CASE REPORT

Moebius Syndrome and Depressor Anguli Oris Muscle Hypoplasia

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Port J Pediatr 2021;52:64-7
DOI: https://doi.org/10.25754/pjp.2021.19327

Abstract

Neonatal asymmetric crying facies is often underrecognized and can be caused by hypoplasia/agenesia of the depressor *anguli oris* muscle of the lip. This condition leads to an asymmetric crying facies, whereas the other functions of the facial muscles, such as frowning, eye closure, and nasolabial fold depth, are normal. It differs from complete facial palsy, which can occur as an isolated or as a part of a syndrome, such as Moebius syndrome. Moebius syndrome is a rare disease characterized by non-progressive congenital palsy of the facial (VII) cranial nerve and external ocular motor (VI) nerve. Other cranial nerves might also be involved. We present the case of a preterm female newborn, born from an uncomplicated vaginal delivery. Prenatal screening tests were normal. Feeding difficulty was noted in the first hour of life. Physical examination showed facial hypomimia, asymmetric face while crying (right and downwards deviation of the mouth angle) and absence of external ocular movements. Clinical diagnosis of Moebius syndrome together with left depressor *anguli oris* muscle hypoplasia was hypothesized. Magnetic resonance imaging showed the bilateral absence of the VII cranial nerve and left VI cranial nerve, which was compatible with the diagnosis.

Multidisciplinary follow-up and early intervention are extremely important to improve the functional prognosis of Moebius syndrome patients, particularly with respect to visual deficits, language, and communication skills.

Keywords: Facial Muscles/abnormalities; Facial Paralysis/congenital; Facial Asymmetry/congenital; Infant, Newborn; Mobius Syndrome/diagnosis

Introduction

Neonatal asymmetric crying facies is often underrecognized, with an estimated incidence of about 5-10 per 1,000 newborns. The defect can occur due to hypoplasia or agenesia of the depressor *anguli oris* muscle of the lip, the most important facial muscle for this movement, which is innervated by branches of the facial nerve.[1,2] Newborn facial asymmetry of the mouth and lips while crying is the core clinical feature. Other functions of the facial muscles, such as frowning, eye closure, and nasolabial fold depth, are normal.[1,2] The left side of the face is affected in nearly 80% of cases.[2] This condition is different from complete facial palsy, which can occur in the newborn due to traumatic or developmental etiologies.[1] In the latest, facial palsy can be observed as an isolated symptom or as part of other syndromes, such as Moebius, CHARGE syndrome, Cayler cardio-facial syndrome, among others.[1,3,4]

Moebius syndrome, also known as congenital facial diplegia or nuclear agenesia, is a rare disease, with a reported prevalence that varies from one in 10,000 to 250,000 neonates.[5-8] Moebius syndrome etiology is unknown. Fetal noxa, such as infections, drug exposure (misoprostol, benzodiazepines, alcohol, cocaine, thalidomide), and trauma as well as genetically determined vascular changes of the rhombencephalon or prenatal ischemic events have been some of the proposed mechanisms.[6,8-10] Although in most cases are sporadic, rather few familial cases with autosomal dominant transmission have been reported.[8,9] Moebius syndrome is a non-progressive pathology characterized by congenital palsy (complete or partial, uni- or bilateral) of the facial nerve (VII) and concomitant paralysis of the external ocular motor nerve (VI), with a limitation of eye abduction and horizontal convergence.[5,6,11,12] Other cranial nerves might be involved, alone or together with other orofacial defects, including orofacial skeleton malformation, thus being responsible for a wide range of clinical presentations.[8,10]

Although some studies report a higher incidence of neurodevelopment disorders and disability in the

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Received: 15/02/2020 | Accepted: 19/10/2020 | Published: 03/01/2021

affected individuals, recent publications indicate normal intellectual development.[10] As illustrated by the present case, despite the difficulty in establishing a prompt and accurate diagnosis, it is nevertheless essential in order to start a multidisciplinary follow-up that will ensure the achievement of the child's full potential.

Case Report

Female newborn at 34 weeks of gestation of a healthy para 2 mother, uncomplicated vaginal delivery, with Apgar scores 9/9/10 at one, five and 10 minutes, respectively. Prenatal care started only after 24 weeks due to pregnancy unawareness. There were no complications during pregnancy, with prenatal screening tests (including fetal ultrasounds) stated as normal. Tramadol and amoxicillin clavulanate were taken at 20 weeks for a urinary tract infection. Parents were non-consanguineous and family history was irrelevant. The newborn was transferred to the neonatal intermediate care unit in the first hour of life due to weak suction reflex, with feeding difficulty. Physical examination showed generalized facial hypomimia, asymmetry of the face on crying, with right and downwards deviation of the mouth angle, epicanthus, and absence of external ocular movements in the horizontal plan. Nasolabial folds and forehead wrinkling were also absent with bilateral eye closure appearing incomplete. Blink, glabella, and oculocephalic reflexes were absent. Generalized hypotonia was also noted, with no other neurological examination findings. No thoracic or limb defects were observed. Cardiac evaluation showed an *ostium secundum* atrial septal defect and a patent *foramen ovale*.

