The androgen receptor CAG repeat and serum testosterone in the risk of Alzheimer's disease in men

We recently reported that the glutamine (CAG) repeat polymorphism of exon 1 of the androgen receptor was associated with Alzheimer’s disease in men from the Oxford region. However, the androgen receptor polymorphism indeed affects Alzheimer’s disease risk rather than being in linkage disequilibrium with the true risk factor, then we should see the effect through androgen receptor actions. The association should, for instance, be influenced by ligands of the androgen receptor. Androgen receptor isoforms are the main, perhaps sole, receptors for the principal mammalian androgens, testosterone and 5α-dihydrotestosterone. On binding ligand, the receptor moves from the cytoplasm to specific compartments of the nucleus (‘nuclear foci’), where it interacts with coactivators and corepressors in the cell specific regulation of numerous genes. We therefore looked for an interaction in Alzheimer’s disease risk of the androgen receptor CAG polymorphism with serum concentrations of total testosterone.

We studied 207 elderly men, 79 with sporadic Alzheimer’s disease (mean (SD) onset age, 70 (9) years) and 128 controls (mean age, 75 (10) years), all from the cohort of the Oxford Project to Investigate Memory and Ageing (OPTIMA). Of the 79 Alzheimer cases, 43 were necropsy confirmed as having Alzheimer’s disease by CERAD criteria (40 ‘definite’ and five ‘probable’) and 34 were diagnosed as ‘probable Alzheimer’s disease’ by NINCDS-ADRDA criteria. All 128 controls were without detectable cognitive dysfunction and with CAMCOG scores of more than 80. Serum concentrations of total testosterone and androgen receptor allele lengths were determined as previously described. 1

Testosterone concentrations were divided into tertiles (69 subjects in each tertile): the lower tertile testosterone was between 13 and 19 nmol/l, and the lower £ 19 nmol/l, the middle between 13 and 19 nmol/l, and the lower < 13 nmol/l. Short androgen receptor alleles were < 20 CAG repeats. Logistic regression analysis was by R.

Results

As expected, short androgen receptor alleles1 and low testosterone2 were associated with Alzheimer’s disease. Controlling for age, odds ratios of Alzheimer’s disease were 2.1 (95% confidence interval, 1.1 to 4.1) (p = 0.025) for short androgen receptor alleles, and 2.2 (1.01 to 4.6) (p = 0.04) for the lower tertile of testosterone. There was a significant trend in the association with Alzheimer’s disease by testosterone tertile (Z = 2.695; p = 0.007), indicating a possible dose related effect of testosterone.

Table 1 shows the unadjusted odds ratios of Alzheimer’s disease for each combination of long or short androgen receptor alleles with each testosterone tertile, taking long alleles with upper tertile testosterone as reference. The odds ratio for short androgen receptor alleles with lower tertile testosterone was 4.2 (1.4 to 13) (p = 0.01). Combining the two at risk subgroups—that is, carriers of short androgen receptor alleles with middle or lower tertile testosterone—versus all the others gave an odds ratio of Alzheimer’s disease of 2.3 (1.1 to 4.8) (p = 0.05), when adjusted for age and for carrier status of apolipoprotein E 4.

Comment

A difficulty with the study of complex diseases such as sporadic Alzheimer’s disease lies in the numerous interactions of each risk gene with other genes, with age and sex, and with the environment. This results in a weak overall effect of each gene and in conflicting results of genetic studies. To resolve the difficulty, we need to examine the interactions that define the ‘relevant subset’ of people at risk for each susceptibility gene.

The association of the glutamine (CAG) repeat polymorphism of the androgen receptor with Alzheimer’s disease appears limited to men. This is unsurprising, given the role of testosterone and androgen receptor actions in memory and with other brain disorders.1, 3

Polyglutamine tracts play an important role in the activity of many transcription factors. The androgen receptor tract is in exon 1, which carries the transactivation domain. Transcriptional activity of the androgen receptor decreases with increasing length of the tract, even within the normal range.3 This effect is cell specific, which suggests that it may reflect interactions with other proteins. The androgen receptor coactivator, ARA24, has been found to be less effective with expansion of the androgen receptor polyglutamine tract. Binding of testosterone to the androgen receptor changes the conformation, releasing it from its cytoplasmic compartment and allowing nuclear translocation. This also permits interactions with coactivators, as well as between the N-and C-terminal domains of the androgen receptor. The polyglutamine tract is involved in several of these interactions.

Our results suggest that the combination of short androgen receptor alleles with lower levels of serum testosterone may increase the risk of Alzheimer’s disease for men. Further study is needed to clarify whether these two potential risk factors interact or act independently. There is a growing appreciation of, first, the influence of sex steroids on Alzheimer’s disease risk1 and, second, the role of sex in Alzheimer’s disease genetics.1, 4, 5

This study therefore merits replication in other, carefully characterised, all male cohorts. To demonstrate an association, large numbers would be needed, either through a collaborative study, using meta-analytical techniques for pooling, or eventually through a meta-analysis.

Acknowledgements

We especially thank all patients and volunteers, members of OPTIMA, the Department of Neuropathology, Radcliffe Infirmary, T James, and M Gaids. We are most grateful to Bristol Myers Squibb, the Medical Research Council, and the Norman Collisson Foundation for financial support.

D J Lehmann, E Hogervorst, D R Warden, A D Smith

Oxford Project to Investigate Memory and Ageing (OPTIMA), Radcliffe Infirmary, Oxford and University Department of Pharmacology, Mansfield Road, Oxford OX1 3QG, UK

H T Butler, J Ragoussis

Genomics Laboratory, Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford

Correspondence to: D J Lehmann; donald.lehmann@pharm.ox.ac.uk

References


7 Seidman SN, Araujo AB, Roose SP, et al. Testosterone level, androgen receptor


Subthalamic nucleus stimulation in a parkinsonian patient with previous bilateral thalamotomy

Stereotactic surgical ablation of the thalamic nucleus (thalamotomy) has long been applied to parkinsonian tremor, rigidity, and levodopa induced dyskinesias. Chronic high frequency deep brain stimulation (DBS) of the thalamus, the globus pallidus internus (GPi), and the subthalamic nucleus (STN) has been widely used as an alternative to ablative surgery in the treatment of Parkinson's disease (PD). STN stimulation has become increasingly popular because it can result in a striking improvement of motor symptoms and the ability for PD patients to pursue the activities of daily living. We report that STN stimulation markedly alleviated axial motor symptoms in a PD patient who had undergone bilateral thalamotomy more than 20 years earlier.

