WAARDENBURG'S SYNDROME*†

REPORT OF A FAMILY

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WAARDENBURG'S syndrome, or more fully the van der Hoeve-Halbertsma-Waardenburg-Klein syndrome, is a combination of ocular and associated anomalies which are always genetically determined and usually show a dominant transmission. The individual features of the syndrome are not of themselves uncommon and the most characteristic of these, outward displacement of the inner canthi, has been described frequently (van der Hoeve, 1916, 1929; Waardenburg, 1930), but Waardenburg was the first to correlate this with dermal, auditory, and iris anomalies. The complete syndrome is rare and the purpose of this communication is to record a family showing all its stigmata in three generations, and to point to a plastic operation to correct the most commonly described feature.

The syndrome, as it was described by Waardenburg (1951), consists essentially of five components.

(1) *Dystopia Canthi*.—Telecanthus, a term proposed by Mustardé (1963), describes an increase in the distance between the medial canthi beyond the normal range. This, combined with lateral displacement of the lacrimal puncta, bringing them to lie in the corneae, yet without any increase in the inter-pupillary (IP) or inter-lateral canthal (ILC) distances, is the most common feature of the syndrome. This abnormal anatomical arrangement causes blepharophimosis, little or none of the medial sclera being visible when the eyes are in the primary position. It also results in elongation of the lacrimal drainage apparatus producing a tendency to epiphora and chronic dacryocystitis (Thorkilgaard, 1962; Galvez Montes, 1958).

Hypertelorism should be distinguished by the increase not only in the inter-medial canthal distance (IMC), but also in the IP distance. This can be expressed as the ratio IMC : IP, which is increased in Waardenburg's syndrome but not in hypertelorism. This ratio has a practical use in that it can be calculated from measurements taken from photographs; these have a close correlation to actual measurements (Partington, 1964), which can be difficult to make, particularly in children.

(2) *Hyperplasia Supercilii Medialis et Radicis Nasi*.—This has been described by Waardenburg as characterized by a high nose-bridge with hypertrichosis of the eyebrows which tend to join in the mid-line (synophrys). The former is seen in extreme degree in the case recorded by Klein (1950), and is demonstrated in the family described below. Although most published cases have had abnormal nose-bridges, this is the most variable feature of the syndrome and many otherwise typical cases have depressed nose-bridges (Fisch, 1959).

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(3) *Heterochromia Iridum Totalis sive Partialis*.—Hypopigmentation and hypoplasia of the iris stroma may be present in one or both eyes. The affected area of the iris presents as a startling white-blue colour caused by scattered areas of white hypoplastic mesenchyme of the anterior iris leaf showing against a dark blue background (Thorkilgaard, 1962).

(4) *Surditas Congenita*.—The deafness found in this syndrome is perceptive in nature and belongs to one of two distinct types. "Type 1" shows almost total deafness with a little residual hearing for the lower range of frequencies, and "Type 2" a moderate degree of deafness with uniform hearing loss for the lower and middle ranges of notes with improvement for the higher notes. The latter type is common in unilateral cases and has not been demonstrated bilaterally. Bilateral deafness can be mixed or Type 1 in both ears. Histological examination of the inner ear and brain-stem has shown absence of the organ of Corti, together with poor myelination and sparse nerve fibres in the cochlear root of the eighth cranial nerve (Fisch, 1959).

(5) *Albinismus Circumscriptus*.—A median white fore-lock may vary in intensity from a few white hairs to the obvious picture found in some cases (Klein, 1950). A transient white fore-lock present at birth and disappearing with age and premature depigmentation of the hair have been described (Galvez Montes, 1958; DiGeorge, Olmsted, and Harley, 1960). Pigmentary upsets have also been demonstrated in the skin producing white patches (Klein, 1950; DiGeorge and others, 1960) and brown (Fisch, 1959).

The first is the most frequently recorded feature and this, together with the white fore-lock, is the most obvious, but the most significant feature for the affected patients is the deafness which is usually a severe handicap. About 2 per cent. of the children in Glasgow's deaf schools have Waardenburg's syndrome in some form.

This is essentially an ectodermal syndrome, the most likely site for the primary fault lying in the neural crest as suggested by Fisch (1959). A developmental abnormality here would account for the association of upsets of pigmentation and defects in the developing ear together with the other lesions which are found.