Due to these findings, the clinical diagnoses of Moebius syndrome together with left depressor *anguli oris* muscle hypoplasia were hypothesized. Magnetic resonance imaging (MRI) showed a bilateral absence of the VII cranial nerve and left VI cranial nerve, together with a flat configuration of the IV ventricle (secondary to the absence of facial colliculi), compatible with the hypothesized diagnosis. Microarray-based comparative genomic hybridization (array-CGH) was normal.

She was discharged at 19 days of age, after progressive feeding improvement, maintaining multidisciplinary follow-ups, particularly in neuropediatrics, developmental pediatrics, ophthalmology, physiatry, and speech therapy.

Currently at 20 months old, she maintains esotropia and facial palsy, with excessive drooling and some feeding difficulties, but with asymmetrical crying facies showing improvement. A gradual tonus improvement during the first months of life was seen, having at 2 years old normal psychomotor development. She maintains speech therapy for excessive drooling and some feeding difficulties and is waiting for ocular surgery. The asymmetric crying facies is presently not very pronounced.

Discussion

Congenital dysfunction of the motor cranial nerves with the nuclei of origin located in the mesencephalon, bulb, or medulla is infrequent.[4] The combination of VI and VII cranial nerves paralysis in infancy is commonly identified as Moebius syndrome, regardless of the additional clinical findings that patients can exhibit (extended Moebius syndrome, in these cases) and that make the syndrome extremely variable in its clinical manifestations.[4,8,13] Although Moebius syndrome is a rare disorder, with a reported incidence of 0.001%-0.002%,[7,13] the number of individuals diagnosed with this syndrome has increased considerably in recent years.[11,14] This might be due to the increased awareness of the disease, with higher diagnosis during the neonatal period.[4] We can also hypothesize that greater accessibility to MRI exams and the identification of new imaging markers can contribute to an earlier establishment of a definitive diagnosis.[15] The disease is characterized by facial hypomimia, frequently with feeding difficulties, and it may also be associated with cranio-oro-facial dysmorphisms and musculoskeletal malformations, including the absence of pectoralis muscle.[5,6] In some series, it has been reported that 10% to 50% of the affected individuals have intellectual disability of variable severity and language disorders, but their intelligence might be underestimated due to the absence of facial expressions. The latter may constitute a relational challenge because of their inability to transmit emotions.[8] Therefore, early diagnosis and intervention is essential for improving the long-term outcome.[6,11]

In the reported case, the newborn presented clinical features compatible with Moebius syndrome diagnosis, such as hypotonia, hypomimia, limitation of horizontal eye movements, neonatal feeding problems, and the presence of epicanthus. In our case, MRI showed a bilateral absence of the VII cranial nerve that does not correlate nor explain the lip asymmetry observed when crying at birth. Neonatal asymmetric crying facies can be due to a variety of different causes being hypoplasia/agenesia of depressor *anguli oris* muscle of the lip the most frequent. In our case, left side affection,

and improvement with time, support the diagnosis hypothesis of concomitant depressor *anguli oris* muscle hypoplasia.[2]

Magnetic resonance imaging also documented the left absence of the VI cranial nerve, although clinical examination showed a bilateral limitation of external eye movements, thus indicating that both abducens nerves should be affected. Since Moebius syndrome is associated not only to cranial nerve nuclei lesions but also with brainstem interconnection pathway defects,[9] we hypothesized that, although abducens right nucleus is visualized, it may be compromised at another level of its intracranial pathway.

In this report, we believe that a combination of Moebius syndrome and depressor *anguli oris* muscle hypoplasia explains the clinical features observed.

Figure 1. Spontaneous crying evidencing hypomimia and facial asymmetry, with a right side and downward angle of mouth deviation. Convergent strabismus and epicanthus were also present.

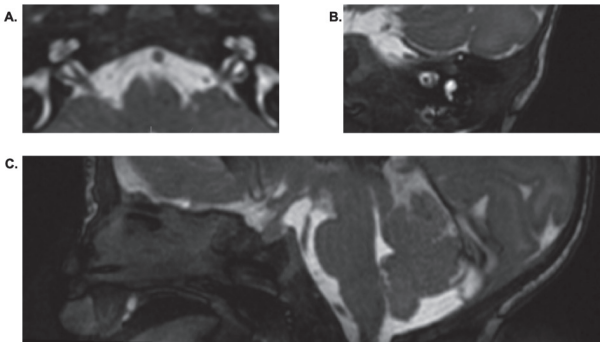

Figure 2. Magnetic resonance T2 3D DRIVE axial plane image reconstructions at the cerebellopontine angle level a) and sagittal plane reconstructions at the internal acoustic canal level b) without the identification of the cisternal or intracanalicular route of the VII cranial nerve, bilaterally; c) sagittal plane image with evidence of the flattening of the fourth ventricle floor, translating the bilateral absence of facial nerve colliculus.

