ACUTE RECURRENT ISOLATED BULBAR PALSY WITH ASYMMETRY A RARE VARIANT OF GUILLAIN- BARRÉ SYNDROME ASSOCIATED WITH ANTIGM3 AND ANTIGT1B ANTIBODIES OF IGG AND IGM SUBCLASS.

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ABSTRACT
Isolated bulbar palsy is a rare variant of Guillain-Barre Syndrome (GBS). Recurrence is even more rare. Antibodies against membrane proteins like GM3 and GT1b have been found only in few patients with GBS variant. Lack of free availability of antibodies and cost effectiveness of test makes diagnostic challenge in developing country like India. We describe a 29 year-old female presenting with acute isolated bulbar weakness with recurrence and asymmetry involving IX, X, and XI cranial nerves with normal reflexes and without limb weakness. Serological testing for antiganglioside antibodies was positive for both IgG and IgM anti-GM3 and anti-GT1b antibodies, suggesting the association of these antibodies with isolated bulbar palsy.

KEYWORDS: Isolated bulbar palsy, recurrence, Guillain –Barré Syndrome.

KEY MESSAGES: Isolated bulbar palsy with recurrence and asymmetry involving cranial nerves IX, X, And, XI with normal peripheral nerve conduction a rare variant of Guillain-Barre syndrome associated with IgG and IgM anti GM3 and anti GT1b antibodies.

INTRODUCTION
Guillain-Barré syndrome (GBS) is characterized by rapidly evolving ascending weakness, mild sensory loss and hypo- or areflexia, progressing to a nadir over up to four weeks. Besides classic presentation of GBS, clinical variants are based on the types of nerve fibers involved (motor, sensory, sensory and motor, cranial or autonomic), predominant mode of fiber injury (demyelinating (AIDP) versus axonal (Acute motor axonal neuropathy (AMAN and acute motor and sensory neuropathy (AMSAN)), and the presence of alteration in consciousness.[1,2] GBS typically present with symmetrical weakness. Variants with regional or a markedly asymmetric distribution also occur but are rare.[1,2]

Most patients present initially with leg weakness and arm weakness (32%) or selective proximal and distal leg weakness (56%) often spreading to the arm while some have onset of weakness in the arms (12%). A descending presentation mimicking botulism, with onset in the face or arms, is less common. Besides prominent weakness, patients are hypo- or areflexia within the first few days but this may be delayed by up to a week. Facial nerve involvement occurs in up to 70% of cases, dysphagia in 40%, and rarely (5%) patients may develop ophthalmoplegia, ptosis, or either suggesting botulism or myasthenia.[1]

Patients with GBS (AIDP) and Miller Fischer syndrome (MFS) demonstrate bulbar weakness.[3,4] Other rare regional forms of GBS, which are associated with bulbar involvement are Pharyngeal –cervical- brachial variant (PCB) occulopharyngeal, polyneuritis cranialis variants and Bicker staff encephalitis.[2,3,6,7] Acute isolated bulbar palsy is a rare variant of GBS and only a few cases have been reported.[8,9,10] This variant does not cause generalized limb weakness as in the acute inflammatory demyelinating polyradiculoneuropathy (AIDP) type, which is the commoner form of GBS. Bulbar palsy usually affects the oropharyngeal muscles especially the bulbar muscles, innervated by IX, IX, XI and XII Th cranial nerves. XI cranial nerve (Accessory nerve) also arises from medulla that has cranial and spinal part; cranial part has pharyngeal supply along with vagus nerve and spinal part innervates sternocleidomastoid and trapezius. Involvement of XI cranial nerve is rare.

reported an acute (PCB) variant of GBS presenting with isolated bulbar palsy.[10] Studies and case reports showed raised Cerebrospinal fluid (CSF) protein, peripheral nerve conduction study and antiganglioside antibodies have been shown to help in the diagnosis of isolated bulbar variant of GBS. In our case raised CSF protein, cranial nerve contrast enhancement on magnetic resonance imaging (MRI) brain and antiganglioside antibodies helped in diagnosing rare variant of GBS. Isolated bulbar palsy with involvement of IX, X, and XI cranial nerve sparing XII with marked asymmetry and recurrence has not been reported as of date.

