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Clinical Report

Pontine Hypoplasia in Carey–Fineman–Ziter (CFZ) Syndrome

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We describe an infant with multiple congenital anomalies including cleft palate and micrognathia, Möbius sequence, developmental delay, myopathy, hydronephrosis, and bilateral clubfeet. These features are consistent with Carey–Fineman–Ziter (CFZ) syndrome (MIM 254940), which has been previously reported in six children (including two sibling pairs). Cranial magnetic resonance imaging (MRI) revealed an unusually small pons, a finding not previously described in CFZ syndrome.

KEY WORDS: Carey–Fineman–Ziter syndrome; Möbius sequence; pontine hypoplasia; congenital myopathy

INTRODUCTION

The Carey–Fineman–Ziter (CFZ) syndrome, first described by Carey et al. [1982], includes a consistent and recognizable phenotype with hypotonia, Möbius sequence, facial anomalies, delayed motor milestones, and failure to thrive [Carey et al., 1982; Schimke et al., 1993; Baraitser and Reardon, 1994]. We report an infant with this syndrome who had notable pontine hypoplasia on neuroimaging. This finding has not been previously recognized as a part of this disorder.

CLINICAL REPORT

A 41-week-male infant was transferred to our neonatal intensive care unit in view of respiratory distress and multiple congenital anomalies. He was the first child born to healthy non-consanguineous parents, age 18 and 19 years. There was no antenatal history of maternal illness or known exposure to drugs/toxins (including misoprostol). A prenatal screening sonogram had documented bilateral clubfeet. The infant was delivered by cesarean section secondary to fetal distress.

The Apgar scores were 3, 5, 6, and 7 at 1, 5, 10, and 15 min, respectively, and the infant required endotracheal intubation due to poor respiratory effort. Physical examination showed a large and wide anterior fontanelle, frontal bossing, downslanting palpebral fissures, small nose, low-set ears, cleft palate, and micrognathia. There was an absence of blink reflex, limitation of extraocular movements, and facial diplegia, consistent with the diagnosis of Möbius sequence. Other abnormalities included a single transverse crease on the right hand, glandular hypospadias, and bilateral talipes equinovarus (Fig. 1). There was generalized hypotonia, and mild flexion contractures were present at the knees. Deep tendon reflexes were weak, but definitely elicitable. The anthropometric measurements including weight, length, and head circumference were between the 50 and 75th percentiles. A renal sonogram showed the presence of left sided hydronephrosis. The karyotype was normal (46,XY).

Although the respiratory illness per se was of minimal clinico-radiologic severity, there was continued need for respiratory support due to central hypoventilation, upper airway instability secondary to cleft palate/micrognathia, and weakness of respiratory muscles. The patient also underwent an initial glossopexy, and later, a tracheostomy to achieve airway stability. A feeding gastrostomy was also placed in view of persistent difficulties in suck–swallow–breathing coordination.

Cranial MRI revealed a small pons and brain stem, and relatively enlarged pre-pontine and the ponto-cerebellar cisterns (Fig. 2). The cerebellar hemispheres, vermis, and the fourth ventricle were normal. The diencephalic structures and cerebral hemispheres were also normal. A muscle biopsy was done at 1 month of age, which showed myopathic features with type I myofiber atrophy (Fig. 3). There were no histopathologic suggestions of a mitochondrial cytopathy; plasma lactate levels were normal. The tissue also tested normal for mitochondrial enzyme complexes I–IV.

DISCUSSION

The CFZ syndrome (MIM 254940) is characterized by hypotonia, Möbius sequence, Pierre Robin sequence, micrognathia, distinctive free, and failure to thrive [Carey et al., 1982; Schimke et al., 1993; Baraitser and Reardon, 1994; Ryan et al., 1999]. Other features include microcephaly [Carey et al., 1982] or relative macrocephaly [Ryan et al., 1999], downslanting palpebral fissures [Carey et al., 1982; Schimke et al., 1993; Ryan et al., 1999] and clubfeet [Schimke et al., 1993; Ryan et al., 1999]. Our patient had all these features, other than having a normal head circumference.

