Syndrome of the month

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The Townes-Brocks syndrome

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The Townes-Brocks syndrome derives its eponymous title from the names of the two authors who, in 1972, described variable anal, hand, foot, and ear anomalies in a father and five of his seven children.¹ Shortly afterwards, similar abnormalities were documented in 19 subjects from four generations of a large Australian family.² Subsequent reports of both familial³⁻⁶ and isolated⁶⁻⁹ cases have established the Townes-Brocks syndrome as a discrete entity and enabled fuller delineation of the phenotype of what appears to be a relatively rare disorder. Individual patients or families or both have been reported from North America,^{1 3 6 8} Australia,^{2 4} Belgium,⁵ Brazil,⁷ and Portugal.⁹

Clinical features

The clinical findings in published cases are summarised in the table. It is important to remember that patients are more likely to be ascertained and correctly diagnosed if they have a serious and cardinal diagnostic feature, such as anal atresia, so that it would be wrong to conclude that the incidence of anal anomalies is necessarily as high as the table suggests. Similarly, other more subtle features such as mild hearing loss or unilateral renal agenesis may well be underdiagnosed. It is also important to note that intrafamilial variation in expression can be quite striking, a point which is considered further in the section on inheritance.

ANORECTAL ABNORMALITIES

These constitute the most characteristic hallmark of this syndrome, being present in 42 of the 44 published

cases. In 13 of these subjects,² the anus was either anteriorly placed (seven females) or surrounded by excess skin (six males) with no functional disturbance. In a further eight cases the anus was stenotic. The remaining 21 children (13 boys and eight girls) had an imperforate anus, usually high (=type 3), which was associated with a rectoperineal or rectovaginal fistula in seven and five cases respectively.

In several cases,^{2 5} it was noted that there was a very prominent midline perineal raphe extending from the site of the anal orifice to the scrotum (fig 1). Glandular hypospadias was present in two boys.^{5 8}

HAND AND FOOT ABNORMALITIES

Abnormalities of the radial ray are reported in

Figure 1 View of the perineum of a newborn infant showing an imperforate anus with a prominent median raphe running forwards to the scrotum.

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approximately 50% of published cases. These consist of (1) preaxial polydactyly ('bifid thumb') with the extra digit sometimes being vestigial, (2) triphalangeal thumb often in association with preaxial polydactyly, (3) hypoplastic thumbs, (4) broad thumbs, and (5) distal ulnar deviation of the thumbs (fig 2). Syndactyly between the second and third fingers and between the third and fourth fingers has been noted in occasional patients.⁵⁻⁹ Radiographs of the hands have also shown absence of the triquetrum¹ and navicular⁷ bones, fusion of the triquetrum and hamate bones,⁴ cone shaped epiphyses,¹ and pseudoepiphyses.¹⁻⁹

Minor abnormalities of the toes have been noted in 25% of published cases. These include clinodactyly of the fifth toes, absence of the third toe, hypoplasia of the third toe, syndactyly between the third and fourth toes, and overlapping of the second, third, and fourth toes (fig 3). Pes planus and rocker bottom feet have also been documented,¹⁻⁶ as have exostoses in a single patient.³

AURICULAR ABNORMALITIES

Overfolding of the superior helix ('satyr ear') is the most characteristic auricular abnormality noted in this syndrome, with 14 of the 44 published cases having one or both ears affected (fig 4). Preauricular tags have been described in 13 cases, six of whom also had uni- or bilateral satyr ears. Three patients have been described as having large ears³ and auricular pits have

Figure 3 The feet of a mother (a) and son (b) showing hypoplastic third toes overlapped by the second and fourth toes.

Figure 2 The hands of subject II.3 in fig 5. An additional digit arising from the base of the right thumb was removed in childhood.

Figure 4 Satyr form of lop shaped ears.

been noted in two patients.^{5 6} Microtia with external auditory atresia has been noted in a single patient.³ Sensorineural hearing loss has been noted in 10 patients, all but one of whom also had auricular abnormalities. Details of the severity of the hearing loss have been provided for two patients who had deficits of 40 and 60 decibels.^{4 5} Ossicular anomalies were found in one patient.⁹

RENAL ABNORMALITIES

In five patients renal hypoplasia has been noted,^{3 5}

and two of these subjects also showed evidence of vesicoureteral reflux. Unilateral renal agenesis was found in a single familial case,⁶ and necropsy studies confirmed bilateral renal dysplastic changes in an isolated case.⁶ It appears that no systematic survey of renal involvement in the Townes-Brocks syndrome has been undertaken.

CARDIAC ABNORMALITIES

Cardiac anomalies have been present in all four isolated cases listed in the table, but have not been

Clinical features in published reports of Townes-Brocks syndrome.

