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Recent Progress in Understanding Congenital Cranial Dysinnervation Disorders

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Abstract

Background—In 2002 the new term congenital cranial dysinnervation disorder (CCDD) was proposed as a substitute for the traditional concept of congenital fibrosis of the extraocular muscles based on mounting genetic, neuropathology, and imaging evidence suggesting that many, if not all, of these disorders result from a primary neurologic maldevelopment rather than from a muscle abnormality. This report provides an update eight years after that original report.

Evidence acquisition—Review of pertinent articles published from Jan 2003 until June 2010 describing CCDD variants identified under PubMed MeSH terms congenital fibrosis of the extraocular muscles, congenital cranial dysinnervation disorders, individual phenotypes included under the term CCDD, and congenital ocular motility disorders.

Results—At present a total of seven disease genes and 10 phenotypes fall under the CCDD umbrella. A number of additional loci and phenotypes still await gene elucidation, with the anticipation that more syndromes and genes will be identified in the future. Identification of genes and their function, along with advances in neuro-imaging, have expanded our understanding of the mechanisms underlying several anomalous eye movement patterns.

Conclusions—Current evidence still supports the concept that the CCDDs are primarily due to neurogenic disturbances of brainstem or cranial nerve development. Several CCDDs are now known to have non-ophthalmologic associations involving neurologic, neuroanatomic, cerebrovascular, cardiovascular, and skeletal abnormalities.

CFEOM to CCDD

During the last half of the 20th century, pediatric ophthalmologists recognized that certain children were born with congenital ocular motility abnormalities associated with fibrotic extraocular muscles. This observation led to the concept of “congenital fibrosis of the extraocular muscles” (CFEOM) because of the assumption that the primary problem was a congenital abnormality of muscle development.[1, 2] The most common of these disorders is Duane retraction syndrome (DRS), although a number of other sporadic and familial congenital ocular motility syndromes were also recognized.

As time passed, evidence accumulated that a number of these syndromes had a neurogenic etiology. Therefore, in 2002 an alternative concept of “congenital cranial dysinnervation disorders” was proposed,[3] shifting the focus away from muscle development and toward a likely neurogenic etiology of congenital abnormalities of ocular muscle and facial innervation. Developments in the last eight years have supported this concept, since all identified genes responsible for CCDDs affect brainstem and/or cranial nerve development. NANOS has now taken up this effort by including CCDDs into its NOVEL Patient Rare

Disease Registry under the topic of Unusual Congenital Ocular Motility Disorders and Strabismus (http://library.med.utah.edu/NOVEL/diseases/rare-registry/view/Unusual_Congenital_Ocular_Motility_Disorders).

The purpose of this brief review is to update the original report proposing the CCDD concept [3] because much has happened over the last eight years. Many of the syndromes described here are uncommon, and a number have autosomal recessive etiologies that make their occurrence more frequent in specific areas of the globe. However, the world's population is mobile as never before, and a patient with any one of these problems can walk into the office of an ophthalmologist or neurologist in America or elsewhere in the world. Therefore, clinicians in our fields should have at least a passing familiarity with the heterogeneous group of syndromes within the concept of CCDD. Not included here (or within the CCDD concept) are myopathies, genetic disorders involving the neuro-muscular junction, or progressive and/or degenerative ocular motility and neurologic problems such as chronic progressive external ophthalmoplegia or spinocerebellar atrophy, even if recognized to have a genetic etiology.

