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Pigment distribution in Waardenburg's syndrome: a new hypothesis*

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Abstract. Two cases of Waardenburg's syndrome are presented. The first case is an example of Waardenburg's type II (without dystopia canthorum) with bilateral sectoral iris heterochromia and fundus bicolor, hyperpigmented skin patches, characteristic facies and deafness. The second case is an example of Waardenburg's type I (with dystopia canthorum) with complete iris heterochromia and characteristic facies. Bilateral glaucoma was also present in the second case. Previously unrecognized details of iris architecture in Waardenburg's syndrome are described. Pigmentation anomalies of the skin are also discussed. It is hypothesized that the ocular pigmentary disturbance in Waardenburg's syndrome is widespread and involves the hyperchromic as well as the hypochromic areas of the eyes. A possible association with glaucoma might be explained by such a hypothesis.

Introduction

Waardenburg's syndrome is an autosomal dominant disorder that has several clinical signs, each with variable penetrance. As originally described, the following features are found (in order of decreasing frequency): lateral displacement of the inner canthi (dystopia canthorum), prominant root of the nose, hyperplasia of the medial brows, iris heterochromia, congenital deafness, and circumscribed hypochromia of the hair (a white forelock). There are also several "Waardenburg's equivalents" that have been described, including circumscribed cutaneous hypochromia (vitiligo), bilateral iris hypochromia, and premature graying of the scalp hair. A facial cleft and/or a highly arched palate is also considered to be part of the syndrome (Waardenburg 1951; Hageman and Delleman 1977; Francois 1982).

DiGeorge et al. (1960) and Fisch (1959) have observed additional facial characteristics that include a prominant jaw (the face being rather square), decreased flare of the alae nasi, a slightly upturned nose, full lips with a prominant "cupid's bow", and an apparent shortening of the distance between the corners of the mouth.

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Goldberg (1966) was the first to describe the iris and fundus findings of the syndrome fully. He observed that the pigment distribution of the fundus is continuous with that of the iris heterochromia, that is, if one iris is hypochromic, the fundus of the same eye would also be hypochromic. Furthermore, if an iris showed only a sector that was hypochromic (heterochromia iridis), then the corresponding sector of the fundus would also be hypochromic.

Since the early literature on Waardenburg's, the syndrome has been divided into type I and type II. The former has the characteristic feature of dystopia canthorum and the latter is without dystopia. There is also a "pseudo-Waardenburg's" with unilateral congenital ptosis and without dystopia canthorum, but this has not been described in consecutive generations. Approximately one-fifth of all patients with "Waardenburg's syndrome" may be type II (Arias 1971). The distinction is most likely a real one because, as Arias points out: (1) there is little overlap in the measurements of the dystopic and non-dystopic groups (Partington 1964); (2) there is no gradation of the dystopia between siblings who have at least one typical sign of Waardenburg's syndrome; (3) dystopia, when it occurs in a family, apparently has complete penetrance. It is important to distinguish between the two types because the penetrance for bilateral deafness is about 25% in Waardenburg's Type I and 50% in Type II (Hageman and Delleman 1977).

Two cases of Wardenburg's syndrome are presented that demonstrate some previously unrecognized aspects of pigmentary distribution. Also, the first published wide-angle fundus photographs of a sectoral heterochromia are included.

Case reports

Case 1

The first patient, a 13-year-old Caucasian male, had no functional complaint when seen for a required eye examination prior to attending a school for the deaf. Pertinent facts from his history included: a "blue spot" that had always been present on his right iris, a severe bilateral hearing loss since infancy, a hyperpigmented spot on his back which had faded considerably since early childhood, and a negative family history of eye disease or of pigmentary disturbances.

He was brunette with normal skin coloration. A hyperpigmented area was present on his right lower eyelid (Figs. 1

and 2), and another faintly hyperpigmented area (measuring 3 × 5 cm) was noted in the sacral region. His facial features were subtly abnormal in that there was hyperplasia of the medial brows, decreased flare of the alae nasi, and the tip of his nose was slightly upturned (Fig. 2). His lips were full with a pronounced "cupid's bow" and the distance between the corners of his mouth appeared shortened. He also had a highly arched palate. There was no dystopia canthorum.

