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 cylosporin 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.[5] 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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Patient details are published with consent

doi: 10.1136/jnnp.2005.071597

Competing interests: none declared

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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 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 ε2, ε3, and ε4) of which APOE ε4 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 gene[3] with or without the APOE ε4 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 previously[3]; the following specific primer was used in a SNaPshot reaction with the length of the tail indicated by the subscript: 5′-T_{31}CAACAGGGCAGAGCCTTGCCCCC-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 $p \leqslant 0.05$.

Results

The distribution of APOE ε2, ε3, and ε4 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 ε4 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 ε4+ versus ε4− 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

Study (population); PMID	AD (n/N)	Control (n/N)	OR (95% CI)	Weight %
Desai (American caucasians; USA); 12 123 847	45/434	41/401		16.33
Desai (African American; USA); 12 123 847	1/54	2/61		0.79
Ingelsson (USA)*; 15 331 159	19/178	5/105		2.40
Wang (China); 15 450 677	2/99	3/113		1.17
Combarros (Spain); 15 286 456	27/321	10/315		3.95
Papassotiropoulos (Greece, Italy); 12 533 085	5/107	6/76		2.86
Papassotiropoulos (Switzerland); 12 533 085	7/94	19/172		5.31
Borroni (Italy); 15 165 699	10/143	10/134		4.10
Kabbara (France); 15 172 102	57/601	57/631		21.51
Kölsch (Germany); 12 232 784	10/115	16/144		5.54
Chalmers (UK)*; 15 106 838	4/86	3/58		1.46
Johansson (Sweden); 15 034 781	54/440	45/398		17.72
Johansson (Sweden)*; 15 034 781	5/93	11/102		4.24
Johansson (Scotland)†; 15 034 781	9/120	11/149		3.88
Present study (Finland)	43/422	24/469		8.73
Total (95% CI)	3307	3328		100.0

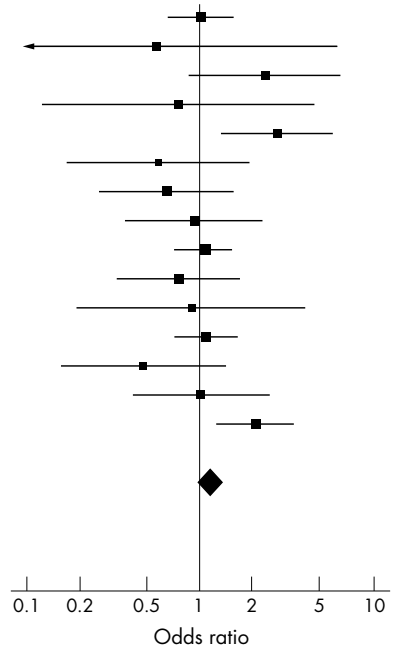

Figure 1 Meta-analysis of the dbSNP:754203 CC genotype carriers. OR and 95% CI of the genotype frequencies are shown. *Autopsy confirmed sample; 54 AD cases confirmed (Ingelsson). †Early onset AD sample. n/N, number of CC genotype carriers/number of subjects. Weight %, weighting proportion in an individual study (used when combining ORs). In the separate pooled analysis of USA and European populations, a pooled effect of CC genotype frequencies was similar to those found in controls (OR 1.17; 95% CI 0.78 to 1.73 and OR 1.16; 95% CI 0.95 to 1.41, for USA and European subjects, respectively). Hardy-Weinberg equilibrium was not re-examined in studies for meta-analysis. PMID, PubMed - indexed for Medline (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi). We did not show allele frequencies of this SNP because the Alzheimer Research Forum (http://www.alzforum.org/home.asp) has previously published OR and 95% CI of allele frequencies of dbSNP:754203 in their meta-analysis.

levels of β amyloid and phosphorylated tau proteins.[5] We conclude that the CYP46 intron 2 polymorphism may influence the risk of developing AD in the Finnish population, although meta-analysis does not support this role on a global scale.

Acknowledgements

The authors are grateful to Ms Petra Mäkinen and Ms Marjo Laitinen for their skilful technical help with the SNP screening and genotyping.

Electronic-database information

The following URLs have been mentioned in this article: PubMed: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi; Applied Biosystems: http://appliedbiosystems.com; RevMan: http://www.cc-ims.net/RevMan/; and the Alzheimer Research Forum: http://www.alzforum.org/home.asp.

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doi: 10.1136/jnnp.2005.071928

The study was supported by the Health Research Council of the Academy of Finland, an EVO grant (no 5772708) from Kuopio University Hospital, and the Nordic Center of Excellence in Neurodegeneration

Competing interests: none declared

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Propriospinal myoclonus with life threatening tonic spasms as paraneoplastic presentation of breast cancer

Myoclonus is a sudden, shock-like, involuntary movement caused by abnormal neuronal discharges. It may be cortical, subcortical, or spinal (segmental or propriospinal).[1] One or a few contiguous spinal segments are involved in segmental myoclonus, while several segments are involved in propriospinal myoclonus since electrical activity spreads upwards and downwards from a spinal generator via propriospinal pathways. Propriospinal myoclonus may be caused by different spinal cord diseases or by drugs.[1 2] Paraneoplastic neurological syndromes are rare immune mediated disorders associated with several types of cancer. Their pathophysiology is incompletely understood, although it is thought that specific antibodies formed against tumours may cross react with nerve cells.

Case report

A 49 year old woman presented with a 9 month history of involuntary, shock-like trunk and leg movements, occurring several times per day. Sporadically, they became prolonged, involved arm muscles, and caused transient respiratory failure. Several unsuc-