

A BRAZILIAN FAMILY WITH BROWN-VIALETTO-VAN LAERE SYNDROME WITH AUTOSOMAL RECESSIVE INHERITANCE

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ABSTRACT - We report the first Brazilian family with Brown-Vialetto-van Laere syndrome. The presence of consanguineous marriages and illness affecting three sisters and one niece support an autosomal recessive transmission. The age at onset of the illness ranged from 12 to 20 years old. The time interval between hearing loss and involvement of other cranial nerves varied from 3 to 12 years. MRI demonstrated bulbar atrophy and also high intensity signal at T2 weighted and fluid attenuated inversion recovery (FLAIR) sequences.

KEY WORDS: Brown-Vialetto-van Laere syndrome, autosomal recessive inheritance, hearing impairment.

Descrição de uma família brasileira com síndrome de Brown-Vialetto-van Laere com herança autossômica recessiva

RESUMO - Descrevemos a primeira família brasileira com síndrome de Brown-Vialetto-van Laere. Os pacientes são três irmãs e uma sobrinha provenientes de casamentos consangüíneos, o que fortalece a hipótese de transmissão autossômica recessiva. A idade de aparecimento dos sintomas variou entre 12 e 20 anos. A latência entre a perda auditiva e o envolvimento de outros nervos cranianos variou de 3 a 12 anos. O estudo de imagem por ressonância magnética demonstrou atrofia bulbar além de alteração de sinal nas seqüências ponderadas em T2 e FLAIR (fluid attenuated inversion recovery).

PALAVRAS-CHAVE: síndrome de Brown-Vialetto-van Laere, herança autossômica recessiva, surdez.

Brown-Vialetto-Van Laere Syndrome – BVVL- (MIM 211530), also called “Progressive Pontobulbar Palsy with Deafness” or “Bulbar Hereditary Neuropathy type I”, is a rare entity with obscure etiologic aspects and several types of inheritance. Since its first description at 18941 there are about 43 cases reported in the medical literature²⁻⁸. The disease is characterized by neurosensorial deafness with a variable involvement of cranial nerves, usually motor components of seventh, ninth to twelfth nerves; besides an upper motor neuropathy. Disease progression varies since a very slow course with motor remitting and relapses until fatal death. Only sporadic cases have been described in Brazil^{9,10}.

We report on a family with several cases of the disease in two generations of consanguineous marriages.

CASES

We examined four subjects of the second and third generation of the kindred (Fig 1).

Case 1 – At age 20, this 55 year female developed slowly progressive bilateral hearing loss and mild behavioral changes, followed years later by dysarthria, dysphagia, reduced visual acuity, muscle wasting and exercise induced shortness of breath. Cognition was normal. Examination demonstrated bilateral temporal optic paleness; best corrected visual acuity of 20/100, absent gag reflex, tongue fasciculation and proximal muscle weakness.

Tonal audiometry demonstrated neurosensory hearing loss with absence of responses on brainstem auditory evoked potential. Needle electromyography showed denervation especially in sternocleidomastoideus and trapezius. Spirometry and electrocardiography were normal. Magnetic resonance imaging of the brain demonstrated bulbar atrophy. Complete blood count and biochemistry tests were unremarkable.

Case 2 – At age 18, this 53 year old female developed bilateral hearing loss and dysarthria. Progressive muscle weakness developed nine years later. Examination demonstrated dysphonia, dysarthria, bilateral facial weakness, reduced gag reflex, tongue paresis and proximal muscle weakness more evident in the lower limbs. Deep tendon

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Received 29 May 2006, received in final form 30 August 2006. Accepted 23 October 2006.

