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Paraneoplastic limbic encephalitis associated with potassium channel antibodies: value of anti-glial nuclear antibodies in identifying the tumour

Limbic encephalitis is characterised by subacute development of short-term memory loss, seizures, confusion and psychiatric features.¹ Paraneoplastic limbic encephalitis is generally associated with small cell lung cancer (SCLC), and around 50% of patients harbour Hu, CV2/CRMP5 or amphiphysin antibodies.¹ Recently, antibodies against voltage-gated potassium channels (VGKC-abs) were identified as a new marker of a non-paraneoplastic, immunotherapy-responsive form of limbic encephalitis.^{2,3} However, the presence of VGKC-ab does not exclude a paraneoplastic cause of limbic encephalitis.¹

We described previously a new antibody called anti-glial nuclear antibody (AGNA), a marker of SCLC shown to be closely associated with paraneoplastic Lambert–Eaton myasthenic syndrome (LEMS).⁴ Here we report on two patients with paraneoplastic limbic encephalitis associated with SCLC and VGKC-ab who also presented AGNA.

Methods

The presence of AGNA was assessed by immunohistochemistry on frozen sections of paraformaldehyde-fixed rat cerebellum in nine patients with limbic encephalitis and SCLC with (n = 2) or without (n = 7) VGKC-ab, and in seven patients with non-paraneoplastic limbic encephalitis and VGKC-ab. To confirm AGNA reactivity, an immunohistochemical competition assay was performed as described previously.⁴ VGKC-abs were detected by radio-immunoprecipitation (cutoff value: 100 pmol/l).²

Case reports

A middle-aged man was admitted to hospital with a 2-week history of behavioural changes and generalised seizures. A neurological examination showed short-term memory loss, confusion and aphasia. Electroencephalography showed slowing in the left temporal lobe. Magnetic resonance imaging (MRI) of the brain showed a hyperintense signal affecting the temporal lobes on T2-weighted images. Examination of the cerebrospinal fluid showed pleocytosis (20 lymphocytes/μl). A chest x ray showed a lung mass. Histological diagnosis of SCLC was made after biopsy of an enlarged groin adenopathy. The patient was treated with valproic acid, pulses of intravenous steroids and chemotherapy, with good control of seizures and remission of the behavioural

problems and aphasia. After 6 months, in the setting of cancer progression, the patient had a relapse of limbic encephalitis (complex partial seizures and agitated behaviour) confirmed by a brain MRI. The patient was treated with repeated pulses of intravenous steroids, with good control of seizures and improvement of the agitation. He died 5 months later from cancer progression.

A middle-aged woman was admitted to hospital with a 2-month history of confusion, memory impairment and seizures. Neurological examination showed moderate short-term memory loss, mild confusion and abulia. Laboratory analysis showed hyponatraemia (118 mEq/l). Chest x ray showed a mediastinal mass confirmed by a computed tomography scan. Electroencephalography disclosed generalised slowing and epileptic activity in both temporal lobes. Cerebrospinal fluid examination and brain MRI were negative. A diagnosis of SCLC was made by transbronchial biopsy of the mediastinal lesion. Seizures did not disappear despite sodium level normalisation and treatment with multiple epilepsy drugs. Eventually the patient evolved to status epilepticus requiring intensive care and induction of barbituric coma. She died several months later from bronchopneumonia.

In both patients, the search for antineuronal antibodies (Hu, Yo, Ri, Ma1 and 2, CV2/CRMP-5, Tr, GAD, and amphiphysin) was negative. VGKC-ab levels were 170 and 220 pmol/l. On immunohistochemistry, serum from both patients showed intense labelling of the nuclei of Bergmann glia in the Purkinje cell layer of the cerebellum (fig 1). The presence of AGNA in our patients' sera was confirmed by the immunocompetition assay.

AGNA immunoreactivity was not detected in the serum of seven patients with limbic encephalitis and SCLC without VGKC-ab and seven patients with non-paraneoplastic limbic encephalitis and VGKC-ab.