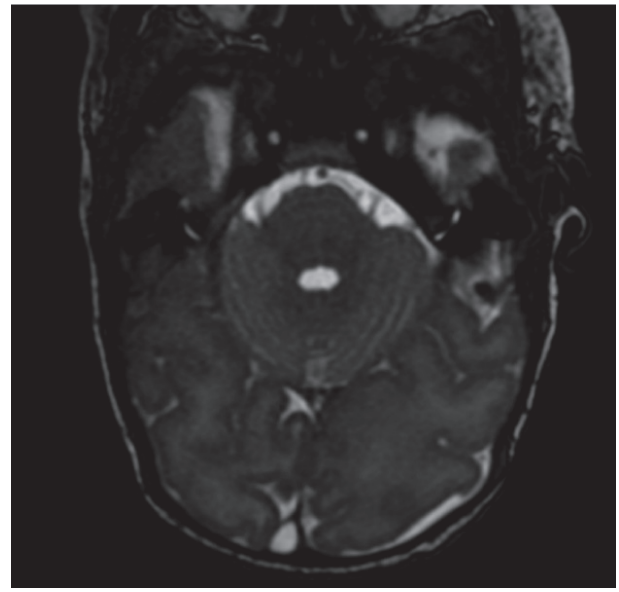

Figure 3. Magnetic resonance T2 3D DRIVE image reconstruction in the axial plane, at the level of the Dorello canal region, suggesting the possible presence of the right VI cranial nerve and its absence on the left side.

WHAT THIS CASE REPORT ADDS

- Agenesia/hypoplasia of the depressor *anguli oris* muscle leads to newborn facial asymmetry of the mouth and lips while crying, whereas the other functions of the facial muscles are normal.
- Complete facial palsy in the newborn can occur due to traumatic or developmental etiologies, the latter isolated or as part of a syndromes such as Moebius, CHARGE, and Cayler cardiofacial.
- Moebius syndrome is a rare disease of unknown etiology, characterized by non-progressive congenital palsy of the facial and external ocular motor cranial nerves.
- Moebius syndrome clinical manifestations are extremely variable and may also be associated with cranio-oro-facial dysmorphisms and musculoskeletal malformations, including the absence of *pectoralis* muscle.
- Multidisciplinary follow-up and early intervention are extremely important to alleviate its consequences, particularly for language and communication skills, so that the child's full potential can be achieved.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

Funding Sources

There were no external funding sources for the realization of this paper.

Provenance and peer review

Not commissioned; externally peer reviewed

Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

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Síndrome de Moebius e Hipoplasia do Músculo Depressor do Ângulo da Boca

Resumo:
A síndrome da assimetria facial com o choro é frequentemente subdiagnosticada no período neonatal, podendo ser devida à hipoplasia ou agenesia do músculo depressor do ângulo da boca, com subsequente assimetria da comissura labial evidenciada pelo choro. As restantes funções musculares faciais, como o franzir da testa, o encerramento palpebral ou a presença de sulcos nasolabiais, são normais. Difere da paralisia facial completa, que pode ocorrer isoladamente ou como parte de uma síndrome, como a síndrome de Moebius. A síndrome de Moebius é uma doença rara, caracterizada por uma paralisia congénita não progressiva do VII par craniano (nervo facial) e do nervo motor ocular externo (VI par). O envolvimento de outros pares cranianos pode, também, ocorrer. Apresentamos o caso de um recém-nascido pretermo, do sexo feminino, nascido por parto eutócico sem complicações. Gravidez tardiamente vigiada, com exames pré-natais sem alterações. Na primeira hora de vida evidenciou dificuldade alimentar. O exame físico mostrou hipomimia facial, assimetria facial no choro, com desvio direito e inferior da comissura labial e ausência de movimentos oculares externos. Assumiu-se o diagnóstico clínico de síndrome de Moebius, associado a agenesia / hipoplasia do músculo depressor do ângulo da boca esquerdo. A ressonância magnética cerebral revelou ausência bilateral do VII par craniano e do VI par craniano esquerdo, achados compatíveis com a hipótese diagnóstica. O acompanhamento multidisciplinar e a intervenção precoce são extremamente importantes para melhorar o prognóstico funcional das crianças com síndrome de Moebius, particularmente no que respeita às perturbações da visão, linguagem e comunicação.

Palavras-Chave: Assimetria Facial/congénita; Músculos Faciais/anomalias congénitas; Paralisia Facial/congénita; Recém-Nascido; Síndrome de Mobius/diagnóstico