Congenital Trismus From Brainstem Dysgenesis: Case Report and Review of Literature

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Trismus refers to any condition inducing limited mouth opening and may present as a result of acquired or congenital pathology. We present the case of a newborn who presented with severe, congenital trismus due to brainstem dysgenesis. We describe the course of his investigations, and a multidisciplinary approach to the management of his care and follow-up. To our knowledge, this is one of the earliest reported cases of congenital trismus attributable to brainstem dysgenesis. A literature review was conducted to provide an overview of the differential pathogenesis as it presents in congenital cases and discuss the complexity of managing congenital trismus due to brainstem dysgenesis in a neonate and infant.

Trismus is a rare form of temporomandibular joint disorders characterized by tonic contractions of the muscles responsible for jaw closure.[1] Although maximal mouth opening varies greatly from person to person, the aperture size can become problematic when it reaches a critical limit of <23 mm.[1,2] Causes of trismus in the pediatric population can be largely divided into acquired and congenital types.[3] Common acquired causes of trismus include infection, trauma, and dental treatment. Congenital-onset trismus is uncommon, and presents with restricted mouth opening at birth. However, if missed or untreated, it can result in complications including poor caloric intake, compromised speech development, irregular facial appearance, and poor oral hygiene.[4] Congenital trismus can be associated with a number of disorders (Fig 1), although in a subset of cases no etiology can be identified. The most common cause of congenital trismus is interalveolar synechiae[1] followed by temporomandibular joint bony ankylosis,[5] distal arthrogryposes,[2,6] Beals–Hecht syndrome,[4,7] and abnormalities of the muscles of mastication.

We report the case of a child with congenital trismus attributable to brainstem dysgenesis and provide a current literature on this condition. We discuss how a multidisciplinary team approach was important to the successful management and neurodevelopmental outcome in this patient.

CASE REPORT

A male term infant of 39 weeks' gestation was born via spontaneous vaginal delivery. Pregnancy was unremarkable with no maternal health concerns. Labor was uneventful with no instrumentation or resuscitation required. Apgar scores were 9 at 1 minute and 9 at 5 minutes. Birth weight was 2.675 kg (3rd–10th percentile). The infant was noted to have limited mouth opening and he developed grunting, drooling,

abstract

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Mr Hong contributed to the critical appraisal of the literature and drafted the initial manuscript; Dr Caulley conceptualized and designed the study and contributed to the initial review of the literature and manuscript revisions; Drs Kohlert, Graham, McMillan, Michaud, and Vaccani contributed to the design of the study and manuscript revisions; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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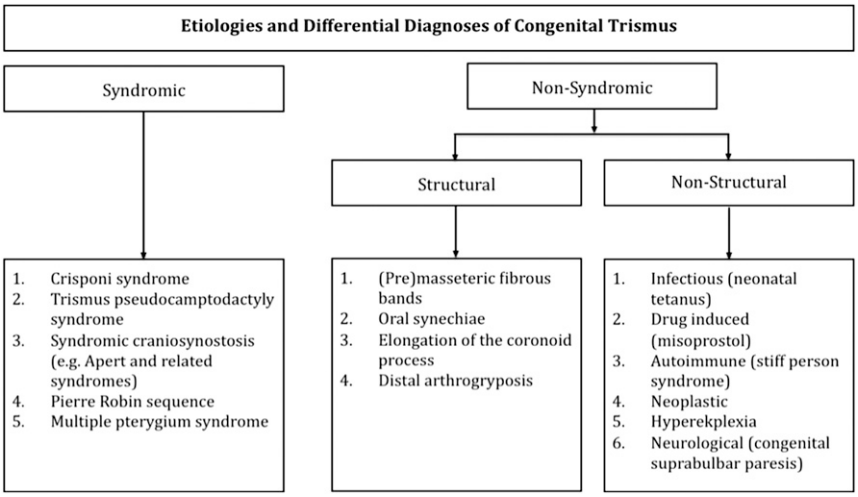

FIGURE 1
Etiologies and differential diagnoses of congenital trismus.

and mild respiratory distress that resolved with oral suctioning. No intervention was required other than intermittent suctioning.

