LEARNING OBJECTIVES
1. Recognize the clinical features that characterize congenital processes which result in restrictive or incomitant strabismus
2. Gain exposure to the genetic basis of complex strabismus
3. Develop an understanding of the surgical management of congenital incomitant strabismus

CME QUESTIONS
1. What clinical characteristics may help to distinguish Type I Duane syndrome from a 6th nerve palsy?
2. What type of anomalous head posture do patients classically adopt in order to maintain binocularity in Type I Duane syndrome, CFEOM1, and congenital Brown syndrome?
3. Which of the CFEOM subtypes is associated with cognitive delay and later onset peripheral neuropathy?

KEYWORDS
1. Congenital Fibrosis of the Extraocular Muscles (CFEOM)
2. Duane Syndrome
3. Brown Syndrome
4. Incomitant Strabismus
5. Congenital Strabismus

INTRODUCTION TO CONGENITAL CRANIAL DYSINNERSATION DISORDERS (CCDDs)
Congenital cranial dysinnervation disorders or CCDDs comprise a group of complex strabismus disorders that result from aberrant innervation or dysinnervation of extraocular muscles. Historically, many CCDDs were thought to be the result of a primary myopathic process that generated incomitant strabismus. Our current understanding, which has been greatly enhanced by the identification of the genetic basis for many of these conditions, is that the underlying etiology for the CCDDs is a primary disruption of innervation of the extraocular muscles with consequent restrictive strabismus.1-3 The ability to recognize the salient clinical features of the CCDDs is essential for appropriate management both non-surgical and surgical, for prognosis, and for work up of associated systemic findings when relevant.

CCDDS WHICH MANIFEST PRIMARILY WITH LIMITATION OF HORIZONTAL MOVEMENT
DUANE SYNDROME
Duane Syndrome is the most frequently observed CCDD and accounts for approximately 4-5% of all strabismus. Familial cases account for 10% of Duane syndrome with a reported range of 5-22%. The underlying pathogenesis stems from a hypoplastic or absent abducens nerve with subsequent aberrant innervation of the lateral rectus by branches of the oculomotor nerve.5-6 Primarily, Duane syndrome occurs sporadically. In familial cases, Duane syndrome is dominantly inherited with the possibility of significant phenotypic variability within families.7 Two Duane associated genetic loci have been identified: the DURS1 locus at 8q13 and the DURS2 locus at 2q31. Mutations in the CHN1 gene (alpha-1-chimerin, OMIM 118423) are responsible for DURS2; the gene encodes a signalling molecule shown to be important for axonal pathfinding in mice.8 The number of genetic syndromes associated with Duane syndrome are myriad. The more commonly encountered associated syndromes are listed in Table 1. (see next page)
Table 1. Clinical Characteristics of Syndromic Duane Syndrome

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Clinical Features</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duane Radial Ray syndrome (Okihiro, acro-renal-ocular)</td>
<td>Radial defect/ Hypoplasia of thenar eminence, deafness, renal dysplasia</td>
<td>SALL4 (OMIM 607343)</td>
</tr>
<tr>
<td>Holt-Oram syndrome</td>
<td>Upper limb/hand anomalies, congenital heart defects</td>
<td>TBX5 (OMIM 601620)</td>
</tr>
<tr>
<td>Townes-Brocks syndrome</td>
<td>Thumb malformation, deafness, imperforate anus</td>
<td>SALL1 (OMIM 602218)</td>
</tr>
<tr>
<td>Bosley-Salih-Alorainy syndrome</td>
<td>Bilateral Type 3 Duane syndrome, deafness, cardiac anomalies, developmental delay</td>
<td>HOXA1 (OMIM 142955)</td>
</tr>
<tr>
<td>Wildervanck syndrome</td>
<td>Deafness, Klippel-Feil anomaly (cervical vertebrae)</td>
<td>unknown</td>
</tr>
</tbody>
</table>

**Clinical Features**
The clinical characteristics typical of Duane syndrome include: complete, less often partial, limitation of abduction, variable limitation of adduction, globe retraction on adduction, narrowing of the palpebral fissure with attempted adduction, and abnormal vertical movements in adduction (Figure 1)(see below). These vertical movements may be described as an upward or downward (upshoots/downshoots) deviation of the eye on attempted adduction. Other aberrant movements such as synergistic divergence or abduction of the eye on attempted adduction have been described.