This 70 year old right handed woman presented for the first time to our university hospital in early 2002. Around 1968, she developed right sided tremor and bradykinesia and was diagnosed with PD. Although she initially responded well to medication, her symptoms progressed, with worsening motor fluctuations including dyskinesia. Left and right thalamotomy, performed in 1976 and 1982 respectively, resulted in marked improvement of her tremor and dyskinesia. She received optimised medication and for the next 10 years was able to continue her job as a secretary. However, she developed slowly worsening postural instability with hesitant and shuffling gait, and suffered occasional falls. Admission examination in March 2002 disclosed no neurological signs apart from parkinsonism. Under the administration of carbidopa/levodopa (4×5.0/50 mg/day), cabergoline (3×1.0 mg/day), amantadine hydrochloride (3×50 mg/day), and DL-threo- DOPS (3×100 mg/day), neither rest tremor nor rigidity were apparent. Her bradykinesia was slight and more pronounced on the left side. Among her parkinsonian disabilities, axial symptoms including postural instability and gait disorder were the most pronounced. In the sitting position, her upper body was...
bent to the left. Without assistance she could not easily stand up, and her feet quickly froze when she attempted to walk forward. Shuffling hesitant steps were more marked on the left side and were particularly evident when turning, initiating gait, and walking backwards (fig 1A). They were not alleviated by visual aids such as stripes on the floor or by use of a serrated walking cane. Her facial expression and speech were slightly affected and she manifested micrographia. On medication, her total and Part III motor scores on the Unified Parkinson’s Disease Rating Scale were 38 and 19, respectively. Magnetic resonance imaging (MRI) revealed no obvious abnormalities except for the surgical lesions produced 20 years earlier in the bilateral thalamic nuclei (fig 1B, C). Because she had experienced occasional transient drug induced dysphoria that disappeared when the dosages were reduced, we concluded that it was not possible to improve her symptoms by pharmacotherapy alone and decided to perform stereotaxy. Prior informed consent was obtained from the patient and her family.

STN stimulation using two ventral contacts (contacts 0 and 1) gave rise to a striking improvement of her axial symptoms. Contacts 0 and 1 were used as cathode (fig 1D) and the pulse generator as anode. After extensive trials, the optimal stimulation parameters were determined to be 130 Hz frequency, 60 μA pulse width, 6.8 V and 2.6 V amplitude at the first and final session, respectively. Under stimulation, she was able to walk up with ease and without assistance, and could initiate gait fluently. Her shuffling hesitant steps almost disappeared even when turning and walking backwards (fig 1E). Compared to preoperative baselines, her total and Part III motor scores were reduced from 38 and 19 to 5 and 5, respectively. She continued to take the same medication at the same doses as before and the beneficial effects of STN stimulation were unchanged at 9 months post-treatment.

Medically intractable PD has been addressed with different types of surgery. Our patient initially underwent staged bilateral thalatomy. Although this procedure produced long lasting benefits and her tremor, rigidity, and dyskinesias were improved, she developed an almost constant bilateral and then unilateral thalamic apraxia with severe contralateral sidedness. STN DBS appears to exhibit greater anti-parkinsonian effects than GPi DBS. Therefore, we chose STN stimulation for our patient. We concluded that it was not possible to improve her symptoms by pharmacotherapy alone and decided to perform stereotaxy. Prior informed consent was obtained from the patient and her family.

Nonetheless, we recognised the long lasting transient drug induced psychoses that disappeared when the dosages were reduced, we concluded that it was not possible to improve her symptoms by pharmacotherapy alone and decided to perform stereotaxy. Prior informed consent was obtained from the patient and her family.

References


Testosterone deficiency in a Parkinson’s disease clinic: results of a survey

It has been shown recently that male patients with Parkinson’s disease who have testosterone deficiency may have symptoms resembling non-motor parkinsonian symptoms. As the similarity between the non-motor symptoms of Parkinson’s disease and the symptoms of hypogonadal non-motor parkinsonian deficiency is so marked, clinicians may fail to recognise and treat testosterone deficiency in patients with Parkinson’s disease. The identification of testosterone deficiency may have a significant impact on the long term course of the disease, as symptoms mistakenly labelled as non-motor parkinsonian manifestations could be relieved more effectively by testosterone replacement than by other treatments. Therefore, in this investigation we examined the prevalence of testosterone deficiency and testosterone deficiency symptoms among a group of patients with Parkinson’s disease presenting to our movement disorders clinic, to assess how commonly undiagnosed symptomatic testosterone deficiency was in this population. A mail-back survey was administered to all the patients seen in the clinic after a 12 month period where patients were seen, examined, and entered into a database. The surveys were returned by 91 of 137 male patients with Parkinson’s disease (66%). The diagnosis of idiopathic Parkinson’s disease was confirmed by a movement disorders specialist who applied the UK Brain Bank criteria and currently recommended guidelines for the diagnosis of Parkinson’s disease. We included in the survey two validated scales—the St Louis testosterone deficiency questionnaire and the Beck depression inventory. Additionally, history of testosterone replacement therapy was obtained including the number of antidepressants the patients were exposed to in a lifetime, number of current antidepressants, history of testosterone deficiency, history of prostate cancer, and history of hormone replacement therapy. Forty two male patients with Parkinson’s disease who returned questionnaires had previously been identified as testosterone deficient by measurements of plasma testosterone concentrations.

The results of the survey are summarised in the table 1. The average age of the male patients was 62 years. Nine per cent of the study population were on testosterone gel replacement therapy. Fifty of the 91 Parkinson’s disease patients were screened with free testosterone levels during the 12 month period of the study. Half of the Parkinson’s disease patients (n = 25) who were screened for testosterone deficiency had a level of <70 pg/ml and were defined as having “low” testosterone. Ninety per cent of all male patients with Parkinson’s disease had a positive St Louis testosterone deficiency questionnaire (positive answers to more than three questions).

