

Imaging of Cranial Nerves III, IV, VI in Congenital Cranial Dysinnervation Disorders

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Congenital cranial dysinnervation disorders are a group of diseases caused by abnormal development of cranial nerve nuclei or their axonal connections, resulting in aberrant innervation of the ocular and facial musculature. Its diagnosis could be facilitated by the development of high resolution thin-section magnetic resonance imaging. The purpose of this review is to describe the method to visualize cranial nerves III, IV, and VI and to present the imaging findings of congenital cranial dysinnervation disorders including congenital oculomotor nerve palsy, congenital trochlear nerve palsy, Duane retraction syndrome, Möbius syndrome, congenital fibrosis of the extraocular muscles, synergistic divergence, and synergistic convergence.

Key Words: Congenital fibrosis of the extraocular muscles, Congenital trochlear nerve palsy, Duane retraction syndrome, Möbius syndrome, Oculomotor nerve palsy

Congenital cranial dysinnervation disorders (CCDDs) are a group of diseases caused by abnormal development of cranial nerve nuclei or their axonal connections, resulting in aberrant innervation of the ocular and facial musculature [1]. Their diagnosis could be facilitated by the development of high resolution thin-section magnetic resonance imaging (MRI). In this review, we describe a method to visualize cranial nerves (CNs) III, IV, and VI and present imaging findings of CCDDs including congenital CN III palsy, congenital CN IV palsy, Duane retraction syndrome, Möbius syndrome, congenital fibrosis of the extraocular

muscles, synergistic divergence, and synergistic convergence.

How to Visualize CNs III, IV, and VI

Cranial nerve imaging is usually performed using thin-section T2-weighted imaging based on gradient-echo imaging or turbo spin-echo sequence, which shows CNs as dark linear structures in contrast to the high signal intensity of surrounding cerebrospinal fluid [2,3].

For the imaging of CNs III and VI, thin-section T2-weighted imaging is performed in an axial plane at the level of the brainstem including the lower midbrain, pons, and upper medulla oblongata [2]. Image resolution (voxel size) of approximately 0.5×0.5 mm in the x-y plane and 0.7 mm of section thickness is sufficient to identify the nerves

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because the mean diameters of CN III has been reported to be 1.8 to 1.9 mm in a previous MRI study [4]. Although the size of CN VI has not been quantitatively measured in previous MRI studies, its diameter is approximately 1.0 mm according to our experience. Therefore, both nerves can be evaluated with a single imaging method using a 1.5- or 3-tesla MRI system. CN III emerges from the anterior surface of the lower midbrain and courses in the anterolateral direction toward the cavernous sinus (Fig. 1A). CN VI emerges from the pontomedullary sulcus, coursing in the anterosuperior direction toward Dorello's canal (Fig. 1B). In addition, CN VII and CN VIII also merge from the pontomedullary sulcus lateral to the root exit of CN VI (Fig. 1B); therefore, these nerves can be evaluated together.

CN IV should be imaged with higher spatial resolution than the other CNs because it is very small (mean diameter, 0.54 mm) [5]. Therefore, image resolution (voxel size) of approximately 0.3×0.3 mm in the x-y plane and 0.3 mm of section thickness is needed to depict CN IV clearly, which can be achieved only with a 3-tesla MRI system. Imaging should be conducted at the level of the lower midbrain and upper pons, including the inferior margin of the inferior colliculus [5,6]. The oblique axial imaging plane is recommended to be perpendicular to the long axis of the aqueduct (i.e., imaging plane being approximately parallel to the course of the CN IV). CN IV exits from the inferior margin of the inferior colliculus and courses in the anterolateral direction toward the ipsilateral tentorium in the perimesencephalic cistern (Fig. 2).

Imaging Findings of CCDDs

Congenital CN III palsy

MR imaging findings of congenital CN III palsy varied from aplasia, hypoplasia, to normal [7-9]. Lim et al. [8] reported that only one out of three patients showed bilateral CN III hypoplasia or hypoplasia of involved extraocular muscles, with normal-sized CN III noted in the two other patients. Kim and Hwang [9] also found unilateral CN III hypoplasia in one out of three patients and reported that the degree of atrophy of the superior, inferior, and medial recti increased with increasing age in the three patients (Fig. 3A-3C), even though the patient number was too small to reach any conclusions.

In addition, brain abnormalities including developmental brain anomaly in the basal ganglia, optic nerve hypo-/dysplasia, pituitary gland malformation, hypoplasia of the midbrain and corpus callosum, septo-optic dysplasia (de Morsier syndrome), ventricular dilatation, and absence of the septum pellucidum have been reported [10-14].

