Oculomotility Disorders Arising From Disruptions in Brainstem Motor Neuron Development

Elizabeth C. Engle, MD

The identification and analysis of pedigrees with rare congenital oculomotility syndromes has led to the definition of the congenital cranial dysinnervation disorders. These disorders appear to result from mutations in genes that are essential to the normal development and/or connectivity of cranial motoneurons. This review highlights the clinical features and genetic etiology of 3 congenital cranial dysinnervation disorders: the human homeobox A1 (HOXA1) syndromes, in which early motoneuron development is disrupted; horizontal gaze palsy with progressive scoliosis, in which there is aberrant axonal targeting onto abducens motoneurons; and congenital fibrosis of the extraocular muscles type 1, in which there is aberrant axonal targeting onto the extraocular muscles.

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This review describes several rare oculomotility disorders and presents some of the accumulating evidence that these disorders result from disruptions in motor neuron development. My interest in the etiology of congenital oculomotility disorders began when a toddler was admitted to the neurology service at Children’s Hospital Boston while I was a senior resident in 1992. He was born with congenital bilateral ptosis and with his eyes fixed in a downward position. He underwent evaluation for myasthenia, mitochondrial disorders, and congenital myopathies. We also asked for our ophthalmology consultants’ opinion and were somewhat surprised when they diagnosed him as having congenital fibrosis of the extraocular muscles (CFEOM), a disorder with which none of us were familiar. We learned that CFEOM had been described in the ophthalmologic literature since the 1800s and was classified as one of the ocular fibrosis syndromes, the most common form being Duane syndrome. In 1992, the diagnoses of the ocular fibrosis syndromes were clinical, and the name arose from the common belief that they resulted from primary fibrosis of the extraocular muscles.1,2

The toddler was a member of a large family in which CFEOM was transmitted as an autosomal dominant trait. In the early 1990s, the Human Genome Project was developing maps of polymorphic short tandem repeat markers across the genome, revolutionizing our ability to perform linkage analysis.3 Therefore, after completion of my residency training and with an interest in neurogenetics, I entered the laboratories of Louis Kunkel, PhD, and Alan Beggs, PhD, to begin research of CFEOM. I had 2 primary goals. The first was to use linkage analysis to map and eventually identify the gene causing CFEOM in the toddler’s family. The second was to determine whether CFEOM might result not from primary fibrosis of the extraocular muscles but rather from errors in the development of brainstem motor neurons and axonal targeting of these muscles. In the intervening years, my laboratory has extended these studies beyond CFEOM to include other forms of ocular fibrosis syndromes and, based on the results from our laboratory and others, we have renamed these syndromes the congenital cranial dysinnervation disorders (CCDDs).4

Collaborating with clinicians worldwide, we have ascertained study participants with mendelian syndromes that include variable forms of congenital
ophthalmoplegia and enrolled these families into our ongoing study. We sort these syndromes by phenotype, considering whether we thought the primary abnormality fell in the distribution of oculomotor, trochlear, or abducens innervated extraocular muscles (Table). We use linkage analysis to map the phenotypes and positional cloning techniques to identify the mutated gene. Once the gene and its spectrum of mutations is defined, we study the role of these normal and abnormal gene products in neurodevelopment. In this review, I highlight the genetic, neuroanatomic, and neurodevelopmental bases of 3 of these disorders: horizontal gaze palsy with progressive scoliosis (HGPPS) and the homeobox A1 (HOXA1) syndromes. They are unable to abduct their eyes and, when they attempt to look inward, there is narrowing of the palpebral fissure secondary to retraction of the globe into the orbit. In the early 1980s, 2 autopsies of individuals with Duane syndrome were conducted at The Johns Hopkins University,6,7 Baltimore, Md, which revealed absence of the abducens nerve, absence of the motor neurons in the abducens nucleus, and aberrant innervation of the lateral rectus muscle by branches of the oculomotor nerve. These autopsies were some of the earliest evidence that the fibrosis syndromes may indeed be neurogenic. Consistent with the Duane syndrome autopsy findings, when high-resolution magnetic resonance (MR) imaging sections through the pons were obtained in a patient with BSAS, no exiting abducens nerve was identified. Patients with BSAS have additional congenital anomalies, including severe bilateral sensory-neural hearing loss secondary to the absence of the cochlea, vestibule, and semicircular canals. This rudimentary inner ear defect is referred to as a common cavity deformity and is often accompanied by absence of the eighth cranial nerve.7 Skull-based computed tomography revealed that most patients had unilateral or bilateral hypoplastic or absent carotid canals, and MR angiograms revealed a variety of internal carotid artery malformations, including bilateral absence of the internal carot-