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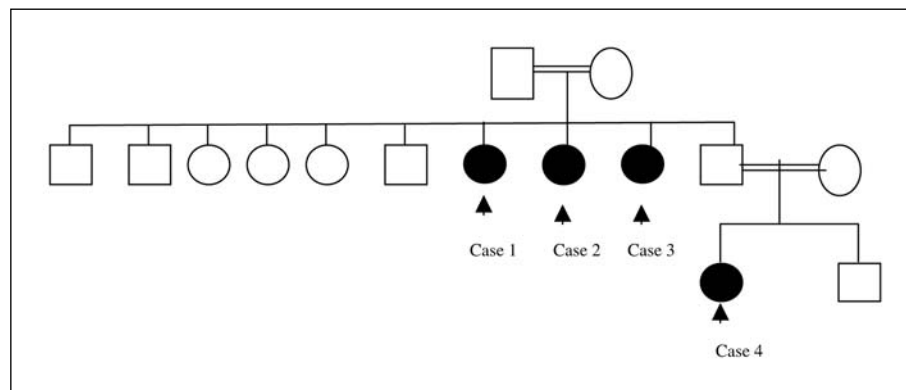


Fig 1. Family pedigree.

reflexes were normal. Audiometry demonstrated neurosensory deafness.

Case 3 – At age 12, this 48 year old female developed hearing loss. At age 15, she presented with dysarthria, dysphagia, dysphonia and mild behavioral changes diagnosed as depression. At age 40 she also complained of exercise induced shortness of breath. Neurological examination she had tongue paralysis with widespread fasciculations, proximal muscle weakness more prominent in the lower limbs with normal deep tendon reflexes. There was no facial weakness. Audiometry demonstrated a severe neurosensory hearing loss with no response on auditory evoked potential. Needle electromyography demonstrated denervation in the genioglossus muscle.

Blood chemistry, electrocardiogram, echocardiography, ergometric tests and spirometry were unremarkable. Cerebrospinal fluid cell count, protein, and glucose were normal. Hematoxylin-eosin stained muscle biopsy was normal. MRI T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences demonstrated a bulbar high intensity signal (Fig 2).

Case 4 – At age 18, this 23-year-old daughter of the brother of three patients described above developed progressive isolated hearing loss. Neurological examination and audiometry demonstrated only bilateral neurosensory hearing loss.

DISCUSSION

BVVL (Bulbar Hereditary Neuropathy type I) is a progressive pontobulbar palsy associated with a neurosensory deafness. Oculomotor and trigeminal involvements are rare^{3,11}. Sensorineural symptom in nearly all cases is the first symptom of the disease. There are only few cases reporting another symptoms preceding deafness. Sathasivam et al. described one patient which the onset of symptoms was slurring of speech and facial weakness¹². Sumners et al. described a girl with limb weakness previous on neurosensory deafness¹³. Hearing loss has been consis-

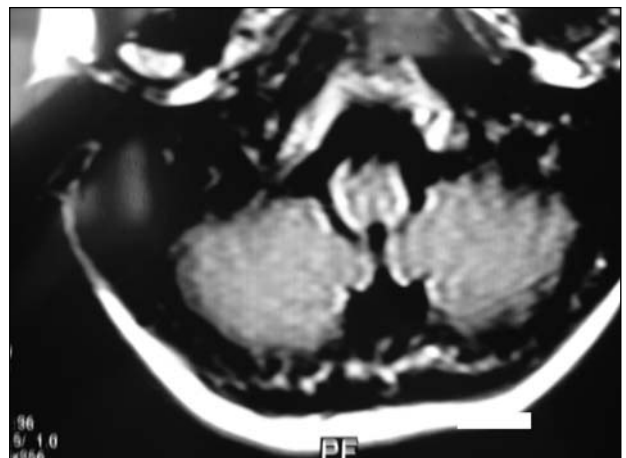


Fig 2. Brain MRI showing bulbar high signal intensity at FLAIR sequence.

tently described at the onset of the disease both in familiar and non- familiar cases.

