Journal of Medical Genetics 1987, **24**, 549–555

The clinical spectrum of the Fraser syndrome: report of three new cases and review

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SUMMARY Three new cases of the Fraser syndrome are presented and 68 published cases are reviewed. A quantitative estimate of the frequency of clinical manifestations is given. Craniofacial abnormalities were reported in all patients, cryptophthalmos in 93%, and syndactyly in 54%. Abnormalities of the ears, nose, genitalia, and urinary system were reported in 44%, 37%, 49%, and 37% of cases respectively. This variability should be taken into account when attempting prenatal diagnosis; a combination of ultrasound and fetoscopy should provide the best approach. Of the reported cases 26% were stillborn and 19% died in the first year of life. Renal and pulmonary malformations were associated with early death.

In the first century AD, Pliny the Elder described a family in which three children were born with a membrane over the eye.[1] This may well represent the first report of autosomal recessive cryptophthalmos. It is now recognised, since Fraser's paper in 1962,[2] that cryptophthalmos may occur with a variety of malformations and as such is known as the Fraser syndrome. François[3] regarded the main features to be cryptophthalmos, anomalies of the head, ears, and nose, syndactyly, and genital abnormalities. This paper reports three new cases and reviews the other published reports in order to give a quantitative estimate of the frequency of the various manifestations of the syndrome.

Case reports

CASE 1

This six month old female was the only child of healthy, non-consanguineous, Caucasian parents. Her mother was well during pregnancy and took no medication. She was born at term with a birth weight of 3·5 kg and multiple malformations were noted at birth. A concave groove extended from the left parietal region to the lateral margin of the left eyelid and the scalp hair extended in this region onto the forehead. The left upper lid was fused with the sclera and the upper row of eyelashes was deficient (fig 1). The right eye was normal. The left ala nasi was notched and the ears were of a simple pattern with partial stenosis of the auditory canals (fig 2). There was bilateral skin syndactyly involving the third, fourth, and fifth digits (fig 3).

After the birth the patient was noted to be tachypnoeic with inspiratory stridor. At microlaryngoscopy and bronchoscopy a partial fusion of the arytenoids and a mild subglottic stenosis were

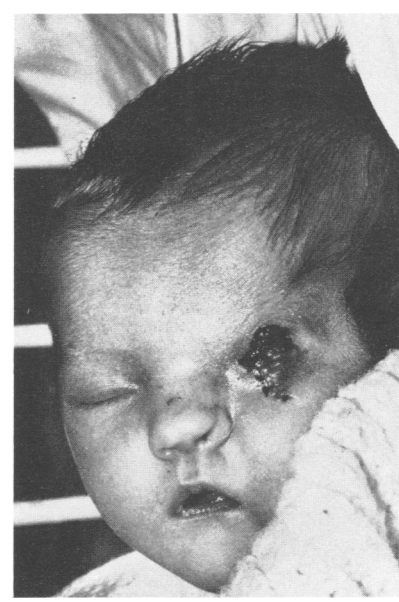

FIG 1 *Facial appearance of case 1 after the initial surgery for cryptophthalmos. Note the extension of hair on left forehead and groove in left ala nasi.*

Received for publication 9 September 1985.
Revised version accepted for publication 25 June 1986.

noted. There was also a tongue tie. The cryptophthalmos was surgically corrected in the second week of life using a procedure reported by Brazier and Collins.[4] Postoperatively the left eye appeared to perceive light.

At one month of age she was noted to have anal stenosis which required dilatation. At this time she also developed a cavernous haemangioma of the lip. Her motor development appeared normal at six months.

Routine haematology, biochemistry, and chromosome analysis, including extended banding, were normal. The electroretinogram showed a well defined response in both eyes and the visual evoked response was normal. The electroencephalogram showed no focal abnormalities and the skull *x* ray was normal except that the left orbit was smaller than the right. Ultrasound of the kidneys showed both were smaller than expected for age but otherwise normal.

