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Review Article

Shifting Paradigms in the Etio-Pathogenesis of Congenital Cranial Dysinnervation Syndrome (CCDD)

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Abstract

Strabismus affects 2–4% of the population and causes loss of binocularity and amblyopia. In the absence of structural brain abnormalities the cause for strabismus remains uncertain. Various research studies have been conducted on the genetic basis involved in etio-pathogenesis of a series of complex strabismus syndromes resulting from mutations in genes necessary for the normal development and connectivity of brainstem ocular motor neurons, including PHOX2A, SALL4, KIF21A, ROBO3, and HOXA1, which is collectively referred to as "congenital cranial dysinnervation disorders," or CCDD. There is growing evidence that complex strabismus can primarily result from aberrant signalling to the extra ocular muscles by neurons in the CNS and hence this terminology to name these complex form of strabismus. This review briefly summarises the shifting paradigms in the understanding of etio-pathogenesis of these CCDD.

INTRODUCTION

The concept of "congenital fibrosis of the extra ocular muscles" (CFEOM) was proposed in view of increasingly common observation by the ophthalmologists where in it was noticed that many children born with disorders of ocular motility had fibrotic extra ocular muscles pointing to a myogenic pathology abnormal neuronal development [1-4]. However there was a shift in the opinion relating to etio-pathogenesis and a neurogenic and genetic basis was emphasized for these group of ocular motility disorders that share common features of dysinnervation to the ocular and facial musculature presently termed as the "congenital cranial dysinnervation disorders" by Gutowski *et al.,* in 2003 [4]. These cases at times pose a diagnostic challenge because of a conserved partial or anomalous paradoxical innervation to the muscles which result in different combinations of involuntary eye movements.

Congenital innervation disorder (CID) syndromes are a group of ocular motor abnormalities associated with congenital loss/abnormality of innervation as proposed by Assaf [5]. The following features are observed in these disorders:

-Congenital defect in the innervation of extra ocular muscles (EOM).

-Present since birth, and non-progressive.

-Unilateral or bilateral.

-Findings are not explained by purely isolated oculomotor nerve palsy/palsies.

-Anatomical muscle changes, including tight muscle.

-Can be associated with synkinesis phenomena and/or co-contraction.

-Abnormal head posture is common.

CCDD syndromes result from mutations in genes essential for correct axonal targeting of the motor neurons (ROBO3), motor neuron development (HOXA1, PHOX2A, and likely SALL4), and correct axonal targeting of the extra ocular muscles (KIF21A) [6].

CCDD's can present with preserved ocular motility or limitation of the same, which is the basis of their categorisation.

The disorders with involvement of ocular movements include:

- Duane Retraction syndrome(DRS)
- Moebius syndrome
- Monocular elevation deficiency (MED)
- Congenital fibrosis of extra-ocular muscles (CFEOM, type1,2,3)
- HOXA1 spectrum
- Horizontal gaze palsy and progressive scoliosis

Disorders without limited ocular motility include:

- Hereditary congenital facial palsy (HCFP)
- Hereditary congenital ptosis (HCP)

The review summarises various disorders classified under the CCDD's, their etio-pathological and genetic basis, clinical manifestations and a brief outline of the management approach to these patients with these disorders. To begin with, a tabulated summary of the genetic basis of various CCDD's has been elaborated followed by emphasis on the more common disorders like DRS, Moebius syndrome and MED and subsequently shifting emphasis on the not so common clinical entities. Table 1 mentions various syndromes, associated genes and clinical features, their inheritance pattern and the innervational abnormalities linked with the CCDDs followed by an elaborative review of each of the enlisted disorders.