Maternal and family history was unremarkable. Parents were nonconsanguineous and had 2 older, healthy children. Initial examination showed that the boy's maximal mouth opening was 10 mm. No other physical abnormalities were noted. Computed tomography of the jaw at 3 months of age revealed no evidence of bony dysplasia, fusion, or dislocation. MRI of the jaw at 3 months of age revealed no signs of ankylosis with no abnormal signal within masseter muscles. MRI of the brain at birth was unremarkable, with no brainstem or cranial nerve abnormalities.

He continued to experience intermittent swallowing and breathing difficulty. He required close monitoring of oxygen saturation and frequent oral and nasal suctioning. The Otolaryngology–Head and Neck Surgery service was consulted for the management of the newborn's trismus and airway, as well as a gastric tube insertion for impaired swallowing ability.

Neurologic examination at birth noted an alert and interactive infant. He demonstrated full extraocular eye movements. Spontaneous facial expression was decreased, although some nasolabial creasing was apparent with facial grimace. He could close his eyes, although his blink rate was decreased. His corneal reflexes were sluggish bilaterally. His tongue could not be visualized due to his trismus and he had a weak and inconsistent gag reflex with oral suctioning. Mild axial hypotonia was noted. He demonstrated good antigravity power with his upper and lower extremities and his deep tendon reflexes were brisk (3+). Electromyography (EMG) at 3 months old noted the right frontalis to show distant, small (<400 μV), polyphasic motor units. EMG of the right masseter and hypoglossus muscle showed rapidly firing, large motor units (some up to 1800 μV) consistent with neurogenic changes. EMG of the vastus lateralis and biceps were normal in morphology and amplitude (600 μV). Muscle biopsy of the left frontalis muscle at 10 months old was nondiagnostic and showed no features of congenital myopathy or dystrophic process. Repeat MRI of the brain (1.5 T) done at 21 months of age revealed no structural abnormalities. Myelination was appropriate for age. Thin sections (0.8 mm) through the brainstem were normal, with cranial nerves V, VII, IX, and XII noted to have a normal appearance.

Genetic testing included sequencing of *cytokine receptorlike factor 1* and *cardiotrophinlike cytokine factor 1* genes for Crisponi syndrome (Center for Medical Genetics and Molecular Medicine, Bergen, Norway), as well as sequencing of the *myosin, heavy chain 8* gene for trismus pseudocamptodactyly syndrome (Molecular Genetics Laboratory, Hospital for Sick Children, Toronto, Canada). All 3 genes were negative for pathogenic variants. Multiplex ligation-dependent probe amplification for these genes was not routinely performed by either laboratory. Single nucleotide polymorphism oligonucleotide array comparative genomic hybridization was normal. The patient and his parents were subsequently enrolled in the Care for Rare Genetic Diseases in Canada research project with informed written consent. A "clinome" next-generation sequencing study targeting 4813 genes known to be involved in human phenotypes (Ilumina Trusight Sequencing Panel) and whole-exome sequencing, both carried out under this research protocol, were unrevealing. In light of the clinical and electrodiagnostic findings, particular attention was placed on all known genes associated with neuromuscular disease, mitochondrial disease, neuronal migration, and neuronal patterning, with no candidate mutations identified. Ophthalmology examination at 2 years old revealed ocular apraxia that had not been appreciated on earlier examinations.

At 27 months old, the patient was admitted to hospital with a foreign-body aspiration requiring intubation. Further testing was performed while he was sedated. Blink study revealed absent ipsilateral R1 and absent ipsilateral and contralateral R2, consistent with bilateral trigeminal neuropathy or neuronopathy.

