Waardenburg syndrome with a fixed dilated pupil

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SUMMARY An unusual case of Waardenburg syndrome associated with a dilated and fixed pupil of the lighter eye is described. Pharmacological investigations were performed to localise the site of the pupillary lesion. A lack of cholinergic reactivity was demonstrated, possibly due to congenital agenesis of the sphincter pupillae. Sympathetic activity was not impaired.

Spiral ganglion agenesis and midline congenital anomalies are common features in Waardenburg syndrome. These lesions as well as the fixed dilated pupil might be due to an embryonal inductive failure.

P. J. Waardenburg delineated a syndrome (Waardenburg, 1951), now bearing his name, consisting of malformation of the inner angle of the eyes, heterochromia iridis, congenital perceptive deafness, and a white forelock. Pupillary anomalies were also described both by Waardenburg (1951) in his original article and by Viswanathan (1973). The present paper describes a pupillary anomaly associated with Waardenburg syndrome (WS) not mentioned previously, namely, a unilateral fixed and dilated pupil.

Case report

A 71-year-old healthy male immigrant from Romania displayed anisocoria, the right pupil being semidilated and not responding to light or accommodation. In addition he had the following features characteristic of WS: Lateral displacement of the medial canthi and lacrimal puncta. The inner distance measured 47 mm (normal 26 to 39 mm) (DiGeorge *et al.*, 1960). The outer canthal and interpupillary distances were within the normal range (96 and 70 mm, respectively). This gave his eyes the appearance of blepharophimosis with partial covering of the medial sclerae (Fig. 1). The lacrimal puncta were also laterally displaced and opened vertically away from the sclera.

Pigmentary changes. (1) Complete heterochromia iridis, the left brown and the right blue (Fig. 1). (2) Heterochromia fundi: pigmentary changes in the

fundi corresponding to those of the iris, with the left fundus darker than the right. Goldberg (1966) described such changes in WS. (3) White forelock: the subject was bald when examined, but a sagittal white skin area was observed on the scalp, supporting his story of a white forelock.

Deafness. Congenital right ear deafness, confirmed by audiometry (Fig. 2). A slight hearing loss was found in the left ear as well, which could be explained by the patient's advanced age. No airborne gap was present.

Broad prominence of the nose, with an oblique furrow beginning at a dimple near the tip of the nose (Fig. 3).

Family history consistent with autosomal dominant transmission of the syndrome, with variable expressivity (Fig. 4).

The ophthalmological examination is summarised in Table 1. Apart from the pupillary changes neurological examination revealed no abnormalities. Metopic sutures or a giant jaw (Fisch, 1959) were not found on *x-ray* examinations.

An association of heterochromia and anisocoria is a common feature in Horner syndrome (Waardenburg *et al.*, 1961), but the lighter iris there belongs to the smaller pupil. The fixed dilated pupil of the present case suggested a parasympathetic lesion in the achromatic iris. Studies were carried out to determine pharmacologically the site of the autonomic abnormality.

Material and methods

The ocular autonomic activity was evaluated by measuring the pupillary diameters in response to

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Fig. 1a, b Frontal and lateral facial photographs of patient. Note the appearance of blepharophimosis, heterochromia iridis, anisocoria, and a broad prominent nose. The furrow on the nose is just seen

different drugs, given as eye drops. The drugs used were: cocaine (4%), hydroxyamphetamine HCl (1%), phenylephrine HCl (5%), guanethidine (1%), pilocarpine HCl (0.01 to 2%), and phospholine iodide (0.06 to 0.12%). All drugs were given in a dose of 50 mcl into the conjunctival sac of both eyes, except for guanethidine, which was administered in a 250 mcl dose over 10 min. Pupillary responses to sympathomimetic drugs and pilocarpine were measured for 1 hour following application; responses to guanethidine were read after 12 hours and to phospholine iodide after 24 hours. The maximal response was recorded for each (Gambill *et al.*, 1967; Korczyn *et al.*, 1976, Laor *et al.*, 1977). The drugs were given 1 week apart, with a background illumination of 200 Lx. Pupillary diameter was measured against a commercial set of black circles while the subject focused at the distance.

