Botulinum toxin type B in blepharospasm and hemifacial spasm

Botulinum neurotoxins (BTXs) inhibit the presynaptic release of acetylcholine causing a chemical denervation that results in sustained muscle weakness and have been used in the past 20 years to induce selective blocking of hyperactive striatal (and smooth) muscles. All the different seven serotypes of BTXs have in common that mechanism of action (block of the neuroexocytosis machinery inside the end plate, responsible for the release of acetylcholine into the neuromuscular junction), acting on different targets. The two commercially available serotypes, botulinum toxin type A and botulinum toxin type B (abbreviated BTX-A and BTX-B, respectively) are reported to act as zinc dependent endoproteases on different intraneuronal target proteins.

The clinical value of BTX-A has been recognised for a long time and is widely demonstrated by hundreds of clinical reports. More recently a clinical usefulness of BTX-B has been reported. Two controlled clinical trials have demonstrated that local intramuscular injections of BTX-B are effective in the treatment of cervical dystonia in patients with BTX-A resistant disease, as well as in patients with BTX-A resistant disease (secondary non-responders). BTX-B was found to be effective in both studies, with a significant improvement observed in all the parameters investigated (severity, disability, and pain); action was found to last as long as 16 weeks. Based on these favourable results, we investigated BTX-B treatment in blepharospasm (BLS), another common form of focal dystonia, and in hemifacial spasm (HFS). Indeed, despite BTX-A being an efficacious treatment for these conditions, a percentage of patients still shows a suboptimal response, particularly in long term treatments. They could, therefore, benefit from the availability of another botulinum toxin serotype.

Blepharospasm
We studied 13 subjects (10 women and 3 men; mean (SD) age at onset 51.5 (15.0) years; mean disease duration 9.1 (8.1) years) with BLS. BLS was diagnosed as idiopathic focal dystonia in 12 patients, and as secondary dystonia in one case. All patients had received BTX-A before, with a moderate to good response. Patients were excluded if they had received a BTX-A injection in the past three months for their BLS. After an informed consent was obtained, four pretarsal injections were placed around each eye; the fixed total dose of BTX-B for each treatment was 937.5 units. This was obtained, four pretarsal injections were placed around each eye, and two around the mouth; the fixed total dose of BTX-B for each treatment was 937.5 units. This was obtained taking 0.3 ml of the previously described solution. Before each treatment, patients were assessed with an objective rating scale for dystonia (Burke-Fahn-Marsden scale, severity factors, items for BLS and mouth averaged; this scale was used in the absence of validated rating scales for HFS); efficacy was assessed at the time of the peak effect with the same objective rating scale and the subjective visual analogue scale reported above. Each patient received a single treatment. Latency and duration of the effect were assessed as above. Results of the trial are reported in table 1.

<table>
<thead>
<tr>
<th>Table 1 Response to BTX-B injections</th>
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<td><strong>BLS</strong></td>
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<td><strong>Before</strong></td>
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<td>Latency to response (days)</td>
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<td>Duration of response (days)</td>
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<td>Objective rating scale (points)</td>
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<td>Subjective visual analogue scale (%</td>
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Results are expressed as mean (SD). *Student’s t test between before and after injection: p<0.001.

and the moment when that any benefit has completely worn off, both as reported by the patient. Each patient experienced an anaphylactic reaction, consisting of Quincke’s oedema, from day two after the injection, though this resolved after treatment with corticosteroids.