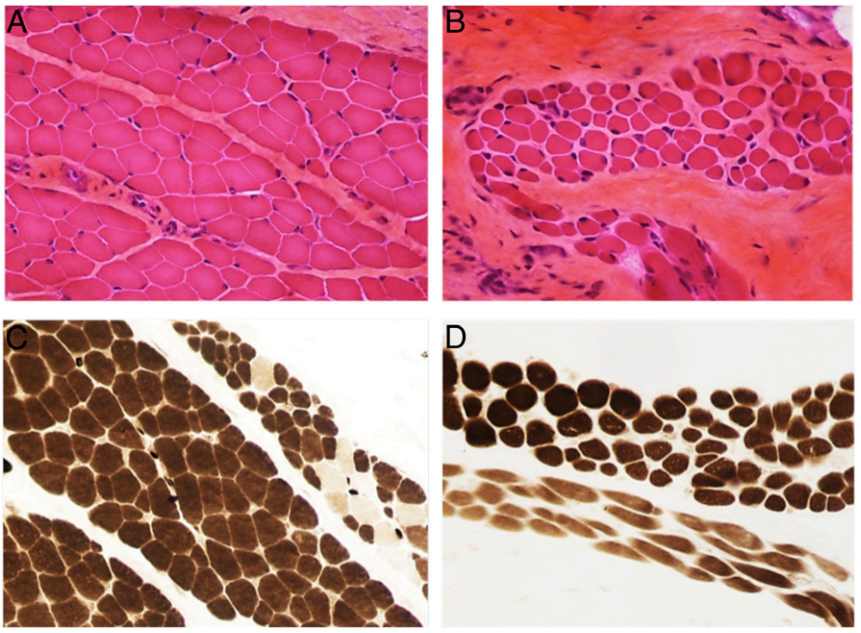

FIGURE 2

Histologic findings of the temporalis muscle biopsy: A, Variation in muscle fiber caliber with several small angulated fibers. B, Entire fascicles with atrophic fibers (when compared with A; both A and B stained with the hematoxylin-phloxin-safran). C, Grouping of type 1 fibers darkly stained with ATPase pH 4.3. D, Entire fascicle composed of darkly stained type 2 fibers with ATPase pH 9.4. (All photos at original magnification of ×400.)

Brainstem auditory evoked potentials noted significant delays in right waves 1, 3, and 5 and left wave 1.

Muscle biopsy of the right frontalis, temporalis, and biceps muscles were completed. The right frontalis muscle showed severe muscle atrophy with very few muscle fibers identified, a significant deterioration when compared with the biopsy made 17 months earlier. The right temporalis muscle showed a significant variation in the caliber of muscle fibers with entire fascicles at times showing atrophic fibers. Several atrophic fibers were angulated. The following stains showed groupings of both fiber types: ATPase pH 9.4 and 4.3, nicotinamide adenine dinucleotide, Periodic acid-Schiff reaction, succinate dehydrogenase, and cytochrome c oxidase. Entire fascicles were composed of the same fiber type. The right biceps muscle was normal. The temporalis muscle biopsy when considered with the previous clinical and electrodiagnostic results confirmed the diagnosis of brainstem dysgenesis, given the extensive neurogenic changes seen (Fig 2).

The child received Botox injections (a total of 3 injections) into the masseter muscles under ultrasound guidance. The child also underwent scheduled physiotherapy to restore jaw mobility and functions. In total, the infant required >3 months of hospitalization and frequent emergency department visits. More recently, the infant has gained some, albeit limited, ability to open his mouth (15 mm). However, his ongoing swallowing difficulties with frequent foreign-body aspirations and respiratory distress eventually necessitated tracheotomy for a definitive airway protection.

Despite his lack of spoken language, his neurodevelopment was otherwise normal. At 2 years old he had >70 sign-language words. He could follow 2-steps command. His gross motor and fine motor skills were normal.

DISCUSSION

Without language restriction, we performed a detailed electronic search of PubMed, Medline, and Embase for studies reporting on brainstem dysgenesis. In consultation with a medical librarian, the following key words and MeSH terms were used in varying combinations: trismus, brainstem dysgenesis, and congenital. The search identified a total of 25 potential studies. We excluded noneligible articles (eg, letters, descriptive studies, non-English articles) after reviewing articles in full text. A total of 4 studies were included in the qualitative synthesis.[8–11]

Brainstem dysgenesis is a rare, clinically heterogeneous, congenital malformation.[8–11] To date, all 4 studies describing this condition have been from a single institution. Clinical manifestations of brainstem dysgenesis include multiple cranial nerve involvement, resulting in bilateral/unilateral facial palsy/diplegia, sucking and swallowing difficulties, velopalatine incoordination, and ocular motor apraxia. Other signs and symptoms include congenital hypotonia and pyramidal tract signs, and unilateral impairment of the auditory brainstem responses on electrophysiological studies. Individuals with congenital brainstem dysgenesis have persistent feeding and speech problems throughout adulthood.

