The telecanthus-hypospadias syndrome

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SUMMARY The telecanthus-hypospadias (BBB) syndrome is characterised by widely spaced inner ocular canthi and hypospadias of variable degree. Heterozygous females have telecanthus. We have summarised the historical and phenotypic findings of 21 patients in seven previous publications. We have also had the opportunity to evaluate personally 12 families with a total of 18 affected males. The most frequent anomalies in patients previously reported are telecanthus 21/21, hypospadias 19/21, cleft lip/palate or uvula 7/21, high, broad nasal bridge 15/15, cranial abnormality 6/21, congenital heart defect 5/21, cryptorchidism 9/21, and mental retardation 11/17. In our series, the most frequent anomalies include telecanthus 18/18, hypospadias 18/18, cleft lip/palate or uvula 8/18, high, broad nasal bridge 10/11, cranial abnormality 12/18, congenital heart defect 3/18, upper urinary tract anomaly 4/9, and mental retardation 10/12. There is also an increased incidence of like-sex twinning, 11/18 in our families. This syndrome must be more common than reflected in published reports. Based upon the observation that males are much more severely affected than females and the lack of male to male transmission, it appears that this condition is most likely to be inherited in an X linked fashion. Further elucidation of the phenotype and documentation of the inheritance is needed. The distinction between the telecanthus-hypospadias syndrome and the G syndrome also needs further clarification.

The telecanthus-hypospadias (BBB) syndrome was first described in 1969 independently by Opitz *et al*¹ in three families (two of the families were from Memphis) and Christian *et al*² in one family. It has been referred to in various reports as the BBB syndrome, the Opitz syndrome, and the hypertelorism-hypospadias syndrome.

The telecanthus-hypospadias syndrome is a disorder characterised by widely spaced inner ocular canthi and hypospadias of variable degree. Additional anomalies are common. Heterozygous females have telecanthus. Inheritance of this condition is most likely to be X linked, but autosomal dominant inheritance with male sex limitation cannot be ruled out.

We summarise the historical and phenotypic findings of 21 patients in seven previous publications.¹⁻⁷ We have also had the opportunity to evaluate 12 families with a total of 18 affected males and have followed some of them for several years.

The purpose of this paper is to elucidate the syndrome further, to analyse data regarding inheritance, and to suggest that twinning and midline structural defects are involved in this condition.

Methods

Telecanthus is a term that refers to an apparently increased distance between the inner ocular canthi. Standards for inner canthal distance by Feingold and Bossert⁸ were used in the evaluation of all patients. These standards are limited by the fact that they only include measurements from birth to 14 years of age. Since a number of factors may affect inner canthal distance, including age, prematurity, epicanthic folds, and cranial contour, we do not feel that inner canthal measurements below the 97th centile completely exclude the diagnosis of the telecanthus-hypospadias syndrome in males nor the heterozygous carrier state in females.

Several previous reports used skull x rays for determination of increased interorbital distance (hypertelorism), but we did not use skull films to evaluate our patients. In addition, some investigators have measured interpupillary distance. However, since 10/39 patients had strabismus, we considered this measurement unreliable in many patients.

All of our 18 patients were examined personally by one of the authors. The diagnosis of the telecanthus-hypospadias syndrome was made in males who had hypospadias, a high, broad nasal

TABLE 1 Historical data.

	21 published cases (10 families)	18 Memphis patients (12 families)	Total patients reported
Race: White	19/21	10/18	29/39
Black	2/21	7/18	9/39
Pregnancy duration <38 weeks	2/12	8/16	10/28
Birth weight <5th centile	1/12	4/15	5/27
Subnormal intellect	11/17	10/12	21/29
Normal chromosomes	5/5	10/10	15/15
Mother with telecanthus	15/15	13/13	28/28
Father with telecanthus	0/11	1/18	1/29
Fetal loss	3/21	5/17	8/38
Like-sex twinning	2/21	11/18	13/39

bridge, a mother with telecanthus, and some degree of displaced canthi. The majority of patients had inner canthal distances greater than the 97th centile for age; for those who had inner canthal distance between the 70th and 90th centiles, other supporting but less specific manifestations helped in confirming the diagnosis.

Results

Table 1 summarises the historical features of 21 previously reported cases and our 18 patients. Of the 39 patients (all male), 29 were white, nine were black, and in one the race was not recorded. Ten of 28 patients were born prematurely. Average maternal and paternal ages were 25 and 30 years respectively. Prenatal growth parameters indicated that 5/27 patients were below the 5th centile for weight at birth and one patient was below the 5th centile for height. None of the patients was noted to have a head circumference below the 5th centile at birth. Subnormal intellect was determined by IQ <70, delayed psychomotor development, or very poor school performance. A total of 21/29 patients about whom we had sufficient information had substantial intellectual impairment. Psychological testing of 11 patients showed an IQ range of 46 to 107.