Comment

The results of our survey indicate that testosterone deficiency is common in the elderly male population seen in a movement disorders clinic setting, and the prevalence is similar to that previously reported in the Baltimore longitudinal study of aging in the normal elderly population and in Parkinson’s disease. As the non-motor symptoms of Parkinson’s disease—including depression, anxiety, fatigue, decreased libido, sexual dysfunction, and a decreased enjoyment in life—directly overlap with those seen in male testosterone deficiency, separating testosterone deficiency from the non-motor symptoms of Parkinson’s disease can be difficult. This separation is important because specific treatment for testosterone deficiency is available and because these symptoms may not respond satisfactorily to antidepressant therapy.

Previous observations of refractory non-motor symptoms of Parkinson’s disease that responded to testosterone replacement suggested that patients were on or had been exposed to an increased number of antidepressants. This study found that testosterone deficiency—and also seen in thyr-roid hormone deficiency—may blunt responsiveness to antidepressants, prompting the investigation of testosterone deficiency. Patients with testosterone deficiency took more antidepressants than those without testosterone deficiency, as well as to examine whether testosterone deficiency scores correlated with the number of antidepressants. Our data suggest a difference in antidepressant use in the testosterone deficient Parkinson’s disease population.
population; however, a prospective study will need to be done to test this observation. Overall, however, depression scores were not high in this study, which may either reflect aggressive treatment of depression in our Parkinson group, or suggest that testosterone deficiency does not present as major depression. Additionally, the study did not specifically screen for patients who were refractory to antidepressant treatment, and for those who had previously received aggressive treatment for depression. We suspect that testosterone deficiency, like thyroid deficiency, will need to be included in future analyses, as this analysis was not designed to determine if testosterone deficiency is a common unrecognized comorbidity.

Testosterone deficiency is a common, treatable, and largely unrecognized form of comorbidity in Parkinson’s disease, and as demonstrated by this study is common in a movement disorders clinic setting. It may go undiagnosed when the symptoms are attributed to the non-motor manifestations of Parkinson’s disease. Additionally, a lack of a history of refractoriness to antidepressants, or lack of a positive depression screening questionnaire, should not dissuade practitioners from checking testosterone levels, as antidepressant responsive “depressive symptoms” seem to be common in testosterone deficiency.

Prospective epidemiological studies on this topic need to be undertaken, as this analysis of clinic patients suffered from both the bias of the researchers interested in testosterone deficiency, and the failure to get 100% return of the surveys. Additionally, a control group will need to be included in future analyses, and better screening devices with increased specificity for patients with Parkinson’s disease and testosterone deficiency will need to be developed. The issue of which type of testosterone assay is best, and how much the testosterone level matters if a patient is symptomatic, will also need to be examined.

Every practitioner who sees patients with Parkinson’s disease should be aware of this common treatable comorbidity. The diagnosis of testosterone deficiency should be confirmed and prostate cancer excluded before initiating treatment.

Acknowledgements
We would like to thank the American Parkinson’s Disease Association and the Department of Neurology and McKnight Brain Institute for their generous support and help with the research described in this report.

M S Okun, G P Crucian
Department of Neurology, McKnight Brain Institute, University of Florida, USA

L Fischer, B L Walter, C M Testa, J L Vitek, M R DeLong
Department of Neurology, Emory University

J Hanfelt
Department of Biostatistics, Emory University

X Huang
Department of Neurology, University of North Carolina, Chapel Hill

Correspondence to: Dr Michael S Okun, Movement Disorders Center, University of Florida, Brain Institute, PO Box 100236, Gainesville, FL 32610, USA; okun@neurology.ufl.edu

References
1 Okun MS, McDonald WM, DeLong MR. Refractory nonmotor symptoms in male patients with Parkinson disease due to testosterone deficiency: a common unrecognized comorbidity.

Table 1 Characteristics of 91 male patients with Parkinson’s disease who returned the questionnaire

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 91)</th>
<th>Free T &lt; 70 pg/ml</th>
<th>Free T &gt; 70 pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 64</td>
<td>71</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>SD 10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Range 40 to 89</td>
<td>55 to 89</td>
<td>44 to 83</td>
</tr>
<tr>
<td>HRT (% of patients)</td>
<td>10%</td>
<td>21%</td>
<td>4%</td>
</tr>
<tr>
<td>Free testosterone level (pg/ml)</td>
<td>19 (45%)</td>
<td>19 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>&gt;70 23 (55%)</td>
<td>0 (0%)</td>
<td>23 (100%)</td>
</tr>
<tr>
<td>Mean</td>
<td>82.1</td>
<td>49.0</td>
<td>109.4</td>
</tr>
<tr>
<td>SD</td>
<td>41.6</td>
<td>13.6</td>
<td>36.7</td>
</tr>
<tr>
<td>Range</td>
<td>4.1 to 196.1</td>
<td>4.1 to 65.7</td>
<td>71.2 to 196.1</td>
</tr>
<tr>
<td>St Louis score</td>
<td>&gt;3 85 (93%)</td>
<td>18 (95%)</td>
<td>22 (96%)</td>
</tr>
<tr>
<td></td>
<td>&lt;3 6 (7%)</td>
<td>1 (1%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Mean</td>
<td>5.9</td>
<td>6.6</td>
<td>5.8</td>
</tr>
<tr>
<td>SD</td>
<td>2.3</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Range</td>
<td>0 to 10</td>
<td>2 to 10</td>
<td>2 to 10</td>
</tr>
<tr>
<td>BDI score</td>
<td>Mean 9.2</td>
<td>10.5</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>SD 6.0</td>
<td>6.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Range</td>
<td>0 to 31</td>
<td>2 to 22</td>
<td>0 to 19</td>
</tr>
<tr>
<td>Number of antidepressants</td>
<td>Current: 51 (56%)</td>
<td>7 (37%)</td>
<td>13 (57%)</td>
</tr>
<tr>
<td></td>
<td>1 37 (41%)</td>
<td>11 (58%)</td>
<td>10 (43%)</td>
</tr>
<tr>
<td></td>
<td>&gt;1 3 (3%)</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Lifetime:</td>
<td>0 35 (38%)</td>
<td>4 (21%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td></td>
<td>2 27 (30%)</td>
<td>10 (53%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td></td>
<td>2 15 (16%)</td>
<td>1 (5%)</td>
<td>6 (26%)</td>
</tr>
<tr>
<td></td>
<td>3 10 (11%)</td>
<td>3 (16%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td></td>
<td>&gt;3 4 (4%)</td>
<td>1 (5%)</td>
<td>2 (9%)</td>
</tr>
</tbody>
</table>

BDI, Beck depression inventory; HRT, hormone replacement therapy; T, testosterone.