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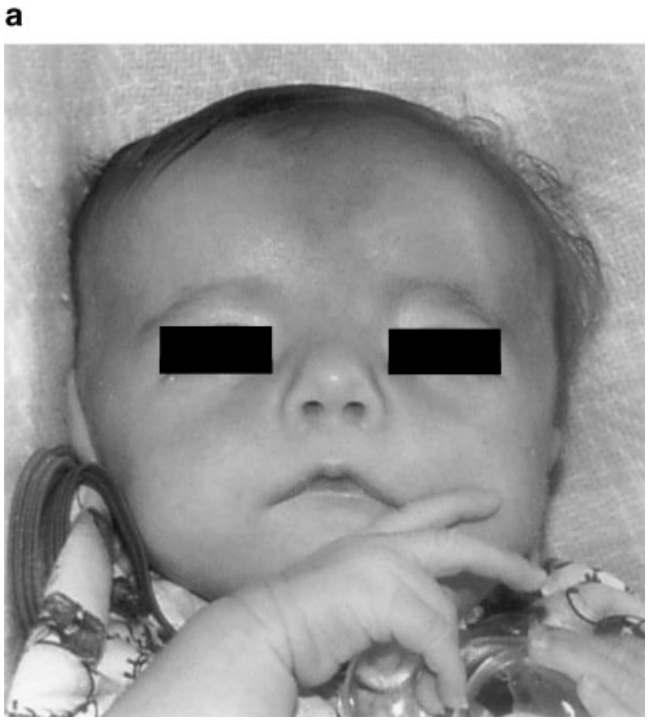

Fig. 1. **a**: Frontal photograph showing frontal bossing, expressionless face during stimulation, and downslanting palpebral fissures. The presence of micrognathia and low-set ears can also be noticed. Tracheostomy was present at the time of the photograph. **b**: Bilateral talipes equinovarus.

The etiopathogenesis of CFZ syndrome is not known. It is believed to be inherited in an autosomal recessive fashion [Carey et al., 1982; Ryan et al., 1999]. Extensive studies on prenatal infections, DNA trinucleotide repeats, and inherited metabolic errors in amino acid, organic acid, lysosomal enzyme, and sterol pathways have remained inconclusive [Ryan et al., 1999]. Parental and patient karyotypes have also been uniformly normal [Ryan et al., 1999]. The electrophysiologic studies show normal conduction in the cranial seventh as well as the peripheral nerves, suggesting that the site of the defect is supranuclear. The presence of feeding problems and central hypoventilation in these patients, and of bulbar palsy in one of the older patients reported by Ryan et al. [1999] suggest an anatomic localization to the brainstem.

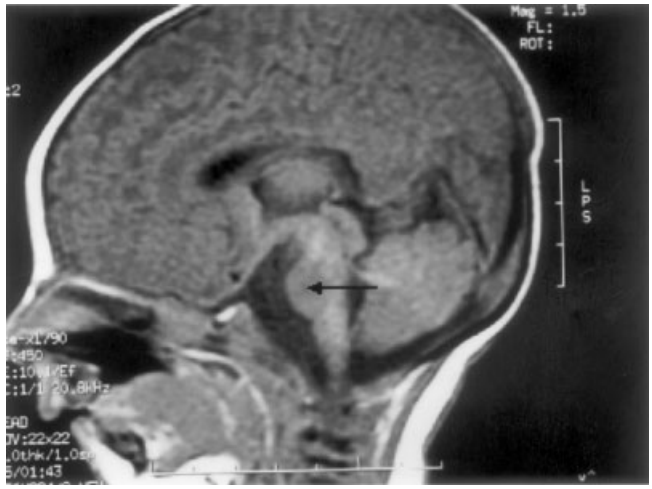

Fig. 2. Cranial MRI in sagittal section showing the pontine hypoplasia (arrow) with secondary prominence of the pre-pontine and ponto-medullary cisterns.

Isolated pontine hypoplasia has not been previously described in CFZ syndrome, although generalized atrophy involving both the cerebral hemispheres and brainstem has been seen in a 20-month-old patient [Ryan et al., 1999]. On the other hand, pontine hypoplasia has been reported in patients with isolated Möbius sequence by several authors [Jaradeh et al., 1996; Lammens et al., 1998; Saint-Martin et al., 1998; Kiratli and Erdener, 2000; Pedraza et al., 2000]. Saint-Martin et al. [1998] recently described an infant with Möbius syndrome and severe pontine hypoplasia, apparently with a

