Lack of association of nephrilysin polymorphism with Alzheimer's disease and Alzheimer's disease-type neuropathological changes

Sporadic Alzheimer's disease is a polygenic disease and the relation between many genetic risk factors and the development of Alzheimer's disease has been controversial. Accumulation of amyloid β-protein (Aβ) in the brain is the neuropathological hallmark and thought to be a key event in the upstream stage of pathological cascade of the disease. Although increased production of Aβ is expected as the pathogenesis of familial Alzheimer's disease due to mutations in presenilin 1, 2, and amyloid β-protein precursor genes, there is no evidence of up regulated synthesis of Aβ in the brains of patients with sporadic Alzheimer's disease. In addition, aging is the most major risk factor for the disease. These findings suggest the possibility that reduction of the catabolic system of Aβ due to aging causes the formation of senile plaques in sporadic disease. Therefore, proteolytic enzymes of Aβ might be related to the development of sporadic Alzheimer's disease.

One of the enzymes responsible for the degradation of Aβ is nephrilysin (NEP). This is a membrane bound metallopeptidase which is expressed in many tissues including the CNS. It cleaves Aβ 1–42 between amino acids 9 and 10 and between amino acids 37 and 38. Reduced mRNA and protein concentrations of NEP in the brain from patients with Alzheimer's disease were reported, suggesting low concentrations of NEP contributed to the accumulation of Aβ. Recent investigation showed that NEP inhibitor infusion into the brain resulted in increased deposition of Aβ, indicating that NEP restricts the catabolic catabolism of Aβ in vivo. There is a dinucleotide repeat polymorphism in the 5' region of the NEP gene. A lower molecular weight allele of NEP gene polymorphism is associated with low amplitude of P300 and increased risk of psychiatric disorders such as alcoholism, conduct disorders of children, and depression. As there is a positive correlation between serum concentration of NEP and psychiatric problems, increased number of dinucleotide repeat of NEP gene is presumed to be related to lower serum concentrations of NEP. Therefore, decreased NEP correlated with dinucleotide repeat polymorphism in the 5' region and might be related to the accelerated accumulation of Aβ through reduced catabolism of Aβ. To verify a role of NEP in the pathogenesis of Alzheimer's disease, we examined the relation of NEP gene polymorphism with the development of Alzheimer's disease and Alzheimer's type neuropathological changes.

Subjects comprised 75 postmortem confirmed patients who had had sporadic Alzheimer's disease (age at death range 62–104 years; mean 85.8 (SD) 7.8 years) and 89 non-demented people (age at death range 65–101 years; mean 85.3 (SD 7.8) years) from a postmortem series at Yokufukai Gen- atric Hospital in Tokyo. There was no significant difference of ages at death between two groups. Non-demented patients were without any neurodegenerative disorders. The clinical and postmortem diagnosis was performed according to criteria of the NINCDS-ADRDA and DSM III-R and the Consortium to Establish a Registry for Alzheimer's disease (CERAD), respectively. We evaluated Alzheimer's disease-type neuropathological changes quantitatively as previously described. Briefly, we counted the densities of the senile plaques, senile plaques with dystrophic neurites and neurofibrillary tangles in the hippocampus and superior temporal gyrus from the brains of all patients. Ten×100 microscopical fields (field size 2.56 mm²) for senile plaques and dystrophic neurites, and 10×200 microscopical fields (field size 0.64 mm²) for neurofibrillary tangles were examined using specimens treated with methenamine-Bodian stain. We extracted genomic DNA from the brain with phenol/chloroform. Genomic DNA was amplified by polymerase chain reaction (PCR) using the primer pairs described by Corrigan et al. The PCR products in the 5' region of the NEP gene was performed with an ALF DNA sequencer II (Pharmacia Biotech). Direct sequence analysis of PCR products of some samples with representative genotypes using ABI PRISM model 310 verified the number of GT repeats (Perkin-Elmer). The apolipoprotein E (ApoE) genotype was also determined.

The distributions of NEP gene polymorphism in patients with Alzheimer's disease and non-demented subjects were examined by χ² test. The same analysis was performed in the subgroups divided by ApoE ε4 status. The correlations between NEP gene polymorphism and the densities of the senile plaques, dystrophic neurites, and neurofibrillary tangles in the hippocampus and superior temporal gyrus in the brains from patients with Alzheimer's disease and non-demented patients, and ages at onset and durations of illness in Alzheimer's disease were examined using Kruskal-Wallis test. We used five sets of data, NEP genotype, NEP allele, longer allele, shorter allele, and the number of sum of GT repeats of two alleles as NEP gene polymorphism to classify our samples. Statistical significance was defined as two tailed probabilities of <0.01. All analyses were performed using the computer software StatView J-4.5 (Abacus Concepts).