Hemifacial spasm
We studied 11 subjects (six men and five women; mean age at onset 64.9 (10.4) years; mean disease duration 5.4 (3.9) years) with primary HFS. All patients had received BTX-A before, with a moderate to good response. Patients were excluded if they had received a BTX-A injection in the past three months for their HFS. After an informed consent was obtained, four pretarsal injections were placed around each eye, and two around the mouth; the fixed total dose of BTX-B for each treatment was 937.5 units. This was obtained taking 0.3 ml of the previously described solution. Before each treatment, patients were assessed with an objective rating scale for dystonia (Burke-Fahn-Marsden scale, severity factors, items for BLS and mouth averaged; this scale was used in the absence of validated rating scales for HFS); efficacy was assessed at the time of the peak effect with the same objective rating scale and the subjective visual analogue scale reported above. Each patient received a single treatment. Latency and duration of the effect were assessed as above. Results of the trial are reported in table 1. Only two patients rated the efficacy of BTX-B as superior to BTX-A and preferred to continue treatment with BTX-B. The drug was generally well tolerated, with the most common adverse effect of BTX-B being pain during the injection, which was reported by 11 of 13 of the patients. Other common side effects of BTX-A treatment, such as ptosis and epiphora, were mild and transient. One patient experienced an anaphylactic reaction, consisting of Quincke’s oedema, from day two after the injection, though this resolved after treatment with corticosteroids.

Competing interests: CC has been reimbursed by Elan, Allergan and Ipsen (manufacturers of different botulinum neurotoxins) for attending several conferences. MFC has been reimbursed by Elan for attending a conference. ARB has been reimbursed by Allergan and Ipsen for attending several conferences.

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References

Persistent bitter taste as an initial symptom of amyotrophic lateral sclerosis
Amyotrophic lateral sclerosis (ALS) is characterised by progressive degeneration of upper and lower motor neurones. Clinical symptoms involve weakness, dysphagia, dysarthria,
and the vaga nerve innervate the posterior third and the epiglottis. It has been shown experimentally and clinically that anaesthesia of the chorda tympani nerve branch results in intensified perception of bitter taste from the posterior tongue, suggesting that the pathway of the chorda tympani normally inhibits the glossopharyngeal and vaga nerve input. In fact, spontaneous bitter taste dysgeusia (phantogeusia) similar to that perceived by our patients was observed in the posterior tongue after anaesthesia of the chorda tympani. Hence it may be speculated that mild sensory neuropathy of the chorda tympani branches may be responsible for our findings. Sensory signs have indeed been described in ALS. However, if at all, they develop relatively late in the disease. Furthermore, the spatial gustatory function test did not show any difference to a control group in our observation, but we believe that future studies may be able to address these issues.

Comment

To our knowledge, dysgeusia has not been described in this disease. The persistent perception of a bitter taste developed as an early sympto of the disease in our patients. In this regard, it resembles the dysgeusia known from ciguatera food poisoning, which is a symptom of the disease in our patients. In this disease, the perception of bitter taste developed as an early symptom. The persistent perception of a bitter taste may be associated with the degeneration of the brain stem solitary tract nucleus in our patients, although further studies may be able to address these issues.

Case reports

Patient 1 was a previously healthy 64 year old woman. Six months before admission, she noticed a persistent bitter taste, dysarthria, and ophthalmoplegia. Several weeks later she noticed a progressive weakness in both legs which spread to both arms within four months. At the time of admission, she had bilateral bulbar weakness, episodes of pallopathy, generalised spasticity, muscle atrophy, weakness, and fasciculations. The plantar reflex was extensor on the left side. The remaining neurological examination was unremarkable.

Patient 2 was a previously healthy 64 year old woman. Six months before admission, she noticed a persistent bitter taste, dysarthria, and ophthalmoplegia. Several weeks later she noticed a progressive weakness in both legs which spread to both arms within four months. At the time of admission, she had bilateral bulbar weakness, episodes of pallopathy, generalised spasticity, muscle atrophy, weakness, and fasciculations. The plantar reflex was extensor on the left side. The remaining neurological examination was unremarkable.

The patients had not taken prescription or non-prescription drugs during the months preceding the symptoms, or at the initiation of symptoms or at the time of admission. Oral hygiene was good in both cases and serostasis was negative. Family history was negative. The occupational and chemical exposure history was unremarkable.

