Syndrome of the month

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Blepharophimosis, ptosis, epicanthus inversus syndrome (BPES syndrome)

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Although von Ammon¹ first used the term blepharophimosis in 1841, it was Vignes² in 1889 who first associated blepharophimosis with ptosis and epicanthus inversus. In 1921, Dimitry³ reported a family in which there were 21 affected subjects in five generations. He described them as having ptosis alone and did not specify any other features, although photographs in the report show that they probably had the full syndrome. Dimitry's pedigree was updated by Owens *et al*⁴ in 1960. The syndrome appeared in both sexes and was transmitted as a Mendelian dominant.

In 1935, Usher⁵ reviewed the reported cases. By then, 26 pedigrees had been published with a total of 175 affected persons with transmission mainly through affected males. There was no consanguinity in any pedigree. In three pedigrees, parents who obviously carried the gene were unaffected.

Well over 150 families have now been reported and there is no doubt about the autosomal dominant pattern of inheritance. However, like Usher,⁵ several authors have noted that transmission is mainly through affected males and less commonly through affected females.⁴⁻⁶ Reports by Moraine *et al*⁷ and Townes and Muechler⁸ have described families where all affected females were either infertile with primary or secondary amenorrhoea or had menstrual irregularity. Zlotogora *et al*⁹ described one family and analysed 38 families reported previously. They proposed the existence of two types: type I, the more common type, in which the syndrome is transmitted by males only and affected females are infertile, and type II, which is transmitted by both affected females and males. There is male to male transmission in both types and both are inherited as an autosomal dominant trait. They found complete penetrance in type I and slightly reduced penetrance in type II.

Clinical features (figs 1 to 6)

BLEPHAROPHIMOSIS

The palpebral fissure is reduced in horizontal dimension. The normal horizontal fissure length in adults is 25 to 30 mm whereas in this syndrome it is usually 20 to 22 mm.¹⁰

PTOSIS

Blepharoptosis literally means a falling of the lids. The palpebral fissure is abnormally small in the

FIG 1 Typical posture assumed because of ptosis. Note narrowing of palpebral fissures and cup shaped right ear.

FIG 2 Same patient as in fig 1. Note telecanthus, smooth skin over eyelids, and flat nasal bridge.

vertical dimension. It is caused by the absence or impairment of the function of the levator palpebrae superioris muscle and is usually bilateral and symmetrical. To compensate for the ptosis, affected

persons assume a characteristic posture with the head tilted backwards, the brow furrowed, and the chin arched upward (figs 1 and 3).

EPICANTHUS INVERSUS

Unlike other types of epicanthus, epicanthus inversus improves only slightly with age. It is characterised by a small skin fold which arises from the lower lid and runs inwards and upwards (fig 2). Associated with this is an increased length of the medial canthal ligament and a lack of the normal depression seen at the internal canthus.

The effect of blepharophimosis, ptosis, and epicanthus inversus is to reduce the size of the palpebral fissure by reducing it in both height and width.

ASSOCIATED OCULAR FEATURES

Telecanthus is seen in the majority of patients. This refers to a lateral displacement of the inner canthus leading to a widening of the intercanthal distance. The interpupillary distance remains unchanged. The eyelids are often covered by smooth skin without eyelid folds and deficient amounts of skin in both eyelids may be found at surgery¹¹ (fig 2).

The eyebrows are increased in their vertical height and they are drawn up into a pronounced convex arch. This is attributed to the stretching of hair bearing skin as a consequence of the constant contraction of the frontalis muscle (fig 3). Abnormalities of the eyelid margin are frequently seen. The margin of the upper lid has a slight S shaped curve and the lower lid usually has an abnormal concavity downwards, particularly laterally where

FIG 3 Affected child, just sitting at 12 months. Note arched eyebrows.

FIG 4 Same patient as in fig 3 with unaffected sibs, who now attends normal school.

an ectropion might occur. Frequently, there is lateral displacement of the upper and lower lacrimal puncta, even more than would be expected from the lateral displacement of the inner canthi.

Occasional ocular findings include microphthal-

mos, anophthalmos, microcornea, hypermetropia, divergent strabismus, nystagmus, amblyopia, and trichiasis. Several authors have commented on the apparent increased frequency of brown eyes in affected persons.¹²

FIG 5 Patient aged two and a half years before surgery.

