Botulinum toxin type B in blepharospasm and hemifacial spasm

Botulinum neurootoxins (BTXs) inhibit the presynaptic release of acetylcholine causing a clinical 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 independently revealed a 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 commonly 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 endopeptidases on different intracellular or extracellular targets.

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 described. Two controlled clinical trials have demonstrated that local intramuscular injections of BTX-B are effective in the treatment of cervical dystonia in patients with BLS 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, probably due to 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, and two around the mouth; 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 from 0% to 100%. Latency of the effect was defined as the time between the injection, which has not been reported in clinical trials on BTX-B. This event might be related to the fact that BTX-B is available in a liquid preparation, which has different biochemical properties than the reconstituted solution of BTX-A. The severe, adverse reaction reported in a single patient with BLS has not been described in previous trials using this compound for cervical dystonia and has rarely been reported in conjunction with BTX-A use; it should, however, not discourage the planning of further dose ranging studies of BTX-B and studies on larger series of patients designed to compare the effect of BTX-B with both placebo and BTX-A in different neurological disorders.

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 well tolerated, with the most common adverse effect being burning pain during the injection, which was reported by 7 of 11 patients. Other common side effects of BTX-A treatment were negligible.

Comment

This open pilot trial, which is the first to use BTX-B in a neurological condition other than cervical dystonia, suggests that BTX-B is an effective and safe treatment for both BLS and HFS. The time course and magnitude of the improvement observed in our study are similar to those reported in trials with BTX-A for the same conditions, while the duration of the effect appears shorter as the mean duration of effect with BTX-A in these neurological conditions is 12–16 weeks. The only peculiar side effect was local pain during the injection, which has not been reported in clinical trials with BTX-B. This event might be related to the fact that BTX-B is available in a liquid preparation, which has different biochemical properties than the reconstituted solution of BTX-A. The severe, adverse reaction reported in a single patient with BLS has not been described in previous trials using this compound for cervical dystonia and has rarely been reported in conjunction with BTX-A use; it should, however, not discourage the planning of further dose ranging studies of BTX-B and studies on larger series of patients designed to compare the effect of BTX-B with both placebo and BTX-A in different neurological disorders.

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.

C Colosimo, M Chianese, M Giovannelli

Dipartimento di Scienze Neurologiche, Università La Sapienza, Rome, Italy

M F Contarino, A R Bentivoglio

Istituto di Neurologia, Università Cattolica del S Cuore, Rome, Italy

Correspondence to: Dr C Colosimo, Dipartimento di Scienze Neurologiche, Università La Sapienza, viale dell’Università 30, 100185 Rome, Italy; carlo.colosimo@uniroma1.it

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,
mastic atrophy and fasciculations, hyper-reflexia, spasticity, Babinski signs, and clonus. Here we report on two patients with sporadic ALS in whom the disease initially presented with a persistent bitter “metallic” taste.

**Case reports**

**Patient 1** was a previously healthy 64 year old woman. Six months before admission, she noticed a persistent bitter taste, dysarthria, and a decrease in appetite. 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 pathological reflexes, generalised spasticity, and 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. At the time of admission, she reported a four month history of a persistent bitter taste confined to the posterior tongue. The taste was noted to intensify after exposure to citric acid (0.01 and 0.02 M), and quinine (0.00016 M). She had a four month history of a “metallic” taste confined to the posterior tongue. The history of the taste prompted a detailed neurological examination. Neurological examination revealed bilateral bulbar weakness, an increased jaw reflex, slow side to side tongue movement, generalised hyperreflexia, and fasciculations. Motor examination revealed normal nerve conduction, and normal F wave latencies. Thus bilateral denervation of the left hand. Neurological examination revealed bilateral bulbar weakness, an increased jaw reflex, slow side to side tongue movement, generalised hyperreflexia, and fasciculations. Motor examination showed active denervation of the left arm. The remaining neurological examination was normal.

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 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 electro-physiological testing showed active denervation, normal nerve conduction, and normal F 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.fnalabs.org/articles/escorial1998.htm](http://www.fnalabs.org/articles/escorial1998.htm)). Treatment with riluzole and α tocopherol was initiated in both patients.