He was emmetropic and had 20/15 vision in both eyes without correction. The remainder of his eye examination, including the visual fields, was normal except for extensive pigmentary anomalies. The conjunctiva and sclera were normally pigmented though there was some increased pigmentation about the scleral emissaria. The right iris was heterochromic. Most of the iris was dark brown and had a thick stroma with partial abolition of the crypts (Figs. 3 and 4). One small sector of this iris was whitish blue, had normal crypts, and a much thinner stroma. The iris pigment epithelium at the pupillary border was normal in both the brown and blue segments. His left iris had only a tiny blue area (Fig. 5 and inset), indicating asymmetry.

Pigmentary abnormalities involved both fundi. Uniform hyperpigmentation extended from the ora serrata to the posterior pole with segmental areas of hypopigmentation. The area of hyperpigmentation involved at least three-quarters of the fundus in both eyes with a somewhat greater extent in the left eye. The areas of hypopigmentation extended, in the right eye, from the fovea to the ora serrata superonasally (Fig. 6). A similar pattern was seen in the left eye (Fig. 7). Figure 8 is an artist's rendition showing the pattern of pigmentation over the entire fundus of both eyes.

Fluorescein angiography showed only mildly decreased choroidal fluorescence corresponding to the hyperpigmented areas, but this was much less drastic than the pigmentary differences seen with the indirect ophthalmoscope or in the color photos. Both the scotopic and photopic electroretinogram were normal.

A biopsy specimen of the hyperpigmented sacral area was taken. The report indicated that hyperpigmentation was present in the basal layer of the skin due to increased melanin. There was no evidence of prominent or increased numbers of melanocytes. We examined the patient's mother and full brother. The skin and ocular pigmentation was normal. In both cases the fundus and iris pigmentation was uniform and the degree of pigmentation was intermediate between our patient's hyperpigmented and hypopigmented areas. His brother did have hyperplasia of the medial brows, decreased flare of the alae nasi and full lips, but no dystopia canthorum.

Case 2

This patient was a 54-year-old Caucasian female who had been diagnosed as having glaucoma 3 years earlier and was referred to us because of elevated intraocular pressure. She complained of gradual visual loss OD as well as intermittent bilateral eye pain. There was a positive family history of glaucoma but the details could not be obtained. She noted only a mild, unilateral hearing deficit.

Her appearance was typical of Waardenburg's type I in that she had prominent dystopia canthorum, decreased flare of the alae nasi, ectopic lacrimal points, and heterochromia iridum (Figs. 9–11). The right iris was whitish blue with normal crypts. The left iris was a medium brown with partial abolition of the crypts.

Her vision was 20/30 OD with a correction of $-1.50+1.25\times10°$ and 20/20 OS with $+0.25+0.50\times174°$. The anterior chamber angle was narrow but open in both eyes. With gonioscopy, the trabecular meshwork in the right (blue) eye was visible up to the scleral spur. Only the anterior portion of the trabecular meshwork was visible in the left (brown) eye, though no peripheral anterior synechia could be seen in either eye. The cup-to-disc ratio was 0.9 in both eyes. She had an intraocular pressure of 52 mm Hg OD and 48 mm Hg OS. Arcuate scotomas were found with Goldmann perimetry in both eyes, but the defects were more extensive in the right (blue) eye.

Discussion

Discussion of case 1

A diagnosis of nevus of Ota (1939) was initially entertained for case 1 because of the hyperpigmentation of the right lower lid (Fig. 1), the absence of both dystopia canthorum and a white forelock, and the apparent lack of a family history of deafness. The abnormally heavy pigmentation of the dark areas of the iris and fundus also suggest a nevus.

However, such a diagnosis would not explain several aspects of this case. These include deafness, characteristic facies, and the highly arched palate. Nor could it account for the abnormally hypopigmented segments of the irides and fundi. In addition, the lack of dystopia canthorum does not prevent a diagnosis of Waardenburg's syndrome; in fact, this is now considered to be a distinct subgroup of the syndrome (type II).

