Evidence for an association between the CSF HVA:5-HIAA ratio and aggressiveness in frontotemporal dementia but not in Alzheimer’s disease

In their recent paper, Soderstrom et al. confirmed their preliminary data suggesting that the CSF HVA:5-HIAA ratio was associated with psychopathic traits and, in particular, violent and aggressive behaviour with childhood onset and adult expression. These findings might indeed reflect changed dopaminergic activity, possibly as a result of serotonergic dysregulation. We hypothesise that their findings might be applicable to other brain disorders characterised by specific behavioural disturbances, including aggression and agitation. Indeed, since several studies have found associations between altered serotonergic neurotransmission and aggression in persons with dementia, we could propose that the CSF HVA:5-HIAA ratio might be associated with aggression in persons with dementia as well. To test this hypothesis, we performed an interim analysis on 102 out of 302 patients who were included in a prospective and longitudinal study on neurochemical and genetic correlates of behavioural and psychological signs and symptoms of dementia (BPSD). The data presented further support a general application of the interesting findings of Soderstrom et al.

Patients with various neurodegenerative forms of dementia were included in this prospective study, and were followed up by means of a neuropsychological and behaviourial assessment every six months. In any case of death, brain autopsy was performed for neurochemical analysis as well as for neuropathological confirmation of the clinical diagnosis. All subjects and their caregivers gave informed consent to participation in the study, which was approved by the local ethics committee.

At baseline, behaviour was assessed by means of a battery of behavioural assessment scales which included the Behavioural Pathology in Alzheimer’s Disease Rating Scale (Behave-AD) and the Cohen-Mansfield Agitation Inventory (CMAI). Lumbar puncture was performed between 9 and 10 am following overnight bed rest and fasting. The first 11 ml of CSF were collected in several polypropylene vials that were immediately frozen in liquid nitrogen and stored at −80°C. Neurochemical analysis was carried out on the CSF fraction containing 6–7.5 ml by means of high performance liquid chromatography and electrochemical detection according to a method recently described. Routine investigation of the CSF included cell count, total protein and glucose analysis, and agar gel electrophoresis of proteins.

For this interim analysis, HVA and 5-HIAA levels were determined in the CSF of 13 participants between aggression and frontotemporal lobe dementia (FTD) and 89 participants with probable Alzheimer’s disease (AD). Spearman Rank Order was used for correlation analysis between the CSF HVA:5-HIAA ratio and BPSD, applying SigmaStat Software (SPSS Science, Erkrath, Germany).

In the AD patient group, no significant correlations were found between the CSF HVA:5-HIAA ratio and Behave-AD clusters, total and global scores, or CMAI clusters (aggressive, physically non-aggressive, and verbally agitated behaviours) and total scores. In persons with FTD, however, the CSF HVA:5-HIAA ratio correlated significantly with the Behave-AD aggressiveness cluster score (r = 0.586; p = 0.033) and with the CMAI verbally agitated behaviour cluster score (r = 0.564; p = 0.041). Despite small sample sizes, effects of treatments were ruled out by comparing the CSF levels of HVA (t-test: p = 0.691), 5-HIAA (p = 0.370), and the CSF HVA:5-HIAA ratio (p = 0.157) between six untreated subjects with FTD and seven subjects with FTD who were receiving atypical antipsychotics.

Our preliminary results revealed an association between aggression and the CSF HVA:5-HIAA ratio in participants with FTD but not in those with AD. More refined neurochemical analyses, including the determination of all catecholamines and serotonin in an extended population of FTD patients, are scheduled. These will allow further testing of the hypothesis that altered serotonergic modulation of dopaminergic neurotransmission leads to BPSD and in particular to aggression. Meanwhile, our findings suggest that the association between the CSF HVA:5-HIAA ratio and aggression as observed by Soderstrom et al. is not limited to violent and aggressive behaviour with childhood onset and adult expression, but may indicate an underlying pathophysiological mechanism that may be common to aggressive symptomatology in other brain disorders, such as frontotemporal lobe dementia.

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References

Extensive radiculopathy: another false localising sign in intracranial hypertension

We read with interest the review by Larner on false localising signs. Among the various false localising signs described in patients with intracranial hypertension (ICHH), radiculopathy is an important manifestation which is probably under-recognized. Many authors have documented subtle features of radiculopathy in patients with isolated intracranial hypertension (IIH). The usual manifestations of radiculopathy in these cases were acral paraesthesias, and backache and radicular pain. Rarely, motor deficits due to radiculopathy caused by ICHT have been described.

