Botulinum toxin type B in blepharoaspasm 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 the 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 endopeptidases on different intramural 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 BLS (burke-fahn-marsden scale), 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 blepharoaspasm (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.

Blepharoaspasm

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 tardive 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 for each treatment was 2500 units (0.8 ml of a solution obtained by adding 0.3 ml of saline to 0.5 ml of the commercially available BTX-B solution). Before each treatment, patients were assessed with an objective rating scale for dystonia (Burke-Fahn-Marsden scale, severity factors, items for BLS); efficacy was assessed at the time of the peak effect (7–14 days after treatment) with the same rating scale and with a visual analogue scale assessment (Patient Global Assessment of Change, in which improvement was subjectively measured from 0% to 100%). Latency of the effect was defined as the time between the treatment and the first detectable clinical effect. Duration of effect was defined as the time between the first detectable clinical effect and the moment when any benefit has completely worn off, both as reported by the patient. Each patient received BTX-B as a single treatment. Additionally, a telephone call was made to the patient each week to assess safety and duration of the effect. Results of the trial are reported in table 1. Overall five 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 phoroptera, were mild and transient. One patient experienced an anaphylactic reaction, consisting of Quincke’s oedema, from day 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 by adding 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 pretarsal treatment injection. 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 than 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 before in 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 other botulinum neurotoxins 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, I-00185 Rome, Italy; carlo.colosimo@uniroma1.it

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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,
muscle atrophy and fasciculations, hyperreflexia, 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 women. Six months before admission, she noticed a persistent bitter taste, dysarthria, and emotional liability. 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 pathologic gait, and 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 women. At the time of admission, she reported a four month history of a persistent bitter “metallic” taste confined to the posterior region of the tongue, whereas the glossopharyngeal nerve, and the vagus nerve innervate the posterior tongue, suggesting that input by the chorda tympani nerve branch results in intensified perception of bitter taste from the tongue after anaesthesia of the chorda tympani. This is in contrast to the finding that bilateral degeneration of the brain stem solitary tract nucleus may be responsible for the dysgeusia in our patients. Interestingly, dysfunction of the autonomic nervous system—which in part 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 further 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

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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 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 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, audiovisual hallucinations (comprising voices), formal thought disorder, and behaviour disorder, 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 score of 51 (positive and negative symptom scale total score).

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, with persistent auditory hallucinations, delusions, 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 gait 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 (500 mg/d) and switched the antipsychotic medication from clozapine to zotepine (25 mg twice daily) 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 gait evoked nystagmus and upward gaze palsy, though attacks of ataxia had neither been reported by the patient nor noticed by the nurses.

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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 ocular motor deficits as well.

At the age of 12 months, a neurological examination of our patient showed saccadic pursuit 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 clozapine showed abnormal 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 increased N-acetylaspartate to creatine ratios in the cerebellar vermis region and left cerebellar hemisphere. On 11C-iomazenil SPECT in July 2002, there was a reduced density of the GABA(A)-benzodiazepine receptor complex in the cerebellum as well as in the frontal dorsolateral and occipital regions.

Comment

This case shows an association between clinically diagnosed episodic ataxia type 2 and schizophrenia. Cessation of ataxia episodes as a response to treatment with clozapine supports the clinical diagnosis of EA2 and rules out alternative pathologies such as SCA6 and EA1, which are known to have only a paraneoplastic basis. 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.

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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 orientated. His pupils were slightly mydriatic bilaterally (8 mm x 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. His grip 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 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 decreased pressure in the lumbar region 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-GD1b 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 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

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

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S Mechtcheriakov, M A Oehl, A Hausmann, W W Fleischhacker University Clinic of Psychiatry, University Clinic Innsbruck, Anichstrasse 35, A-6020, Innsbruck, Austria

S Boesch University Clinic of Neurology, Innsbruck

M Schacke University Clinic of Radiology I, Innsbruck

E Donnemiller University Clinic of Nuclear Medicine, Innsbruck

Correspondence to: Dr S Mechtcheriakov; s.mechtcheriakov@uibk.ac.at
both ophthalmoplegia and gait disturbance. The left ventriculogram resembled a takotsubo, a transient shape of left ventricular hypertrophy in response to emotional stress. The synovial fluid and synovial biopsy findings were negative for the cause by many investigators.