Because it was not possible for us to examine more than two other family members, a hereditary pattern could not be determined with certainty, though the characteristic facies of the patient's brother are suggestive of this disease. History alone is not always helpful because of the low penetrance of deafness and the often inconspicuous nature of the other Waardenburg syndrome features, especially when the white forelock is absent.

Fig. 1. Case 1. Hyperpigmented area on right lower lid and upturned nose

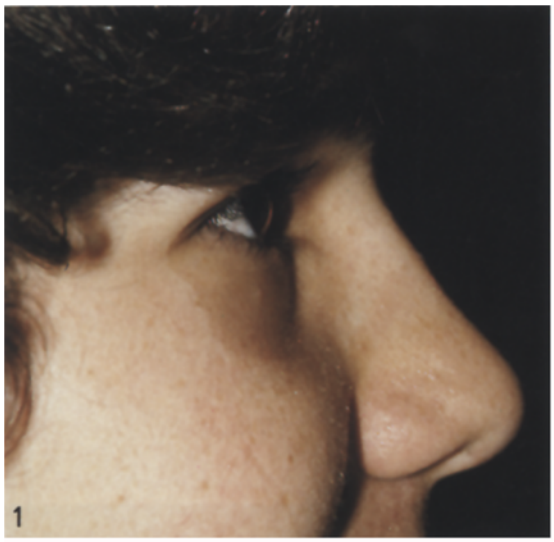
Fig. 2. Case 1. Hyperplasia of the medial brows and decreased flare of the alae nasi

Fig. 3. Case 1. Right iris with sectoral pigment defect

Fig. 4. Case 1. Higher magnification of right iris. Small flecks of pigment are present at the edge of the defect and appear to be confined to the anterior border layer when viewed with a stereobiomicroscope

Fig. 5. Case 1. Left iris with smaller hypopigmented area (*arrow*). *Inset*: Higher magnification