Huber provided a classification scheme which is helpful in clinically stratifying patients with Duane syndrome. In Type I Duane syndrome, the affected eye shows limited abduction with typically normal adduction. In Type II Duane syndrome, the affected eye shows limited adduction with typically normal abduction. In Type III Duane syndrome, the affected eye demonstrates limitation of both abduction and adduction. These limitations of movement result in incomitant strabismus. Type I Duane syndrome will demonstrate an esodeviation worse in the field of action of the eye which cannot abduct. Type II Duane syndrome will demonstrate an exodeviation worse in the field of action.

Figure 1. External photographs of a 17 year old girl with Duane syndrome Type I affecting the left eye. Nine fields of gaze are shown. There is inability to abduct the left eye with narrowing of the palpebral fissure on adduction.
of the eye which cannot adduct. The incomitance for Type
III Duane syndrome will vary depending on the degree of
limitation. Patients often will have an anomalous head
posture to achieve a position of gaze that allows them to see
binocularly. Strabismus may or may not be present when
the head is in the primary position.

In general, we do not routinely obtain neuroimaging in
both pediatric and adult patients with a clear history of a
congenital strabismus and with the salient clinical features
of Duane syndrome on exam. For infants in whom it may
be more difficult to establish whether there is a change
in eyelid position with horizontal movement of the eye
or globe retraction, and therefore difficult to distinguish
between Duane syndrome and an acquired 6th nerve palsy,
neuroimaging may be pursued in some cases. Typically,
congenital 6th nerve palsy is rare.

MANAGEMENT
Patients with Duane syndrome will often present with
uncorrected refractive error and amblyopia. In particular,
anisometropia and astigmatic error are often present. A
thorough eye examination which includes a cycloplegic
refraction in children or manifest refraction in adults is an
important aspect of the non surgical treatment of patients
with Duane syndrome.

Surgery is generally considered when there is a horizontal
deviation in primary gaze, when there is a significant
anomalous head position or torticollis, and when there
is concern regarding the cosmesis associated with up/
downshoots or marked globe retraction of the affected
eye. There are a number of treatment strategies which
have been proposed for the management of Duane
syndrome. Recession of a horizontal rectus muscle, primary
transposition of the vertical rectus muscles, combined
recession of a horizontal muscle with transposition of the
vertical rectus muscles and botulinum toxin injection of
a horizontal rectus muscle have all been employed in the
treatment of Duane syndrome. Recessions are more
commonly performed rather than resections. The preferred
approach at Boston Children’s Hospital is medial rectus
recession combined with superior rectus transposition for
Duane Type I as opposed to the traditional vertical rectus
transposition surgery. This approach allows the surgeon
to relieve medial rectus restriction while also expanding
the field of binocular vision by improving abduction of the
eye. Addressing the medial rectus restriction is particularly
important for adult patients for whom the muscle will
often appear tighter than in pediatric patients given the
contracture of the medial rectus over time. Although only
the superior rectus muscle is transposed, hypertropias post-
operatively are relatively uncommon.

ADDITIONAL CCDDS WITH PRIMARY LIMITATION
OF HORIZONTAL MOVEMENT
In addition to Duane syndrome, there are several additional
CCDDs that manifest primarily with limitation of horizontal
movement. The clinical features of these conditions are
summarized in Table 2 (see below). In contrast to classic,
non-syndromic Duane syndrome, these conditions are
associated with significant systemic findings. Recognition
of the systemic associations and appropriate referral for these
findings is essential. Often the broader evaluation may be
initiated by the treating ophthalmologist who may be the
first to establish the underlying diagnosis in these patients.