Obied et al reported two patients with extensive radiculopathy due to ICHT: one individual had IIH and the other had cerebellar venous sinus thrombosis. Both persons had papilloedema, marked visual impairment, and flaccid areflexia quadriparesis with normal MRI of brain, brainstem, and cervical spinal cord. The electrophysiological findings were consistent with radiculopathy. Both individuals initially received intravenous immunoglobulin for Guillain–Barre syndrome, without benefit, but they responded well to lumbo-peritoneal shunting. We also encountered two such cases with angiographically proven cerebral venous sinus thrombosis.

The most likely mechanism at the basis of radiculopathy appears to be similar to that of other cranial neuropathies in ICHT—that is, mechanical compression of nerve roots, due to elevated CSF pressure distending the subarachnoid space. Documented enlargement of spinal subarachnoid space and distended root pouches in a patient with radicular pain and areflexia due to IIH supports this view. Radiculopathy secondary to ICHT has been reported almost exclusively in patients with IIH or cerebral venous sinus thrombosis. Other causes of ICHT may not induce a diffuse increase in pressure in both intracranial and intraspinal compartments, and are unlikely to manifest as radiculopathy.

The constellation of flaccid-areflexic quadriparesia and papilloedema may be misdiagnosed as Guillain–Barre syndrome with papilloedema. Careful analysis of the evolution of symptoms, estimation of CSF pressure, and appropriate vascular imaging should help to correctly identify the cause of ICHT.

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References
Role of entacapone in later Parkinson’s disease not yet established

The study by Brooks and Sagar,1 along with a number of previous others, demonstrates benefit for the catechol-O-methyltransferase (COMT) inhibitor entacapone when compared with placebo in Parkinson’s disease (PD). However, this is insufficient evidence to justify the authors’ conclusion that “it appears logical to employ levodopa combined with entacapone routinely”. The important issue is not whether entacapone is more efficacious than placebo, but whether it is more or less clinically effective and cost effective than the other available treatments for patients with PD that is no longer adequately controlled by levodopa alone. Other available agents—including dopamine agonists and monoamine oxidase type B (MAO-B) inhibitors—have also shown efficacy when compared with placebo. The paper would have benefited from a balanced discussion of the merits of entacapone compared with these other available treatment options.

Such a discussion is likely to be inconclusive, however, as there is a dearth of reliable evidence on the best treatment for PD, at any stage of the disease, since very few trials directly comparing active treatments have been undertaken.2 Companies are reluctant to undertake such trials, as it is not in their commercial interests to risk studies that might show their product to be inferior to that of a competitor. For this reason, independently funded trials—such as the current PD MED trial in the UK—should be supported to provide the reliable evidence on comparative efficacy needed to enable clinicians to make informed treatment decisions. Analysis, presentation and interpretation of the results of independent studies are also likely to be more objective than those of commercial studies. The potential for bias in commercial trials has recently been highlighted by systematic reviews and journal editors—for example “systematic bias favours products which are made by the company funding the research”1—and “scientific studies can be manipulated in many ways to give results favourable to companies”.3

There are problems with the trial reported by Brooks and Sagar, and these are common to many PD trials, which are generally poor methodologically.4 In a progressive condition such as PD, it is important to evaluate the long term effects of treatment, and six months follow up is inadequate. The outcome measures used should reflect the impact of treatment on the patients’ own perception of their functioning and quality of life, not that of clinicians as with the Unified Parkinson’s Disease Rating Scale (UPDRS).

It is unclear how well the data obtained from off-on diaries correlates with global quality of life, and how to treat (ITT) analysis was not performed, since patients who withdrew from treatment were excluded from the analysis—ITT analysis requires such patients to be followed up and included in the analysis according to the arm to which they were allocated even if they have withdrawn from allocated therapy.5 Near 50% more patients (24.1% v 16.5%) dropped out of the entacapone arm than from the placebo arm and, in progressive diseases such as PD, dropout bias tends to favour the active treatment.6 Thus, although COMT inhibitors are welcomed as additional treatment options in PD, large, rigorously conducted comparative trials, assessing the long term impact on patient-rated measures of quality of life, are still needed to define their role in routine clinical practice.

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Competing interests: We are investigators in the PD MED trial and thus have a vested interest in obtaining the results of independent studies are also likely to be more objective than those of commercial studies. The potential for bias in commercial trials has recently been highlighted by systematic reviews and journal editors—for example “systematic bias favours products which are made by the company funding the research”1—and “scientific studies can be manipulated in many ways to give results favourable to companies”.3

References

Portal-systemic shunts, manganese, and parkinsonism

I read with interest the article by Yoshikawa and colleagues.1 The authors reported the case of a 44 year old woman with hereditary haemorrhagic telangiectasia (Rendu-Osler-Weber disease) involving the liver, who had raised serum concentrations of manganese, hyperintense areas in the basal ganglia on T1 weighted magnetic resonance images, and levodopa unresponsive parkinsonism. Naturally, I agree that the parkinsonism in this case is most probably related to portal-systemic (portal-venous) shunts. There are, however, two points that deserve clarification.