### THE HUMAN HOXA1 SYNDROMES

The human HOXA1 story began in our laboratory when collaborators identified an autosomal recessive syndrome that included abnormal ocular motility in 4 Saudi Arabian pedigrees.7 We subsequently named this BSAS in recognition of the collaborators who defined the phenotype. Bosley-Salih-Alorainy syndrome is recessive, requiring an individual to harbor 2 mutated copies of the gene to express the phenotype, and all 4 of the Saudi pedigrees were consanguineous, with affected individuals being the offspring of first- or second-cousin marriages. Once this phenotype was defined, we realized we had previously enrolled a Turkish patient with similar findings who was the only child of his first-cousin parents.

Individuals with BSAS are born with bilateral Duane syndrome. They are unable to abduct their eyes and, when they attempt to look inward, there is narrowing of the palpebral fissure secondary to retraction of the globe into the orbit. In the early 1980s, 2 autopsies of individuals with Duane syndrome were conducted at The Johns Hopkins University, Baltimore, Md, which revealed absence of the abducens nerve, absence of the motor neurons in the abducens nucleus, and aberrant innervation of the lateral rectus muscle by branches of the oculomotor nerve. These autopsies were some of the earliest evidence that the fibrosis syndromes may indeed be neurogenic. Consistent with the Duane syndrome autopsy findings, when high-resolution magnetic resonance (MR) imaging sections through the pons were obtained in a patient with BSAS, no exiting abducens nerve was identified. Patients with BSAS have additional congenital anomalies, including severe bilateral sensory-neural hearing loss secondary to the absence of the cochlea, vestibule, and semicircular canals. This rudimentary inner ear defect is referred to as a common cavity deformity and is often accompanied by absence of the eighth cranial nerve.7 Skull-based computed tomography revealed that most patients had unilateral or bilateral hypoplastic or absent carotid canals, and MR angiograms revealed a variety of internal carotid artery malformations, including bilateral absence of the internal carot-

### Table. The Congenital Cranial Dysinnervation Disorders

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Abbreviations: ABDS, Athabascan brainstem dysgenesis syndrome gene; AD, autosomal dominant; AR, autosomal recessive; BSAS, Bosley-Salih-Alorainy syndrome gene; CFEOM, congenital fibrosis of the extraocular muscles; HOXA1, homeobox A1; OMIM, Online Mendelian Inheritance in Man; ellipses, information not known.


†Parentheses indicate that this is a proposed disease gene in 1 patient that has not been confirmed in additional patients.
The congenital cranial dysinnervation disorders (CCDDs). Schematic representation of extraocular muscle (EOM) innervation in healthy individuals and in those with 3 of the CCDDs. In the normal wild-type state (A), the globe is moved by the 4 recti and 2 oblique EDMs, and the eyelid is elevated by the levator palpebrae superiors (LPS). Throughout the illustration, the oculomotor nucleus (blue) is composed of 5 motor subnuclei that send their axons in the oculomotor nerve (blue) and divide into a superior branch that innervates the LPS and superior rectus (SR) muscles, and an inferior branch that innervates the medial rectus (MR), inferior rectus (IR), and inferior oblique (IO) muscles. The trochlear nucleus (brown) sends its axons in the trochlear nerve (brown) to innervate the superior oblique (SO) muscle. The abducens nucleus (green) is composed of motoneurons and interneurons. The motoneurons send their axons in the abducens nerve (green) to innervate the lateral rectus (LR) muscle. The interneurons send their axons in the medial longitudinal fasciculus (MLF) (green), which crosses the midline to innervate neurons in the MR subnucleus of the contralateral oculomotor nucleus. In addition, crossed input onto the abducens nucleus is shown (magenta). The pathology of the human homeobox A1 (HOXA1) syndromes (BSAS/ABDS [Bosley-Salih-Alorainy syndrome/Athabascan brainstem dysgenesis syndrome]) (B), horizontal gaze palsy with progressive scoliosis (HGPPS) (C), and congenital fibrosis of the extraocular muscles type 1 (CFEOM1) (D) are presented. Aberrant or missing nuclei, nerves, and muscles are shown with hatched vs solid lines. The region of the rhombomere defects in the homeobox A1–related syndromes is hatched in red. The oculomotor, trochlear, and abducens nerves and the medial longitudinal fasciculus are labeled only when abnormal. Adapted with permission from *Pediatric Research.* 

