OCULAR MANIFESTATIONS OF NOONAN SYNDROME

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SUMMARY

Noonan syndrome is a genetic condition inherited in an autosomally dominant manner, characterised by congenital heart disease, short stature, abnormal facies and the somatic features of Turner's syndrome, but a normal Karyotype.

The ophthalmological and orthoptic findings on 58 patients with Noonan syndrome are reported. External features were hypertelorism (74%), downward sloping palpebral apertures (38%), epicanthic folds (39%) and ptosis (48%). The orthoptic examination revealed strabismus in 48%, refractive errors in 61%, amblyopia in 33%, and nystagmus in 9% of cases.

Sixty-three per cent of cases had anterior segment changes consisting of: Prominent corneal nerves (46%), anterior stromal dystrophy (4%), cataracts (8%) and panuveitis (2%). Fundal changes occurred in 20% of the study group, including optic nerve head drusen, optic disc hypoplasia, colobomas and myelinated nerves.

Forty-seven per cent required non surgical treatment and a further 16% had undergone surgery for strabismus or ptosis. Only three patients had no visual defects. With such a high incidence of ophthalmic abnormalities it is clearly important that children with Noonan syndrome are screened by an ophthalmologist at an early age.

The diagnosis of Noonan syndrome is made purely on clinical grounds. Unlike Turner's syndrome, which is phenotypically similar, no chromosomal abnormalities have been detected. The lack of any laboratory test to confirm the diagnosis has hampered the recognition of this syndrome. The first case was probably described by Kobylinski¹ in 1883 but such cases were varyingly called Status Bonnevie Ullrich or 'Male Turner's syndrome'. It was not until 1963 that Dr. Jacqueline Noonan² identified this group as a separate condition. Opitz³ subsequently proposed the name Noonan syndrome to avoid further confusion. The key to the diagnosis is an individual with

typical facies (Fig. 1), right sided cardiac abnormalities and normal chromosomes. The main features of the 151 patients seen by the multidisciplinary team, including the 58 patients reviewed here, are listed in Table I. This variability of expression led to a suggestion that a scoring system should be introduced to aid the diagnosis⁴, and this was used to confirm the diagnosis in the study group patients.

This syndrome has an autosomal dominant pattern of inheritance with a high (about 50%) new mutation rate. It

Fig. 1. Noonan Child.

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Table I. Main General features of Noonan Syndrome found in 151 individuals examined

Feature	%
Cardiac Defect	88
Pulmonary Stenosis	62
Hypertrophic Cardiomyopathy	20
ASD, VD, AVD	13
Cardiac Surgery	20
Skeletal	
Chest Abnormalities (Pectus carinatus superior & Pectus excavatum inferior)	95
Joint Hyperextensibility	50
Webbed Neck	22
Short stature—Mean Bone delay	2.0 years
Skin & Hair	
Prominent Fetal Pads on hands and toes	67
Abnormal hair (Thick & curly or sparse)	40
Schooling	
Attending Normal School	84
Other	
Undescended Testes	67
Feeding difficulties	95
Bleeding abnormalities	58
Hepatosplenomegaly	26
Hearing Loss (Otitis Media)	38

Table II. Summary of the External Facies observed in 58 patients with Noonan Syndrome. Where less than 58 patients were examined, the number examined is indicated in parentheses

External Feature	No.	%
Hypertelorism	43	74
Downward Sloping palpebral apertures	22	38
Epicanthic Folds	22 (56)	39
Ptosis	22 (56)	48
Lower Lid Retraction	2 (56)	4
Proptosis	1 (56)	2
Orthoptic Findings		
Strabismus	28	48
—Esotropia	13	22
—Exotropia	10	17
—Mixed	1	2
—Vertical	4	7
Abnormal Binocular Vision	21	36
Amblyopia	18 (55)	33
Nystagmus	5	9
Head Turn	1	2
Refractive Errors	33 (57)	61

Angle
Degrees

Fig. 2. Histogram showing the range of palpebral fissure angles. The mean angle for the two eyes is shown. The normal range is taken as 0–5 Degrees.¹⁵

Fig. 3. Histogram showing the range of refractive errors.

is common to find minor anomalies or partial expression of this syndrome in other family members. The exact incidence of Noonan syndrome is unknown but has been estimated at between one in 1000 and one in 2500 live births⁵ for severely affected cases. When Mendez and Opitz⁶ reviewed the literature they found that eye abnormalities were the commonest consistent finding being present in

Table III. Ophthalmic findings observed with Noonan Syndrome. The number of patients examined is in parentheses

Ophthalmic Findings	No.	%
Anterior Segment Changes	30 (48)	63
Panuveitis	1 "	2
Corneal Pannus formation	4 "	8
Peripheral Sclero-cornea	1 "	2
Corneal Opacity	2 "	8
Prominent Corneal Nerves	22 "	46
Persistent Pupillary Membrane	1 "	2
Cataract	1 (53)	2
Marked Lens Vacuolation	10 (53)	6
Fundal Abnormalities	10 (51)	20
Coloboma disc or retinal	2 "	4
Swollen discs/Disc Drusen	2 "	4
Myelinated Nerves	1 "	2
Optic Disc Hypoplasia	2 "	4
Situs Invertus	1 "	2
Tortuous Vessels	3 "	6

95% of the 121 individuals reviewed. Reports in the ophthalmic literature have been limited to individual case reports.^{7,8,9} This study was undertaken to produce a comprehensive review of the ocular features of Noonan syndrome.

