X linked dominant congenital isolated bilateral ptosis: the definition and characterisation of a new condition

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Abstract

Aims—To characterise the inheritance of ptosis in one particular pedigree.

Methods—The pedigree was analysed clinically and genetically to assess the mode of inheritance and to ascribe a gene locus for the condition.

Results—Affected members of the pedigree have bilateral symmetrical congenital isolated ptosis, a condition which is linked to genetic markers on the X chromosome in this family.

Conclusion—A pedigree with dominantly inherited congenital bilateral ptosis is presented. The pedigree exhibits X linked dominant inheritance. A new ophthalmic condition was thereby characterised—namely, X linked dominant congenital isolated bilateral ptosis.

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Congenital isolated ptosis can be unilateral or bilateral, although it is possible that much unilateral ptosis is in fact markedly asymmetric bilateral ptosis. Controversy exists as to the underlying cause of congenital ptosis. While there is little doubt that there is abnormal muscle present in the vestigial levator palpebrae superioris, (LPS), implying a myogenic component,[1] the term congenital levator dystrophy is a misnomer because (i) there is no progression in the condition, and (ii) there is little histological evidence of a dystrophic process.[2] There is a growing body of evidence to suggest that the ptosis is due to a failure of neuronal migration or development with muscular sequelae.[3 4]

There have been many reports of hereditary ptosis in the literature. It is not always easy to dissect out the precise phenotype but many undoubtedly relate to blepharophimosis ptosis epicanthus inversus syndrome (BPES). Von Ammon first described this condition in 1831.[5] Vignes described hereditary epicanthus in 1889.[6] Small *et al* demonstrated linkage for BPES to 3q22–23.[7] This was later refined to 3q23 by Messiaen *et al.*[8] Piemontese *et al* have demonstrated that both BPES type I (BPES in association with decreased female fertility) and BPES type II (normal fertility) map to this region.[9]

Briggs described an extensive pedigree in 1919 with autosomally dominant ptosis in six generations.[10] The ptosis was remarkably symmetrical and there was only one skipped generation, although this case was not evaluated and therefore could have had decreased expressivity. The author comments that one of the pedigree had blepharophimosis so this may be a BPES pedigree. Stuckey described a family with autosomally inherited ptosis but the clinical details are sketchy.[11] However, the photograph that accompanies his paper clearly depicts blepharophimosis and the individuals also look as though they have epicanthus inversus.

Ptosis and purpura simplex were co-inherited in members of a pedigree reported by Fisher *et al.*[12] However, ptosis and purpura simplex segregated independently in two individuals, perhaps denoting linkage rather than a common genetic defect. There was male to male inheritance of ptosis in this family, excluding X linkage and mitochondrial inheritance.

Other hereditary conditions that incorporate congenital ptosis are congenital fibrosis of the extraocular muscles (CFEOM) types I, II, and III. These similar conditions have been linked to loci on chromosomes 12, 11, and 16 respectively.[13–15] They are characterised by congenital ptosis and external ophthalmoplegia. There is phenotypic heterogeneity within families[16] and there is also evidence of locus heterogeneity outside the loci on chromosomes 11 and 12 which may be explained by the recent description of CFEOM III.[15 17]

Engle *et al* have also described a family with dominantly inherited congenital isolated ptosis which was first reported by Cohen in 1972.[4 18] They demonstrated linkage to markers that were defined cytogenetically to the region 1p32-p34.1. This family is different from the one we describe in three important ways. (i) The phenotype is asymmetrical, with the ptosis being either unilateral or bilateral, (ii) there are skipped generations denoting reduced penetrance or variable expression, (iii) the inheritance is autosomal and not sex linked. The autosomal recessively inherited muscle-eye-brain disease (MEB) has recently been linked to the same area. MEB patients are severely mentally retarded with characteristic ocular abnormalities, congenital muscular dystrophy, and a polymicrogyria-pachygyria type neuronal migration abnormalities.[19] Ptosis is not a feature of MEB, but it is interesting to note that there may be genes involved in neuronal migration in this area of chromosome 1.

There are numerous hereditary causes of acquired ptosis such as progressive external ophthalmoplegia (PEO), oculopharyngeal muscular dystrophy (OPMD), Kearns-Sayre syndrome (KSS), and myotonic dystrophy; however, the subject of this paper is congenital ptosis.

Figure 2   (A) Male member of the pedigree showing bilateral symmetrical congenital ptosis. (B) Female member of the pedigree showing bilateral symmetrical congenital ptosis.