Fig. 6. Case 1. Wide-angle photograph of right fundus showing sectoral pigment distribution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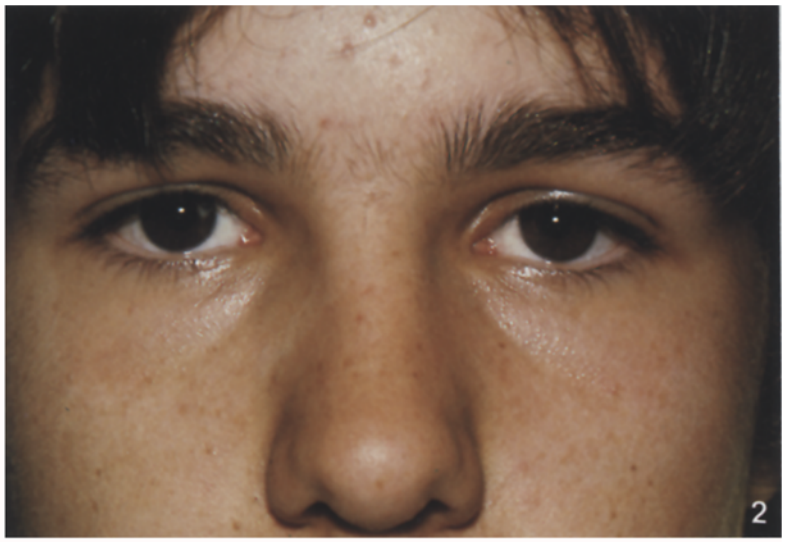
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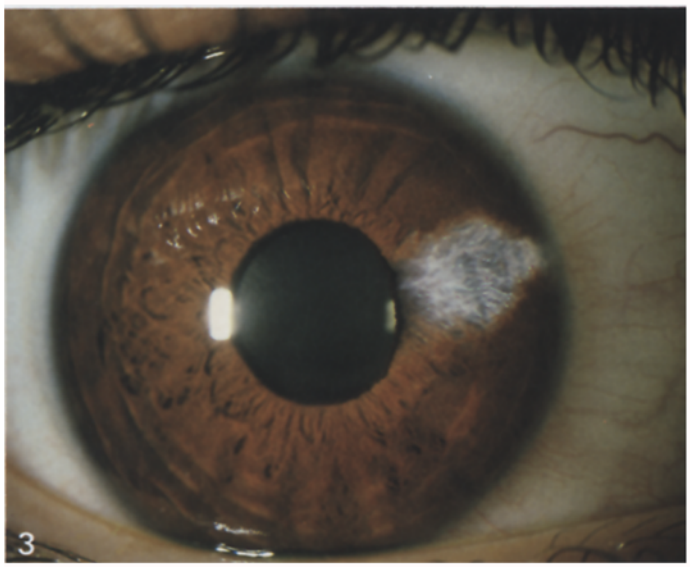
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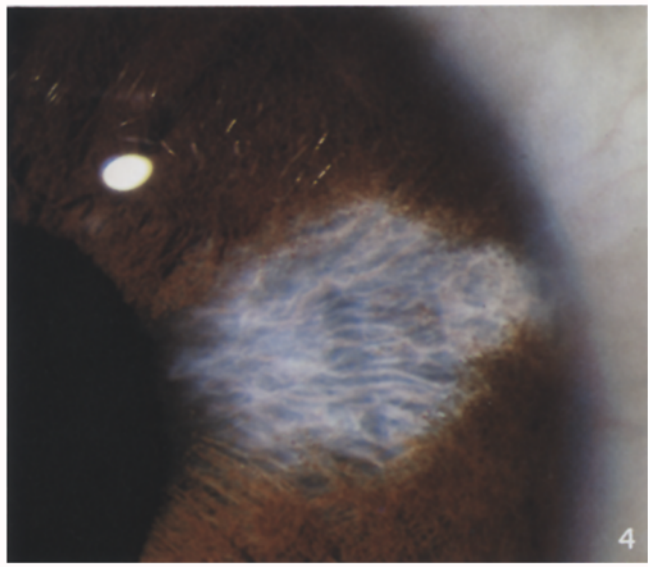