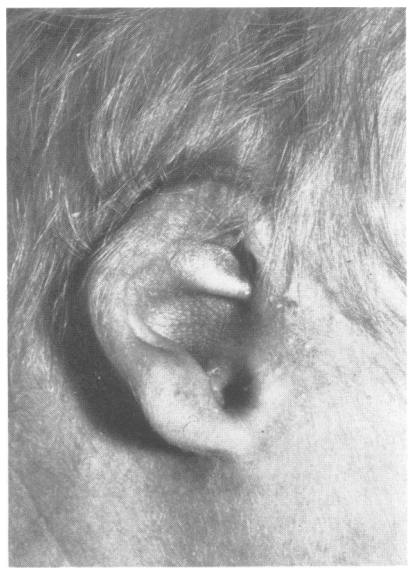

FIG 2 *The external auditory meatus in case 1 is in a lower position than normal in relation to the pinna and is reduced in diameter.*

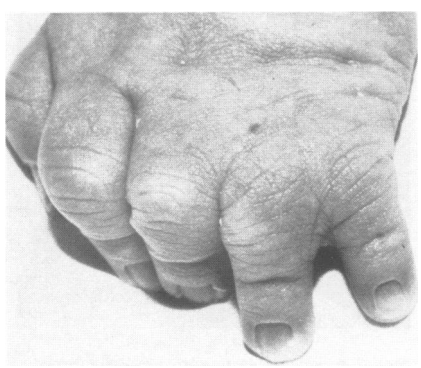

FIG 3 *Soft tissue syndactyly present in case 1.*

CASE 2

This one year old male infant was the second living child of healthy, non-consanguineous parents. The first pregnancy had resulted in a stillbirth in which no abnormalities were found; the second produced a healthy female child. The third resulted in a miscarriage at 18 weeks.

He was born at term by elective Caesarian section after an uneventful pregnancy. The birth weight was 4·23 kg. At birth there was a bradycardia and he required resuscitation. The Apgar scores were 4, 4, and 8 at one, five, and 10 minutes respectively. Hypoglycaemia on the first day required intravenous therapy.

A number of abnormalities were present (fig 4), most of which were noted at birth. There was bilateral microphthalmia with a coloboma in the left eye. The right eye was rudimentary with a cystic mass lying adjacent to the globe. There was facial

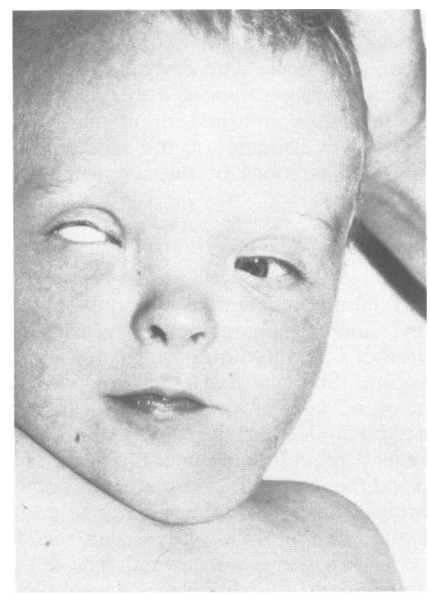

FIG 4 *Facial appearance in case 2. The right eye is rudimentary and has a cystic swelling lying adjacent to the optic globe. Microphthalmia and an iris coloboma are present on the right.*

asymmetry and redundant skin was noted over the neck and shoulders. Bilateral auditory canal stenosis was present. The nipples were widely spaced. Dextrocardia with normal heart sounds was noted. The pelvis was small and the right testis undescended. The thumbs were proximally placed and hypermobile.

Initially he was extremely hypotonic, but by nine months there was some improvement in tone. His motor development at nine months was assessed to be at a three month level. His hearing was normal. There was no vision in the right eye, but the left eye responded to light. His physical and mental development in the first year has been retarded.