The genotypic and allelic frequencies of the NEP gene in Alzheimer's disease and non-demented patients are shown in table 1. Five types of alleles, which represent 19–23 GT repeats and nine genotypes, were found in our samples. There were no significant differences in the frequency of NEP genotypes between Alzheimer's disease and non-demented patients. A lower molecular weight allele of NEP gene is presumed to be associated with the densities of the senile plaques, dystrophic neurites, or neurofibrillary tangles in the hippocampus or superior temporal gyrus in our samples. There was no correlation between NEP genotype and ages at onset or durations of illness. The results remained non-significant when we performed similar analysis using the other types of NEP polymorphism such as longer allele, shorter allele, and the number of sum of GT repeats of two alleles to classify our samples. The genotype, longer allele, shorter allele, or the number of sum of GT repeats of two alleles were not associated with the genotype or allele of ApoE ε4 status. The ApoE ε4 allele was significantly associated with Alzheimer's disease (p=0.0001). To our knowledge, this is the first study to examine the genetic relation between a catalytic enzyme of Aβ and sporadic Alzheimer's disease. Although the present study does not demonstrate association of NEP with the development of Alzheimer's disease, we examined the relation of NEP gene polymorphism with the development of Alzheimer's disease and Alzheimer's type neuropathological changes.

Table 1  Distributions of NEP polymorphism in patients with Alzheimer's disease (AD) and non-demented patients

<table>
<thead>
<tr>
<th>NEP genotype</th>
<th>19/19</th>
<th>19/20</th>
<th>19/21</th>
<th>20/20</th>
<th>20/21</th>
<th>20/22</th>
<th>20/23</th>
<th>21/21</th>
<th>21/23</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD (n=75)</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Non-demented (n=89)</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>51</td>
<td>14</td>
<td>51</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Table 2  NEP genotype and the densities of SDs, NPs, and NFTs in the hippocampus and superior temporal gyrus, ages at onset and durations of illness in Alzheimer's disease

<table>
<thead>
<tr>
<th>NEP genotype</th>
<th>19/19</th>
<th>19/20</th>
<th>19/21</th>
<th>20/20</th>
<th>20/21</th>
<th>20/22</th>
<th>20/23</th>
<th>21/21</th>
<th>21/23</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippocampus:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPs</td>
<td>9.8</td>
<td>10.9</td>
<td>15.4</td>
<td>9.9</td>
<td>10.2</td>
<td>0.1</td>
<td>11.4</td>
<td>11.7</td>
<td>21.3</td>
<td>0.60</td>
</tr>
<tr>
<td>NPs</td>
<td>9.1</td>
<td>9.7</td>
<td>13.1</td>
<td>8.9</td>
<td>10.0</td>
<td>0.0</td>
<td>5.7</td>
<td>11.5</td>
<td>18.8</td>
<td>0.45</td>
</tr>
<tr>
<td>NFTs</td>
<td>26.3</td>
<td>17.4</td>
<td>29.1</td>
<td>27.1</td>
<td>27.2</td>
<td>0.5</td>
<td>12.1</td>
<td>29.4</td>
<td>34.7</td>
<td>0.38</td>
</tr>
<tr>
<td>Superior temporal gyrus:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPs</td>
<td>20.7</td>
<td>31.0</td>
<td>57.6</td>
<td>42.3</td>
<td>30.7</td>
<td>1.3</td>
<td>52.3</td>
<td>33.0</td>
<td>63.8</td>
<td>0.46</td>
</tr>
<tr>
<td>NPs</td>
<td>13.0</td>
<td>9.9</td>
<td>14.0</td>
<td>13.1</td>
<td>10.8</td>
<td>0.6</td>
<td>19.5</td>
<td>19.5</td>
<td>21.8</td>
<td>0.52</td>
</tr>
<tr>
<td>NFTs</td>
<td>4.6</td>
<td>2.4</td>
<td>1.9</td>
<td>4.0</td>
<td>2.0</td>
<td>0.0</td>
<td>4.7</td>
<td>12.6</td>
<td>8.5</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Age at onset: 85.0 74.3 80.3 78.4 81.7 58.0 82.0 86.5 0.23

Duration of illness: 8.0 9.0 3.3 6.5 7.4 4.0 5.0 5.0 0.48

Values are means. The density represents the average counts in 2.56 mm² for SPs and NPs, and in 0.64 mm² for NFTs. NEP=nephrilysin gene; AD=Alzheimer's disease; SPs=senile plaques; NPs=senile plaques with dystrophic neurites; NFTs=neurofibrillary tangles.
disease or Alzheimer’s-type neuro-pathological changes, we suppose that the investigation of the catalytic system of Aβ is important for four reasons. Firstly, it links to elucidation of the mechanism of accumulation of Aβ. As NεP is thought to be a main peptidase which degrades the Aβ in the brain, it is necessary to examine the influence of the NεP gene on the severity of the senile plaques and dystrophic neurites to search for a role of cleavage of Aβ in the deposition of Aβ. Secondly, this research contributes in clarifying a role for senile plaques and dystrophic neurites in the development of Alzheimer’s disease. Thirdly, the detection of key molecules in the degradation of Aβ might directly lead to the treatment of Alzheimer’s disease. Fourthly, recent analyses disclosed that families with late onset Alzheimer’s disease are linked to genetic markers near the insulin degrading enzyme gene, which is thought to be one of the catalytic enzymes of Aβ. Genes of the degradating enzymes of Aβ such as the NεP gene still remain potential risk factors for sporadic Alzheimer’s disease. The examination of other polymorphisms in the NεP gene or multivariate analysis taking in the related gene except ApoE which modifies the processing of Aβ might detect potential correlation of the NεP gene with Alzheimer’s disease.