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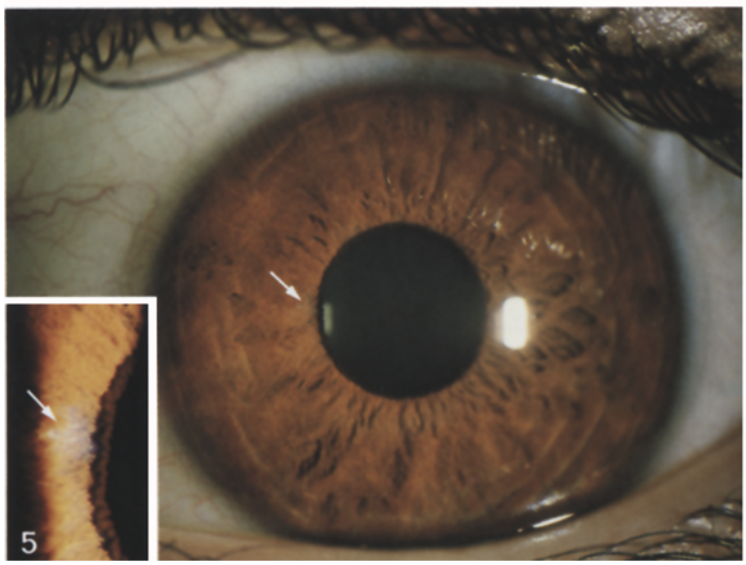
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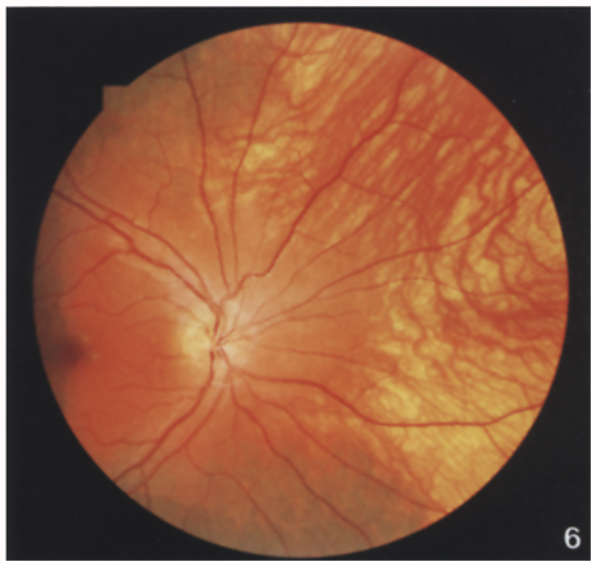
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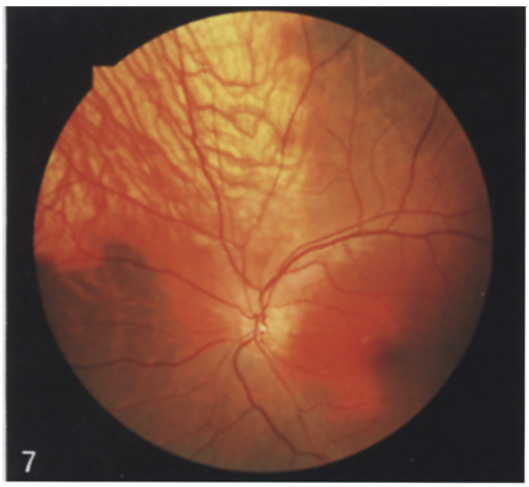

