Organisation of the sympathetic skin response in spinal cord injury

With much interest we read the article of Cariga et al who studied the capacity of the isolated spinal cord to generate a sympathetic skin response (SSR). We appreciate this comprehensive and well designed study, which encouraged us to suggest some of our own ideas. The authors recorded the palmar and plantar SSR to peripheral nerve electrical stimulation (median or supraorbital nerve above the lesion, and peroneal nerve below the lesion) in 29 patients with spinal cord injury (SCI) at various neurological levels and in 10 healthy control subjects. In complete SCI no SSR could be evoked below the lesion. It was concluded that the spinal cord isolated from the brain stem could not generate an SSR. Furthermore, the authors assume that supraspinal connections are necessary for the SSR.

The sudomotor response below a complete SCI has been widely studied in the past. However, the question whether the isolated spinal cord can generate SSRs is still under discussion. Wallin et al obtained sudomotor responses in complete SCI after manual pressure applied to the anterior abdominal wall. In SCI, the authors have shown, using microneurographic recordings from postganglionic axons in skin nerves, that several stimuli applied caudal to the lesion site induce bursts of neural impulses that contain sympathetic outputs of spinal origin. Previnaire et al recorded the palmar and plantar sudomotor responses in complete SCI during cystometry and found a sudomotor activation during bladder contraction.

In a recent study we focused on sudomotor pathways in patients with complete SCI. Below the level of lesion the tibial and the pudendal nerve were stimulated electrically whereas the palmar and plantar SSR were recorded. Tibial nerve stimulation was not obtainable in 4 patients due to technical reasons. Plantar SSRs after pudendal nerve stimulation were obtained in patients with lesions at L1 and more caudal. SSRs after pudendal nerve stimulation evoked plantar SSRs in patients with complete cervical and thoracic SCI. No SSRs after pudendal nerve stimulation were obtained in patients with lesions at L1 and more caudal. SSRs following pudendal nerve stimulation in complete SCI above the level L1 are probably mediated by supraspinal connections. We conclude “that treatment may improve or restore intellectual functions.” As was mentioned by the authors, one of us (AMC) has previously described the prevalence of potentially reversible conditions, with 13.2% of cases having a potentially reversible cause, while only 3% fully resolved on treatment. In that review of the literature, as in the study by Hejl et al, most of the studies originated from secondary or tertiary centres. In a recent meta-analysis by AMC, where a much higher proportion of studies than previously emanated from either outpatient departments or were community based, it was shown that regardless of potential reversibility, the true prevalence of reversed dementias is actually less than 1%.

We thus feel that although it is important to diagnose and treat concomitant conditions in patients suffering from cognitive decline, one should exercise great caution in describing possible causes of cognitive decline and dementia as either potentially or fully reversable.

**Reversible dementias**

The concepts of potentially reversible cognitive impairment in general, and the reversible dementias in particular, remain controversial. The prevalence of these conditions depends to a great extent on the definitions used and on the population studied. Also, the definition of those cases with potentially reversible conditions that actually do reverse remains a critical aspect in assessing these conditions.

In our article, Hejl et al present the results of a prospective study to investigate the prevalence of potentially reversible causes of cognitive decline in consecutive patients presenting to a tertiary medical centre memory clinic. The description that they provide of a large cohort provides an important contribution to our understanding of this condition. However, as was mentioned by the authors in the discussion, the rather high prevalence (19%) of potentially reversible causes detected must be regarded with some caution. Also, while no data are presented regarding the follow up of those patients where a potentially reversible cause was identified, the authors nevertheless conclude “that treatment may improve or restore intellectual functions.”

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**References**


**Authors’ reply**

We are grateful for the opportunity to comment on the important issue raised by Dr Dwolatzky and Dr Clariﬁeld regarding the true prevalence of reversible dementias. In our paper we investigated the prevalence of potentially reversible aetiology and comorbidity in 1000 consecutive patients referred to an outpatient memory clinic based in neurology. In the whole group of patients with cognitive symptoms, 11% met the criteria for potentially reversible condition. However, in patients meeting the clinical criteria for dementia, the prevalence was only 23%. Thus, potentially reversible conditions are most common in patients with cognitive symptoms, less common in patients meeting the criteria for dementia, and comparatively common as comorbidity in both groups.

