Fazio Londe syndrome: A treatable disorder

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Abstract

Fazio Londe Syndrome is a rare neurological disorder presenting with progressive bulbar palsy with respiratory failure. Initially considered to have an unrelenting course, is now found to be due to mutations in the SLC52A3 gene which encodes the intestinal (hRFT2) riboflavin transporter in some children. We report an 11-year-old child with features of Fazio Londe syndrome who presented to our Institute with respiratory failure.

Key Words

Fazio Londe disease, hereditary motor neuronopathy, spinal muscular atrophy

Case Report

An 11-year-old male child presented with a history of chest pain, breathlessness of 2-weeks duration. He had a history of difficulty in swallowing liquids that progressed to involve solid foods. Child was treated at a local hospital as bronchopneumonia and was shifted to our Institute with endotracheal intubation and inotropic support.

History revealed a neurological illness with difficulty in swallowing liquids and solids, nasal regurgitation to liquids, nasal twang 2 years ago. He was treated as post-diptheritic bulbar palsy and had a residual bulbar weakness. Other details were not available. Child was ambulant and was apparently normal until 3 months back when he developed respiratory distress and was treated at a local hospital prior to referral. He had a past history of dog bite 3 months ago for which he received five doses of ARV. He was born out of a non-consanguineous marriage. The antenatal, natal, postnatal histories were insignificant. His elder sibling was healthy. This child was immunised appropriate for age. There was no family history of any neurological illness or sibling death.

Child was afebrile. His vital signs were stable. Examination of the cardiovascular system revealed a short systolic murmur in the left para sternal region. Neurological examination revealed normal sensorium. He had bilateral facial weakness and palatal paralysis. His extra-ocular movements were full and pupils were normal. He had continuous drooling of saliva to the extent of intermittent dehydration. He had wasting of small muscles of both hands with polyminimyoclonus. Tone was normal and reflexes were brisk. Power in all four limbs was 3/5. There was no gynecomastia and testicular volume was normal.

Complete blood count, urea creatinine and liver enzymes were normal. His chest X-ray and CT chest were suggestive of pneumonitis. Echocardiography showed patent foramen ovale. Thyroid profile, serum levels of calcium, pyruvate, lactate, ammonia and CPK were normal. His blood gases were within normal limits. Corneal smear was negative for rabies antigen. Barium swallow was normal. Multiple attempts for weaning were not successful and the child underwent tracheostomy in view of the need for continued ventilatory support due to respiratory muscle weakness. He was on antibiotics for his respiratory infection.

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Examination of the tongue during one of the reintubation attempts revealed atrophy with fasciculations. His hearing evaluation was normal. Pulmonary function tests revealed a restrictive pattern. At this time of the hospital stay it was decided to work up for neurological illness causing predominant respiratory muscle weakness with bulbar involvement. MRI brain with entire spine screening was normal. PCR for Survival motor neuron gene (SMN gene exon 728) was negative. Nerve conduction study (NCS) was normal. Electromyography (EMG) showed spontaneous fibrillations potentials with high amplitude polyphasic potentials and incomplete pattern of interference. All these suggested a neurogenic pathology. His muscle biopsy revealed neurogenic atrophy and vitamin B12 levels were normal. Diagnosis of a variant of Spinal Muscular Atrophy was considered as the bulbar involvement was more prominent than proximal muscle weakness.

Child was extubated after 40 days of mechanical ventilation. A final diagnosis of Fazio Londe disease was made. With recent evidence of Fazio — Londe (FL) disease being treated with Riboflavin, the child was started on Riboflavin therapy. Child was reviewed after 6 months of follow-up. His speech was normal without nasal twang. Other cranial nerves were normal. He was able to swallow liquids and solid food without difficulty. He had no drooling of saliva. Power in all four limbs was 4/5. Tone and reflexes were normal. His muscle wasting persisted. He was able to walk on his own. He did not have any polyminimyooclonus on review.

Discussion

Respiratory failure in children is commonly due to primary respiratory or cardiac illness in the intensive care unit. Although the child had pneumonitis it was too minimal to cause a refractory respiratory failure. There was no cardiac lesion and the sensorium was normal. All these factors pointed to a neurological cause of respiratory failure. Clinical signs of progressive bulbar palsy, NCS findings, EMG, muscle biopsies were the clues for the diagnosing to anterior horn cell disease. In the absence of hearing loss a diagnosis of FL was considered.

The possibilities considered were — hereditary motor neuronopathy (HMN) type I (Brown Vialetto Van Laere syndrome -BVVL), type II, Fazio Londe disease, Kennedy disease and juvenile form of Tay Sach disease. Absence of sensorineural hearing loss did not favor BVVL. Absence of gynecomastia or testicular atrophy did not suggest Kennedy disease. Due to the absence of radiologically evident cerebellar atrophy, juvenile Tay Sach was not considered though hexosaminidase A levels could not be tested.

In some patients FL has been found to be caused by mutations in the SLC52A3 gene which encodes the intestinal (hRFT2) riboflavin transporter.[1] Plasma flavin levels and acyl carnitine levels have been found to be low in some children. But the response to riboflavin is independent of the flavin levels. Recent literature has shown that both BVVL and FL are the same disease entity and absence of hearing loss in FL is the major difference between them. FL is said to present in the first decade of life while BVVL presented in the 2nd decade of life.

Literature has documented the same homozygous mutation in siblings presenting with BVVL and FL.[2]

In Fazio Londe disease, motor neuron in cranial nerve nuclei may be progressively impaired and decreased in number, with resultant progressive bulbar paralysis and little or no accompanying anterior spinal cord involvement. Riboflavin in the dose of 10-15 mg/kg/day has been used successfully and the time for response may vary up to months in some children. [3] Improvement in the muscle power can be seen as early as a few days and it has been documented to facilitate early recovery from respiratory paralysis even in patients on tracheostomy.[3] Bulbar paralysis is only one facet of progressive motor neuron disease in many of these patients, and pathologic study confirms widespread degenerative changes in the brainstem. Morphologic involvement of anterior horn cells has been demonstrated, despite the absence of clinical signs. Of the cranial nerves cranial nerve VII is almost always affected. Cranial nerve XII is usually affected pathologically, and clinical manifestations are apparent in the early onset patients. Involvement of extraocular movements is usually rare. Bulbar impairment is indicated by dysarthria, dysphagia and facial diplegia.

There are three subtypes as described in literature. A very rare autosomal dominant form, two variants with autosomal recessive inheritance. One with early onset of respiratory symptoms and rapid progression to death and another with late onset respiratory symptoms with protracted course. This child probably belongs to the autosomal recessive late onset type. Treatment is usually supportive. Riboflavin has been used with promising results.

FL presents much earlier with rapidly progressive disease with stridor, facial weakness and weakness of the upper limbs and leads to death by 18 months due to the respiratory failure. For better results riboflavin needs to be started at the earlier stages of the disease.[4] Although the mechanism how riboflavin is useful in FL is not clear there is now undeniable evidence for the use of riboflavin in the delay in the progression of illness which was considered an unrelenting illness in the past.

In conclusion, though rare, neurological causes of respiratory failure should be thought of when dealing with a case especially the rare variants of common diseases. It is worth trying this simple therapy with riboflavin for FL even in the absence of genetically proved mutation as the therapy is harmless.

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