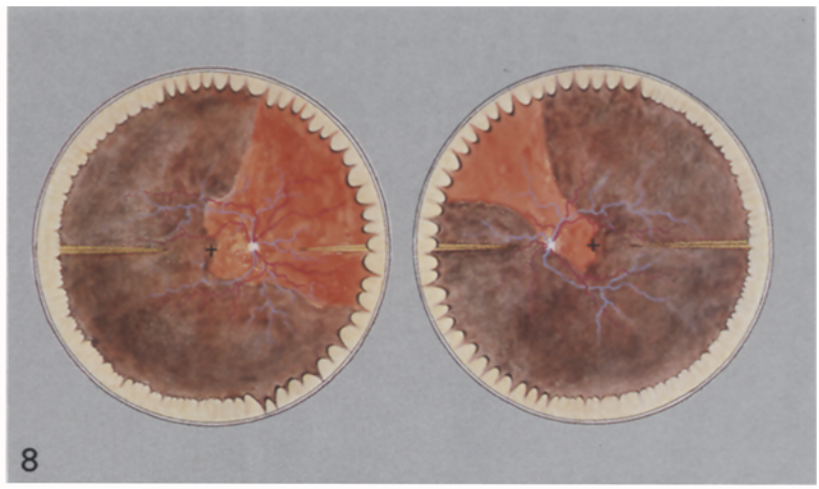

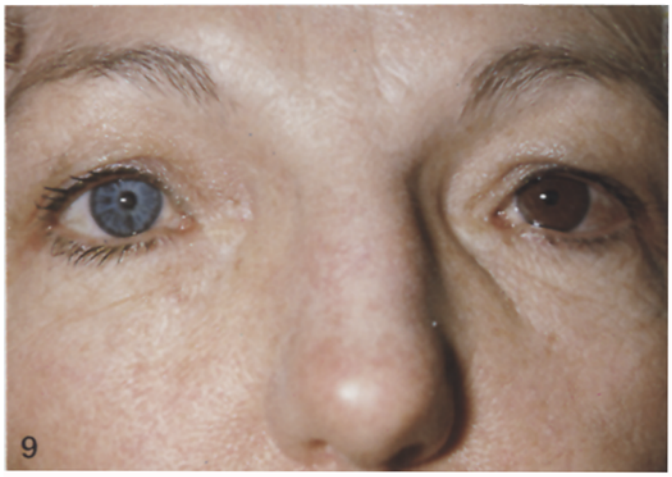

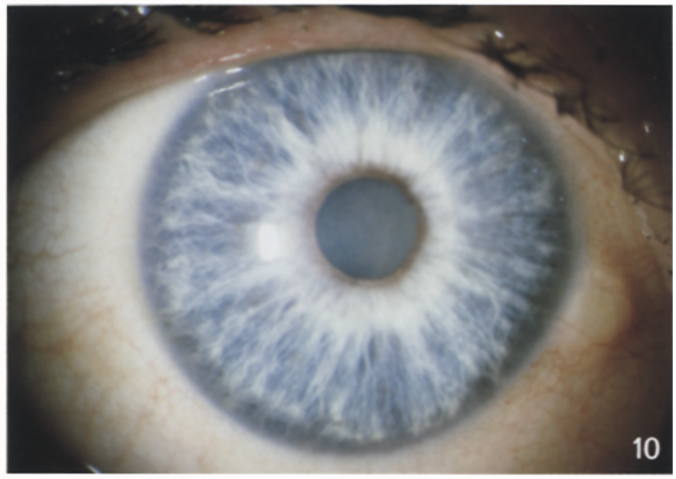

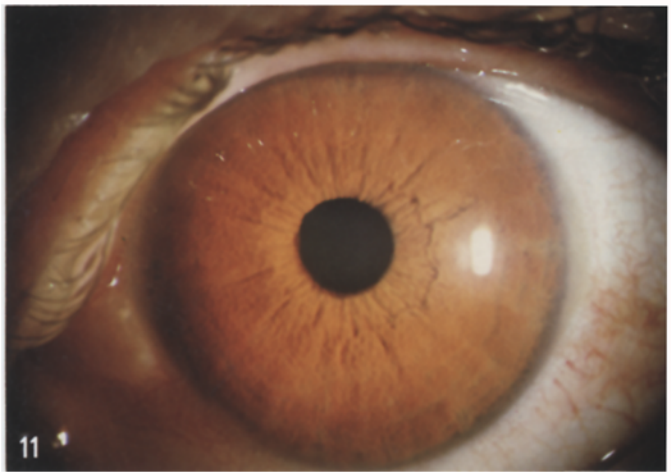

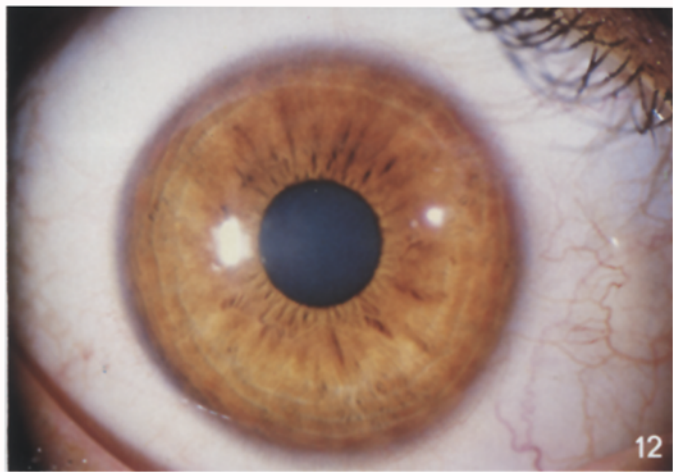

Fig. 7. Case 1. Left fundus

Fig. 8. Case 1. Drawing of entire right and left fundi

Fig. 9. Case 2. Total heterochromia, dystopia canthorum, and decrease flare of the alae nasi (medial brows have been plucked)

Fig. 10. Case 2. Right iris

Fig. 11. Case 2. Brown left iris with monotonous coloration

Fig. 12. Normal light-brown iris. Compared to Fig. 11, there is considerable variation in color from the darker pupillary zone to the lighter iris root

Iris details of cases 1 and 2

Waardenburg's syndrome has classically been considered to be a disorder of pigmentary deficit (i.e., an albinoid condition), with the darker eye being normal (Bard 1978; Delleman and Hageman 1978; Hageman 1980; Reed and Border 1967). While the hypopigmented areas of the irides in both of our patients are distinctly abnormal with their steel gray-

blue color so characteristic of Waardenburg's syndrome, the brown areas also appear abnormal when examined closely.

The hyperpigmented parts of the irides in case 1 are much darker than one would expect for someone with such a light skin color. Further, upon close examination of the border of the hypopigmented segment with a slit lamp (Fig. 4), one gets the impression that the pigment is confined entirely to the anterior border layer. This is more apparent with direct examination and is not fully represented in the two-dimensional color photographs. It is as though the pigment were merely "dusted over" the surface of what would otherwise have been an entirely pale blue iris.