First, it is not entirely clear whether their fig 2 (left panel) shows portal-systemic or arteriovenous shunts. The authors say that the figure shows a selective angiogram of the superior mesenteric artery. If that were the case, there should not be a “feeding artery” involved in the intrahepatic shunts (as they state in the legend to fig 2). Instead, the figure would show the portal venous phase of the angiogram and show a feeding artery (the hepatic artery) and arteriovenous (not portal-systemic) shunts. Interestingly, there is evidence to suggest that both types of shunt may be involved in the development of neurological complications in the presence of an intact (or mostly preserved) hepatic parenchyma.2 Thus excessive quantities of potentially toxic substances (for example, manganese) passing directly from the gut to the systemic circulation through portal-systemic shunts could be rapidly cleared by a normal liver as long as the hepatic arterial blood flow is adequate.

Second, Yoshikawa and colleagues claim that the parkinsonism of their patient was induced by manganese. While this is a reasonable working hypothesis, the authors provide no direct evidence supporting such a statement. The fact that manganese was raised does not necessarily imply that manganese played a key role in the pathogenesis of parkinsonism. Indeed, their patient lacked clinical features often seen in cases of manganese induced parkinsonism (for example, cock walk and propensity to fall backwards).

Levodopa unresponsive parkinsonism is a well known manifestation of chronic non-Wilsonian hepatocerebral degeneration.3 Although blood concentrations of ammonia were within the normal range in the case reported by Yoshikawa and colleagues, the possibility of manganese induced parkinsonism occurring particularly after meals was not investigated.

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References

Authors’ reply

We are pleased to have an opportunity to comment on the important issues raised by Dr de la Fuente-Fernández regarding a case of hereditary haemorrhagic telangiectasia.
with parkinsonism. Raised serum manganese combined with the abnormal findings in cranial magnetic resonance imaging and abdominal angiography were the rationale for our conclusion that the parkinsonism in our patient was induced by manganese that had accumulated because of portal-systemic shunting.

After the angiogram: the angiogram of the superior mesenteric artery presented in our manuscript showed a dilated feeding artery, a dense mottled hepatogram, and early filling of the hepatic vein. These findings concerned the arterial phase. The intrahepatic arteriovenous shunts were definite diagnostic evidence of hereditary haemorrhagic telangectasia but not of portal-systemic shunts. We therefore agree with Dr de la Fuente-Fernández that we should have presented another angiogram in the portal phase showing a hypoplastic portal vein with abnormal vessels between the mesenteric and inferior vena cava to confirm the portal-systemic shunt.

About the parkinsonism: after the failure of treatment by levodopa, we took other measures to relieve the parkinsonism; for example, we persuaded the patient to avoid manganese-rich foods such as blueberries. Fortunately, her serum manganese gradually decreased below the normal upper limit during the next six months, and her neurological symptoms became less prominent. All elevation of parkinsonism in inverse proportion to serum manganese concentrations suggests that the parkinsonism in this case may have been caused by manganese accumulation, and that the patient was in the early stage of manganese intoxication in which neurological symptoms were incomplete and partially reversible.

About transient hyperammonaemia: we searched for cases of hyperammonaemia related parkinsonism, and finally found a case with portal-systemic encephalopathy and parkinsonism which disappeared after treatment of the portal-systemic shunting.1 The mechanism of parkinsonism in that case is currently open to debate, as hyperammonaemia is generally thought to cause disturbance of consciousness or negative myoclonus rather than parkinsonism. We do not deny the possibility that our patient may have had a transient increase in serum ammonia, though it seems unlikely when there had never been a disturbance of consciousness.

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Intraventricular assessment of preoperative electrographic recordings

The paper by Song et al describes the placement of intraventricular arrays with endoscopic assistance for preoperative electrographic recordings for epilepsy surgery. The 4.2 mm outer diameter rigid endoscope was introduced up to the temporal ostium from where the arrays were advanced until a point of resistance was felt.

In our paper we reported the use of a 1.2 mm outer diameter semirigid endoscope to explore the contents of the ventricles prior to electrode placement, with direct visualization and assessment of the final electrode position, which helped us obtain appropriate pre-resection electrographic recordings. Perhaps it would be more convenient to use semirigid endoscopes or slim fibrescopes to fully visualise the ventricle as well as flexible arrays to avoid electrode displacement resulting in unintentional cerebral lesions.

