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Clinical Report

Severe Congenital Myopathy With Möbius, Robin, and Poland Sequences:
New Aspects of the Carey–Fineman–Ziter Syndrome

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We report a boy with severe congenital myopathy, Möbius–Poland sequence, Robin sequence, and severe developmental delay. We consider this patient to have Carey–Fineman–Ziter syndrome. Since this is only the seventh case reported, this case helps to define further the consistent manifestations of this recognizable phenotype. Additionally our patient shows laryngostenosis, intermittent episodes of high blood pressure and Poland sequence as important clinical symptoms.

KEY WORDS: Carey–Fineman–Ziter syndrome; Möbius–Poland sequence; Robin sequence; congenital myopathy

INTRODUCTION

The Carey–Fineman–Ziter syndrome (CFZ, OMIM 254940) is an apparently autosomal recessively inherited disorder consisting of the combination of non-progressive congenital myopathy with Möbius and Robin sequence, facial anomalies, and growth delay, first described by Carey et al. [1982]. Mental development has been described as normal or delayed. Only six children with CFZ syndrome, two sib pairs [Carey et al., 1982; Ryan et al., 1999] and two sporadic cases [Schimke et al., 1993; Baraitser and Reardon, 1994] have been reported in the literature so far.

Here, we report a 3-year-old boy with striking similarities to the previously described cases.

CLINICAL REPORT

The boy was born as the first child of non-consanguineous healthy German parents. There is no family history of myotonic dystrophy and clinical examination of the parents was normal. The pregnancy was complicated by polyhydramnios from 33 weeks gestation on. At 38 weeks of gestation the boy was delivered spontaneously without any complications. Birth weight was 2,615 g (<5th centile), length 50 cm (50th centile), head circumference 35 cm (75th centile), Apgar-scores were 6/7/9. An unusual facial appearance with Robin sequence and cleft palate were diagnosed at birth. The facial anomalies further included frontal bossing, hypertelorism, epicanthus, as well as a prominent nose. He was also noted to have a myopathic facies with bilateral VI and VII-cranial nerve palsy. His right pectoralis major muscle was absent, combined with an ulnar deviation of the right hand (Fig. 1). The boy was hypotonic and had persistent feeding problems. A removal palatal plate was adapted. However, due to recurrent episodes of obstructive apneas intubation was necessary at the age of 7 months, which was followed by tracheotomy at the age of 8 months, and intermittent ventilation has since been necessary. Laryngoscopy performed at 8 months revealed a laryngostenosis.

At the age of $2\frac{4}{12}$ years nocturnal ventilation was still necessary during episodes of pulmonary affection. There still was marked muscular hypotonia. He had global developmental delay. The head circumference decreased to the 25th centile. Length and weight were at the 25th and 50th centile, respectively. He was not able to sit and supported walking had not been achieved. There was no speech. Gavage feeding was still necessary due to dysphagia. On neurological examination no pathological reflexes were present. He was suffering from recurrent episodes of pneumonia. He had several febrile convulsions.

MRI of the brain performed at the age of 2 months was normal. At the age of 19 months a follow-up scan was performed which showed enlarged ventricles caused by reduction of frontal white matter (T2-sequence) in globus pallidum bilaterally, right thalamus, and hypothalamus. In addition medulla oblongata appeared to be thin. There were no CNS calcifications.

Because of his extreme muscular weakness, a muscle biopsy was performed at the age of 10 months. Except for focal broadening of the endomysial soft tissue lightmicroscopy, enzyme-histochemistry, and electronmicroscopy revealed normal skeletal muscle. Immunohistochemical investigation showed expression of neural cell adhesion molecule (N-CAM) in about 10% of muscle fibers and of the neonatal isoform of the myosin heavy chain (MHCn) in 1–5% of muscle fibers (normal range for both parameters: expression in 1–0% of muscle fibers). Taken together, the above results are non-specific signs of developmental delay.

He has had intermittent high blood pressure with facial flush and increased sweat production. The origin of the arterial hypertension is unknown, a catecholamine-secreting tumor has been excluded.

GTG-banded chromosome analysis (550 bands per haploid genome) showed a normal male karyotype (46,XY).

DISCUSSION

In 1982 Carey et al. reported a brother and a sister with Möbius sequence, Robin sequence, hypotonia, unusual facial appearance, and growth delay. Due to a non-progressive

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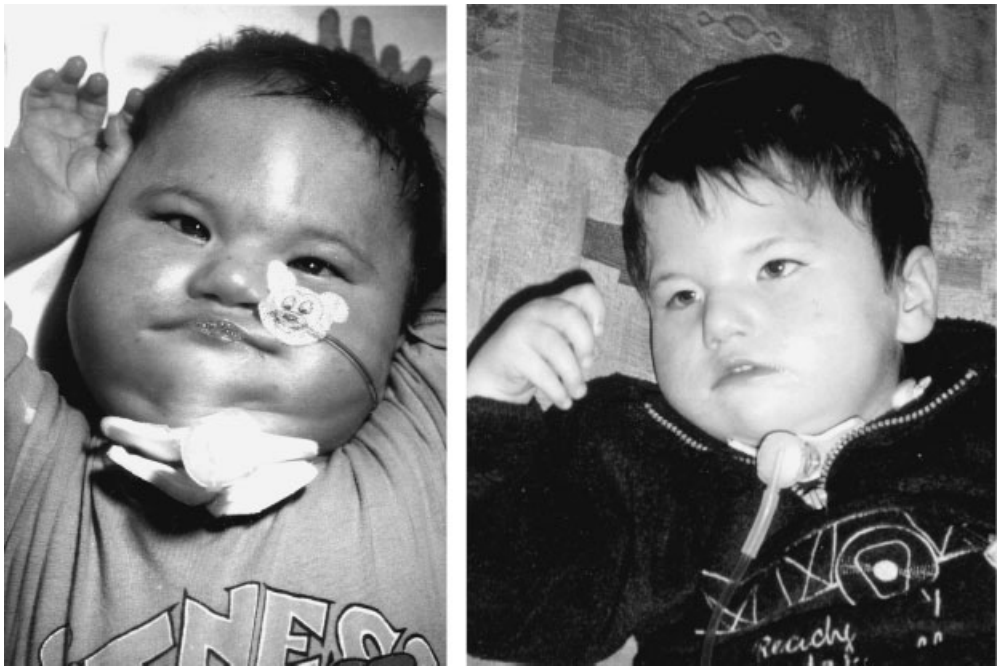