These clinical entities are:

A. Duane Retraction Syndrome

Isolated Duane retraction syndrome (DRS) is the most common CCDD, typically unilateral with female predisposition and is a congenital non-progressive ocular motility defect. Its most common type 1 is characterised by limited abduction with variable limitation of adduction along-with globe retraction and narrowing of the palpebral fissure (Figure 1a,b) [6]. Primary absence or hypoplasia of the abducens nerve with dysinnervation of the ipsilateral lateral rectus by a branch of the oculomotor nerve has been known in its etio-pathogenesis [7-9]. Patients with DRS reveal CID of the lateral rectus muscle which results in abnormal muscle structure, loss of muscle function, co-contraction, and contraction against a tight muscle. Neurogenic etiology for DRS has been documented by electrophysiological, pathological and neuroradiological studies which is further strengthened by the association of DRS with synkinesis phenomena such as Marcus Gunn jaw-winking [7, 8,10,11]. Hypoplastic abducens nucleus with absent 6th nerve on the affected side in a DRS type 1 patient was first reported by Matteuci [12]. The abducens nucleus reveals no motor neuron cell bodies without intra-axial fibers within the brainstem [12]. The DURS1 locus (MIM %126800; Mendelian Inheritance in Man) was observed following overlapping cytogenetic abnormalities on chromosome 8q13 in multiple patients with syndromic DRS including disruption of a carboxypeptidase A6 gene, CPAH [13]. Linkage analysis of families suggested DURS2 locus by segregating dominant DRS (MIM#604356) with patients commonly manifesting with bilateral involvement and vertical movement anomalies [6]. CHN1 gene is responsible for 3rd and 6th nerve axon pathway development but is uninvolved in sporadic DRS [9,10]. SALL4 gene, which is involved in abducens nerve, limbs, and heart development is involved in syndromic DRS [11] and is associated with Holt–Oram and acro-renal-ocular syndromes [17]. Linkage

Table 1: Genetic basis of CCDDs.

Syndrome	Gene	*Inh.	Associated features	Innervational abnormality
Non syndromic Duane retraction syndrome Familial DS	*CHN1*	AD	Type 1 or 3 DRS & vertical motility anomalies	Abnormal CN VI & III with/ without SO hypoplasia
Syndromic DRS Duane radial ray (Okihiro) Arco-renal-ocular syndrome Townes-Brock syndrome	*SALL4* *SALL4* *SALL1*	AD AD AD	DRS, radial ray± Hearing Loss DRS, radial ray, kidney defects Imperforate anus, hearing loss, thumb malformation ± DRS	Hypoplastic /absent CN VI, aberrant innervation of LR muscle
HOX mutations Bosley-Salih-Alorainy syndrome Athabaskan brain dysgenesis HoxB1	*HOXA1* *HOXA1* *HOXB1*	AR AR AR	DRS, SNHL, Cardiac malformation, autism Horizontal gaze restriction, SNHL, Facial weakness Esotropia, Cranial nerve VII palsy, HL	Non-innervated EOM, Hypoplastic cranial nerve VI, Hypoplastic /absent ICA, double aortic arch, absent CN VII
Horizontal gaze palsy with progressive scoliosis (HGPPS)	*ROBO3*	AR	Horizontal gaze limitation, scoliosis	Flattened pons with midline cleft
CFEOM CFEOM 1 CFEOM2 CFEOM3	*KIF21A* *PHOX2A* *TUBB3*	AD AR AD	Restrictive ophthalmoplegia, blepharoptosis Ptosis, restrictive ophthalmoplegia, exotropia, poorly reactive pupils Variable unilateral blepharoptosis, ophthalmoplegia	Hypoplastic CN III >VI, Hypoplastic LPS, SR Hypoplastic EOM, large LR, absent CN III & VI

Abbrevations: *Inh: Inheritance; AR: Autosomal Recessive; AD: Autosomal Dominant; CN: Cranial Nerve; SO: Superior Oblique; SNHL: Sensory Neural Hearing Loss; HL: Hearing Loss; LPS: Levetor Palpebrae Superioris; SR: Superior Rectus; EOM: Extra Ocular Muscle; LR: Lateral Rectus; ICA: Internal Carotid Artery

Figure 1 Child with bilateral DRS. Note the restriction of abduction bilaterally and retraction of the palpebral aperture on adduction.

analysis of pedigrees with Bosley–Salih–Alorainy syndrome (a condition with bilateral DRS and systemic findings) is localised to the gene on chromosome 7p15.2, encompassing the HOXA gene cluster [18]. Functional MRI has added to in depth analysis of this group of CCDD's [14]. Most DRS patients do not need any surgical intervention and remain asymptomatic [12]. However, 80 % patients with abnormal head posture benefit from eye muscle surgery but the successful restoration of normal ocular motility is unlikely [12] Surgery in DRS aims to improve face turn, alignment in primary gaze, globe retraction, to eliminate upshot and to maintain ocular rotations [12]. Most DRS patients compensate well for the disorder and do not require further management [12]. Transposition procedures improve abduction in a few cases with some compromise on adduction [19]. Fixation of lateral rectus to the lateral orbital wall with transposition of the vertical muscles can be performed in patients with severe DRS associated with up shoots and down shoots on adduction [19].