Waardenburg's syndrome is inherited as an autosomal dominant and no sex-linkage has so far been demonstrated. The degree of penetrance of its various aspects has been estimated by Waardenburg as:

- Dystopia canthi—90 per cent.
- Prominentia radialis nasi—78 per cent.
- Hyperplasia supercilii medialis—45 per cent.
- Heterochromia iridum (partial or complete)—25 per cent.
- Surditas congenita—20 per cent.
- Albinismus circumscriptus—17 per cent.

By the nature of its inheritance only a small percentage of those affected show all the features.

Material

The family described consists of three generations (Figs 1 and 2, opposite).

Generation II, 1. The most obviously affected member is a man now aged 34 years, who shows the complete syndrome. He has dystopia canthi, treated by operation in childhood, a high nose-bridge with heavy eyebrows which are prematurely greying, heterochromia iridum—the right iris being brown with a blue spot and the left iris blue, perceptive deafness in the left ear, and a median white fore-lock. He has only two children, both of whom are affected.

FIG. 1.—Family tree.

FIG. 2.—Three of the cases described (the father and his two children), all of whom have had a cosmetic operation.

Generation III, 2. His daughter, now aged 7 years, had presented with dystopia canthi (Fig. 3, overleaf), prominent nose-bridge, and perceptive deafness in both ears with mutism, but no abnormality in skin or hair pigmentation. A cosmetic operation to correct the dystopia canthi was performed at the age of 5 years. Before operation the IMC : IP ratio was 0.76 and after operation 0.67.

Generation III, 1. His son, aged 9 years, was noted at birth to have dystopia canthi which was corrected at the age of one year. The IMC : IP ratio before operation was 0.779 and after operation 0.67. His other features are prominence of the nose-root, with synophrys, patchy pigmentation of the limbs, and severe bilateral perceptive deafness with mutism.

FIG. 3.—The girl at the age of 4 years, before operation.

He was found to be deaf when almost a year old and has had a hearing aid since that time.

Generation I, 1. The other affected case indicated in Fig. 1 was the children's paternal grandmother (now deceased). She had dystopia canthi, a high nose-bridge, heterochromia iridum, and almost constant bilateral epiphora.

Despite their stigmata the two children are happy and well-adjusted and are responding well to education at a deaf school. They have reasonable auditory acuity with their hearing aids, but they have a limited vocabulary and communicate mainly by signs. The most disabling feature of this syndrome is, undoubtedly, the severe deafness, yet the children's parents and the children themselves seem less concerned by this than by their appearance and they were anxious to have cosmetic operations performed as soon as possible.

Operation

The proposed site of the new medial canthus is marked on the skin and four small skin flaps are raised lateral to this as described by Mustardé (1963, 1966). The medial canthus is then brought up to its new position and the flaps are transposed and sutured.

Subsequent removal of the sutures reveals a neat canthoplasty without the noticeable scarring and epicanthal folds which may be produced by contracture of scar tissue in other forms of operation. Cicatricial epicanthal folds cannot occur since any residual scar is linear and runs through the canthus.

Genetic Studies

Chromosome counts and photographic analysis did not reveal chromosomal aberrations in any of the affected members of generations II and III, or in the wife of II, 1 (Fig. 1). Normal chromosome patterns have been found in other affected children (Partington, 1964).

Comment

The family described has four affected cases in three generations and is presented to show one case with the complete syndrome associated with others with the incomplete syndrome, expressing varying features. Although in this pedigree there is an obvious association between the cases, the individual features of this syndrome

tend to be expressed in apparently sporadic cases and their association is not always obvious. Apparently sporadic cases can usually be proved to be part of a pedigree, but difficulty in demonstrating this may be found unless it is appreciated that other members of the family showing the syndrome may show different features. We see many cases with the partial syndrome and it is important to appreciate the hereditary nature of these anomalies. It is interesting that, despite the varying penetrance and varying expression, even within a pedigree, the separate features are usually fully expressed (as in the case of the children described above), even though they may present as isolated phenomena.

The full Waardenburg's syndrome is rare, but cases showing apparently isolated features which can be linked through a pedigree are not uncommon.

Summary

A family of three generations with four cases showing Waardenburg's syndrome is described and an effective operation for correction of dystopia canthi, the most obvious feature of the syndrome, is suggested.

One of the operations described above was performed by Dr. M. W. Paterson and another by Mr. J. C. Mustardé. We are grateful to Dr. Malcolm Ferguson Smith, who carried out extensive genetic studies on this family.

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