**Comment**

To our knowledge, dysgeusia has not been described in this disease. The persistent perception of bitter taste may be an early symptom of the disease in our patients. In this regard, it resembles the dysgeusia known from ciguatera food poisoning, which is thought to produce a bitter taste by blocking sodium channels. However, other sensory symptoms were absent, both clinically and electrophysiologically. The chorda tympani branch of the facial nerve carries taste sensations from the anterior two thirds of the tongue, whereas the glossopharyngeal nerve and the vagus 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 vagus 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 chorde 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 confirm our finding that bilateral degeneration of the brain stem solitary tract nucleus may be responsible for the dysgeusia in our patients. Interestingly, dysfunction of the autonomous nervous system, which in ALS is also regulated by the solitary tract nucleus—has been described in ALS, supporting the view that this disease may be a multisystem disorder. Thus dysgeusia may indicate brain stem involvement in the disease. As a bulbar onset of ALS is an important predictor of the disease course, our finding may also be of prognostic value. We cannot provide a definite neuroanatomical basis for our observation, but we believe that future studies may be able to address these issues.

G C Petzold, K M Einhäupl, J M Valdueza
Department of Neurology, Charité Hospital, Humboldt University, Schumannstr 20/21, 10098 Berlin, Germany

Competing interests: none declared

Correspondence to: Dr Petzold; gabor.petzold@charite.de

**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 pathogenesis of schizophrenia and facilitate the search for susceptibility genes for this disorder.

To our best knowledge, there have been no previous reports about an association between 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 paranoid 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, auditory hallucinations, formal thought disorder, and behaviour disorganisation, as well as negative symptoms such as blunted affect, poor rapport, and lack of spontaneous speech. He was diagnosed as having paranoid schizophrenia (ICD-10: F20.0) and showed a PANSS (positive and negative symptom scale) total score of 117 (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 admission in April 2001. At this admission he was suffering from severe psychosis (paranoid delusions, auditory 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 gaze 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 clobazam (1000 mg/d) and celexzapine (400 mg/d). This led to both a complete elimination of the extrapyramidal symptoms, we began treatment with clozapine (400 mg/d) and switched the antipsychotic to risperidone (6 mg/d) which led to a slight improvement in his psychotic symptoms. 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 disorders—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 risperidone. He remained stable on this treatment.

Further follow up investigations undertaken monthly until December 2002 the psychotic symptoms remained unchanged (fig 1) and there was no recurrence of the ataxia attacks.
Association of cardiomyopathy caused by autonomic 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 afebrile and had no respiratory difficulty. On neurological examination, he was fully oriented. 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 maxillary strength was preserved, deep tendon reflexes were absent in the four extremities. The plantar responses were flexor. There was no definite involvement of sensory function. Ataxia was also 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 a decreased protein per high power field and an increased protein level of 82 mg/dl. Aetiological investigations, including anti-GM1, anti-GM2, anti-GD1a, anti-GM1b, anti-GT1a, anti-GQ1b, anti-GD1b, anti-GQ1b titre, were all negative. Results of thyroid function tests, angiotensin converting enzyme level, c-ANCA, p-ANCA, anti-acetylcholine receptor antibody, serum electroimmunofluorescence, 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 the 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 combination with clinical findings, led to the diagnosis of cardiomyopathy associated with Miller Fisher syndrome.

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

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

<table>
<thead>
<tr>
<th>Date</th>
<th>PANSS</th>
<th>Quetiapine 400 mg/d</th>
<th>Olanzapine 400 mg/d</th>
<th>Acetazolamide 500 mg/d</th>
<th>Zetepine 400 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jun 95</td>
<td>67</td>
<td>40</td>
<td>40</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Apr 01</td>
<td>50</td>
<td>40</td>
<td>40</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Jul 01</td>
<td>50</td>
<td>40</td>
<td>40</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Oct 01</td>
<td>30</td>
<td>40</td>
<td>40</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Nov 01</td>
<td>20</td>
<td>40</td>
<td>40</td>
<td>30</td>
<td>42</td>
</tr>
</tbody>
</table>