Congenital CN IV palsy

Sato [15] first reported significantly smaller superior oblique muscle in patients with congenital superior oblique palsy. She also found more severe hypertropia in the primary position and loose tendon on traction test under general anesthesia in patients with smaller superior oblique muscle belly on MRI. Demer et al. [16] also reported absent or atrophic superior oblique muscle in superior oblique palsy. Superior oblique hypoplasia has been reported in familial cases [17].

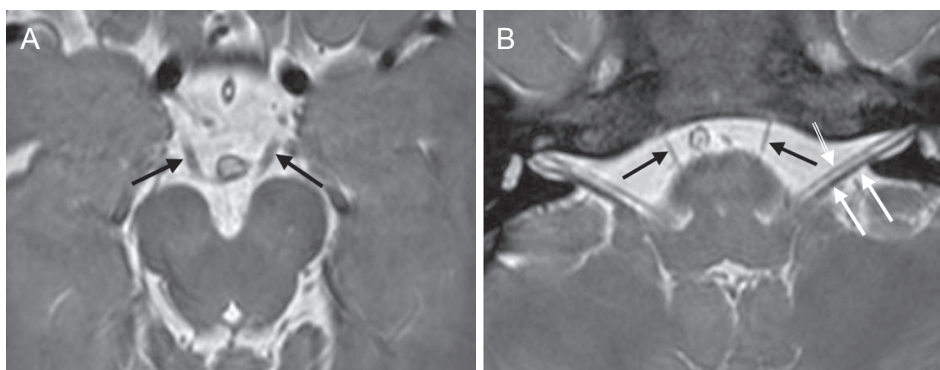


Fig. 1. Normal cranial nerve (CN) III and VI. (A) Axial magnetic resonance image at the level of the lower midbrain shows the cisternal segments of CN III (arrows) as linear dark structures coursing in the anterolateral direction toward the cavernous sinus. (B) Axial magnetic resonance image at the pontomedullary junction shows the cisternal segments of CN VI (black arrows) coursing in the anterosuperior direction toward Dorello's canal. CN VII (double arrow) and CN VIII (white arrows) are also well identified.

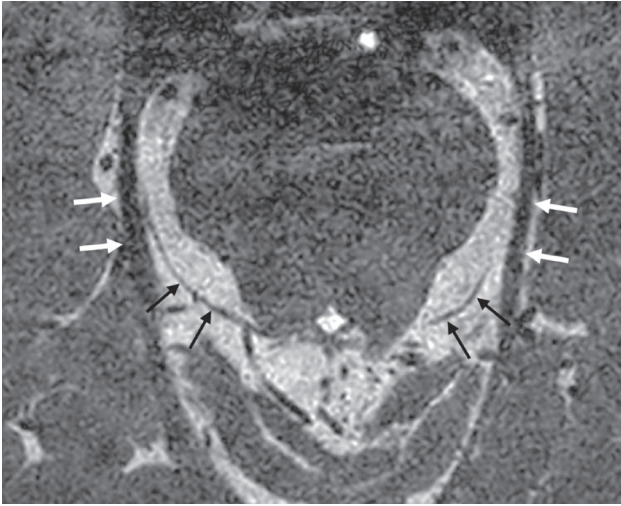


Fig. 2. Normal cranial nerve IV. Axial magnetic resonance image at the level of the inferior colliculus shows the cisternal segments of cranial nerve IV (thin arrows) exiting from the posterior aspect of the brainstem and coursing in the anterolateral direction toward the tentorium (thick arrows).

In 2010, Choi et al. [5] first consistently visualized CN IV using high-resolution 3-tesla (3T) MRI. Kim and Hwang [18] first reported absent CN IV in 10 patients with hypoplasia of the superior oblique muscles with congenital CN IV palsy and asserted that congenital CN IV palsy with superior oblique hypoplasia also can be classified as a CCDD based on documentation with MRI (Fig. 4A-4C). Yang et al. [6] demonstrated that 73% of 97 patients with congenital CN IV palsy showed CN IV aplasia and variable degrees of superior oblique hypoplasia. Patients without CN IV showed more frequent head tilt (96% vs. 81%) at an earlier onset before 1 year of age (80% vs. 29%) and a larger degree of hypertropia on ipsilateral head tilt. Patients with CN IV more frequently showed inferior oblique overaction and dissociated vertical deviation.