METHOD

This study was conducted as part of a larger multi-disciplinary research project into Noonan syndrome. To recruit patients a letter was sent to all consultant paediatricians, paediatric cardiologists and clinical geneticists in the United Kingdom, asking for the names of any patients with Noonan syndrome under their care and permission to contact their families. The first 58 patients recruited were included in this study. The diagnosis of Noonan syndrome was confirmed by the paediatrician (MS) who also used a scoring system⁴ to aid diagnosis. A full orthoptic examination was conducted by the senior orthoptist (LK), and included visual acuity assessment, autorefraction, cover test, synoptophore and stereo acuity. A facial photograph was taken to measure the inner canthal to zygomatic ratio,¹⁰ and the angle of the palpebral fissures. If the former ratio exceeded 0.28 (97th Percentile from a group of normal children) this was considered indicative of hyper-

Fig. 4. Prominent corneal nerves. A similar appearance is found all the way round the limbus in both eyes. They can easily be traced to the central corneal region.

telorism. The ophthalmic examination commenced with a subjective or objective refraction with cycloplegia (Cyclopentolate hydrochloride 1%) where appropriate. A significant refractive error was taken to be hypermetropia greater than +2.00 Dioptres, myopia greater than -0.75 Dioptres and astigmatism greater than ± 1.00 Dioptre. This was followed by an external examination and a slit-lamp examination. All patients then underwent a mydriatic fundal examination (using g. Tropicamide 1% & g. Phenylephrine hydrochloride 10% if Cyclopentolate had not already been instilled.)

RESULTS

The age of the study patients ranged from one year to 40 years with a mean age of 10 years. 83% were less than 16 years old. Thirty-three were males and 25 females. The main external features are listed in Table II. Of the 58 patients in this study, all underwent the paediatric and orthoptic examination, though in three cases it was not possible to accurately assess visual acuity. Furthermore, one case failed to attend for any refractive assessment, two failed to attend for the external and internal ophthalmic examination and five failed to return for their post mydriatic fundal examination. In 10 cases, including the two who failed to attend this part of the examination, it was not possible to examine them on the slit-lamp. The

results have been adjusted to take account of this and where the case numbers are less than 58 the number actually examined is indicated in parentheses. The most consistent finding was hypertelorism which was documented in 43 cases. Epicanthic folds of the epicanthus palpebralis type were present in 22 (of 56) cases. The palpebral fissures were downward sloping in 21 patients (Fig. 2) but varied between -11.5 and $+8^\circ$.

Ptosis was present in 27 cases of which 16 measured at least 2 mm. The ptosis was usually symmetrical. In three cases ptosis surgery had been undertaken. Manifest strabismus was present in 28 cases of which 46% were esotropia, 36% exotropia, 14% had a vertical element and 4% were mixed. Of the 21 with abnormal binocular function, eight showed no potential for binocular vision at any distance, six had established anomalous retinal correspondence and seven had intermittent strabismus with suppression. Amblyopia defined as occurring when there is a reduction of two or more lines on the Snellen chart, was present in 18 (of 55) cases. Refractive errors of all types were common and the spectrum of refractive errors is shown in Figure 3.

A variety of abnormalities in the anterior and posterior segments were identified and these are listed in Table III. Increased visibility of the corneal nerves was seen in 22 (of 48) patients. The number and extent of the nerves that were visible varied between patients but was similar between the two eyes of one individual. The nerves were most visible nearest the limbus and became more translucent as they approached the central cornea. In 13 of these 22 patients there were more than 10 nerve fibres visible at the limbus and at least one extended into the central cornea. The most advanced case had a corneal dystrophy beside an extensive number of prominent corneal nerves (Fig. 4) that extended into the central region. The anterior stroma had a granular appearance that was more marked centrally. In addition in the anterior stroma there were small discrete circular areas of marked granularity. The appearances were similar in both eyes. Corneal sensation was intact and the visual acuity was unaffected. The corneas of the child's parents were normal. The appearance of the corneal dystrophy remained unchanged over the next two years. In the second patient similar discrete opacities were present on the endothelium in a geographic area just above the visual axis in one eye only. The rest of the anterior chamber in both of these patients was normal. Changes in the lens were noted in four (of 53) patients. A moderately dense asymmetric mixed nuclear and cortical cataract was noted in a severely affected 14 month old who had severe pulmonary stenosis that required a pulmonary valvotomy. In three others marked vacuolation of the lens was noted.