FIG 6 Same patient as in fig 5, after three operations, the last one at 18 years. She has secondary amenorrhoea.

NON-OCULAR FEATURES

A flat, broad nasal bridge occurs frequently (fig 2). There is one report of a bony deficiency with absent supraorbital ridges and an absent nasoglabellar angle.¹¹ High arched palate has been reported in a few cases.^{4,13} Protruding, simple, or cup shaped ears have been reported occasionally¹⁴ (fig 1). Smith¹⁵ has suggested some may have generalised hypotonia. Cardiac defects have been reported.¹⁶ Intellectual development is usually normal although mild mental retardation has occasionally been reported.¹⁷ Delay in sitting alone often occurs during the first year of life, mostly because the infant tilts its head in order to see and then falls backwards. Psychological problems secondary to the altered facial appearance do occur.¹⁸ Many Caucasian children are teased because they look Oriental and some are diagnosed initially as having Down's syndrome.

INFERTILITY

There is a high incidence of menstrual irregularity and infertility in females. Although primary hypogonadism has been suggested as a cause of the female infertility,⁹ it appears to be responsible in only a few cases, with the cause in most remaining unknown. Townes and Muechler⁸ reported a family where all affected females had primary ovarian failure. They had a normal female karyotype and normal breast development, and pubic and axillary hair was scant but in the normal female distribution. Laparoscopy revealed a small uterus and small atrophic ovaries. There was raised serum testosterone, serum luteinising hormone, and follicle stimulating hormone and after administration of cyclical oestrogen and progesterone therapy regular withdrawal bleeding occurred. However, Jones and Collin¹⁹ reviewed 37 known cases, and of the six females of child bearing age two had normal menstrual periods, three had scanty irregular periods with no definite cycle, and one had primary amenorrhoea. One of the women with normal periods had had a child and one woman with irregular periods had had three miscarriages. Primary hypogonadism with raised gonadotrophins and low oestrogen and progesterone was evident in only one but four others had abnormal hormone function which was difficult to interpret.

It has also been suggested that the infertility is an autosomal dominant sex limited trait transmitted by males and affecting females only, similar to the type of inheritance described in the Stein-Leventhal syndrome.²⁰

Differential diagnosis

The differential diagnosis includes those conditions in which ptosis or blepharophimosis is a major

feature. Therefore, congenital simple ptosis, ptosis with external ophthalmoplegia,²² Noonan syndrome,²³ Marden-Walker syndrome,²⁴ Schwartz Jampel syndrome,²⁵ Dubowitz syndrome,²⁶ and Smith-Lemli-Opitz syndrome²⁷ must all be considered.

Inheritance

Autosomal dominant transmission is well established. Differentiation of the syndrome into two types by Zlotogora *et al*⁹ shows that penetrance 100% in type I where there is transmission by males only and affected females are infertile. In type II penetrance is 96.5% and transmission occurs through both sexes. Zlotogora *et al*⁹ also found there was a deviation from the expected sex ratio among children of affected fathers in both types. In type I most of the children were males and most male offspring were affected, whereas in type II, most of the children were females and most of the female offspring were affected.

Although distinction between the two types is important for counselling females about the likelihood of being fertile, if the rate of new mutations is as high as 50%, as suggested by Jones and Collin, then counselling of isolated cases is extremely difficult.

Pathogenesis

In 1930 Waardenburg,²⁸ after studying the embryology of human fetuses, proposed that the ocular defect in this syndrome occurred during the third month of intrauterine life. This would coincide with the critical period in the development of the ovaries and the initial formation of the uterus through Müllerian duct fusion.

Management/treatment

Many children require early surgery because of the visual difficulties associated with the ptosis and blepharophimosis. As distinct from other conditions associated with ptosis, there is very little improvement in the appearance and function with age.

Surgery is far more difficult than for isolated ptosis because of the associated epicanthus inversus, the variable degree of blepharophimosis, and the frequent finding of deficient eyelid skin. Early surgery is recommended to minimise being teased at school, although the final results of surgical correction may be better in older children and in adults.²⁹ Surgery is started between the ages of three and five years, although severe ptosis may require earlier correction.

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Many surgical techniques have been described but most seem to involve initial canthal surgery to improve the blepharophimosis before ptosis correction is possible.¹⁰ However, combined surgery has been used in children with less severe manifestations.³⁰

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