Moebius syndrome

This syndrome consists of congenital complete or partial facial nerve palsy with or without paralysis of other cranial nerves (most commonly an abducens paralysis) and often associated with other malformations of the limbs and orofacial structures (Figure 2a,b) [20]. Esotropia is common and needs to be differentiated from strabismus fixus [6]. The syndrome has been variably labeled as congenital facial diplegia, nuclear agenesis, congenital nuclear hypoplasia, congenital oculofacial paralysis, and congenital abducens-facial paralysis [20].

Criteria for diagnosing Moebius syndrome include [20].

(1) Complete or partial facial nerve paralysis which is an essential criteria.

(2) Limb malformations (syndactyly, brachydactyly or absent digits, and talipes) are often present.

(3) The additional clinical features which aid in diagnosis include bilateral or unilateral ocular nerve palsies (commonly of the abducens (VI) and less commonly the oculomotor (III) and trochlear (IV) nerves); hypoplasia of the tongue owing to hypoglossal (XII) nerve paralysis; swallowing and speech difficulties owing to trigeminal (V), glossopharyngeal (IX), and vagus (X) nerve palsies; malformations of the orofacial structures (bifid uvula, micrognathia, and ear deformities); other anomalies of the musculoskeletal system, for example, Klippel-Feil anomaly, absence of the sternal head of the pectoralis major, rib defects, and brachial muscle defects.

Most cases of Moebius syndrome are sporadic without any evidence of a known environmental etiological factor and there is not much evidence to support autosomal dominant mode of inheritance, however, the syndrome may result from a new dominant mutation [21-24]. Reciprocal translocation between chromosomes 1 and 13, t (lp34; 13ql3) has also been reported [20]. It is likely quite heterogeneous in origin and may have more than one genetic and/or developmental etiology with HOXA1 and TUBB3 mutations noted in atypical Moebius phenotypes [18,25].

Most ophthalmologists recommend delaying surgery for strabismus because the condition frequently improves with age and ocular surgical procedures have been successful in some patients with Moebius syndrome [26]. Some strabismologists believe that patients with Moebius syndrome are not optimal candidates for transposition surgeries [27]. In view of combined restrictive and paralytic strabismus in these patients, transposition surgery may be problematic if restrictions are enhanced [27]. Vertical rectus transposition is now recommended as a first choice procedure because large medial rectus recessions if performed will further weaken the adduction commonly associated with gaze palsies as also observed in these patients [27]. Medial rectus recession may be considered as a second surgery for residual esotropia if it persists after 1st surgery [28]. In older patients, insertion of a gold weight into the eyelid may allow lid closure to protect the cornea [29].

Monocular Elevation Deficiency (MED)

MED, also known as double elevator palsy (DEP), is inability to elevate one eye in both adduction and abduction, resulting in relative hypotropia of that eye. MED may be congenital or acquired via restrictive or paretic etiology. Combined palsy of the inferior oblique (IO) and superior rectus (SR) muscles is unlikely; paresis of the SR muscle alone is sufficient to produce the

Figure 2 Patient with Moebius syndrome with bilateral abduction deficiency, esotropia and lagophthalmos due to facial nerve aplasia.

clinical manifestations of the disease [30]. A significant number of patients with congenital MED show synkinesis phenomena such as Marcus Gunn jaw-winking [31,32]. Dissociated vertical deviation (DVD) is noted in 29% of MED patients suggesting innervational rather than anatomical aetiology [30]. The disorder is classified into three subtypes: 1) restrictive form, with positive forced duction test (FDT) for elevation, normal elevation forced generation test (FGT), and elevation saccadic velocity, often an extra or deeper lower eyelid fold on attempted upgaze and poor or absent Bell phenomenon; 2) paretic form with elevator muscle weakness, free FDT, reduced elevation FGT and saccadic velocity, in which the Bell phenomenon is often preserved; and 3) a combination form, presenting with positive FDT for elevation and reduced FGT and saccadic velocity for elevation [33].