Results

The sympathomimetic drugs caused an increase in diameter in the right 'fixed' dilated pupil of 21 to

28% and in the left pupil of 100 to 133%. There was a concomitant increase in the palpebral fissure. Pilocarpine (0.02%) constricted the normal left pupil to a diameter of 2.5 mm, phospholine iodide (0.06%) to a diameter of 2 mm. The right pupil did not react to either drug, even at concentrations of 2% and 0.12% respectively. Both pupils reacted to guanethidine; the right one contracted to a diameter of 6 mm and the left one to 2.5 mm. These results are summarised in Table 2.

Discussion

The concurrence of heterochromia and anisocoria is a common sign in Horner syndrome which appears in infancy (Waaardenburg *et al.*, 1961). In the present case the sympathetic innervation of the abnormal pupil is intact. The dilator muscle responded to the direct adrenergic agonist, phenylephrine, as well as to hydroxyamphetamine, which acts through release of catecholamines from sympathetic terminals. Moreover, norepinephrine was spontaneously released from the ocular sympathetic nerves in both

eyes; guanethidine caused miosis and cocaine dilated both pupils. Thus the diminished pigmentation of the abnormal iris and fundus is not likely to be due to a latent Horner syndrome. The reaction of the pupil to adrenergic and sympatholytic agents also

eliminates mechanical factors as an explanation for its immobility in response to light.

In the absence of local ocular causes fixed dilated pupils are usually caused by interruption of the parasympathetic innervation to the iris. Acquired lesions of the parasympathetic pathway to the eye either have no effect on or increase the response to cholinergic agonists. However, in our patient the ab-

Fig. 2 Audiometry of patient. There is complete right ear deafness, with mild hearing loss on the left

X—Left ear, air conduction; ▽—left ear, bone conduction;
□—right ear, air conduction; ○—right ear, bone conduction

Fig. 3 Oblique furrow on right side of nose is seen

Fig. 4 Pedigree of Family P. The proband is the only survivor of 5 siblings; the others have died of unknown causes at the ages mentioned. According to the subject the father had a white forelock and heterochromia iridis. Brother II₂ was severely affected. He was deafmute and had heterochromia iridis, a white forelock, and a cleft lip. Siblings II₂, II₄, and II₅ as well as the father are said to have had 'little eyes', resembling those of the proband, possibly implying dystopia of the medial canthi. The inheritance is most likely due to autosomal recessive inheritance with variable penetrance

Table 1 Ophthalmological status

	Right eye	Left eye
Conjunctivae	Normal	Normal
Cornea	Normal	Normal
Anterior chamber	Normal	Normal
Intraocular pressure (mmHg)	21–22	19–21
Pupil	Semidilated (7 mm) fixed to light and attempted convergence	3 mm (200 lx) Normal light and near responses
Iris	Blue; stromal atrophy; intact pigment layer	Brown, normal
Lens	Posterior capsular cataract	Normal
Fundus	Myopic disc	Myopic disc
Visus		
Distance	– 3.50 DS + 2.00 cyl. axis 180° 6/12	– 2.00 DS + 2.00 cyl. axis 180° 6/9
Reading	+ 3.50 DS Jaeger 5	+ 3.5 DS Jaeger 1

Table 2 Pupillary diameter (mm) after various drugs

	Right pupil	Left pupil
Resting diameter (200 Lx)	7	3
Phenylephrine 5%	9	7
Cocaine 4%	8.5	6
Hydroxyamphetamine 1%	8.5	7
Pilocarpine 0.08%	7	3
0.02%	7	2.5
0.03–2%	7	<2
Phospholine iodide 0.06–0.12%	7	<2
Guanethidine 1%	6	2.5

normal pupil did not respond even to high concentrations of cholinomimetic drugs (Table 2). Neither did he have accommodation. Thus we conclude that the sphincter pupillae does not exist (or does not contain cholinergic receptors, an unlikely alternative).

Both pupillary muscles develop from the optic cup and do not require automatic induction (Kronfeld, 1969); rather, the autonomic nerves are attracted to the eye by the developing optic cup (Arey, 1966). Thus one could postulate agenesis of the ciliary ganglion in this patient. Goldberg's (1963) patient with WS associated with congenital aganglionic colon suggests that parasympathetic ganglion agenesis may occasionally also occur at other sites.

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