Fundal changes (Table III) were present in 10 (of 51) cases and only interfered with vision in one case. Both of the children with the optic disc hypoplasia were severely affected by the Noonan syndrome and difficult to examine. The first case of optic disc hypoplasia was in a seven year old child. The vision was reduced to 6/18 right and

(a)

(b)

(c)

6/36 left with mixed astigmatism. Confrontational fields showed an inferior field defect. He also had bilateral ptosis, horizontal nystagmus and prominent corneal nerves. Computerised axial tomography of the ventricles and basal cisterns was normal as was an ERG. The second case was 19 years old. The vision could only be measured with a Catford Drum because his concentration and co-operation was so poor. This was found to be reduced to 6/18. He has undergone two squint operations for a convergent squint. No further investigations have been carried out. In two cases swollen optic discs were observed consistent with buried optic disc drusen. Bilateral deep intra-retinal haemorrhages that formed partial rims around the optic discs were present in the first case (Fig. 5). A CAT scan confirmed the presence in the second case. Fluorescein angiography confirmed the absence of a neovascular complex in both cases.

DISCUSSION

This study agrees with the findings of Mendez and Optiz⁶ that ocular abnormalities are one of the commonest and

Fig. 5. *Buried Optic Disc Drusen.* (a) & (b) Colour photograph and fluorescein Angiogram showing haemorrhage around the Disc. (c) CAT scan showing the bilateral Optic disc Drusen.

most consistent features of Noonan syndrome occurring in our series in 95% of all cases. A similar spectrum of ocular features have been documented in Turner's and Down's syndromes and would appear to be part of the manifestations of craniofacial malformations (Fig. 5). Distinguishing features of Noonan syndrome include a higher incidence of ptosis, downward rather than the upward slanting palpebral fissures which occur in Down's syndrome and the presence of prominent corneal nerves. Though the overall incidence of strabismus in the three syndromes is similar, esotropia predominates in Turner's and Down's syndrome (84% and 90% respectively¹¹⁻¹⁶), whereas this made up only 48% of our study group.

Corneal abnormalities consisting of corneal opacities were known to occur in Turner's syndrome,¹² and were observed in two Noonan syndrome patients. However, prominent corneal nerves were found in 54% of the patients and is a new finding in Noonan syndrome. Neurofibromatosis is known to occur more commonly in Noonan patients¹⁷ than the general population and prominent corneal nerves are known to occur in 65% of such

Fig. 6. Comparison of the main ophthalmic features of Noonan, Turner and Down's Syndromes.

patients.¹⁸ However, only one patient of ours had neurofibromatosis and there were no visible corneal nerves in this case. Because of this association between neurofibromatosis and Noonan syndrome and the discovery of similar corneal nerves, gene linkage studies with the neurofibromatosis I locus were undertaken. However no linkage was found. There is little pathological information explaining why the corneal nerves become prominent.

Table IV. Management Summary. Orthoptic treatment consisted of occlusion therapy and does not include those patients who are just attending the orthoptic department for review. The findings of those patients who had not previously attended an ophthalmic department are also presented

	No.	%
Surgery	9	16
Squint	5	
Ptosis	3	
Syringe & Probing	1	
Non-Surgical Treatment	27	47
Spectacles	22	38
Orthoptic Treatment	5	9
Attended Eye Department	30	52
Never seen by eye Department	28	48
Normal Eye examination	11	39
Undetected Refractive error	6	22
Undetected Squint	9	32
Ptosis	2	7

Bleshey¹⁹ showed that in patients with keratoconus the nerves appeared thickened due to a change in the basement membrane around what appeared normally structured nerves. The increased prominence does not seem to alter their function as no patients in our study group appeared to have reduced corneal sensitivity. As the stromal dystrophy was observed in the case which had the greatest number of prominent corneal nerves, it may be that the dystrophy is a result of the abnormal corneal nerves.

Of the 58 patients, 27 (47%) required non surgical treatment predominantly consisting of prescribing glasses and occlusion therapy for amblyopia. A further nine (16%) had undergone surgery for strabismus, ptosis or blocked nasolacrimal duct (Table IV). Of concern to us was the observation that 28 of the patients had not attended an ophthalmology department before. Amongst this group 17 (61%) were found to have either a refractive error, including a myope of -6.25, a hypermetrope of +8.5 and a child with a +4.50 cylinder, or a significant squint or ptosis. It is likely that because these children often have serious cardiac and feeding problems when young this overshadows any ocular problems the child may have. Only one of the 58 patients appeared to be below normal intelligence and was attending a special school. Most of the other children were of normal intelligence and were attending normal schools. This makes the detection and correction of the

above conditions especially important to ensure that they realise their full potential.

In summary 95% of patients with Noonan syndrome had some ocular abnormality. Amongst these there is a considerable variety of disorders found, but the most frequent are hypertelorism, refractive errors, strabismus and anterior segment changes including prominent corneal nerves and less commonly cataracts and fundal changes. With such a high incidence of ocular abnormalities, it is clearly important for all children with Noonan syndrome to have a detailed visual assessment in infancy.

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Key words: Amblyopia, Cataracts, Corneal Nerves, Corneal Dystrophy, Down's Syndrome, Epicanthic Folds, Hypertelorism, Myelinated Nerves, Neurofibromatosis, Optic Disc Drusen, Palpebral Apertures, Ptois, Squint, Strabismus, Turner's Syndrome, Uveitis, Noonan Syndrome, Nystagmus.

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