
Other features	–	–	D	–	–	–

N=normal milestones, B=behavioural problems, normal intellect. D=severe congenital deafness.

behaviour problems, the medical records revealed that the six children referred to the neurosurgical unit for assessment of trigonocephaly were healthy and of normal development. Table 2 summarises the clinical features in this group.

Discussion

Clinical details of twelve children with trigonocephaly are presented, six with multiple malformations and six with an isolated skull anomaly. Based as it is on the experience of a referral paediatric hospital, the distribution almost certainly bears little relationship to the true incidence of the two types. A prominent metopic ridge in an otherwise normal child may not be brought to medical attention and the child is unlikely to be referred unless there is concern about the cosmetic aspects. Of those seen at our hospital with uncomplicated trigonocephaly, the outcome seemed satisfactory whether or not surgery was employed. There was evidence of the deformity improving with age though surgery should not be ruled out. Smith[10] has emphasised that even in cases of deformity due to intrauterine compression improvement with age is not invariable, while bone resection at an early stage has a very low morbidity in good hands and can permit normal skull growth. Parents whose child is trigonocephalic but developing normally should be reassured. In our cases and other published cases intellect was normal. It is probable that the congenital deafness in case 9 was coincidental.

The cases of simple trigonocephaly had dysmorphic features similar to those of the complex cases. In particular, orbital hypotelorism, telecanthus, and upward slanting palpebral fissures should be regarded as being consequent upon the malformation of and around the lower part of the metopic suture. It might be best to regard these as a 'trigonocephaly sequence' rather than multiple features of a specific syndrome.

Antley *et al*[9] have discussed the full spectrum of features of the C syndrome. Table 1 shows that the features in the first five children reported here fit closely with those described previously. However, the 'characteristic palate' is not invariable. Nevertheless, broad alveolar ridges are useful in diagnosis as is the striking softness of the ears in some cases.

Case 3 was distinguished by a large hairy naevus on the forearm. Also, the child had severe congenital mitral stenosis which led to an early death. This is a rare malformation which is difficult to diagnose clinically though is recognised readily by echocardiography. It is possible that this anomaly contributed to death in other reported cases.

Survival is poor in the presence of complex trigonocephaly, but parents should not be advised to anticipate early death in view of the survival to adulthood of cases 1 and 2. These two are the oldest sufferers to be described in detail. Features of note are the profound retardation and short stature. Case 1 also had delayed puberty of uncertain cause, while case 2 adopted a stooped posture in part due to a degree of joint limitation.

Parental consanguinity in one case, albeit in a family from an inbred population, and an affected sib pair add further weight to earlier suggestions of autosomal recessive inheritance. However, caution is necessary. Trigonocephaly with its attendant dysmorphic features and mental retardation may result from a variety of chromosome disorders which draws attention to the relative non-specificity of this 'syndrome'. Case 6 is of particular interest in this respect. The karyotype was reported normal by a reputable cytogeneticist, whereupon the clinical features were accepted as being typical of Opitz C syndrome. It was by chance that the chromosomes were examined by a second laboratory and the small de novo deletion indentified.

In the light of this experience, we suggest that cases of trigonocephaly be divided into isolated trigonocephaly, a usually trivial and sporadic deformity, and complex trigonocephaly. A proportion of the latter appear to result from an autosomal recessive gene defect which should be called Opitz C syndrome. Even after the exclusion of chromosome anomaly, it is probable that this syndrome is heterogeneous and that the risk of recurrence will fall substantially below 1 in 4. A recurrence risk of the order of 10% would be reasonable advice until an empirical risk is established.

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