

Abnormalities of the Oculomotor Nerve in Congenital Fibrosis of the Extraocular Muscles and Congenital Oculomotor Palsy

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PURPOSE. High-resolution magnetic resonance imaging (MRI) can now directly demonstrate innervation to extraocular muscles and quantify optic nerve size. A quantitative MRI technique was developed to study the oculomotor nerve (CN3) and applied to congenital fibrosis of extraocular muscles (CFEOM) and congenital oculomotor palsy.

METHODS. The subarachnoid portions of the CN3s were imaged with a 1.5-T MRI scanner and conventional head coils, acquiring heavily T₂-weighted oblique axial planes 1-mm thick and parallel to the optic chiasm. Thirteen normal subjects, 14 with CFEOM, and 3 with congenital CN3 palsy were included. Digital image analysis was used to measure CN3 diameter, which was correlated with motility findings.

RESULTS. In CFEOM, CN3 diameter was bilaterally subnormal in eight subjects, unilaterally subnormal in three subjects, and normal in three subjects. Mean \pm SD CN3 diameter in CFEOM was 1.14 ± 0.61 mm, significantly smaller than the diameter in normal subjects, which measured 2.01 ± 0.36 mm ($P < 0.001$). CN3 diameter variably correlated with clinical function. One subject with congenital CN3 palsy showed bilateral CN3 hypoplasia, but CN3 diameter was normal in two other subjects with congenital CN3 palsy.

CONCLUSIONS. Unilateral or bilateral hypoplasia of CN3 is quantitatively demonstrable using MRI in many cases of CFEOM and occasionally in congenital CN3 palsy. Variations in CN3 diameter in CFEOM and congenital CN3 palsy suggest mechanistic heterogeneity of these disorders that may be clarified by further imaging and genetic studies. (*Invest Ophthalmol Vis Sci*. 2007;48:1601-1606) DOI:10.1167/iovs.06-0691

Since the discovery of x-rays, imaging has been useful in diagnosis of disease. Although computed x-ray tomography (CT) or magnetic resonance imaging (MRI) have been widely used in many specialties, the use of imaging has been limited in evaluation of strabismus. Neuropathic strabismus has been conventionally diagnosed by clinical ocular motility. In the evaluation of neuropathic strabismus, the head is frequently

imaged to find large brain abnormalities and less often to evaluate cranial nerves (CNs) and extraocular muscles (EOMs).

Technical improvements in MRI now afford opportunity for detailed study of the functional anatomy of EOMs and nerves in the orbits of living subjects,¹ and CNs can be imaged against the surrounding cerebrospinal fluid as they exit the brain stem.² Imaging by MRI has been used to demonstrate various diseases in the brain and orbit, including abnormalities of the rectus pulleys,³⁻⁹ CNs in neuropathic strabismus,^{5,10} and optic nerve size.^{5,11,12} This study was conducted to examine the utility of high-resolution MRI for the quantitative measurement of the oculomotor nerves (CN3s) at the midbrain in subjects having congenital neuropathic strabismus, including congenital fibrosis of extraocular muscles (CFEOM) and congenital oculomotor (CN3) palsy, and to correlate CN3 size with clinical findings.

CFEOM is a typically nonprogressive disorder of ocular motility including blepharoptosis. The term of "congenital cranial dysinnervation disorders" (CCDDs) has been proposed to include several congenital neuromuscular diseases characterized by abnormal eye, eyelid, and/or facial movement.¹³ There has been an ongoing debate as to whether CFEOM is a primary myopathic or neurogenic disorder. The classic concept was of primary myopathy based on the clinical finding of mechanical restriction on forced duction testing, with pathologic reports of EOM fibrosis.¹⁴⁻¹⁸ The alternative primary neurogenic hypothesis was based on the frequent association of CFEOM with Marcus-Gunn jaw-winking phenomenon and synergistic divergence¹⁹⁻²³ and an absence of superior division of CN3 and its corresponding α motor neuron in an autopsy of a patient with CFEOM.²⁴ Marcus-Gunn jaw-winking is a synkinesis associating jaw movements with upper lid position, due to misinnervation of the levator palpebrae superioris by trigeminal innervation normally destined for a muscle of mastication. The recent findings that gene mutation in the developmental kinesin *KIF21A* is the cause of CFEOM1 and mutation in *PHOX2A* is a cause of CFEOM2²⁵ support the neuropathic hypothesis.²⁶⁻²⁹ According to the neuropathic hypothesis, CFEOM1 results from primary maldevelopment of CN3, CFEOM2 from CN3 and trochlear nerve maldevelopment, and Duane's retraction syndrome (DRS) from abducens nerve (CN6) maldevelopment.^{30,31} Congenital CN3 palsy may be considered a variant of CFEOM if both are categorized within the newly defined concept of CCDDs.