Discussion

The diagnosis of classical limbic encephalitis is made in the setting of subacute onset of short-term memory loss, seizures and behavioural changes, imaging or pathological evidence of involvement of the limbic system, and exclusion of other potentially confusing diagnoses.¹ Patient 1 fulfilled the criteria for classic limbic encephalitis of definite paraneoplastic origin.¹ The clinical syndrome of patient 2 was initially attributed to a severe hyponatraemia, a common finding in limbic encephalitis associated

with VGKC-ab.^{2,3} However, when the sodium level was normalised, the clinical syndrome did not improve and the brain MRI ruled out permanent hyponatraemia-related brain damage. A normal MRI does not rule out the possibility of limbic encephalitis. Normal brain MRI, including fluid-attenuated inversion-recovery and diffusion-weighted imaging, may repeatedly be seen in patients with autopsy-proved paraneoplastic limbic encephalitis (F Graus, unpublished data).

The clinical significance of the VGKC-ab levels in our patients is not clear. Some authors consider the cut-off value in the diagnosis of VGKC-ab-associated limbic encephalitis to be 400 pmol/l,² but reports of patients with epilepsy and encephalopathy with lower titres⁵ suggest that the clinical relevance of VGKC-ab titres has to be better defined.

Our patients' sera presented AGNA defined by robust immunoreactivity with the nuclei of Bergmann glia, an astrocyte population localised in the cerebellar cortex around the Purkinje cells.⁴ We identified AGNA as a marker of SCLC rather than paraneoplastic neurological syndromes. However, we observed a tight association between AGNA and voltage-gated calcium channel antibodies in the setting of SCLC. We found that among 35 patients with SCLC and voltage-gated calcium channel antibodies (LEMS 30, paraneoplastic cerebellar degeneration 5), 18 (51%) had AGNA whereas this antibody was not detected in a series of 19 patients with non-paraneoplastic LEMS, nor in 100 of 113 patients without paraneoplastic neurological disorders and SCLC.⁴

In this study, we found AGNA in two patients with limbic encephalitis, SCLC and VGKC-ab. No AGNA reactivity was found in patients with limbic encephalitis, SCLC without VGKC-ab, or in those with non-paraneoplastic limbic encephalitis and high titres of VGKC-ab. The characteristic immunoreactivity of AGNA was not reported in any patient from the two series of patients with VGKC-associated non-paraneoplastic limbic encephalitis,^{2,3} although both were published before our description of AGNA. These data suggest that, in the setting of SCLC, the immune mechanisms that trigger AGNA are closely associated with those responsible for the generation of antibodies against neuronal membrane channels.

In conclusion, in patients with a clinical diagnosis of limbic encephalitis and positive VGKC antibodies, irrespective of the titre, the presence of AGNA should be evaluated because its detection must prompt the search for lung cancer. Future studies will confirm the association between AGNA and channel antibodies in patients with paraneoplastic neurological syndromes.

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Figure 1 Frozen section of paraformaldehyde-fixed rat cerebellum immunoreacted with the serum of patient 1. There is intense labelling of the nuclei of Bergmann glia in the Purkinje cell layer typical of anti-glial nuclear antibody. Magnification $\times 200$.

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BOOK REVIEWS

The whole picture of dementia: seeing the elephant in the room

Edited by Julian C Hughes, Stephen J Louw, Steven R Sabat. Published by Oxford University Press, Oxford, 2005, £75.00 (soft cover), pp 302. ISBN 0-19-856614-X

There's an old story about three blind men who encounter an elephant in a field. Each man touches a different part of the creature—its side, its tusks and its trunk—and misidentifies the elephant. This truncated version of a classic parable reminds us that we often fail to create the time in our own lives (and in our professional journals) to share the stories that remove our own intellectual blindness and view our world in its full complexity.

In *Dementia: mind, meaning, and the person*,¹ we are reminded that western medicine, which dissects the universe into smaller, more easily studied parts, is often guilty of the myopia of the three blind men; when considering patients with dementia in our care, rarely do we see the whole elephant in the room. Biological reductionism can provide some relief from disease,

but as Michael Bavidge writes in chapter 2, "The shape of a human life ... is not purely biological matter" (p 42). By ignoring the totality of the human illness experience, western medicine often fails to treat the entire person. As the editors argue, "What is required is whole sight. People should be treated as wholes, with attention not only to their biology, but also to their psychology, their social and ethical concerns, and the cultural and spiritual aspects of their lives" (p 4).