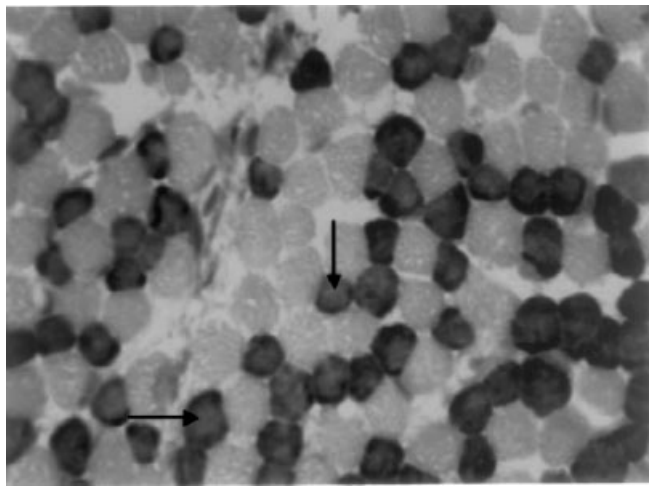

Fig. 3. Muscle biopsy showing type I myofiber (arrows) atrophy (original magnification 250×; Myosin stain for slow fibers).

disruption between the normal mesencephalon and a thin medulla. These findings, being relatively limited to the pons, do not resemble neocerebellar dysgeneses such as pontoneocerebellar hypoplasia [Barth, 1993; Mamourian and Miller, 1994; Saint-Martin et al., 1998]. Contrarily, neuroimaging and autopsy studies seem to favor a prenatal ischemic insult involving the proximal sixth intersegmental artery during a critical vulnerable period between the 5th and 6th weeks of embryonic life [Wilson et al., 1982; Bavinck and Weaver, 1986; Brill et al., 1987; D'Cruz et al., 1993; St. Charles et al., 1993; Yoon et al., 1997; Ghabrial et al., 1998; Lammens et al., 1998]. Indeed, several lines of evidence suggest the presence of a zone of vascular vulnerability in the paramedian region of the developing brain stem. This area remains avascular for protracted periods during fetal life and could be vulnerable to ischemia in the event of hypoperfusion. Secondly, the somatic efferent nuclei in this area have a high rate of metabolic activity, which could render these to be particularly susceptible to hypoxia. Thirdly, it has been suggested that the blood vessels in this area may have relatively poor interstitial support, and this may give rise to an increased risk of hemorrhage [Leong and Ashwell, 1997].

The hypotonia in CFZ syndrome has been attributed to a congenital non-progressive myopathy. Ryan et al. [1999] described myopathic histologic features with type II fiber predominance in one of their two cases. Similar findings of a generalized non-specific myopathy were also described by Schimke et al. [1993]. The muscle biopsy in our patient showed type I fiber atrophy, a finding commonly associated with congenital myopathies such as congenital muscle fiber type disproportion myopathy (CMFTD). Type I fiber atrophy is considered diagnostic for CMFTD in the presence of typical clinical characteristics (which are present in our patient): motor developmental delay due to muscle hypotonia and weakness, and facial, neck, and respiratory muscle involvement [Imoto and Nonaka, 2001]. Interestingly, abnormal suprasegmental influences of the brainstem on the developing motor unit during the histochemical stage of muscle development (20–28 weeks gestation) may alter the rate of maturation of striated muscle or may cause abnormal proportions and relative sizes of fiber types. These features may serve as useful markers of upper motor neuron disease during early muscle development [Sarnat, 1986].

Many clinical features in CFZ syndrome may only be secondary effects of muscle weakness during development. Facial weakness may give rise to altered mandibular movement, consequent mandibular hypoplasia, and Pierre Robin sequence [Carey et al., 1982]. Similarly, clubfeet and other joint contractures are seen non-specifically in myopathies of prenatal onset, associated with paucity of fetal movements [Gordon, 1998]. Hydronephrosis and hypospadias, however, have not been described previously in this disorder. It remains to be seen if these features are individual to our patient or indicate pleiotropy.

We speculate that CFZ syndrome, instead of being a distinct nosologic entity, may actually be the severe end of the spectrum in Möbius syndrome. A prenatal ischemic insult to the developing brainstem, possibly earlier in timing or wider in distribution, may explain the association of Möbius sequence and myopathy. Further studies to evaluate these patients for linkage to 3q21-22 (marker D3S1292) and the *SOX14* gene, as have been described in Möbius sequence [Wilmore et al., 2000], may be helpful.