Lee et al. [19] performed a morphologic study of CN IV and superior oblique muscle in three groups of control and CN IV palsy with and without CN IV and showed a positive correlation between the diameter of CN IV and the superior oblique volume in controls and in the nonparetic sides of congenital CN IV palsy. However, they found no linear correlation between CN IV diameter and superior oblique volume in the paretic side of congenital CN IV palsy patients with CN IV. In another morphologic study, Yang et al. [20] showed significantly smaller superior oblique muscle volume of the paretic side in patients without CN IV. The cutoff value of the superior oblique muscle

volume ratio for diagnosing CN IV absence was 0.75 (sensitivity, 98.9%; specificity, 95.0%) in patients with congenital CN IV palsy. These results suggest that the ratio of paretic/normal side superior oblique volume could be very useful for predicting CN IV absence in congenital CN IV palsy.

Some patients with congenital CN IV palsy without CN IV can develop diplopia for the first time in their 60s or 70s. A patient could develop diplopia after a phacoemulsification of cataract under topical anesthesia [21]. In such cases, the diagnosis of congenital CN IV palsy could be challenging, and MRI could be helpful for the correct diagnosis [22]. Rarely, a patient without CN IV presents with transient diplopia and might show no significant superior oblique underaction on versions [23]. More interestingly, a patient showed superior oblique underaction on the contralateral side to CN IV aplasia [24]. Therefore, a 3T MRI system with a suitable protocol to visualize CN IV could sometimes be essential for correct diagnosis.

Okanobu et al. [25] reported the lateral rectus split into superior and inferior portions in the posterior orbit in one (4%) of 26 patients with congenital CN IV palsy.

Duane retraction syndrome

Duane's retraction syndrome (DRS) is characterized by congenital abduction limitation, palpebral fissure narrowing on adduction caused by retraction of the globe, and upshoots or downshoots on adduction [26]. There are three types of this syndrome: abduction limitation in type 1 DRS, adduction limitation in type 2 DRS, and limited abduction and adduction in type 3 DRS [27]. There have been pathologic reports of type 1 and 3 DRS in which the abducens nuclei and CN VI were hypoplastic or absent from the brainstem, and the lateral rectus muscle was innervated by CN III branches [28,29]. Parsa et al. [30] first reported the absence of CN VI in a patient with type 1 DRS using MRI. Kim and Hwang [2] first reported that the presence of CN VI depends on the type of DRS: CN VI is absent in type 1 DRS (Fig. 5A and 5B), present in type 2 DRS, and can be either present or absent in type 3 DRS patients. Later, Demer et al. [7] found that CN VI was small or absent in the affected orbit, and CN III was in continuity with CN VI, suggesting aberrant innervation of the lateral rectus muscle by CN III. Six years later, Kim and Hwang [31] found that CN VI was present in all 13 eyes of 12 patients with type 2 DRS. However, Denis et al.

[32,33] found a severely hypoplastic orbital CN VI in a patient with type 2 DRS in whom they could not identify the cisternal portion of CN VI. Yonghong et al. [34] also found a hypoplastic CN VI in a patient with type 2 DRS. However, their image of CN VI before it was abruptly cut off in the cistern appeared to have a normal diameter compared to the contralateral side (serial images were not shown). Yang et al. [35] gathered 31 more patients with type 3 DRS and found that CN VI was absent or hypoplastic in 31 eyes (91%) and present in three eyes (9%). Patients with CN VI showed more adduction limitation than those without CN VI [35]. DRS without CN VI could be familial [36].

MRI could be very helpful for the diagnosis of DRS as follows. Firstly, patients with DRS can be misdiagnosed with traumatic CN VI palsy if abduction limitation is found after head trauma associated with traffic accident [37]. Secondly, the diagnosis of DRS could be more challenging in children if they only show abduction limitation [38]. Thirdly, patients with DRS can suddenly develop diplopia for the first time later in life and could be misdiagnosed with CN VI palsy or Miller-Fisher syndrome [39]. Lastly, patients with DRS can show atypically variable eye

movements [40]. A patient without CN VI showed limited adduction and abduction most of the time, but he could fully abduct the eye with maximal effort, in contrast to most patients with DRS [40]. In patients who did not previously recognize abnormal eye movement, a diagnosis of DRS could be challenging. A patient with DRS might show a severely discrepant abduction limitation between upgaze and downgaze [41]. A patient might show coexistence of different types of DRS and could be misdiagnosed with congenital horizontal gaze palsy [42]. MRI could be very helpful for the differential diagnosis of abduction limitation with such abnormal atypical eye movements.

Okanobu et al. [25] reported the lateral rectus split into superior and inferior portions in the posterior orbit in two (40%) of five patients with DRS.