The goal of surgery is to improve the position of the affected eye in primary gaze, by increasing the field of binocular vision [34]. Indications for surgery include vertical deviation in primary gaze, deviation-induced amblyopia, diplopia in primary gaze, and restricted binocular fields [34]. Inferior rectus recession, Knapp procedure, partial tendon transposition, and combined procedure are different surgical procedures in the management of monocular elevation deficiency (MED) [34].

The Human HOXA1-Related Syndromes: Bosley-Salih-Alorainy Syndrome (BSAS) and Athabascan Brainstem Dysgenesis Syndrome (ABDS)

Affected children with this syndrome manifest with bilateral Duane syndrome, congenital sensorineural deafness secondary to bilateral absence of the cochlea, semicircular canals, and vestibule suggesting common cranial nerve involvement, malformations of the internal carotid arteries (unilateral hypoplasia to bilateral agenesis), delayed motor milestones and autism spectrum disorder (ASD) [35,36]. ABDS children manifest with horizontal gaze restriction, sensorineural deafness, central hypoventilation, mental retardation, and subsets have facial weakness, vocal cord paralysis, and conotruncal heart defects, including tetralogy of Fallot (TOF) and double aortic arch and delayed motor development with MRI suggestive of internal carotid artery anomalies [37]. Genomic analysis pointed BSAS to region of chromosome 7 encompassing the *HOXA* gene cluster [38]. Homozygous truncating *HOXA1* mutation that result in complete loss of *HOXA1* function cause more diffuse error in hindbrain segmentation leading to aberrant abducens and inner ear development [39,40]. Differences in genetic background or environment between the Turkish, Saudi Arabian and Native American populations account for phenotypic variability between these two syndromes [18]. These syndromes are now called the *HOXA1* related syndromes because the common loss of *HOXA1* gene leads to brainstem dysgenesis and cortical dysfunction in these patients. These manifestations suggest new functions of this gene in humans unlike what has been demonstrated in vivo in mice with *HOXA1* mutations [39].

Horizontal gaze palsy with progressive scoliosis (HGPPS)

HGPPS is a rare autosomal recessive disorder first documented in consanguineous Greek pedigrees wherein the patient manifests with absent horizontal eye movements and develops severe progressive scoliosis starting in infancy or childhood [41]. Bi-allelic mutations in the roundabout homolog of Drosophila 3 *(ROBO3*) gene cause horizontal gaze palsy with progressive scoliosis (HGPPS; OMIM 607313) [42]. ROBO3is a large gene which encodes a cell adhesion molecule containing five extracellular immunoglobulin-like motifs, three fibronectin-like motifs, a transmembrane domain, and an intracellular tail containing signalling motifs [43]. ROBO3 is expressed in the human fetal hind brain and shares homology with *roundabout* genes which directs the axons in developing *Drosophila*, zebrafish, and mouse [44]. Human ROBO3 is most closely related to mouse *ROBO3* (Rig1), and its mutations lead to complete loss of gene function manifesting with failure of spinal commissure axons to cross the midline [44]. 24 distinct mutations located in different domains of the ROBO3 gene have been described [44-47]. Splice-site mutation i.e. a homozygous missense mutation (c.3319A>C) next to the splice donor site of exon 22 of the *ROBO3* gene, homozygous deletion of 31bp (c.2769_2779del11, 2779+1_+20del20) spanning the splice donor site of exon 17 of the *ROBO3* gene leading to an altered splicing and an insertion/deletion mutation in the *ROBO3* gene in have been reported in patients of three consanguineous families from Turkey and Saudi Arabia by a study conducted by Alexandar E Volk *et al.,* [48]. MRI has identified hypoplasia of the Pons and medulla with an unusual anterior and posterior midline cleft in the medulla giving a butterfly like bifid appearance in axial sections [44]. However, optic chiasma and corpus callosum appear normal with shortening of anterior posterior diameter of pons and medulla and cerebellar peduncles is observed [49]. Somatosensory and motor evoked potentials show responses predominantly on the same side of stimulation on functional MRI [44]. Electrophysiological studies have suggested that the corticospinal and dorsal somatosensory tracts do not cross the midline in HGPPS patients causing midline medullary clefts in these patients [43]. Congenital absence of horizontal gaze with preserved adduction in convergence, saccades, and vestibulo-ocular or optokinetic responses is observed [50]. Vertical eye movements are mainly unaffected [45,50]. Patients have been reported with horizontal and pendular low amplitude nystagmus [45,46,51], asynchronous blinking [47,50], and bilateral synergistic convergence without pupil constriction upon attempting to gaze horizontally to one side or the other [47]. Visual fields, pupil function, accommodation, and anterior and posterior segments of the eye are usually normal without any deterioration in visual acuity [47]. Apart from motor impairment and subnormal intelligence in a few patients, cognitive functions are usually unaffected [45,47,50,52] . Failure of axons together with that of commissural fibers of the abducent inters nuclear neurons which fail to cross the midline during development has been presumed to be a possible pathogenetic mechanism in this disorder [53].