The study was supported in part by a Health Science Research Grant (to MY) from the Ministry of Health and Welfare, Japan and in part (to NS) from the Japan Society for the Promotion of Education, Science, Sports and Culture.

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One of the authors (Y IT) has served as a consultant to an advisory board for a drug company. The other authors have no potential conflicts of interest to disclose.

Association between high production of interferon-γ (IFN-γ) and gene and age at onset of idiopathic Parkinson’s disease

Although the pathogenesis of progressive degeneration of nigrostriatal dopaminergic neurons in Parkinson’s disease remains uncertain, cytokines are thought to contribute to the development of the disease. 1 Interferon (IFN-γ) is one of the Th1 cell derived multi-functional cytokines and seems to influence neuronal differentiation and to increase in inflammatory and neurodegenerative diseases. 2 Immunohistochemical studies showed an increase of IFN-γ expression in nigral astrocytes of patients with Parkinson’s disease. 3 This increase of IFN-γ concentration may be a trigger for the disease or a compensatory response. It was reported that IFN-γ producing capacity in whole blood cultures of untreated parkinsonian patients decreased compared with sex and age matched healthy controls. 4 This supports the idea that IFN-γ may increase in Parkinson’s disease as a compensatory response. Concerning genetic polymorphisms in the IFN-γ gene, the production of IFN-γ measured in peripheral blood mononuclear cell cultures may correlate with dinucleotide CA repeat polymorphism in the first intron of the IFN-γ gene. 5 In vitro production of IFN-γ is higher in

Human T lymphotropic virus type I (HTLV-I) associated myelopathy acquired through a liver transplant

Subacute myelopathy (HAM/TSP) is the main neurological manifestation of human T lymphotropic virus type I (HTLV-I) infection. 1 This virus is endemic in central Africa, Caribbean countries, and Japan. It is transmitted sexually through contact, during lactation, and by blood transfusions. The risk of seroconversion after blood transfusion is 40%–60%. Around 5% of the carriers will develop clinical manifestations; only 0.3% of them will have a myelopathy. Immunosuppression enhances the risk of infection, reduces the latency, and accelerates the clinical picture. We have reviewed the first documented case of HTLV-I infection through an organ transplantation in a western country. In another organ recipient the vehicle of the virus was the blood transfused during the surgical procedure.

A 44 year old woman developed alcoholic cirrhosis and hepatocarcinoma. On 5 October 1998, she received a liver transplant followed by cyclosporin treatment (175 mg/day). The donor was an apparently healthy young man who died after brain injury. Eighteen months later, the patient complained of progressive weakness in her legs. In the next 3 months a rapidly evolving paraparesis with a T6 sensory level, pyramidal signs, and bladder dysfunction became evident. She was admitted to another hospital. The CSF contained 37 white cells/ml, 93 mg/ml protein, and 43 mg/ml glucose. Serological tests for neurotropic virus were negative. On T2 weighted MRI a diffuse hyperintense of the cervicothoracic spinal cord was seen. The rest of the data from an extensive investigation were non-contributory. She was transferred to our institution on 3 August 2000. Other than a complete paraplegia no neurological abnormalities were found. Somatosensory evoked potentials after median nerve stimulation were normal but they were abolished after posterior tibial nerve stimulation. In the CSF there were 9 white cells/ml, 133 mg/ml protein, and 43 mg/dl glucose. Serological tests for HTLV-I (enzyme linked immunosorbent assay (ELISA) and western blotting) were positive in blood and CSF, and the polymerase chain reaction was positive in blood. Tests were negative for HTLV 2 and VIH. The patient had a pulse of intravenous methylprednisolone (1g/day/5 days) and a course of interferon (3 MU/day/1 month) without any improvement in her neurological status.

We have conducted a retrospective serological survey for HTLV-I antibodies in archival blood samples from the patient before the transplantation, from the liver donor, and from the blood donors. All the samples were negative except one donor who received blood from the liver donor. He was a multiorgan donor (both kidneys, liver, heart, and corneas). A follow up of all the recipients is in progress.

The prevalence of HTLV-I infection in the endemic area was found to be 5% and 30% in western countries. 2,3 Disease or Alzheimer’s-type neuro-pathological changes or sporadic Alzheimer’s disease. 4,5 It was reported that 15 out of 153 recipients of renal transplants were HTLV-1 positive. They did not develop HAM/TSP or any HTLV-I related disorder during a follow up period of 10 years. By contrast, the case we are reporting here indicates that HTLV-1 infection may have devastating consequences for some immuno suppressed organ recipients. This emphasises the necessity for a systematic survey of its antibodies in all potential donors despite the low current prevalence of HTLV-I infection in western countries.

