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Bulbar Syndrome as Atypical Presentation of Transthyretin Familial Amyloid Neuropathy Associated with First Bite Syndrome: Possible Causal Relationship

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Abstract

Hereditary transthyretin amyloidosis (ATTRv, v for variant) is an autosomal dominant disease, due to a mutation in transthyretin (TTR) gene. Some mutations determine predominantly peripheral and autonomic neuropathy, others prevalent cardiomyopathy or mixed phenotype. In non-endemic areas, rare forms of predominantly motor neuropathies have also been described. Herein, we report on a patient with ATTRv presenting with pure motor neuropathy, mainly characterized by bulbar signs, and an associated First Bite Syndrome (FBS). Our patient differs from those reported in the literature for the isolated clinical involvement of cranial nerves in the bulbar district and the concomitant presence of FBS. We hypothesize an associated autonomic neuropathy, with involvement of the sympathetic fibers directed to the parotid gland to justify FBS, even if a random association cannot be excluded. At clinical follow-up, 14 months after the beginning of therapy with patisiran, the patient presented with stable neurological conditions and treatment with botulinum toxin provided complete relief from parotid pain for 4 months. Our case widens the spectrum of ATTRv with predominantly motor neuropathy and suggests a possible association with FBS.

Keywords: First Bite Syndrome; ATTRv; motor neuron disease like; botulinum toxin treatment.

Introduction

Hereditary transthyretin amyloidosis (ATTRv, v for variant) is an autosomal dominant disease, due to a mutation in transthyretin (TTR) gene [1]. TTR is made up of four identical subunits, primarily synthesized and assembled in the liver, responsible for transporting thyroxine and retinol binding protein complex. Point mutations in TTR gene induce destabilization and dissociation of the TTR tetramer, leading to abnormally folded monomers that aggregate into amyloid fibrils and deposit at extracellular level of different organs. Some mutations determine predominantly peripheral and autonomic neuropathy, others prevalent cardiomyopathy. Finally, there are mutations responsible for a mixed phenotype [2]. The phenotype depends on geographic location, causative

gene mutation and age at onset. Furthermore, for each TTR gene mutation, phenotype may change, even within the same family [3]. In endemic areas (Portugal, Sweden, Japan, Brazil), a length-dependent small-fibers polyneuropathy with dysautonomia is the most frequent encountered phenotype [4].

In non-endemic areas, subjects with ATTRv and atypical phenotypes of neuropathy have been reported, including length-dependent all-fibers sensorimotor polyneuropathy mimicking chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [5], upper limbs onset multifocal neuropathy [6], ataxic neuropathy [7] and motor neuropathy [8,9]. Rare forms of predominantly motor neuropathies, mimicking amyotrophic lateral sclerosis (ALS), have also been described in association with different mutations [8-14]. Herein, we report on a patient with ATTRv, bearing a missense mutation causing an amino acid change from proline with serine at codon 44 of the TTR protein, presenting with pure motor neuropathy, mainly characterized by bulbar signs, and an associated First Bite Syndrome (FBS). The patient has also cardiac involvement as her sister, affected by the same mutation. Treatments with patisiran and botulinum toxin are also discussed.

Case Presentation

An Italian 79-years-old woman was referred to our neurological outpatient clinic for paroxysmal stabbing pain in the parotid regions, more severe on the right side. The bilateral pain started 5 years before, and occurred simply thinking of a meal or at contact with food. Initially, the pain subsided within 5 minutes from the beginning of each meal, but later it persisted (although decreasing) throughout the meal. The patient suffered from the same pain in case of intense emotions and crying. There was no history of injury or surgery in the head and neck. Furthermore, 6 months before our neurological evaluation, the patient started developing progressive dysarthria, dysphagia to liquids and trouble moving the bolus inside the mouth. Her past medical history was positive for bilateral carpal tunnel syndrome and surgical evacuation of acute post-traumatic subdural hematoma, without neurological sequelae.

In her family history, the father died at 78 of heart attack and the mother died at 82 years of congestive heart failure due to clinically suspected amyloidosis. The neurological assessment revealed atrophy and fasciculations of the tongue, and dysarthria. No objective sensory deficits at the orofacial region were detected. At the upper limbs, atrophy of right thenar eminence was present. The strength of the lower limbs was normal. Light touch and pinprick sensation were reduced only in the first 3 fingers of the right hand. Vibratory sensation was unremarkable. Deep-tendon reflexes were normal, except for achilleous reflexes that were reduced. The parotid regions were not visibly swollen.