Mothers of affected males were examined. All 28 mothers had increased inner canthal measurements

or were described as having telecanthus clinically (table 2). Two of our patients were adopted and the mothers were unavailable for examination. Fig 1 is a photograph of the mother of three affected males. Her inner canthal distance is 3.5 cm, which is on approximately the 97th centile, and she appears clinically telecanthic. Fathers of affected males were also examined for telecanthus and hypospadias. Only one father had an increased inner canthal distance (4.0 cm), but this appeared to be a separate, isolated dominant characteristic in his family. Both his sister and her daughter also had telecanthus. The mother of the proband in this family appeared to be the carrier of the condition.

An interesting finding was the high incidence of like-sex twinning in these families. Opitz *et al*¹ reported monozygotic twins affected with telecanthus and hypospadias. Gonzalez *et al*⁴ reported a family with three sets of like-sex twins who were related to the proband. Two of our patients are monozygotic twins who are concordant for the syndrome. A third patient has an affected male twin of unknown zygosity (both have been lost to follow up). A fourth patient has a normal male twin of unknown zygosity. Of seven other patients with first or second degree relatives who are like-sex twins, the zygosity is uncertain.

Table 3 lists some of the clinical features of the 21 previously reported patients and our 18 patients. Age at examination varied from birth to 34 years. All 39 patients either had increased inner canthal measurements for age or were described as being clinically telecanthic (table 4). Thirty-seven of 39 patients had hypospadias of variable degree (table 5). Approximately one-third of patients showed postnatal growth deficiency. Of the 18 patients who had cranial abnormalities, seven were scaphocephalic, two brachycephalic, two oxycephalic, and the remainder had unspecified asymmetry. In addition, seven patients had prominent metopic sutures. Of the 14 patients with cleft lip/palate, 12 had bilateral cleft lip and palate, and two had unilateral cleft lip

TABLE 2 Inner canthal distances of mothers of patients.

15 mothers of 21 published cases:
8 at ≥97th centile
1 at 85th centile
1 at 80th centile
5 described as having telecanthus; no measurements given
15 mothers of 18 Memphis patients:
6 at ≥97th centile
2 at 75th centile
5 described as having telecanthus; no measurements given
2 information unavailable

FIG 1 Mother of three affected males. Note telecanthus.

TABLE 3 Clinical data.

	21 published cases (10 families)	18 Memphis patients (12 families)	Total patients reported
Telecanthus	21/21	18/18	39/39
Hypospadias	19/21	18/18	37/39
Weight <5th centile	4/10	5/17	9/27
Height <5th centile	4/10	5/17	9/27
Head circumference <5th centile	8/15	2/16	10/31
Cranial abnormality	6/21	12/18	18/39
Cleft lip/palate	7/21	7/18	14/39
High, broad nasal bridge	15/15	10/11	25/26
Congenital heart defect	5/21	3/18	8/39
Upper urinary tract anomaly	0/6	4/9	4/15
Cryptorchidism	9/21	2/18	11/39

and palate. Seven additional patients were noted to have a bifid uvula. Cardiac defects of various types were present in eight patients (table 6). Intravenous pyelograms in six previously reported patients were normal. However, 4/9 patients we examined had abnormal IVPs. Two patients had bifid, medially displaced ureters, one patient had duplication of the calyceal system, and one patient had duplication of the ureter with reflux.

Other phenotypic characteristics of the 39 patients not listed in table 3 include epicanthic folds (7), strabismus (10), posteriorly rotated or anomalous ears (18), high arched palate (9), micrognathia (7), diastasis recti (9), inguinal hernias (8), hypoplastic scrotum (3), cleft scrotum (4), and imperforate anus (3).

FACIAL APPEARANCE

Males with the telecanthus-hypospadias syndrome have an oval face with a narrow forehead and

TABLE 4 Inner canthal distances of patients.

21 published cases:
20 at >97th centile
1 described as having telecanthus; no measurements given
18 Memphis patients:
10 at >97th centile
1 at 90th centile
2 at 80th centile
2 at 75th centile
2 at 70th centile
1 with telecanthus by photograph

TABLE 5 Hypospadias.

	21 published cases	18 Memphis patients	Total
First degree	7	5	12
Second degree	4	6	10
Third degree	6	4	10
Degree not specified	2	3	5

TABLE 6 Cardiac defects.

	21 published cases	18 Memphis patients	Total
Coarctation of aorta	1	1	2
Ventricular septal defect		1	1
Atrial septal defect	1		1
Patent ductus arteriosus	2		2
Pulmonary valvular insufficiency		1	1
Heart murmur, 'aberrant artery'	1		1

occasionally a prominent metopic suture. Telecanthus with a high, broad nasal bridge is typical, while epicanthic folds and cleft lip/palate may also be present. Fig 2 is a photograph of family 1 showing the mother and her three sons and fig 3 is the family pedigree. The mother (II.10) has telecanthus (ICD=3.5 cm) and normal intelligence. The oldest son (III.4) has telecanthus (ICD=3.8 cm), bilateral cleft lip and palate, hypospadias, cranial asymmetry, and subnormal intellect. The younger boys (III.7 and III.8) are identical twins with telecanthus (ICD=3.5 cm and 4.0 cm), bilateral cleft lip and palate, scaphocephaly, hypospadias, and subnormal intellect. Fig 4 shows the twins at 10 years of age with their mother.