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Relation between the high production related allele of the interferon-γ (IFN-γ) gene and age at onset of idiopathic Parkinson’s disease

Although the pathogenesis of progressive degeneration of nigrostriatal dopaminergic neurons in Parkinson’s disease remains uncertain, cytokines are thought to contribute to the development of the disease. 1 Interferon (IFN-γ) is one of the Th1 cell derived multi-functional cytokines and seems to influence neuronal differentiation and to increase in inflammatory and neurodegenerative diseases. 2 Immunohistochemical studies showed an increase of IFN-γ expression in nigral astrocytes of patients with Parkinson’s disease. 3 This increase of IFN-γ concentration may be a trigger for the disease or a compensatory response. It was reported that IFN-γ producing capacity in whole blood cultures of untreated parkinsonian patients decreased compared with sex and age matched healthy controls. 4 This supports the idea that IFN-γ may increase in Parkinson’s disease as a compensatory response. Concerning genetic polymorphisms in the IFN-γ gene, the production of IFN-γ measured in peripheral blood mononuclear cell cultures may correlate with dinucleotide CA repeat polymorphism in the first intron of the IFN-γ gene. 5 In vitro production of IFN-γ is higher in
people homozygous for allele 122 (12 CA repeats, named allele 2 by Pravica et al) and allele 6 by Awata et al' than in those of other genotypes. Therefore, we investigated the CA repeat polymorphism of the IFN-γ gene in 170 patients with idiopathic Parkinson's disease (102 women and 68 men, aged 64.2 (SD 9.7) years; onset, 55.5 (SD 10.6) years; disease duration 8.7 (SD 5.2) years). As controls, 157 healthy people were selected from the annual health examination at a city clinic. The control group was matched for age (mean: 62.5 (SD 8.7) years), sex ratio (98 women and 59 men), and birth place (Kyoto and Osaka prefectures) with the patients. All participants were Japanese. The study protocol was approved by the institutional ethics committees and informed consent was obtained from every patient. The CA repeat polymorphism was analyzed according to a previous report.1 The result is shown in table 1. Using χ2 analysis (combined rare alleles “116”, “118”, “130”, and “132”), no significant difference was found in allele distribution between the Parkinson’s disease and control groups (p=0.86). When patients were divided into two groups (early onset and late onset disease), pc was obtained by multiplying the p value by two. No significant difference was found between patients with early onset Parkinson’s disease and controls (pc=0.23) or between those with late onset Parkinson’s disease and controls (pc=0.17). However, the allele distribution was significantly different between early onset (<50 years) and late onset (≥50 years) disease (χ2=14.5, df=5, pc=0.028). The frequency of allele 122 was lower in those with early onset Parkinson’s disease than in those with late onset Parkinson’s disease. Carriership analysis also showed a low allele 122 carrier frequency in patients with early onset compared with late onset disease (χ2=4.62, df=1, pc=0.039). Although the genetic polymorphism of IFN-γ does not seem to be a risk factor for Parkinson’s disease, a lack of high producer allele 122 may affect the onset of disease. The allele 122 may be part of a haplotype that also includes functionally relevant polymorphisms. Our findings support the idea that the increase of IFN-γ concentration in the brain of patients with Parkinson’s disease might be a compensatory mechanism rather than a trigger of the disease. Thus, IFN-γ may help in delaying the progress of the disease.

Table 1: IFN-γ allele and carriership frequencies in patients with Parkinson’s disease (PD) and in healthy controls as well as in patient subgroups whose ages of onset are early (<50 y) and late (≥50 y).

<table>
<thead>
<tr>
<th>Allele (bp):</th>
<th>PD n (%)</th>
<th>Control n (%)</th>
<th>Early onset PD n (%)</th>
<th>Late onset PD n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td>1 (0.3)</td>
<td></td>
<td>1 (0.3)</td>
<td></td>
</tr>
<tr>
<td>118</td>
<td>2 (0.6)</td>
<td></td>
<td>3 (0.8)</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>52 (15.3)</td>
<td>61 (13.1)</td>
<td>3 (19.3)</td>
<td></td>
</tr>
<tr>
<td>122</td>
<td>157 (46.2)</td>
<td>143 (45.5)</td>
<td>23 (23)</td>
<td>122 (50.8)</td>
</tr>
<tr>
<td>124</td>
<td>19 (5.6)</td>
<td>6 (1.3)</td>
<td>35 (35)</td>
<td>29 (12.1)</td>
</tr>
<tr>
<td>126</td>
<td>27 (7.4)</td>
<td>32 (7.9)</td>
<td>28 (28)</td>
<td>65 (27.1)</td>
</tr>
<tr>
<td>129</td>
<td>9 (2.6)</td>
<td>8 (2.5)</td>
<td>1 (1)</td>
<td>8 (3.3)</td>
</tr>
<tr>
<td>130</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>132</td>
<td>6 (1.8)</td>
<td></td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>340</td>
<td>314</td>
<td>284</td>
<td>210</td>
</tr>
</tbody>
</table>

Carriership: 122 carrier 117 (68.8) 109 (69.4) 28 (56) 89 (74.2) 122 non-carrier 53 (31.2) 48 (30.6) 22 (44) 31 (25.8) Total 170 157 50 120

For combined alleles 116, 118, 130, and 132, allele frequency: early onset PD d f 0.028. Carriership frequency: early onset PD χ2=4.62, df=1, P<0.039.

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Autonomic dysreflexia due to neurogenic bladder dysfunction; an unusual presentation of spinal cord sarcoidosis

Clinical involvement of the CNS in sarcoidosis is seen in about 5% of patients.1 The most common affected sites are the basal leptomeninges and the region of the floor of the third ventricle. However, primary involvement of the spinal cord is much less common.1 It may cause serious neurological deficits below the affected level of the lesion. Here we describe a case of spinal cord sarcoidosis with an unusual presentation: autonomic dysreflexia due to neurogenic bladder dysfunction.