Investigations showed a normal karyotype, normal full blood count, and a negative TORCH screen. Radiological examination, including ultrasound scanning, confirmed the presence of dextrocardia and bilateral microphthalmia. An ultrasound scan of the kidneys was normal.

CASE 3

This male infant was the first child of healthy, unrelated, Caucasian parents. The pregnancy had been complicated by three episodes of antepartum bleeding and the biparietal diameter was noted to be increased at 37 weeks' gestation. The maternal α fetoprotein was in the normal range at 16 weeks. There was no history of medication or infection during pregnancy. The patient was born at 39 weeks' gestation by induced forceps delivery and he weighed 2·7 kg at birth.

Multiple malformations were noted (fig 5). He was hydrocephalic with widely spaced sutures and a tense anterior fontanelle. The left eye was absent with fusion of the eyelids, and the hair on the left forehead extended down to the lateral margin of the left eyebrow. The left nostril was absent, the palate was high, and the ears low set. There was a micropenis with undescended testes and the anus was imperforate. A single umbilical artery was noted.

A TORCH screen for congenital infection was negative and the karyotype was normal. A CT brain scan showed holoprosencephaly with enlargement of the ventricular space.

In view of the holoprosencephaly the hydrocephalus was not shunted and the infant died at 47 days. Necropsy showed that both optic nerves were present, that the right eye was of normal size, but that the left eye was completely absent. The central canal of the spinal cord was grossly distended producing a hydromelia. There were no abnormalities of the cardiovascular or respiratory systems. The thymus and larynx were hypoplastic. The anus was imperforate with an associated rectal atresia.

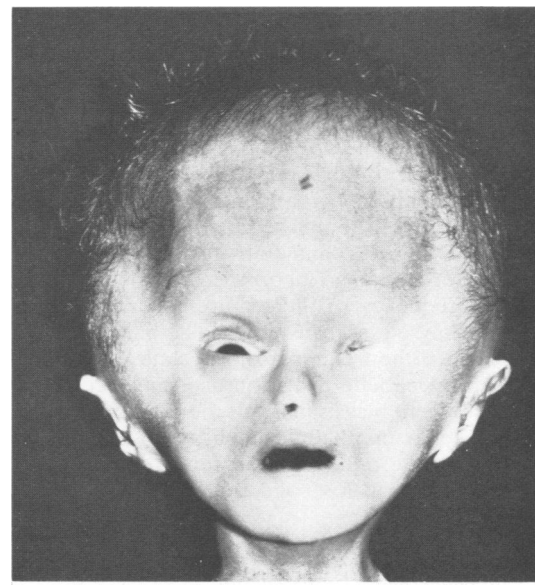

FIG 5 *Facial appearance in case 3. Note the cryptophthalmos and absent nostril. The macrocephaly is secondary to hydrocephalus.*

The right kidney was absent and there was a duplex system on the left side. Both ureters drained separately into the bladder; however, that on the lower side crossed over to the right before entering the bladder. Both testes were present in the abdomen.

Following the infant's death the parents received genetic counselling and had fetoscopy at 17 weeks in the next pregnancy. The fetus appeared to have normal eyes and genitalia and was shown to have a normal fetal karyotype on a fetal blood sample. Diagnostic ultrasound scan was normal. A healthy female child has subsequently been delivered.

Discussion

The patients reported in this paper illustrate the range of variation in the Fraser syndrome. Cryptophthalmos is an important feature of the syndrome, but is not always present. It occurred in the first and third patients of our series, but not in the second. The degree of microphthalmia varied from anophthalmia in the third patient to a normal size globe in the first. Digital anomalies were present in only the first and second patients. The degree of cerebral abnormalities varied. Holoprosencephaly was present in the third patient whereas in the first patient there was normal psychomotor development at six months and no apparent cerebral abnormality.

The variability in the syndrome is important when considering prenatal diagnosis by fetoscopy or when counselling families on the prognosis of the condition. This prompted us to review the published reports and to determine the relative frequencies of the clinical features in the Fraser syndrome.

