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Lateral medullary syndrome with anti-neuronal antibodies (anti-Ta/Ma2) in primary Sjögren’s syndrome

Sir, A 61-year-old Irish female with known primary SS, presented to the emergency department with a 3-h history of sudden-onset vertigo, vomiting, diplopia, ataxia and hemi-facial sensory loss. She had a long-standing history of polyarthralgia and sicca symptoms with a hypergammaglobulinaemia (IgG 25 g/l) and positive ANA, anti-Ro and anti-La antibodies and therefore met the diagnostic criteria for SS. Six months earlier she had an acute psychotic episode secondary to cerebral vasculitis with cerebrospinal fluid (CSF) oligoclonal bands and three small hyperintense foci in the frontal lobe on MRI of the brain. Past medical history included Grave’s disease, immune thrombocytopenic purpura and coeliac disease. She admitted to poor compliance with prescribed HCQ (400 mg daily), mycophenolate mofetil (MMF) (500 mg twice daily), prednisolone (5 mg daily) and olanzepine (2.5 mg daily). On examination, she was alert and orientated. There was sensory loss to all modalities on the left side of her face and right leg, left-sided cerebellar signs (nystagmus, dysmetria, dysdiadokokinesis and truncal ataxia) and a left Horner’s syndrome, consistent with a left lateral medullary syndrome.

Haematological, biochemical and inflammatory indices were within normal limits (ESR 27, CRP < 5). CSF exhibited no evidence of infection. Serology demonstrated high titres of ANA, anti-Ro and anti-La antibodies. LAC, aCL and anti-dsDNA antibodies were absent. Serum western blotting for anti-neuronal antibodies was strongly positive for the anti-paraneoplastic Ma2 (PNMA2, also known as anti-Ma2/Ta) antibody only. Anti-aquaporin4 antibodies—associated with Devic’s disease and recently suggested as a myelopathic association of SS—were negative [1].

MRI brain revealed two discrete foci of high signal intensity in the left medulla and left cerebellar hemisphere (Fig. 1). These were thought to be due to cerebral vasculitis rather than thromboembolism, given a normal echocardiogram and absence of aPLs. Despite the presence of anti-Ma2/Ta antibodies, a malignancy screen (CT chest, abdomen and pelvis, mammography, tumour markers, serum electrophoresis and urine Bence Jones protein) did not reveal evidence of neoplasia. There were no clinical or radiological features suggestive of lymphoma.

The patient was treated with intravenous methylprednisolone (300 mg) for 5 days and six courses of cyclophosphamide (1 g/kg...
Table 1. Anti-neuronal antibody with the associated paraneoplastic neurological syndrome and most common underlying tumour

<table>
<thead>
<tr>
<th>Anti-neuronal</th>
<th>Molecular weight, kDa</th>
<th>Paraneoplastic neurological syndrome</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-Hu (ANNA 1)</td>
<td>35–38</td>
<td>Cerebellar syndrome, encephalomyelitis, sensory neuropathy</td>
<td>SCLC</td>
</tr>
<tr>
<td>anti-Yo (PCA 1)</td>
<td>34, 52 and 62</td>
<td>Cerebellar syndrome</td>
<td>Ovary, breast</td>
</tr>
<tr>
<td>Anti-Ri (ANNA 2)</td>
<td>66</td>
<td>Encephalomyelitis, sensory neuropathy</td>
<td>Various</td>
</tr>
<tr>
<td>anti-CV2 (CRMP5)</td>
<td>128</td>
<td>Stiff person syndrome, encephalomyelitis</td>
<td>Breast, SCLC</td>
</tr>
<tr>
<td>anti-Amphiphysin</td>
<td>37 and 40</td>
<td>Cerebellar syndrome, brainstem encephalomyelitis</td>
<td>Various</td>
</tr>
<tr>
<td>anti-Ma2 (PNMA 1 or 2)</td>
<td>40</td>
<td>Limbic encephalitis, cerebellar syndrome, brainstem encephalomyelitis</td>
<td>Testicular</td>
</tr>
</tbody>
</table>

SCLC: small cell lung cancer; ANNA 1 or 2: anti-neuronal nuclear antibody type 1 or 2; PCA1: anti-Purkinje cell antibody type 1; CRMP 5: collapsin response mediator protein type 5; PNMA 1 or 2: paraneoplastic Ma2 antigen type 1 or 2.

**Fig. 1.** MRI of the brain: (a) axial and (b) sagittal sections. Two foci of high signal intensity are seen in the left medulla (dashed arrow) and left cerebellar hemisphere (white arrow).

Each month for CNS vasculitis with good response. Repeat MRI brain at 7 weeks, demonstrated diminution of the left cerebellar lesion and the absence of new lesions. Thereafter, she continued on maintenance MMF. At 1-year follow-up, the patient was in complete clinical remission with only a mild residual trigeminal neuralgia.

Peripheral nervous system disease involvement occurs in ~25% of the patients with SS and manifests commonly as a sensory neuropathy. However, the prevalence of CNS involvement in SS is controversial, attributed perhaps to differences in diagnostic criteria, selection and referral bias. The lateral medullary syndrome results from occlusion of the vertebral artery, with or without extension to the posterior inferior cerebellar artery. Vasculitis is a rare cause but has been reported in SLE [2, 3], Behçet’s syndrome [4] and relapsing polychondritis [5]. To our knowledge the syndrome has not been reported in association with SS.

