Child's Nerv Syst (1994) 10:347–349

CASE REPORT

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Familial infantile myasthenia: a neuromuscular cause of respiratory failure

Received: 28 December 1992
Revised: 11 May 1993

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Abstract Acute respiratory failure can be the product of any of a great number of muscular, neuromuscular, and neurologic causes. The family history may be extremely helpful in narrowing the differential diagnosis. We report the case of a girl who, during the course of a slight upper respiratory infection, presented with acute respiratory failure requiring mechanical ventilation. The family history was significant for a brother who had arthrogryposis and died at 15 h of life, also from respiratory failure. The patient herself had a history of palpebral ptosis in the evening. The absence of electromyographic and muscle biopsy abnormalities and the patient's positive response to anticholinesterase therapy supported the diagnosis of familial infantile myasthenia. We emphasize the importance of considering the myasthenic syndromes in the differential diagnosis of acute respiratory failure, since appropriate therapy can rapidly resolve the symptoms. Furthermore, an accurate diagnosis allows appropriate genetic counseling for the hereditary forms.

Key words Congenital myasthenia
Neuromuscular disease
Respiratory failure

Introduction

Familial infantile myasthenia is an autosomal recessive disorder that is clinically characterized by ophthalmoparesis, feeding difficulty during early infancy, muscular weakness following exercise, and attacks of apnea precipitated by crying, vomiting, or fever [2]. Affected neonates have hypotonia at birth, and many of them require mechanical ventilation. Arthrogryposis may also be present [5]. Paroxysms of weakness and apnea occur repeatedly throughout infancy and adolescence. While the symptoms tend to abate with age, they occasionally recur in adulthood [3].

We describe a girl who from birth experienced feeding difficulty, easy fatigability, hypotonia, and, subsequently, life-threatening episodes of respiratory failure.

Case report

Sara L., a 2570-g (3rd percentile) infant girl was delivered at term by cesarean section to healthy, unrelated parents. The pregnancy had been remarkable for a paucity of intrauterine fetal movements. An ultrasonogram at the 16th week of gestation had further demonstrated that the fists were closed and that polyhydramnios was present. At the time of birth, the girl was noted to have distal articular rigidity, flexion of the hands, long, tapered fingers, and hypotonia.

The patient was fed through a nasogastric tube for the first 15 days of life on account of her easy fatigability and the absence of a sucking reflex. Because the easy fatigability persisted, she was subsequently given a feeding bottle with a wide-bore nipple. At 2 months, she showed hypotonia during the course of a viral respiratory infection. At 4 months, she supported her head and the mother reported that her subsequent psychomotor development was normal.

At 13 months, she was hospitalized for an episode of apnea that was complicated by generalized hypotonia and perioral cyanosis. The preceding day, the girl had experienced the onset of rhinitis and high fever. The neurological findings were reportedly within normal limits. During this hospitalization, the girl had two further episodes of apnea, hypotonia, and cyanosis during meals. However, all assessments, including arterial blood analysis, serum chemistry, and cortisol, adrenocorticotropic hormone, and insulin tests were normal.

One month later, she was hospitalized again for respiratory difficulty, extreme pallor, loss of consciousness, generalized hypotonia, bradycardia, and myoclonus. When she had a second, similar crisis, the child was transferred in a soporific state to the intensive care unit of our hospital, where she was placed on a mechanical ventilator. A careful interview of the parents revealed palpebral ptosis and poor head control in the evening. A younger brother, who died at 15 h of life from respiratory failure, had arthrogryposis.

On physical examination, the patient's weight was 7 kg (<3rd percentile) and her height was 75 cm (25th percentile). There was facial muscular weakness, a high-arched palate, a small jaw, and generalized hypotonia. The deep-tendon reflexes were present and bilaterally equal. Routine hematologic and serum electrolyte studies and urinary organic acids were normal. Aminoacidemia, aminoaciduria, and the serum carnitine level were normal. An electroencephalogram demonstrated slow waves. A transfontanellar ultrasonogram was normal. An electromyogram showed no signs of muscular injury. Ultrastructural and histochemical studies of a biopsy specimen from the quadriceps muscle showed no abnormalities. Clinical and electromyographic findings in the mother were also within normal limits. An assay for anti-acetylcholine re- ceptor (AChR) antibodies was negative.

