the authors lent further support to their hypothesis by showing that the depicted anatomical region was also affected in published cases of either RBD or symptomatic narcolepsy due to circumscribed brain stem lesions.

Future research, of course, has to establish the presumed connection of narcolepsy and RBD in larger collectives of patients. Methodologically, such studies may apply advanced neuroimaging techniques, such as voxel-based morphometry and diffusion tensor imaging, which have recently been introduced for structural evaluation of the brain in neurological disorders. It might be interesting to compare groups of narcoleptics with and without RBD with regard to the integrity of fibre tracts involved in the generation of muscle atonia—that is, those originating from the pontine tegmentum and descending via the medial medulla to motor neurones.⁴

Looking at the topic in question from a different angle, one may choose to study patients with Parkinson's disease, multiple system atrophy and dementia with Lewy bodies. All these synucleinopathies are known to be associated with RBD, with one third of patients with Parkinson's disease and about 80% of patients with multiple system atrophy and dementia with Lewy bodies being

affected.^{5–7} Interestingly, apart from excessive daytime sleepiness, sleep episodes and hypnagogic hallucinations, sleep-onset REM periods on the Multiple Sleep Latency Test have repeatedly been described in the neurodegenerative disorders mentioned, which were especially prevalent in patients with concomitant RBD.⁸ The remarkable association of these features, especially the finding of multiple sleep-onset REM periods, is reminiscent of primary narcolepsy, and helped in coining the term “narcolepsy-like phenotype”.⁸ In the future, using voxel-based morphometry and diffusion tensor imaging, we could compare well-characterised groups of patients with and without RBD, with and without a narcolepsy-like phenotype, and with a combination of both. Although changes in different brain regions are to be expected because of the multifocal pathophysiology of the synucleinopathies, it may be speculated that fibre tracts and neurone populations located in the suggested “common pathway for narcolepsy and RBD” are exclusively affected in patients showing both syndromes.

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REFERENCES

- 1 Schenck CH, Mahowald MW. Motor dyscontrol in narcolepsy: rapid-eye-movement (REM) sleep without atonia and REM sleep behavior disorder. *Ann Neurol* 1992;**32**:3–10.
- 2 Nightingale S, Orgill JC, Ebrahim IO, et al. The association between narcolepsy and REM behaviour disorder (RBD). *Sleep Med* 2005;**6**:253–8.
- 3 Mathis J, Bassetti C, Hess CW. Isolated mediotegmental lesion causing narcolepsy and REM sleep behaviour disorder (RBD). A case evidencing a common pathway in narcolepsy and RBD. *J Neurol Neurosurg Psychiatry* 2007;**78**:427–9.
- 4 Baumann CR, Bassetti C. Hypocretins (orexins) and sleep-wake disorders. *Lancet Neurol* 2005;**4**:673–82.
- 5 Gagnon JF, Bédard MA, Fantini ML, et al. REM sleep behavior disorder and REM sleep without atonia in Parkinson's disease. *Neurology* 2002;**59**:585–9.
- 6 Plazzi G, Corsini R, Provini F, et al. REM sleep behavior disorders in multiple system atrophy. *Neurology* 1997;**48**:1094–7.
- 7 Boeve BF, Silber JH, Ferman TJ, et al. REM sleep behavior disorder and degenerative dementia. *Neurology* 1998;**51**:363–70.
- 8 Arnulf I. Excessive daytime sleepiness in parkinsonism. *Sleep Med Rev* 2005;**9**:185–200.