REFERENCES

Baraitser M, Reardon W. 1994. New case of the Carey–Fineman–Ziter syndrome. Am J Med Genet 53:163–164.

Barth PG. 1993. Pontocerebellar hypoplasias. An overview of a group of inherited neurodegenerative disorders with fetal onset. Brain Dev 15:411–422.

Bavinck JN, Weaver DD. 1986. Subclavian artery supply disruption sequence: Hypothesis of a vascular etiology for Poland, Klippel–Feil, and Mobius anomalies. Am J Med Genet 23:903–918.

Brill CB, Peyster RG, Keller MS, Galtman L. 1987. Isolation of the right subclavian artery with subclavian steal in a child with Klippel–Feil anomaly: An example of the subclavian artery supply disruption sequence. Am J Med Genet 26:933–940.

Carey JC, Fineman RM, Ziter FA. 1982. The Robin sequence as a consequence of malformation, dysplasia, and neuromuscular syndromes. J Pediatr 101:858–864.

D'Cruz OF, Swisher CN, Jaradeh S, Tang T, Konkol RJ. 1993. Mobius syndrome: Evidence for a vascular etiology. J Child Neurol 8:260–265.

Ghabrial R, Versace P, Kourt G, Lipson A, Martin F. 1998. Mobius' syndrome: Features and etiology. J Pediatr Ophthalmol Strabismus 35:304–311; quiz 327–328

Gordon N. 1998. Arthrogryposis multiplex congenita. Brain Dev 20:507–511.

Imoto C, Nonaka I. 2001. The significance of type 1 fiber atrophy (hypotrophy) in childhood neuromuscular disorders. Brain Dev 23: 298–302.

Jaradeh S, D'Cruz O, Howard JF Jr, Haberkamp TJ, Konkol RJ. 1996. Mobius syndrome: Electrophysiologic studies in seven cases. Muscle Nerve 19:1148–1153.

Kiratli H, Erdener U. 2000. Poland–Moebius syndrome: A case report. Jpn J Ophthalmol 44:679–682.

Lammens M, Moerman P, Fryns JP, Schroder JM, Spinnewyn D, Casaer P, Dom R. 1998. Neuropathological findings in Moebius syndrome. Clin Genet 54:136–141.

Leong S, Ashwell KW. 1997. Is there a zone of vascular vulnerability in the fetal brain stem? Neurotoxicol Teratol 19:265–275.

Mamourian AC, Miller G. 1994. Neonatal pontomedullary disconnection with aplasia or destruction of the lower brain stem: A case of pontoneocerebellar hypoplasia? AJNR Am J Neuroradiol 15:1483–1485.

Pedraza S, Gamez J, Rovira A, Zamora A, Grive E, Raguer N, Ruscalleda J. 2000. MRI findings in Mobius syndrome: Correlation with clinical features. Neurology 55:1058–1060.

Ryan A, Marshall T, FitzPatrick DR. 1999. Carey–Fineman–Ziter (CFZ) syndrome: Report on affected sibs. Am J Med Genet 82:110–113.

Saint-Martin C, Clapuyt P, Duprez T, Ghariani S, Verellen G. 1998. Mobius sequence and severe pons hypoplasia: A case report. Pediatr Radiol 28:932.

Sarnat HB. 1986. Cerebral dysgeneses and their influence on fetal muscle development. Brain Dev 8:495–499.

Schimke RN, Collins DL, Hiebert JM. 1993. Congenital nonprogressive myopathy with Mobius and Robin sequence—the Carey–Fineman–Ziter syndrome: A confirmatory report. Am J Med Genet 46:721–723.

St. Charles S, DiMario FJ Jr, Grunnet ML. 1993. Mobius sequence: Further in vivo support for the subclavian artery supply disruption sequence. Am J Med Genet 47:289–293.

Wilmore HP, Smith MJ, Wilcox SA, Bell KM, Sinclair AH. 2000. *SOX14* is a candidate gene for limb defects associated with BPES and Mobius syndrome. Hum Genet 106:269–276.

Wilson ER, Mirra SS, Schwartz JF. 1982. Congenital diencephalic and brain stem damage: Neuropathologic study of three cases. Acta Neuropathol 57:70–74.

Yoon K, Yoo SJ, Suh DC, Lee YA, Kim KS, Choe G. 1997. Mobius syndrome with brain stem calcification: Prenatal and neonatal sonographic findings. Pediatr Radiol 27:150–152.