RESEARCH PAPER

Serum antigliadin antibodies in cerebellar ataxias: a systematic review and meta-analysis

Chi-Ying Lin,1 Min-Jung Wang,2 Winona Tse,1 Rachel Pinotti,3 Armin Alaedinir,4 Peter H R Green,4 Sheng-Han Kuo5

ABSTRACT

Background Gluten sensitivity refers to prominent immunological responses to gluten, usually in conjunction with elevated levels of serum antigliadin antibody (AGA). The association between AGA and cerebellar ataxias has been inconsistently reported.

Methods We performed a systematic literature search and a meta-analysis to study the weighted pooled OR of idiopathic cerebellar ataxia (IDCA) cases to controls or to hereditary ataxia (HA) for AGA seropositivity using fixed effect model.

Results Eleven studies were included, with a total of 847 IDCA cases, 1654 controls and 445 HA cases. IDCA cases had fourfold higher odds than controls (OR 4.28, 95% CI 3.10 to 5.90) and twofold higher odds than HA cases (OR 2.23, 95% CI 1.45 to 3.44) of having AGA seropositivity. Sensitivity analysis excluding the most weighted study, which accounted for 69% of the total weight, still showed similar associations (IDCA vs controls, OR 3.18, 95% CI 1.79 to 5.67 and IDCA vs HA, OR 1.72, 95% CI 1.03 to 2.86, respectively). The subgroup analysis showed that, when compared with controls, IDCA cases of both East Asian and Western countries had approximately threefold to fourfold higher odds to have AGA seropositivity (OR 3.41, 95% CI 1.67 to 6.97 and OR 4.53, 95% CI 3.16 to 6.49, respectively), suggesting the lack of ethnic heterogeneity. The odds of AGA seropositivity for HA cases was not significantly higher than controls (OR 1.41, 95% CI 0.82 to 2.44).

Conclusion Our study indicates the association between AGA and IDCA, across different geographic regions.

INTRODUCTION

The differential diagnosis of cerebellar ataxia is broad, including hereditary and degenerative causes, and few disease-specific treatments are available. Immune-mediated cerebellar ataxias are characterised by serum or cerebrospinal fluid antibody positivity, mild or absence of the cerebellar atrophy on structural neuroimaging at the initial stage and the responsiveness to immunomodulatory therapy.1 2 Established immune-mediated cerebellar ataxias are relatively rare, among which gluten ataxia has been reported to be the most common. Gluten ataxia refers to cerebellar ataxia associated with gluten sensitivity, a prominent immunological response to gluten intake, for which the human body produces abnormally high titres of serum antigliadin antibodies.3 4 Gluten sensitivity is considered a gluten-related disorder separate from coeliac disease, which is characterised by the presence of antibodies to tissue transglutaminase 2 (TTG2) and inflammatory changes in the small intestine.5 Patients with gluten sensitivity lack these changes; however, might have evidence of alterations in intestinal permeability.6 The presence of antibodies to gliadin is considered to represent a form of gluten sensitivity.7 Patients with cerebellar ataxia with antigliadin antibodies could respond to gluten-free diet or immunoglobulin therapy,8 representing a treatable form of cerebellar ataxia.

Antigliadin antibodies are generated in response to gluten proteins existing in wheat, rye and barley, among which antigliadin antibody (AGA) is most studied in patients with cerebellar ataxia.9 AGA has been reported in 43% of otherwise idiopathic cerebellar ataxia (IDCA) cases; however, AGA is also found in up to 12% controls and in 13% hereditary ataxia (HA) cases.9 10 When comparing with controls, IDCA cases are thus more commonly reported to have AGA seropositivity.10 However, these results have been inconsistently replicated.11 12 Several factors such as ethnic backgrounds and different methodologies used for AGA detection have been postulated to explain the discrepancy between studies,12 but there is no systematic review for these important questions. Therefore, we performed a meta-analysis to examine the association between AGA seropositivity and cerebellar ataxia and to investigate the factors accounting for the discrepancies between studies.