A 42 year old woman began to have a slowly progressive spastic gait, left hand numbness, urinary urgency/frequency, and voiding difficulty which worsened for a year. She underwent C2–7 laminoplasty for a relief of C4–6 cervical disc herniation where mild cord swelling was present. However, her gait difficulty ameliorated only for 2 weeks. Two months later she became unable to walk without an aid. Spinal MRI disclosed C2–7 cord swelling. She also developed bilateral hilar lymphadenopathy, ocular uveitis, and an increased serum concentration of angiotensin converting enzyme (ACE). Endoscopic lymph node biopsy showed non-caseating epithelioid granuloma. These findings and the clinical features confirmed the diagnosis of spinal cord sarcoidosis. She underwent steroid pulse therapy (1000 mg/day of intravenous methylprednisolone over 3 succeeding days) and started taking oral prednisolone (80 mg/day) with benefit. Steroids were tapered to 40 mg every other day and 4 mg per week until referred to our hospital. However, her gait difficulty relapsed together with urinary urgency, incontinence and voiding difficulty. She had constipation but no orhtostatic hypotension. On admission to our hospital, she was in a state of sepsis and C4–5 tetraparesis, which was dominant in the legs. Deep tendon reflexes were brisk with positive Babinski’s signs. Sensations for pin prick and proprioception were decreased bilaterally below the C4 dermatome. Routine laboratory data were normal. Examination of CSF showed normal cell count (lymphocyte 1 mm/l) but mildly increased protein content (42 mg/dl). The ACE concentration was normal both in the serum and CSF. Spinal MRI disclosed C2–7 cord swelling which appeared as low signal intensity on T1 weighted images and high signal intensity on T2 weighted images (fig 1). Gadolinium-DTPA images showed contrast enhancement in the C2–5 intramedullary region which extended longitudinally through the surface of the spinal cord. She again underwent three courses of steroid pulse therapy and started taking oral prednisolone (40 mg/day) and cyclosporin A (200 mg/day), which gradually ameliorated her neurological symptoms.

However, she began to have a sudden onset of severe, throbbing headache which was accompanied by conjunctival congestion, facial flushing, lacrimation, and congestion of the nose, without evidence of sketetal muscle spasms or bowel contraction. Just before the attacks she felt only slight bladder sensation. Measurement of the blood pressure showed an extreme hypertension (190/100 mm Hg) without increasing heart rate (60 beats/min), although it showed a normal value between these attacks. On the first attack emergent brain CT disclosed no subarachnoid hemorrhage and 5 mg of sublingual nifedipine was applied. Autonomic dysreflexia was suspected and the bladder was catheterised, which showed a urine volume of 650 ml. These treatments ameliorated all of her symptoms and the hypertension within 30 minutes. We performed urodynamic studies which showed voluntary voided volume of 79 ml with low maximum and average flow rates. She had a postvoid residual volume of 350 ml (normal<30 ml). On EMG-cystometry, the first sensation was 350 ml (normal<100 ml) and the maximum bladder capacity was

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A detrusor-sphincter dyssynergia was noted at the end of bladder filling. When asked to void after the detrusor hyperreflexia, her detrusor pressure increased slightly with poor urinary flow although the reaction seems to be milder than autonomic dysreflexia. The patient was taught clean intermittent self-catheterisation and started taking oral prazosin hydrochloride, a selective α1-antagonist, with benefit. During autonomic dysreflexia, concentrations of plasma noradrenaline (norepinephrine) increase and other substances—such as neuropeptide Y—may also increase in certain regions. The bladder neck (internal urethral sphincter) is innervated by sympathetic nerve and abundant with α1A/D-adrenergic receptors. The α1-antagonists relax both vascular (mainly α1B) and urethral (mainly α1A/D) smooth muscles, which may account for the amelioration of both autonomic dysreflexia and neurogenic bladder dysfunction in the patient. 

1 Stern BJ, Krumholz A, Johns G, et al Sarcoi- 
2 Sakakibara R, Hattori T, Uchiyama T, et al. Visc-
eurodynamic and sphincter motor unit potent-
as analyses in Parkinson’s disease and multi-
4 Mathias CJ, Frankel HL. Autonomic disturb-
who stands to gain sums of money, often larger than he or she has ever handled before the accident. The social and cultural factors they so well describe are real; but the production of symptoms’ ultimately depends on the conscious will of the claimant in providing a defensive posture, for severity, duration, and the consequent disabilities and loss of earnings. In litigation practice, deliberate exaggeration is common. It is misleading to inculpate society alone, and insisting the patients to deny their exercise of free choice.

