Strabismic syndromes and syndromic strabismus - a brief review

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Strabismus can be found in association with congenital heart diseases, for examples, in velocardiofacial (DiGeorge) syndrome, Down syndrome, mild dysmorphic features, in CHARGE association, Turner syndrome, Ullrich-Turner syndrome, cardiofaciocutaneous syndrome.¹⁻⁴ Some types of strabismus is heritable (e.g. infantile esotropia syndrome), particularly the ones associated with multisystem disorders, e.g. Moebius syndrome, Prader-Willi syndrome, craniofacial dysostoses, and mitochondrial myopathies.⁵ Due to the complexities that a case of strabismus may pertain to, it is worthwhile to get to know more about the strabismic syndromes and syndromic strabismus. This brief review -as its name implied- does not attempt to cover every angle of the syndromic conditions, but offers a refreshment on our knowledge about more prevalent strabismus-related syndromes.

Duane’s syndrome

Duane’s syndrome or Duane’s retraction syndrome (DRS) is one of the most recognized strabismic syndrome which is genetic in nature. The incidence of DRS is 0.1% in population, and it comprises 1-4% of all strabismus cases.⁶ It has a preponderance of left eye involvement and the reason for this is unknown. The gene responsible for DR is located at chromosome 2, 4, 8, and 22 (to be more specific: 2q31, 8q13, and 22q11).⁷ The occurrence of cleft palate, Klippel-Feil anomaly, sensorineural hearing loss, and DRS are genetically linked.⁶ DRS is also associated with velocardiofacial syndrome.¹ From these findings we can conclude that basically the DRS may present in association with certain viscerocranium anomalies.

DRS pathology involves congenital anomaly of the sixth cranial nerve’s nuclei (in the form of hypoplasia) with aberrant innervation from the third cranial nerve nuclei (an extra branch of the inferior division of the oculomotor nerve to the lateral rectus).⁸ Paradoxical innervation of the lateral rectus muscle causes simultaneous contraction of both medial and lateral recti during adduction, causing the retraction of the globe into the orbita.⁶ Both DRS and congenital fibrosis of extraocular muscles can be categorized under incomitant strabismus and fibrosis of the extraocular muscles.⁶ In type 1 Duane’s syndrome, the abduction saccadic velocity is reduced significantly, while the adduction one is moderately affected.⁹ DRS can be associated with hyperopia.⁶ Interestingly, despite no significant psychophysical feature changes were identifiable (except for hyperopia), the coronal optic nerve cross-sectional area were reported significantly smaller than normal.¹⁰

The wide variety of DRS clinicopathologic features demands classification for guiding the management of the condition. The Huber’s classification of DRS is: (i) type I - limited abduction with normal to near normal adduction; (ii) type II - limited adduction with normal to near normal abduction; and (iii) type III - limited abduction and adduction.⁶ Type I of DRS is further classified based on the deviation in their primary position into: IA - esotropia; IB - exotropia; and IC - orthotropia.¹¹
Craniofacial asymmetry can be found in DRS due to long standing torticollis. Thus it is of utmost importance to deal with the syndrome in timely manner. When anomalous head posture was used as a marker for successful surgical intervention, horizontal muscle recession was beneficial in 93% of cases. This procedure is relatively simple, therefore the recognition and timely management of DRS become a determinant in the success of surgery.

**Brown's syndrome**

Normally, when the inferior oblique contracts while the globe is adducted, the superior oblique tendon should be relaxed and its tendon passively lengthens. However, this is not the case in Brown’s syndrome. Brown’s syndrome is also known as superior oblique tendon sheath syndrome, with limited elevation in adduction, thus giving an impression (pseudopalsy) of the inferior oblique. CT-scan revealed thickening and inflamed reflected part of the superior oblique.

Brown’s syndrome can be hereditary or acquired. The acquired type of the syndrome can be induced by trauma involving orbital throclea. It can also be caused by paranasal sinus mucocele extending into the orbit or orbital venous malformation. Glaucoma implant (Molteno), cataract surgery due to myotoxicity by local anesthetic agent (albeit rare), and blepharoplasty may be associated with acquired Brown syndrome. Children with this syndrome often assume an anomalous head posture in the form of head tilt.

Patients with congenital Brown syndrome, may overtime be stable or resolve spontaneously, thus requiring no surgical intervention, especially whose primary position orthotropic (instead of hypotropic). Seventeen percents of the cases present with compensatory head posture, which were completely amenable surgically. Surgical management of this condition usually involves superior oblique tenotomy or tenectomy, however, post-operative complication of cyclovertical deviation can be very disturbing for the patients and can be very difficult to treat. In this case, where multiple surgeries failed, partial or sectoral monocular occlusion therapy can alleviate patients with diplopia.

**Möbius’ syndrome**

The symptoms of Möbius’ syndrome can already be identified soon after birth. Several loci were associated with this syndrome: 13q12.2-q13, 3q21-q22, and 10q21.3-q22. In this syndrome, there is the paralyses of bilateral sixth, seventh, and twelfth cranial nerves. Congenitally, this syndrome may be associated with the loss of innervation to the extraocular muscles, which can also occur in other muscles, hence called congenital innervation dygenesis syndrome (CID). Histologic examination showed hypoplastic abducens, facial and hypoglossal nerves. Underaction of the lateral rectus in Möbius’ syndrome can reach up to -4, whereas the underaction at adduction -3, therefore esotropia is one of several features of the Möbius’ syndrome. Bilateral talipes equinovarus and syndactyly may be found in association with Möbius’ syndrome.