Patients and methods

PATIENTS

The pedigree was noted by one of us (AGT) as part of his oculoplastic practice. Detailed assessment of their phenotype was made and blood taken for DNA extraction and cytogenetic analysis. These procedures were undertaken with informed consent and the relevant ethical approval.

Family members were approached and assessed. A full ocular history, medical history, and family history were obtained. The patients were then examined for corrected visual acuity, ocular motility, and lid function. Undilated funduscopy was also performed to assess the macula and optic disc.

Results

CLINICAL DESCRIPTION

The pedigree has 21 affected members and 73 unaffected members; there are six affected males and 15 affected females. There are 37 unaffected males and 36 unaffected females. There is no evidence of male to male transmission and all daughters of affected males are affected.

The pedigree studied exhibits dominantly inherited congenital isolated bilateral ptosis and is represented in Figure 1. An affected male and female member of the pedigree are depicted in Figure 2. Both have bilateral symmetrical ptosis, in particular there is no evidence of blepharophimosis or epicanthus inversus. The patients have bilateral ptosis that results in an abnormally low lid position that almost impinges on the visual axis in the primary position of gaze (superior margin reflex distance of ≈ 0 mm). Patients have minimal levator function bilaterally, <5 mm, associated with an absent upper lid skin crease. They have pronounced frontalis overaction and a characteristic chin-up head posture. Ocular motility is normal in most cases but there is some reduced upgaze in some affected family members (Table 1). Pupillary reactions are normal. Corrected visual acuity is normal with no evidence of prevalent amblyopia in either affected or unaffected members. The patients have a good Bell's response and have been treated with bilateral brow suspension with autologous fascia lata using the Crawford method.

Discussion

We subjected the pedigree to linkage studies. Microsatellite analysis of markers in the region Xq24-Xq27.1 gives a LOD score of 2.88, con-
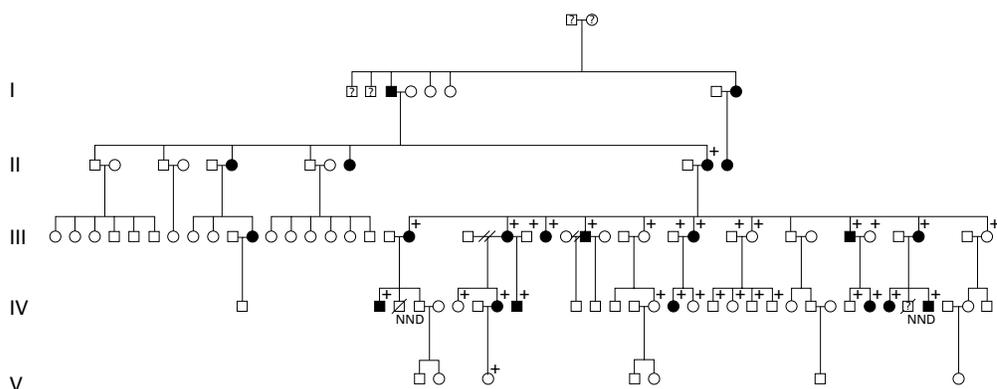

Figure 1   Ptosis pedigree. + = Denotes sample taken for analysis. NND = neonatal death.

Table 1   Summary of the clinical findings on examination of affected family members

Patient	II:11	III:19	III:21	III:25	III:30	III:35	III:38	IV:2	IV:8	IV:9	IV:15	IV:25	IV:26	IV:28
Ocular motility	RU	N	N	RU	N	N	RU	N	N	RU	N	N	N	N
Strabismus	N	N	N	N	N	N	N	N	N	N	N	N	N	RET 30 PD RHypoT 2 PD
Levator function (mm)	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5
Amblyopia	No	No	No	No	No	No	No	No	No	No	No	No	No	RE only

RU = reduced upgaze; N = normal; RET = right esotropia; RHypoT = right hypotropia; PD = prism dioptres.

firming X linked inheritance.[20] As can be seen from Figure 2, the phenotype is identical in both males and females. Because the expressivity is the same in males and females this is one of very few truly X linked dominant conditions and therefore defines a new condition—namely, X linked dominant congenital isolated bilateral ptosis. There are no reports of X linked isolated ptosis in the literature. There is often a vague family history of ptosis in patients with congenital ptosis which might implicate recessive inheritance or reduced penetrance. One might speculate that there are other pedigrees with X linked dominant ptosis that have not been fully assessed, or that an X linked recessive form of mutation in the same gene might be easily missed in routine clinical practice. Both recessive and dominant inheritance due to different mutations in the same gene have been reported, as in OPMD.[21]

The underlying defect in congenital ptosis may be intrinsic to the levator palpebrae superioris (LPS) or there may be failure to innervate the developing LPS with a secondary effect on its development/maturation. This defect could be at the origin of the motorneurons in the single midline central caudal subnucleus in the rostral third nerve nucleus, or there may be failure of migration involving the branch of the superior division of the oculomotor nerve that supplies the LPS.