Spatial gustatory function testing with sodium chloride (0.04 and 0.32 M), sucrose (0.07 and 0.32 M), citric acid (0.01 and 0.02 M), and quinine (0.00016 M) was undertaken. Although both patients described the perception of a bitter taste throughout the examination, the test did not reveal hypogeusia for any quality. In both cases, routine blood chemistry and cerebrospinal fluid studies were normal. Tests for paraneoplastic autoantibodies (Hu, Yo, Ri, Ma, Ta, CV2) were negative. Cranial and spinal magnetic resonance imaging showed mild bilateral atrophy of the precentral gyrus in both patients. Motor evoked potentials revealed slowed central conduction. Peripheral electrophysiological testing showed normal nerve conduction, normal motor conduction, and normal N1 wave latencies. Thus motor neuropathy with multifocal conduction block, cervical myelopathy, and paraneoplastic motor neurone disease could be excluded. A diagnosis of clinically definite ALS was made, based on the revised El Escorial criteria ([http://www.wfnals.org/articles/escorial1998.htm](http://www.wfnals.org/articles/escorial1998.htm)). Treatment with rifuzole and α tocopherol was initiated in both patients.

References


Schizophrenia and episodic ataxia type 2

The frequent co-occurrence of degenerative cerebellar pathology and schizophrenia, as well as the recently reported increased association rate between autosomal dominant ataxias and major psychosis, strongly suggests the involvement of the cerebellum in the pathophysiology of schizophrenia. The analysis of associations between psychosis and neurodegenerative diseases may improve our understanding of the pathophysiology of schizophrenia and the periodic autosomal dominant ataxias, such as episodic ataxia type 1 and type 2 (EA1 and EA2). We present a case of a young man who has been diagnosed with paraneoplastic and schizophrenia (ICD-10: F20.0) and episodic ataxia type 2.

Case study

The patient, a man aged 27 years, was first admitted to our hospital with psychotic symptoms in June 1995. He presented with paranoid delusions and delusions of reference, acute hallucinations (commenting voices), formal thought disorder, and behaviour disorganisation, as well as negative symptoms such as blunted affect, poor rapport, and lack of spontaneity. He was diagnosed as having paranoid schizophrenia (ICD-10: F20.0) and showed a PANS (positive and negative symptom scale) total score of 177 (fig 1).

The patient was initially treated with risperidone (6 mg/d) which led to a slight improvement in his psychotic symptoms. After discharge from our hospital in September 1995 he regularly attended our outpatient clinic. Despite treatment with risperidone and later with haloperidol decanoate (20 mg/2 weeks), he continued to have chronic psychotic symptoms, which persisted until his admission in April 2001. At this admission he was suffering from severe psychosis (paranoid delusions, acoustic hallucinations, formal thought disorder, and behaviour disorganisation) and negative symptoms (fig 1). Antipsychotic treatment with quetiapine (800 mg/d; 4 weeks) and subsequently with amisulpride (600 mg/d; 4 weeks) did not lead to any improvement in the psychosis. At this time, a neurological investigation showed gazed evoked nystagmus and upward gaze palsy, though attacks of ataxia had neither been reported by the patient nor noticed by the nurses.

Because of persistence of the psychotic symptoms, we began treatment with clozapine (1500 mg/d) and noted a slight improvement of the deterioration in psychosis over the next four weeks despite sufficient serum levels of clozapine. At that time the first severe ataxia attacks appeared. They were manifested by gait ataxia, dysarthria, and slight intention tremor of the upper extremities and persisted for at least several hours. After other causes of cerebellar dysfunction—such as inflammatory, toxic, and vascular—had been excluded, the patient was diagnosed as having episodic ataxia type 2 because he met the following clinical diagnostic criteria: duration of episodes (hours to days), gait and stance ataxia, interictal absence of most symptoms (except oculomotor deficits). Consequently, we began treatment with acetazolamide (200 mg twice daily) and switched the antipsychotic medication from clozapine to potent lorazepam (400 mg/d). This led to both a complete elimination of ataxia episodes and a gradual amelioration of the psychotic symptoms. At the time of discharge six weeks later, the total PANS score was 90. At all subsequent follow up investigations undertaken monthly until December 2002 the psychiatric symptoms remained unchanged (fig 1) and there was no recurrence of the ataxia attacks.

