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Case Report

Moebius sequence: radiological approximations to molecular disturbances: an overview ☆,☆☆

Daniel José Palma-Martínez[a], *Valentina Mejía-Quiñones*[b,*], *Ana María Granados-Sánchez*[c]

[a] *General practitioner, Fundación Valle del Lili, Av. Simón Bolívar - Carrera 98 # 18 - 49, Cali - Colombia*
[b] *Fundación Valle del Lili, Av. Simón Bolívar - Carrera 98 # 18 - 49, Cali, Colombia*
[c] *Radiology Department, Fundación Valle del Lili, Cali, Colombia*

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ABSTRACT

Moebius sequence is one of the rarest congenital cranial nerve abnormalities. Approximately 300 cases have been recorded in medical literature usually from single case report. Frequently characterized by either partial or complete agenesis of the VI and VII cranial nerves, Moebius sequence is also accompanied by vascular abnormalities and other alterations such as an aberrant or hypoplastic posterior fossa. We present 3 patients with Moebius sequence and their clinical and radiological features along with a discussion of their diagnostic approximations. The 3 patients (1 male and 2 females) with ages ranging from 24 days to 7 years in both outpatient and inpatient settings in a high complexity health center. Clinical and radiologic diagnosis with magnetic resonance imaging showed to be consistent with Moebius sequence. Moebius sequence initial diagnosis is based exclusively on nonunified clinical criteria, and there is an apparent genetic pattern of inheritance. Diagnostic clues include the child's inability for proper facial expressions, affectations in eye convergence, or diminished functional hearing. A radiological approach through the use of specific MRI sequences is often warranted in order to not only approximate cranial nerve abnormalities but also accompanying structural malformations.

Introduction

Moebius sequence is a nonprogressive congenital disorder of the cranial nerves (CN), characterized by a partial or total, unilateral or bilateral absence of CN VI and VII. Prevalence in the United States has been reported as 0.002%-0.0002% of all births [1]. Approximately 300 cases have been described in English-speaking literature. The disease was originally reported by von Graefe in 1880 in a case of congenital facial diplegia, the condition was further defined by Paul Julius Möbius, a German neurologist [2].

The definition and diagnostic criteria for Moebius sequence has varied throughout its history. Von Graefe and

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* *Corresponding author*.
E-mail address: valentina.mejia@fvl.org.co (V. Mejía-Quiñones).
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Möbius regarded only those patients with congenital facial diplegia and bilateral abducens nerve palsy as a true Moebius sequence. In 1939, Henderson broadened the criteria and included patients with unilateral congenital facial paralysis [3].

Herrera et al. describe the neuroimaging findings of Moebius sequence in the largest group of patients, they introduced the term "sequence" because it defines a cascade of secondary events after initial ischemia during the embryonic period, which is the most accepted etiology of the syndrome [4].

Moebius sequence is characterized by a child's lack of facial expression, difficulty swallowing, poor suction, ptosis or inability to close the eyes alongside the inability to abduct them. In other presentations, the hypoglossal nerve may be involved, resulting in paralysis of the mouth and tongue musculature. Involvement of the oculomotor and trigeminal nerves has also been reported [5]. The cerebellum, hypothalamus and pituitary gland may also be affected as well as oculofacial and limb malformations [6].

Below we present 3 clinical cases of pediatric patients diagnosed with Moebius sequence and the radiological findings characteristic of this congenital disorder.

