PostScript

LETTERS

Blindness in a case of tetanus

Tetanus is a major public health concern and an important cause of death worldwide despite being largely preventable. Although endemic in the developing world, vaccination has rendered it rare in the developed world. Recently, however, an outbreak of tetanus in injecting drug users in England and Scotland has occurred.¹

Intensive care treatment has significantly lowered mortality from tetanus, although the multisystem effects of *Clostridium tetani* infection, as well as prolonged critical illness, continue to provide major therapeutic challenges.²

Here we describe the sub-acute onset of headache and blindness in a patient with severe tetanus. Clinical and neurological features were consistent with posterior reversible encephalopathy syndrome (PRES, previously known as reversible posterior leucoencephalopathy syndrome³), which to our knowledge has not previously been described in a case of tetanus. We suggest that the pathophysiology of PRES in this case is multifactorial and incompletely understood.

Case report

A 27 year old female intravenous/subcutaneous heroin user was admitted with a 12 h history of generalised muscular stiffness, intermittent sweats, and progressive difficulty in mouth opening. On examination, she had risus sardonius and trismus with less than 5° of mouth opening. She had paroxysms of severe sweating although afebrile, and had multiple involuntary self-terminating tonic spasms of neck retraction and trunk extension with no loss of consciousness. She had multiple skin abscesses consistent with infected injection sites.

A clinical diagnosis of severe tetanus was made, later supported by a low tetanus antitoxin titre suggestive of inadequate immunity, and by the growth of mixed *Clostridia* species from injection site abscesses.

Immediate management included administration of intravenous benzylpenicillin and metronidazole, and placement of a nasogastric tube. Intravenous anti-tetanus immunoglobulin was administered and the infected skin lesions debrided.

The patient was transferred to the intensive care unit and commenced on a magnesium sulphate infusion for increasing frequency of spasms, aiming for a level of 2-4 mmol/l. Infusions of low dose morphine and midazolam failed to control attacks, and she suffered a respiratory arrest. She was intubated, sedated with increased morphine and midazolam, and paralysed with atracurium.

Over the following week, our patient developed worsening cardiovascular instability with severe and rapid swings in blood pressure between 80/40 and 230/130 mm Hg. These peaks and troughs were maintained for hours at a time despite attempts at control using esmolol boluses followed by a labetalol or noradrenaline infusion as indicated.

She had a sustained sinus tachycardia of 120-150 bpm throughout the peaks, falling to ~70 bpm with labetalol. Over her 26 day period of critical care, she suffered multiple nosocomial infections from which she made good recovery. Prior to transfer to a medical ward, the magnesium infusion was stopped and she was changed to oral methadone and diazepam.

Two days later, she complained of a severe occipital headache and of visual disturbance with "shapes and colours" in front of her eyes. Although she did not report visual loss, she was unable to count fingers or recognise specific colours, and could only see shadows. Her pupils were dilated to 7 mm but reacted briskly to light; there were no other focal neurological findings. On the previous morning, she had had one documented hypertensive tachycardic episode with blood pressure 186/90 mm Hg and pulse 130 bpm. An MRI was performed (fig 1A,C) which revealed bilateral occipital lobe hyperintensities. The bright signal on diffusion weighted images (DWI) corresponded with a low signal on the apparent diffusion co-efficient (ADC) maps which indicated some irreversible damage. Her rapid clinical improvement to normal visual acuities over 7 days with marked radiological improvement in 2 weeks

(fig 1B,D) makes PRES the most likely diagnosis.

Before discharge, the patient received tetanus immunisation, and was confirmed as being HIV negative and hepatitis C positive.

Discussion

PRES has been described in a variety of clinical situations including hypertensive encephalopathy, treatment with cytotoxic chemotherapy, eclampsia, post partum, and with immunosuppression following organ transplant.³ It represents cerebral endothelial cell dysfunction and the development of reversible vasogenic oedema classically in the parietal-occipital lobes, and is diagnosed according to clinicoradiological criteria.³ The original series of PRES published in the *New England Journal of Medicine* in 1996,³ showed incomplete recovery both clinically and radiologically in some patients and further studies have confirmed this and that DWI hyperintensities and ADC hypodensities may correspond to irreversible ischaemia. This is the first case of PRES associated with tetanus reported in the literature to our knowledge.