LBP-1c/CP2/LSF gene polymorphism and risk of sporadic Alzheimer’s disease

The 4 allele of apolipoprotein E (ApoE) accounts for an estimated 45–60% of the genetic risk for late onset sporadic Alzheimer’s disease, suggesting that it may be possible to identify other genetic loci that could account for the remaining risk associated with this disease. Recently, a biallelic polymorphism (G/A) in the 3’ untranslated region (UTR) of the transcription factor LBP-1c/CP2/LSF (for brevity, CP2) has been implicated in Alzheimer’s disease susceptibility with the 3’-UTR A allele being associated with a reduction in the risk of sporadic Alzheimer’s disease.4–6 The CP2 gene is a plausible candidate for influencing Alzheimer’s disease risk: it is located near the CP2 polymorphism in a sample of sporadic early onset and late onset cases.6 In early studies, we investigated the potential association of the CP2 polymorphism in a sample of sporadic early onset and late onset cases along with age and sex matched control subjects from southern Italy.5

The Alzheimer’s disease group consisted of 166 patients (62 men and 104 women) from the Apulia region with a mean (SD) actual age of 69.4 (10.3) years, including 93 patients with sporadic late onset disease (age at onset >70 years; mean age 78.1 (4.9) years; 64 women and 31 men), and 71 patients with sporadic early onset disease (age at onset <70 years; mean age 63.7 (4.3) years; 50 women and 21 men). A clinical diagnosis of probable Alzheimer’s disease was made according to the NINCDS/ADRDA criteria.5 The age at
onset of Alzheimer’s disease symptoms was estimated by semi-structured interviews with the patients’ caregivers. The non-demented age, sex, and ethnically matched control group comprised 225 unrelatred caregivers (72 men and 153 women), spouses, friends, neighbours, or volunteers, consecutively examined between June 1998 and October 2002 in our centre. Their mean age at the time of the study was 71.3 (10.4) years. The healthy subjects included 193 individuals of 70 years of age (130 women and 63 men) and 32 of <70 years (23 women and nine men).

The ascertainment, diagnosis, and collection of cases and controls has been described in detail elsewhere. The study protocol was approved by the ethics committee of the University of Bari. Informed written consent was obtained from all subjects or their relatives before blood samples were collected. Genomic DNA was extracted from peripheral blood samples using Cod 1796828 (Roche Diagnostics kit). APOE genotypes were determined as previously described. CP2 polymorphism was analysed on a Lightcyler system using specifically designed hybridisation probes (sensor probe: 5’-GGCTTTGATGCCTGAGTCG-3’, reverse primer: 5’-TCAGCTTCGCTGGACATGC-3’ forward primer). Polymerase chain reaction (PCR) amplification was undertaken using 200 ng of genomic DNA, 50 pmol each primer (5’-GACAGAATTTGCCTGCTGCCC-3’, reverse primer; 5’-TCAGCTTCGCTGGACATGC-3’ forward primer), 2.5 mM MgCl2, 1×DNA master hybridisation probes (Roche Diagnostics). The amplification conditions were 95°C for two minutes, and 38 cycles of 94°C for five seconds, 58°C for 15 seconds, and 72°C for 10 seconds. After amplification, the temperature was raised to 94°C for 30 seconds, lowered to 40°C at 20°C/s of temperature transition rate, and held at 40°C for one minute. A melting curve analysis profile was obtained by raising the temperature to 80°C at 0.05°C/s while collecting fluorescence data continuously. The melting temperatures were 60°C for the 3’-UTR G allele and 66°C for the 3’-UTR A allele.

### Table 1

| Genotype and allele frequencies of LBP-1c/CP2/LSF gene 3’ UTR polymorphism in patients with Alzheimer’s disease and non-demented age and sex matched controls |
|---|---|---|---|---|---|---|
| **Age at onset and at collection (SD) years** | **Genotype, n (frequency (95% CI))** | **Allele, n (frequency (95% CI))** |
| **All cases of Alzheimer’s disease (n = 166)** | 67.6 (10.8) | 19 | 0.03 (0.01 to 0.05) | 19 | 0.06 (0.03 to 0.09) |
| **All controls (n = 225)** | 71.3 (11.4) | 216 | 0.04 (0.01 to 0.07) | 0 | 0.0 (0.0 to 0.0) |
| **LOAD (>70 years) (n = 95)** | 76.1 (4.4) | 86 | 0.09 (0.05 to 0.15) | 9 | 0.17 (0.12 to 0.22) |
| **EOAD (<70 years) (n = 71)** | 61.5 (4.5) | 61 | 0.98 (0.94 to 1.02) | 0 | 0.0 (0.0 to 0.0) |
| **Controls (>70 years) (n = 193)** | 77.8 (5.2) | 184 | 0.05 (0.01 to 0.09) | 9 | 0.16 (0.11 to 0.21) |
| **Controls (<70 years) (n = 32)** | 64.1 (4.3) | 0 | 0.0 (0.0 to 0.0) | 9 | 0.16 (0.11 to 0.21) |