Paraneoplastic neurological syndromes (PNS) are remote effects of malignancy on the nervous system. New diagnostic criteria for PNS have been proposed which include six onconeural antibodies: anti-Hu, Yo, Ri, CV2, amphiphysin and Ma2/Ta antibodies, that indicate the presence of a ‘definite’ PNS, even in the absence of a detectable tumour (Table 1) [6]. There have been 36 reported cases of patients with anti-Ma2/Ta antibodies; tumours were diagnosed in 32 patients (89%) [7]. These antibodies are predominantly seen in male patients with testicular germ cell tumours (75%) and are most frequently associated with limbic encephalitis (64%) and brainstem cerebellar syndromes (39%) [7]. Less commonly, anti-Ma2/Ta antibodies were associated with lung 9%, breast 9%, non-Hodgkin’s lymphoma 3% and ovarian tumours 3% [7]. PNS pre-dated the tumour diagnosis in 82% of the cases (range 2–36 months) and developed after diagnosis in 18% of the cases (range 1 month to 14 years) [7]. Therefore, anti-Ma2/Ta antibodies in patients with brainstem or limbic symptoms warrant rigorous investigation for neoplasia.

Serum anti-neuronal antibodies are significantly more frequent in SLE patients compared with individuals with other rheumatic diseases or healthy controls [8]. Among SLE patients, serum and CSF anti-neuronal antibodies were significantly more frequent in those with cerebral involvement [8]. This study included two SS patients with cerebral disease and one had positive serum anti-neuronal antibodies. CSF anti-neuronal antibodies have been observed to decrease post-successful-treatment of CNS-SLE [9]. In a series of 71 SS patients with cerebral involvement, only one patient had anti-neuronal antibodies (anti-Hu) and this patient developed a small cell lung carcinoma 3 years later [10].

CNS involvement in SS is uncommon. Anti-neuronal antibodies may be associated with paraneoplastic disease; however, their significance in the context of autoimmunity is unclear. We have described a case of lateral medullary syndrome secondary to cerebral vasculitis associated with SS and positive anti-neuronal antibodies (anti Ma2/Ta), who remains well at 1-year follow-up with no evidence of malignancy and will continue to be monitored.

![Rheumatology](https://academic.oup.com/rheumatology/article-abstract/48/9/1174/178788/1174)

**Rheumatology key message**
- The spectrum of CNS-SS may include the lateral medullary syndrome and may be associated with anti-neuronal antibodies in the apparent absence of neoplasia.

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Comment on: Investigation of candidate polymorphisms and disease activity in rheumatoid arthritis patients on methotrexate

Sir, With great interest we read the article of Lee et al. [1] in which associations between candidate polymorphisms and disease activity in RA patients on MTX were assessed. Hereby, the minor allele of the single nucleotide polymorphism (SNP) within the ATIC gene (rs4673993), which is in linkage disequilibrium (LD) with rs2372536, was associated with low disease activity [28-joint disease activity score (DAS28) ≤3.2] in a cohort of patients on MTX monotherapy. Previously, our group found an opposite association of the homozygous wild-type of the SNP ATIC 347 C>G (rs2372536) with good clinical response to MTX monotherapy at 6 months [2]. Notably, this comparison is based on the assumption that rs4673993 is a proxy for rs2372526 due to LD [1]. We agree with the authors that differences in study population, study design and relatively small sample size in both studies could be causative factors for observing opposite findings. However, additional important points should be taken into account.

We understand that the authors do not have data regarding the effect of MTX on DAS28 over time and that hereby no association between disease activity at baseline and treatment outcome could be analysed. However, we would underline that disease activity (DAS) at baseline before treatment on MTX determines an important part of the response [3, 4]. Specifically, our reciprocal comparison in multivariate regression analyses of 17 polymorphisms and 24 non-genetic factors in the Best cohort cervied that a genetic variant of 1.2 with a 95% CI of 0.8, 1.6 illustrates a range of values for what the mean decrease might be if the entire population could be studied instead of just the sample. Generally, estimated effect sizes and CIs are more informative about application of findings than statistical outcomes, like P-values. Consequently, a clinician becomes more involved into the results of a pharmacogenetic study and could evaluate its own clinical decision-making in, for example, additive value of genotyping patients based on these estimates.

Only a small number of studies have been performed concerning rs467393 and/or rs2372536 in the ATIC gene and MTX therapy outcome. Therefore, replication, (ideally) meta-analyses and performance of prospective study design in large cohorts are warranted to demonstrate the legitimate predictive value of these variants for assessment of disease activity and/or treatment outcome on MTX.

Disclosure statement: T.W.J.H. is co-inventor on a patent that predicts patient responsiveness on MTX. H.-J.G. holds patents EP 06119819.8 and US 60/840,973 related to a pharmacogenetic prediction model for MTX. He is also a consultant for Cypress Bioscience, San Diego, USA and for PGx Health, Newton (MA), USA. All other authors have declared no conflicts of interest.

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