Disorders affecting predominantly ocular motility

Duane Retraction Syndrome (DRS)

DRS is the most common of all CCDD ocular motility patterns and is characterized most commonly (in DRS type 1) by limited abduction with variable limitation of adduction together with retraction of the globe and narrowing of the palpebral fissure. This ocular motility pattern is generally sporadic, typically unilateral, and more common in females. The underlying mechanism is primary absence or hypoplasia of the abducens nerve (CN6) with dysinnervation of the ipsilateral lateral rectus by a branch of the oculomotor nerve (CN3). [4–6]

Up to 10% of DRS cases may be familial, including autosomal dominant inheritance in several distinct syndromes. The DURS1 locus (MIM #126800; Mendelian Inheritance in Man; <http://www.ncbi.nlm.nih.gov/omim>) was defined after finding overlapping cytogenetic abnormalities on chromosome 8q13 in multiple patients with syndromic DRS and may reflect a complexity of cytogenetic causes, including disruption of CPAH.[7, 8] The DURS2 locus was defined by linkage analysis of families segregating dominant DRS (MIM #604356), and affected individuals commonly have bilateral involvement and associated vertical movement anomalies. The responsible gene, *CHN1*, is involved in ocular motor axon path finding in the development of CN6 and, to a lesser extent, CN3.[9, 10] *CHN1* mutations were not found in a cohort of individuals with sporadic DRS.[11]

Duane-Radial Ray Syndrome (DRRS or Okihiro syndrome; MIM #607323) is characterized by DRS with hand and, in some cases, upper extremity anomalies and variable expression of cardiac, renal, hearing, and vertebral abnormalities. It is caused by mutations in the *SALL4* gene, which is thought to be involved in the patterning of several embryonic structures such as abducens nerve, limbs, and heart.[12, 13] DRS may also be associated with other developmental problems such as the *HOXA1* spectrum, while limited abduction and globe retraction can also occur as part of a more complicated congenital ocular motility syndromes such as CFEOM1.

CFEOMtype 1 (CFEOM1; MIM#135700)

This is the most common CFEOM phenotype. It is autosomal dominant and has been reported worldwide [14] with primary clinical features including bilateral ptosis and severe restriction of up gaze so that neither eye is able to reach midline (Figure 1).[15,16] Down gaze and horizontal movements are variably restricted. Misdirected eye movements are

common, including bilateral convergence on attempted up gaze (synergistic convergence) and globe retraction with attempted globe movement. Autopsy study and careful orbital imaging show profound atrophy of levator and superior rectus, variable reduction in the size of other extraocular muscles, absent orbital motor nerves, and optic nerves that are reduced 30–40% in cross section.[16] CFEOM1 is caused by heterozygous missense mutations in *KIF21A*, a gene that encodes a kinesin microtubule-associated protein associated with anterograde organelle transport in neuronal cells.[15]

CFEOM type 2 (CFEOM2; MIM #602078)

The main clinical features of this autosomal recessive syndrome are bilateral ptosis and absent adduction, up gaze, and down gaze, creating the appearance of bilateral oculomotor nerve palsies (Figure 2).[17] Abduction is present although generally incomplete, and pupils often are variable in size and shape and unreactive to light even though they react correctly to pupillary pharmacologic agents.[18] Neuroimaging shows that the oculomotor nerves are absent bilaterally.[18] The syndrome is caused by homozygous loss-of-function mutations in the *PHOX2A* gene, [17] a homeodomain transcription factor that is prominently expressed in developing oculomotor and trochlear motor neurons and is essential to their survival. In mouse, *Phox2a* also regulates the expression of two catecholaminergic biosynthetic enzymes essential for the differentiation and maintenance of the noradrenergic neurotransmitter phenotype. [19–21]

CFEOM type 3 (CFEOM3)

This disorder is autosomal dominant, and the ocular motility findings are similar to CFEOM1 except that it is more variable and sometimes associated with the ability to elevate the eyes above the midline (Figure 3 and 4).[22] It is now known to be caused by heterozygous mutations in at least two genes, *TUBB3* (CFEOM3A; MIM #600638) [23] and rarely *KIF21A* (CFEOM3B).[24]