The degree of brainstem dysfunction in our patient was severe as demonstrated clinically as well as by electrodiagnostic testing and microscopic analysis of facial muscles. Clinical onset was also presumably quite early in gestation, as indicated by degree of congenital trismus. Despite this, MRI of the brainstem and cranial nerves was surprisingly intact. A limitation of our neuroimaging was that it did not include tractography, as this is not performed as part of routine clinical care at our hospital. Tractography may have provided information pertaining to the integrity

of the corticospinal tract, which did show some clinical involvement in our patient given his brisk deep tendon reflexes. However, tractography would not have provided any information pertaining to the integrity of brainstem nuclei or cranial nerves, which, in our opinion, is the more likely site of the lesion in brainstem dysgenesis.

Syndromic causes of congenital trismus have been reported, including Crisponi syndrome,[12–18] trismus pseudocamptodactyly syndrome,[6,19–25] syndromic craniosynostosis,[26] atypical Pierre Robin sequence,[27–29] and multiple pterygium syndrome.[29] Crisponi syndrome is a rare, autosomal recessive disorder due to cytokine receptorlike factor 1 gene mutations characterized by inability to suckle and swallow due to facial and bulbar weakness, excessive startle and trismuslike facial contractions, apneic spells, episodic unexplained fevers, and camptodactyly.[12–18] Trismus pseudocamptodactyly syndrome is an autosomal dominant syndrome caused by myosin, heavy chain 8 mutations characterized by severe restriction of mouth opening, camptodactyly, shortness of leg flexor muscles, and foot deformities.[6,19–25] Our patient described in this article did not meet the criteria for any of the previously reported genetic causes of congenital trismus. Importantly, exome sequencing did not identify any mutations in genes encoding proteins known to be involved in brainstem nuclear migration and development.

Structural malformations, acquired or of a genetic origin, have also been reported in the literature as a possible etiology of congenital trismus. These commonly include (pre) masseteric fibrous bands,[30–32] oral synechiae,[4,33] distal arthrogryposis,[34] and elongation/hypertrophy of the coronoid process.[35,36] Other causes of congenital trismus include neonatal tetanus,[37–39] drug induced,[40] autoimmune,[41] neoplastic,[42] and neurologic (congenital suprabulbar paresis).[43] Neonatal tetanus is still prevalent in the developing world with high morbidity and mortality, but is rare in the Western world.[38,39] Exposure to misoprostol in the first trimester of pregnancy has also been associated with birth defects and congenital trismus.[40] In the case of our patient, there was no radiologic evidence to suggest structural malformations as a possible cause and there was no evidence of birth defects, and the mother denied taking any medications other than prenatal vitamins.

CONCLUSIONS

The patient described in the present report represents one of the earliest known cases of congenital trismus attributable to brainstem dysgenesis. Genetic testing, including whole-exome sequencing, did not identify a genetic cause for brainstem dysgenesis, supporting the theory that brainstem dysgenesis may arise from an early fetal insult (eg, vascular disruption) at a critical stage of brainstem development and neuronal migration. Only through electrophysiological studies (ie, blink reflex, brainstem auditory evoked response) in conjunction with a diagnostic muscle biopsy, we were able to arrive at the firm diagnosis of brainstem dysgenesis.

Managing this patient was challenging due to the absence of previously established guidelines. Evaluating the need for emergency intubation and surgical intervention was the first priority. The child responded favorably to Botox injections and physiotherapy.