Nerve conduction studies showed the absence of compound muscle action potential (CMAP) of right median nerve, a reduced CMAP of left median nerve and both ulnar nerves, and the absence of sensitive action potential (SAP) of right median nerve. The concentric electric needle examination demonstrated neurogenic signs at tongue and distal muscles of upper limbs, with fibrillation potentials, and motor unit action potentials characterized by prolonged amplitude and duration. Autonomic function tests (tilt-test, Valsalva ratio, deep breathing, hand-grip and SSR response) were normal. Laboratory tests showed an elevated NT-proBNP (324 mg/L) with a normal renal function. Electrocardiogram displayed sinus rhythm, normal atrio-ventricular and intraventricular conduction. Transthoracic echocardiography detected a not dilated left ventricle with increased and uniform wall thickness (17 mm), myocardial granular sparkling, normal systolic function but a diastolic restrictive dysfunction and mild diffuse pericardial effusion without any tamponade sign (7 mm). 99mTc-PYP scintigraphy showed a myocardial grade 3 Perugini uptake [15], confirming the presence of cardiac amyloidosis. Serum and urine immunofissaxion together with normal serum free light chain ratio excluded a hematological disorder.

TTR genetic testing revealed a heterozygous mutation in exon 2 (c.130C>T) resulting in p.Pro44Ser substitution and confirming the diagnosis of ATTRv. To investigate the parotid pain, the patient underwent head and neck magnetic resonance imaging (MRI), focusing on the parotid glands, the parapharyngeal space, and the course of glossopharyngeal nerves, which did not reveal any underlying lesion. Ultrasound study ruled out parotid stones or parotid ducts enlargement. The patient refused to undergo parotid biopsy. Paroxysmal parotid pain was suggestive of FBS, generally described as a complication of upper cervical region surgery and rarely as idiopathic. The patient began therapy with patisiran and, after 9 months, neurological symptoms were unmodified. Paroxysmal parotid pain was still present. Taking into consideration the possible pathogenic mechanism of the FBS [16], we performed an intraglandular injection of botulinum toxin type A (BTA) in the right side, because the patient complained a pain rated 10/10 at numeric rating scale (NRS) on the right side and 3/10 on the left side. Under ultrasound guide, 33 units of BTA (Mertz), diluted into 1 mL of 0.9% sodium chloride solution, were injected into the right parotid gland, fractionated into 3 doses of 11 units. After two weeks, the patient had a complete resolution of her right parotid pain.

After 2 months and half, gradual pain during the first few bites of food recurred. Three months post-injection, the pain increased in severity also in the untreated side (NRS 8/10 in the right side and 6/10 in the left side), thus both sides were treated. Under ultrasound guide, 40 units of BTA (Mertz) were injected into the right parotid gland, fractionated into 3 doses, and 30 units, also fractionated into 3 doses, in the left parotid gland. The second treatment provided

complete relief from pain in both sides for 4 months and the patient returned for a third injection after 5 months. At clinical follow-up, 14 months after the beginning of therapy, the patient did not present worsening of bulbar symptoms. Moreover, sensory-motor and autonomic symptoms did not occur. Neurologic assessment was unchanged. Nevertheless, nerve conduction studies revealed a sub-clinic axonal sensory polyneuropathy at lower limbs, while autonomic function tests were normal.

Extended evaluation of the proband's family

After our proband's diagnosis, genetic test was proposed to the other members of her family. The patient has one son and two daughters. Her son had a negative genetic test, while the daughters were positive, but with no symptoms. The proband's brother, instead, refused genetic testing. The proband's sister, a 75-years-old woman, has a history of paroxysmal atrial flutter and carries a pacemaker for a complete atrioventricular block with asystole, occurred one year earlier.

Transthoracic echocardiography detected a not dilated left ventricle with an increased and uniform wall thickness (16 mm), myocardial granular sparkling, normal systolic function but a diastolic restrictive dysfunction and mild diffuse pericardial effusion. 99mTc-PYP scintigraphy showed myocardial Perugini grade 3 uptake too. TTR genetic testing confirmed the presence of the same mutation of the proband. Regarding neurological features, she has been complaining of numbness, tingling and pain in the fingers of both hands, especially the thumb, the index and middle fingers, for 15 years. Neurological assessment revealed hypotrophy of bilateral thenar eminence, reduced light touch and pinprick sensation in the first finger of both hands and positive Tinel's sign. Nerve conduction studies showed only bilateral carpal tunnel syndrome. Autonomic function tests were normal. So, having a heart involvement, she was treated with Tafamidis 61 mg/die.

Discussion

We describe a patient affected by ATTRv, with unusual neurological phenotype mimicking ALS, associated with FBS. Cases of predominantly motor neuropathies mimicking ALS have already been described, due to different mutations (Table 1) and, occasionally, immunoglobulin light chain amyloidosis (AL amyloidosis) [17]. However, case reports regarding the involvement of cranial nerves in the bulbar district are few [18]. Goyal et al. reported two unrelated patients with atypical features of tongue atrophy and fasciculations, in the setting of a severe sensory-motor neuropathy [9]. Lozeron et al. observed a patient with motor phenotype, characterized by amyotrophy, weakness at upper limbs and bulbar signs [14]. Riboldi et al. described a subject with distal limbs paralysis, atrophy, fasciculations, dysphagia, and dysarthria [13].