Dementia is a process that raises crucial questions about our attitudes to illness, ageing and even personhood itself. This erudite volume explores those questions in great depth, laying out not only a theoretical framework for comprehending the changes wrought by ageing of the brain but also an ethical framework that reminds us to respect the lives of the deeply forgetful and not to allow our moral understanding to flag as the patients undergo a slow metamorphosis.

Readers will also find helpful practical guidance in the volume. Strong emphasis is placed on the merits of narrative medicine as a method that can be used to create multi-dimensional models of health and illness while simultaneously remembering the individual. Indeed, in Cleveland, we are launching StoryBank—a community digital multimedia repository of patient narratives (memes) of illness that will be processed in parallel with tissues and extracted DNA (genes) in our BioBank—which is predicated on the same principles enumerated in this volume. The book teaches that, even from a purely biological perspective, genes must be viewed as evolving structures that interact with environment over time. Hence, our call for holism in dementia scholarship is one echoed in the book: an integrative–evolutionary–narrative medicine that appreciates how genes and memes interact in social and natural environments throughout history to create the individual and collective stories of age-associated cognitive challenges. The book also emboldens us to consider profound paradigm shifts in our understanding and attitude towards dementia. Perhaps we should abandon the concept of Alzheimer's disease: a stigmatising and arguably clinically misleading label that reduces an ageing person's story to a purely scientific framework. This year, the 100th anniversary of the first case report on Alzheimer's disease, offers us a chance to reflect deeply on the eponym and imagine richer stories of ageing of the brain than the quest for magic bullets and neurological immortality.

From the book, we took the lesson that today's healers must widen their perception to include the "elephant in the room" rather than view patients as having degenerating brains. George Lakoff *et al*² have suggested in their book *Don't think of an elephant* that partisan political discourse should be reframed conceptually and linguistically; here, we agree with the authors of this fine volume that our discourse about dementia must think of the whole elephant.

Peter Whitehouse, Danny George, Sylvia Krinsky

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The Clinical Neuropsychiatry of Stroke, 2nd edn

Edited by Robert G Robinson. Published by Cambridge University Press, Cambridge, 2006, £85.00, pp 453. ISBN 0-521-84007-4

The Clinical neuropsychiatry of stroke is the most comprehensive textbook ever published on the neuropsychiatric complications of stroke. The practical relevance of the information included in this text is illustrated by the finding that depression is one of the strongest predictors of disability and mortality after stroke, whereas anosognosia is a strong predictor of poor improvement after rehabilitation. This second edition was published 8 years after the first, and the amount of new information included makes it almost a different book.

To name just a few of the new additions, there is a thorough discussion on the problems of diagnosing depression in patients with stroke, a new section on transcranial magnetic stimulation treatment, and a new chapter on the pharmacological prevention of post-stroke depression. The book also includes a number of empirical studies carried out by Professor Robinson's research team, which have not yet been published. Among other interesting studies, there is an analysis on the specificity and sensitivity of psychological and autonomic symptoms of depression in a large series of patients with stroke, a comparison of inclusive versus substitutive approaches to diagnose depression in stroke, a new study on the association between depression, cognitive deficits and response to antidepressant treatment, a comparison of cognitive deficits in early versus late-onset post-stroke depression, and the results of a pharmacological treatment study of anosognosia after stroke.

The discussion on the phenomenology, prevalence, assessment, course, clinical and biological correlates, outcome and treatment of depression after stroke covers about half of the book. The remaining half provides a detailed description of other neuropsychiatric conditions of stroke, such as mania, anxiety disorders, psychosis, anosognosia, catastrophic reaction, apathy, aprosody, irritability and aggression, and emotional lability. Being a single-authored book, there are virtually no overlaps between chapters. The case vignettes are very illustrative and the many figures helpful.

In conclusion, Professor Robinson has written the most comprehensive and didactic textbook on the neuropsychiatric disorders of stroke. This book is not only a necessary lecture for anybody involved in clinical care and research in stroke, but sets a standard on how to write textbooks on neuropsychiatric disorders for other neurological disorders as well.

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CORRECTION

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I Kleffner, E B Ringelstein, P Young, *et al*. Susac's syndrome: effective combination of immunosuppression and antiplatelet treatment (*J Neurol Neurosurg Psychiatry* 2006;**77**:1335). The last author of this article is P Young and not T-U Niederstadt as published. The correct author list is therefore: I Kleffner, E B Ringelstein, N Stupp, T-U Niederstadt, P Young. We apologise for this error.