Clinical cases

Patient 1

Male patient 4-year-old, third child, born from a 28-year-old mother with a normal pregnancy with no pathologies or reports of any abortive measures during it. Prior to delivery, the mother coursed with an unspecified initiation of preterm labor after which there were no other abnormalities. Due to postbirth respiratory distress, the patient was hospitalized in the NICU for 46 days. A pulmonary valve stenosis was detected. The patient presented with neurological development delays alongside with a suction-deglution disorder, hipotony, and general malnutrition. Physical examination revealed malformation of the left auricular pavilion, bilateral optic nerve coloboma, bilateral conductive sensorineural hearing loss, respiratory distress, and gastroesophageal reflux with the need of gastrostomy. CT scan revealed changes secondary to loss of left hemisphere cerebellum, brainstem and pons volume alongside a concavity of the floor of the IV ventricle. MRI of the brain (SIEMENS 1.5 T) was performed using sagittal FLAIR sequences in T1, axial sequences in T1, T2, diffusion sequences (ADC and TRACEW), susceptibility, coronal and ADC. Later following administration of contrast medium (1.8 cc of Gadobutrol); axial images and MPR in T1 CISS and coronal CISS were taken, which showed an adequate differentiation of the white and gray matter, with symmetrical sulci and gyri. Additionally it revealed a corpus callosum of normal morphology and intensity and a normal-appearing pons, vermis, peduncles and cerebellar hemispheres. However, asymmetry was observed in the cerebral hemispheres, which was slightly smaller in the right side, this being more evident in the cerebral peduncles, a non-specific hyperintensity in the right basal ganglia, and a right temporal arachnoid cyst. Finally, a bilateral absence of cranial nerves VI and VII was observed, fulfilling the diagnosis of Moebius sequence (Fig. 1).

Patient 2

The patient is a 2-year-old female at the time of diagnosis, daughter of a mother in her second pregnancy, initiating prenatal controls during a late date in her pregnancy. The mother denied exposure to psychoactive and abortive substances. During the pregnancy, the patient's mother coursed with hypertensive disorders and during the final stages of pregnancy with eclampsia. The patient was born by cesarean delivery. The patient presented with suction-deglution disorder, neurodevelopmental delay and bilateral sensorineural hearing loss. MRI (SIEMENS 1.5 T) was performed with sagittal FLAIR sequences were performed in T1, axial sequences in T1, T2, diffusion sequences (ADC and TRACEW), susceptibility, coronal and in ADC, and after the administration of contrast medium (1.8 cc of Gadobutrol); axial images and MPR in T1 were taken that evidenced a corpus callosum of normal morphology and intensity. However, secondary to volume loss greater than expected for age a prominence of sulci, gyri, and subarachnoid spaces was visualized. Additionally, a prominent IV ventricle was observed with flattening of its roof alongside a decrease in mesencephalon, pons, peduncles and cerebellar vermis volume bilaterally. Finally, an absence of cranial pairs VI and VII was observed bilaterally (Fig. 2).

Patient 3

The third patient was a 10-month-old female child at diagnosis, born from a mother in her second pregnancy and product of an undesired pregnancy. The mother reported initial attempts with abortive measures using prostaglandin analogues in between her 7th and 10th week of pregnancy. There were no other complications during pregnancy, delivery was initially without complications although the patient later during her first day of age developed a convulsive disorder. Later on, due to psychomotor development delays the patient was suspected yet never diagnosed with autism. MRI of the brain (SIEMENS 1.5 T) was performed using sagittal FLAIR sequences in T1, axial sequences in T1, T2, diffusion sequences (ADC and TRACEW), susceptibility, coronal and ADC were taken, which showed a thinning of the corpus callosum alongside pons and brainstem volume reduction. Gyri were also shown to be reduced in prominence, there was cerebellar hypoplasia with prominent cerebellar cortex alongside a reduced mesencephalon. Later following administration of contrast medium (1.8 cc of Gadobutrol); axial images and MPR in T1 CISS and coronal CISS showed bilateral absence of the VII cranial nerve confirming Moebius sequence as a diagnosis (Fig. 3).