The present study was conducted with high-resolution MRI to evaluate CN3 and its brain stem origin in congenital CN3 palsy and CFEOM and to correlate the findings with ocular motility in the same subjects.

METHODS

High-resolution MRI was performed in volunteers who gave written informed consent to a protocol conforming to the Declaration of Helsinki and approved by governing institutional review boards. Paid normal control subjects were recruited by advertising, and subjects

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with CFEOM were recruited through an ongoing genetic study. Subjects with congenital CN3 were recruited from the clinics and from ongoing genetic studies. All normal and affected subjects underwent complete ophthalmic examination of corrected visual acuity, ocular motility, eyelid structure and function, binocular alignment, anterior segment anatomy, and ophthalmoscopy. Ophthalmic histories were obtained from subjects, with corroboration of previous ocular surgeries from operative records when possible. In addition to the preceding examinations, subjects with CFEOM and CN3 palsy also underwent measurement of palpebral fissure height and levator function, with video recording of ocular versions, eyelid motility, and an attempt to elicit Bell's phenomenon of involuntary supraduction on attempted eyelid closure.

The diagnosis of CFEOM required that subjects be born with non-progressive ophthalmoplegia and ptosis.²⁷ We classify CFEOM by clinical ocular motility findings. Classic CFEOM is phenotypically defined to be CFEOM1, typified by congenital bilateral ophthalmoplegia and blepharoptosis, with the eyes partially or completely fixed in infraduction, with supraduction limited to below central gaze.^{24,30,32} Molecular genetic confirmation of the cause of CFEOM1 was obtained in some of the current subjects with CFEOM1.⁵

There are also nonclassic phenotypes of CFEOM. Subjects with unilateral CFEOM, or who could supraduct one or both eyes above central gaze were classified as having CFEOM3. If one family member satisfied criteria for CFEOM3, we classified all other members of that family as having CFEOM3.³⁰ CFEOM2 is very rare, having to date been found only in consanguineous families in the Middle East.^{25,33,34} Since we could not study any subjects with CFEOM2, we classified all subjects with atypical CFEOM as having as CFEOM3.

For subjects who did not exhibit the CFEOM phenotype, we classified those who were born with deficient elevation, adduction, and/or depression of the globe with or without ptosis as having congenital CN3 palsy. We excluded from the category of subjects with congenital CN3 palsy those who exhibited concurrent abducens or superior oblique palsy.

Orbital and brain MRI was performed with a 1.5-T scanner (Signa; General Electric, Milwaukee, WI). Imaging was performed with an array of surface coils embedded in a transparent face mask (Medical Advances, Milwaukee, WI) incorporating illuminated fixation targets, to avoid eye motion artifact.^{35,36} The head was stabilized in the supine position by tightly fastening the surface coil mask to the face with headbands and fixing the mask to the scanner gantry with foam cushions and tape. These measures avoided head rotation during scanning. An adjustable array of illuminated fixation targets was secured in front of each orbit with the center target in subjective central position for each eye and, in selected cases, in secondary and tertiary gaze positions. Imaging at and posterior to the orbital apex in some subjects was performed using the standard head coil. When surface coils were used, images of 2-mm thickness in a matrix of 256×256 were obtained over a field of view of 6 to 8 cm for a resolution in plane of 234 to $312 \mu\text{m}$, respectively. Axial scout images were obtained, as well as quasicoronal images perpendicular to the long axis of the orbit, and quasisagittal images parallel to the long axis of the orbit. Heavily T_2 -weighted (know as FIESTA or CISS) imaging of the skull base region was conducted in 60 contiguous 1-mm-thick slices in the plane of the optic chiasm and major cranial nerves that innervate the orbit.^{2,5,37} In-plane resolution was $195 \mu\text{m}$ over a 10-cm field of view (matrix 512×512) with 10 excitations.

