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Brown-Vialetto-Van Laere Syndrome-report of three cases.

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Abstract

Brown-Vialetto-Van Laere syndrome is a rare disease with progressive ponto-bulbar palsy and sensorineural deafness first described in 1894. There is only one earlier case report from Saudi Arabia. Here we report three cases with literature review.

Keywords: Brown-Vialetto-Van Laere syndrome, Autosomal recessive inheritance, Hearing impairment, Hypotonia.

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Introduction

Brown-Vialleto-Van Laere Syndrome (BVVLS) (OMIM No.211530), also called "Progressive Pontobulbar Palsy with sensorineural Deafness" or "Bulbar Hereditary Neuropathy type I", is a rare entity with unclear etiology aspects and several types of inheritance. Its first description was by Charles Brown in 1894.

Following cases were described by Vialetto and Van Laere in 1936 and 1966 respectively. The number of reported cases, though mentioned in some articles is not precisely addressed as it seems to be under reported. Also some mixing with other syndromes as Fazio–Londe and Madras disease was made [1].

Different patterns of inheritance were described. Majority of the familial cases demonstrate autosomal recessive inheritance [2], although autosomal dominant and X-linked modes of inheritance were described in individual cases.

The two major differential diagnoses for BVVLS are Fazio-Londe disease and Juvenile Amyotrophic Lateral Sclerosis (JALS). Fazio–Londe disease (OMIM 211500), also called " Bulbar Hereditary Neuropathy type II" has been considered distinct from BVVLS because of the absence of deafness [3]. JALS presented at a younger age in sporadic cases, with mixed upper and lower motor neuron signs, bulbar palsy but sensorineural deafness is not a feature of this condition [4].

We report 3 cases of BVVLS, highlighting several unusual features of our case compared with those reported in the literature. To our knowledge, this will be the first case series and the second report after that published in July 2012 [5] with BVVLS reported from Saudi Arabia.

Case report

Case 1: A three years and four months old girl had first hearing impairment at the age of two years. Four months later, she started to have speech difficulty, which started by decreased volume of speech followed by complete loss of previously acquired vocabulary without regression in her cognitive functions. Few months later, she started to have difficulty with swallowing, for solid food initially, followed by liquids as well. She lost weight and became physically weaker than before. Following that, ambulation became troublesome and before admission to the hospital she became wheelchair bound. She was admitted to Pediatric Intensive Care Unit (PICU) where she continued to have breathing and swallowing problems. She was intubated and mechanically ventilated. Several trials of extubation were unsuccessful, so tracheostomy tube was sited but she continued to require 24 ***hour*** ventilatory support. A gastrostomy tube was inserted for nutritional support. Her parents noted that she ha***d*** droopy eyelids. There was no history of seizures. She used to have tachycardia and swinging in her blood pressure.

Her second degree consanguineous parents were healthy. Her birth was uneventful. She attained her developmental milestones at appropriate ages till the age of two years. No other family members had neurological symptoms or hearing deficits.

The patient's general appearance was that of a weak and slim girl. The neurological examination revealed equal reactive pupils, normal fundi, partial ptosis, no restriction of her extra ocular movements, exaggerated jaw reflex, bilateral facial diplegia with flattening of nasolabial folds, no facial expressions to stimulations; she is not responsive to loud sounds. Her tongue was central, non atrophic with visible fasciculations. She ha***s*** axial and appendicular hypotonia, mild generalized muscular weakness with

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power range of 3 - 4/5 all over and tremulous hand movements bilaterally. Deep tendon reflexes were 1+ on biceps, 2+ on brachioradialis, 0-1 in the knee, 4+ in the ankle with downgoing plantars with bilateral 3-4 clonus beats at the ankle joints. There was no fasciculation in muscles except tongue. Her sensory examination seemed equally intact. She seemed to be of normal intelligence.

The following investigations were normal**:** routine hematology and biochemistry including thyroid function tests, creatine kinase, serum and cerebrospinal fluid (CSF) lactate and pyruvate levels, Tandem MS, organic acid analysis of urine, lysosomal enzyme screening.

CSF showed increased protein with no cells. Magnetic resonance imaging (MRI) of brain was initially normal, repeated MRI with fine brain stem cuts showed mild global brain atrophy and hyperintense signals at the region of vestibular and cochlear nuclei and the inferior cerebellar peduncle. Brainstem auditory evoked potentials (BAEP) showed absent III, IV and V waves. Motor and sensory nerve conduction velocities revealed *absent sensory nerve action potential (SNAP)* in the right median, right ulnar, and sural nerves, low compound motor action potentials amplitudes *(CMAP)* and slow conduction velocities *(CV)* in all segments of The right ulnar, right median, right facial and tibial nerves. Repetitive nerve stimulation studies of the right median nerve *showed* normal results. EMG examinations of the selected muscles did not show evidence of abnormal spontaneous activity. No Motor Unit Potentials (MUPs) were observed in these muscles. No fasciculation potentials were recorded.