The pedigree of family 2 is illustrated in fig 5. Fig 6a is a photograph of an eight year old black male (III.7) with telecanthus (ICD=4.75 cm), hypospadias, and learning disabilities. His mother's (II.5) inner canthal distance is 4.0 cm and she is of normal intelligence (fig 6b). The boy's grandmother (I.6)

FIG 3 Pedigree of family 1. Note high incidence of like-sex twinning.

also has telecanthus. An uncle (II.12) has the telecanthus-hypospadias syndrome, four aunts (II.6, II.7, II.8, II.9) have telecanthus, and two of these aunts have cleft lip and palate. Two of the telecanthic aunts each has a son with the telecanthus-hypospadias syndrome (III.5 and III.10).

Discussion

INHERITANCE

In our series there were three kindreds which contained multiple affected members. The nine

FIG 2 Mother and her three affected sons. Note telecanthus, cleft lip and palate, and similar facial appearance in each son.

FIG 4 III.7 and III.8 at 10 years with their mother.

remaining patients were singleton cases, all of whom had mothers with some degree of telecanthus. After analysing the pedigrees of all 39 patients it appears that the telecanthus-hypospadias syndrome is most likely to be inherited in an X linked fashion. There has been no well documented male to male transmission either in patients previously reported or in our families. This may be because of decreased reproduction secondary to genital anomalies and the

high incidence of mental retardation. Only one of our patients has reproduced and he has three normal sons. A possible incidence of male to male transmission was noted by Opitz *et al*,¹ but there was insufficient clinical information since they had not been examined. Stoll *et al*⁹ reported a father and son who had telecanthus and hypospadias. However, their facial characteristics were not similar to others with the BBB syndrome. The five month old son

FIG 5 Pedigree of family 2.

FIG 6 (a) Affected eight year old (III.7). Note telecanthus and high, broad nasal bridge. (b) Mother (II.5) of boy pictured in fig 6a. Note telecanthus.

had a flat, broad nasal bridge, anteverted nares, and a facial appearance which more closely resembles that of the G syndrome.

Heterozygous females exhibit telecanthus, occasional mild facial dysmorphism, and normal intelligence. One of our families contains two sisters who have cleft lip and palate in addition to telecanthus (fig 5). This observation that females are much less severely affected than males also supports X linked inheritance. However, autosomal dominant inheritance with male sex limitation is still a possibility.

INCIDENCE AND DIFFERENTIAL DIAGNOSIS

Only 21 cases of the telecanthus-hypospadias syndrome have been published. We have personally evaluated 18 additional patients. This syndrome seems to be more common than reflected by published reports.

Differential diagnosis includes the G syndrome, which is characterised by telecanthus, hypospadias, cleft lip and palate, mental retardation, flattened nasal bridge, anteverted nares, laryngo-oesophageal abnormalities, and respiratory or swallowing difficulties. Inheritance of this disorder is thought to be autosomal dominant. Male to male transmission has been documented in the G syndrome.^{5 10} The phenotypic similarities and differences of these two syndromes are discussed in papers by Funderburk and Stewart⁵ and Cordero and Holmes.⁶ The G syndrome has many characteristics in common with the BBB syndrome. Distinguishing features include the laryngo-oesophageal abnormalities and respiratory or swallowing difficulties in the G syndrome. None of our patients had these findings. Additionally, the facial appearance in these two syndromes is

different. Patients with the BBB syndrome have a high, broad nasal bridge while those with the G syndrome have a flat nasal bridge and anteverted nares. An increased incidence of like-sex twinning seen in our patients has not been noted in the G syndrome families.

Telecanthus is a prominent feature in several other conditions including Aarskog, Waardenburg, Robinow, and Noonan syndromes. These, however, are readily distinguished clinically from the telecanthus-hypospadias syndrome.

Reed *et al*¹¹ reported eight patients who were said to have the hypertelorism-hypospadias syndrome but were not included in our review. Three of the patients were brothers who probably had the autosomal recessively inherited Elshah-Waters syndrome (branchioskeletogenital syndrome). Another of the patients (EG, family II) had facial features more consistent with the G syndrome than the BBB syndrome. The four remaining cases lacked sufficient clinical data and photographs to be certain of the diagnosis.

In a letter to the editor, Miller *et al*¹² reported a newborn with the hypertelorism-hypospadias syndrome who had a laryngotracheo-oesophageal cleft. Minimal clinical data were given and there was no photograph. This infant probably had the G syndrome although without further information the diagnosis remains uncertain.

Conclusion

In summary, 21 subjects with the telecanthus-hypospadias syndrome have been described in seven publications. We have evaluated 18 patients in 12

families with this syndrome. The most common features are telecanthus, hypospadias, cranial abnormality, cleft lip/palate, congenital heart defect, and mental retardation. The most likely form of inheritance appears to be X linked; however, autosomal dominant inheritance with sex limitation cannot be ruled out. Future studies should include psychological testing and careful evaluation for renal and cardiac anomalies. Evaluation of additional families and DNA studies will help to establish the inheritance and clarify the distinction between the telecanthus-hypospadias and the G syndromes.

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