### Results

Statistical analysis was done using Pearson χ² tests to make genotype and allele comparisons, and a test for data agreement using Hardy-Weinberg principles. Allele frequencie ies were determined by allele counting. To express variances of allele and genotype frequencies, we used 95% confidence intervals (CI), calculated by Wilson’s formulae. Differences among age at onset of Alzheimer’s disease symptoms in relation to different CP2 genotypes were calculated using the Mann–Whitney test. To evaluate whether the association between Alzheimer’s disease and CP2 genotypes was homogeneous in all ApoE strata we used a permutation test for Pearson’s correlation coefficient, using 10,000 permutations. To evaluate whether there was a difference in the allele frequency between affected subjects and controls, we used a test for data agreement using 10,000 permutations. To evaluate whether the association between Alzheimer’s disease and CP2 genotypes was significant in the Alzheimer patients and the controls, the A allele had a mean age of onset lower than those carrying the G allele (mean age at onset: A allele, 64.8 (12.2) years; G allele, 68.0 (9.4) years), although this difference was not statistically significant (t = 0.9, p = 0.35). Furthermore, the Alzheimer patients bearing the A allele had a mean age of onset lower than those carrying the G allele (mean age at onset: A allele, 64.8 (12.2) years; G allele, 68.0 (9.4) years), although this difference was not statistically significant (t = 0.9, p = 0.35). We did not find any significant differences in rates between CP2 alleles and Alzheimer’s disease among ApoE allele strata.

### Comment

The major finding of the present study is that the A allele of the 3’-UTR CP2 gene polymorphism increases the risk of sporadic Alzheimer’s disease (OR = 2.97), without interaction with ApoE alleles. After stratification for age at onset, this effect was statistically significant only in patients with early onset disease (<70 years), whereas in late onset disease (≥70 years) there was a difference in the A allele frequency between affected subjects and controls (though this did not reach statistical significance).

### References

Lambert et al reported an association between the CP2 polymorphism and sporadic Alzheimer’s disease in French and British populations, and a similar trend in a north American population. The combined analysis of the three independent populations suggested a protective effect of the A allele (OR = 0.58), that decreased with age (OR = 0.43 before 70 years; OR = 0.52 between 70 and 80 years; OR = 0.83 after 80 years). More recently, Taylor and colleagues found similar results, detecting a significant protective effect of the A allele (OR = 0.59) in 216 neuropathologically confirmed patients with late onset disease and 301 controls from the United Kingdom. Finally, Luedeking-Zimmer et al found that the frequency of the A allele was higher in controls than in cases (0.07 ± 0.05), suggesting a moderate protective
effect of the CP2 polymorphism against the risk of Alzheimer’s disease (OR = 0.65). 1

To the best of our knowledge, this is the first report suggesting a risk of Alzheimer’s disease linked to the CP2 A allele, and the contrasting results of our study are, at present, difficult to explain. However, Lambert et al did not observe a significant protective effect of the A allele in the US population, 2 and we recently provided a novel finding that the ApoE ε4 allele frequency decreases according to a geographic trend from northern to southern Europe. 2 We hypothesize that the variability in the association between the A allele and Alzheimer’s disease can be related to ethnic and geographical variations: from 0.09 to 0.07 of A allele frequency in healthy controls from the UK, France, and north America, to only 0.02 in southern Italy. 3, 4 It is also possible that a moderate effect associated with the CP2 polymorphism is caused by its non-random association with a functional mutation present somewhere in the gene. Finally, it is possible that there is linkage disequilibrium between another biologically relevant locus on chromosome 12. The possible role of the A allele as a risk factor for sporadic Alzheimer’s disease, suggested by the lower mean age at onset of Alzheimer’s disease in patients with the A allele than those carrying the G allele, though this difference was not significant. We found no interaction between CP2 polymorphism and ApoE alleles in relation to Alzheimer’s disease risk, and this finding is consistent with previous results. 1, 2

In conclusion, our data support CP2 as a candidate gene for sporadic Alzheimer’s disease, and we recently provided a novel approach to the treatment of mania. It is possible that the power of suggestion, or a “placebo” effect, contributed to the observed effect. Care was taken not to relay to the patient a sense of expectation of an improvement in mood, and extra contact with staff following the procedure was minimised. It is unlikely that the immediate improvement in symptoms reflected a change in behaviour secondary to adverse effects of the procedure. Vertigo was the only side effect experienced by the patient, and all sense of vertigo had resolved within 10 minutes of the procedure. The use of the YMRS provided a standard for comparison of the severity of her symptoms before and after stimulation and served to provide a marked reduction in manic symptoms.

Caloric vestibular stimulation represents a novel approach to the treatment of mania. It is possible that it exerts its effect on mood through stimulation of motor and neural circuits. Following caloric vestibular stimulation, functional magnetic resonance imaging shows widespread, mainly contralateral activation of diencephalic and cortical regions which include the basal ganglia, insula,

References


Vestibular stimulation in mania: a case report

Caloric vestibular stimulation is a common clinical procedure, routinely employed during testing of vestibulocochlear nerve function. The procedure involves stimulation of vestibular afferents by the application of cooled water to the tympanic membrane. Vestibular afferents are concentrated in a small area of the diencephalon and cortex, including areas believed to be involved in the regulation of mood. In accordance with these observations, imaging studies have shown widespread though largely contralateral hemispheric activation following the procedure.

Caloric vestibular stimulation has been associated with a rapid but short lived improvement in stroke induced functional deficits, 5 but the effect of the procedure on psychiatric symptomatology has not been reported. In the case described here, an improvement in manic symptoms was observed after caloric vestibular stimulation in a 29 year old woman with a 10 year history of bipolar affective disorder. The patient was admitted to an acute psychiatric ward with several weeks of increasingly elevated and irritable mood. Her symptoms fulfilled DSM-IV criteria for a manic episode. Resistance to pharmacotherapeutic drug use and intolerance of side effects had limited effective management of her condition. Previous episodes of mania had often responded to ECT. At the time of admission her treatment regimen included olanzapine and carbamazepine. Carbamazepine had been started following the identification of abnormal thyroid function tests on routine testing.

The patient did not respond to increases in antipsychotic drugs or to a course of right unilateral ECT given three times a week. She withdrew consent for ECT when no improvement was noted after the treatments. At this point, a review of published reports suggested that left caloric vestibular stimulation might reduce the severity of the maniac symptoms through modulation of mood related neural circuits. A trial of caloric vestibular stimulation was felt by staff to represent her general level of symptoms during the past two months.