Duane radial ray syndrome (Okiihiro syndrome, OMIM 607323)

Duane radial ray syndrome is the dominant association of uni-/bilateral DRS with uni-/bilateral dysplasia of thumb, radial bone and artery, and hypoplasia of pectoral muscle.

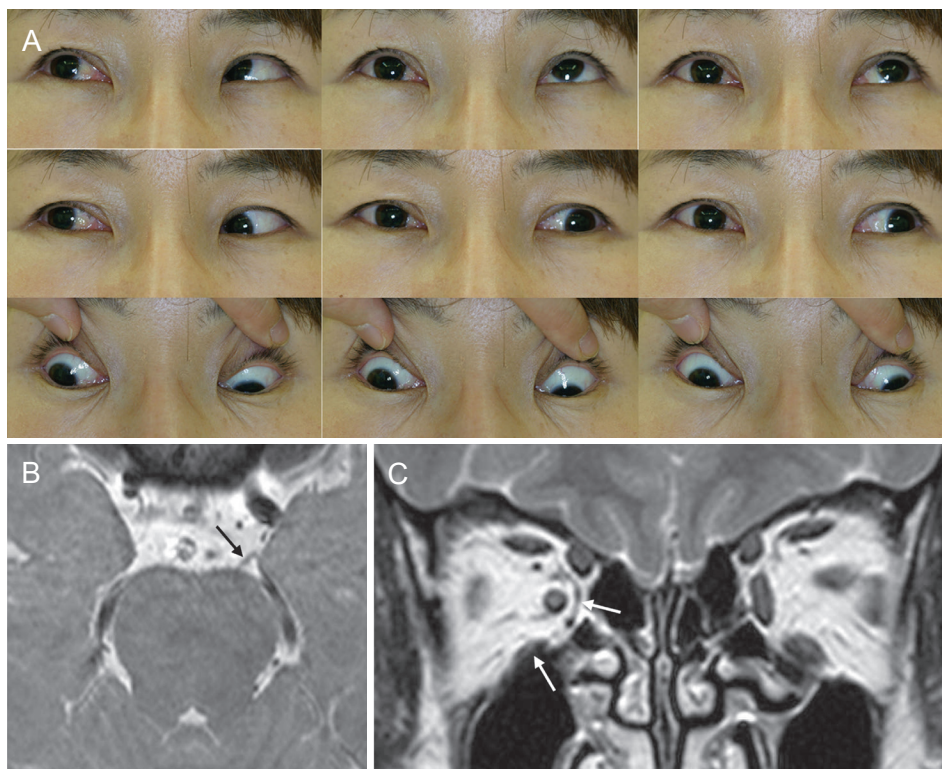


Fig. 3. Congenital cranial nerve (CN) III agenesia. (A) Ocular versions show limited elevation, adduction, and depression of the right eye. (B) Axial magnetic resonance image shows normal left CN III (arrow). Right CN III is not observed. (C) Orbital coronal magnetic resonance image shows atrophy of the right medial rectus and right inferior rectus (arrows).