Digital MRI images were transferred to computer (Macintosh; Apple Computer, Cupertino, CA), converted into 8-bit tagged image file format (TIFF), and quantified with the program Image J 1.34s (available by ftp at zippy.nimh.nih.gov/ or at <http://rsb.info.nih.gov/ij/>; developed by Wayne Rasband, National Institutes of Health, Bethesda, MD). Careful examination was made of multiple contiguous sections, including CN3 at the midbrain. We measured the widest CN3 diameter in consecutive planes with Image J.

RESULTS

Normal Subjects

Thirteen normal volunteers, 3 male and 10 female, underwent MRI. Control subjects were of age 22.2 ± 4.3 years (mean \pm SD; range, 17–33). All control subjects had normal ocular and lid motility and visual acuity in each eye correctable to 0 logarithm of the minimum angle resolvable in arc min [log-MAR] (20/20) or better. In all normal subjects, it was possible in oblique, axial heavily T_2 -weighted MRI images to resolve and measure the diameter of CN3 in multiple adjacent image planes (Fig. 1). Mean CN3 diameter in normal subjects was $2.01 \pm 0.36 \text{ mm}$ (\pm SD, Fig. 2).

Neuropathic Strabismus

Congenital Fibrosis of the Extraocular Muscles. Characteristics of subjects with CFEOM are summarized in Table 1. These 14 individuals represent eight pedigrees. Subjects 1 and 4 had CFEOM1 and harbored R954W and R954Q amino acid substitutions, respectively, in *KIF21A*.⁵ Subjects 8 and 9 met the clinical criteria for CFEOM1 but with additional clinical features not reported with *KIF21A* mutations and molecular genetic testing did not identify a *KIF21A* mutation (Engle EC, unpublished data, 2006). Subjects 2, 3, 5, 6 7 and 10 to 14 had CFEOM3, and all but subject 5 were tested for *KIF21A* mutations and were negative. Nine subjects had bilateral congenital blepharoptosis and bilateral congenital ophthalmoplegia. Three subjects had unilateral congenital ptosis and unilateral congenital ophthalmoplegia. Two subjects exhibited unilateral ptosis and bilateral congenital ophthalmoplegia. Atrophy of the levator palpebrae superioris (LPS) and superior rectus EOMs, small or absent orbital motor nerves, and significant reduction in optic nerve size associated with CFEOM were observed and have been described in detail in a previous paper.⁵

Most ophthalmoplegic eyes showed hypoplasia of the ipsilateral subarachnoid CN3. In eight subjects with CFEOM, CN3 was bilaterally hypoplastic (Fig. 3). Unilateral CN3 hypoplasia was observed in subjects 2, 6, and 14. In subject 2, unilateral right blepharoptosis and ophthalmoplegia correlated with unilateral right CN3 hypoplasia. In subjects 6 and 14, however, CN3 hypoplasia was ipsilateral to the unilateral blepharoptosis, whereas ophthalmoplegia was bilateral. Bilaterally normal CN3 diameter was found in subjects 8, 9, and 13. Subjects 8 and 9 are from one pedigree, and although they met the criteria for CFEOM1, they also exhibited total ophthalmoplegia, bilateral facial palsy, and bilaterally normal CN3s. Subject 13 had CFEOM3 and bilaterally normal sized CN3, yet left unilateral blepharoptosis and ophthalmoplegia.

Subject 4 with CFEOM1 had bilateral blepharoptosis, and A-pattern exotropia with convergence on attempted supraduction and divergence on attempted infraduction. Subject 4's palpebral fissure narrowed in adduction and widened in abduction. She could not supraduct either eye even to the midline. Mean CN3 diameter in CFEOM was $1.12 \pm 0.73 \text{ mm}$, significantly smaller than normal diameter of $2.01 \pm 0.36 \text{ mm}$ ($P < 0.001$, Fig. 2).