In addition to the three patients reported in this paper, 65 patients were identified from a comprehensive search of published reports. There were 34 males, 28 females, and four in whom the sex was either undetermined or unspecified.

The frequency of the features of the syndrome were analysed in two ways. The initial analysis determined the frequency of the clinical features in the total 68 patients. This approach might contain an ascertainment bias as many of the reports have been published in ophthalmic publications and tend to emphasise the ophthalmic features. To correct for this possible bias a second analysis was carried out looking at the frequency of clinical features in 23 affected sibs of 16 probands. This is summarised in table 1. On the whole, the frequencies of clinical features in affected sibs corresponded well with the frequencies in the probands and in the total group.

TABLE 1 *Frequency of selected clinical features reported in 16 probands and 23 affected sibs.*

	Probands (n=16)		*Sibs (n=23)*		*Total series (%)*
	No	*%*	*No*	*%*	
Cryptophthalmos	16	100	21	91	93
Atresia or stenosis of EAM	2	13	2	9	15
Renal hypoplasia/ agenesis	7	44	8	35	37
Clitoral hypertrophy	4	25 (F)	3	13 (F)	
Cryptorchidism	1	6 (M)	2	9 (M)	
Syndactyly	10	62	11	48	54
Laryngeal stenosis	4	25	5	22	21

Cryptophthalmos was the most frequent feature of the syndrome. It was present in 63 patients (93% of the total). In 39 patients (57%) it was bilateral and in 17 (25%) it was unilateral. In the remaining seven patients where cryptophthalmos was present, the authors did not state whether it was bilateral or unilateral.

Craniofacial abnormalities were seen in all cases of the Fraser syndrome (table 2). One of the most characteristic signs was the extension of scalp hair from the lateral forehead to the lateral eyebrow on the affected side. This feature was present in 23 patients (34% of the total). It was often accompanied by a depression of the underlying frontal bone and sometimes extended to involve the alae nasi as it did in the first case reported in this paper (fig 1).

A variety of abnormalities of the ears have been described including defects of the middle ear, atresia of the external auditory meatus, cup shaped ears, low set ears, and fusion of the posterior auricle to the scalp. Ear abnormalities were found in 30 patients (44% of the total). The commonest ear abnormality was atresia of the external auditory meatus, which was seen in about one-third of those with ear abnormalities. An example of this abnormality is seen in our first patient (fig 2).

Abnormalities of the urinary tract were reported in 25 patients (37% of the total) (table 3). In each

TABLE 2 *Craniofacial features reported in 68 cases of the Fraser syndrome.*

Craniofacial features reported	*No of cases*	*% of total cases*	*References*
Cryptophthalmos	63	93	
Unilateral	17	25	3, 5, 7, 12, 14, 20, 21–23, 33, 35, this report
Bilateral	39	57	3, 6–11, 13, 16–19, 21–32, 34, 36–38
Not stated whether unilateral or bilateral	7	10	2, 7
Extended hair growth on forehead (from lateral forehead to lateral eyebrow)	23	34	6, 8, 9, 11, 13–19, 21, 24, 30, 32, 35–37, this report
Facial asymmetry	7	10	3, 5, 8, 32, 35, 37, this report
Abnormalities of ear	30	44	
Atresia or stenosis of external auditory canals	10	15	3, 7, 10, 17, 18, 21, 35, this report
Defects of middle ear	5	7	2, 18
Other*	28	41	2, 3, 5–10, 15–18, 21, 22, 35, 37, this report
Abnormalities of nose	20	37	3, 6–10, 13, 14, 17, 18, 21–23, 27–30, 32, 35, 36, this report
Midline fissure including nose, upper lip, and tongue	7	10	2, 6
Dental abnormalities	5	7	3, 6, 16, this report
Occasional features			
Lacrimal duct defect	6	9	2, 15, 29
Coloboma of upper lid	4	6	6, 7, 35, this report
Cleft lip and palate	3	4	7, 12, 18
Cleft palate alone	2	3	3, 6
Tongue tie	4	6	14, 18, 21, this report
Potter facies	3	4	5, 15