Dr Dwolatzky and Dr Clariﬁeld report that in their future meta-analysis for publication in 2005 the “true” prevalence of reversed dementia is less than 1%. With reference to our results in patients with dementia we are not surprised about the very small prevalence of truly reversed dementia.

As we have already discussed in our report, both the setting of the study and the deﬁnition of potentially reversible conditions may influence the prevalence found. Also a systematic search for potentially reversible conditions in other settings, the study provides evidence that potentially reversible conditions are not rare. They were most common in younger patients and in patients with mild cognitive symptoms not sufﬁciently severe to meet international criteria for dementia. The most frequent potentially reversible conditions were depression, hydrocephalus, alcohol dependence syndrome, metabolic disorders, and space occupying lesions. Even if treatment of these conditions may not always lead to full reversal of cognition, as in our study, they may reveal a higher prevalence than retrospective studies. Thus, even though one cannot apply our ﬁndings directly to the conditions in other settings, the study provides evidence that potentially reversible conditions are not rare.

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Neuropathology of Hashimoto's encephalopathy

Doherty et al have recently reported in this journal on a case of Hashimoto's encephalopathy clinically mimicking Creutzfeldt–Jakob disease, and presented a neuropathological analysis of a brain biopsy in this case revealed spongiform change and sparse mononuclear infiltrates in perivascular spaces, the authors suggested that Hashimoto's encephalopathy is an encephalitic process. We have previously described a necropsy case of Hashimoto's encephalopathy showing lymphocytic vasculitis of veins and venules of the brain stem, supporting the hypothesis that vasculitis represents the morphological substrate of Hashimoto's encephalopathy. Doherty et al have challenged our diagnosis and stated that the term vasculitis should be reserved for lesions with inflammation and fibrinoid necrosis of arterial vessels.

Lymphocytic vasculitis is a generally accepted pathological subtype covered by reviews and standard textbooks. It is characterised by the presence of lymphocytes within the vessel wall and is encountered in Wegener's disease, systemic lupus erythematosus, and Behcet's disease, to name but a few conditions. That the diagnosis is more difficult than for necrotising arteritis does not, however, imply that lymphocytic vasculitis does not exist, and our case certainly belongs in this vasculitis category.

Additional support for the vasculitic basis of Hashimoto's encephalopathy comes from other reports on this condition where there has been ongoing diagnostic demonstration of vasculitis. More recent experimental evidence for a vasculitic pathogenesis involves the identification of α-enolase as an autoantigen of Hashimoto's encephalopathy, because anti-α-enolase antibodies are present in various autoimmune vasculitic diseases such as systemic lupus erythematosus and ANCA associated vasculitis, and because α-enolase is highly expressed in the endothelium.

Based on the histological figure and the description provided by Doherty et al, we express some reservations over the presence of the changes. True spongiform changes, usually encountered in prion diseases, are present in the neuropil between nerve cell bodies, whereas the perineurial spaces described by Doherty et al more closely resemble shrank artefacts which may be particularly pronounced in small biopsy specimens. In addition, we would like to point out that vasculitis is typically focal and may have been missed in this case.

In conclusion, we feel that the available clinical, pathological, and experimental evidence suggests that vasculitis underlies a substantial proportion of cases of Hashimoto's encephalopathy. However, additional careful necropsy studies are required to determine whether other pathological processes contribute to the clinical picture.