References

Comment
This case shows an association between clinically diagnosed episodic ataxia type 2 and schizophrenia. Cessation of ataxia episodes as commonly diagnosed episodic ataxia type 2 and this case shows an association between clinical and autonomic 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.
conjunction with the previous episode of chest tightness, led us to suspect acute coronary syndrome, and we undertook coronary angiography. Although the coronary arteries were free of any lesions, a left ventriculogram showed severe hypokinesia in the antero-lateral, apical, and diaphragmatic segments, with an ejection fraction of 34%. Provocative vasospasm was not confirmed. Maximum creatine kinase MB release was 8.0 ng/ml (normal < 5.0 ng/ml). A left ventriculogram on the 13th hospital day showed an improvement in the hypokinesia, with an ejection fraction of 44%. There were no specific abnormal findings on myocardial biopsy. Serum noradrenaline (norepinephrine) concentrations were increased to 810 ng/l, 1160 ng/l, and 549 ng/l on the seventh, 14th, and 78th day, respectively (normal 90–420 ng/ml). Thallium-201 scintigraphy on the ninth day showed only mild hypoperfusion in the lateral wall; however, 123I-metaiodobenzylguanidine (MIBG) scintigraphy done on the 12th day revealed a decrease in uptake in the anterior, inferior, and lateral walls [A]. The patient had recovered by the 70th day [B].

**Figure 1** MIBG (metaiodobenzylguanidine) myocardial scintigrams on the 12th day (A) and the 70th day (B). On the 12th day, MIBG uptake was reduced in the anterior, inferior, and lateral walls [A]. The uptake had recovered by the 70th day [B].

**Comment**

In this case, serum anti-GQ1b antibody was negative despite its common association with Miller Fisher syndrome. However, we feel that the triad of ataxia, areflexia, and ophthalmoplegia in association with dissociation of protein and cytological findings in the CSF and the absence of specific findings on cranial MR imaging and MR angiography is sufficient to justify our diagnosis of the Miller Fisher syndrome. Autonomic dysfunctions consisting of sinus tachycardia, increased serum noradrenaline, and decreased MIBG uptake were noted in this case. As these dysfunctions were reversible and paralleled the severity of the Miller Fisher syndrome, they probably have the same aetiology. Because 123I-metaiodobenzylguanidine is a physiological analogue of noradrenaline, and is actively transported into the noradrenaline granules of sympathetic nerve terminals by uptake-1, decreased MIBG uptake in the early phase suggested the involvement of cardiac autonomic nerves. Normal findings on coronary angiography, as well as unremarkable findings on thallium-201 scintigraphy, ruled out ischaemic cardiomyopathy. Thus autonomic dysfunction in the cardiovascular system was considered to have been an important factor in the present case.

Takotsubo shaped cardiomyopathy is a unique heart syndrome characterised by reversible left ventricular apical wall motion abnormalities with chest symptoms, ECG changes, and minimal myocardial enzymatic release mimicking acute myocardial infarction without coronary stenosis.4 The syndrome is named “takotsubo shaped” cardiomyopathy as it has often been reported in Japan and the unique configuration of left ventriculogram resembles a takotsubo, a Japanese word describing an octopus pot.1 The left ventricular wall motion abnormality observed in the present case can be included in the takotsubo shaped cardiomyopathy category because of its reversible course and other clinical characteristics. Although the detailed aetiology of this syndrome remains unclear, enhanced sympathetic activity or vasospasm are considered to play a role in the development of contraction abnormalities.1 Three cases of Guillain-Barré syndrome with irreversible left ventricular dysfunction have previously been reported.12 13 In all these cases, the apical regions were mainly involved. In two of the three cases, MIBG scintigraphy was done and showed decreased uptake around the apex in both cases.14

To our knowledge, this is the first report of a case of Miller Fisher syndrome with reversible cardiomyopathy caused by impairment of the autonomic nervous system. This cardiac syndrome may easily be missed because of its transient nature, with minimal abnormalities on routine laboratory findings. However, careful cardiac examination including ECG, left ventriculography, and MIBG scintigraphy may lead to the identification of further cases of Miller Fisher syndrome showing this cardiac complication.