Discussion

Brain stem ischemia during embryogenesis is the most accepted etiology of Moebius sequence. Hemorrhage and uterine contractions produced by abortive substances have been associated with Moebius sequence [4,7,8]. Genetic is believed

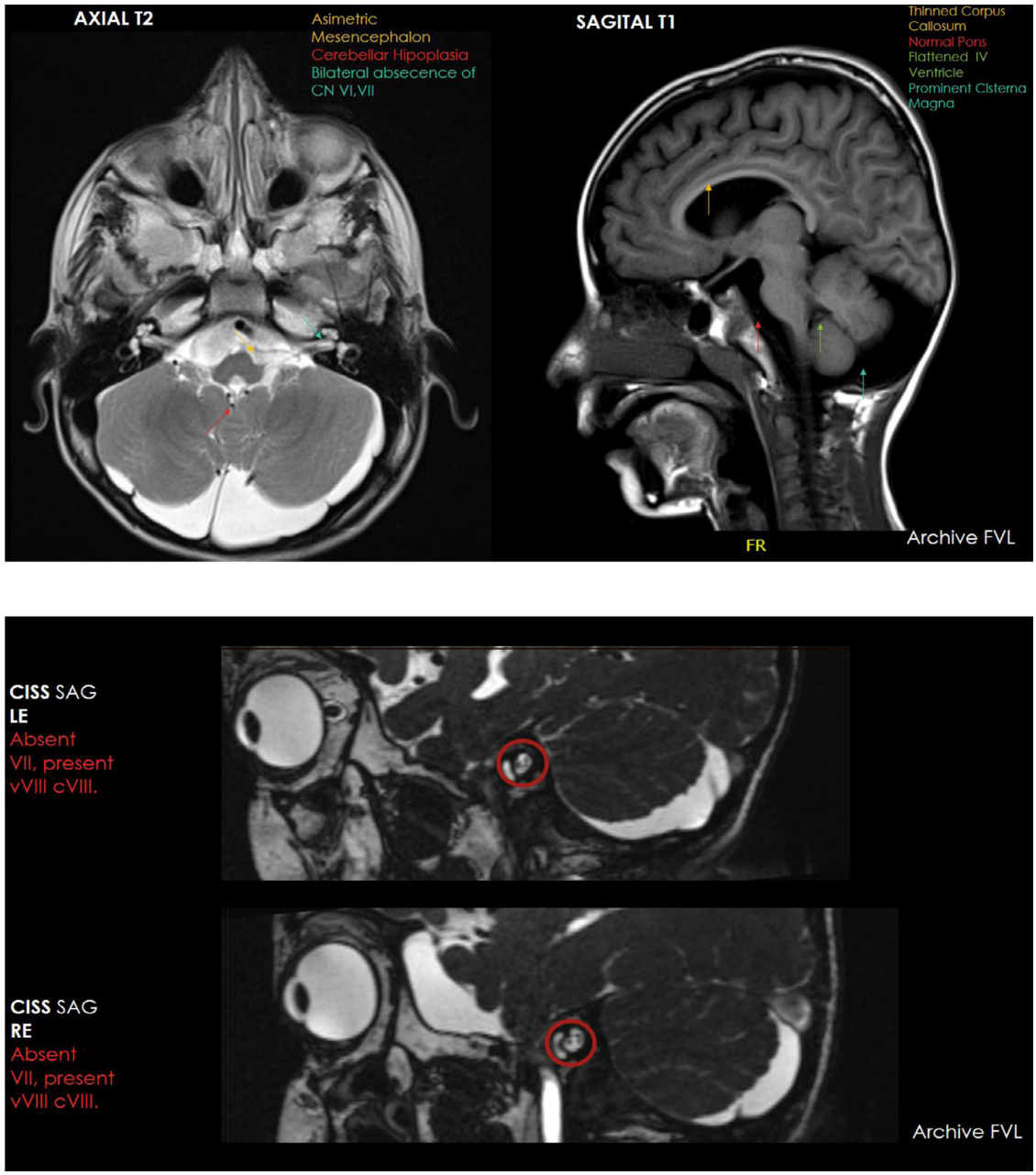

Fig. 1 – Male patient 4-year-old, third child, born from a 28-year-old mother with a normal pregnancy with no pathologies or reports of any abortive measures during it. Axial slices in T2 an example of asymmetric mesencephalon, cerebellar hypoplasia, bilateral absence of CN VI and VII. Sagittal slices in T1 with a thinned corpus callosum, normal pons, flattened IV ventricle, and prominent cisterna Magna. Sagittal slices in CISS (LE) which shows an absent VII, and absent VII (RE).

to be important for the development of Moebius sequence, 2 different loci at 3q21-q22 and 10q have been reported, as well as mutations in the PLXND1 and REV3L genes [4,9].

