

Four cases of brown-vialetto-van laere syndrome from Iran: Clinical and electrophysiologic findings

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Keywords

Brown-Vialetto-Van Laere Syndrome, Progressive Pontobulbar Palsy, Sensorineural Deafness

Abstract

Brown-Vialetto-Van Laere syndrome (BVVLS) is a rare neurological disorder. We report our finding about four patients clinically and electrophysiologically diagnosed as BVVLS and denoted their clinical features with comparison to previous reports. The first symptom was bilateral hearing loss and the onset of other cranial nerves involvement varied between 0-15 years. Our patients represented some rare features like upper motor neuron signs in one patient and two cases interestingly developed some clinical improvement. This is the first report of BVVLS from Iran. Our patients which represent Caucasian population had generally similar features like previously reported cases.

Introduction

Brown-Vialetto-Van Laere syndrome (BVVLS) or progressive pontobulbar palsy with deafness is a rare degenerative disorder characterized by slow or rapid onset progressive bilateral deafness and cranial nerve involvement, usually motor components of the 7, 9, 10, 11 and 12.¹⁻⁵ Spinal motor nerves and less commonly upper motor neuron may be involved.^{1,2,4} This syndrome was first described in 1894 by Brown and subsequently by Vialetto in 1936 and Van Laere in 1966.^{6,7} Sathasivam reviewed all reported cases until 2007 and was able to retrieve 58 cases.⁸ By now, no case has ever been reported from Iran. Herein, we report 4 Iranian cases of

BVVLS seen from 1999 to 2008 with significant clinical improvement in some of them and we tried to find similarities and differences of our patients who all had Caucasian ethnicity with previously reported patients with BVVLS.

Patient 1

A 17-year-old female, unmarried and student presented with speech problem and progressive hearing loss since the age of 12. She was admitted in our hospital in 1999 with liquid dysphagia and progressive weight loss in the last 6 months. She also reported irregularity in menstruation recently. Her parents were first cousins and four siblings had no problem. Systemic examination was unremarkable except left tympanic membrane perforation. She was mentally normal and there was bilateral facial and cervical flexor weakness. The tongue was atrophic with fasciculation and gag reflex was diminished and the limbs were atrophic with mild proximal weakness. Deep tendon reflexes (DTRs) and sensory exams were within normal limits. Biochemical lab tests revealed no abnormality; but on audiometry, there was severe bilateral sensorineural hearing loss. Electromyography and nerve conduction studies (EMG-NCV) were compatible with motor neuron disease with prominent involvement of cranial muscles; in addition, repetitive nerve stimulation was negative. Other investigations including chest X-ray, brain magnetic resonance imaging (MRI) and abdomino-pelvic sonography were normal.

Patient 2

This 17-year-old girl was admitted for the evaluation of slowly progressive dysphagia and choking from 6 months before admission in 2000.

She also complained of proximal weakness in upper extremities from 2 weeks ago. She had an episode of febrile seizure at the age of 3 and slowly progressive hearing loss from the age of 12. Her 3 brothers and 2 sisters were healthy and parents were non-consanguineous. Physical examination was normal. On neurologic exam, there was bifacial weakness, diminished gag reflex, atrophic tongue with fasciculation and proximal weakness. Routine laboratory tests, peripheral blood smear, creatine phosphokinase (CK), and lactate dehydrogenase (LDH) were all normal, as well as cerebrospinal fluid (CSF) analysis. There was bilateral low frequency sensorineural hearing loss on pure tone audiometry (PTA) and motor neuron involvement mainly in cranial innervated muscles on EMG-NCV. Other investigations including chest X-ray, brain MRI, Tensilon test, repetitive nerve stimulation (RNS) and abdomino-pelvic sonography were negative and genetic testing did not show deletion in SMN1. One year after the beginning of gabapentin, 900 mg/day, she reported some improvement in dysphonia and dysphagia, which continued for the next 4 years, when she was lost to follow up.

Patient 3

This 21-year-old female was admitted in December 2008 because of hoarseness, difficulty in swallowing, choking and fatigue in the recent 3 months. She had weight loss, difficulty in walking and bilateral hearing loss since 2 years ago which aggravated gradually. She also reported chronic bifrontal throbbing headache that was more prominent in mornings and history of several generalized tonic clonic seizures in the past few years. In the last months, she occasionally had mild dyspnea during sleep. Her 4 brothers and 1 sister were healthy and parents were non-consanguineous.

She was alert and of normal intelligence. There was bifacial weakness, wasted tongue with fasciculation, diminished palatal and left vocal cord movements and nasal speech. Weakness particularly in neck and proximal limb girdle and bilateral pes cavus were noted. Routine lab tests, creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and acetylcholine receptor antibody disclosed no abnormality. Findings of brain MRI, chest CT-scan and abdomino-pelvic sonography were unremarkable. There was bilateral low frequency sensorineural hearing loss and electrodiagnostic study was compatible with anterior horn cell disease.

Patient 4

A 22-year-old female, presented with hoarseness, sore throat, dysphagia, and hearing loss from 3 years before our first visit in December 2008. In the last 2 months, weakness developed over lower and then upper limbs associated with muscle wasting, fasciculation and exertional dyspnea. She reported 2 episodes of seizures at the age of 11 and her parents were first cousins and all 4 sisters and her brother were healthy. She was mentally normal with bifacial weakness, wasted tongue and fasciculation (Fig. 1), palatal weakness, reduced motor force more in lower limbs, bilateral foot drop and generalized brisk DTRs. Plantar reflexes were downward. Sensory and cerebellar exams were unremarkable. Lab data revealed hypochromic microcytic

anemia with normal serum iron and total iron binding capacity. In addition, brain MRI was normal. PTA showed bilateral low frequency sensorineural hearing loss and normal tympanometry. Nerve conduction studies were normal and EMG of limbs and tongue muscles was compatible with motor neuron disease. One year after the treatment with 900 mg gabapentin, her swallowing subjectively improved and motor strengths became completely normal. No change in speech and hearing was seen.