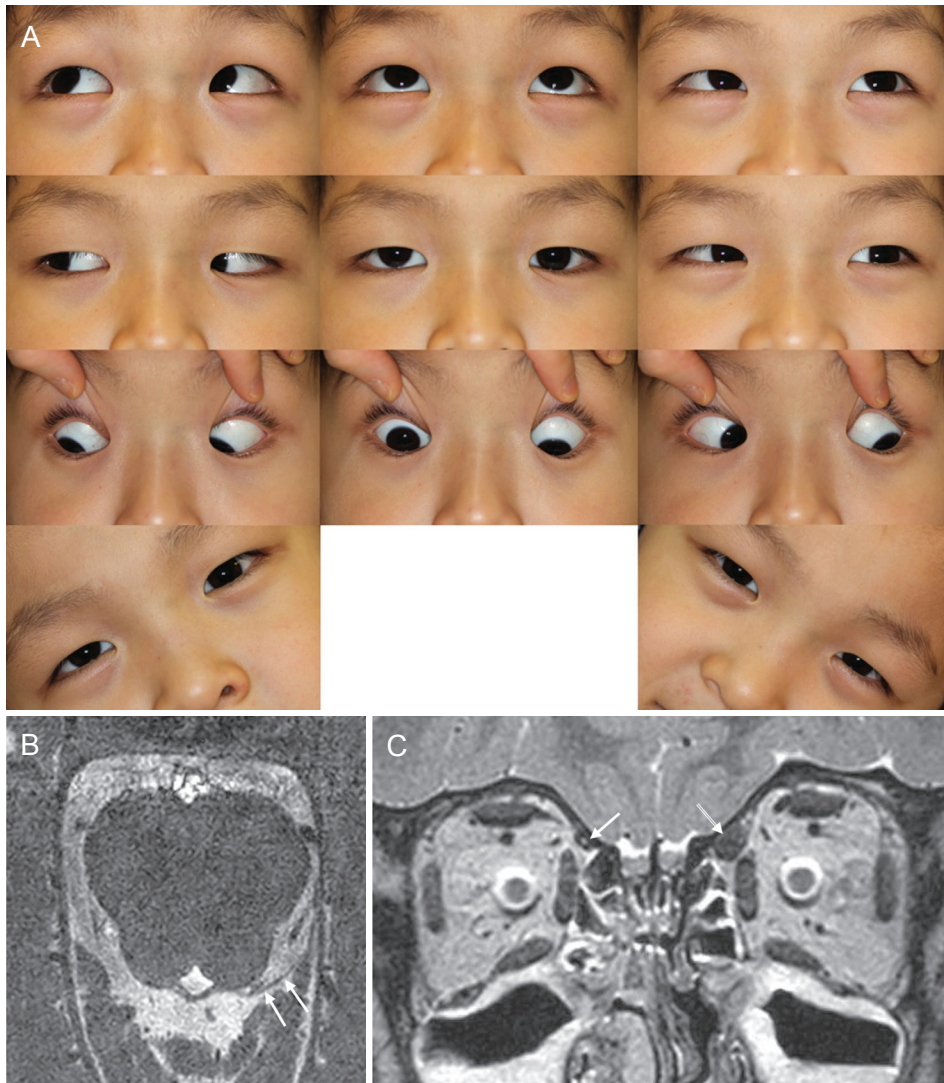


Fig. 4. Congenital cranial nerve (CN) IV agenesis. (A) Ocular versions show right hypertropia and limited depression both in downgaze and adduction in the right eye. (B) Axial magnetic resonance image shows normal left CN IV (arrows). Right CN IV is not identified. (C) Orbital coronal magnetic resonance image shows atrophy of the right superior oblique muscle (arrow). Compare with the left superior oblique (double arrow).

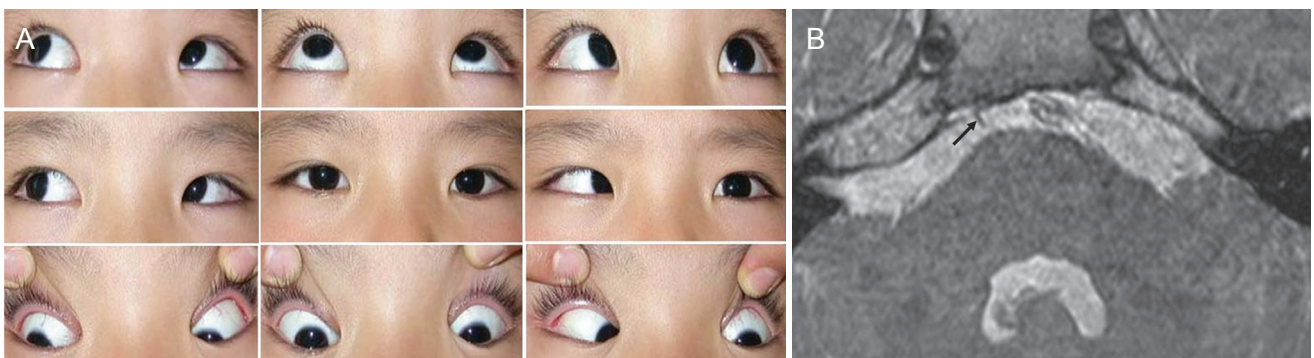


Fig. 5. Duane's retraction syndrome type 1. (A) Ocular versions show limitations of adduction and abduction and fissure narrowing on adduction in the left eye. (B) Axial magnetic resonance image at the pontomedullary junction shows normal right cranial nerve VI (arrow). Left cranial nerve VI is not identified.

It can result from heterozygous *SALL4* mutations [43]. MRI in five patients with Duane radial ray syndrome showed intraorbital and intracranial small to absent CN VI and normal intracranial CN III, optic nerve, and extraocular muscles [43]. In some orbits, a CN III branch closely approximates the lateral rectus [43].