Figure 1 123-iodobenzylguanidine (MIBG) 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 positive despite its common association with Miller Fisher syndrome. However, we failed to identify aetiology of this syndrome remains unclear. In the present case, MIBG scintigraphy was done and showed decreased uptake around the apex in both cases.

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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 Hyper-sensitivity 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.2

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

ventriculography, and MIBG scintigraphy may lead to the identification of further cases of Miller Fisher syndrome showing this cardiac complication.

M Oomura, T Yamawaki, H Oe, H Moriwaki, K Miyashita, H Naritomi Cerebrovascular Division, Department of Internal Medicine, National Cardiovascular Centre, S-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan
Correspondence to: Dr Hiroshi Naritomi; hnaritomi@hsp.ncvc.go.jp
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; Qa = 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 (< 250 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 probably 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.

S Kastenbauer, H-W Pfister
Department of Neurology, Klinikum Großhadern, Ludwig-Maximilians University, Marchioninistr 15, 81377 Munich, Germany

M Wick
Department of Clinical Chemistry, Klinikum Großhadern, Munich, Germany

Correspondence to: Dr Kastenbauer; stefan@kastenbauer.de

References

Another adverse effect of aspirin: bilateral vestibulopathy

Widely used for more than 2000 years, salicylic acid has numerous beneficial effects. It may also lead to several adverse reactions, affecting for instance the auditory system. Persistent dysfunctions of the vestibular system, however, has not yet been described. We report a patient who took 5–6 g aspirin a day for three days for arthralgia. Subsequently, he felt unsteady and had oscillopsia while walking, but no tinnitus or hypacusis. 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 teacher took 5–6 g aspirin a day for three days to treat his arthralgia, 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 and his vision was blurred. 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. Though he had had monoclonal 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 unsteady. He could not walk with the eyes closed. His goal pursuit was worsened. However, his hearing was normal, and he had no cerebellar signs.

Electronystagmography revealed a significant bilateral caloric hyporesponsiveness (peak slow-phase velocity of the caloric nystagmus during irrigation with 44°C warm water: right ear, 2°/s; left ear, 5°/s; and with 30°C cold water: right ear, 5°/s; left ear, 3°/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 possible causes of bilateral vestibulopathy (antibodies against inner ear structures, anti-nuclear antibodies, anticytoplasmic antibodies, rheumatic factor, vitamin B-12, folic acid, and so on), as well as high resolution magnetic resonance imaging of the cerebello-pontine angle and labyrinth were normal. As mentioned above, testing of the serum revealed the presence of monoclonal IgG lambda gammopathy (total protein 8.7 g/dl; normal range 6.0 to 8.0 g/dl); IgG concentration 28.2 g/dl (normal range 7.0 to 16.0 g/dl).

Comment

Pathophysiologically, the patient’s complaints are fully explained by bilateral vestibulopathy: the oscillopsia is caused by a defect of the vestibulo-cerebellar reflex, and the unsteadiness by a defect of the vestibulospinal reflexes, especially in darkness when vision cannot substitute for absent vestibular function. The time course of symptom development following the ingestion of a high dose of aspirin provides strong evidence that the isolated and persistent bilateral vestibulopathy was caused by the drug. Although aspirin induced bilateral vestibulopathy has not been reported before, it is likely that other patients taking aspirin have developed it, as bilateral vestibulopathy is often overlooked.

For more than 150 years it has been known that high doses of salicylates can cause tinnitus, loss of absolute acoustic sensitivity, and alterations of perceived sounds, which may develop in the initial days of treatment. It is also known that the susceptibility of individual subjects to salicylate induced inner ear toxicity varies greatly, but why this is so is unclear. Various attempts have been made to explain the toxic effects of salicylic acid. Otoacoustic emissions have been used to show that salicylates cause changes in the mechanosensory functioning of the cochlea; in particular, spontaneous emissions are decreased. Histopathological animal studies have revealed significant changes of only the outer hair cell lateral membrane. In vitro experiments have shown that the fast motile responses of outer hair cells are reduced. As regards the underlying mechanisms, aspirin seems to directly inhibit the mechanoelectrical transduction process by partitioning the salicylate molecules in the hair cell membrane. These latter findings suggest to us 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.

M Strupp, K Jahn, T Brandt
Department of Neurology, Klinikum Großhadern, Marchioninistrasse 15, Ludwig-Maximilians University, 81377 Munich, Germany

Correspondence to: Dr Michael Strupp; mstrupp@nefo.med.uni-muenchen.de

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