A congenital form of myasthenia was suspected, but given the abundant respiratory secretions, the previously reported episode of bradycardia, and the possibility of provoking adverse muscarinic side effects (increased bronchial secretions, bradycardia, atrioventricular block, etc.), the intravenous edrophonium (Tensilon) test was not performed. Instead, pyridostigmine bromide therapy was instituted at a dose of 10 mg p.o. t.i.d., with complete symptomatic resolution in 3 days. The therapy has subsequently been adjusted to match the increase in the patient's weight. For the past 2 years, the evening dose has been substituted by a slow-release preparation of pyridostigmine bromide.

At present, Sara is 3 years old and well. Even when afflicted with acute febrile episodes, she manifests no weakness or apnea. A transient episodes of palpebral ptosis occurred on only one occasion, which was associated with her mistakenly having been given only one-sixth of her usual daily dose.

Discussion

In our patient, hypotonia and acute respiratory failure triggered by fever or infection were recurrent clinical presentations. They were so significant as to require the assistance of mechanical ventilation. Pertinent positive findings in the case history included: a younger brother with arthrogryposis who died during the first hours of life from respiratory failure; the reported scarcity of the patient's intrauterine movements; the presence of polyhydramnios and hypotonia; feeding difficulty during the neonatal period; and the presence of slight bony and articular abnormalities, such as a high-arched palate and flexures of the hands at birth. In the setting of acute respiratory failure under conditions of stress, these findings strongly suggest a genetically-transmitted muscular or neuromuscular disorder [6].

The absence in the mother of clinical or electromyographic manifestations, including cataracts, ruled out congenital myotonic dystrophy. Furthermore, the absence of histochemical or ultrastructural abnormalities of the muscle biopsy excluded the diagnosis of a congenital myopathy, and the normal serum lactate and pyruvate levels and the normal muscle biopsy findings excluded the mitochondrial myopathies. Last, the clinical, histologic, and electromyographic data excluded the diagnosis of a spinal muscular atrophy, such as Werdnig-Hoffmann disease.

The patient history, the normal laboratory studies, and the absence of histochemical or ultrastructural muscle abnormalities point to the diagnosis of a myasthenic syndrome. This diagnosis was confirmed by the progressive, rapid remission of the symptomatology following the institution of anti-cholinesterase therapy.

Myasthenia may be classified [1] as: acquired, autoimmune (myasthenia gravis, Lambert-Eaton syndrome); congenital (Table 1); toxic (botulism and drug-induced disorders); or transient (in newborn of mothers affected by myasthenia gravis).

In our patient, the historical (normal mother, brother who died in the neonatal period secondary to respiratory insufficiency), clinical, and laboratory data suggest congenital myasthenia (Table 1).

The absence of a predominance of type 1 fibers or of type 2 fiber atrophy [1] on histochemical examination of the muscle points to familial infantile myasthenia. That arthrogryposis is associated with this disease [4, 5] suggests that Sara's younger brother had been similarly affected.

The clinical and family histories of our patient emphasize the importance of neonatal intensive care and appropriate use of mechanical ventilation during crises. If instituted promptly, they not only encourage a favorable outcome, they also allow one to have at one's disposal the necessary time to arrive at a precise diagnosis. A precise diagnosis is imperative in order to make a realistic prognosis, provide appropriate genetic counseling to the fam-

Table 1 Classification of the genetic disorders of neuromuscular transmission

	Mode of genetic transmission
Familial infantile myasthenia	Autosomal recessive
End-plate acetylcholine receptor deficiency	Autosomal recessive
Slow-canal syndrome	Autosomal dominant
End-plate acetylcholinesterase deficiency	X-linked recessive

ily, and possibly, institute specific pharmacologic therapy. Furthermore, adequate and early physical therapy is indispensable; it can resolve most cases of arthrogryposis, obviating eventual corrective surgical intervention [6].

Admittedly, familial infantile myasthenia is a rare disease, but it is probably not always diagnosed; therefore, its incidence is probably underestimated, as the family history of our patient demonstrates. Given the ease of performing the diagnostic Tensilon test and the efficacy of anti-cholinesterase therapy, this genetic condition must be considered in subjects with respiratory insufficiency and feeding difficulty when these are associated with neuromuscular signs such as palpebral ptosis and arthrogryposis.

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