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Parkinsonism and persistent vegetative state after head injury

Matsuda et al recently reported three patients with a persistent vegetative state (PVS) after severe head injury who, after recovering from prolonged disturbance of consciousness, presented parkinsonian features (mainly rigidity and hypokinesia) which improved after levodopa treatment.1 MRI studies showed lesions in the dorsolateral midbrain and cerebral peduncles suggesting axonal injury involving the dopaminergic system (substantia nigra and cerebral peduncles area). Similar observations were made in a series of 125 patients with severe vegetative state following head injury (survival time 1–10 years). Nineteen of 49 patients surviving in fully developed or mild recovery stages of PVS initially presented with severe to moderate, mainly symmetrical, parkinsonian symptoms (amnesia, rigidity, hypokinesia, convergence disorders). Following levodopa treatment, 11 patients showed incomplete and four full improvement of both the PVS and parkinsonism, while four patients showed complete recovery from both syndromes. However, in 15 patients—despite good recovery from the initial PVS and other neurological symptoms (spasticity, frontal and cerebellar symptoms), and long term levodopa treatment—a progressive parkinsonian syndrome (rigidity, hypokinesia) developed in six patients this was associated with unilateral or bilateral resting tremor. In MRI studies done in 34 patients, 32 showed unilateral or bilateral lesions in the midbrain involving both the dorsolateral tegmentum and the cerebral peduncle.2

Neuropathological studies were undertaken in 32 patients surviving without essential improvement of the PVS for at least two months after head injury. Parkinsonian syndromes were severe in seven, moderate in five, and mild in four. In addition to older caudate and putaminal necroses or reversed striatum (n = 6), globus pallidus and thalamus (n = 8), all brains revealed multiple lesions in the rostral brain stem with unilateral or bilateral focal lesions in the substantia nigra, vascular lesions in the lateral and ventrolateral midbrain in seven, and symmetrical post-axonic cellular depletion and gliosis or unilateral necroses in the substantia nigra in one case each. In nine cases, there was a good correlation between the severity of clinical parkinsonian signs and the severity and extent of nigral lesions; three patients showed severe parkinsonian signs associated with only mild nigral damage, but there was severe bilateral damage to the globus pallidus in two. In four patients the expression of clinical parkinsonian signs was more severe than the anatomical lesions, in particular the damage to the substantia nigra. The distribution pattern of the brain stem lesions correlated with the sequelae of transtentorial shifting caused by increased intracranial pressure; direct or “primary” traumatic lesions to the oral brain stem usually cause acute death, as seen in two young men with rupture of the diencephalon and acute haemorrhage into the substantia nigra or midbrain following severe and acute fatal head injuries. However, in rare patients with long-term survival following head injury, symmetrical necrosis of the substantia nigra without a clinical parkinsonian syndrome has been reported.3

The clinical phenotype of post-traumatic parkinsonism often resembles that in post-encephalitic parkinsonism, both showing akinesia, rigidity, hypomimia, rare tremor, and optomotor and vegetative disorders. Both the lesion pattern and the therapeutic efficacy of long term levodopa treatment suggest a dysfunction of the striato-nigral dopaminergic system which, however, may show progressive compensation in some patients with long lasting PVS after severe head injury.

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REFERENCES

Authors’ reply
We greatly appreciate the thoughtful comments offered by Dr Jellinger, and his interest in our report of three cases in a persistent vegetative state (PVS) after severe head
injury, who recovered from a prolonged disturbance of consciousness after they were given levodopa.

This finding reports that in cases of prolonged post-traumatic coma the brains showed multiple lesions of primary and secondary traumatic origin and that the highest incidence of lesions was found in the rostral brain stem. These were considered to be almost exclusively of secondary origin, resulting from cerebral and peripheral circulatory disorders, post-traumatic oedema, and increased intracranial pressure. Primary (direct) traumatic lesions to the rostral brain stem usually cause acute death. In contrast to this report, the brain stem injuries in our cases suggested by MRI may have been the primary traumatic lesions. All these cases showed high intensity lesions in the dorsolateral midbrain on T2 weighted MRI. These findings implied that the midbrain was injured by tentorial compression induced by translatory and rotatory acceleration when the cranium was struck in its sagittal axis, or by postrotatory damage. MRI findings, particularly in the acute stage, are useful for evaluating primary brain damage. 1

Furthermore, another distinctive feature of our cases was that the anatomical distribution of the lesions was not multifocal but was localised in the cerebral peduncle or the dorsolateral midbrain, implying diffuse axonal injury involving the substantia nigra or the ventral segmental area.1 The neuroradiological findings, the clinical features of extra-pyramidal dysfunction, and the efficacy of levodopa treatment all strongly suggest that the dopaminergic pathways were selectively damaged in these patients. Such patients may have required permanent medication; an example is case 1 in our report, whose recovery was sustained even after the levodopa treatment was discontinued. Some patients may need levodopa only as a trigger agent at the start of treatment to interrupt the vicious cycle of exhaustion of neurotransmitter. However, discriminating which cases fall into this category is very difficult and withdrawal of medication involves ethical problems.