**Figure.** The congenital cranial dysinnervation disorders (CCDDs). Schematic representation of extraocular muscle (EOM) innervation in healthy individuals and in those with 3 of the CCDDs. In the normal wild-type state (A), the globe is moved by the 4 recti and 2 oblique EDMs, and the eyelid is elevated by the levator palpebrae superiors (LPS). Throughout the illustration, the oculomotor nucleus (blue) is composed of 5 motor subnuclei that send their axons in the oculomotor nerve (blue) and divide into a superior branch that innervates the LPS and superior rectus (SR) muscles, and an inferior branch that innervates the medial rectus (MR), inferior rectus (IR), and inferior oblique (IO) muscles. The trochlear nucleus (brown) sends its axons in the trochlear nerve (brown) to innervate the superior oblique (SO) muscle. The abducens nucleus (green) is composed of motoneurons and interneurons. The motoneurons send their axons in the abducens nerve (green) to innervate the lateral rectus (LR) muscle. The interneurons send their axons in the medial longitudinal fasciculus (MLF) (green), which crosses the midline to innervate neurons in the MR subnucleus of the contralateral oculomotor nucleus. In addition, crossed input onto the abducens nucleus is shown (magenta). The pathology of the human homeobox A1 (HOXA1) syndromes (BSAS/ABDS [Bosley-Salih-Alorainy syndrome/Athabascan brainstem dysgenesis syndrome]) (B), horizontal gaze palsy with progressive scoliosis (HGPPS) (C), and congenital fibrosis of the extraocular muscles type 1 (CFEOM1) (D) are presented. Aberrant or missing nuclei, nerves, and muscles are shown with hatched vs solid lines. The region of the rhombomere defects in the homeobox A1–related syndromes is hatched in red. The oculomotor, trochlear, and abducens nerves and the medial longitudinal fasciculus are labeled only when abnormal. Adapted with permission from *Pediatric Research.*

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and ABDS, are the first human mendelian syndromes to result from homozygous mutations in a HOX gene and from mutations in a 3′ HOX gene critical for the development of the head and central nervous system. The internal carotid artery and cardiac outflow defects found in these patients have not been reported in the mouse models; targeted examinations of these mice should reveal whether these were missed or whether the expression of human HOXA1 differs from that of mouse Hoxa1. The mental retardation and autism in the patients with ABDS and BSAS is also notable. Expression of HOXA1 has not been reported above the developing brainstem and, if this holds true, it suggests that proper brainstem development is essential to later cognitive development.

HORIZONTAL GAZE PALSY WITH PROGRESSIVE SCOLIOSIS

Similar to BSAS/ABDS, HGPPS is an autosomal recessive syndrome most often found in offspring of consanguineous parents, and individuals with this syndrome are born with restricted horizontal gaze. In HGPPS, the congenital gaze restriction is co-inherited with progressive scoliosis, which can begin in the first year of life and typically becomes severe in the first decade.12,13 Horizontal gaze palsy with progressive scoliosis was first mapped to 11q23-q25 in a Saudi Arabian and an Indian pedigree by members of the Jen laboratory at the University of California–Los Angeles.12 We had enrolled a pedigree that also mapped this region and significantly reduced the critical region, and so our 2 laboratories established a collaboration to study HGPPS and identify the mutated disease gene.13

Neuroimaging and electrophysiological studies of HGPPS revealed unexpected findings.13 Magnetic resonance imaging of affected individuals from pedigrees that were otherwise asymptomatic, despite this extensive hindbrain and spinal cord miswiring, this suggests that these axons find their intended target, albeit on the ipsilateral rather than contralateral side. In summary, HGPPS represents a later developmental defect than the HOXA1 syndromes and demonstrates that horizontal gaze abnormalities can result from aberrant axonal targeting of cranial motoneurons.