TUBB3 is a component of microtubules, and the phenotype of an individual harboring a *TUBB3* mutation depends in part on the specific heterozygous missense mutation. Some mutations can be non-penetrant, while others result in isolated CFEOM3, and in these individuals the ocular phenotype is quite variable, including individuals with only absent up gaze. Other mutations can cause CFEOM3 in association with facial palsy, peripheral neuropathy, wrist and finger contractures, and intellectual, social, and behavioral impairments. Orbital imaging of individuals with *TUBB3* mutations [25] is similar to that found in CFEOM1 resulting from *KIF21A* mutations.[26] Brain magnetic resonance imaging (MRI) can reveal corpus callosum and anterior commissure dysgenesis.[23]

Patients have been described with a syndrome that looks similar to CFEOM1, although generally without complete restriction of up gaze, who do not harbor mutations in *TUBB3*. Several of these individuals do harbor one of the common mutations in *KIF21A*, and this syndrome is referred to as CFEOM3B. Both *TUBB3* and *KIF21A* have a role in directing growing cranial nerves to a correct termination in extraocular muscles. A CFEOM3C variant (MIM #609384) has been recognized in three generations of a single family where all affected members carry a reciprocal translocation involving chromosomes 2q and 13q.[27]

HOXA1 spectrum (MIM#601536)

This autosomal recessive syndrome consists most notably of bilateral DRS type 3 (with limited adduction as well as absent abduction), deafness, and internal carotid and cerebrovascular malformations, sometimes with autism (Figure 5).[28–30] Some individuals may have associated intellectual disabilities, facial weakness, and/or central hypoventilation. [31] Neuroimaging revealed absence of the abducens nerve bilaterally and almost

completely absent development of the hearing and vestibular apparatus in the petrous bone. [28–30] The syndrome is due to homozygous mutations in *HOXA1* that probably cause loss of rhombomere 5 and an early and profound brainstem patterning defect.[28] *HOXA1* mutations were not found in cohorts of individuals with sporadic DRS [32] or Moebius syndrome.[33]

Horizontal Gaze Palsy and Progressive Scoliosis (HGPPS; MIM #607313)

This syndrome is marked neurologically by complete or almost complete bilateral horizontal gaze limitation with full vertical gaze, variable convergence, variable congenital nystagmus, and normal lids except for asynchronous blinking.[34] The other obvious clinical feature is scoliosis that begins in early childhood and is commonly rapidly progressive and severe (Figure 6).[35] Neuroimaging shows intact abducens nerves bilaterally but deep anterior and posterior clefts in the medulla and low pons, a large 4th ventricle, and no decussation of corticospinal tract, medial lemniscus, or superior cerebellar peduncle.[36, 37] HGPPS is an autosomal recessive syndrome caused by mutations in *ROBO3*, [38] a gene that promotes decussation of developing neural tracts in the pons, medulla, and spinal cord (at least in the mouse [39]).

Moebius syndrome (MBS; MIM#157900)

Moebius syndrome is the eponym reserved for congenital facial weakness associated with restricted horizontal eye movements. Facial weakness is usually bilateral and asymmetric; limited horizontal eye movements always affect abduction and commonly adduction, while vertical gaze is affected in rare cases. Esotropia is common, convergence is variable, Bell's phenomenon is intact, nystagmus is rare, and ptosis is not characteristic. It is frequently accompanied by other non-ocular and facial features such as lingual and/or pharyngeal dysfunction, craniofacial dysmorphism, and limb malformations. In most patients, Moebius syndrome is sporadic, although *HOXA1* and *TUBB3* mutations can result in atypical Moebius phenotypes.[23, 28] Moebius syndrome is likely quite heterogeneous in origin and may have more than one genetic and/or developmental etiology.