In recent neuropathological and neuroradiological studies on PVS after traumatic brain injury,2,3 the most common structural abnormalities were diffuse axonal injury involving the corpus callosum, the dorsolateral aspect of the rostral brain stem, and the thalamus.4 Although the clinical features will vary in such cases, a take-home message which we learned from our three cases is that in any group of patients with PVS after severe head injury there may be some whose dopaminergic systems may have been selectively damaged; such individuals may respond to levodopa treatment. It is necessary to accumulate a great deal more clinical experience and data to elucidate the pathogenesis and pathophysiological mechanism of post-traumatic PVS. We respect Dr Jellinger’s careful observations and descriptions of his cases of prolonged post-traumatic coma, and look forward to further views from him on this topic.

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References


BOOK REVIEWS

Year book of neurology and neurosurgery 2003


Every year, countless journals publish myriad neurology and neurosurgery papers. There is immense attraction in the notion of a single volume yearbook that selects and comments upon the best. So, how well does the Yearbook of neurology and neurosurgery succeed in informing about significant advances in knowledge on a particular subspecialty area for 2003? The editors draw their selection from a survey of 500 journals, with something from most of those with big impact. Thirty seven associate editors assisted by reviewing the various subspecialty areas; of these all except 11 come from North America, of whom 9 are neurosurgeons rather than neurologists, an intriguing imbalance.

Papers selected cover every conceivable subspeciality, and sometimes the inconceivable. New gene mutations abound, illuminating beyond schizophrenia and a syndrome with effectively treatable, notably, but not exclusively electroconvulsive therapy (ECT).

For those interested in the cerebral basis of psychiatry, a condition with the main presenting signs of mutism, immobility, negativeism, posturing, stereotypy, and echo-phenomena cannot fail to attract attention, and the many faces of catatonia (title, chapter 3) are an olla podrida of neuropsychiatry. It is refreshing to find reference to Leonhard’s work and the cycloid psychoses in a text from American authors, who are thoroughly appreciative of the European literature on their subject, and shly critical of DSM-IV. Their overall conclusions are clear: Catatonia is a common, almost disappeared from the literature, and currently 2002;58:1321-2.

M Donaghy

Reference


Catatonia: a clinician’s guide to diagnosis and treatment


This nicely produced book reviews one of the historically most interesting, but clinically still very important, disorders of neuropsychiatry. Catatonia, described by Kalischer in the latter half of the 19th century, was hijacked by Kraepelin to be incorporated into his concept of dementia praecox, and almost disappeared from the literature in the first half of the 20th century, being finally eclipsed by the introduction of effective psychotropic drugs thereafter. But, as Fink and Taylor explore here, catatonia as a diagnosis is still a diagnostic challenge, with causes far beyond schizophrenia and a syndrome with the best treatment, notably, not exclusively electroconvulsive therapy (ECT).

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New Oxford textbook of psychiatry, vols 1 and 2

The New Oxford textbook is the latest and largest from the Oxford textbook of psychiatry's stable. The book was originally published in 2000 and has recently appeared in paperback. This is the best modern British textbook of psychiatry. It is over 2000 pages long and comes in two stout volumes. The international editorship is led by Michael Gelder, Emeritus Professor of Psychiatry at Oxford, with Spanish (Jaun Lopez-Ibor) and American (Nancy Andreasen) co-editors. The book is inevitably based on a myriad of individual contributions although the choice of contributor and standard of editing is exemplary.

The first volume covers general issues and the scientific basis of psychiatry, including a number of reviews of neurobiology. Interestingly, psychodynamic contributions have a separate section. The remainder of the first volume is taken up with coverage of the clinical syndromes of adult psychiatry, including substantial coverage of dementia.

The second volume includes review of special topics with a number of articles on aspects of the psychiatry and medical conditions. This includes a useful chapter on neurological disease by Maria Ron, and on epilepsy by Monty E. The remaining part of the second volume addresses the psychiatric subspecialties as well as having a substantial section on psychiatric treatments, both pharmacological and non-pharmacological.

This book does much more than its title would suggest. Although mainly concerned with magnetic resonance imaging (MRI) in stroke, the text actually covers single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging as well and would appear to be one of the best chapters ever written on computed tomography (CT) in stroke. The approach and content reflect the predominance of neurologists among the editors and authors, with only a few radiologists, and is really aimed at neurologists and stroke physicians.

The scene is set in the first chapter with a discussion of the limitations of clinical diagnosis of stroke and the specific role that imaging can play in diagnosing the type and cause of stroke. There is a superb chapter on CT in acute stroke, which exemplifies how the role of imaging in any diagnostic process should be evaluated. Separately, there is a chapter on CT evaluation of cerebral blood flow, a useful and practical introduction to MRI, discussion of conventional structural MR techniques such as T2, FLAIR, and gradient echo sequences, and a section on MR angiography. Much of the rest of the book (about half of it) is given over to diffusion and perfusion MRI, including its evaluation in animal models, concepts of identifying the ischaemic penumbra, evaluation of transient ischaemic attacks, selection of patients for new therapies and drug development trials, and finally a chapter on MR spectroscopy and a (very short) chapter on functional MRI after stroke.