The diagnosis of Moebius sequence is often made clinically through results found in the physical examination. Additional imaging studies can be performed, MRI being the most used. MRI shows absence or hypoplasia of the sixth cranial nerve. Involvement of the VII CN (uni- or bilaterally) is the most common radiological feature along with IX hypoplasia [4]. An associated finding may be bilateral calcifications in the regions of the VI CN nuclei. However, these calcifications are not specific to the disease [10]. In addition, it has been found that the brain stem may appear hypoplastic, with a straightening of the floor of the IV ventricle [5,6].

Dysinnervation disorders make part of the principal differential diagnosis of Moebius sequence which includes congenital, sporadic or familial, primary and secondary dysinnervation, MR imaging can show diverse findings and these findings will be essential to establish the origin of facial paralysis [4,11].

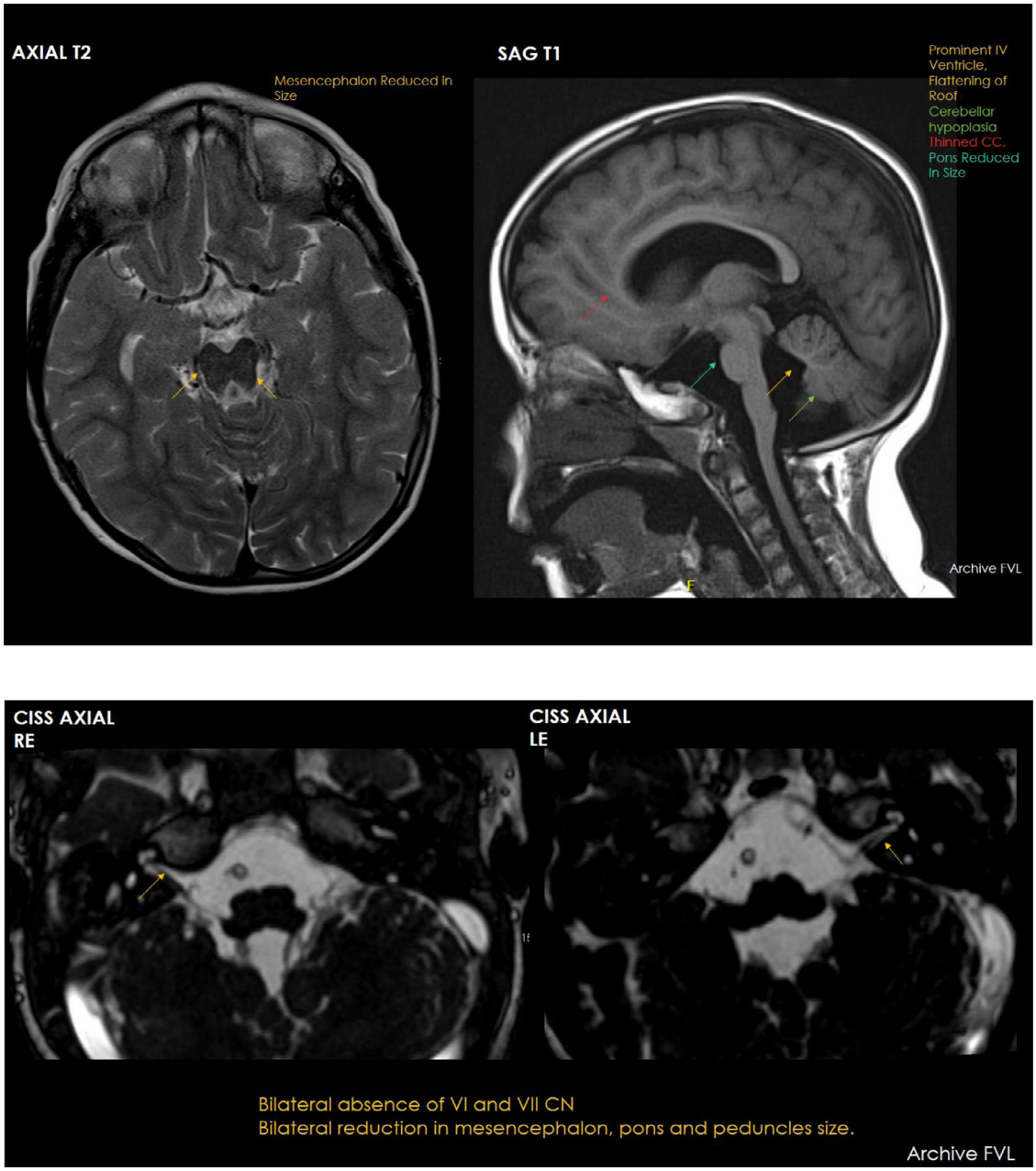

Fig. 2 – The patient is a 2-year-old female patient at the age of diagnosis, the patient presented with suction-deglution disorder, neurodevelopmental delay and bilateral sensorineural hearing loss. Axial slices in T2 which shows mesencephalon reduced in size. Sagittal slices in T1 with prominent IV ventricle, flattening of the roof, cerebellar hypoplasia, thinned CC, and pons reduced in size. Sagittal slices in CISS RE and LE an example of bilateral absence of VI and VII CN and bilateral reduction in mesencephalon, pons, and peduncles size.

Several reports have described the radiological characteristics of Moebius sequence. In a study by Carta et al. 7 patients with Moebius sequence underwent brain MRI and stem evaluation, high-resolution T2 images (FIESTA) and diffusion tensor images were acquired. In all 7 patients, the cranial nerves VI and VII were hypoplastic. DTI analysis showed a lack of uniformity in the brainstem and in the cerebellar peduncles. When compared to controls, there was hypoplasia in both the mesencephalon (6 cases) and the brainstem [12].

Additionally, Srinivas et al. reported 1 case of Moebius sequence in a 2-year-old girl with difficulty in bilateral convergence and facial weakness in the left side. MRI findings included absence of bilateral abducens nerve and absence of left facial nerve. In addition, there was absence of the anterior inferior cerebellar artery and absence of bilateral facial colliculi [13].

Pedraza et al. reported 3 patients with Moebius sequence and found a straightening of the fourth ventricle floor that reflects bridge and stem hypoplasia. The medial colliculus was