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References

Authors’ reply
We thank Drs Paulus and Nolte for their interest in our case report, which we offered as a lesson in the potential for a clinical picture to indicate pathology other than that expected. Consequently, the histological finding did raise the prospect of an encephalitic process in Hashimoto’s disease. However, additional careful necropsy studies are required to determine whether primary or secondary. Whether primary or secondary, the difficult judgment does require—spongiform change is easily recognised by vacuoles in the neuropil; in contrast to their contention, these are regularly accompanied by neuronal cytoplasmic change, in our case of parenchymal inflammation and fibrinoid necrosis of arterioles. The concurrence of atrophy with the spongiform appearance (no matter what the cause) in our case further lowered our threshold for submitting the tissue for definitive/prion protein studies in the clinical setting of rapidly evolving cognitive decline. We hope the correspondents would agree that such would be simply good clinical practice, especially in a patient like ours without a helpful history of Hashimoto’s thyroiditis or anti-thyroid peroxidase antibodies. As to their assertion that we “challenged” our diagnosis of vasculitis (which we point out was followed by a question mark in the title of their own report!), we felt that the previous subarachnoid haemorrhage and apparently diffuse involvement of the subarachnoid spaces that they described suggested that the venular lymphocytic infiltrates could be secondary to haemorrhage, or be a manifestation of a meningoecephalitis (possibly autoimmune) as a true primary vasculitis. According to the textbook they cite, the entities of Wegener’s disease, systemic lupus erythematosus, and Behcet’s disease, to use their examples, are all characterised primarily by true arteritis with necrosis, not by the lymphocytic venulitis which may accompany it. Drs Paulus and Nolte are correct that in our small biopsy, vasculitis may have been missed. The authors may also be correct that the pathogenesis of Hashimoto’s encephalopathy involves vasculitis. We stand firm in our position, however, that to make a histological diagnosis of vasculitis requires the exclusion of other factors, such as haemorrhage or tissue inflammation, in which lymphocytic diapedesis through venules is physiological. Moreover, the novel finding in our case of perivascular inflammation does raise the prospect of an encephalitic process in Hashimoto’s encephalopathy, independent of any effect on blood vessels, whether primary or secondary. We thank Drs Paulus and Nolte for pointing out the interesting paper by Ochi et al, and look forward to future elucidation of the role of α-enolase in Hashimoto’s encephalopathy. Perhaps those of us with tissue from cases of Hashimoto’s encephalopathy will need to collaborate in that regard, to expand their studies on serum from patients with this condition. Finally, we want to reiterate the importance of a broad differential diagnosis in evaluating patients with rapid decline in cognition, and with vasculitis, arteritis, and microglial, and pathological examination of vascular cells on brain biopsy. That was the overarching point of our paper.

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References

BOOK REVIEWS

Management of stroke: a practical guide for the prevention, evaluation and treatment of acute stroke, 2nd edition


This textbook exemplifies the recent and dramatic changes in the approach to the management of acute stroke. Whereas in the past stroke was seen as untreatable, this book sees stroke as an emergency warranting acute treatment. As the authors state in the introduction, “A positive attitude towards stroke is critical. Patients with cerebrovascular disease should be considered to have an illness that can be treated successfully.” This admirably emphasises the approach that sees stroke not as an untreatable “cerebrovascular accident” (a term that should be expunged from medical texts) but as a “brain attack,” a term the authors use to emphasise the need for rapid diagnosis and evaluation of acute suspected stroke.

Despite giving the impression of being a brief guide, almost all aspects of emergency stroke treatment are covered, starting with organisation of stroke services and proceeding to diagnosis and emergency treatment. There is also a chapter devoted to stroke prevention. The text is divided into 13 chapters, followed by a reference list and an index, which includes the tables and figures. The text is illustrated with computed tomography and magnetic resonance imaging scans and is interspersed throughout with very helpful
summary tables. Advice is clearly given and where there is controversy, the authors do not hesitate to discuss both sides of the argument. There is an emphasis on medical care during the first few days after a stroke. Rehabilitation is quite rightly introduced as an integral part of the management of patients with stroke, but not really explored, being only allocated a few paragraphs. Hence, the book is clearly not intended to be a comprehensive guide to the totality of multidisciplinary acute stroke management.

Measuring only 6 x 4 x 2 cm, this book is small enough to fit in a white coat pocket. This suggests that the book is designed to be carried around by the medical student, resident, or even the acute care nurse nowhere in the book do the authors make clear their intended audience and neither do they say whether it is intended to be a pocket sized handbook or a detailed textbook that happens to be small. Certainly the size of the book is an advantage, and the numerous tables will undoubtedly prove useful for the busy clinician or the student revising for exams. However, the lack of colour detracts from the attractiveness of the text and the binding prevents the book from opening well. It also needs a more durable cover as it will quickly become dog-eared from being frequently stuffed in and out of a pocket.

