1.2.4 OPHTHALMOLOGICAL ABNORMALITIES

Ocular abnormalities are well documented in patients with NPS[6 62 81 95].

1.2.4.1 Glaucoma

Glaucoma is a complication which has only recently been confirmed as a feature of NPS, although it is mentioned in passing in some earlier reports[6 36 81 96-98]. Lichter et al. described the co-segregation of open-angle glaucoma and NPS in two large families[96]. The age at diagnosis of glaucoma ranged from birth to 54 years with an average age at diagnosis of 32. The maximal intraocular pressure in the family members with glaucoma ranged from 23 to 55 mm Hg. All those with glaucoma had a normal slit-lamp examination and wide-open drainage angles. In addition to open-angle glaucoma, in some individuals ophthalmological examination also revealed pigmentary glaucoma and ocular hypertension with and without pigment dispersion syndrome; iris processes; bilateral Krukenberg spindles; and iris transillumination defects. In one individual with bilateral congenital glaucoma, there were defects in Descemet membrane. Some individuals also had refractive errors. All patients with glaucoma also had NPS, as did all but one of the patients with ocular hypertension.

Vollrath et al. studied 4 unrelated families in whom NPS and open angle glaucoma co-segregated[36]. Two of these families had previously been described by Lichter et al[96].

The patient described by Bennett et al. with congenital glaucoma was also deaf and these anomalies had been ascribed to maternal rubella[81].

1.2.4.2 Lester's sign.

In 1936, Mark Lester reported an abnormality of the iris in several affected members of a family with NPS[25]. He described a zone of pale pigmentation around the circumference of the iris, and a darker part centrally around the pupil, which was roughly a cloverleaf shape. This was more pronounced in blue eyes than darker eyes and Lester himself was uncertain as to the significance of this sign. In o

Flickinger and Spivey discussed what they term Lester's line and they felt that this was not a valid part of the syndrome [99]. The iris is embryologically derived from both mesodermal and ectodermal tissue. There are two layers derived from the mesoderm element. The superficial mesodermal layer extends from the ciliary border to the collarette (or circulus minor), whereas the deep mesodermal layer extends from the ciliary border to the pupillary edge. The superficial layer ends at the collarette in an irregular, zigzag line, or frill. Flickinger and Spivey felt that the description of the iris anomaly given by Lester was consistent with the normal configuration of the collarette. They proposed that the dark pupillary margin of the iris described by Lester might have been due to the deeply pigmented ectodermal layer visible through the thin, deep mesodermal layer. They found similar appearances in the eyes of 11 out of 100 normal controls examined. Lichter et al. agreed that Lester's sign was probably a normal variant[96] and some authors agree[8 72], although other authors continue to report its presence in patients with NPS[54]. Lichter et al. did, however, note iris processes in 7 out of 14 patients (grade 1-4) and grade 1 iris processes in one unaffected relative[96]. Cosack's family survey showed that the appearance of the iris described by Lester could also be seen in family members without NPS[100].

1.2.4.3 Other ophthalmological abnormalities

Congenital cataracts were reported in three members of a large pedigree described by Hawkins[62]. However, 2 of these patients lacked features of NPS. Adult-onset cataracts have been reported in one patient[96]. Keratoconus[54], microcornea[3] and microphakia[3] have also been described in NPS patients, albeit in single cases.

1.4.3.8 *LMX1B* and the eye

Lmx1b has also been shown to play an important role in the development of the anterior segment of the eye in mice[172]. *Lmx1b* is first expressed in the periocular mesenchyme, and later expressed in the extraocular muscles, corneal stroma, corneal endothelium, iris and ciliary body stroma, and the trabecular meshwork. In the absence of functional Lmx1b protein, the anterior segment fails to develop properly, with prominent phenotypes including an absence of the ciliary body and iris stroma and a characteristic corneal dysplasia. Analysis of the molecular markers expressed

in the anterior segment suggest that a primary function of *Lmx1b* may also be to regulate the composition of the extracellular matrix postnatally, which if defective, may lead to secondary defects. These findings provide further evidence supporting an etiological role of *LMX1B* mutations in the development of glaucoma in NPS patients, and emphasise the importance of *Lmx1b* in the development of the anterior chamber.