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Episodic ataxia in this patient obviously follows an autosomal dominant trait. The patient's mother suffers from cerebellar atrophy with severe gait and limb ataxia, dysarthria, and oculomotor deficits. Her father is reported to have had oculomotor deficits as well.

At the age of 12 months, a neurological examination of our patient showed saccadic pursuits and vertical spontaneous nystagmus. Since the age of 18 months, spells of gait and stance ataxia have been described (15 to 20 minutes long, one to four times in four to six weeks). At the age of three years and nine months, a neurological investigation showed gaze evoked nystagmus, saccadic pursuit, and absence of optokinetic nystagmus (both horizontal and vertical). At that age a suspicion of migraine was raised but not confirmed. At the same time abnormal EEG patterns with sharp waves over the left temporal lobe were reported.

Recent EEGs done before, during, and after treatment with clonazepam showed abnormal bilateral theta-delta activity (4–7 cps and 2–3 cps) in the temporal and parietal regions. Magnetic resonance (MR) imaging done in 1995, 1997, and 2001 showed no signs of atrophy or cerebral signal alteration. Proton MR spectroscopy done in July 2001 revealed decreased N-acetylaspartate to creatine ratios in the cerebellum and regions in the temporal and parietal regions. Recent association studies have shown that decreased ST segments in leads V3–V5. These findings, in addition to normal CT angiography, supports the clinical diagnosis of EA2 and EA1, which are known to have only a paroxysmal cerebellar syndrome.

Figure 1
Positive and negative syndrome scale scores, treatment with antipsychotic agents, and the frequency of episodes of ataxia.

Association of cardiomyopathy caused by autosomal nervous system impairment with the Miller Fisher syndrome

We report a case of Miller Fisher syndrome associated with reversible left ventricular wall motion abnormalities similar to takotsubo shaped cardiomyopathy.

Case report
A 58 year old man was admitted to our hospital because of ataxia, ophthalmoplegia, and dysarthria. He had a 10 year history of hypertension. Four weeks before admission, he had common-cold-like symptoms. Ten days before admission, he developed difficulties with walking and speaking. The next day he was unable to walk or lift his eyelids. He was admitted to another hospital, where he was diagnosed as having a brain stem infarct. During admission, he developed tightness in the chest for three to four days, which improved spontaneously. Because of exacerbation of his neurological symptoms, he was transferred to our hospital.

On initial physical examination, his blood pressure was 158/106 mm Hg and his heart rate was 108 beats/min and in regular rhythm. He was afibrile and had no respiratory difficulty. On neurological examination, he was fully orientated. His pupils were slightly mydriatic bilaterally (right 6 mm, left 6.5 mm) and the light reflex was absent on both sides. Complete ophthalmoplegia and peripheral facial palsy were observed bilaterally. He had severe dysarthria with restricted movements of the soft palate and tongue. Although his neck strength was preserved, deep tendon reflexes were absent in the four extremities. The plantar responses were flexor. There was no definite involvement of sensation or motor function. Ataxia was observed in the four extremities.

Routine laboratory tests were normal except for a slightly increased white blood cell count. Cerebrospinal fluid obtained on the first hospital day showed an increased protein level of 82 mg/dl. Aetiological investigations, including anti-GM1, anti-GM2, anti-GD1a, anti-GD1b, anti-GT1a, anti-GQ1b, anti-GD1b, anti-GQ1b, and anti-GT1b titres, were all negative. Results of thyroid function tests, angiotensin converting enzyme level, c-ANCA, p-ANCA, anti-acetylcholine receptor antibody, serum electroimmunophoresis, and polymerase chain reaction analysis for CSF tuberculosis and herpes simplex virus were all normal. Serum titres of influenza A and B, measles, mumps, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, rubella, and mycoplasma were also normal. Cranial magnetic resonance (MR) imaging and MR angiography showed no abnormal lesions. EEG findings were normal. Nerve conduction studies showed decreased F wave persistence in the arms. Motor and sensory nerve conduction velocities were well maintained.