CFEOM

It is a type of CCDD phenotype and is classified based on the presence of congenital eye movement disorder that primarily affects function of the extra ocular muscles in the oculomotor nerve distribution [54,55] It is further sub-classified as CFEOM1, CFEOM2, or CFEOM3 based on specific phenotypic features [6]. Three CFEOM genetic loci (FEOM1, FEOM2, and FOM3) have

been mapped of which *KIF21A* and *PHOX2A* are referred to as the FEOM1and FEOM2 genes, respectively [10]. A phenotypic and genotypic correlation exists, such that most individuals with CFEOM1 harbour *KIF21A* mutations, most individuals with CFEOM2 harbour *PHOX2A* mutations, and those with CFEOM3 map to the FEOM3 locus (a locus with unidentified disease causing gene) [56].

CFEOM1 (MIM135700)

A patient with CFEOM1 phenotype (MIM135700) presents with congenital non-progressive bilateral external ophthalmoplegia, where both eyes are downward (infraducted) with limitation of elevation above the horizontal midline along-with congenital bilateral ptosis with papillary sparing [38]. The etio-pathogenesis lies in the absence of the superior division of the oculomotor nerve (CNIII) and the corresponding motor neurons in the mid brain oculomotor nucleus with marked abnormalities of the levetor palpebrae superioris (LPS) and SR muscles, confirmed on high-resolution MRI of the brainstem and orbit [57]. These findings suggest that *FEOM1* gene, mapped to centromeric region of chromosome 12 [58], now referred to as the *FEOM1* locus is of prime importance in the development of superior division of the oculomotor nerve & is likely important for axonal targeting of the extra ocular muscles. *KIF21A (*Developmental kinesin*)* gene contains 38 exons and encodes a 1674 amino acid protein [56]. Structurally it resembles classical kinesin with three domains namely motor, stalk, and tail (which carries an unknown cargo [59]. Interaction between these three domains results in homo- or heterodimerization [59]. Heterozygous mutations in this gene in patients with *CFEOM1* inhibit dimerization of *KIF21A* to itself or another binding partner, or may interfere with the ability of *KIF21A* to move into and out of an active state resulting in inhibition of *KIF21A* to deliver its un identified moiety that it carries from the oculomotor neurons to the synapse of the developing neuromuscular junction of the extra-ocular muscle [56].

CFEOM2 (MIM 602078)

This disorder results from aberrant axonal targeting of the extra ocular muscles by a branch of the oculomotor nerve [60]. It is autosomal recessive syndrome characterised by bilateral ptosis and absent adduction, up gaze, and down gaze mimicking bilateral third nerve palsies [60]. Abduction is incomplete, anisocoria with non reacting pupils to light with preserved reactions to drugs [61]. MRI reveals absence of third nerve bilaterally [56] genotypically, homozygous loss-of-function mutations in the *PHOX2A* gene (previously termed ARIX, also identified in an Iranian pedigree) [61]. A home domain transcription factor that is prominently expressed in developing oculomotor and trochlear motor neurons nearly indispensible for their survival. Linkage analysis mapped CFEOM2 to chromosome11q13, referred to as the *FEOM2 l*ocus [62].