Table 1. Familial amyloid neuropathy mimicking motor neuron disease

	Age/ gender	TTR Variant	Presenting symptoms	Motor signs	Sensory symptoms	Autonomic symptoms
Ando 1993 [10] n=2	1:33/M 2:59/M	Met30 Met30	Muscle wasting Mild sensory	ND	Yes	ND
Yoshioka 2001 [11] N=1	56/M	Met30	Blurred vision	Muscle atrophy and weakness of UL and LL, with distal predominance and marked fasciculation	Yes	Erectile dysfunction and dysuria
Salvi 2003 [12] n=2	1:27/F 2:45/F	Leu68	1. Muscle twitching and cramps 2. Limb weakness	1: Symmetrical weakness of UL + LL and distal muscle wasting 2: distal wasting of UL and LL, fasciculation, and strength reduction in the four limbs	1: Yes 2: Yes	1: Orthostatic hypotension; gastro-urinary symptoms 2: Impaired autonomic function test

Riboldi 2011 [13] n=1	63/M	Phe78	LL weakness and dysphagia	Bulbar signs Hand weakness with diffuse fasciculation, and atrophy of the right arm. Bilateral mild proximal muscle weakness in the LL, with a particular atrophy in the distal regions	No	Erectile dysfunction
Cappellari 2011 [8] n = 1	71/M	Leu64	Sensory-motor symptoms and fasciculations	ND	Yes	+
Lozeron 2013 [14] n=1	50/M	Met93	Asthenia, intermittent postural hand tremor and tongue fasciculations	Fasciculations and muscular atrophy of tongue and small hand muscles, dysarthria. Strength was reduced both distally and proximally in the UL and distally in the LL	No	Erectile dysfunction
Goyal 2015 [9] n=2	1:75/F 2:60/M	Val127 Met30	Sensory loss at four limbs Diffuse weakness	Diffuse weakness with severe distal-greater-than-proximal weakness; tongue atrophy and fasciculations; dysarthria and dysphagia	Si	No
Our case	79/F	Ser44	Dysarthria, dysphagia Paroxysmal pain in parotid region	Tongue atrophy	No	No

LL: lower limbs; **ND**: not determined; **UL**: upper limbs

Quattrini et al. reported a case of AL amyloidosis with motor neuropathy, mimicking lower motor neuron disease [17]. Our patient differs from those reported in the literature for the isolated clinical involvement of cranial nerves in the bulbar district. Ikeda et al. described a Japanese patient with late onset familiar amyloid polyneuropathy, characterized by bulbar palsy and sensorimotor neuropathy [18]. The neuropathological studies demonstrated transthyretin-amyloid deposits in the hypoglossal nerve roots. It is possible to hypothesize that also in our patient dysarthria and dysphagia have the common pathogenesis of amyloid deposits in caudal cranial nerves.

Another feature that distinguishes our case from the other descriptions is the concomitant presence of FBS. FBS is a rare facial pain syndrome, characterized by severe paroxysmal pain in the parotid region, triggered by the first bite of each meal and diminishing in severity with subsequent bites. Most cases of FBS occur as a complication of surgery at the upper cervical region involving the inferior temporal fossa, the parapharyngeal space or the deep lobe of the parotid gland [19]. FBS may be due to neoplastic process of the parotid gland, parapharyngeal space and submandibular gland [19]. Finally, few cases of idiopathic FBS have been reported [20].

Until now, no cases of FBS associated with ATTRv have been described in literature. Regarding the pathophysiology, several evidence support the hypothesis that FBS develops as a result of damage to the sympathetic innervation of the parotid gland, with an imbalance of parotid gland autonomic innervation. Intense contraction of myoepithelial cells, due to cross-stimulation of the receptors by parasympathetic release of acetylcholine, results in pain at first few bites [16]. This theory is the basis for the use of

botulinum toxin (BT) in the treatment of FBS. In our case, after 9 months, disease-modifying treatment with patisiran stopped the progression of motor signs, without effects on FBS, while BT injection provided a complete relief from pain.

ATTRv neuropathy is generally characterized by an involvement of the autonomic fibers. Our patient presented first with a pure motor neuropathy, mainly characterized by bulbar signs, and subsequently developed a sub-clinic sensory and autonomic neuropathy. So, it is reasonable to hypothesize an associated autonomic neuropathy, with involvement of the sympathetic fibers directed to the parotid gland. Unfortunately, the patient refused to undergo parotid biopsy, so we could not assess the possible presence of amyloid in the gland.

However, since idiopathic FBS cases have been reported in the literature [20], a random association cannot be excluded, although the simultaneous presence of two different rare diseases in the same subject is unlikely.

Conclusions

Within the same family, genetic heterogeneity of ATTRv determined one case of prevalent cardiac involvement and one case with unusual neurological phenotype mimicking ALS, associated with FBS. This description widens the spectrum of ATTRv with predominantly motor neuropathy and suggests a possible association with FBS.

Ethical considerations: The case report was written after getting the patient's informed consent, according to our hospital policy to obtain patients' data for clinical practice and research.

Conflict of Interest: Each author declares that he/she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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