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REVIEW

Ophthalmic features of Turner's syndrome

AKO Denniston and L Butler

Abstract

Turner's syndrome is one of the most common of all chromosomal abnormalities and is associated with significant ophthalmic morbidity. Turner's 1938 account included two patients with strabismus, and hitherto the condition has generated more interest among orthoptists than ophthalmologists. This systematic review of the literature seeks to redress the balance. Based on the pooled data of 274 patients with Turner's syndrome, it is the most complete evaluation so far of the prevalence and severity of ophthalmic problems in this population. This includes both a systematic review of the ophthalmic literature (via Medline) and the much larger body of work available in the orthoptic literature. Finally, we consider recent progress that enables the ophthalmologist to progress from the simple recognition of a phenotype to the correlation of genotypic variations with embryogenesis and consequent features of that phenotype.
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Department of Ophthalmology Birmingham and Midland Eye Centre, City Hospital Birmingham, UK

Correspondence: AKO Denniston Department of Ophthalmology Birmingham and Midland Eye Centre, City Hospital Dudley Road, Birmingham B18 7QU, UK
Tel: +121 554 3801
Fax: +121 554 3801
E-mail: alastair@denniston.org

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Introduction

Turner's syndrome is a chromosomal abnormality, affecting about 1 in 2000 live female births.[1] Although it is associated with significant ophthalmic morbidity, this is usually underestimated and often goes unrecognised. Delay in orthoptic and ophthalmic input increases the risk of amblyopia and long-term visual impairment. This review considers the genetics, diagnosis, and management of Turner's syndrome.

Turner's syndrome has been recognised since the 1930s when Otto Ullrich and Henry Turner described female subjects with the association of short stature, sexual infantilism, webbed neck, and cubitus valgus.[2] The first description, at least of primary ovarian failure, was probably by Morgagni in 1761.[3] However, it was not until 1959 that the chromosomal nature of the condition was described.

Genetics and Pathogenesis

Turner's syndrome is best known for the XO karyotype, more accurately described as 45, X. In fact, this represents only half the patients with Turner's syndrome. A further 15% are mosaics having both 45, X and a normal cell line, that is, 45, X/46, XX. The remainder demonstrates a range of abnormalities of the X chromosome including partial deletions and ring chromosomes. In the majority of cases (60%), it is the paternal X chromosome that has been lost during meiosis. As yet, no risk factors for this chromosomal loss have been identified; maternal age is not a risk factor.[4] The 45, X karyotype arises in 3% of all conceptions, but results in spontaneous abortion in 99% of cases.

The Turner's phenotype arises from X-linked genes that escape inactivation. Important among these are the short-stature-homeobox (SHOX) gene, mutations of which result in such well-recognised features like short stature and Madelung deformity (a skeletal abnormality of the distal forearm).[5,6] Candidates for causing the gonadal dysgenesis include USP9X, RPS4X, and DIAPH2. USP9X is of particular ophthalmic interest since its homologue in *Drosophila* (fruit fly) is involved in the development of the eye as well as the ovary.[7,8]

Systemic features

The normal foetal ovary contains 7 million oocytes that rapidly reduce to 2 million at birth, 500 000 at menarche and 10 000 at menopause. In Turner's syndrome, this appears to be accelerated so that by 2 years of age, there are almost no oocytes left. This premature gonadal aging results in 'streak' ovaries. Consequently, there is delay or failure of puberty, amenorrhoea, and infertility.[9,10] Interestingly,

the rare instances of pregnancy that do occur show increased rates of chromosomal aberrations such as trisomy 21 (Down's syndrome) and, in one case, an identical Turner's karyotype to the mother.[11,12]

Short stature is almost universal.[13] Additional features are common[14–20] and are listed in Table 1. Interestingly, the individual's phenotype appears to be dependent on the exact genotype and even the parental origin of the remaining X chromosome. For example, although intelligence is normal in most patients, those with the ring X chromosome (ie 45, X/46, X,r(X)) do show mental retardation.[21] Additionally, those who have inherited a paternal X chromosome (45, Xp) appear to do well with regard to social adjustment, verbal and executive function skills but relatively poorly on visuospatial memory tests. In contrast, those with a maternal X chromosome (45, Xm) did well with regard to visuospatial memory, but poorly with verbal memory.[22,23]

Ocular features

Ocular abnormalities are common in this syndrome, but are underestimated and often neglected. Only two case series have been published in the ophthalmic literature[24,25] representing a total of 54 patients. However, search of the orthoptic literature revealed a further four series that contribute another 220 patients.[26–29] The results of these series are collected in Table 2 and the pooled data analysed.