Subject 5, a 15-year-old boy with left CFEOM3, showed absence of the right CN3 at the midbrain. He had undergone ptosis surgeries three times on the left eye, and strabismus surgeries twice. He had normal ocular motility in his right eye, and nearly total ophthalmoplegia in his left. His pupils were equal and reacted normally to light. Although we could not demonstrate subject 5's right CN3 at the midbrain, the right inferior division of CN3 and nerves to the right medial rectus and inferior rectus muscles were well defined in an MRI of the orbit. Subject 5's most recent MRI showed large acoustic neuromas and multiple other intracranial tumors, suggesting neurofibromatosis type 2.³⁸

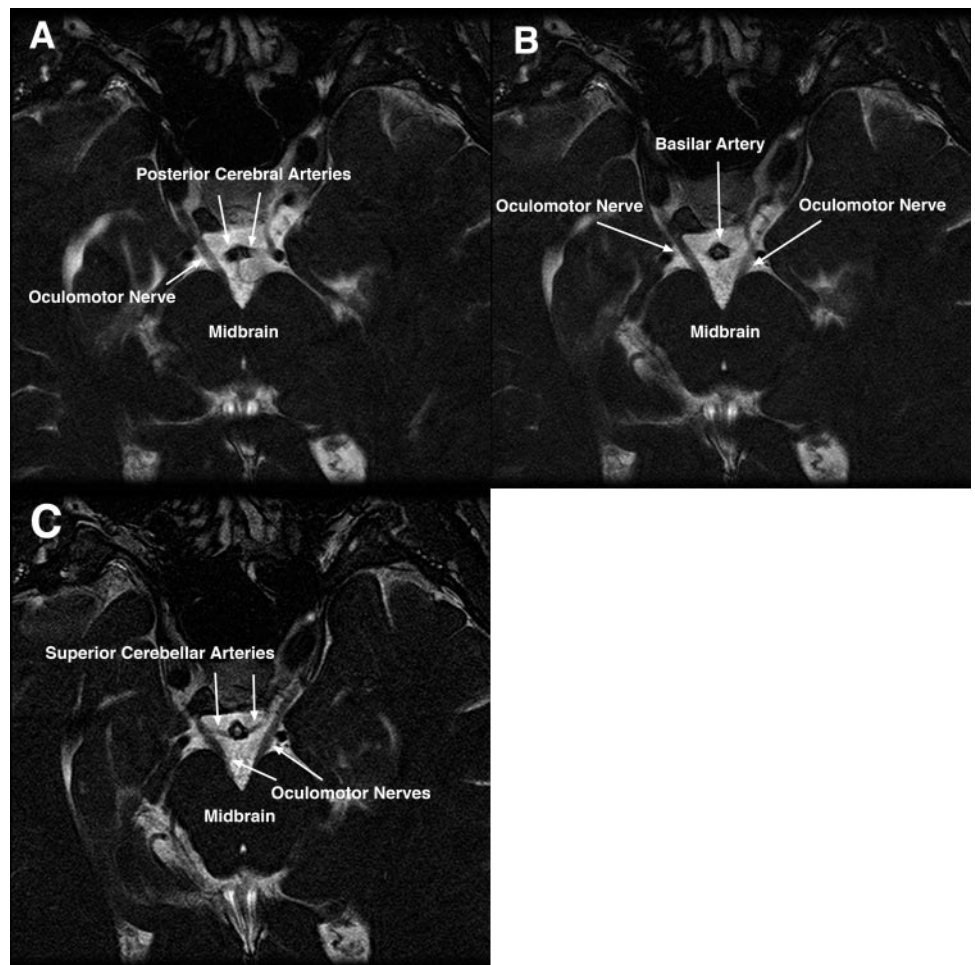


FIGURE 1. In this set of three contiguous 1-mm-thick oblique axial planes parallel to the optic chiasm, normal oculomotor nerves are easily found exiting the brain stem between superior cerebellar arteries and posterior cerebral arteries. Images are in rostral-to-caudal sequence.

Subject 6, a 26-year-old woman, had limited elevation, adduction, and depression of the left eye and only limited elevation on adduction in the right eye. Subject 6's MRI showed left

but not right CN3 hypoplasia compatible with the asymmetric ocular motility. Intraorbital branches of the inferior division of CN3 were readily identifiable in Subject 6's right but not left orbit.