Limbic encephalitis

Limbic encephalitis: extension of the diagnostic armamentarium

Christian G Bien

Diagnostic spectrum of limbic encephalitis

The highly specific tests for anti-Hu, anti-Ma, anti-amphiphysin and anti-CV2/CRMP5 antibodies have been an important tool in the diagnosis of paraneoplastic limbic encephalitis (PLE).¹ The testing procedure for these antibodies is two tiered. Firstly, patients' sera are incubated with brain slices from a paraformaldehyde-perfused animal (usually rat or monkey). Specific binding patterns to brain cells allow the identification of the above-named “well-characterised” antibodies. After this immunohistochemical test, a confirmatory blotting test is performed on the brain homogenate (in comparison with a

positive control) or on the suspected antigen as recombinant protein. For both techniques, testing of serum is more sensitive than testing of cerebrospinal fluid (CSF). The antibodies detected in this way react with intracellular antigens. They portend a poor outcome. A relevant limitation, however, is that 40% of patients with PLE do not harbour any of these antibodies.¹

The diagnostic spectrum of limbic encephalitis was considerably broadened by the detection of antibodies against voltage-gated potassium channels in association with (usually) non-paraneoplastic limbic encephalitis (NPLE). These

antibodies are diagnosed in serum by radioimmunoprecipitation. On standard immunohistochemical analysis, strongly positive sera stain the molecular layer of rat cerebellum. The prognosis of affected patients is good with consequent immunotherapy.²

In the paper by Bataller *et al* (see p 381),³ the Philadelphia group summarises its most recent experience on autoantibody testing in cases with the clinical syndrome of limbic encephalitis. They report on several patients with PLE found to harbour in their sera and CSF novel antibodies reacting with rat brain neuropil in the molecular layers of the hippocampus and cerebellum on immunohistochemical analysis. Importantly, this reactivity could be picked up only if slices were prepared from a brain that had not been perfused but instead had been immersed in paraformaldehyde for several days. The staining pattern was more easily detected with CSF than with serum. The antigens recognised by these antibodies have not yet been determined, and no consistent banding pattern on western blotting has been identified. Most patients had ovarian teratomata or thymic tumours. They had a mostly

favourable outcome after tumour treatment and immunotherapy.

These data on patients harbouring antibodies against cellular membrane structures (ie, voltage-gated potassium channel antibodies and the newly discovered "neuropil antibodies") introduce a new borderline into the subclassification of patients with limbic encephalitis. In addition to PLE and NPLE, cases of limbic encephalitis can now be subdivided into poorly and favourably treatable cases. Clinicians will increasingly ask for this novel testing procedure. Future experience alone will show how well it will be to transfer this method as routine practice in other laboratories, especially as no confirmatory test is yet available. Replication studies on the neuropil antibodies will therefore be very welcome.

The neurologist will still make the tentative diagnosis of limbic encephalitis if an adult patient newly develops limbic symptoms and shows an otherwise unexplained mediotemporal magnetic resonance imaging-T2/fluid-attenuated

inversion recovery hyperintensity⁴ or fluorine-18 fluorodeoxyglucose positron emission tomography hypermetabolism. In this situation, a tumour search considering the risk factors of the individual patient is mandatory. Ideally, comprehensive antibody testing is performed in a specialised laboratory. If a tumour is found, it should be treated immediately. Thereafter (and in all tumour-negative cases immediately), immunotherapy should be introduced. In antibody-positive cases, additional investigation for tumours often associated with this particular antibody may become necessary, and the treatment prognosis can be better pre-estimated.

Hopefully, diagnostic tools, prognostic data and treatment options will become available for the still insufficiently characterised group of (so far) "antibody negative" cases with NPLE⁵ (which also stands out in Bataller's paper). Future studies may add to the diagnostic armamentarium for these cases, as has been achieved by the present work for the PLE subgroup.

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REFERENCES

- 1 Gultekin SH, Rosenfeld MR, Voltz R, *et al.* Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. *Brain* 2000;**123**:1481–94.
- 2 Vincent A, Buckley C, Schott JM, *et al.* Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain* 2004;**127**:701–12.
- 3 Bataller L, Kleopa KA, Wu GF, *et al.* Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry* 2007;**78**:381–5.
- 4 Urbach H, Soeder BM, Jeub M, *et al.* Serial MRI of limbic encephalitis. *Neuroradiology* 2006;**48**:380–6.
- 5 Bien CG, Schulze-Bonhage A, Deckert M, *et al.* Limbic encephalitis not associated with neoplasm as a cause of temporal lobe epilepsy. *Neurology* 2000;**55**:1823–8.