Although written by MR enthusiasts, the text is tempered with some discussion of the drawbacks of MR, such as poorer patient accessibility (compared with CT) and problems of metallic foreign bodies. It also makes the point that, despite the huge interest in MR diffusion and perfusion imaging, the precise thresholds of defining irreversibly damaged tissue and tissue at risk are yet to be determined. Some aspects of stroke MRI are not dealt with in much detail, for example classification or interpretation of white matter lesions (frequently found in stroke patients), or the identification and interpretation of microhaemorrhages on MR and how they might influence decisions regarding stroke treatment, or on using diffusion imaging to identify lesions in patients with milder strokes (say, within intervals after acute stroke (that is, not just the first few hours)). There is very little on practical issues (perhaps reflecting the neurology rather than the radiology approach such as how one assesses a stroke patient who is unable to speak prior to MR to make sure that it is safe for the patient to go into the magnet, and how one manages the patient while in the machine with respect to factors such as oxygenation.

Some of the authors express personal views that not all readers will agree with. For example, in the chapter on assessment of a transient ischaemic attack (TIA), the authors suggest that the definition of a TIA should be changed to one based on the presence or absence of certain imaging features. Although this clearly represents a personal opinion expressed by the authors, it is an interesting suggestion to change a classification that is so fundamental to stroke epidemiology and clinical practice is that only those with access to an MR scanner with diffusion imaging will be able to correctly diagnose a TIA using this new classification. Not only that, but the diagnosis of TIA might be dependent on the ability of the local radiologist or clinician to spot subtle features of recent ischaemia on diffusion images and the timing of scanning after symptom onset.

I found it a little disappointing that a proportion of the perfusion images were presented in black and white when this is one technique which really requires colour display for proper interpretation and appreciation.

In summary, this is a useful textbook, particularly for neurologists or stroke physicians who need to understand more about imaging and its role in patient characterisation, decision making, and assessment of treatments in acute stroke. It’s not just about MR and everybody with an interest in stroke should read the chapter on clinical efficacy of CT in acute cerebral ischaemia. Although 250 pages it is easily digestible and yet also a useful reference. At £80.00 I think compared with other books on MR and on stroke it represents good value for money.

M Sharpe

The parallel brain: the cognitive neuroscience of the corpus callosum

Roger Sperry’s research on the cognitive abilities of split-brain patients following callosal section is a landmark in the study of brain-behaviour relationships. His studies firmly established the role of the corpus callosum in inter-hemispheric information transfer. What have we learned more recently about the role of the corpus callosum in cognition? In this book Eran Zaidel (originally one of Sperry’s students) and neurologist Marco Iacoboni present 22 chapters based on a 1996 NATO Advanced Science Institute that attempt to answer this question. The central focus is on the classic problem of why reaction time to respond to a light flashed in either visual field differs according to whether the ipsilateral or contralateral hand is used to respond (known as the Poffenberger effect, after the psychologist who described it in 1912). This is thought to reflect callosal information transfer between the hemispheres; the book uses anatomical, physiological, and behavioural perspectives to address the question of what information is transferred and how the transfer might work. Many chapters are accompanied by commentaries and editorial comment, giving a flavour of the debates and controversies in the field.

Perhaps reflecting the long interval between the original conference and this book, more recent studies that use functional neuro-imaging techniques to investigate callosal function are relatively poorly represented. However, there is still much of interest in this otherwise comprehensive volume. The chapters generally have a basic scientific focus, but chapters on multiple sclerosis, dyslexia and alexia, schizophrenia, and attention deficit hyperactivity disorder also contain much that will interest the practicing clinician.

G Rees

Magnetic resonance imaging in stroke

This book does much more than its title would suggest. Although mainly concerned with magnetic resonance imaging (MRI) in stroke, the text actually covers single photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging as well and would appear to be one of the best chapters ever written on computed tomography (CT) in stroke. The approach and content reflect the predominance of neurologists among the editors and authors, with only a few radiologists, and is really aimed at neurologists and stroke physicians.

The scene is set in the first chapter with a discussion of the limitations of clinical diagnosis of stroke and the specific role that imaging can play in diagnosing the type and cause of stroke. There is a superb chapter on CT in acute stroke, which exemplifies how the role of imaging in any diagnostic process should be evaluated. Separately, there is a chapter on CT evaluation of cerebral blood flow, a useful and practical introduction to MRI, discussion of conventional structural MR techniques such as T2, FLAIR, and gradient echo sequences, and a section on MR angiography. Much of the rest of the book (about half of it) is given over to diffusion and perfusion MRI, including its evaluation in animal models, concepts of identifying the ischaemic penumbra, evaluation of transient ischaemic attacks, selection of patients for new therapies and drug development trials, and finally a chapter on MR spectroscopy and a (very short) chapter on functional MRI after stroke.