Surgical intervention of choice in both Möbius and Duane’s syndrome is recession of the medial rectus with vertical rectus transposition.

**Marcus-Gunn (jaw-winking) phenomenon**
Strabismus occur in 36% of Marcus-Gunn syndrome.\textsuperscript{30} This syndrome is associated with concomitant esotropia, ptosis, and jaw winking phenomenon.\textsuperscript{31} It can also be associated with Williams-Beuren\textsuperscript{32} and CFEOM syndrome.\textsuperscript{33} Double elevator palsy occurred in 25% of the cases\textsuperscript{34}, whereas superior rectus palsy in 23%.\textsuperscript{34} The mesencephalic root of the trigeminal nerve (motoric to the mastication muscles), is linked to the muscles of the oculomotor nerve, including to the eyelid levator in this condition.\textsuperscript{31} Other aberrant connectivities, such as trigemino-abducens\textsuperscript{35} and congenital abnormality within the otolith-oculomotor pathway\textsuperscript{36}, may accompany the phenomenon.

For the ptosis, bilateral fascial suspension is considered to be the treatment of choice in this syndrome\textsuperscript{30, 34, 37}, with some advocating unilateral levator excision.\textsuperscript{34, 37} Amblyopia occurred in 34%\textsuperscript{30} to 59%\textsuperscript{34} in this syndrome.

**Nystagmus compensation (blockage) syndrome**

Around 5% of patients with congenital esotropia had this condition.\textsuperscript{38} The syndrome is characterized by early onset esotropia with pseudoparalysis of the abducens nerves. It is called pseudoparalysis because the esotropia is due to convergence (or non-convergence esodeviation\textsuperscript{39}), in order to block the nystagmus from occurring (in primary and abduction position).\textsuperscript{38} The asymmetric type of this syndrome may manifests itself in the form of asymmetric concomitant horizontal deviations (dissociated horizontal deviation or DHD) dependent on the fixing eye.\textsuperscript{40}

Surgical management by recessing the rectus muscle (in this case the medial one) retroequatorially or pre-equatorially\textsuperscript{41-44}, or with additional resection of the lateral rectus\textsuperscript{45}, can be employed in the syndrome.\textsuperscript{41, 42} While they work for dissociated vertical deviation (DVD), this posterior fixation procedures’ results in nystagmus compensation syndrome have been inconclusive, unfortunately.\textsuperscript{46}

**Noonan’s syndrome**

In this congenital heart disease syndrome, strabismus were found in 48% of the cases, of which 80% were horizontal strabismus.\textsuperscript{47} Superior oblique tendon absence may also be found,\textsuperscript{48} this indicate that vertical incomitant strabismus with or without anomalous head posture may be present.

External eye anatomy-related abnormalities in the syndrome include: hypertelorism (74%), downward sloping palpebral apertures (58%), epicanthic folds (59%), ptosis (48%).\textsuperscript{47} Aside from strabismus, the orthoptic findings are: refractive errors (61%), amblyopia (53%), and nystagmus (9%) of cases.\textsuperscript{47} Anterior segment involvement include: prominent corneal nerves (46%), anterior stromal dystrophy (4%), cataracts (8%) and panuveitis (2%).\textsuperscript{47} Fundal changes occurred in 20% of the study group, including optic nerve head drusen, optic disc hypoplasia, colobomas and myelinated nerves.\textsuperscript{47}

**Other syndromes**

Other syndromes related to strabismus include congenital fibrosis of the extraocular muscles (CFEOM), fat adherence syndrome, inferior rectus muscle contracture syndrome, and Marfan’s syndrome. The syndromes are each briefly described below.

CFEOM showed (from MRI) hypoplasia of the oculomotor, abducens, trochlear nerves, and the extraocular muscles.\textsuperscript{8} It can also be associated with agenesis of the corpus callosum, colpocephaly,
hypoplasia of the cerebellar vermis, hydrocephalus, pachygyria, encephalocele and/or hydrancephaly.\textsuperscript{33} Rarely, it is coexists with Marcus-Gunn jaw-winking phenomenon.\textsuperscript{33}

In fat adherence syndrome restrictive strabismus is present, which is amenable by homologous temporal fascia transplant for globe fixation.\textsuperscript{49} The syndrome is an important cause of restrictive strabismus following retina surgery.\textsuperscript{60, 61} Another condition would be the inferior rectus muscle contracture syndrome. Its prevalence is 7\% according to one study.\textsuperscript{52} Under exploration, peribulbar part of the muscle is usually normal, however the retrobulbar part may be fibrotic and showing segmental enlargement in MRI.\textsuperscript{53} In one unusual case, spontaneous recovery from the consecutive hypotropia occurred.\textsuperscript{64}

Strabismus also occurred in around 11\%\textsuperscript{55} to 19\% of individuals with Marfan syndrome, usually in the form of exotropia, followed by esotropia and other forms.\textsuperscript{56} Perhaps due to its nature of connective tissue disorder, media rectus pulley instability was discovered in the syndrome.\textsuperscript{57}

\textbf{Summary}

We have briefly discussed some systemic or regional conditions related to strabismus. Surgery is usually a viable option for treating some conditions above. Nonetheless, when strabismus is a part of a more widespread syndrome (like in Noonan’s), or with mesencephalic etiology (like in CFEOM), the treatment becomes difficult, if not impossible at all, and therefore patient education of their condition should be very carefully done.
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