Table 1 Systemic features of Turner's syndrome

Age	*Systemic features*
Neonate	Dorsal oedema of hands and feet Low birthweight Reduced length
Child/Adult	*Habitus*—Short stature, webbed neck, low posterior hairline, broad chest with apparent wide spacing of the nipples, cubitus valgus (wide carrying angle), hyperconvex fingernails *Facies*—Small mandible, prominent ears, high arched palate *Cardiovascular*—Bicuspid aortic valves, aortic coarctation, aortic stenosis, mitral valve prolapse, anomalous pulmonary venous drainage, hypertension *Renal*—Pelvic kidney, horseshoe kidney, double collecting system, agenesis *Gonadal*—Absent or late puberty, amenorrhoea, infertility, streak ovaries *Metabolic*—Thyroid dysfunction, diabetes mellitus (type II) osteoporosis, dyslipidaemia, liver function test abnormalities *Neurological*—Sensorineural deafness, delayed motor development, delayed language skills *Psychological*—Dependence, delayed emotional maturity, negative body image

Table 2 Cumulative ophthalmic and orthoptic case-series of patients with Turner's syndrome

Series	*Wesson*[26]	*Raab*[27]	*Troupe*[28]	*Adhikary*[25]	*Chrousos*[24]	*Masters*[29]	*Total*	*%*
Year	1974	1974	1981	1981	1984	1990	2003	
N	11	7	25	24	30	177	274	
Genetics if known		5XO		15XO	23XO			
(mosaic = m)		+2m		+5m	+7m			
Amblyopia		1/7		10/24	4/30	30/95	45/156	29%
Strabismus	5/11	3/7	6/25	9/24	10/30	58/177	77/274	33%
Phoria only	3/11	2/7	13/25			49/104	67/147	46%
Exotropia	2/11	1/7	5/25	1/24	2/30	12/166	23/263	9%
Esotropia	2/11	1/7	1/25	8/24	8/30	33/166	53/263	20%
Hypertropia	2/11	1/7	0/25	0/24	0/30	6/166	9/263	3%
Hypermetropia	2/11			10/24	5/30	48/177	65/242	27%
Myopia						23/177	23/177	13%
Reduced accommodation		5/5				27/76	32/81	40%
Convergence insufficiency	9/11		15/25			32/104	56/140	40%
Nystagmus					1/30	11/104	12/134	9%
Ptosis				7/24	5/30	34/165	46/219	21%
Epicanthus				11/24	3/30	42/104	56/158	35%
Hypertelorism					3/30		3/30	10%
Antimongoloid palpebral fissures	2/11				3/28	3/47	8/86	9%
Red-green deficiency	3/9		1/25		3/30	13/177	20/241	8%
Presenile cataract				1/24	0/30	2/42	3/96	3%
Congenital glaucoma				0/24	0/30	1/42	1/96	1%
Blue sclera				0/24	0/30	2/42	2/96	2%

Horizontal and vertical tropias may coexist and thus sum to more than total strabismus. Some of the orthoptic studies only collected eye movement data resulting in more limited data for other ocular features.

The cumulative data shown here now permit more accurate estimation of the prevalence of ophthalmic morbidity in the Turner's syndrome population. For some of the features considered, the existing measures are satisfactory. For example, although ametropia is very common (around 40%), this is probably adequately dealt with by community optometrists. However, the high rate of amblyopia (almost 30%) and strabismus (33%) is of greater concern. There is a danger that parents and community doctors may concentrate exclusively on the 'medical' features of Turner's syndrome, resulting in delayed recognition of strabismus and developing amblyopia. The high prevalence of these conditions would argue for early systematic screening of children with Turner's syndrome. This could initially be by orthoptists with appropriate onward referral to an ophthalmologist.