Fig. 1. Propositus at the age of 1 and 3 years, respectively presenting with myopathic facies, frontal bossing, hypertelorism, epicanthus, and an unusual shaped nose with broad nasal bridge, short columella, and short philtrum. Note the ulnar deviation of the right hand.

myopathy motor development was delayed. Intelligence was considered as normal. The authors used this sib pair to illustrate the Robin sequence as a consequence of neuromuscular syndromes. Four other children with a similar phenotype have since been described, confirming the validity of the syndrome [Schimke et al., 1993; Baraitser and Reardon, 1994; Ryan et al., 1999]. For the definition of rare syndromes every single case report is important since they may help evaluating the clinical spectrum of the entity. Microcephaly was only described by Carey et al. [1982], but could not be confirmed in the later reports. Our patient and case 1 described by Ryan et al. [1999] are normocephalic, but the head circumference had decreased in the first year of life. Scoliosis and talipes are regarded as important manifestations of the CFZ syndrome by Ryan et al.

TABLE I. Main Clinical Manifestations in Patients With CFZ Syndrome

	Carey et al. [1982]				Ryan et al. [1999]		
Manifestation	Patient 1	Patient 2	Schimke et al. [1993]	Baraitser and Reardon [1994]	Patient 1	Patient 2	Our patient
Gender	m	f	m	m	m	f	m
Polyhydramnios	−	−	−	−	−	+	+
Delivery at term	+	+	+	+	+	+	+
Birthweight	2,600g	2,620g	3,100g	2,700g	2,800g	2,750g	2,615g
Short stature	+	+	+	−	−	−	−
Microcephaly	+	+	−	−	−	−	−
Facial weakness	+	+	+	+	+	+	+
Ophthalmoplegia	+	+	+	+	?	+	+
Ptosis	+	+	+	+	−	+	+
Downslanting palpebral fissures	+	−	+	+	+	+	−
Triangular nose	+	+	+	+	+	+	−
Small jaw	+	+	+	+	+	+	+
Cleft palate	+	+	+	−	−	−	+
Feeding/swallowing problems	+	+	+	+	+	+	+
Nocturnal ventilation	−	−	+	−	−	+	+
Hypotonia	+	+	+	+	+	+	+
Developmental delay	−	−	−	−	+	+	+
Seizures	−	−	+	−	+	−	+
Scoliosis	+[a]	+	−	−	−	+	−
Talipes equinovarus	−	−	+	+	−	+	−
Brachydactyly	+	+	+	+	?	+	−
Hypoplastic pectoral muscles	Bilateral	Bilateral	Bilateral	Bilateral	−	−	−
Poland sequence	−	−	−	−	−	−	+

−, absent; +, present; ?, unspecified.
[a]Personal communication J.C. Carey.

[1999], but they were only found in three of the seven children. We suggest that these symptoms only represent the severity of the hypotonia and poor movement abilities during pregnancy. Therefore, they cannot be regarded as constant features of the CFZ syndrome (Table I). In our case laryngostenosis could be the consequence of endotracheal intubation and might therefore not be a primary feature of the CFZ syndrome.

The children reported by Carey et al. [1982], Schimke et al. [1993], and Baraitser and Reardon [1994] have bilateral hypoplasia of the pectoral muscles. In our patient we found a Poland sequence with unilateral aplasia of the right pectoralis muscle, which we believe to be part of the syndrome independently from the overall muscle condition.

We suggest that the mental development and prognosis in patients with CFZ syndrome must be considered with reserve, since in three of the seven cases, including our case and case 1 of Ryan et al. [1999] who died at the age of 8 months, developmental delay is present. Robin sequence in conjunction with the neurological findings present in CFZ patients do favor respiratory difficulties. Whether developmental delay is a primary symptom of the CFZ syndrome or a secondary complication due to possible episodes of hypoxemia remains unclear at the moment.

Apart from the myopathic facies, our patient has only slight facial resemblance to the other children reported, but this is also true for the oldest patient described by Carey et al. [1982]. Therefore, we suggest that facial appearance might not be an invariable feature in this syndrome.

The delineation of the CFZ syndrome from the heterogeneous Möbius–Poland sequence [Parker et al., 1981] is especially important because of the different clinical and genetic implications. So far there are no known laboratory findings specific for the CFZ syndrome and muscle biopsy shows only mild, non-specific myopathic changes [Carey et al., 1982; Schimke et al., 1993, our patient]. Despite the fact that only seven patients were reported, congenital nonprogressive myopathy, Möbius sequence and Robin sequence, hypotonia, delayed motor development and facial anomalies must be considered as major criteria of the CFZ syndrome. All these symptoms are present in our patient. Furthermore, we suggest low birth weight as another consistent finding which might also be an expression of the poor muscle mass. Additional symptoms of CFZ syndrome that have not been described before may be intermittent high blood pressure episodes of unknown origin and Poland sequence as present in our patient.

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