Otological examination before the caloric stimulation revealed an intact tympanic membrane and a clear external auditory canal. A flexible tube (14 gauge) was attached to a 50 ml syringe and introduced into the left auditory canal to a depth of 2 cm; 50 ml of cold water (4°C) were then introduced into the canal over a period of two to three minutes. Run off was collected in a kidney dish. The procedure was repeated after 72 hours.

The YMRS was applied by nursing staff involved in the patient’s care at the following times: before vestibular stimulation, and at 10 minutes, 20 minutes, 60 minutes, 6 hours, 24 hours, and 48 hours after the procedure.

The procedure was well tolerated; the patient described minimal local discomfort and a sense of vertigo. Horizontal nystagmus occurred towards the right. Within two minutes of termination of the procedure the patient described a slowing of thoughts and speech and a lowered mood. She remained on the examination couch until all sensation of vertigo had passed (approximately 10 minutes). During this period she was calm, cooperative, and appropriate in behaviour. There was an obvious reduction in speed and volume of speech and a reduction in spontaneous laughter and movement. These observations corresponded to a reduction in YMRS score of 32 (pre-stimulation) to 10 (post-stimulation).

Upon returning to the ward, she remained appropriate in her behaviour and interactions with staff and other patients. The patient described a lasting lowering of mood and slowing of thoughts and quickly became embarrassed when reminded of some of the behaviours she had shown before stimulation. Staff noted a gradual increase in her manic symptoms from approximately 24 hours post-stimulation, and after 72 hours her YMRS score was similar to that observed before the procedure (fig 1). The vestibular stimulation was readministered, and a dramatic and sustained partial reduction in symptoms again occurred, followed by a slow return towards baseline.

Comment

This case describes an impressive and relatively sustained improvement in manic symptoms following left caloric vestibular stimulation. It is possible that the power of suggestion, or a “placebo” effect, contributed to the observed effect. Care was taken not to relay to the patient a sense of expectation of an improvement in mood, and extra contact with staff following the procedure was minimised. It is unlikely that the immediate improvement in symptoms reflected a change in behaviour secondary to adverse effects of the procedure. Vertigo was the only side effect experienced by the patient, and all sense of vertigo had resolved within 10 minutes of the procedure. The use of the YMRS provided a standard for comparison of the severity of her symptoms before and after stimulation and served to provide a marked reduction in manic symptoms.

Caloric vestibular stimulation represents a novel approach to the treatment of mania. It is possible that it exerts its effect on mood through stimulation of motor and neural circuits. Following caloric vestibular stimulation, functional magnetic resonance imaging shows widespread, mainly contralateral activation of diencephalic and cortical regions which include the basal ganglia, insula, thalamus, and motor cortex. Following caloric vestibular stimulation, functional magnetic resonance imaging shows widespread, mainly contralateral activation of diencephalic and cortical regions which include the basal ganglia, insula, thalamus, and motor cortex.
cingulate gyrus, prefrontal, and parieto-temporal areas. These areas have also been implicated in disorders of mood, and some laterality of mood is suggested by neuroimaging and lesion studies that link depression to left cerebral impairment and mania to right cerebral impairment. Thus impulses transmitted by vestibular afferents in response to caloric vestibular stimulation may reach previously underactive neural pathways, so restoring a balance to previously impaired mood circuits.

Transient resolution of stroke induced deficits has been documented following caloric vestibular stimulation.6 These effects have lasted only minutes, and patients who have responded to the procedure have shown a reduced response to subsequent stimulations. The sustained response observed in this case may have been because neuronal hypofunctioning was present in the absence of overt neuronal damage as occurs following stroke.

This case report, which requires replication, describes a sustained reduction in manic symptoms following left caloric vestibular stimulation; this may have occurred through the activation of previously hypofunctioning neural circuits. Whether the observed improvement in symptoms corresponds to a normalisation of cerebral perfusion, as illustrated by positron emission tomography and functional magnetic resonance imaging, remains to be seen. Further research in the area may yield an alternative treatment for mood disorders, and provide an avenue for clarification of the neural pathways involved in the regulation of mood.

M J Dodson
Department of Psychological Medicine,
University of Otago, Dunedin, New Zealand;
michael.dodson@stonebow.otago.ac.nz

References

Hand weakness onset Guillain–Barré syndrome

Landry’s 19th century report gives the impression that Guillain–Barré syndrome (GBS) is characterised by ascending weakness. This clinical picture is now called “Landry’s ascending paralysis.” Indeed, muscle weakness in GBS does usually begin in the legs, progressing to the trunk, arms, and cranial regions. However, several clinical variants are now recognised in which weakness initially begins in other areas. Four patients with acute polyneuropathy were reported initially to have had muscle weakness in the hands. In two of these, Campylobacter jejuni infection had preceded the neurological symptoms, and serum anti-GM1 antibody was detected in the others. To determine the frequency and clinical features of hand onset GBS, we reviewed the medical records of 464 consecutive patients with the disease. Eleven had been treated at our hospital, the others were referred to our laboratory from other hospitals for antiganglioside antibody tests. Hand onset GBS was diagnosed when the first symptom that a GBS patient recognised was hand weakness. Paraesthesiae and other sensory symptoms may have preceded hand weakness, but patients who developed weakness in both the hands and legs on the first day of illness were excluded.

We found that 33% of the patients reviewed had hand onset GBS. frequent initial symptoms were weak hand grip and clumsy fingers. Paraesthesiae in the hands or all four limbs had preceded hand weakness in eight of them. Three patients presented with facial palsy, diploria, or blurred vision on the day of hand weakness onset. Weakness was limited to the hands and arms and throughout the acute phase of illness in four patients (12%), while it spread to the legs in the others. Assisted ventilation was required for four patients (12%). Compared with the other patients, those with hand onset GBS more often had a history of preceding diarrhoea, had antiganglioside IgG antibodies, and, less frequently, had sensory disturbance (table 1). Of the autoantibodies present, anti-GM1, anti-GM1b, and anti-GD1a IgG were significantly associated with hand onset GBS.