**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.1 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.1 To our knowledge, only two cases of aseptic meningitis induced by amoxicillin with or without clavulanic acid have been reported.2 3 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.

www.jnnp.com
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 edema, 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: leukocyte 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; Qsu 13.4 (1000 × CSF albumin.serum albumin, normal < 7.4); IgG index 9.38 (1000 × CSF IgG/serum IgG); oligoclonal 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 type 1 or type 3 hypersensitivity mechanism, as no specific IgE to amoxicillin (< 0.35 IU/ml) or immune complexes interacting with C1q (< 2.4 IU/ml) were detected in his serum or CSF. Without further treatment, he recovered completely within one week.

Comment
On the basis of the history and findings (two identical episodes of high fever and headache shortly after intake of the prophylactic antibiotic, and sterile CSF pleocytosis at least during the second episode), we diagnosed probable amoxicillin/clavulanic acid induced aseptic meningitis. However, we could not find any evidence suggesting an underlying type 1 or type 3 hypersensitivity reaction. Further studies are therefore warranted.

References

Another adverse effect of aspirin: bilateral vestibulopathy

In the 1850s John Phlox first described the symptoms of aseptic meningitis. When aspartic meningitis after treatment with amoxicillin was described in 1955, it was thought that this adverse reaction was due to a direct toxic effect of the antibiotic. However, in 1999, it was reported that a patient who took 5–6 g aspirin a day for three days for arthritis, subsequently felt unsteady and had oscillopsia while walking, but no tinnitus or hypacusis. His MRI scan was normal. Caloric irrigation revealed a bilateral vestibulopathy which was most probably caused by the direct effect of aspirin on the vestibular hair cells.

Case report
A 61-year-old woman took 5–6 g aspirin a day for three days to treat her arthritis, but no other drugs during this period. Two or three days later he felt unsteady while walking. This problem was worse on uneven ground and in the dark. During head movements and while walking he perceived apparent motion of the visual scene when he was unsteady. Hearing was normal and he did not complain of tinnitus. He had not had vertigo or hearing problems previously, and his family history was also unremarkable. He had had monosymptomatic (IgG lambda) gammopathy for five years, a bone marrow biopsy proved normal, and thus his condition had been diagnosed as “monoclonal gammopathy of unknown significance.”

As all his symptoms persisted, he came to our dizziness unit nine months later. The Halmagyi–Curthoys test (head impulse test to evaluate the function of the semicircular canals) was pathological and revealed a dynamic deficit of the horizontal semicircular canal bilaterally. Romberg testing showed increased sway which worsened when the eyes were closed. His gait was broad based and also worsened with the eyes closed. However, his hearing was normal, and he had no cerebellar signs.

Electromyography revealed a significant bilateral caloric hyporeponsiveness (peak slow–phase velocity of the caloric nystagmus during irrigation with 44°C warm water: right ear, 5°/s; left ear, 5°/s; and with 30°C cold water: right ear, 5°/s; left ear, 5°/s). Further, the pre- and postrotatory nystagmus lasted less than three seconds and showed a gain of < 0.2. Hearing tests, including an audiogram, were normal. Blood tests for other infections were negative, and magnetic resonance imaging of the cerebello-pontine angle and labyrinth were normal. As regards the underlying mechanisms, aspirin seems to directly inhibit the mechanoelectrical transduction process by partitioning the calyceate molecules in the membrane of hair cells. These latter findings suggest that this newly described adverse reaction to aspirin may be related to our patient’s monoclonal IgG lambda gammopathy. The raised IgG concentration could have promoted such partitioning of the molecules in the hair cell membrane, assuming they are able to enter the endolymphatic space. However, this does not explain the isolated impairment of the vestibular function.

From a clinical point of view, it is relevant to consider this additional adverse effect of aspirin, especially as it is unpredictable owing to varying individual susceptibilities. If a patient has taken higher dosages of aspirin and complains of dizziness, his vestibular function should be tested for bilateral vestibulopathy.
Persistent bitter taste as an initial symptom of amyotrophic lateral sclerosis

G C Petzold, K M Einhäupl and J M Valdueza

*J Neurol Neurosurg Psychiatry* 2003 74: 687-688
doi: 10.1136/jnnp.74.5.687-a

Updated information and services can be found at:
http://jnnp.bmj.com/content/74/5/687.2

**References**

This article cites 6 articles, 2 of which you can access for free at:
http://jnnp.bmj.com/content/74/5/687.2#BIBL

**Email alerting service**

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

**Notes**

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/