Unlike many textbooks of this type of book, the text is extensively referenced, with 688 separate references, reflecting the large evidence base behind the current rational treatment of stroke. This has the disadvantage that references occur nearly every sentence tend to interrupt the flow of text, giving the impression that one is reading a list of facts. If the text is really meant to be used to guide treatment, rather than to be read at leisure to gain understanding of the topic, perhaps a recommended reading list of a few key articles at the end of each chapter might be more useful.

The text is clearly orientated towards the North American market. For example, it is assumed that suitable patients will be treated with intravenous tissue plasminogen activator (tPA). This has not yet been licensed in most other parts of the world, but the algorithm detailing the assessment of patients with thrombolysis will prove useful elsewhere when tPA eventually receives a license outside North America. The text does deal with many other acute approaches to treatment that can be adopted without embracing thrombolysis, for example the treatment of metabolic disturbances and raised intracranial pressure. Another difficulty is that the use of some North American terms may grate slightly with those more used to the British equivalent: for example, ‘emergent’ rather than ‘emergency’ is used throughout. Many North American terms such as emergency department are written in full only once, then used abbreviated (ED) throughout the book. A list of the many abbreviations would help with this problem.

In conclusion, this is a useful book on acute stroke management, which will appeal especially to the North American market. The next edition will hopefully be more user-friendly with a better layout, improved binding, and som e colour.

Z E Brown, M M Brown

Diseases of the nervous system: clinical neuroscience and therapeutic principles


The third edition of this well known book is subtitled Clinical neuroscience and therapeutic principles. This signifies that it is not a textbook of clinical practice, but a reference book founded on pathophysiology. So how well does it succeed? With 221 authors writing 129 chapters some unevenness is inevitable. It is a tribute to the editors’ tight grip that the overall coverage of neurological disease is suitably comprehensive.

I particularly liked the introductory section which highlights contemporary trends in understanding neurological disease processes, the principles of restoring function after damage, and “windows on a working brain”. This is the section of the book that I chose to read for pleasure, simply for a succinct and thoughtful view as to where neurology is going outside our own specialty. And throughout the book, there is excellent coverage of background issues ranging from the chemical bases of addiction and alcoholism, to host responses to infection, to pathophysiology of cerebral circulation, to the cellular basis of epilepsy, and to repeat trinucleotide expansions.

Inevitably one can take issue with aspects of subject matter coverage, particularly in their treatment with antipsychotic drugs. The author argues that this new book is justified by the rapidly expanding knowledge base of psychopharmacology for psychosis and schizophrenia.

This book has the same qualities as its big brother. The simple and beautifully conceived graphs make the book highly readable while conveying information that is at the cutting edge of contemporary neuroscience. The latest theories of mechanisms of “atypicality” are presented, including Kapur’s rapid dissociation theory, as are the modes of action of the new generation of so-called dopamine system stabilisers, exemplified by aripiprazole. Given that the latter has not yet been launched in the UK, this volume can be expected to be ahead of the field. There is less new information on mood stabilisers, although some extended discussion of the use of atypical antipsychotics in mood disorders.

Those who already have a copy of Essential pharmacology may be tempted to upgrade. New readers may be drawn to a thin, attractively presented volume. However, some concern must be expressed at the practice of releasing new material in this way. This book is not cheap for its size and the third edition of Essential pharmacology cannot be far behind.

J Hollyman

Essential pharmacology of antipsychotics and mood stabilizers


This short book is an update of the two chapters from the second edition of Stahl’s larger textbook Essential pharmacology that deal exclusively with psychosis and schizophrenia and their treatment with antipsychotic drugs. The author argues that this new book is justified by the rapidly expanding knowledge base of psychopharmacology for psychosis and schizophrenia.

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C Bench

Essential pharmacology