Table 1 Comparison of clinical and serological features

<table>
<thead>
<tr>
<th>Initial symptoms</th>
<th>Hand weakness (n=33)</th>
<th>Others (n=431)</th>
<th>p Value</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, range)</td>
<td>43 (14 to 78)</td>
<td>44 (0 to 88)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>22/11</td>
<td>262/169</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Preceding symptoms:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>19 (58)</td>
<td>151 (33)</td>
<td>&lt;0.001</td>
<td>3.4 1.4 to 3.8</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11 (33)</td>
<td>174 (40)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>9 (27)</td>
<td>156 (36)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Neck weakness</td>
<td>14 (42)</td>
<td>221 (51)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Sensory deficits</td>
<td>10 (30)</td>
<td>211 (49)</td>
<td>0.03</td>
<td>2.7 0.1 to 0.6</td>
</tr>
</tbody>
</table>

All gangliosides tested

<table>
<thead>
<tr>
<th>Gangliosides</th>
<th>Hand weakness (n=33)</th>
<th>Others (n=431)</th>
<th>p Value</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GM1</td>
<td>20 (61)</td>
<td>106 (25)</td>
<td>&lt;0.001</td>
<td>3.4 1.4 to 3.8</td>
</tr>
<tr>
<td>GT1a</td>
<td>3 (9)</td>
<td>2 (0.4)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GD1a</td>
<td>10 (30)</td>
<td>65 (15)</td>
<td>0.01</td>
<td>2.1 0.9 to 4.7</td>
</tr>
<tr>
<td>GD1b</td>
<td>6 (18)</td>
<td>37 (9)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GT1b</td>
<td>9 (27)</td>
<td>75 (17)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>GQ1b</td>
<td>3 (9)</td>
<td>2 (0.4)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Differences between groups were examined with the z2 or Fisher’s exact test. CI, confidence interval; F, female; M, male; NS, not significant (p value >0.5); OR, odds ratio.

Hand onset GBS patients (n = 25) who had Campylobacter jejuni infection had preceded the neurological symptoms, and serum anti-GM1 antibody was detected in the others. Of the autoantibodies present, anti-GM1, anti-GM1b, and anti-GD1a IgG were significantly associated with hand onset GBS. Antecedent C jejuni infection was proven by serological assay (n = 19) or stool culture (n = 2) in 20 (61%) of the patients with hand onset GBS.

Hand onset GBS patients (n = 25) who had Campylobacter jejuni infection, or who often had a history of previous gastrointestinal symptoms but rarely cranial nerve involvement or sensory disturbance. Although most patients had received either intravenous immunoglobulin within two weeks of onset, seven showed irreversible neurological damage at the last consultation. Moderate or mild weakness remained in the arms and legs of four patients (from four to 22 months after onset), and weakness mainly remained in the upper limbs of three (from two to four months after onset). Results of nerve conduction studies done within two weeks of weakness onset were available for 10 patients: five had predominant axonal disturbance and the others showed unclassified findings. In contrast, the eight patients who had neither antiganglioside IgG nor evidence of a preceding C jejuni infection often had a history of previous respiratory infection and sensory disturbance. All had received plasmapheresis or intravenous immunoglobulin and, except for one, had no or only mild weakness 12 months after onset. The exception required assisted ventilation at nadir and still had moderate distal weakness and amyotrophy in the legs six months after onset. Results of nerve conduction studies were available for four patients who had neither antiganglioside IgG nor evidence of a preceding C jejuni infection; all of these had a primary demyelinating disturbance.

In the larger population, we confirmed previous findings that hand onset GBS is related to C jejuni enteritis and anti-GM1 antibody, although the cases reported had either C jejuni or anti-GM1 antibody. Furthermore, we found that hand onset GBS is characterised by pure motor symptoms and the presence of IgG antibodies against GM1b and GD1a, as well as those against GM1. Residual symptoms were frequent in the C jejuni or autoantibody related populations, but no statistical analysis was made of outcome. In contrast, one quarter of the patients with hand onset GBS had no evidence of previous C jejuni infection or antiganglioside IgG. Antecedent respiratory infection symptoms and sensory involvement were characteristic, and those patients tended to have better outcomes than the others.

It is noteworthy that motor deficit remained only in the arms during the course of the illness in the four hand

www.jnnp.com
onset GBS patients, two of whom were positive for C. jejuni serology and antiganglioside IgG. Another patient who developed acute pure motor neuropathy following C. jejuni enteritis was reported to have localized weakness in his hands and anti-GM1 IgG. Although that patient had preserved tendon reflexes in the four limbs, a serial electrophysiological study confirmed the diagnosis of an axonal variant of GBS, indicating that anti-GM1 IgG and C. jejuni infection are related to hand-predominant weakness in GBS. It is also noteworthy that the six patients who had hand onset GBS had an initial diagnosis of cervical spondylosis (n = 4), lacunar infarction (n = 1), or brachial plexus neuritis (n = 1) on hospital admission. Frequent hand function problems have been reported even in mildly affected GBS patients who could walk unaided at nadir. Early treatment has been suggested in such cases. Recognition of the clinical characteristics of hand onset GBS may lead to a good prognosis because individuals can be given specific treatment as early as possible.

Acknowledgements

This research was supported in part by a grant-in-aid from the Uehara Memorial Foundation, a grant for scientific research (B) (KAKENHI 14370210 to NY) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a research grant for neuroimmunological diseases from the Ministry of Health, Labour and Welfare of Japan.

I Mori, M Kaga, K Hirata, N Yuki
Department of Neurology, Dokkyo University School of Medicine, Kitakobayashi BBQ, Mibu, Shimotsuga, Tochigi 321-0293, Japan

Correspondence to: Dr Michiaki Kaga, kagamik@ dokkyo-med.ac.jp

References


Lack of association between interleukin-1β polymorphism (−511) and ischaemic stroke

A growing body of evidence suggests an important role for interleukin 1 (IL-1) in the pathogenesis of brain damage following cerebral ischaemia. Central administration of IL-1 exacerbates brain damage, and over-expression of the IL-1 receptor antagonist (IL-1Ra) or blockade of IL-1 converting enzyme activity reduces infarct size dramatically (reviewed by Tzouzianis et al). Clinical studies suggest there is intrathecal IL-1 production early during stroke. A single nucleotide polymorphism in the promoter region of IL-1β at position −511 resulting in C→T transition influences the protein production, and IL-1β−511T carriers are reported to be higher producers of IL-1β than IL-1β−511C carriers. In the study described here we investigated whether IL-1β polymorphism (−511) can be involved in the genetic susceptibility to ischaemic stroke. We studied 183 consecutive patients with ischaemic stroke presenting to our stroke unit and 180 control subjects without a history of stroke. Control subjects were recruited from spouses of the patients, from individuals admitted to the university hospital for any reason other than neurological diseases, and from persons randomly selected from the community of our town. All patients, controls, and their parents had to be of white extraction.