Numerous case reports[30–35] have suggested additional associations (Table 3). While of interest, such isolated associations may arise by chance and cannot determine the frequency or significance of any association.

It is important to realise that classical X-linked recessive disease may occur in the Turner's female. This may be a trap for the unwary ophthalmologist who rules out a diagnosis on the basis of gender. This is demonstrated by the high prevalence of colour vision abnormalities (8%), which is at a level typical of the male, rather than the female, population. In addition, the authors know of patients with Turner's syndrome and X-linked congenital stationary night blindness, and of Turner's with Duchenne's muscular dystrophy.

Table 3 Ocular features of Turner's syndrome

From pooled case series	*Additional features in case reports*
Common (>25%)	Conjunctival lymphoedema[31]
Amblyopia	Keratoconus[33]
Strabismus	Anterior segment dysgenesis[37]
Reduced accommodation	Anterior lenticonus[30]
Convergence insufficiency	Retinal neovascularization[34]
	Choroidal neovascular [35] membrane[35]
Uncommon (5–25%)	Retinal detachment[32]
Ptosis	
Epicanthus	
Hypertelorism	
Antimongoloid palpebral fissures	
Red-green deficiency (male incidence)	
Nystagmus	
Rare (<5%)	
Presenile cataract	
Congenital glaucoma	
Blue sclera	

Hitherto few reports have provided detailed karyotypic information. As karyotype and genetic analysis improves it may become possible to more accurately match ophthalmic phenotype with an individual's genotype (akin to the relative success with systemic phenotype/genotype matching[35]). One thorough ophthalmic and chromosomal examination of four girls with mosaic Turner's syndrome demonstrated anterior segment abnormalities including glaucoma and abnormal irides (Rieger malformation). Interestingly, although mosaicism was observed in all four cases, there was variation in the cell line type, that is, with residual Y chromosome material (45,X/46,X,idic(Y)) in two cases, with a ring X chromsome (46,X,r(X)) in another and with an extra X chromsome (47,XXX) in the fourth. Given this variation in karyotype the authors speculate as to whether it is the direct effect of mosaicism *per se* on the embryogenesis of the anterior segment that gives rise to these abnormalities.[36,37]

Management

Patients with Turner's syndrome require multidisciplinary care. This is normally coordinated by a paediatrician, with appropriate input from endocrinologists, cardiologists, nephrologists, psychologists, and others. Valuable support and information for patients and their families are available from the Turner Syndrome Support Society (www.tss.org.uk).

As discussed above, the prevalence of ocular morbidity would argue for greater routine ophthalmic input, for example early orthoptic screening with onward referral to an ophthalmologist where indicated. General treatment strategies include hormone replacement (both growth hormone and oestrogen), This may impact the ophthalmologist since concern has been voiced over possible ophthalmic sequelae. Koller *et al*[38] reported two non diabetic patients with Turner's syndrome who developed retinal changes mimicking diabetic retinopathy when treated with growth hormone. The authors note previous hypotheses suggesting a role for growth hormone in the pathogenesis of diabetic retinopathy. However, neovascular changes may be seen in Turner's syndrome in the absence of exogenous growth hormone.[33] It should also be noted that the increased prevalence of type II diabetes mellitus (with attendant ophthalmic complications) in Turner's population requires care in regard to exogenous growth hormone and monitoring of glycaemic tolerance.[18,39]

Conclusion

An increased awareness of the ophthalmic features of Turner's syndrome should enable earlier detection and treatment of sight-threatening conditions. This review provides a more accurate estimate of the prevalence and severity of the ophthalmic sequelae of this syndrome. Recent advances in the understanding of this condition are enabling progression from a simple description of a syndrome to the correlation of genotypic variations with embryogenesis and consequent features of that phenotype.

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