Disorders with normal ocular motility

Hereditary Congenital Facial Palsy(HCFP)

This syndrome causes an autosomal dominant, isolated facial weakness that is often asymmetric and bilateral and is distinct from Moebius syndrome in that ocular motility is full. Postmortem pathological studies have shown reduced number of neurons within the facial nerve motor nuclei and poorly developed facial nerve roots. Two genetic loci, termed HCFP1 (MIM %601471) and HCFP2 (MIM %604185), have been defined but neither gene has been identified yet; there does not appear to be any major phenotypic differences between the loci.[40–42]

Hereditary Congenital Ptosis

Hereditary congenital ptosis is defined as isolated drooping of the upper eyelid with no accompanying ocular features. Bilateral involvement is common but unilateral cases have been reported. Severity of ptosis ranges from mild to severe and can be asymmetric in bilateral cases. There are currently two loci mapped by linkage analysis: an AD locus on chromosome 1 ([43]; PTOS1; MIM %178300) and one X-linked locus.[44]

Discussion

In 2002, the CCDD concept included 10 syndromes, two confirmed genes, and 14 genetic loci. Eight years and over 80 articles later, seven genes are now recognized to cause 10

phenotypes (Table 1) and another six syndromes are associated with at least 11 genetic loci (Table 2). Every CCDD gene characterized since 2002 has been associated with neuronal development at the nuclear, brainstem, or peripheral nerve level, supporting the hypothesis that CCDDs are neurogenic in origin.[3]

With genotypic definitions have come better phenotypic characterizations, including the realization that syndromes caused by different genetic mutations may present confounding clinical similarities. For example, DRS most commonly occurs sporadically but can be caused by heterozygous [10, 15] or homozygous [28–30] mutations of several genes. The CFEOM1 [15] and CFEOM3 [23] phenotypes can be quite similar, and severe horizontal gaze restriction is a hallmark of both HGPPS [34] and the *HOXA1* spectrum.[30]

Some CCDDs include non-ocular abnormalities. For example, CFEOM3 due to *TUBB3* mutations can be associated with a peripheral neuropathy, joint contractures, and intellectual and behavioral disabilities.[23] We now realize that ocular motility and other clinical aspects of these syndromes are variable, even within families where presumably the genetic status is relatively homogenous. Thus, some patients with *HOXA1* mutations may lack ocular motility abnormalities or deafness, two of the cardinal clinical features.[30] Perhaps most importantly, certain CCDD diagnoses may call attention to important but clinically unapparent features of a syndrome such as cerebrovascular maldevelopment and congenital heart disease in the *HOXA1* spectrum.[28–30]

These disorders are uncommon but not so rare that they cannot appear in any clinician's office anywhere in the world. NANOS has recently created the NOVEL Rare Disease Registry under which there is now a category for Unusual Congenital Ocular Motility Disorders. The NANOS website now contains a link (http://library.med.utah.edu/NOVEL/diseases/rare-registry/view/Unusual_Congenital_Ocular_Motility_Disorders) by which any clinician can make contact with the stewards, Drs. Thomas M. Bosley and Elizabeth C. Engle, and eventually submit clinical descriptions and genetic material for analysis. We encourage everybody to participate because this sort of broadly based effort will likely be necessary to clinically and genetically characterize new CCDDs.

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Figure 1. CFEOM1 phenotype. A. Primary position showing marked bilateral ptosis. B. Primary position with lids held showing resting globe position. Both eyes remain infraducted below midline. C. Attempted up gaze showing inability to reach midline with convergence of the visual axis (synergistic convergence).

Figure 2.
CFEOM2 phenotype. A. Primary position showing bilateral ptosis and exotropia. B. Primary position with lids held showing resting globe position. C. Patient with right face turn and holding left upper lid to clear pupillary axis. D. Miotic irregular pupil.

Figure 3. CFEOM3B phenotype. All images are in primary position. A. Patient has unilateral ptosis and esotropia. B. Patient has severe bilateral ptosis in primary position despite with marked frontalis effort. C. Same patient as B in primary position with lids held showing resting globe position marked by exotropia and bilateral infraduction.

Figure 4.

CFEOM3A phenotype. A. Primary position. B. Right gaze with absent adduction and slight down shoot OS. C. Left gaze with absent adduction, slight down shoot OD, and limited abduction OS. D. Attempted upgaze showing limitation OU with OS unable to reach midline and with development of an esotropia. E. Down gaze fixing OD with slight downward movement OD and only outward movement of non-fixing OS. F. Down gaze fixing OS with slight downward movement OS and only outward movement of non-fixing OD.