Möbius syndrome

Möbius syndrome is a complex abnormal development of the lower brainstem resulting in congenital abduction deficit, orofacial and limb malformations, musculoskeletal defects, and mental retardation [44]. Ouanounou et al. [45] reported a hypoplastic dorsal pons corresponding to the location of the facial colliculus and CN VI complexes, absent middle cerebellar peduncles, prominent superior cerebellar peduncles, small internal auditory canals, and a normal supratentorial brain. Pedraza et al. [46] emphasized straightening of the fourth ventricle floor caused by loss of the facial colliculi. Dooley et al. [47] reported calcification in the floor of the fourth ventricle. Pandey et al. [48] and Verzijl et al. [49] reported an absent CN VII. Fons-Estupina et al. [50] found compromised CN VII (100%), VI (85%), XII (40%), VIII (25%), or IX (60%) in 20 patients with Möbius syndrome. Dumars et al. [51] reported three patients with congenital complete ophthalmoplegia, ptosis, and facial diplegia. MRI showed markedly hypoplastic extraocular muscles, intraorbital motor nerves, and posterior bony orbit [51]. However, CN III, VI, VII, and VIII were normal [51]. Jiao et al. [52] also found bilaterally absent CN VI, VII, and IX in one patient and bilaterally absent CN VI and VII in another patient with Möbius syndrome. Park et al. [53] reported a patient with coexisting bilateral

Duane retraction syndrome and unilateral Möbius syndrome resulting in horizontal gaze palsy and unilateral facial palsy. They found absent bilateral CN VI and absent unilateral CN VII on the side with Möbius syndrome [53]. Some patients may show bilateral absence of CN VI and VII (Fig. 6A and 6B).

Congenital fibrosis of the extraocular muscles

Congenital fibrosis of the extraocular muscles (CFEOM) is characterized by congenital restrictive ophthalmoplegia, more severe in vertical eye movement, with or without ptosis. CFEOM can be categorized into eight complex strabismus of CFEOM1A, CFEOM1B, CFEOM2, CFEOM3A, CFEOM3B, CFEOM3C, CFEOM4 (Tukel syndrome), and CFEOM5 [54-61]. CFEOM1 is diagnosed if all affected family members show the classic phenotype with bilateral involvement [54,55]. CFEOM2 is characterized by bilateral ptosis and fixed exotropia with autosomal recessive inheritance and *ARIX* gene mutation on chromosome 11q13 [56]. CFEOM3 is a genetically as well as phenotypically heterogeneous disorder with variable clinical features. Such patient can show more unilateral involvement, can raise the eyes above midline, or might not have ptosis [54,55].

Kim and Hwang [4] reported medial and/or superior rectus muscle atrophy, bilateral hypoplasia of CN III, and absent CN VI in two patients with CFEOM and synergistic divergence (Fig. 7A-7C). Because CN VI was absent only on the side of synergistic divergence, they suggested that hypoplasia of CN III is related with CFEOM. Bosley et al. [58] also reported similar findings of absent CN III and atrophy of the levator palpebrae superioris, medial/superior/inferior recti, and inferior oblique muscles. Demer et al.

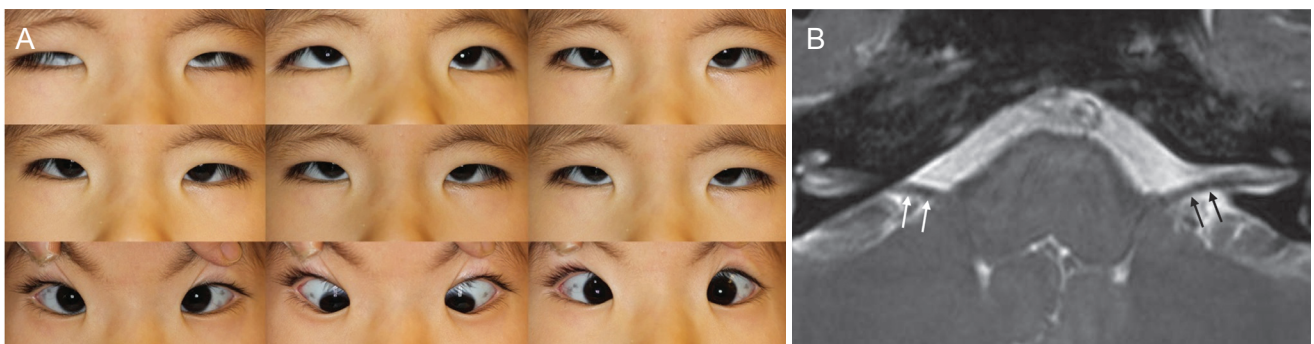


Fig. 6. Bilateral Möbius syndrome. (A) Ocular versions show limitation on abduction in both eyes. (B) Axial magnetic resonance image at the lower pons shows normal cranial nerve VIII bilaterally (white and black arrows). Cranial nerve VI and VII are not observed bilaterally. Refer to normal VI and VII in Fig. 1B.