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ABBREVIATION

EMG: electromyography

REFERENCES

1. Dhanrajani PJ, Jonaidel O. Trismus: aetiology, differential diagnosis and treatment. *Dent Update*. 2002;29(2):88–92, 94
2. Nevakari K. 'Elipsio prearticularis' of the temporomandibular joint. A pantomographic study of the so-called physiological subluxation. *Acta Odontol Scand*. 1960;18(2):123–170
3. Shires PM, Chow G. Trismus in the paediatric population. *Dev Med Child Neurol*. 2015;57(4):339–343
4. Hirano A, Iio Y, Murakami R, Fujii T. Recurrent trismus: twenty-year follow-up result. *Cleft Palate Craniofac J*. 1994;31(4):309–312
5. Poulsen P. Restricted mandibular opening (trismus). *J Laryngol Otol*. 1984;98(11):1111–1114
6. Markus AF. Limited mouth opening and shortened flexor muscle-tendon units: 'trismus-pseudocamptodactyly.' *Br J Oral Maxillofac Surg*. 1986;24(2):137–142
7. Dworkin SF, Huggins KH, LeResche L, et al. Epidemiology of signs and symptoms in temporomandibular disorders: clinical signs in cases and controls. *J Am Dent Assoc*. 1990;120(3):273–281
8. Castilla-Fernández Y, Boix H, Macaya A, Vázquez E, Gratacòs M, Roig-Quilis M. Brainstem dysgenesis during the neonatal period: diagnosis and management. *J Perinat Med*. 2013;41(4):445–453
9. Armangue T, Macaya A, Vazquez E, Jurado MJ, Roig-Quilis M. Central hypoventilation and brainstem dysgenesis. *Pediatr Neurol*. 2012;46(4):257–259
10. Boix H, Ortega-Aznar A, Vazquez E, Salcedo S, Roig-Quilis M. Brainstem dysgenesis in an infant prenatally exposed to cocaine. *Pediatr Neurol*. 2010;42(4):295–297