Although written by MR enthusiasts, the text is tempered with some discussion of the drawbacks of MR, such as poorer patient accessibility (compared with CT) and problems of metallic foreign bodies. It also makes the point that, despite the huge interest in MR diffusion and perfusion imaging, the precise thresholds of defining irreversibly damaged tissue and tissue at risk are yet to be determined. Some aspects of stroke MRI are not dealt with in much detail, for example classification or interpretation of white matter lesions (frequently found in stroke patients), or the identification and interpretation of microhaemorrhages on MR and how they might influence decisions regarding stroke treatment, or on using diffusion imaging to identify lesions in patients with milder strokes (say, within intervals after acute stroke (that is, not just the first few hours)). There is very little on practical issues (perhaps reflecting the neurology rather than the radiology approach such as how one assesses a stroke patient who is unable to speak prior to MR to make sure that it is safe for the patient to go into the magnet, and how one manages the patient while in the machine with respect to factors such as oxygenation.

Some of the authors express personal views that not all readers will agree with. For example, in the chapter on assessment of a transient ischaemic attack (TIA), the authors suggest that the definition of a TIA should be changed to one based on the presence or absence of certain imaging features. Although this clearly represents a personal opinion expressed by the authors, it is an interesting suggestion to change a classification that is so fundamental to stroke epidemiology and clinical practice is that only those with access to an MR scanner with diffusion imaging will be able to correctly diagnose a TIA using this new classification. Not only that, but the diagnosis of TIA might be dependent on the ability of the local radiologist or clinician to spot subtle features of recent ischaemia on diffusion images and the timing of scanning after symptom onset.

I found it a little disappointing that a proportion of the perfusion images were presented in black and white when this is one technique which really requires colour display for proper interpretation and appreciation.

In summary, this is a useful textbook, particularly for neurologists or stroke physicians who need to understand more about imaging and its role in patient characterisation, decision making, and assessment of treatments in acute stroke. It’s not just about MR and everybody with an interest in stroke should read the chapter on clinical efficacy of CT in acute cerebral ischaemia. At just over 250 pages it is easily digestible and yet also a useful reference. At £80.00 I think compared with other books on MR and on stroke it represents good value for money.

J M Wardlaw

Cortex and mind: unifying cognition

Joaquin Fuster is a distinguished American neuroscientist whose work has explored the neurophysiology of cognition, largely in animals, but with the ultimate goal of understanding how the human mind is implemented in the brain. His own research has focused particularly on the neural basis of working memory, revealing “memory” cells in the prefrontal cortex that help to retain the information an animal must “keep in mind” if it is to act appropriately after a delay—like the position of a rewarded well. At the heart of the prefrontal memory cells are a key component of an extensive cortical network required to maintain working memory, which also involves...
The bard on the brain: understanding the mind through the art of Shakespeare and the science of brain imaging


One of the great challenges of popular science writing is to convey a coherent and consistent impression of scientific ideas while avoiding confusing, specialist terminology. The most useful tools for this task are metaphor and pictures. The Dana Press, publisher for the Charles A Dana Foundation, has as its mandate “the provision of information about the personal and public benefits of brain research”. With The bard on the brain, they have chosen to use the voice of William Shakespeare, the master craftsman of metaphor, to introduce the areas of human cognition that have attracted the most attention in recent functional imaging research. The bard’s general line of argument suggests that interwoven and sometimes identical networks are involved in each of these cognitive functions, which are therefore far less well localised and less distinct than much of our contemporary quasi-phenomenological thinking suggests: no cognitive function has a fully dedicated cortical area or network; conversely, a cortical network or representation is at the disposition of any and all functions.

This view has a good deal of appeal; perception is in part the reactivation of memory, attention is expressed in the changing content of perception, language and intelligence emerge from the categories that perceptual memory creates...and yet other observations, like the role of the medial temporal lobes in acquiring declarative memories, or of the fusiform gyrus in face perception or inferior parietal lobe in spatial awareness, seem to call for a more finely differentiated theory of cortical function than Fuster’s general model of argument suggests.

Fuster’s main thesis condemns him to repeat himself at times as he works through the roster of our cognitive functions, and he tends to a rather abstract style. But there is much fascinating information to be found here—I particularly enjoyed the closing chapters on language and intelligence—and anyone who is used to locating cortical functions on colourful scans will find cause for thought in these pages.

A Zeman

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Testing, common neurological presentations, for example headache and weakness, specific neurological conditions, for example multiple sclerosis and cerebrovascular disease, neurological trauma, paediatric neurological emergencies, pregnancy related neurological emergencies, neurotoxicology, and brain death. So, it attempts a comprehensive coverage.