CFFEOM3 (MIM 600638)

CFEOM3 is an autosomal dominant disorder with clinical manifestations similar to CFEOM1except for retained ability to elevate the eyes above midline in a few cases [63]. Heterozygous mutations in at least two genes, *TUBB3* (CFEOM3A; MIM #600638), a component of microtubules [25] and rarely *KIF21A* (CFEOM3B) have been found to be mutated in these cases Other manifestations noted in these patients include facial palsy, peripheral neuropathy, wrist and finger contractures, and intellectual, social, and behavioural impairments [6]. Corpus callosum and anterior commissure dysgenesis have been reported on neuro imaging [25]. A CFEOM3C variant (MIM % 609384) has been described wherein a reciprocal translocation in chromosome 2q and 13q have been documented in 3 subsequent generations of a family [64]. Literature is scanty pertaining to surgical management of patients with CCDD's [65-69]. Large recessions with/without adjustable suture technique, resections, tenotomise, myectomies, fixation of a muscle to the orbital wall, and botulinum toxin injection are the surgical modalities for managing CCDD's [66,67]. Resections are generally avoided, in the management of CFEOM [67,69]. The need for multiple surgical procedures should be clearly explained to the patients emphasizing the under-correction after single surgical procedure and early surgery should be considered in adults in view of more tight and friable muscle in this group of patients unlike paediatric age group [66-69].

Two disorders are associated with normal ocular motility:

Hereditary congenital facial palsy (HCFP) HCFP is bilateral, autosomal dominant disorder presenting with isolated asymmetric facial weakness [70-72]. Reduced number of neurons within the facial nerve motor nuclei and poorly developed facial nerve roots has been observed on pathological examination. *HCFP1* (MIM %601471) and *HCFP2* (MIM %604185) are the genetic loci associated with the disorder [18,70].

Hereditary congenital ptosis (HCP)

Bilateral asymmetric mild to severe isolated upper eye lid ptosis without associated ocular features are the presenting features of HCP [73,74]. Two loci have been mapped by linkage analysis namely an autosomal dominant (AD) locus on chromosome 1 (*PTOS1*; MIM %178300) and other X-linked locus [73]. Electromyography studies have suggested paradoxical innervation of superior oblique muscle in some patients with absence of trochlear nerve without hypoplastic or atrophic superior oblique muscle in patients with Brown's syndrome thus pointing to neurogenic etiology [75,76].

DISCUSSION AND CONCLUSIONS

Seven genes are now recognized to cause 10 phenotypes of CCDD's and six syndromes are associated with at least 11 genetic loci [4]. CCDDs are neurogenic in origin [77]. Which can be supported by a genetic basis wherein a gene is responsible for nuclear, brainstem and peripheral nerve development [4]? MRI has shown reliable observations that the EOMs are stabilized without slipping over the globe in relation to the orbit is that they pass through structures known as the rectus "pulleys of Miller." which constitute the fundamental origin of EOM and act as effective mechanical origins of the rectus EOMs causing their paths to change systematically with gaze [78]. High resolution MRI provides microscopic resolution of EOM and orbit [77,79]. DRS which was earlier considered misinnervation of the lateral rectus by a branch of the oculomotor nerve can now be confirmed

radio logically [14,80-83] Additionally, a common observation reported in DRS is a double-headed LR muscle whose superior and inferior divisions of the global layer are typically separated and act at scleral insertion points separated by several millimetres vertically [14] has now also been reported in normal individuals. It is now routinely possible to demonstrate the motor nerve entries into EOM's [14,77]. High resolution magnetic resonance imaging in multiple gaze positions can now routinely demonstrate the size, paths and contractile states of EOMs along-with motor nerve entries into EOMs [14,77,79,84]. Preoperative evaluation of orbits, EOM functional anatomy by imaging would become significantly important in the management of these complex strabismus syndromes in the near future. Strabismus and ocular motility disorders are in the zone of paradigm shift wherein the EOM anatomy is being evaluated in functional terms and genetic basis of this group of ocular motility disorders is being comprehensively studied for focussed, evidence based management.

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