Figure 5.

HOXA1 Spectrum phenotype. A, B, C. Right gaze, primary gaze, and left gaze of a girl with bilateral Duane retraction syndrome type 3. Note up shoot OS on attempted left gaze. D. Axial CT bone windows of the same patient showing almost no development of the petrous bones except for mastoid air cells. E. MR angiogram of the Circle of Willis in the same patient showing absent left internal carotid artery and relatively large caliber of the basilar and both posterior cerebral arteries.

Figure 6.

HGPPS phenotype. A. Primary position. B. Attempted right gaze showing complete gaze palsy. C. Attempted left gaze showing complete gaze palsy. D. Moderately severe scoliosis concave right. E. Hypoplasia of the pons. F. Deep anterior and posterior clefts in the medulla causing the classic “butterfly medulla” appearance.

Table 1

Genes associated with CCDDs

Gene(s)	Phenotype	Main neuro-ophthalmologic features	Other features
<i>CHN1</i>	DURS2	DRS, often bilateral and associated with vertical motility abnormalities	
<i>SALL4</i>	DRRS	DRS	Variable hand and upper extremity anomalies; variable cardiac, renal, auditory, and vertebral abnormalities
<i>KIF21A</i>	CFEOM1	Bilateral ptosis; bilateral severe limitation of up gaze OU with less severe limitations in other directions.	
	CFEOM3B	As above but up gaze limitation typically not as severe	
	CFEOM3A	Variable uni- or bilateral ptosis and limitation of up gaze that may not be as severe as CFEOM1; bilateral, asymmetric restrictions in other directions OU	
<i>TUBB3</i>	CFEOM3A plus	Similar to or more severe than CFEOM3A; when more severe the findings are bilateral and eyes are exotropic	Peripheral neuropathy; facial palsy; wrist and finger contractures; and/or intellectual, social, and behavioral impairments
<i>PHOX2A</i>	CFEOM2	Bilateral severe ptosis and bilateral palsies of adduction, elevation, and depression with significant exotropia; occurs rarely without exotropia	
<i>HOXA1</i>	BSAS	Bilateral DRS type 3 or horizontal gaze palsy	Deafness AU; variable cerebrovascular and cardiovascular anomalies
	ABDS	As above	Often more severe phenotype, including facial weakness and central hypoventilation
<i>ROBO3</i>	HGPPS	Complete or almost complete horizontal gaze palsy	Scoliosis, usually severe

Table 2

Loci associated with CCDDs

Genetic loci	Phenotype	Main neuro-ophthalmologic feature	Other features
13q12.1 (cytogenetic; 1 family)	CFEOM3C	Bilateral ptosis and bilateral limitation of up gaze typically not as severe as CFEOM1; bilateral, asymmetric restrictions in other directions OU; bilateral exocyclotorsion	Facial dysmorphism; mental retardation
22pter (cytogenetic in 3 patients)	DRS	DRS	
DURS1 (cytogenetic)	DRS	DRS	Contiguous gene deletion syndrome, usually with additional findings.
1p22 (cytogenetic in 2 patients)	MBS	Lower motor neuron facial weakness, often bilateral and asymmetrical; variable restriction of horizontal eye movements	Presumed contiguous gene deletion syndrome with variable ptosis, dysmorphism, developmental delay, Poland syndrome, etc
13q12.2-q13 (cytogenetic in 1 family)		As above	Variable flexion finger contractures
3q21-q22	HCFP1	None	Isolated dysfunction of the facial nerve
10q	HCFP2	None	Isolated dysfunction of the facial nerve
1p34.1-p32	PTOS1	Isolated unilateral or bilateral ptosis	
Xq24-q27.1	PTOS2	Isolated unilateral or bilateral ptosis	