*Includes cupped, low set, undeveloped, and fused ears.

case renal hypoplasia or agenesis was seen. Often abnormalities of the ureters or bladder accompanied the renal agenesis and on two occasions cystic dysplasia of the kidneys was also noted. It is possible that the frequency of urinary abnormalities might be higher, as some of the earlier reports did not include radiological investigations of the patients or pathological examination of stillbirths. Renal hypoplasia has been reported as a cause of oligohydramnios and Potter facies.[5]

Abnormalities of the genital tract were reported in 33 patients (49% of the total). In four of these the sex of the patient could not be adequately determined.[7 18] The commonest abnormality in the female patients was clitoral hypertrophy, whereas the commonest abnormality in the male patients was cryptorchidism. In spite of the high frequency of genital abnormalities, there have been no endocrinological studies reported in this syndrome. None of the patients reported has reproduced, and it is likely that there would be a very considerable reduction in fertility as a result of the genital abnormalities.

A number of other clinical features have been described (table 4). Syndactyly was reported in 37 patients (54% of the total). This involved soft tissues only and was usually relatively minor in comparison to the other malformations. No particular pattern of syndactyly emerged from published reports. Laryngeal stenosis was reported in 14 patients (21% of the total). As our first patient showed, the combination of laryngeal stenosis and pulmonary hypoplasia may rapidly lead to respiratory failure.

Although the reported abnormalities are numerous they do not involve each system equally. Cardiovascular malformations are unusual and have only been reported in four cases: dextrocardia (this report), univentricular heart,[5] atrial septal defect,[10] and ventricular septal defect.[37] Similarly, cerebral malformations are unusual. Our third patient represents the first report of hydrocephalus, hydromelia,

TABLE 3 *Abnormalities of the genitourinary system in 68 cases of Fraser syndrome.*

Clinical features	*No of cases*	*% of total cases*	*References*
Abnormality of urinary tract·	25	37	
Renal hypoplasia or agenesis	25	37	2, 3, 5, 7–10, 14–17, 21, 22, 37, this report
Abnormality of ureters	11	16	3, 7–9, 14, 15, 21, 22
Abnormality of bladder	7	10	7, 10, 15, 22
Cystic dysplasia of kidneys	2	3	7, 21
Abnormality of genital tract	33	49	
Indeterminate sex	4	6	7, 18
		% female	
Abnormalities in females	15	54	2, 3, 5–8, 17, 22, 35
Clitoral hypertrophy	11	39	2, 6, 8, 17, 22, 35, 36
Bicornuate uterus	4	14	2
Vaginal atresia	4	14	5, 7, 8
Cystic ovaries	3	11	5, 22
Rudimentary uterus	1	4	35
Undifferentiated genital tubercle	1	4	5
Unspecified	1	4	
		% male	
Abnormalities in males	14	41	3, 6, 7, 9, 10, 21, 37, this report
Cryptorchidism	8	24	3, 6, 7, 9, 10, 21, this report
Underdeveloped penis	7	21	3, 7, this report
Hypospadias	1	3	6

TABLE 4 *Other clinical features reported in 68 cases of Fraser syndrome.*

Clinical features	*No of cases*	*% of total cases*	*References*
Syndactyly of fingers	37	54	2, 3, 5–11, 13–15, 17, 22, 25
Laryngeal stenosis/atresia	14	21	2, 5, 7, 9, 10, 15, 17, 18, 22, this report
Umbilical hernia/exomphalos	8	12	7, 18, 21, 35, 37
Pulmonary hypoplasia	5	7	5, 7, 15, 25
Anal stenosis/atresia	4	6	7, 15, this report
Others			
Hypoplastic or absent thumbs	3	4	5, 7, this report
Club foot	3	6	8, 35
Microcephaly	2	3	3, this report
Congenital heart defect	4	6	5, 10, this report
Umbilical displacement	4	6	2

and holoprosencephaly in this syndrome. Previous reports have been limited to microcephaly[3] (this report) and myelomeningocele.[32]