In our case, the onset of PRES was preceded by one recorded episode of sustained hypertension 24 h previously. For

Figure 1 (A,B) FLAIR imaging from 4 days after onset of blindness and 2 weeks later showing the diffuse occipital lobe hyperintensities and the marked improvement in 2 weeks. (C, D) Transverse DWI and T2 weighted image. The T2 image from 2 weeks after onset of symptoms shows some residual cortical abnormalities.

1 week prior to this, the patient had been normotensive with minimal fluctuations in blood pressure. The mechanism of PRES in this case is likely to be primarily related to the tetanus toxin mediated sympathetic hyperactivity, resultant hypertension, and failure of cerebral perfusion pressure, or blood flow autoregulation. The fact that the patient developed the clinical features of headache and blindness during the recovery phase of her illness is surprising. Hypomagnesaemia has been implicated in the pathophysiology of cyclosporin and cisplatin induced PRES.⁴ Magnesium sulphate is a presynaptic neuromuscular blocker, blocks sympathetic catecholamines, and has been used to reduce autonomic disturbance and spasms.⁵ It has been found to be an effective adjunct to control autonomic disturbance, spasms, and rigidity.³ Our patient had been on a magnesium sulphate infusion until the day of discharge to the ward when it was suddenly stopped. It may be that this played a role in providing some protection from cerebral vasogenic oedema during the sympathetic surges that had occurred during the most severe period of illness.

This case illustrates the difficulties in clinical management of tetanus particularly in relation to autonomic dysfunction. It also highlights the need for improved vaccination provision particularly in at risk groups such as intravenous drug users, and reminds us that tetanus remains an important but rare disease in the UK requiring rapid diagnosis and expert management.

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References

- 1 Ongoing outbreak of tetanus in injecting drug users. *Health Protection Agency CDR wklly* 2004;14:11.
- 2 Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. *Br J Anaesth* 2001;87:477–87.
- 3 Hinchey J, Chaves C, Appignani B, et al. A reversible posterior encephalopathy syndrome. *N Engl J Med* 1996;334(8):494–500.
- 4 Ito Y, Arahata Y, Goto Y, et al. Cisplatin neurotoxicity presenting as reversible posterior leucoencephalopathy syndrome. *Am J Neuroradiol* 1998;19:415–17.
- 5 Attygale D, Rodrigo N. Magnesium sulphate for control of spasms in severe tetanus. *Anaesthesia* 1997;52:956–62.

Association of CYP46 intron 2 polymorphism in Finnish Alzheimer's disease samples and a global scale summary

Cholesterol 24S-hydroxylase (CYP46; Gene ID: 10858) in chromosome 14q32.1 plays a key role in the hydroxylation of brain cholesterol to 24-hydroxycholesterol.¹ This

primary cholesterol elimination product can be transported through the blood-brain barrier. 24S-hydroxycholesterol is in vitro conditions neurotoxic and may contribute to neurodegeneration.²

The gene for apolipoprotein E (APOE), a major cholesterol-transporting plasma protein, is expressed as three different polymorphic allelic forms (APOE ϵ 2, ϵ 3, and ϵ 4) of which APOE ϵ 4 is associated with an increased risk of Alzheimer's disease (AD). A small amount of cholesterol exits via an APOE mediated pathway through the cerebrospinal fluid.¹ Because depletion of brain cholesterol levels reduces the generation of β amyloid protein in the brain and cholesterol lowering drugs may reduce the risk of dementia,¹ we tested the hypothesis that the previously examined single nucleotide polymorphism dbSNP:754203 in the CYP46 gene³ with or without the APOE ϵ 4 allele was associated with AD in a Finnish population. Further, we performed a meta-analysis of the CYP46 dbSNP:754203 polymorphism using all reported findings of similar association studies on Medline (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) up to April 2005 to evaluate the true global effect of the polymorphism as a susceptibility factor for AD.

The study population was examined in the Department of Neurology, Kuopio University Hospital.⁴ The ethical committee of University Hospital approved the study. The subjects consisted of 422 AD patients (mean age of onset 72 ± 7 years; 293 (69%) women) and 469 controls (mean age at examination or death 70 ± 5 years; 284 (61%) women), who had no signs of cognitive decline on interview or neuropsychological testing. There was a positive family history of AD in 36% of AD patients, but inconclusive evidence of autosomal dominant transmission. If a reliable family history was not available, the disease was termed sporadic. All AD subjects underwent a comprehensive clinical evaluation during which a clinical diagnosis of probable AD was made according to the NINCDS-ADRDA criteria. There were 68 AD patients (16% of all AD cases) with onset at 65 years of age or below, 63 of whom were screened for known AD mutations in APP, PSEN-1, or PSEN-2 genes. Although no such mutations were found, it is still possible that some of these patients may carry rare variants of these genes.

