



Skin reactions after intramuscular injection of Botulinum toxin A: A rare side effect

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Occurrence of CJD 22 years after hGH administration is in line with the peak risk approximately 20 years after exposure calculated from a large hGH-iCJD series in the UK,² whereas the mean incubation period in French hGH recipients was considerably shorter at 9–10 years.³ Differences of infectivity in hormone lots have been suggested as an explanation for this finding.

Some unusual circumstances and clinical features also deserve comment. First, iCJD associated with hGH has, so far, only been reported after administration of non-commercial hormone. The reports available, however, have excluded patients treated with commercially prepared hormone; hence, there are insufficient data on the CJD rate in these patients.^{2,3} Second, the administration period of hGH and disease duration were both short for iCJD patients even though comparable cases have been reported in previous literature.^{2,7}

In summary, this is the first CJD case from Austria in a patient having received hGH and only the third iatrogenic case detected in this country. The recognised iatrogenic risk (cadaveric hGH 22 years before onset) and the neuropathological confirmation of CJD meet the WHO criteria for definite iCJD, although the possibility of a sporadic methionine-homocysteine juvenile CJD case without causal relation to hGH treatment cannot be definitely ruled out.

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APPENDIX

Histopathological examination

The total fixed brain weight was 1408 g. Macroscopically, moderate diffuse cerebral and cerebellar atrophy was observed. In addition, there were signs of diffuse oedema. On coronal sections, the cortical ribbon of the insular and parietal cortices was narrowed. Histology showed characteristic spongiform change, moderate neuronal loss and gliosis in cerebral cortex and basal ganglia (see Supplementary figure). The cerebellar cortex was severely affected with marked spongiform change of the molecular layer and neuronal loss of the granule cell layer (see Supplementary figure). The Purkinje cells and brain stem nuclei were comparatively better preserved. Immunohistochemistry using the antibody 12F10 (Cayman, Ann Arbor, Michigan, USA) revealed strong pathological prion protein (Pr^{Sc}) deposits in cerebral and cerebellar cortices, and basal ganglia in a diffuse synaptic pattern (see Supplementary figure). In the brain stem nuclei, only discrete Pr^{Sc} deposits were demonstrable. There were no Pr^{Sc} plaques neither in the cerebellum nor in the cerebral cortex or white matter. These features confirmed the diagnosis of Creutzfeldt-Jakob disease (CJD). Due to the recognised iatrogenic risk (due to human growth hormone), the disease was classified as definite iatrogenically transmitted CJD, according to World Health Organisation criteria.

Skin reactions after intramuscular injection of Botulinum toxin A: a rare side effect

The use of Botulinum toxin (BTX) has been constantly increasing over the past years, not least on account of obtaining the license for the treatment of facial lines. It has proven a safe drug with only a few adverse effects. Local irritations at the injection site are not uncommon, whereas more widespread and generalised exanthemas were first described in 1992.¹ One dramatic case documents a lethal outcome due to treatment with a mixture of BOTOX® (BTX-A) and lidocaine.² In accordance with databases from the companies Allergan and Ipsen (SPC BOTOX®, Allergan, December 2005; SPC, DYSPORT®, Ipsen Pharma, April 2006), skin reactions seem to be a rare phenomenon with a frequency of less than 1:1,000. The Ipsen database (January 2007) mentions 5 cases of local and 4 cases of more widespread redness, bulging and pruritus in Germany, as well as 11 cases abroad. Here, we report on two further cases of rapid-onset skin reactions after injection of two different BTX-A products.

CASE 1

A 49-year-old woman developed a left-sided spastic hemiparesis after cavernoma extirpation in 1997. Successful treatment of the spastic arm muscles was carried out with BOTOX® for about 5 years and with DYSPORT® for the last 4 years. She did not receive any other medication. Injection intervals ranged from 3 to 9 months. During the treatment session in April 2006, we applied a total dose of 1,000 Units DYSPORT® (250 MU into the left biceps muscle, 250 MU into the left flexor pollicis longus and extensor carpi radialis muscles, 500 MU into the left flexor digitorum superficialis muscle). Within 6 hours after intramuscular injection of BTX-A, a segmental or “pseudosegmental” fine-spotted pruriginous exanthema emerged in the region of the entire left shoulder, arm and left breast. Fever or other additional symptoms did not occur. Allergological tests, such as prick tests, and an intracutaneous test were normal. Treatment with DYSPORT® was repeated 3 months later with a dose reduction of 50% without any adverse effects. At a later visit, she received 1,000 Units DYSPORT®, which was well tolerated.

CASE 2

A 63-year-old man presented with right-sided limb spasticity due to a stroke 7 years ago. The patient received a stable medication consisting of gabapentine, tramadol, tetrazepam, clopidogrel and atorvastatin. From 2003, he was successfully treated with injections of 900–1,100 Units DYSPORT® at regular intervals of 3 months. In 2006, the therapy was changed to BOTOX®. Within



Figure 1 Photograph of the skin reaction as described in Case 2 about 1 hour after injection into the right brachial muscle. Informed consent was obtained for publication of this figure.

minutes after the first injection of 100 MU BOTOX® into the left brachial muscle, the patient felt generally unwell and had autonomic symptoms such as paleness and an urge to urinate for more than 30 minutes, which is uncommon for a vasovagal reaction. Blood pressure and heart frequency remained stable. Approximately 30 minutes later, the patient also developed a "pseudo-segmental" small-spotted and partially confluent exanthema (fig 1). The rash resolved completely without any specific therapy over the course of 1 day. Intracutaneous and prick tests for both BOTOX® and DYSPORT® were unremarkable. Three months later, the patient was treated with 1,100 Units DYSPORT® again and tolerated re-exposure without relapse.