Congenital Oculomotor Palsy. Of three subjects with congenital CN3 palsy, only subject 15, a 21-year-old woman with congenital exotropia, showed bilateral hypoplasia of the subarachnoid portion of CN3 (Fig. 4). She exhibited marked limitation of adduction and depression in her right eye and moderate limitation of depression and adduction in her left eye. Bell's phenomenon was present, and the pupils were equal in diameter. The other two patients with congenital CN3 palsy showed normal CN3 diameters.

DISCUSSION

Orbital imaging, particularly using MRI, has broadened understanding of the anatomy and physiology of the EOMs and their associated connective tissues.^{39,40} In living humans, it is now possible to image at near microscopic resolution the physiologic changes associated with conjugate eye movements, vergence, and accommodation.⁴¹ Ophthalmologists have traditionally diagnosed congenital neuropathic strabismus relying on the ocular motility examination. In this study, we were able to quantify CN3 diameter at the midbrain of normal subjects and subjects with congenital neuropathic strabismus.

The CN3 is easily imaged as it exits the midbrain (Fig. 1). Most subjects with CFEOM studied here exhibited CN3 hypoplasia. Hypoplasia of CN3 supports the neuropathic rather than myopathic origin of CFEOM. Nevertheless, direct imaging of CN3 indicates substantial heterogeneity in this neuropathol-

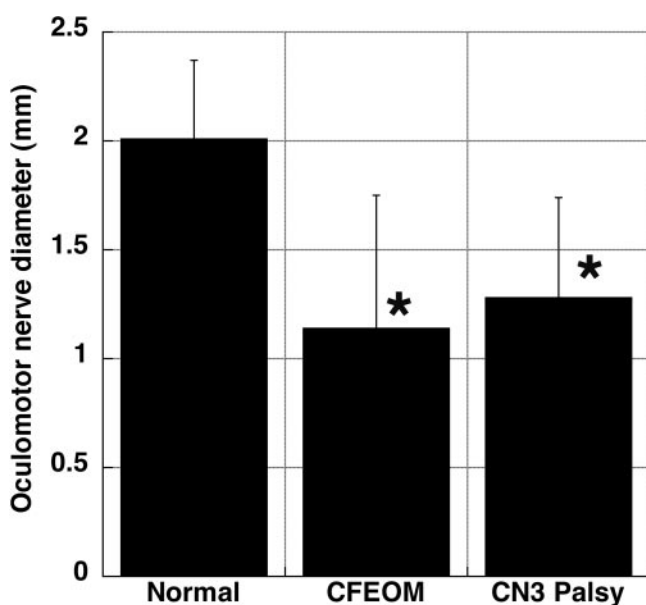


FIGURE 2. Mean diameter of the subarachnoid portion of the oculomotor nerve (CN3). *Significantly subnormal for CFEOM and congenital CN3 palsy ($P < 0.001$), but the abnormality in CN3 palsy was noted only in subject 15.

TABLE 1. Characteristics of Subjects with CFEOM

Subject	Pedigree	Age (y)	Sex	<i>KIF21A</i> Mutations		Ptosis	Ophthalmoplegia	Other Abnormalities	CN3 Diameter (mm)	
				Type	Present				Right	Left
1	A	28	M	CFEOM1	+	Bilateral	Bilateral	Nystagmus	0.44*	0.35*
2	B	39	M	CFEOM3	—	Right	Right	Right amblyopia	0.83*	1.41
3	B	13	F	CFEOM3	—	Bilateral	Bilateral	Bilateral Marcus-Gunn jaw-winking	0.98*	1.05*
4	C	35	F	CFEOM1	+	Bilateral	Bilateral	Nystagmus	0.44*	0.28*
5	D	15	M	CFEOM3	N/A	Left	Left	Nystagmus; bilateral retinal folds; left cataract; acoustic neuroma	0*	1.05*
6	E	26	F	CFEOM3	—	Left	Bilateral		2.01	1.05*
7	E	57	F	CFEOM3	—	Bilateral	Bilateral	Left high myopia	0.87*	0.70*
8	F	15	M	CFEOM1	—	Bilateral	Bilateral	Congenital facial palsy; retrognathia; bilateral maxillary hypoplasia	2.01	2.11
9	F	13	M	CFEOM1	—	Bilateral	Bilateral	Congenital facial palsy; high arch palate; supernumerary molar tooth	2.36	2.18
10	G	67	F	CFEOM3	—	Bilateral	Bilateral	Right cataract	0.55*	0.70*
11	G	48	F	CFEOM3	—	Bilateral	Bilateral		1.14*	1.25*
12	H	32	M	CFEOM3	—	Bilateral	Bilateral	Right amblyopia	1.14*	1.14*
13	H	39	F	CFEOM3	—	Left	Left	DVD; left amblyopia	1.58	1.49
14	H	17	M	CFEOM3	—	Bilateral	Bilateral	Nystagmus; right optic nerve hypoplasia	1.25*	1.49