11. Roig M, Gratacòs M, Vazquez E, et al. Brainstem dysgenesis: report of five patients with congenital hypotonia, multiple cranial nerve involvement, and ocular motor apraxia. *Dev Med Child Neurol*. 2003;45(7):489–493
12. Crisponi G. Autosomal recessive disorder with muscle contractions resembling neonatal tetanus, characteristic face, camptodactyly, hyperthermia, and sudden death: a new syndrome? *Am J Med Genet*. 1996;62(4):365–371
13. Uzunalic N, Zenciroglu A, Beken S, et al. Crisponi syndrome: a new mutation in CRLF1 gene associated with moderate outcome. *Genet Couns*. 2013;24(2):161–166
14. Hakan N, Eminoglu FT, Aydin M, et al. Novel CRLF1 gene mutation in a newborn infant diagnosed with Crisponi syndrome. *Congenit Anom (Kyoto)*. 2012;52(4):216–218
15. Dessì A, Fanos V, Crisponi G, Frau A, Ottonello G. Isolated 'sign of the horns': a simple, pathognomonic, prenatal sonographic marker of Crisponi syndrome. *J Obstet Gynaecol Res*. 2012;38(3):582–585
16. Cosar H, Kahramaner Z, Erdemir A, et al. Homozygous mutation of CRLF-1 gene in a Turkish newborn with Crisponi syndrome. *Clin Dysmorphol*. 2011;20(4):187–189
17. Nannenberg EA, Bijlmer R, Van Geel BM, Hennekam RC. Neonatal paroxysmal trismus and camptodactyly: the Crisponi syndrome. *Am J Med Genet A*. 2005;133A(1):90–92
18. Accorsi P, Giordano L, Faravelli F. Crisponi syndrome: report of a further patient. *Am J Med Genet A*. 2003;123A(2):183–185
19. Mercuri LG. The Hecht, Beals, and Wilson syndrome: report of case. *J Oral Surg*. 1981;39(1):53–56
20. O'Brien PJ, Gropper PT, Tredwell SJ, Hall JG. Orthopaedic aspects of the trismus pseudocamptodactyly syndrome. *J Pediatr Orthop*. 1984;4(4):469–471
21. Teng RJ, Ho MM, Wang PJ, Hwang KC. Trismus-pseudocamptodactyly syndrome: report of one case. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi*. 1994;35(2):144–147
22. Nagata O, Tateoka A, Shiro R, Kimizuka M, Hanaoka K. Anaesthetic management of two paediatric patients with Hecht-Beals syndrome. *Paediatr Anaesth*. 1999;9(5):444–447
23. Gasparini G, Boniello R, Moro A, Zampino G, Pelo S. Trismus-pseudocamptodactyly syndrome: case report ten years after. *Eur J Paediatr Dent*. 2008;9(4):199–203
24. Carlos R, Contreras E, Cabrera J. Trismus-pseudocamptodactyly syndrome (Hecht-Beals' syndrome): case report and literature review. *Oral Dis*. 2005;11(3):186–189
25. Pelo S, Boghi F, Moro A, Boniello R, Mosca R. Trismus-pseudocamptodactyly syndrome: a case report. *Eur J Paediatr Dent*. 2003;4(1):33–36
26. Holmes AD, Wright GW, Meara JG, Heggie AA, Probert TC. LeFort III internal distraction in syndromic craniosynostosis. *J Craniofac Surg*. 2002;13(2):262–272
27. Giurgea I, Raqbi F, Nihoul-Fékété C, Couly G, Abadie V. Congenital microgastria with Pierre Robin sequence and partial trismus. *Clin Dysmorphol*. 2000;9(4):307–308
28. Denion E, Capon N, Martinot V, Pellerin P. Neonatal permanent jaw constriction because of oral synechiae and Pierre Robin sequence in a child with van der Woude syndrome. *Cleft Palate Craniofac J*. 2002;39(1):115–119
29. Parashar SY, Anderson PJ, David DJ. An unusual complication of mandibular distraction. *Int J Paediatr Dent*. 2006;16(1):55–58
30. Visscher SH, Schortinghuis J, Bos RR. Congenital mandibular hypomobility: a rare condition with little consensus—a case report. *J Oral Maxillofac Surg*. 2009;67(2):444–447
31. Adams C, Rees M. Congenital trismus secondary to masseteric fibrous bands: endoscopically assisted exploration. *J Craniofac Surg*. 1999;10(4):375–379
32. Skinner AM, Rees MJ. Congenital trismus secondary to masseteric fibrous bands: a 7-year follow-up report as an approach to management. *J Craniofac Surg*. 2004;15(5):709–713
33. Verdi GD, O'Neal B. Cleft palate and congenital alveolar synechia syndrome. *Plast Reconstr Surg*. 1984;74(5):684–686
34. Reiss JA, Sheffield LJ. Distal arthrogryposis type II: a family with varying congenital abnormalities. *Am J Med Genet*. 1986;24(2):255–267
35. Isberg A, Isacsson G, Nah KS. Mandibular coronoid process locking: a prospective study of frequency and association with internal derangement of the temporomandibular joint. *Oral Surg Oral Med Oral Pathol*. 1987;63(3):275–279
36. Turk AE, McCarthy JG, Nichter LS, Thorne CH. Moebius syndrome: the new finding of hypertrophy of the coronoid process. *J Craniofac Surg*. 1999;10(1):93–96
37. Chatterjee S, Hemram S, Bhattacharya S, Khuntdar BK. A case of neonatal tetanus presented within 24 hours of life. *Trop Doct*. 2013;43(1):43–45
38. Gürkan F, Boşnak M, Dikici B, et al. Neonatal tetanus: a continuing challenge in the southeast of Turkey: risk factors, clinical features and prognostic factors. *Eur J Epidemiol*. 1999;15(2):171–174
39. McMillen SG. "No uncommon disease": neonatal tetanus, slave infants, and the southern medical profession. *J Hist Med Allied Sci*. 1991;46(3):291–314
40. Vauzelle C, Beghin D, Cournot MP, Elefant E. Birth defects after exposure to misoprostol in the first trimester of pregnancy: prospective follow-up study. *Reprod Toxicol*. 2013;36:98–103
41. Damásio J, Leite MI, Coutinho E, et al. Progressive encephalomyelitis with rigidity and myoclonus: the first pediatric case with glycine receptor antibodies. *JAMA Neurol*. 2013;70(4):498–501
42. Nakano H, Mori Y, Mano T, et al. Diagnosis and treatment of an infant case with temporomandibular joint osteoarthritis caused by tumor. *Oral Maxillofac Surg*. 2010;14(2):119–121
43. Wilson MC, Laskin DM. Surgical management of limited mouth opening associated with congenital suprabulbar paresis: report of a case. *J Oral Maxillofac Surg*. 2009;67(3):650–652

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