<table>
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<tr>
<th>Syndrome</th>
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<tbody>
<tr>
<td>Horizontal Gaze Palsy with Progressive Scoliosis</td>
<td>Limitation of horizontal gaze and aggressive scoliosis</td>
<td>ROBO3 (OMIM 608630)</td>
</tr>
<tr>
<td>Athabaskan Brain Dysgenesis syndrome</td>
<td>Limitation of horizontal gaze, deafness, developmental delay, central hypoventilation, cardiac anomalies Patients of Native American ethnic origin</td>
<td>HOXA1 (OMIM 142955)</td>
</tr>
<tr>
<td>Hereditary Congenital Facial Paresis</td>
<td>Esotropia, bilateral facial palsy</td>
<td>HOXB1 (OMIM 142968)</td>
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CONGENITAL FIBROSIS OF THE EXTRAOCULAR MUSCLES (CFEOM)

Congenital fibrosis of the extraocular muscles refers to several rare strabismus disorders characterized by non-progressive ophthalmoplegia and blepharoptosis. This condition is hypothesized to result from dysinnervation of the extraocular muscles innervated by the oculomotor and/or trochlear nerves. Three dominant (FEOM1, 3, 4) and one recessive (FEOM2) CFEOM genetic loci have been mapped. The kinesin family member KIF21A (OMIM 608283), the homeodomain gene PHOX2A (OMIM 602078), and a b-tubulin gene TUBB3 (OMIM 602661) have been identified as the FEOM1, FEOM2, and FEOM3 genes, respectively. These genes contribute to neuronal differentiation, axonal trafficking, and axonal pathfinding. Genetic testing for each of these genes is commercially available. The clinical features of the subtypes of CFEOM are described below.

CFEOM 1

CFEOM 1 is the most common and is inherited in an autosomal dominant manner from mutations in KIF21A and rarely TUBB3 genes. These mutations affect innervation by the superior division of oculomotor nerve. Clinical features include bilateral blepharoptosis and eyes infraducted with limited vertical movement (Figure 2) (see below). Consequently, many patients will adopt a chin-up head posture. Horizontal movement may be unaffected. Associated features include Marcus-Gunn jaw winking. Optic nerve abnormalities have been reported including excavation of the optic nerve or optic nerve hypoplasia. High resolution MRI imaging of the orbit has revealed hypoplastic oculomotor and abducens nerves and atrophy of the levator and superior rectus muscle complex.

Figure 2. External photographs of a 6.5 year old girl with CFEOM1. Note the marked chin up position. Nine fields of gaze are shown. The eyes are fixed in downgaze with inability to elevate the eyes. Horizontal movement of the eyes is intact.
CFEOM 2

CFEOM 2 has autosomal recessive inheritance secondary to mutations in the PHOX2A gene and affects both the superior and inferior divisions of the oculomotor nerve. Clinical features include a large angle fixed exotropia with blepharoptosis of varying severity. There is phenotypic heterogeneity with respect to the degree of vertical misalignment ranging from full vertical movements to unilaterally or bilaterally supra/infraducted eyes. A distinguishing feature of CFEOM 2 is the presence of pupillary abnormalities both in size and also in responsiveness. Neuroimaging findings of absent oculomotor and trochlear nerves and enlarged lateral rectus muscles have been reported.

CFEOM 3

CFEOM 3 is autosomal dominantly inherited from mutations in TUBB3 and rarely KIF21A genes. Clinical features of this subtype are more variable and may include unilateral or bilateral blepharoptosis and ophthalmoplegia with heterogeneity in the limitation of vertical eye movements. Optic nerve anomalies may be present. Importantly, CFEOM 3 may have associated systemic findings including developmental delay and late onset peripheral neuropathy.

Neuroimaging findings including hypoplasia of the oculomotor nerve with variable atrophy of extracocular muscles. Tukel syndrome describes a condition characterized by a CFEOM3 phenotype with hand anomalies; the genetic basis for Tukel syndrome has not been identified to date.

CFEOM WITH INTELLECTUAL DISABILITY

A novel phenotype of CFEOM co-segregating with polymicrogyria and cognitive dysfunction has been described. This is secondary to mutations in a b-tubulin gene TUBB2.