Results

3.1.27 Ophthalmological findings

3.1.27.1 Lester's sign

Lester's sign was seen in 53.7% of patients (64/119). When present, it was usually but not always bilateral. Rather than the clover-leaf pattern first described by Lester, the pattern more resembled a flower shape of darker pigmentation of the iris around the pupil (see fig. 3.29). Lester's sign was not any more frequently seen in those with glaucoma or ocular hypertension (7/14).

3.1.27.2 Glaucoma and ocular hypertension

In the patient group overall, 9.6% (8/83) had glaucoma and 7.2% (6/83) ocular hypertension. These data include patients with a previous history of glaucoma or ocular hypertension and those found to have raised intraocular pressure when examined in the study, but only when this raised intraocular pressure was confirmed by an optician or ophthalmologist. Since glaucoma and ocular hypertension are age-related conditions, as expected, their frequencies were higher in older age groups. In patients over 40 years, 16.7% (7/42) had glaucoma and 11.9% (5/42) had ocular hypertension. The mean age at which glaucoma or ocular hypertension had been detected was 47.9 years (23 – 78 years)

Table 3.4 Frequency of ocular hypertension and glaucoma

Glaucoma	Overall	>=18 years	>=40 years
Normal IOP	69/83 (83.1%)	63/77 (81.8%)	30/42 (71.4%)
Ocular Hypertension	6/83 (7.2%)	6/77 (7.8%)	5/42 (11.9%)
Glaucoma	8/83 (9.6%) (40 unknown)	8/77 (10.4%) (12 unknown)	7/42 (16.7%) (2 unknown)

Other ophthalmological findings included bilateral cataracts but these were in a woman of 72 years (44.1) and a unilateral cataract in a diabetic woman (8.8). One

child was noted to have a left persistent pupillary membrane (31.2) and a woman who also had glaucoma had a unilateral posterior vitreous detachment (26.1). One patient had had operations for bilateral squint (29.1)

Discussion

4.2.4 Ophthalmological features

This is the first study to have assessed the frequency at which glaucoma occurs in NPS and the presence of glaucoma or ocular hypertension in 29% (12/42) of patients over 40 confirms that this is a significant problem in NPS patient. However, this aspect of NPS is treatable and therefore screening for glaucoma in NPS patients must be strongly encouraged. It is also of interest that the onset is earlier in NPS patients than in the general population[178] with the average age of onset in this study being 48 years and the earliest age of detection at 23 years. It would therefore be sensible to suggest that all patients with NPS are screened for glaucoma on a 2 yearly basis, the screening including the measurement of intraocular pressure, examination of the optic discs and an assessment of visual fields.

Only patients with glaucoma and ocular hypertension were recorded in this study. This leaves a potential group of patients who could have normal pressure glaucoma, consisting of abnormal disc cupping and visual field defects, undetected. It has been suggested that there may be a role for LMX1B in the regulation of collagen surrounding the optic nerve[179]. NPS patients could, therefore, have a predisposition to develop glaucoma at what would be generally considered normal intraocular pressures. This is another reason why screening should not be restricted to the measurement of intraocular pressure only.

In this study, Lester's sign was seen in 54% of patients, and in Lester's one literature review was seen in 42%[11]. It is now widely accepted that the iris configuration characteristic of Lester's sign is not pathognomonic of NPS and may be seen in the general population, although to a considerably lesser degree[99]. However, there are other iris appearances which may be seen in the general population but are much more common in particular syndromes, such as the stellate iris that is commonly seen in Williams' syndrome[130]. The expression of LMX1B in the anterior chamber of the developing eye together with the iris abnormalities seen in

lmx1b -/- mutant mice[172] supports the suggestion that Lester's sign is indeed a feature of NPS, albeit a non-specific one.

As previously discussed, it seems that diminished levels of ***LMX1B*** fail to fully induce expression of the *COL4A4* gene, resulting in disruption of the type IV collagen fibrils of the glomerular basement membrane. The trabecular meshwork of the anterior chamber of the eye is similar to basement membrane and also contains type 4 collagen, as do the connective tissues in the area around the optic disc[179]. The lamina cribrosa is a sieve-like perforation in the posterior part of the sclera, which allows passage of the retinal nerves and central retinal vessels and preserves a pressure gradient between the intraocular and extraocular space. It is considered the primary site of glaucomatous damage to the optic nerve. If there is an abnormality in the collagen in this structure and in the trabecular meshwork then these alone, or together, could predispose to glaucoma in NPS[179].