prominent retinal myelinated fibers in Japan. *Mov Disord* 2005;20:380–2.

- 5 Shimazaki H, Takiyama Y, Sakoe K, et al. A phenotype without spasticity in sarsin-related ataxia. *Neurology* 2005;64:2129–31.

Qualitative evidence of anti-Ri specific intrathecal antibody synthesis and quantification of anti-Ri antibodies in serial samples from a patient with anti-Ri syndrome

Anti-Ri associated paraneoplastic neurological syndrome was initially described in patients suffering from breast or lung malignancy and presenting with opsoclonus, myoclonus, and ataxia.¹ Since anti-Ri antibodies have been reported to react both with central neuronal cells and with tumour tissue of patients with anti-Ri antibodies and breast cancer,¹ they are believed to reflect an autoimmune process.

Case report

Ten years after treatment for breast cancer, a 66 year old woman presented with complete horizontal gaze palsy to the right, jaw opening and neck dystonia, and slight ataxia of the upper extremities. No opsoclonus or myoclonus was observed. Four months previously a relapsing tumour in the lymph nodes of the right axilla had been treated with extirpation and radiotherapy; afterwards the patient was discharged on tamoxifen. MRI of the brain was normal. CSF cell count and protein were normal and no malignant cells were observed. Increased IgG index (1.1) indicated intrathecal antibody synthesis. Anti-Ri serum antibodies were detected by immunoblot with recombinant Ri protein. Apart from the gaze palsy, the patient improved after high dose treatment with methylprednisolone for 3 weeks. However, despite concurrent immunosuppressive treatment with cortisone and azathioprine, the patient developed truncal instability, slight appendicular ataxia, cervical dystonia, and severe tetraspasticity and became wheelchair bound. MRI of the cervical myelon revealed signs suggestive of myelopathy. Repeated, extensive searches found no hint of tumour relapse. Therapy with cyclophosphamide (700 mg/m² with a 6 week gap between courses) resulted in improvement of symptoms. The patient is able to walk some steps with help and jaw opening dystonia has also improved, but the gaze palsy is unchanged.

Isoelectric focusing and affinity blotting were performed as previously described.² Briefly, serum and CSF pairs were adjusted to equal IgG concentrations of 20 mg/l. Furthermore, we applied the patient's serum in serial concentrations of total IgG of 40–2560 mg/l. Focused antibodies were blotted onto nitrocellulose membranes which had been previously loaded (50 µg/10 cm²) with recombinant Ri antigen (constructed by standard methods³ in a baculovirus expression system). Bound antibodies were detected with peroxidase conjugated goat anti-human IgG (Dianova, Hamburg, Germany) diluted 1:1000. As controls, six CSF/serum pairs from patients with paraneoplastic neurological syndromes (PNS) other than anti-Ri syndrome and intrathecal synthesis of total IgG were investigated (anti-CV2 syndrome, anti-Hu syndrome, and anti-Yo syndrome).

ELISA detection of anti-Ri IgG serum antibodies was performed by standard methods described elsewhere.⁴ Briefly, plates were coated with recombinant Ri antigen (20 µg/ml) and incubated with the patient's sera, diluted 1:1600. Bound anti-Ri IgG antibodies were detected by peroxidase conjugated goat anti-human IgG antibodies (Dianova), diluted 1:5000. Sera of 31 patients with neurological symptoms not compatible with PNS were investigated as controls.

Discussion

Detection of oligoclonal bands of total IgG exclusively in CSF and not in the corresponding serum is taken to indicate an intrathecal inflammatory process. In previous studies we provided qualitative evidence of anti-HuD and anti-Yo specific intrathecal antibody synthesis by demonstrating specific oligoclonal bands in CSF.² Using this approach, we now investigated a serum/CSF pair from a patient with an atypical anti-Ri syndrome. We found anti-Ri specific oligoclonal bands exclusively in CSF (fig 1B) but not in the corresponding equilibrated serum of the patient with Ri-syndrome. Weaker and less frequent oligoclonal bands were detected in the patient's serum with higher concentrations of total IgG (160–2560 mg/l).

We observed clear negative results in control serum/CSF pairs of six patients suffering from clinically and serologically unambiguous non-Ri paraneoplastic neurological syndromes, confirming the high specificity of the affinity blot. In a previous study,³ a disproportionately high concentration of anti-Ri antibodies in the CSF compared to serum in most patients was revealed by semi-quantitative methods. These authors suggested intrathecal production of paraneoplastic neuronal autoantibodies as

the most likely explanation for the elevated CSF/serum ratios. In our present study, we confirm this assumption of intrathecal anti-Ri specific autoantibody synthesis with qualitative data. Using ELISA, the CSF specific anti-Ri index was 5.6, strongly indicating intrathecal anti-Ri specific antibody synthesis by a semi-quantitative method and confirming our qualitative results. In conclusion, these data provide further evidence that anti-Ri specific antibodies are produced by B cell clones in the central nervous system.