For both patients, the same antiseptic (Cutasept®, 2-propanolole) and the same materials (gloves, needles) were used as before and also for the re-exposure. An intravascular injection as a further potential cause of their condition was excluded by aspirating the syringe for all muscles. BOTOX® and DYSPORT® were dissolved with saline according to the manufacturers' recommendations. Serum anti-BTX antibodies were not checked in either patient. Both patients had not experienced allergic reactions before.

Skin reactions after intramuscular injections of BTX-A can be attributed to allergic, pseudoallergic and intolerance reactions.

The classification by Coombs and Gell differentiates between four types of allergic reactions.³ Type I leads to an immediate IgE-mediated allergic response after re-exposure of special antigens, whereas type II involves an antibody-dependent activation of either the classical pathway of the complement system or of NK-cells/macrophages within 12 hours. The most characteristic feature of type III hypersensitivity is the immunocomplex-mediated response to antigens within hours with consecutive activation of the complement system. Type IV hypersensitivity is also known as delayed-type hypersensitivity that is mediated by sensitised cytotoxic T-cells. Symptoms typically take 2–3 days to develop. Pseudoallergic reactions are considered when symptoms occur promptly after exposure (direct histamine release) without allergic background. Effects are typically dose-dependent and there is no history of sensitisation by definition. An intolerance reaction is a result of an imbalance in the histamine-releasing and histamine-degrading pathways.

The time course in Case 1 would be in keeping with either an accelerated Coombs and Gell's type IV hypersensitivity mechanism or an intolerance reaction. Disease progression in Case 2 may be associated with an IgE-mediated anaphylactic type I reaction. Negative prick and intracutaneous tests in both cases argue against a type I reaction. However, the variable clinical presentation of both cases suggests different causative mechanisms.

BTX as a biopharmaceutical product exhibits an immunogenic potential. BOTOX® and DYSPORT® contain a crystalline complex of purified toxin and a binding protein (haemagglutinin). They also comprise human serum albumin and lactose (DYSPORT®). Human serum albumin can contribute to allergic reactions, but most reactions occur when administered systemically; for example, after an intravenous infusion. The role of lactose and the BTX-haemagglutinin complex remains speculative. Either described BTX-A preparation is capable of inducing the formation of antibodies after recurrent exposure. BTX-A antibodies can cause protein neutralisation and presumably general immune effects such as anaphylaxis. Although anaphylactic reactions due to therapeutic proteins are getting rare due to the purity of biopharmaceuticals, neutralisation may have more serious implications because of protein inactivation. The immunogenicity of proteins is influenced by several factors, including its biochemical structure (eg denaturation through oxidation), storage conditions, contaminants in the preparation, dose and frequency of treatment, place of application and genetic predisposition of patients.⁴

The reasons for skin rash currently remain unknown.^{1–6} Based on available data, no conclusion can be drawn concerning the risk of skin reactions between different preparations. Taken together, users of BTX should be aware of possible idiosyncratic reactions, such as skin rashes due to intramuscular injections.

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Parkinson's disease with Onuf's nucleus involvement mimicking multiple system atrophy

Urinary frequency, urgency and nocturia are common complaints in Parkinson's disease (PD). The hypothesis most widely proposed to explain neurogenic bladder symptoms in PD is that cell loss in the substantia nigra may cause detrusor hyperactivity due to a loss in the D1 receptor-mediated tonic inhibition of the micturition reflex, although other causes including anti-parkinsonian medication cortical effects have been considered.¹ We present the clinical and pathological findings of a patient with parkinsonism who presented with prominent dysautonomia and a poor response to dopaminergic medications and was considered to have possible multiple system atrophy parkinsonism (MSA-P). Pathological examination revealed that the patient had PD with α -synuclein pathology in the Onuf's nucleus (ON).

CASE REPORT

A 52-year-old male presented with a 12-month history of urinary frequency and urgency in 1999. Examination revealed no prostate enlargement. Urodynamic studies showed evidence of bladder instability and obstruction, with flexible cystoscopy not showing any abnormalities. Two years later, he started to slow down in his movements, shuffle and complain of stiffness. He had a stooped posture, a frozen facial appearance, reduced blinking and mild limb rigidity. Deep tendon reflexes were brisk, with equivocal plantar responses. Orthostatic hypotension was found with a greater than 20 mm systolic blood pressure drop on standing for 2 minutes. Eye movements were normal, and cognition was intact. A MRI brain scan showed mild generalised atrophy with a few non-specific white matter lesions and the MRI scan of the spinal cord was normal. Repeat urodynamic studies showed deterioration with a hypo-compliant bladder, with further evidence of bladder instability and obstruction. Tamsulosin and ropinirole (up to 15 mg/day) did not provide any symptomatic benefit. A clinical diagnosis of MSA-P was considered and his bladder symptoms worsened over the next 2 years with occasional episodes of urge incontinence. A trial of levodopa in 2003 was ineffective and all anti-parkinsonian medications were discontinued. Over the next 2.5 years, the patient deteriorated rapidly with marked bradykinesia, frequent falls due to poor balance and continuing urgency, frequency and incontinence of urine. His bowel function alternated between diarrhoea and constipation, but there was no faecal incontinence. He died 8 years after the onset of bladder symptoms from aspiration pneumonia at the age of 59 years.