Reference	No of cases	Sex		Anorectal anomaly	Thumb anomaly	Auricular anomaly	Hearing loss	Foot anomaly	Renal anomaly	Other abnormalities
		M	F							
<i>Familial cases</i>										
Townes and Brocks ¹	6	4	2	6	4	6	4	5		
Reid and Turner ²	19	12	7	19	5	5				
Kurnit <i>et al</i> ³	9	5	4	9	2	9	1	2	4	
Walpole and Hockey ⁴	2	1	1	2	1	1	1			
De Vries-Van der Weerd <i>et al</i> ⁵	2	2		1	2	1	2	2	2	
Barakat <i>et al</i> ⁶	2		2	2	2	2	2	1	2	
<i>Isolated cases</i>										
De Pina-Neto ⁷	1		1	1	1	1	1			Atrial septal defect
Hersh <i>et al</i> ⁸	1	1		1	1	1	1			Hypospadias Tetralogy of Fallot
Barakat <i>et al</i> ⁶	1		1		1	1		1	1	Truncus arteriosus Ventricular septal defect
Ferraz <i>et al</i> ^{9*}	1		1	1	1		1			Ventricular septal defect
Total	44	25	19	42	20	27	13	11	9	

*The patient reported by Ferraz *et al*⁹ had a distant family history of hearing loss.

recorded in any of the familial cases. This suggests that the four isolated cases, one of whom died after cardiac surgery in infancy,⁶ may have had a disorder other than the Townes-Brocks syndrome. The finding of congenital heart disease in a familial case would greatly strengthen the argument of those who contend that cardiac abnormalities fall within the phenotypic spectrum of this condition.⁷⁻⁹

Differential diagnosis

Anorectal malformations may occur in association with numerous other malformations¹⁰ and as part of a very large number of syndromes.¹¹ Among these, the disorder likely to feature most prominently in the differential diagnosis of the Townes-Brocks syndrome is the VATER association, in which there is a high incidence of anal atresia (56%), renal dysplasia or agenesis (44%), and congenital heart defects (73%).¹² Anomalies of the ears (39%) and thumbs (28%) occur less commonly. In an isolated case, distinction between the almost invariably sporadic VATER association and the Townes-Brocks syndrome may be very difficult. The presence of vertebral defects or tracheo-oesophageal malformations or both would strongly favour the former diagnosis.

Naveh and Friedman¹³ have described two sibs born to consanguineous parents who showed variable combinations of anal atresia, congenital heart disease, renal anomalies, and short thumbs. Both of these children were mentally retarded, a point which serves to distinguish this probable autosomal recessive condition from the Townes-Brocks syndrome in which intelligence is normal.

There is at least one report¹⁴ of anal anomalies in children believed to have the Holt-Oram syndrome, which shares with the Townes-Brocks syndrome both a high incidence of thumb anomalies and autosomal dominant inheritance. However, the precise diagnosis in the children reported by Silver *et al*¹⁴ is not absolutely clear and in general the Holt-Oram syndrome can usually be distinguished from the Townes-Brocks syndrome by the absence of both anal and auricular abnormalities.

Finally, many of the features of the Townes-Brocks syndrome, including preauricular tags, anal atresia, and cardiac and renal malformations, are also seen in children with partial trisomy 22¹⁵ (the cat eye syndrome) so that careful chromosome studies are indicated, particularly if ocular abnormalities are present.

Inheritance

Autosomal dominant inheritance is well established with several examples of male to male transmission.^{1-3, 5} However, it is difficult to determine from available published reports whether penetrance is complete. The parents of the girl described by Ferraz *et al*⁹ were examined and showed no abnormality. The maternal grandfather had bilateral sensorineural deafness, a short fifth finger, and bilateral polycystic kidneys, findings which prompted the authors to suggest that he might also have had the condition. This man had a total of seven children and nine grandchildren of whom only one, the female proband, was affected.

In the very large pedigree reported by Reid and

Figure 5 Pedigree of a family with the Townes-Brocks syndrome. * = personally examined.

Turner,² several alleged gene carriers were identified only by the presence of excess perianal skin. Confirmation of intrafamilial variability in this disorder is provided by the pedigree of a family known to the authors (fig 5). The proband (III.1) presented with an imperforate anus, satyr ears, and overlapping toes, and was found to have unilateral renal agenesis. In contrast, his maternal aunt (II.3) had abnormalities involving only the thumbs and toes. The maternal grandmother (I.2), who could not be examined, was alleged to show only mild hypoplasia of the third toes with overlapping of the second and fourth toes.

Thus, the prevailing uncertainty concerning the expression of this syndrome and its full phenotypic spectrum illustrates the importance of careful documentation and assessment of every family, not only for academic purposes, but also for the detection of less obvious features, such as hearing loss and renal anomalies, so that appropriate treatment can be initiated.

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