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Ferrari replies:
Pearce’ completes the biopsychosocial model(s) of whiplash by recognising factors that we could not, for lack of space, include, although they have been discussed in detail elsewhere. Illness behaviour is the end result of many factors, including pathophysiological processes, experience biased interpretations of abnormal versus normal bodily sensations, and environmentally influenced attributions affecting further expressions of illness behaviour. In most cases, the sum effects of these factors is often considered to be normal behaviour. Thus, we gather most whiplash patients are victims, not so much of the collision, but of a system that endangers their health. It is further clear that the day has come to view the whole beast that is whiplash. Researchers that assert that psychosocial factors do not primarily determine the outcome of illness behaviour in patients with whiplash, or that the primary determinants are to be found in the microscopic nature of the cervical spine are simply too wrong to be given any further credence or consideration. There are so many “facets” to whiplash, that the whiplash injury itself becomes of less importance when we desire to understand the larger range of illness behaviour, and why it evolves.

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NOTICE


Chen ZY, Denney RM, Breakfield XO. Norrie disease and MAO genes: nearest neighbours. Hum Med Genet 1995; 4:1729–37 was misquoted in the second sentence of paragraph 8 of the above letter. The sentence should read “The gene is flanked by the MAO-A and MAO-B loci”.

CORRECTION


Freeman MD, Croft AC. Late whiplash syndrome. Lancet 1996; 348:125.


This book claims to examine objectively the basic pharmacological and clinical aspects of the use of benzodiazepines. The agenda is clearly laid out in the introduction where the editors emphasise that the valuable use of these compounds in neurological disorders was overlooked because of the “political turmoil and confusion about the use of benzodiazepines in psychiatry”. In practice the book primarily sets out to make the case for benzodiazepines as acceptable pharmacological treatments for epilepsy, with seven out of 13 chapters devoted to this specific topic. The consensus statement in the introduction suggests that the origins of the publication were a workshop organised by the editors on the use of benzodiazepines in epilepsy, although this is not explicitly stated. Clearly, the balance of the book is heavily weighted towards the treatment of epilepsy and as such the reader is left a little misleading. This is not a book for the general physician or psychiatrist looking for an overview of the clinical pharmacology of benzodiazepines. The first five chapters examine the pharmacological properties of benzodiazepines, their anxiolytic activity, and their utility in the management of anxiety and sleep disturbance. These are not all written with equal objectivity. The chapter on the management of sleep disorders delivers a clinically relevant and balanced review and includes ecletic, practical advice. By contrast, the chapter on the use of benzodiazepines in anxiety disorders focuses on these compounds to the exclusion of other interventions. Whereas the potential problems of tolerance and dependence are acknowledged, the problems of cognitive and emotional dysfunction are not. There is also little mention of SSRI antidepressants, despite their proved efficacy in anxiety disorders and limited discussion of the relation between drug and non-drug treatments. The epilepsy chapters present short expert reviews of specific clinical indications for benzodiazepines with some new pharmacoeconomic data. In summary, this is a really specialist text with a general title that is most relevant for and likely to be read by clinicians treating patients with epilepsy.

Christopher Bench


Stem cells, like the ancient Chinese ruyi sceptre, mean different things for different people. For doctors and patients they are a future gold mine and a haven from the dot com carnage. But for the scientists working with them, well, the scientists are not quite sure what stem cells are. Some chapters in MS Rao’s edited collection “Stem cells and CNS development” attempt a definition of a “true” stem cell, but like fragments of the True Cross, they are elusive. Stem cells should be capable of infinite division (but stopping just short of immortality), reproducing themselves as a might differentiated specialised progeny, remaining quiescent until required, and capable, when transplanted, of recognising exactly what tissues are lacking or diseased, turning into them (and into just the right numbers, migrating to the required area, and incorporating themselves into new, new fully functional host tissues.

Is there a neural stem cell, analogous to the haemopoietic stem cell? The progeny of a haemopoietic stem cell only have to be released into the circulation. If we can find a source of neural stem cells, can their progeny be expected to incorporate equally easily into the immensely complex and variable nervous system? Will we be able to discover the factors needed to drive stem cell differentiation in the directions needed to produce the specific progeny required for a particular application? If the neuroblastoma and glioma models are any guide towards the treatment of epilepsy and as such the current state of play in the practical application of haemopoietic stem cells is anything to go by, we may have to wait a while before neural stem cells will be curing diseases.

The reader will find all these topics dealt with in Rao’s compendium. It is fully referenced, and provides a comprehensive and valuable snapshot of where things are now. Hopefully, its readers’ copy will not, like this review copy, have 15 pages missing, and seven duplicated.

Geoffrey Raisman


It is difficult to think of any medical book that has done so much to raise the profile of a specialty as Organic Psychiatry, its guide to neurosis by Alwyn W Lishman has done for neuropsychiatry. The third edition of Organic Psychiatry, published in 1997, will remain a classic for many years to come. Its focus on the clinical description of neuropsychiatric syndromes and the clarity and elegance of the writing will ensure that it is a tribute to the book that, as in the cases of popular literary works, a film should be based on it, or in this case two videos, a workbook, and an answer book. By contrast with the Hollywood tradition that renders the book of the film obsolete, this teaching package requires the reader to go back to the original source to get the best of the other components of the package.