Usually the term opsoclonus-myoclonus syndrome (OMS) is used to describe a paraneoplastic syndrome associated with anti-Ri antibodies.¹ Opsoclonus and myoclonus were never observed in our patient. Other studies on larger groups of anti-Ri patients described a wide spectrum of multifocal disorders; Pittcock¹ reported on four patients with jaw opening dystonia, as seen in the patient featured in this report. These widespread clinical findings reflect the broad distribution of the Ri antigen in the central nervous system.³

In the present study, quantification of circulating anti-Ri antibodies over a period of 28 months with ELISA revealed a clear decrease, together with improvement in paraneoplastic neurological symptoms during treatment with cortisone and azathioprine (fig 1A). Later deterioration due to myelopathy was not reflected by an increase in anti-Ri antibody titre, possibly due to immediate immunosuppressive therapy with cyclophosphamide. These data are in rough agreement with previous findings describing a correlation between the concentration of anti-Hu antibodies and improvement in paraneoplastic neurological symptoms.⁴ Unfortunately, no serum sample from the time before the onset of neurological symptoms was available. The decline in Ri-specific antibody levels as well as the clinical

Figure 1 (A) Decrease in anti-Ri antibody concentration in serial serum samples (dilution 1:1600), spanning an observation period of 28 months from diagnosis of anti-Ri syndrome to the end of immunosuppressive treatment. Antibody concentration is shown as optical density (OD) in ELISA employing recombinant Ri protein as antigen. Line indicates average OD of controls (31 non anti-Ri patients). (B) Results of affinity blotting after isoelectric focusing of CSF/serum pair (total IgG: 20 mg/l) demonstrating anti-Ri specific oligoclonal bands exclusively in CSF but not in the patient's serum. A blot of the patient's serum with a concentration of total IgG of 640 mg/l revealed only weak and less frequent oligoclonal bands. CSF, cerebrospinal fluid; S, serum; pH range: bottom pH 10, top pH 3.

improvement could be also related to effective treatment of the tumour and eradication of the antigenic stimulus. Nevertheless, neoplasm treatment and immunosuppressive therapy could be a way to improve neurological symptoms in anti-Ri associated syndrome.

In conclusion, this is the first qualitative evidence of intrathecal anti-Ri specific antibody synthesis. Together with the positive correlation between the decrease in anti-Ri antibodies and immunosuppressive treatment, these results further support the hypothesis of autoimmunity in the pathogenesis of anti-Ri antibody associated neurological symptoms. In addition to ocular abnormalities and cerebellar ataxia, dystonic disorders such as jaw opening dystonia and cervical dystonia, should focus the clinician's attention on a possible underlying anti-Ri syndrome, even when a malignancy dates back several years.

Acknowledgements

We are indebted to Christiane Rasiah for providing the recombinant Ri protein and Caecilia Peschel for her excellent technical assistance.

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Patient consent was obtained for the publication of these details

doi: 10.1136/jnnp.2005.062489

Competing interests: none declared

References

- 1 Pittock SJ, Lucchinetti CF, Lennon VA. Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. *Ann Neurol* 2003;53(5):580-7.
- 2 Stich O, Graus F, Rasiah C, et al. Qualitative evidence of anti-Yo-specific intrathecal antibody synthesis in patients with paraneoplastic cerebellar degeneration. *J Neuroimmunol* 2003;141(1-2):165-9.
- 3 Buckanovich RJ, Posner JB, Darnell RB. Nova, the paraneoplastic Ri antigen, is homologous to an RNA-binding protein and is specifically expressed in the developing motor system. *Neuron* 1993;11(4):657-72.
- 4 Rauer S, Czygan M, Kaiser R. Quantification of circulating anti-Hu antibody in serial samples from patients with paraneoplastic neurological syndromes: possible correlation of antibody concentration and course of neurological symptoms. *J Neurol* 2002;249(3):285-9.
- 5 Dropcho EJ, Kline LB, Riser J. Antineuronal (anti-Ri) antibodies in a patient with steroid-responsive opsoclonus-myoclonus. *Neurology* 1993;43(1):207-11.

Parkinsonism and dementia due to gliomatosis cerebri mimicking sporadic Creutzfeldt-Jakob disease (CJD)

We describe a patient presenting with the clinical phenotype of sporadic CJD and very extensive brain abnormalities on MRI. The final diagnosis was gliomatosis cerebri (GC) and was only proven after a second cerebral biopsy.