SURGICAL MANAGEMENT OF STRABISMUS IN CFEOM

Literature regarding surgical approach and detailed surgical outcomes are limited. Surgery may include large resections, tenotomies, myectomies, fixation of a muscle to the orbital wall, and botulinum toxin injection. More specifically, for the marked restriction of elevation of the eyes, at Boston Children’s Hospital, we typically perform a weakening procedure of the superior oblique muscles (tenotomy) coupled with large resections of the inferior rectus muscles. We have found resection of the superior rectus muscle to be less useful in treating the vertical misalignment. Although classically for restrictive strabismus, resections are generally avoided, in the management of CFEOM, large resections of the horizontal rectus muscles may be necessary. Patients should be counseled that multiple strabismus procedures may be needed as undercorrection is common in spite of an aggressive surgical approach. In our experience, adult patients undergoing surgery have tighter and more friable muscles than the pediatric patients who are being treated surgically for CFEOM. Therefore, we counsel our patients that earlier surgery may be more beneficial.

MANAGEMENT OF BLEPHAROPTOSIS IN CFEOM

The primary consideration in repair of blepharoptosis in this condition is the risk of post-operative exposure keratopathy given the limitation of vertical eye movements. The frontalis sling procedure is an effective, conservative method of ptosis repair for these patients.

CONGENITAL BROWN SYNDROME

Congenital Brown syndrome is characterized by limitation of elevation of the eye in adduction passively or actively (Figure 3). There may be a downshoot of the eye in adduction and an associated chin up posture to maintain binocularity however, a true superior oblique overaction is not generally observed. The underlying etiology is unclear and the congenital form of this condition may fall into category of CCDDs. Traditionally, the mechanism of Brown syndrome is considered to be secondary to restricted movement of the superior oblique tendon or trochlear abnormalities and consistent with this, forced duction testing is positive with adduction and elevation of the eye. Whether this occurs secondarily as a consequence of aberrant innervation is unclear. Spontaneous resolution of congenital Brown syndrome is uncommon.
In comparison to patients with congenital Brown syndrome, the etiologies for acquired Brown syndrome are myriad including inflammatory causes associated with systemic disease, traumatic causes, and iatrogenic causes after orbital or ocular surgery.\textsuperscript{36} In a study of 85 patients with congenital and acquired Brown syndrome, Wright\textsuperscript{36} observed several features which appeared to distinguish congenital from acquired causes of Brown syndrome: acquired cases are more likely to have a large hypotropia in primary position compared with congenital cases and this is more pronounced in those cases secondary to a trauma. Further in this cohort, amongst the acquired cases, excluding traumatic cases, 16% of patients experienced spontaneous resolution of their strabismus.\textsuperscript{36} Amongst some of the patients with spontaneous resolution were pediatric patients diagnosed with idiopathic acquired Brown syndrome.

SURGICAL MANAGEMENT OF CONGENITAL BROWN SYNDROME
The mainstay of treatment involves a weakening procedure of the superior oblique without creating a secondary superior oblique palsy. Complete tenotomy of the superior oblique tendon is likely to result in an iatrogenic superior oblique palsy therefore more a conservative expansion of the superior oblique tendon is preferred. Techniques to elongate the superior oblique tendon may include split thickness lengthening of the tendon, z-myotomy of the tendon, or placement of a tendon expander including the Wright silicone expander or suture spacer. Our preferred technique involves the use of a non-absorbable polyethylene suture suture spacer.\textsuperscript{37-38}

Figure 3. External photographs of a 6 year old girl with congenital Brown syndrome right eye. Nine fields of gaze are shown. There is limitation of elevation of the right eye in adduction.

CME ANSWERS
1. Globe retraction on adduction, narrowing of the palpebral fissure with attempted adduction, and abnormal vertical movements in adduction are clinical features associated with Duane syndrome as distinct from a 6\textsuperscript{th} nerve palsy. Further, a congenital 6\textsuperscript{th} nerve palsy is rare and therefore a history of a limitation of abduction since infancy in addition to the above clinical findings would support the diagnosis of Type I Duane syndrome.
2. Duane syndrome Type I- head turn towards the affected side; CFEOM1- chin up head position; Brown syndrome- chin up head position
3. CFEOM3

REFERENCES