Cerebral infarction was defined as a focal neurological deficit of sudden onset that persisted beyond 24 hours, documented by brain computed tomography or magnetic resonance imaging, indicating the presence of infarction or the absence of haemorrhage.

Stroke aetiology was defined according to the TOAST criteria: 66 patients had large vessel disease, 50 had small vessel disease, 49 had cardioembolic stroke, and 18 had stroke of undetermined aetiology.

Arterial hypertension was diagnosed when its presence was documented in the medical records or if two or more readings of blood pressure were >160 mm Hg (systolic) or >95 mm Hg (diastolic) before the onset of stroke or three months later. Diabetes mellitus was diagnosed if the patient gave a history of diabetes or was taking insulin or an oral hypoglycaemic agent. A patient was defined as a current smoker if there was a history of cigarette smoking during the last five years.

Genomic DNA was extracted from peripheral blood using a commercially available kit from Qiagen. Interleukin-1β polymorphism (−511) was detected using the polymerase chain reaction and restriction enzyme digestion as described elsewhere. All subjects gave informed consent and the local ethics committee approved the study protocol.

The sample size was calculated with a power of 80% at the 0.05 significance level. The characteristics of study subjects and distribution of IL-1β genotype are shown in table 1.

There was no significant difference between stroke patients and controls in age and sex. Allele frequency in both controls and patients was in Hardy-Weinberg equilibrium (p = 0.32 for controls, p = 0.40 for stroke patients).

There was no significant difference between stroke patients and controls in IL-1β genotype distribution. There was also no relation between IL-1β polymorphism and any particular stroke subtype: large vessel disease, for TT, 7/66 (10.6%); small vessel disease, 6/50 (12.0%); cardioembolic stroke, 7/49 (14.3%) (p = 0.24, χ² test).

Comment

We failed to find a relation between IL-1β polymorphism (−511) and ischaemic stroke in this Polish population. Recently Seripa et al investigated the same polymorphism in an Italian population of 110 stroke survivors and 101 healthy controls and also did not find any significant association between IL-1β polymorphism (−511) and stroke, although they showed a significantly higher frequency of the IL-1Ra 1/1 genotype in stroke survivors than in controls.

Several issues should be taken in account in interpreting the results of our study. First, cytokines do not work alone, but in a network. Therefore a genetic predisposition to produce anti-inflammatory cytokines (for example, IL-10 or IL-1Ra) could interfere with the biological effects of IL-1.

Second, we did not examine another IL-1β polymorphism in exon 5 at position +3953 which could determine IL-1β synthesis.

Third, we cannot exclude the possibility that IL-1β polymorphism (−511) is associated with one particular stroke subtype; however, in our study we found no relation between IL-1β polymorphism and large vessel disease, small vessel disease, or cardioembolic stroke. From our point of view, there is currently a lack of strong evidence indicating a functional association between IL-1 and any particular stroke subtype.

Fourth, IL-1 may be linked to inflammatory mechanisms of atherogenesis. Hypertension and smoking play an important role in the pathogenesis of atherosclerosis. In our study the incidence of hypertension and smoking was higher in stroke patients than in controls, and the frequency of the TT allele was higher in smokers than in non-smokers (15.4% v 7.9%, p = 0.018) and in subjects with hypertension than in those without (10.3% v 7.7%, p = 0.48).

Atherosclerosis is related to

Table 1 Distribution of risk factors and IL-1β genotypes in patients and controls

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Stroke patients (n = 183)</th>
<th>Controls (n = 180)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean (SD))</td>
<td>65.2 (14.7)</td>
<td>64.8 (14.8)</td>
<td>0.80</td>
</tr>
<tr>
<td>Male</td>
<td>81 (44.3)</td>
<td>69 (38.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypertension</td>
<td>139 (76)</td>
<td>94 (52.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>33 (18)</td>
<td>32 (17.8)</td>
<td>0.59</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>15 (8.2)</td>
<td>9 (5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Current smoker</td>
<td>47 (25.7)</td>
<td>21 (11.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IL-1β genotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>94 (51.4)</td>
<td>87 (48.3)</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>69 (39.7)</td>
<td>79 (43.9)</td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>20 (10.9)</td>
<td>14 (7.8)</td>
<td></td>
</tr>
<tr>
<td>T allele frequency (%)</td>
<td>29.8</td>
<td>29.7</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Values are n (%) unless stated otherwise.
large vessel disease; however, in our study the IL-1 genotype distribution did not differ significantly between patients with large vessel disease and controls.

Fifth, further studies are needed that are focused on achieving sufficient power to detect a possible smaller allelic relative risk (<2).

In conclusion, our results do not support the hypothesis that IL-1β polymorphism (−511) is associated with ischaemic stroke.

Acknowledgement
This study was supported by a grant from Medical Committee of Collegium Medicum, Jagiellonian University.

References
Subthalamic nucleus stimulation in a parkinsonian patient with previous bilateral thalamotomy
S Goto, K Yamada and Y Ushio

*J Neurol Neurosurg Psychiatry* 2004 75: 164-165

Updated information and services can be found at: [http://jnnp.bmj.com/content/75/1/164](http://jnnp.bmj.com/content/75/1/164)

**References**
This article cites 7 articles, 4 of which you can access for free at: [http://jnnp.bmj.com/content/75/1/164#BIBL](http://jnnp.bmj.com/content/75/1/164#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](http://group.bmj.com/group/rights-licensing/permissions)

To order reprints go to: [http://journals.bmj.com/cgi/reprintform](http://journals.bmj.com/cgi/reprintform)

To subscribe to BMJ go to: [http://group.bmj.com/subscribe/](http://group.bmj.com/subscribe/)