The package, which also includes the Organic Psychiatry book, is described as a teaching resource in neuropsychiatry for self paced learning and is aimed at English speaking students. The book and videotapes contain seven modules: examination of the neuropsychiatric mental state, investigations (EEG, imaging, and neuropsychology), head injury, epilepsy, infection, dementia, and movement disorders. The various modules are introduced by Professor Goldberg, who interviews the contributing neuropsychiatrists, in a setting somewhat reminiscent of Bird and Fortune, emphasising the importance of taking a careful history and making a differential diagnosis. The workbook provides a brief background to these modules and directs the student to the Lishman for further reading and to the relevant section of the video. After each module the student is invited to answer questions and feedback is provided in the workbook.

We are warned that the modules do not provide exhaustive coverage, as they have been selected for their relevance. However, the pace seems rather idiosyncratic and I suspect that it has been dictated to some extent by the availability of patients.

The package is a team effort and many well known neuropsychiatrists are seen interviewing patients in the workbook, but are not always related to the clinical material on the tapes. All in all, this is a very valuable teaching package for trainees in different areas of clinical neuropsychology. In the face of technology, the publishers will consider producing a CD Rom version in the future.

Maria A Ron


Post-traumatic stress disorder (PTSD) did not enter the psychiatric lexicon until 1980 when the American Psychiatric Association’s DSM-III proposed operational diagnostic criteria for a group of stress related disorders. Nevertheless, it is clear from previous descriptive studies that the symptoms which are now associated with PTSD were often and consistently recognised in victims of trauma, particularly involving military conflict. The impetus to the establishment of PTSD as a diagnostic concept came from studies on veterans of the Vietnam war. Since the 1980s there has been a steady growth in the frequency with which PTSD is diagnosed, facilitated by a broadening of the diagnostic criteria, particularly the nature of the precipitating aetiological trauma. Several sceptics have also related the increased tendency to diagnose the condition to a growth in the
trade in litigation, actively promoted by the legal profession.

The popularity of the diagnostic concept has been matched by an explosion of published papers, so this book is a timely review which enables clinicians and lawyers to keep up advances in understanding the aetiology and management of the condition. Like most authoritatively books the quality is uneven and there is some overlap between several chapters. The strength of the book lies mainly in the chapters on treatment. There are useful contributions from Barbara Rothbaum on psychological treatments and from Stein et al on pharmacotherapy. There is also a good article by Martin Derick on psychological debriefing. This has become a popular form of intervention after trauma but its effectiveness is uncertain and at present its widespread use cannot be justified. More research needs to be undertaken to identify victims who are likely to develop PTSD and to distinguish them from those who are more resilient and who do not require any form of psychological intervention.

This book is aimed at the reader who is up to date, and comprehensive summary of the current state of knowledge on PTSD. It deserves to be widely read by neurologists, psychiatrists, psychologists, and personal injury lawyers, all of whom have patients who may consult a growing number of victims of trauma.

GEOFFREY LLOYD


This multi-author book aims to improve the management of patients with spasticity in two ways. It provides a clear and clinically relevant account of the underlying neurophysiology that will help clinicians understand the nature and genesis of the problem. And it provides a critical and up to date review of much of the relevant clinical evidence. Some parts of the book are weak, but this book will not mislead and is good value for money.

One weak area in the book is the coverage of the measurement of spasticity. There is one chapter devoted to the topic, by one of the editors, yet this chapter does not make any reference to the Tardieu scale, which forms an important part of the next chapter on physiotherapy management. The next edition should ensure at least adequate cross reference. There is little discussion of the indirect measure of spasticity, measuring the consequences of spasticity such as reduced range of movement, pain, frequency of spasms, or the difficulty experienced by carers in activities. It is these measurements which are being used in modern trials. It would be helpful to include a review of measures used in the evaluation of the management of spasticity, especially because this will be the main clinical interest in measurement.

Two excellent chapters cover the explanation of the neurophysiology and the pharmacological management of spasticity, both draw heavily on evidence which is heartening. High quality evidence is lacking in many other areas, but the discussion of matters such as seating and the use of intrathecal baclofen does draw on experience, and is clearly written. In practice most clinicians will need to learn from direct experience, but if good teachers are not easily available then this text will give a good start to the learning curve.

Some chapters do not use all the evidence that is available. The chapter on orthoses focuses too much on being a catalogue of available orthoses, with any critical evaluation of their utility. The chapter on chemical neurolysis similarly fails to list the various anatomical options. There are certainly studies, including a large randomised controlled trial from The Netherlands that investigate the use both of orthoses and neurolysis and this study is not referenced. There are several studies investigating the use of ankle-foot orthoses.

Finally there is a good chapter on the use of botulinum toxin, its only and inevitable weakness being that some studies are omitted because more evidence is being published regularly. However, it is sensible and accurate and will be a sound basis for action in most cases.

In summary this book covers almost all aspects of spasticity that doctors, therapists, nurses and other clinicians may be interested in. Its use of evidence is good, although it could be improved. It cannot substitute for being taught by someone with clinical experience, nor can it substitute for keeping up to date through continuing professional development but if spasticity management is only a part of your workload (rather than being your specialty) then this book will give a good foundation for clinical practice for the next few years.

DERICK WADE


It was not so many years ago that a diagnostic approach to dementias was limited to the exclusion of potentially reversible causes. It is becoming increasingly clear that clinicians now need to be able to differentiate not only between reversible and irreversible causes but also between the primary degenerative dementias themselves. The past decade has seen great advances in our understanding of the basic science of the dementias, particularly Alzheimer’s disease, bringing us not only a theoretical basis for different symptomatic conditions in different dementias, but also the promise of future therapies that may act directly on the molecular underpinnings of these diseases.