The extraocular muscles constitute a separate allotype of muscle with distinctive properties. They have been shown in rats to express a different myosin heavy chain and in rabbits to express different proportions of troponin isoforms.[22–24] They are immune from some muscle disorders such as Duchenne muscular dystrophy whereas they are among the first to be affected in others such as OPMD, mitochondrial myopathies, and myasthaenia gravis. The LPS is defective in isolated ptosis. Of the extraocular muscles, the LPS is supplied by a branch of the superior division of the oculomotor nerve. The superior division also supplies another extraocular muscle, the superior rectus (SR) whose primary function is to elevate the globe. The origins of the superior division of the oculomotor nerve are in two separate subnuclei of the third nerve nucleus. Both LPS muscles receive their supply from a single midline central caudal subnucleus in the rostral third nerve nucleus. In contradistinction, each SR muscle is supplied from a contralateral subnucleus. Each superior division of the oculomotor nerve, therefore, has components from (i) a single midline subnucleus which sends fibres to the LPS, and (ii) the contralateral subnucleus that sends fibres to the SR. The fact that the superior division of the oculomotor nerve has dual origins and supplies two separate muscles with different functions can give anatomical clues as to the site of any putative pathophysiological defect. If the embryogenesis, migration, or function of the superior division of the oculomotor nerve was affected as a whole then one would postulate that there would be abnormality of SR function as well as a defect in LPS function; this is not seen in isolated ptosis (but may be seen in double elevator palsy). The reduced upgaze in four of the 14 affected family members that were examined may be a manifestation of SR involvement. If there was a defect in one half of the midbrain, affecting the subnucleus subserving the SR and half of the subnucleus supplying the LPS, then there would be contralateral effects on the SR but bilateral effects on the LPS. If there was a defect in the central subnucleus which supplies both LPS via both oculomotor nerves then there would be bilateral sequelae, bilateral ptosis as opposed to unilateral ptosis.

Bilateral ptosis could, therefore, be explained by a fault in the central third nerve subnucleus that supplies both LPS. Unilateral ptosis, which is far more common in the wider population, can be explained by an asymmetrical outflow from the central, single midline nucleus that supplies the LPS, giving rise to asymmetric phenotypic sequelae—namely, unilateral ptosis. Alternatively, the fault could reside in the branch of the superior division of the oculomotor nerve that supplies the LPS; this could be defective unilaterally or bilaterally, giving unilateral or bilateral ptosis. We have disregarded Muller's muscle or its (sympathetic) innervation as the site of the primary pathology because the degree of ptosis seen when this muscle's function is defective is much less, as in Horner's syndrome.

There is evidence of neuronal misdirection from a variety of other conditions. Work on CFEOM type I by Engle *et al*[3] has suggested that this condition is caused by an absence of the central caudal third nerve subnucleus and an associated absence of the superior division of the oculomotor nerve which fails to develop and innervate the structures that it normally supplies—the LPS and the SR. Postmortem studies on one patient with CFEOM type I failed to find either the central caudal subnucleus (which would ordinarily supply the LPS), or the superior division of the oculomotor nerve or the SR or the LPS. Other cranial nerves that supply extraocular muscles were noted to have fewer fibres than matched controls.

There is also misdirection of nerve fibres in Duane syndrome,[25 26] inherited levator-medial rectus synkinesis[27] and Marcus Gunn jaw winking patients, a condition that may be familial.[28] Brodsky *et al* report a case of "congenital ocular fibrosis syndrome" in association with Marcus Gunn jaw winking and synergistic divergence—the simultaneous abduction of both eyes on attempted lateral gaze.[29] This provides at least two concurrent examples of neuronal misdirection. Similarly, Wang *et al* postulate that in CFEOM II there is failure of development of the motor divisions of the entire third nerve giving ptosis and an exotropic ophthalmoplegia.[14]

In conclusion, we have characterised a new ophthalmic condition—namely, X linked dominant congenital isolated bilateral ptosis. The recruitment of further families with this condition might help to isolate the gene responsible and this may provide an insight

into the development and pathology of extraocular muscles and the genes that affect them.

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