CFEOM TYPE 1

The toddler I met as a neurology resident was born with bilateral ptosis and bilateral ophthalmoplegia with his eyes fixed downward and has a CCDD syndrome we now refer to as CFEOM1. We gained significant insight into CFEOM1 by conducting the postmortem examination of the brain and orbit of an elderly affected family member of the toddler.16 We found that the superior division of the oculomotor nerve and the corresponding motoneurons in the oculomotor nucleus were absent. This branch of the oculomotor nerve innervates the levator palpebrae superioris and superior rectus muscles that elevate the eyelid and eye, respectively, and these muscles were aplastic. This suggested that the etiology of CFEOM1 may be the oculomotor analogue of Duane syndrome, and both may be neurogenic in nature.

We mapped the CFEOM1 gene to the pericentromeric region of chromosome 12 and, after enrolling many additional pedigrees with CFEOM1 from around the world, identified the mutated gene as KIF21A, a member of the kinesin family of molecular motors.17 Kinesins transport cargo along microtubules in an anterograde direction. They are responsible for anterograde axonal transport in neurons, moving cargo from the neuronal cell body to the growing or mature synapse. There are at least 45 human kinesins that transport different cargoes, including mitochondria, vesicles, and protein complexes. The structure of the KIF21A kinesin is predicted to be similar to classic kinesin, with a motor, tail, and stalk domain. The motor domain interacts with tubulin; typically, 2 kinesins homodimerize or heterodimerize, allowing the 2 motor domains to “walk” down the microtubule tract. The tail domain is where the cargo is typically carried, and KIF21A and KIF21B are the only kinesins known to have a series of WD40 repeats in their tails. The cargo of KIF21A, however, is not yet known. The stalk domain is a flexible connection between the
tail and the motor that contains several coiled-coil regions implicated in protein-protein interactions. These domains are likely to be important to KIF21A dimerization, and the coiled-coil domains closer to the tail may also interact with specific cargo.

Remarkably, among the 61 probands with CFEOM1 for whom KIF21A mutations have been published, only 8 different KIF21A mutations, altering only 4 amino acids, have been reported. Fifty-nine of the probands harbor mutations that alter 1 of 3 amino acid residues in the third coiled-coil region of the stalk, and, of these, all but 5 probands have mutations that alter the arginine at amino acid residue 954. The remaining 2 unrelated probands harbor a mutation that alters an amino acid residue at the end of the motor domain.17 The nature of these mutations suggests that the CFEOM1 phenotype results from altered function of KIF21A rather than from loss of function of 1 allele. These mutations may result in an inability of KIF21A to dimerize normally or may disrupt its ability to bind to specific cargo critical to the development of oculomotor axons. Future work should lead to an understanding of how these mutations disrupt KIF21A function to result in the CFEOM1 phenotype. Identification of the KIF21A cargo may provide insight into the normal and abnormal development of the oculomotor nerve. Our current hypothesis, however, is that CFEOM1 results from absent or aberrant delivery of a cargo from the motoneuron cell body to the growth cone that is critical to the development of the oculomotor nerve.

CONCLUSIONS

The identification and analysis of pedigrees with rare congenital oculomotility syndromes has led to the definition of the CCDDs. These disorders appear to result from mutations in genes that are essential to the normal development and/or connectivity of cranial motoneurons. These genetic defects can lead to disruption in early motoneuron development, aberrant axonal targeting onto motoneurons, and aberrant axonal targeting onto the extraocular muscles. The identification and study of additional CCDD genes are likely to continue to provide knowledge about the pathogenesis of oculomotor disease and development of the human brainstem.

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REFERENCES


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