On the basis of the neurological findings, we established a diagnosis of Miller Fisher syndrome. The patient was treated with a 12 litre plasma exchange over six days, followed by high dose intravenous gamma globulin (400 mg/kg/day for five continuous days).

There was no chest pain during admission to our hospital; however, an ECG on the first hospital day showed sinus tachycardia with slightly elevated ST segments in leads V3–V5. T waves were inverted in leads I, II, AVL, and V3–6 on the fifth day. These findings, in
both ophthalmoplegia and gait disturbance. The 130th day with marked improvement in lateral walls in the early phase (fig 1A). MIBG decrease in uptake in the anterior, inferior, and scintigraphy done on the 12th day revealed a absence of specific findings on cranial MR protein and cytological findings in the CSF and the triad of ataxia, areflexia, and ophthalmoplegia as it has often been reported in the absence of specific findings on cranial MR imaging. MIBG scintigraphy done on the 12th day revealed a decrease in uptake around the apex and cancelled the appointment with the dentist. Five weeks before, he had already had to cancel the planned operation, because he had exactly the same (but more severe) signs and symptoms, also approximately six hours after the intake of one tablet of 500 mg amoxicillin plus 125 mg clavulanic acid (Augmentan®, SmithKline Beecham) as antibiotic prophylaxis before a cardiovascular division, Department of Internal Medicine, National Cardiovascular Centre, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

**References**


**No evidence of type 1 or type 3 hypersensitivity mechanism in amoxicillin/clavulanic acid induced aseptic meningitis**

Drug induced aseptic meningitis has been reported in response to various agents, in particular non-steroidal anti-inflammatory drugs, intravenous immunoglobulins, anti-CD3 monoclonal antibody (OKT3), and antibiotics. Hypersensitivity reactions (especially type 1 and type 3) have been invoked as the cause by many investigators. This hypothesis is supported by the detection of immune complexes in the serum or cerebrospinal fluid (CSF) of some patients. To our knowledge, only two cases of aseptic meningitis induced by amoxicillin with or without clavulanic acid have been reported. We report a third case of probable amoxicillin induced aseptic meningitis where we performed laboratory studies for type 1 or type 3 hypersensitivity mechanisms.

**Case report**

A 62 year old man presented to our hospital because of fever (up to 40°C) and severe headache for four days. Both had begun approximately six hours after the intake of one tablet of 500 mg amoxicillin plus 125 mg clavulanic acid (Augmentan®, SmithKline Beecham) as antibiotic prophylaxis before a planned dental surgical procedure. He had discontinued the antibiotic after two tablets and cancelled the appointment with the dentist. Five weeks before, he had already had to cancel the planned operation, because he had exactly the same (but more severe) signs and symptoms, also approximately six hours after the intake of one tablet of amoxicillin/clavulanic acid. Following discontinuation of the prophylactic antibiotic (after two tablets), the fever and headache had subsided over the course of three weeks without any treatment.
Tests were not performed during that episode. He could not remember having taken amoxicillin/clavulanic acid before that first occasion. He did not report any accompanying “allergic” signs, such as facial oedema, conjunctivitis, or rash during either of the two episodes, and he had no previous history of allergy or connective tissue disorder.

His neurological status was unremarkable, and in particular there was no neck stiffness. His physical status was also normal except for a body temperature of 38.2°C. Cranial computed tomography revealed no abnormalities. CSF examination showed the following results: leucocyte count 54 cells/µl (82% lymphocytes, 12% monocytes, 4% lymphoid cells, 2% granulocytes); glucose 62 mg/dl (serum 98 mg/dl); protein 94 mg/dl; Qm 13.4 (1000 × CSF albumin/serum albumin, normal < 7.4); IgG index 9.38 (1000 × CSF IgG/serum IgG); oligodendroglial bands negative. Bacterial and fungal cultures from CSF were negative. Blood analyses were also normal except for a slightly raised C reactive protein (1.1 mg/dl, normal < 0.5 mg/dl). Additional investigations did not support an underlying aseptic meningitis. However, we could not find any evidence suggesting an underlying aseptic meningitis. Fur-