+, presence and —, absence of detected *KIF21A* mutation. N/A, mutation testing was not performed; DVD, dissociated vertical deviation.

* Significantly subnormal CN3 diameter.

ogy, and the possibility of a primary myopathy cannot be excluded entirely.

In CFEOM, the CN3 diameter at the midbrain was poorly correlated with clinical CN3 function. Notable absence of this correlation was evident in subjects 5, 8, 9, and 13. In subject 5 with CFEOM, we could not demonstrate the right CN3 at the midbrain despite normal ocular motility. However, subject 5 had bilateral acoustic neuromas and other intracranial tumors suggestive of neurofibromatosis 2, with distortion of the brain stem, and normal CN3 branches were evident in subject 5's right orbital MRI. This finding suggests that CN3 may have

exited the brain stem in some atypical location in Subject 5. Subjects 8 and 9 were unusual cases combined with facial paralysis. Subject 13 had a normal-sized CN3.

Although CFEOM is typically unaccompanied by other abnormalities, there have been several reports of CFEOM in association with central nervous system disorders. Previous reports include patients with sporadic CFEOM in association with Marcus-Gunn jaw-winking phenomenon,^{20–22} synergistic divergence,^{20,23} and monocular elevation during tooth brushing due to aberrant regeneration between the nerve to the superior rectus and the trigeminal nerve.⁴² In this study, two subjects exhibited bilateral facial paralysis. There have been several reports of CFEOM with Möbius syndrome, a congenital facial palsy with abduction deficit.^{34,43} It is possible that CFEOM and Möbius syndrome have etiologic overlap. However, the normal CN3 in CFEOM with facial palsy suggests that the condition may have a different etiology than typical CFEOM.

The term CCDDs has been proposed to include a group of congenital neuromuscular diseases characterized by abnormal eye, eyelid, and/or facial movement.¹³ The CCDDs includes DRS, CFEOM, Möbius syndrome, HGPPS, congenital ptosis, congenital CN3 palsy, congenital trochlear palsy, and congenital facial palsy. These CCDDs may share similar developmental etiologies, but the shared etiologies may nevertheless be diverse.

Though a significantly smaller mean CN3 diameter than normal was observed in congenital CN3 palsy, this effect was noted in only one of three such subjects who had markedly hypoplastic CN3 at the midbrain. Two cases of congenital CN3 palsy had normal subarachnoid CN3 size. Nevertheless, the finding of even occasional subarachnoid CN3 hypoplasia similar to those in CFEOM suggests that some cases of congenital CN3 palsy may be variants of CFEOM. It would be informative

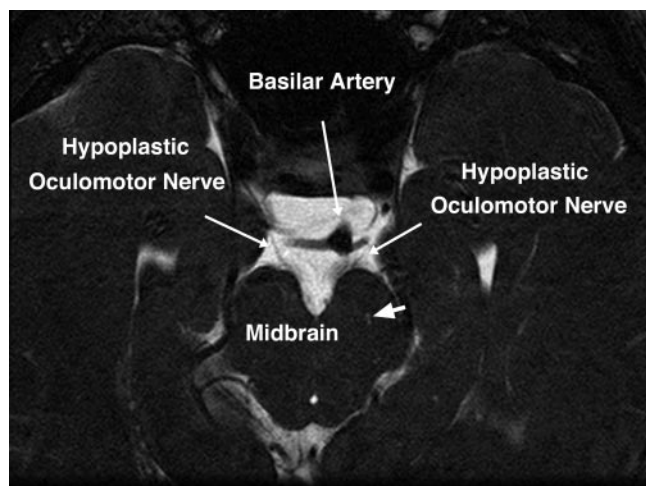


FIGURE 3. Oblique, axial heavily T₂-weighted MRI of subject 4 with classic CFEOM shows bilaterally hypoplastic oculomotor nerves at the midbrain.