This sense of pigment "dusting" limited to the anterior border layer is reinforced by the brown iris of case 2. Here, the iris is actually a light-brown color and might be casually interpreted as normal. However, comparison with a truly normal light-brown iris (Fig. 12) from another subject revels some striking differences. The color and texture of the Waardenburg iris (Fig. 11) are very monotonous with partial abolition of the crypts. By comparison, the color of the normal light brown iris is varied, being darker in the vicinity of the collarette where the iris is thickest and becoming quite pale at the thin iris root. A variation in color is to be expected in a light-brown iris because melanocytes are scattered throughout the iris stroma and the shade of brown depends upon iris thickness. Such variation in color would not occur if the pigmentation was limited to the anterior border layer. If the pigmentation was limited to the anterior border layer, then iris color would depend only on this layer and it would be independent of iris thickness and, therefore, would have the monotonous color and texture seen in our patients.

Skin pigmentation

Abnormal skin hyperpigmentation as well as hypopigmentation has been described occasionally with Waardenburg's syndrome. Two cases have been reported with a black forelock (Arias 1971; Ellis 1931), and hyperpigmented rings have been noted surrounding the vitiligo spots in some patients.

Glaucoma

Although glaucoma has not been considered to be an associated finding in Waardenburg's syndrome, Waardenburg's very first patient (the proband of his pedigree 1) did have bilateral open angle glaucoma as well as bilateral iris hypochromia (Waardenburg 1951). One might conjecture whether this was acquired and related to local manifestations of his systemic disease. The patient's brother also had glaucoma but no manifestations of Waardenburg's syndrome, thus a fortuitous development of familial open angle glaucoma is the most realistic possibility. A third patient (the brother of the proband in pedigree 2) had bilateral glaucoma and bilateral blue irides, but his only other possible manifestation of the syndrome was hypertelorism.

Our second patient had advanced bilateral glaucoma. While her iridocorneal angles were narrow, the glaucoma was more advanced in the blue eye where the angle was wider, her entire trabecular meshwork being visible to the scleral spur in the blue eye.

Previous reports have not demonstrated any predisposition toward the development of glaucoma among patients with manifestations of this disease or their families. Our few cases do not represent an adequate statistical base for anything but conjecture. Only a few patients of the many who were at risk that were reported in the literature had glaucoma (Waardenburg 1951; DiGeorge et al. 1960; Goldberg 1966; Hageman and Delleman 1977; Lian et al. 1968; Partington 1964; Reed and Boder 1967).

One might postulate that since ocular and dermal melanocytes are derived from the embryonic neural crest and since the iris stroma and the trabecular meshwork develop from the same cell line (Ozanics and Jakobiec 1982), a defect in pigmentation might lead to developmental abnormalities in these structures much as it does in the organ of Corti (Fisch 1959).

As a parallel thought, oculodermal melanocytosis represents another condition of abnormal pigment distribution, which involves neural crest-derived tissues. Acquired glaucoma has been described in several of these cases (Doherty 1927; Fishman and Anderson 1962; Foulks and Shields 1977; Weiss and Krohn 1971). This is probably not a simple pigmentary dispersion glaucoma but is thought to be due to an abnormal trabeculum (Fishman and Anderson 1962). Only the melanotic eye is affected in this disorder, apparently because the pigment defect is localized.

Based on a detailed examination of skin and iris pigmentation in the above two cases of Waardenburg's syndrome, it is proposed that there is a more generalized pigmentary distribution defect than has previously been suspected. Not only are the hypopigmented areas of the uveal tract abnormal, but the hyperpigmented areas may be abnormal as well.

Such a hypothesis would explain the following features of the syndrome:

1. Hyperpigmentation and hypopigmentation could be a part of the syndrome, as with our case 1. This has now been reported by several authors.

2. Deafness, in unilateral cases, would not necessarily be more prominent on the side of the hypochromic eye since both eyes are abnormal. Indeed, no association between unilateral deafness and the hypochromic eye has been found (Hageman 1977).

3. Because the iridocorneal angle structures are largely neural crest in origin, the possibility of a predisposition towards glaucoma should be investigated if adequate cases for a statistical study can be gathered.

4. The only postmortem study of Waardenburg's syndrome was limited to the organ of Corti. Thus, additional histopathologic studies are needed to fully understand to ocular ramifications of this disease.

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