[7,59] reported hypoplastic or absent CN III and VI in the orbit, misdirection of the inferior division of CN III to the lateral rectus muscle, reduced cross section of optic nerves, severe atrophy of levator palpebrae superioris and superior recti, and variable degree of atrophy of other extraocular muscles in CFEOM1 associated with mutations in six patients with CFEOM1 with *KIF21A* mutation. Lim et al. [8] assessed the subarachnoid portions of CN III. Mean CN III diameter in CFEOM was 1.14 mm, significantly smaller than in normal subjects (mean, 2.01 mm). Demer et al. [7] evaluated 13 CFEOM3 patients with *TUBB3* mutations and found variable asymmetric levator palpebrae superioris and superior rectus atrophy correlated with ptosis, limited supraduction, and small orbital motor nerves. Extraocular muscles showed variable hypoplasia, except the superior oblique muscle. They suggested that CFEOM3

phenotype is more variable than that of CFEOM1 and is often asymmetric. In addition, lateral rectus muscle misinnervation by a branch of CN III is a common feature of DRS and CFEOM1.

Some patients with CFEOM have central nervous system malformations, including agenesis of the corpus callosum, brainstem atrophy, cerebellar hemisphere atrophy, absence of the cerebral peduncle in the midbrain, colpocephaly, hypoplasia of the cerebellar vermis, expansion of the ventricular system, pachygyria, encephalocele, and/or hydrancephaly. Pich et al. [60] reported colpocephaly, pachygyria, corpus callosum agenesis, cerebellar vermis hypoplasia, encephalocele, and/or hydrancephaly in four patients with CFEOM. Harissi-Dagher et al. [61] reported atrophy of the cerebellar hemisphere, brainstem, thalamus involving the lateral geniculate body, and the optic radiation.

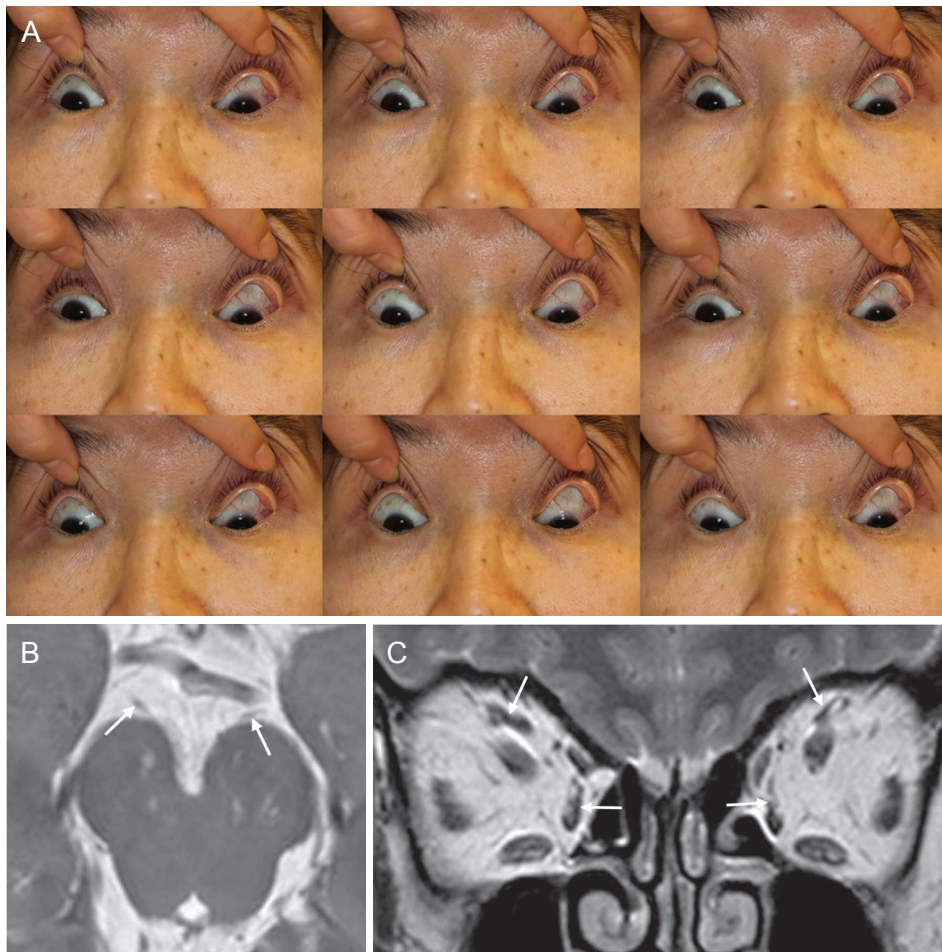


Fig. 7. Congenital fibrosis of the extraocular muscles in both eyes. (A) Ocular versions show limited ductions of both eyes. (B) Axial magnetic resonance image shows bilateral small-sized cranial nerve III (arrows), suggesting hypoplasia. (C) Orbital coronal magnetic resonance image shows mild atrophy of the right superior rectus and right medial rectus and severe atrophy of the left superior rectus and left medial rectus (arrows).