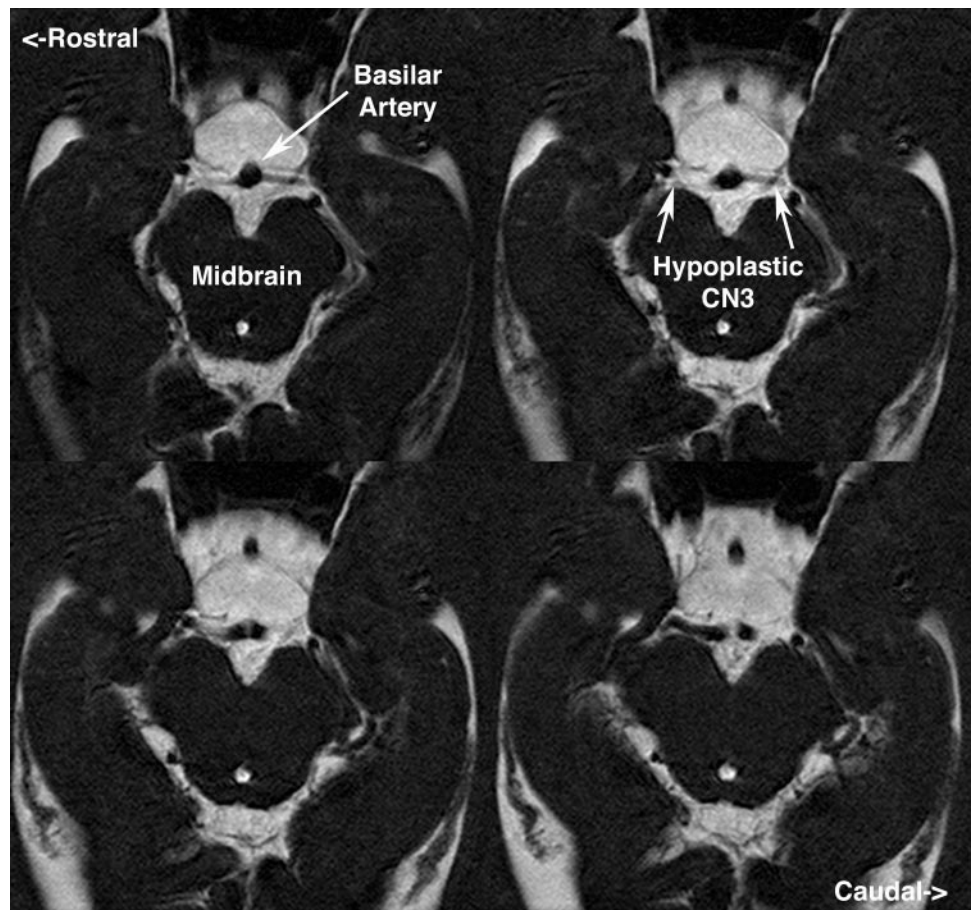


FIGURE 4. Bilateral hypoplasia of the subarachnoid portion of CN3 in subject 15, a 21-year-old woman with congenital oculomotor palsy. Four contiguous, 1-mm-thick MRI oblique axial image planes, obtained with heavy T₂-weighting, are presented in rostral-to-caudal sequence.

to seek genetic evidence of the causative mutations for CFEOM in congenital CN3 palsy. Cases of CFEOM and congenital CN3 palsy are currently diagnosed by clinical findings. In both CFEOM and CN3 palsy, there is marked interindividual variability in CN3 size. In CFEOM3, there may even be differences on the left and right sides in the same subject. This variability suggests that there may be even further heterogeneity in the pathogenesis of these disorders than is currently recognized. This heterogeneity may include both variability of penetrance and expressivity of causative genetic mutations, multiple mutations having differing mechanisms and possible nongenetic causes. Further direct imaging study of CN3 will be helpful in distinguishing the multiple possible pathogenetic mechanisms of CFEOM and congenital CN3 palsy.

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