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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 semi-facial sensory loss. She had a long-standing history of polyarthralgia and sicca symptoms with a hypergammaglobulinaemia (IgG 25g/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 (500mg) 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 Molecular weight, kDa</th>
<th>Paraneoplastic neurological syndrome</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-Hu (ANNA 1) 35–38</td>
<td>Cerebellar syndrome, encephalomyelitis, sensory neuropathy</td>
<td>SCLC</td>
</tr>
<tr>
<td>anti-Yo (PCA 1) 34, 52 and 62</td>
<td>Cerebellar syndrome</td>
<td></td>
</tr>
<tr>
<td>Anti-Ri (ANNA 2) 55 and 80</td>
<td>Ophthalmoplegia, cerebellar syndrome, brainstem encephalomyelitis</td>
<td></td>
</tr>
<tr>
<td>anti-CV2 (CRMP5) 66</td>
<td>Encephalomyelitis, sensory neuropathy</td>
<td></td>
</tr>
<tr>
<td>anti-Amphiphysin 128</td>
<td>Stiff person syndrome, encephalomyelitis</td>
<td></td>
</tr>
<tr>
<td>anti-Ma (Ma1) (PNMA 1 or 2) 37 and 40</td>
<td>Cerebellar syndrome, brainstem encephalomyelitis Various</td>
<td></td>
</tr>
<tr>
<td>anti-Ta (Ma2) (PNMA 2) 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).

Letters to the Editor

Richard P. Barlow

I read with interest the recent article by Colaco et al. [1], which highlighted the significance of anti-neuronal antibodies in the context of paraneoplastic syndromes. The authors emphasized the importance of these antibodies as markers of disease activity, and their association with both neurological and hematological malignancies.

One aspect of their discussion that I would like to highlight is the role of anti-neuronal antibodies in predicting treatment response. Colaco et al. noted that patients with anti-neuronal antibodies are more likely to achieve complete remission with immunosuppressive therapy, compared to those without these antibodies. This finding underscores the importance of early recognition and appropriate management of paraneoplastic syndromes.

Another important point is the potential for anti-neuronal antibodies to serve as surrogate markers for underlying malignancy. The authors reported that antineuronal antibodies were present in 25% of patients with malignant tumours, raising the possibility that these antibodies could be used as a diagnostic tool in the evaluation of patients with neurological symptoms.

Finally, the study by Colaco et al. also stresses the need for multidisciplinary approaches in the management of paraneoplastic syndromes, highlighting the importance of collaboration between neurologists, oncologists, and other specialists.

In conclusion, the article by Colaco et al. provides valuable insights into the role of anti-neuronal antibodies in paraneoplastic syndromes, and underscores the importance of early recognition and comprehensive management of these conditions.

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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 [8-join 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 347C>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 led to a predictive model for MTX efficacy, in which DAS at baseline was scored as most predictive. Scores for prediction of response regarding DAS at baseline were about three times larger than ATIC rs2372526 [4].

Secondly, in contrast with what Lee et al. have reported in their discussion, analyses by our group revealed that all results remained similar when performed with and without inclusion of non-Caucasian patients [2]. In this way, both cohorts of patients in the article of Lee et al. and our article are ethnically comparable.

Also, regarding the LD between rs4673993 and rs2372536 (D' = 1 and r² = 0.96), additional information about linkage could be important in demonstrating genetic variation in the ATIC gene. Namely, the SNP ATIC 347C>G (rs2372536) represents a TAG-SNP, meaning that given an r² of ~1 there is no loss of power when analysing this tag SNP. This SNP represents indirectly six SNPs including rs4673993 (www.hapmap.org). In general, limitation of effort and costs of association studies could be reduced by taking tag SNPs into account [5].

Finally, we would like to comment on the use of correction for multiple testing. In the article of Lee et al., the likelihood for false-positive results is calculated by the false-positive report probability (FPRP) as reported by Wacholder et al. [6]. With this approach, estimation of a priori probability based on previous studies can lead to the calculation of posterior probability. In the study of Lee et al. the prior probability is estimated based on one odds ratio (OR), as reported by our group. However, with this single OR it is difficult to evaluate the prior probability (and eventually the FPRP) since it is an indirect (due to LD) and contradictory effect size. Ideally, the prior probability in order to calculate the FPRP is based on a well-done meta-analysis and hereby a calculated prior estimated OR [7].

We agree with the authors that applying the Bonferroni correction is conservative. In general, multiple corrections are focused on a certain chosen level of significance. However, the reporting of effect size and confidence interval (CI) may be more informative than the blunt P-values. Regarding pharmacogenetics in RA and adequate sample size, a mean decrease in DAS for a specific 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 rs4673993 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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