Figure 1. Atrophic tongue with fasciculation in patient 4

Discussion

BVVLS is a rare neurological disorder considered as a type of motor neuron disorders which is characterized by bilateral hearing loss (the most common presenting symptom) accompanied by a variety of other mainly motor cranial nerve dysfunction. In spite of rarity, the disease has widespread distribution and cases have been reported in the literature from Europe followed by Asia and South America. Female to male ratio is approximately 3:1.⁹ The age of onset of the syndrome varies from infancy⁴ to the third decade;¹⁰ but is more common in the first and second decades.¹¹ Disease duration varies from 0 (death at the presentation) to 45 years.¹¹ The main cause of death is respiratory failure.

The diagnosis is mainly based on clinical features and electrophysiological studies and no diagnostic biochemical or genetic defect has been reported. Recently a noteworthy progression has made by Peter Green et al.,¹² as they identified C20orf54 gene located in 20p13 in a study of seven families with BVVLS (9 cases which 4 had no consanguinity), although the function of the gene in the nervous system is still not known. Previously search for the mutations associated with spinal muscular atrophy (SMA) has been done in two patients including the survival motor neuron (SMN) gene and neuronal apoptosis inhibitory protein (NAIP) gene which was negative.⁸

Half of the cases reported in the last century were sporadic,¹³ in the familial cases the vast major inheritance was autosomal recessive; in some families autosomal dominant inheritance^{2,14,15} or probable X-linked inheritance has been postulated.² All 9 cases reported by Green¹² had recessive mutations (homozygous or compound heterozygote, nonsense or missense mutations).

Table 1. Clinical feature of our patients with Brown-Vialetto-Van Laere syndrome

Case No	sex	Family history	Age at onset of deafness (year)	Age at onset of other cranial nerve involvement (year)	UMN* signs	Affected cranial nerves							associated features	
						3	5	6	7	8	9 10	11		12
1	female	-	12	17	-	-	-	-	+	+	+	+	+	Menstrual irregularity
2	female	-	12	17	-	-	-	-	+	+	+	+	+	-
3	female	-	19	21	-	-	-	-	+	+	+	+	+	epilepsy
4	female	-	19	19	+	-	-	-	+	+	+	+	+	epilepsy

*UMN: upper motor neuron

Herein we presented 4 cases of BVVLS which consanguinity was present in 2 of them (cases 1 and 4). The age of initial symptoms varied between 12 and 20. The clinical features and other characteristics of our patients are summarized in table 1.

The first presentation of all cases was hearing loss either isolated or accompanied by other neurological deficits (like speech problem in case 1 and difficulty in walking and weight loss in case 3). Other first presentations rather than hearing loss have rarely been reported in the literature; however, hearing loss has eventually developed in all. Abarbanel et al. noted a girl with weakness of right foot dorsiflexion and then progressive hearing loss 7 years later.¹⁶ Summers et al. depicted difficulty climbing stairs in a young girl one year before onset of deafness, but he also suggested madras type of anterior horn cell disorder as an alternative diagnosis.¹⁷ Finally, slurred speech⁶ and respiratory failure^{4,18} have been reported as rare initial symptoms. The latter occurred at the age of 7 years.

Madras type of motor neuron disorder closely resembles BVVLS and is almost confined to southern India.¹⁹ In contrast to BVVLS, there is male preponderance or equal distribution, rare familial inheritance, more reported lower and upper motor neuron (UMN) signs (more than 75% of patients) and a benign course.^{17,19,20} Both syndromes have hearing loss and lower cranial nerve involvement in common.

UMN signs are infrequent in BVVLS, although this happened in one of our cases (case 4). Another rare feature of the disease is epilepsy which was seen in two of our cases (cases 3 and 4). Previously, only two cases have been

described with this finding.⁴

The clinical course of BVVLS is variable. The usual course reported in most cases is gradual deterioration followed by periods of stability or abrupt worsening. Four of the previously reported cases showed some improvement: two in spontaneous activities and swallowing following steroid therapy¹ and two others from respiratory failure.^{10,14} Clinical improvement developed in two of our cases was mainly in swallowing with great recovery of motor strength to normal function in case 4. Whether this is related to effect of gabapentin or the course of disease itself is unknown. Grandis et al.¹⁴ showed evidence of improvement in motor and even sensory action potentials which are unusual in typical motor neuron disease.

CSF analysis in four cases revealed no abnormality. Brain MRI in cases did not show any abnormal changes; however, atrophy of brain stem and cerebellum, hyperintensity in the brain stem, cerebellar peduncles and subcortical white matter has been previously reported,⁸ all were non-specific changes. The genetic study of our three patients revealed four novel *C200RF54* mutations which was published elsewhere.²¹ In conclusion, this is the first report of BVVLS from Iran. Patients presented with hearing loss as initial symptom and developed gradual deterioration mainly in bulbar and motor function in their clinical course, although some improvement was noted in two of them. Hopefully, in the recent future, molecular studies will clarify a better concept of the disease pathogenesis.

Conflict of Interest

Authors have no conflict of interests.

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