Case 2

18 months old boy got cardiac arrest while on full ventilator support. He was the outcome of spontaneous vaginal delivery after an uneventful full term pregnancy to first cousin healthy parents denying any similar cases in the family. The baby was growing well until the age of 9 months when he got croup like episodes that was diagnosed as bronchiolitis needing hospital admission that was followed by symptomatic improvement. Few weeks later the child got stridor and needed intubation.

He stayed on ventilator for a week then was discharged in stable condition. On follow up, he was initially noticed to have minimal increase of appendicular tone. He started to lose previous cooing and began to have drooling followed by loss of facial expressions. He was readmitted with facial diplegia, stridor, generalized weakness and decreased tone.He was examined by laryngoscope revealing vocal cord paresis after which he got cardiac arrest and was intubated.

Quickly he became flobby, unable to sustain normal breathing; necessitating full ventilatory support. Examination at that time revealed severely hypotonic child at both truncal and appendicular levels with generalized paucity of movements. His pupils were reactive to light; but there were restrictions of movements with preserved corneal reflexes. There was facial diplegia and loss of response to sounds. Later baby was unable to turn head to the sides. Fasciculations were noticed on the tongue. Reflexes were normal on the upper limbs and exaggerated on the lower limbs. Plantars were equivocal and sensations were intact. His S1 and S2 were normal with soft abdomen and no organomegaly. The child got hypertension that was controlled by Atenolol. He got bilateral exposure keratitis that was treated successfully.

Initial MRI brain was reported normal in the initial hospital, then in a tertiary one it was reported as having changes in the brainstem, the medial longitudinal fasciculus, the cerebellar peduncle, the central tegmentum and the hypoglossal nuclei. No involvement of the supratentorial white matter. The changes were supportive of diagnosis of ALS.

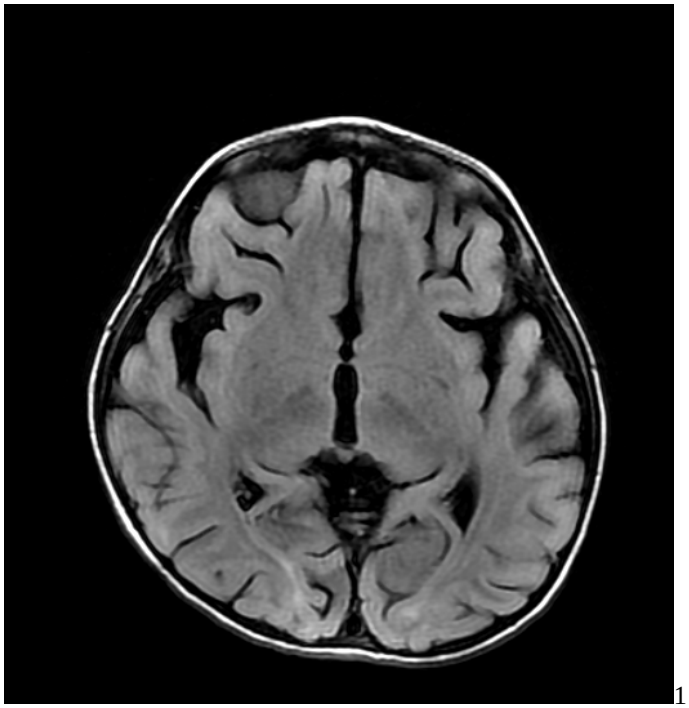
Test for spinal muscular atrophy (SMA) was negative, Electromyography (EMG) was not conclusive and Creatine Kinase (CK) was within normal limits. His electrolytes were normal. His Auditory Evoked Potentials were flat. The diagnosis of BVVL syndrome was considered.

The parents initially were rejecting and denying the diagnosis. Unfortunately the mother was pregnant and just gave delivery when the boy was around 10 months and the outcome was case 3.

Case 3

11 months old girl died in another hospital while she was on full ventilatory support. She was an outcome of spontaneous vaginal delivery and a product of full term unremarkable pregnancy to the same parents mentioned above. She developed normally till the age of 7-8 months when she started to have hypotonia, loss of response to sounds and decreased power with stridor, drooling and loss of facial expressions. She was taken to a secondary hospital where she ran a similar but shorter course compared to her elder brother and she died at an earlier age.

The parents were counseled and they were told that both siblings must have had the same disease. They started to accept the diagnosis.