GBS is considered as an acute onset, usually monophasic immune-mediated disorder of the peripheral nervous system, but recurrence does occur in 1-3% of subgroup of population.[11,12] Recurrent GBS (RGBS) has been described as a rare entity with distinct characteristics. RGBS defined two or more episodes that fulfilled the NINCDS criteria for GBS, with a minimum time between episodes of 2 months (when fully recovered in between) or 4 months (when only partially recovered).[11] Recurrences occur more frequently in patients under 30, with milder symptoms and in MFS.[11,12] Here we report a case of acute isolated bulbar palsy with asymmetry and recurrence involving IX, X, and XI th cranial nerves associated with anti GM3 and anti GT1b antibodies a rare variant of GBS with diagnostic challenge in clinical practice.

CASE HISTORY

28 year-old female presented with dysarthria, hoarseness of voice, difficulty in swallowing both liquids and solids, and nasal regurgitations of 2 weeks duration (second week of September 2013). The bulbar symptoms were acute onset evolved over a week and were then non-progressive. She did not experience any limb weakness, unsteadiness, facial asymmetry or any antecedent infection. There was no sensory symptoms, facial or limb weakness. She noticed mild diurnal variation of symptoms.

Neurological examination showed marked bulbar palsy involving the pharyngeal and palatal muscles. Laryngoscope showed bilateral adductor palsy (left >right). There was no facial weakness and neck flexion was strong. Limb muscle power was generally normal; grade 5/5 with normal deep tendon reflexes and normal sensations, and plantar responses were down-going bilaterally. Cerebrospinal fluid (CSF) examination was normal. Neostigmine test showed mild improvement in dysphagia. Peripheral nerve conduction study with repetitive nerve stimulation was normal. Computed tomography of chest and Magnetic resonance imaging (MRI) brain plain, vascular work up was negative. Diagnosis of bulbar palsy secondary to neuromuscular junction disorder was considered. In view of bulbar palsy being static and response to Neostigmine intravenous immunoglobulin was not given. She was started on pyridostigmine 60 mg twice daily; she showed improvement and was discharged. Ryles tube was removed after 1 month, she noticed mild dysphagia for liquids; there were residual 20% symptoms.

She presented with recurrence of symptoms in February first week 2014, after four and half months of initial presentation, with preceded severe unilateral headache on left side, pain was of squeezing type with radiation to the neck region and dysphagia with nasal regurgitation. Examination showed uvula was pulled towards right side, palatal movement reduced bilaterally, with sagging of palatal folds left more than right (figure 1a) with impaired posterior pharyngeal wall sensation (right – 25% impaired, left –50%). There was selective weakness of sternocleidomastoid (Right SCM 0/5, left SCM 4/5, medical research council grading) and trapezius muscles right >left (figure 1b).

Figure 1: a showing bilateral palatal weakness left > right, deviation of uvula towards right suggestive of bilateral IX, X cranial nerve palsy with asymmetry.

Figure 1: b showing winging of scapula right> left (Marked by black arrow) suggestive of Trapezius weakness indicating involvement of accessory nerve (XI cranial nerve).
Clinically a diagnosis of asymmetric bulbar palsy involving IX, X, and XI cranial nerve was considered. CSF examination done with in a week of onset of illness showed lymphocyte predominant pleocytosis (white blood cell of 10 cell/mm), protein level of 48mg/dl (normal range 15-45mg/dl), and sugar of 70mg/dl (normal range 40-60mg/dl) with absent malignant cells. Creatine phosphokinase, Angiotensin converting enzyme inhibitors (ACEI), Acetylcholine receptor antibody (ACRa), anti ro and anti la antibody was in normal range. Nerve conduction study repeated twice was normal. MRI brain with gadolinium contrast showed enhancement of IX, X cranial nerves. (Figure 2).

Serological testing for anti-ganglioside IgG and IgM antibodies against GM1, GM2, GM3, GD1a, GD1b, GT1b, GQ1b, antigen were performed. GT1a test was not done in our case. The patient’s serum was strong positive for anti-GT1b and anti GM3 antibodies (table1).

Table 1: showing antiganglioside antibodies observed in our case.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>IgM</th>
<th>Ig G</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM1 (GM1)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>GM2 (GM2)</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>GM3 (GM3)</td>
<td>Strong positive</td>
<td>Positive</td>
</tr>
<tr>
<td>GD1a (GD1a)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>GD1b (GD1b)</td>
<td>Borderline</td>
<td>Negative</td>
</tr>
<tr>
<td>GT1b (GT1b)</td>
<td>Very strong positive</td>
<td>Strong positive (+++)</td>
</tr>
<tr>
<td>GQ1b (GQ1b)</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Diagnosis of acute isolated bulbar variant of GBS with asymmetry involving IX, X and XI was considered. Intravenous immunoglobulin (IVIg) at dose of 0.4gm/kg/day was administered for five days, she responded day 2 of IVIg, Ryles tube was removed after 1 week. At 1-month follow up she had mild weakness of right trapezius, which was of normal power at 2 months follow up. She was followed for a period of one and half years and is absolutely asymptomatic with no recurrence.