In addition to analysing the frequency of the clinical features in the reported cases, an attempt was made to analyse the prognosis and survival for patients with this syndrome. Thirty-seven patients (54% of the total) survived for a year or longer. Eighteen patients (26%) were stillborn and 13 (19%) died within the first year of life. Most of the infant deaths occurred in the first week of life and were associated with renal and respiratory malformations. The frequency of renal malformations was higher in those dying in the first year (52%) compared to those surviving the first year (22%). Similarly, pulmonary or laryngeal malformations were found in 39% of the non-survivors and in 14% of the survivors. There was little indication from published reports what the life expectancy might be for those who survive the first year. The oldest reported patient was 35 years of age.[13]

Overall, the prognosis for vision was very poor. In most cases there was no assessment of visual function and in few cases has there been surgical correction of cryptophthalmos. In 18 patients, including this report, a pupillary response to light was reported.[3 11 13 14 16–19 26 28 29 31 32 35–37] Of these, one patient with bilateral cryptophthalmos was taught to distinguish coloured lights,[18] one could detect moving objects,[35] one could 'count fingers at 18 inches' in the eye affected by partial cryptophthalmos, and one was reported to have 1/20 vision in the affected eye. In the first patient reported in this paper the patient was noted to respond to light and had a normal electroretinogram after surgical correction of the cryptophthalmos.

Although abnormalities of the ear are common, hearing is usually normal. In five of the 10 patients with atresia of the external auditory meatus no assessment of hearing was reported. In the other five (this report)[17 18 35] hearing was clinically normal. Formal audiometry has only been reported in one patient[35] and in that case was found to be normal.

There is little information concerning the mental development of surviving children. In the 37 children who survived more than one year, mental retardation was reported in seven (this report)[3 11 18 35 38] and normal intelligence in five.[3 17 28 33 37] In the remainder, no indication of psychomotor development was given.

Diagnosis of the syndrome should be straightforward when the four cardinal features of cryptophthalmos, abnormalities of the ear and nose, syndactyly, and genital malformations are present. When cryptophthalmos is absent the diagnosis will be more difficult but the pattern of associated abnormalities should still allow the diagnosis to be made. When cryptophthalmos is the only external abnormality it is important to investigate the patient for underlying urinary or genital abnormalities. Cryptophthalmos without associated malformations has been reported as an autosomal dominant trait. Coover[39 40] and Magruder[41] both reported two generation families with cryptophthalmos, and Goldberg[42] mentioned a four generation family with five affected members. Unfortunately these reports were published some time ago and there have been no illustrated reports recently.

The basic defect in the Fraser syndrome is unknown. The condition, however, is inherited as an autosomal recessive disorder. The review of published reports showed consanguinity in nine families who produced 17 affected children, and 11 unaffected, non-consanguineous couples produced two or more affected children. Thus, couples face a high recurrence risk and may wish to consider prenatal diagnosis. In our third case, Fraser syndrome was excluded by fetoscopy and ultrasound. Since then Feldman *et al*[43] have reported a positive prenatal diagnosis of Fraser syndrome using ultrasound to show the presence of microphthalmia and hydrocephalus. The published reports suggest that microphthalmia is not a constant feature and ultrasonography should be used to look for a wide range of malformations apart from the eye defect. Many of these malformations could be difficult to diagnose by ultrasound alone and a combined approach, using both ultrasonography and fetoscopy, appears to offer the best option in prenatal diagnosis at present.

We would like to thank Mr D Taylor and Mr Butler for referring the first case, Dr Semmens for referring the second case, and Dr Franklin for referring the third case. We would also like to thank Mrs Melanie Barham for secretarial assistance. Dr Patton is supported by a fellowship from the Child Health Research Trust.

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