In summary, selective CN III hypoplasia and corresponding extraocular muscle hypoplasia are the key imaging features of CFEOM.

Synergistic divergence

Synergistic divergence is an adduction deficit with bilateral simultaneous abduction on attempted gaze to the action field of the medial rectus muscle. There have been no pathologic reports of synergistic divergence. Kim and Hwang [4] reported MRI findings of two patients with CFEOM and synergistic divergence as an absent CN VI on the side of synergistic divergence and bilateral hypoplastic CN III on the side of CFEOM. In addition, they found atrophy of the medial rectus muscle and/or superior rectus muscles [4]. Both patients showed a normal size of the inferior rectus muscle [4]. Park et al. [62] reported orbital mass and atrophy of the inferior and the medial rectus muscles in an 11-month-old girl with unilateral enophthalmos, restricted eye movement, and synergistic divergence. Pathologic examination of the orbital mass showed choroid plexus, arachnoid tissue, dura mater, and brain parenchyma. Jiao et al. [52] found an enlarged branch of the inferior division of CN III to the medial rectus muscle and possibly absent branch to the inferior rectus muscle. Jiao et al. [52] did not mention the size of the medial rectus muscle, and their figure did not show any significant atrophy of the medial rectus muscle. Oystreck et al. [63] reported 30% of maximum cross sectional size of the medial rectus muscle compared to the contralateral side in three patients with synergistic divergence. They mentioned that CN III was present in one patient.

Variable synergistic divergence

A patient can show either normal adduction or synergistic divergence in addition to restricted eye movement compatible with CFEOM. Kim and Hwang [64] reported one such patient and the MRI findings of bilateral hypoplasia of CN III and absent CN VI on the affected side of synergistic divergence. In addition, bilateral medial and superior rectus muscles were atrophic.

Synergistic convergence

Synergistic convergence is an abduction deficit with bilateral simultaneous adduction on attempted gaze to the

action field of the lateral rectus muscle. Since Kim and Hwang [65] first reported such eye movement in a patient with CFEOM, there have been many reports not only with CFEOM, but also with horizontal gaze palsy with progressive scoliosis and brain stem dysplasia [66-68].

Kim and Hwang [65] first reported bilateral absent CN VI and hypoplastic CN III in a patient with bilateral synergistic convergence and CFEOM. In addition, bilateral superior rectus muscles were severely atrophic, and bilateral medial rectus muscles were mildly atrophic [65]. Peh et al. [66] reported a patient with bilateral synergistic convergence and full vertical eye movement. They found slightly hypoplastic CN III, normal CN VI, and normal extraocular muscles. Khan et al. [67] reported a similar patient with bilateral synergistic convergence and full vertical eye movement with kyphoscoliosis, in whom they found anterior midline cleft in the pons and medulla and small pons and cerebellar peduncles typical of horizontal gaze palsy and progressive scoliosis. CN III and VI and all extraocular muscles were normal in size [67]. Jain et al. [68] reported a similar patient with bilateral synergistic convergence and full vertical eye movement and kyphoscoliosis. MRI showed normal CN III, VI, and all extraocular muscles. In addition, there was a variable degree of deep midline cleft of the pons, known as the split pons sign.

Conclusion

In summary, the imaging findings of CCDDs are as follows.

Congenital CN III palsy:

- Variable with aplasia, hypoplasia, or normal CN III

Congenital CN IV palsy:

- No definite abnormality: 27%
- CN IV aplasia with variable degree of superior oblique hypoplasia: 73%
- Superior oblique aplasia: rarely
- Splitting: one of 26 (4%)

Duane retraction syndrome (congenital cranial dysinnervation syndrome related with CN VI):

- Type 1: absent CN VI
- Type 2: present CN VI
- Type 3: variable presence of CN VI

- Splitting: two of five patients (4%) with Duane retraction syndrome

Möbius syndrome:

- Mostly CN VI and VII aplasia

Congenital fibrosis of extraocular muscles:

- Mostly CN III hypoplasia and the corresponding extraocular muscle hypoplasia

Synergistic divergence and synergistic convergence:

- Mostly CN VI aplasia

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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