If clinicians are to be able to make these clinical distinctions and initiate appropriate therapy, then unless they are neurologists with a specialist interest in dementias, they may need a little help. Robert Green’s book, Diagnosis and management of Alzheimer’s disease and other dementias, provides that help and a whole lot more. Although in its introduction Dr Green claims that his manual is aimed at the primary care physician it is also informative and useful enough to provide evidence for neurologists in training and neurologists whose area of specialisation lies outside the realm of dementias.

One of the greatest difficulties in reviewing this publication has been to find what was missing. For several weeks this volume has been carried around in my briefcase with regular checks to see if it included certain aspects of the management of dementing illnesses. From the appropriate dose of vitamin E, the debate on the use of ginko biloba, the use of CSF biomarkers in diagnosis, to advice on handling the emotionally charged issue of driving, each time, this small book was informative.

Essentially, the book is divided in four parts. The first, on general aspects of dementing disorders, opens with definitions and the epidemiology of dementias. The following section on the evaluation of the older patient with cognitive impairment emphasises issues such as the importance of taking a corroborative history, and the assessment of functional capabilities or activities of daily living. The appropriateness of ancillary investigations such as neuroimaging, neuropsychology, CSF analysis, and electroencephalography are discussed as well as aspects of a bedside mental status examination. If I had one minor quibble it would be the absence of instructions for my own test of neuropsychological function that can be used at the bedside. Although we all know that we should assess short term memory, few of us can administer a simple list learning task at the bedside or in the clinic. The book concludes with a chapter on cognitive disorders not due to Alzheimer’s disease and is particularly useful in detailing the differentiation of Alzheimer’s from delirium, depression, frontotemporal dementia, and dementia with Lewy bodies.

Part two of the book is devoted to Alzheimer’s disease, its genetics, natural history, neuropathology, and treatment options. In the third part, practical and behavioural issues are addressed and it is here that we really benefit from the experience accumulated by Dr Green and his team in Boston in caring for many patients and their families through the course of these devastating illnesses. The final section of the book is devoted to resources for clinicians and families, over 400 references, and a comprehensive index.

In summary, on the basis of its content, this book is well written, well structured, comprehensive, and above all useful. For me however, its strongest feature is in making all this into a slim volume measuring only 19×10 cm, which was easily carried around in my case.

RICHARD PERRY


David Kline and Alan Hudson wrote Nerve injuries, a work of exceptional importance which was published in 1995. In this work they are joined by Daniel Kim and present an atlas of operative exposure with a discussion of methods of repair of nerves; this is a companion volume to the earlier work.

Nineteen chapters describe the anatomical relations of the peripheral nerves in the upper and lower limbs, of the brachial plexus, of the intrapelvic course of the femoral and sciatic nerves, and of the nerves of the abdominal wall. Five chapters describe methods of nerve transfer or of nerve repair, a further chapter is dedicated to neurolysis, one

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chapter is dedicated to intraoperative neurophysiological work, and there is chapter dedicated to technical questions for the treatment of nerve sheath tumours.

There is a lengthy appendix, of some 100 pages, with photographs of anatomical dissections. These, from Dr Kim, are of the highest quality.

This work is more than a surgical companion. The detailed description of the relation between peripheral nerve trunks and adjacent axial structures, the relation of anatomical variation makes it relevant to any clinicians engaged in the diagnosis of patients with disorders of peripheral nerves most especially to those engaged inclined towards interventional work. The descriptions of the course and relations of nerves of cutaneous sensation in the lower limb and of the nerves of the abdominal wall is particularly good and of direct relevance in the treatment of patients who have had accidental damage to those nerves. Too often these patients present with severe pain, and, because of ignorance, the importance of the distribution, and the location of those sensory disturbances, inappropriate treatment is commenced.

The careful description of the exposure for operations of thoracic outlet syndrome serves to remind all of the potential seriousness of this procedure. I particularly liked the chapters describing exposure of the suprascapular and the circumflex nerves, of the course and variations of the sciatic and of the femoral nerves and most especially the account of David Kline’s own operation, the posterior or subscapular approach to the most proximal segment of the spinal nerves passing to the brachial plexus and upper limb.

Of the technical chapters describing intraoperative compound nerve action potential recordings, a particular contribution from David Kline is especially good.

The work is greatly enhanced by Dr Kim’s photographs of dissections. This is important and valuable work. I would suggest that it is essential reading for surgeons engaged in this work but that its interest extends well beyond that group. There are inevitably errors which will require attention when the work comes to revision, figure 1.11 does not demonstrate the correct relation of the spinal accessory nerve to the uppermost spinal nerves, figure 13.8 showing the course of the posterior interosseous nerve requires attention. Set against the whole these are very minor blemishes.

The authors are to be congratulated on producing an important book which does indeed act as a “companion surgical dissection text or atlas” to their earlier work, which in fact goes well beyond.

ROLFE BIRCH
Lack of association of neprilysin polymorphism with Alzheimer's disease and Alzheimer's disease-type neuropathological changes

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