DISCUSSION

Isolated bulbar palsy is a uncommon regional variant of GBS, First reported by O’ Leary et al. in 1996.\(^{[13]}\) Our case presented with isolated bulbar palsy with recurrence. Initial presentation there was symmetrical involvement of bilateral IX, and X the cranial nerves. Subsequent recurrence occurred after four and half months with involvement of bilateral IX, X, and, XI Th cranial nerves and showed marked asymmetry, clinically and radio logically. Studies showed that in RGBS there seems to be accumulating deficit in subsequent episode.\(^{[11]}\)

There are only few published case studies of RGBS worldwide. Studies showed that males were more affected than females; recurrence was common in younger age (mean age 34.2). Kuitwaard K et al all reviewed 32 recurrent GBS patients, who had a total of 81 episodes, study showed that genetic or immunological host factors may play an important role in recurrent GBS, and recurrences occur more frequently in patients under 30, with milder symptoms and in MFS\(^{[15]}\) There are only few case reports of isolated bulbar palsy but no reports of recurrence. To our knowledge we believe our case is the first reported isolated bulbar palsy involving IX, X and XI cranial nerve with recurrence and asymmetry in young female.

We retrospectively consider that initial presentation as the milder form of isolated bulbar variant of GBS as she presented after 2 weeks of illness and was in plateau phase, and there was recovery of her bulbar symptoms by 80%. Diurnal variation of symptoms, subjective positive Neostigmine test, negative peripheral nerve conduction study and normal CSF proteins laid to improper diagnosis initially. We think diurnal variation of symptoms in our case was due to accumulation of secretions in piriform fosse leading to worsening in evening hours. Antiganglioside antibody was not done initially because of non-availability of test freely or of cost factor. Involvements of accessory (XI th cranial nerve) in subsequent presentation led to the weakness of sternoleidomastoid and trapezius mimicking neck and proximal arm weakness similar to pharygeo-cervical – brachial variant of GBS. Our case does not fit to the diagnostic criteria for PCB variant given by Benjamin R wakerley et al\(^{[14]}\) that modified Rooper et al criteria. Absence of areflexia or hyporeflexia in arm, normal nerve conduction study, asymmetric presentation and recurrence clearly differentiated from PCB variant.

Although the patient did not have any antecedent infection during both episodes this has been described in many cases of GBS and is not a major criterion in diagnosing GBS. As bulbar palsy can be a main symptom in many neurological disorders, it is important to determine that other differential diagnoses like bulbar...
onset neuromuscular junction disorder, botulism, polymyositis, brainstem lesion, behcets disease, sarcoidosis, all of which have been excluded. In our case, gadolinium contrast MRI brain not only ruled out structural lesion but showed, 9,10,11 bulbar cranial nerve enhancement (Right>left) demonstrating inflammatory pathology.

A diagnosis of acute GBS was made based on clinical, CSF and contrast MRI brain. Peripheral nerve conduction study was inconclusive in our case. Further our clinical diagnosis was confirmed by antiganglioside antibody specific for isolated bulbar palsy. Serological and clinical data reported in literature showed GM3 and GT1b antibody against IgG subclass in isolated bulbar palsy.[13] To our knowledge, there is only two other case report of isolated bulbar palsy with positive anti-GM3 and -GT1b antibodies against IgG in the literature.[8,10] Our case showed a very strong positive anti GT1b and anti GM3 antibodies for both IgM and IgG subclass. The current report of our patient adds further to the literature and highlights the usefulness of comprehensive antiganglioside antibody testing to aid in understanding the pathogenesis of this rare condition and also aid in situations where diagnosis is challenging with absence of sensor motor signs in limbs and negative peripheral nerve conduction study.

CONCLUSION

Isolated bulbar palsy may be the first or only manifestation of GBS. One need to clearly differentiate isolated bulbar palsy involving IX, X and, XI cranial nerves from pharygeo-cervical brachial variant of GBS. Antiganglioside antibodies detection is mandatory in recurrent isolated bulbar palsy with negative peripheral nerve conduction for early diagnosis and management of GBS.

REFERENCES

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