A 55 year old female accounts clerk presented in March 2004 with a history of approximately 6 weeks of memory disturbance. She had trouble recalling her children's birthdays and recent conversations, and performing familiar tasks at work. Her husband also noted some change to her personality, in that she was more gregarious and less cautious than usual. This was in addition to a background of several months' sleepiness where she would sleep soundly overnight and also require a sleep regularly during the day. There had been no alteration to her weight or appetite during this time. Just prior to initial review she experienced two unexplained episodes of urinary incontinence. Headache was never a feature.

Her medical history was only remarkable for hypothyroidism, treated with thyroxine replacement, and there was no relevant family history.

Physical examination revealed extrapyramidal features with hypomimia and a monotonous hypophonic voice. Her gait demonstrated mild bilateral (asymmetric) reduction in arm swing. Ocular movements were normal. She displayed mild bilateral bradykinesia, but there was no axial or limb rigidity or tremor. Power, co-ordination, reflex examination including plantar responses, and sensation were all normal. She was distractible, had difficulty sequencing tasks, and demonstrated concrete interpretation of common proverbs. In addition, stimulus sensitive myoclonic jerks of both upper limbs were noted. There was no pathological startle response. Her Folstein minimal state examination score was 26/30 with one error in orientation and calculation and two errors in recall. However, the frontal assessment battery score was markedly impaired with a score of 8/18. A formal neuropsychological assessment was undertaken confirming severe memory impairment (immediate and delayed story recall scores in the 2nd centile), attention difficulties (digit span memory score in the 9th centile), and evidence of frontal lobe dysfunction (semantic and phonemic fluency scores in the 1st centile). General physical examination was normal, in particular there was no lymphadenopathy or organomegaly, and breast examination was normal.

Baseline biochemistry, haematology, and inflammatory markers were normal. Voltage gated potassium channel antibodies and anti-neuronal (Yo, Hu, Ri) antibodies were not detected. Copper studies and blood lactate were normal. Chest x ray was normal. An EEG demonstrated an excess of intermittent delta activity over both hemispheres, but with a retained normal background post-central alpha rhythm at 9-10 Hz. Neither epileptiform features nor periodic complexes were identified.

Brain MRI demonstrated striking, relatively symmetrical abnormalities affecting predominantly grey matter structures (fig 1). The most prominent feature was symmetrical bilateral basal ganglionic and thalamic enlargement with signal alteration (fig 1, arrows). These structures demonstrated increased signal on T2 weighted images and decreased signal on T1 weighted images with no enhancement following intravenous gadolinium administration. Remarkable sparing of the adjacent white matter tracts, for example, the internal capsules and anterior commissure, was seen. The hippocampi were also affected with the right being more dramatically enlarged. The only infratentorial involvement was in the tectum of the midbrain and a small area of the dorsal medulla oblongata. In view of the extensive

Figure 1 Axial T2 weighted MR images demonstrate relatively symmetrical abnormality of the thalami (long arrow), lentiform nuclei (short arrow), and heads of the caudate nuclei (arrow head). There is enlargement of the involved structures and markedly increased T2 signal.

imaging abnormalities with focal swelling supratentorially, it was felt that a cerebral biopsy was the most useful investigation to help obtain a formal diagnosis despite the need to quarantine the surgical instruments afterwards. CSF examination, including an assay for the 14-3-3 protein, was considered but not undertaken in view of concerns with the focal areas of swelling.

In view of the clinical presentation coupled with the imaging abnormalities (although extensive), sporadic CJD was considered. A limited right temporal biopsy was undertaken to assess for the presence of prion related and other pathologies. Tissue was examined locally and sent to the regional CJD surveillance unit. No evidence of prion disease was found on histopathologic or western immunoblot examination. Unfortunately, the rest of the tissue did not provide a specific pathological diagnosis on this limited biopsy.

The patient's state fluctuated considerably, but overall a progression was evident with deepening difficulty in memory and planning. Complex partial seizures consisting of speech, behavioural arrest, and automatism were witnessed. These attacks were controlled well initially with sodium valproate. Due to the continued deterioration, a craniotomy and right temporal lobe excision biopsy were undertaken. The biopsy appearances were consistent with a diffusely infiltrating intrinsic neoplasm composed of glial cells (astrocytes). The pattern of involvement was that of a diffusely infiltrating glioma most consistent with WHO grade II. Together with the MRI evidence of involvement of more than two cerebral lobes, this was diagnostic of GC.

The patient was discharged following the second biopsy procedure without complication. At this time, although remaining ambulant, she required significant prompting and help from her husband in tasks of daily living. However, within several weeks her seizures became difficult to control and she became increasingly somnolent. Radiotherapy planning had commenced but after a prolonged seizure she recovered poorly and was admitted to the