The exception is Gallai's case¹⁴ with no evidence of hearing loss during the lifetime, although autopsy showed axonal loss on the 8th nerve roots. Interval of time between hearing loss and the involvement of other cranial nerves has been variable from simultaneous involvement (5 cases)¹⁴⁻¹⁶ to a latency of 30 years¹⁷ as shown in Table. In our series, the time interval between hearing loss and involvement of other cranial nerves varied from 3 to 12 years. The disease progresses from a very slow course with motor remitting and relapses to death⁸. Fazio-Londe disease (Bulbar Hereditary Neuropathy type II) is the closest related syndrome but considered distinct from BVVL syndrome because of the absence of deafness¹⁸. Bolthausen et al. described a similar disease, but with different aspects from the BVVL: autosomal dominant inheritance and predominant presentation of vocal alteration with dysphonia and intermittent changes on voice pitch¹⁹. Madras variant of motor neuron dis-

Table. Clinical summary of familiar reported cases of BVVL* (adapted from Mégarbané et al.¹⁵).

Authors	Gender	Age of onset of deafness (years)	Age of onset of cranial nerves disability (years)	Time between deafness and cranial nerves disability	Age of death (years)	Consanguinity	Inheritance
Present report	3 F	20, 18, 12	20, 27, 15	0, 9, 3	-	+	AR
Ramachandran et al., 2004	2 F	7, 8	10, 11	3, 3	-	+	AR
Megarbane et al., 2000	3 M	2.5, 2.5, 3.5	2.5, 2.5, 3.5	0, 0, 0	-7, 11	+	AR
Davenport et al., 1994	1 F	Childhood	18	?	-	-	AD
Hawkings et al., 1991	1 F	12	13	1	17	-	AR
Gallai et al., 1981	1 M, 1 F	2, 1.5	14, 1.5	12, 0	-2	-	AR
Lombaert et al., 1976	1 M, 1 F	Childhood, 17	?/25	?/8	19, 25	-	AR
Boudin et al., 1971	2 F	11, 14	?/?	?/?	?	-	AR
Van Laere, 1967	1 M	13	20	7	?	-	AD? XL
Van Laere, 1966	1 F	10	10	0	?	-	AR
Vialetto, 1936	1 F	0	30	30	?	-	AR
Vialetto, 1936	1 F	16	35	19	?	-	AR
Total	6 M, 14 F	Mean-10 Median-10	Mean-15 Median-14	Mean-6.2 Median-3	6 deaths	3 consanguineous families	AR 10AR, 2AD, 1XL

F, female; M, male; AR, autosomal recessive; AD, autosomal dominant; XL, X-linked.

ease presents with an early onset of muscle and bulbar involvement, with deafness occurring in two thirds of the patients^{9,20}. Some authors consider Madras variant as clinical spectrum of the same disease^{13,20}. Three cases of the present series have proximal muscle weakness, supporting this hypothesis. Madras variant, however, is sporadic condition with a benign clinical course.

Dyspnea has been reported in sporadic and familial cases of BVVL, especially in younger male patients^{18,21}. This finding can be severe although there are reports of spontaneous improvement⁸. Cases 1 and 3 presented with dyspnea as a fluctuating symptom, although with mild functional impairment and normal pulmonary function tests.

Lombaert described in 1976²² severe neuronal changes in the brainstem reticular formation, but the reason for the fluctuating pattern is unknown. Several types of inheritance have been described in BVVL: autosomal dominant or an alternative X linked^{23,24} autosomal recessive¹⁵, besides sporadic cases and even from autoimmune origin^{25,26}. The cases described in Brazil were all sporadic^{9,10}, and the present series is the first with a clear autosomal recessive inheritance: the pedigree showing two generations of consanguineous marriages in which all affected

were females, strongly suggests this hypothesis. All cases described in the medical literature to date did not show any abnormality on imaging studies. We have found, however, a high intensity brainstem signal in the MRI (Case 3, Fig 2) suggestive of involvement of the pyramidal tract.

In conclusion, we have reported a family with consanguineous marriages where three brothers and one niece meet diagnostic criteria of BVVL. The inheritance of the illness is compatible with autosomal recessive transmission. One of our patients had hyperintensity of the brainstem in the topography of the pyramidal tract. This is the first described Brazilian familial case of BVVL.

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