The editors consider it to be symptom based, although this is not always achieved. It has many tables, good illustrations, and management of algorithms with “pearls and pit falls” at the end of every chapter.

The neurological examination is done poorly, particularly the cranial nerves. This needs to be done with pictures of the lesions, their causes, and the anatomy, based around the common emergency presentations in A&E. Although the authors disagree with some of the advice given, most of the text is reliable and clear. (For instance, in the chapter on myasthenia gravis, it states “useful gauges include pulse oximetry, peak expiratory flow and PCO2 measurement”, which are all poor gauges of impending ventilatory failure and vital capacity is the most important measurement in this respect.)

The most disappointing feature is that the chapters are not adequately focused on emergency conditions. The chapter on movement disorders covers virtually the whole spectrum of chronic movement disorders without specifically concentrating on the commoner acute presentations, such as drug induced dystonia with oculogyric crisis and hemiballisms, which are likely to come to A&E. Unfortunately the editors and authors have failed to produce a sufficiently concise account of emergency conditions to make this book really useful. It needs to be much briefer and appropriately focused to achieve this book really useful. It needs to be much

D Hilton-Jones

Duchenne muscular dystrophy, 3rd edn


Quite simply, this monograph is essential reading for anybody involved with this devastating condition, and indeed for those involved with any form of muscular dystrophy, whether in the clinic or in the laboratory. Duchenne muscular dystrophy (DMD) is the archetypal dystrophy. It is because the clinical course is so stereotyped that it was the first of the dystrophies to be defined clearly, over a century ago. The historical journey from the first clinical descriptions to our present state of knowledge forms the core of this book, with side branches relevant to the identification of other specific forms of dystrophy, particularly the limb girdle dystrophies. The nihilist may suggest that all of this knowledge has as yet failed to find a cure, but for the clinicians intimately involved with these patients we can now do more than ever to provide an improved quality of life. There is of course great hope that “genetic engineering” will lead to a cure, but patients and their families cannot live on hope alone and Professors Emery and Muntoni have elegantly summarised present management options.

The second edition was published in 1986, a matter of months before the identification of the gene involved in the disease process and its protein product dystrophin. Within a few years it became apparent that dystrophin and dystrophin associated proteins have a fundamental role in various forms of muscular dystrophy, and for a while it looked as if there might be a common mechanism of membrane fragility due to dysfunction of these membrane associated proteins. Then abnormal cytosolic proteins were found in some forms of limb girdle dystrophy and it became clear that there was no simple single disease mechanism. Despite that, altered function of membrane proteins is clearly of fundamental importance in many dystrophies and Muntoni has been at the forefront of recent discoveries relating to altered glycosylation of the membrane protein z-dystroglycan in various forms of congenital and adult onset limb girdle dystrophies.

There is no need to describe the individual chapters in detail. In brief, the monograph covers the history of the disease (Emery being a noted medical historian), clinical features, then abnormal dystrophin. Dystrophin is considered first, and then clinical practice is kept up to date by his being joined by Muntoni for this timely third edition.

All those involved in the management of DMD will find something of value in this book. Some patients and families may also want to dip into it. Those interested in the history of medicine, the growth of interest in and the clinical importance of dystrophin in various forms of congenital and adult onset dystrophia muscular dystrophies, will find it a fascinating story.

Let us hope that a fourth edition, detailing the successes of genetic engineering, will not be too far off, but in the meantime there is much that can be done to alleviate the consequences of this truly awful condition.

D Hilton-Jones

Mental and behavioral dysfunction in movement disorders


It was not long ago that the basal ganglia were considered to be structures sub-served motor function, they represent driver and affect and are re-represented cortically and which propel our very being.

M Trimble

Corrections

doi: 10.1136/jnnp.2003.029074corr1

In the review by Rockwood in the May issue of JNNP (K Rockwood. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer’s disease. J Neurol Neurosurg Psychiatry 2004;75:677–85) there is an incorrect entry on the x axis each of the tables in figure 1. The sixth entry should read 0.25, instead of 0.3. The correct table can be viewed at http://www.jnnp.bmjournals.com/cgi/content/full/75/5/677/DC1

doi: 10.1136/jnnp.2003.034876corr1

The authorship list of the letter entitled emotion process in the minimally conscious state, by Bekinschtein et al (JNNP May 2004;75:788), was incorrectly printed as T Bekinschtein, J Niklison, L Sigman, F Manes, R Leiguarda, J Armony, A Owen, S Carpintiero, and L Olmos. The correct order is as follows: T Bekinschtein, R Leiguarda, J Armony, A Owen, S Carpintiero, J Niklison, L Olmos, L Sigman, F Manes.