We genotyped dbSNP:754203 T to C substitution in intron 2 by using the ABI PRISM SNaPshot Multiplex assay and ABI 3100 Genetic Analyzer (<http://appliedbiosystems.com>). Amplification primers for dbSNP:754203 have been described previously³; the following specific primer was used in a SNaPshot reaction with the length of the tail indicated by the subscript: 5'-T₃₁CAACAGGGCAGAGCCTTGCCCC-3'. Genotype frequencies were in Hardy-Weinberg equilibrium in cases and controls. APOE genotyping was determined by a standard method.⁴ Meta-analysis was carried out with RevMan 4.2 software (<http://www.cc-ims.net/RevMan/>). Fixed and random effects meta-analyses were performed depending on the heterogeneity of the effects. Pooled and individual study effects were estimated by applying a maximum likelihood estimation technique. Binary logistic regression analyses were carried out with SPSS version 11.5 and the level of statistical significance was set at $p \leq 0.05$.

Results

The distribution of APOE ϵ 2, ϵ 3, and ϵ 4 alleles in the AD patients and controls was 0.02/0.51/0.47 and 0.04/0.80/0.16, respectively; this result was consistent with that previously found in the same population.⁴ The APOE ϵ 4 allele was significantly associated with AD (OR 4.8, 95% CI 3.8 to 6.0; $p < 0.001$) and age at onset was 3 years earlier for ϵ 4 versus ϵ 4- patients (71 v 74 years of age, $p < 0.001$). In logistic regression tests, the subjects were also divided on the basis of APOE genotype into APOE4 carriers and non-carriers.

We found a significant difference ($p = 0.015$) in the distribution of dbSNP:754203 CC, CT, and TT genotypes between all AD subjects and controls. We also observed a significant association between the dbSNP:754203 CC genotype and AD in all and APOE4+ subjects (311 AD patients and 129 controls). The age and sex adjusted odds ratio for the risk of AD in the carriers of the dbSNP:754203 CC genotype was 2.13 (95% CI 1.25 to 3.62; $p = 0.005$) and 3.58 (95% CI 1.21 to 10.56; $p = 0.021$) compared with the CT/TT genotypes for all and APOE4+ subjects, respectively. In the subgroup of patients with onset at 65 years of age or below, the distribution of dbSNP:754203 genotypes did not differ significantly from controls, but it did differ in the subgroup with onset at 65 years of age or above. However, the highest significance was achieved when all study material was considered together. For meta-analysis of dbSNP:754203, 15 case-control studies including this one were pooled, resulting in 3307 cases and 3328 controls (fig 1). A fixed effects meta-analysis was performed since the likelihood ratio test did not provide significant evidence of between study heterogeneity ($\chi^2 = 20.49$, df 14; $p = 0.12$). In the pooled analysis of different ethnic populations, a pooled effect of CC genotype frequencies in AD cases was very similar to those found in controls (OR 1.16; 95% CI 0.97 to 1.38).

Comment

This candidate gene based association study of the CYP46 gene in a large series of AD patients and controls implicated the CYP46 intron 2 CC genotype as a possible risk factor for Finnish AD patients. For maximum power in statistical tests, we primarily used all AD and control material together, but since the APOE polymorphism is an established risk factor for AD we also determined the effect of APOE genotypes on possible CYP46 association with AD.

There are several contradictory studies describing either risk, no association, or even a beneficial effect for dbSNP:754203 and AD (fig 1). Although allele/genotype frequencies of dbSNP:754203 and AD may be population or geographic specific, the meta-analysis argues against the hypothesis that dbSNP:754203 plays a crucial role in the interaction between the CYP46 gene and AD (fig 1). Since the relevant variation dbSNP:754203 is intronic, it is not clear how it influences the function of the respective enzyme. It may be in linkage disequilibrium with an as yet unidentified functional variant on CYP46 coding exons or promoter region. Interestingly, dbSNP:754203 was not associated with 24S-hydroxycholesterol/cholesterol ratios in CSF of AD patients.⁵ However, the dbSNP:754203 polymorphism correlated with increased β amyloid load in brain tissues as well as with increased CSF