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Case report

Brown–Vialetto–Van Laere syndrome; variability in age at onset and disease progression highlighting the phenotypic overlap with Fazio-Londe disease

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Abstract

We report four siblings showing features of a pontobulbar palsy, a mixed spinal and upper motor neuropathy and variable deafness. The observation of affected males and females born to consanguineous first cousin parents suggests autosomal recessive inheritance. Two children presented in the first 16 months of life with stridor and died of respiratory failure by the age of 2 years. Hearing loss was not apparent in these infants. In contrast, 2 further siblings developed a bulbar palsy in their sixth year followed by the onset of deafness and features of an anterior horn neuropathy with corticospinal tract involvement. They exhibited a relatively slow but relentless decline over a period of several years. These cases highlight the phenotypic overlap of Brown–Vialetto–Van Laere syndrome with Fazio–Londe disease. Rather than representing two separate disorders, our findings suggest the possibility of a single disease entity which may usefully be considered a form of juvenile amyotrophic lateral sclerosis.

Keywords: Brown–Vialetto–Van laere syndrome; Fazio–Londe disease; Bulbar palsy; Deafness; Juvenile amyotrophic lateral sclerosis

1. Introduction

Pontobulbar palsy with deafness, known as the Brown–Vialetto–Van Laere syndrome (MIM 211530), is a rare disorder characterised by bilateral sensorineural hearing loss in association with other cranial nerve palsies, usually involving the motor components of the 7th and 9th–12th cranial nerves, and a mixed spinal and upper motor neuropathy. A similar disorder, Fazio–Londe disease (MIM 211500) has been considered distinct from Brown–Vialetto–Van Laere syndrome because of the absence of deafness. We describe a family illustrating a marked variability in the age at onset and subsequent disease progression and compare these findings with those of earlier reported cases.

1.1. Child A

This child was born after a normal pregnancy and delivery weighing 3.37 kg. He sat at 6 months, walked at 9 months and had single words with appropriate social skills at 1 year of age. At this time he presented to the local paediatric service with stridor, bilateral ptosis and an expressionless face. Vocalisation, hearing and eye movements appeared normal. No other muscle weakness was

Abbreviations: CT, computerised tomography; NCS, nerve conduction studies; EMG, electomyography; SMN, survival motor neuron; MRI, magnetic resonance imaging; dB, decibel; Hz, Hertz; FVC, forced vital capacity; CPAP, continuous positive airway pressure; ALS, amyotropic lateral sclerosis; CSF, cerebrospinal fluid.

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evident. Within a month of presentation he exhibited a loss of head control and 3 months into his illness he developed breathing difficulties with respiratory failure requiring tracheostomy and ventilatory support. By age 16 months he was unable to vocalise and manifested a rapidly progressive truncal weakness with preserved power in the limbs. Cranial CT, nerve conduction studies (NCS), electromyography (EMG) and muscle biopsy were reported as normal. He did not undergo formal hearing assessment. Six months after presentation he died from respiratory failure. A diagnosis of Fazio–Londe disease was made.

1.2. Child B

This female child was born following a normal pregnancy and delivery with a birth weight of 3.15 kg. Early development was normal. She passed a hearing test at 9 months. At age 1 year she was walking and had a few single words. At 16 months she presented with stridor which was worse on exertion. Indirect laryngoscopy demonstrated vocal cord paralysis. She had normal vision and hearing, full eye movements and no truncal or limb weakness. One month after presentation she experienced swallowing difficulties and exhibited facial weakness with ptosis and some proximal muscle weakness. There was no ophthalmoplegia, visual disturbance or concern about her hearing. Her parents declined further investigation. Over the next 4 months she experienced progressive truncal and limb weakness and frequent cyanotic episodes. Her parents refused ventilatory support and she died of respiratory failure aged 23 months.

1.3. Child C

She first presented at 5 years of age with a history of stridor, reduced facial movements, poor vision. Past medical history was unremarkable with a normal pregnancy and birth history, a birth weight of 3.17 kg and normal developmental milestones. Her general health had been good and intelligence was felt to be above average. At this time she was noted to have a slight ptosis, normal pupils and a full range of eye movements. She had reduced facial expression and tongue fasciculation but a normal gag reflex. She had inspiratory stridor at rest. She walked with a normal gait, had good proximal and distal power and retained muscle bulk. Her deep tendon reflexes were generally brisk. There were no other pyramidal signs. She had a mild tremor of the arms bilaterally. Cranial CT was normal and EMG of right deltoid and sensory NCS from sural nerve were unremarkable. Laryngoscopy revealed paralysis of the vocal cords with a normal trachea and glottis. Visual evoked responses and electroretinogram were unremarkable.

Over the next year she developed difficulty with chewing and swallowing. There was a loss of the gag reflex and increasing swallowing difficulties necessitated nasogastric feeding and subsequently gastrostomy. At this point her stridor had resolved and gross motor function was unchanged. At 7 years of age she was noted to have a progressive hearing loss. Pure tone audiometry demonstrated a moderate-to-severe sensorineural deficit and she was fitted with a hearing aid. At 11 years, she experienced increasing facial weakness and was unable to close her eyes. Stridor was present on exertion but not at rest. She was still able to make sounds but was now using sign language to communicate. Gait and motor function unchanged. Testing for an SMN gene deletion and abnormal fragment on 4q as seen in fascio-scapulo-humeral muscular dystrophy was negative.

At 13 years she was experiencing daytime somnolence due to obstructive sleep apnoea. She had difficulty maintaining head position and climbing stairs. Two months thereafter she underwent tonsillectomy. At this time there was a gradual deterioration in gross motor function although she was still ambulant. She had difficulty tolerating enteral feeds. She demonstrated symptomatic hypoventilation and increasing drowsiness. A month after operation she was admitted to intensive care with respiratory collapse requiring ventilatory support. Examination revealed reduced bulbar function with a poor cough and respiratory muscle weakness. She was unable to stand independently but could walk with support. She had reasonable hand function and was still able to write and sign. She exhibited a marked ptosis with an external ophthalmoplegia and dysconjugate eye movements. She had muscle wasting greater in the upper than lower limbs, reduced power proximally greater than distally, brisk reflexes, bilateral ankle clonus and up-going plantar responses.

One month after admission to intensive care a tracheostomy was sited but she continued to require 24-h ventilatory support. She experienced rapid progression of her muscle weakness and by this time had no head control. MRI of the brain and upper spinal cord was normal. Repeat EMG showed chronic partial denervation with bursts of paroxysmal fibrillation. Nerve conduction studies were normal. At 14, her condition had deteriorated further. She had no antigravity movements at the shoulder, elbow, hip or knee and was now unable to use her hands to sign. She had a further loss of voluntary eye movements, her only spontaneous movement being an up-gaze of the left eye.

1.4. Child D

This female child was born after a normal pregnancy and delivery. Early development was unremarkable. She presented with stridor, weak voice, myopathic facies, tongue fasciculation and hearing loss aged 7 years. Again, vocal cord paralysis was seen on indirect laryngoscopy. Pure tone audiometry demonstrated hearing loss in both ears across a range of frequencies (50 dB in right and 35 dB in the left at 250 Hz and 35 dB on both sides at 8000 Hz). Parents refused further neurophysiological investigation, muscle biopsy or brain imaging.