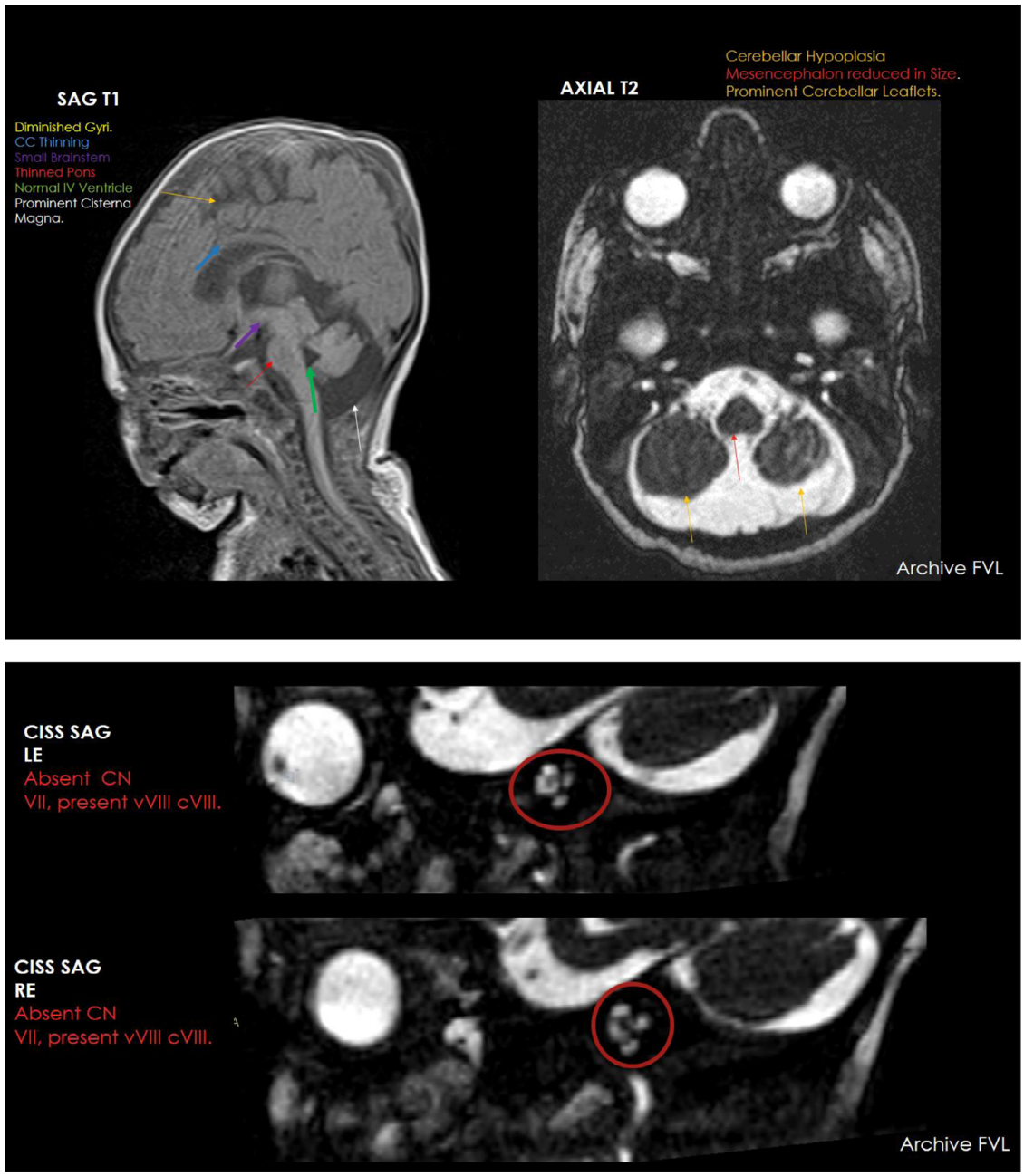

Fig. 3 – Female child of 10 months of age at time of diagnosis, born from a mother in her second pregnancy, the mother reported initial attempts with abortive measures using prostaglandin analogues in between her 7th and 10th week of pregnancy. Sagittal slices in T1 an example of diminished Gyri, CC thinning, small brainstem, thinned pons, and prominent cisterna Magna. Axial slices in T2 with cerebellar hypoplasia, mesencephalon reduced in size, and prominent cerebellar leaflets. Sagittal slices in CISS (LE and RE) which shows an absent VII.

absent at the level of the pons, suggesting hypoplasia of LV and VII. Finally, he found an absence of the median eminence in the medulla oblongata, suggesting a hypoplasia of the hypoglossal nuclei [6].

Conclusion

Moebius sequence initial diagnosis is based exclusively on nonunified clinical criteria, and there is an apparent genetic pattern of inheritance yet there are various mechanisms by which the cranial nerve structures and adjacent anatomical structures are damaged. Diagnostic clues include the child's inability for proper facial expressions, affectations in eye convergence, or diminished functional hearing. A radiological approach with specific MRI sequences is often warranted in order to not only approximate cranial nerve abnormalities but also accompanying structural malformations. The radiological approach becomes important, since it allows detecting additional alterations in a clinical diagnosis. Imaging techniques

are not the most specific way of understanding this entity, while gene sequencing and molecular characterization might show an improved accuracy for diagnosis. In addition, an approximation of the genetic and molecular pathways affected can be made from imaging findings which in turn can complement and further generate an understanding of this condition.

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