Figures 1. MRI brain of Case 1: *Mild to moderate generalized brain tissue volume loss.*

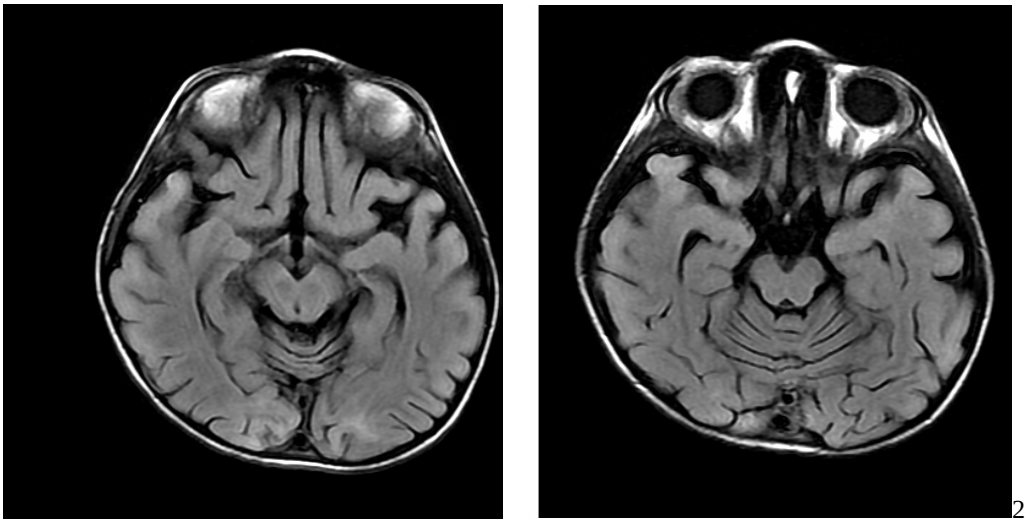


Figure 2. *Bilateral symmetrical high signal foci on FLAIR that are seen at cerebellum peduncle of uncertain significance*

Discussion

The clinical neurological findings of sensorineural deafness, facial diplegia, tongue fasciculations, upper motor neuron and lower motor neuron signs point to a lesion in the lower brain stem and a higher cortical one, and this combination is consistent with the syndrome of progressive pontobulbar palsy with sensorineural deafness (Brown Vialetto Van Laere syndrome). Other brainstem lesions, e.g. tumors, infections, cranial nerves and muscle diseases should be excluded using appropriate investigations.

BVVLS age of onset falls into a wide range from early infancy to the fourth decade, most of the reported cases fall between the first and second decade. Cognitive func-

tions are not affected in this syndrome; although coincidental finding of mental retardation in a child with BVVLS with dysmorphic features was reported in one case [6].

Madras motor neuron disease (MMND) was originally described by Meenakshisundaram et al in 1970. It is characterized by sensorineural deafness, atrophy and weakness of distal muscles of upper and lower limbs, dysarthria, bilateral facial palsy, bulbar palsy and visual impairment with optic atrophy. Occasional recessive inheritance is described and the disease has a slowly progressive course than BVVLS. Furthermore the sex distribution is different, males outnumbering females and commonly found in South India as a sporadic. Madras motor neuron disease has attracted considerable interest in view of its characteristic features of involvement of facial, bulbar and hypoglossal cranial nerve nuclei, lower and upper motor neuron signs in the limbs with associated sensorineural deafness. Clinical features of both disorders clearly overlap and it is thus possible that they represent more or less related disorders.

Breathing abnormalities have been reported in some cases of the BVVL syndrome in the form of central sleep apnea (CSA) and obstructive sleep apnea (OSA) due to the brain stem affection or weakness of the respiratory muscles due to affection of the spinal motor nerves, which can result in acute respiratory failure with anoxic cardiac arrest [7], Breathing abnormalities needed to be assessed early on in any patient with this syndrome [8]. This seems to be the case in our above mentioned 2 siblings.

Although many cases are sporadic, about 50% are familial, and most suggest autosomal recessive inheritance. Few affected families have demonstrated an inheritance pattern compatible with autosomal dominant or X-linked inheritance. Therefore, genetic heterogeneity seems a possibility. Some advocated early administration of Riboflavin with the hope of either delaying the progression and or change natural history [9].

A report on a 3 years old patient with Mutation in the *C20orf54* Gene did not benefit from steroids, immunoglobulins, and riboflavin [10].

Brown-Vialetto-Van Laere syndrome should be considered in patients with sensorineural hearing loss and pontobulbar palsy. Patients should be screened for riboflavin deficiency and a therapy with riboflavin may provide effective treatment in some affected patients [10].

In conclusion, we have reported 2 families with consanguineous marriages.

The first family had a 40 months old girl affected at the age of 2 years and her manifestations progressed with time. The other family had 2 siblings, an 18 months old boy who was affected at nearly 9 months of age and died at 1 1/2 years. His sister developed the disease at 8 and died at 11 months of age. All had sensorineural hearing loss and pontobulbar palsy.

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