METHODS

Data sources and searches

The methodology used for the systematic review and meta-analysis followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (www. prisma-statement.org). C-YL and RP composed a comprehensive search strategy using both subject headings and all relevant keywords, including antigliadin antibody, cerebellar ataxia and gluten. The search was executed in the MEDLINE, EMBASE and SCOPUS databases from their inception through 15 April 2017, with the goal of identifying all published material relevant to AGA in cerebellar ataxias. Google Scholar was also searched and the first 100 pages of search results were reviewed to identify additional relevant materials. All results from the databases as well as selected results from Google Scholar were uploaded to COVIDENCE.
and the result set was de-duplicated. The detailed search strategy is provided in online supplementary file 1.

**Study selection and quality assessment**

Study selection was conducted independently by two independent reviewers (C-YL and S-HK) according to predetermined eligibility criteria. The eligibility criteria were designed to be relatively broad and inclusive, as studies related to cerebellar ataxias with serological testing for AGA were expected to be relatively uncommon. We thus included both case-control and cross-sectional studies with patients diagnosed with IDCA, HA and/or healthy controls who received AGA serological testing. The exclusion criteria were as follows: a single case report, review articles, lack of measurement of AGA and studies not written in English. The primary outcome of interest was the presence or absence of serum AGA. It is required that the IDCA cases of the recruited studies should have no other known causes of the cerebellar ataxias, including genetics. Age was not considered as a factor for study exclusion because the majority of the current published studies did not specify study subjects’ individual demographics.

Studies from the search were initially screened on the basis of their titles and abstracts. Incongruent decisions (ie, one voted for ‘yes’ to include for the full-text review and the other voted for ‘no’) and controversial opinions (eg, one or both voted for ‘maybe’) between the two independent reviewers were then resolved by the third reviewer (WT). The studies identified based on the title and abstract screening were then included for full-text review. The full-text review was again performed by two independent reviewers (C-YL and S-HK) and any disagreement between the two reviewers was resolved by the third reviewer to reach the consensus for making the final decision of the inclusion for qualitative assessment. Newcastle-Ottawa Quality Assessment Scale Adapted for Cross-Sectional Studies was used for assessment of the study selection, comparability and outcome, and articles rated 7 stars or above on the scale were considered good quality and included for the meta-analysis.

**Data extraction**

The OR of each included study was calculated by a single reviewer (C-YL). Calculating the OR required the number of the patients and controls in the exposure (with AGA) and non-exposure groups (without AGA), respectively; if the original study used the percentage for the prevalence of AGA seropositivity, the percentage would be converted to the subject number. The decimal would be rounded up to an integer as the original study used the percentage for the prevalence of AGA seropositivity, the percentage would be converted to the subject number. The decimal would be rounded up to an integer as the subject number. While all 11 studies measured both AGA IgA and IgG, only two studies specify in the results separately for AGA IgG for pooling effect in the primary analysis because IgG typically stands for the antibody indicative of long-standing immunity and could more reliably reflect the long-term gluten sensitivity. We did not have sufficient sample size to independently evaluate AGA IgA and cerebellar ataxia.

**Data synthesis and statistical analysis**

Our primary analysis is the pooled OR of IDCA cases to controls (OR_{I/C}) and secondary analysis is the pooled OR of IDCA cases to HA cases (OR_{I/H}). The rationale of performing secondary analysis is that HA could serve as a disease control against the possibility that the subclinical pre-existing cerebellar disease due to genetic and neurodegenerative factors may predispose the cerebellum to immunological damages. The pooled effects were presented as OR with 95% CIs, and the studies were weighted using the Mantel-Haenszel test for pooled OR. We quantified the statistical heterogeneity by calculating I^2 statistics (ie, the percentage of the total variation across the studies due to effect size heterogeneity) between studies. An I^2 value of 0% indicates no observed heterogeneity; 25% is low, 50% is moderate and 75% is high heterogeneity. The heterogeneity was considered significant if the heterogeneity p value was <0.05. We used fixed effects model with the assumption that the study sample, method and effect sizes were not different across the included studies. We performed the meta-analyses using STATATA V14. In addition, we further explored the geographic regions where the patients were recruited/studies were conducted since it would reflect information regarding ethnicity differences. We assessed publication bias by inspecting the shape of the funnel plot for the log OR against the log OR SE, and by performing the Egger test.

**RESULTS**

Our search identified 206 citations (figure 1). After removing duplicate records, 159 unique citations entered the process of title and abstract screening, of which 133 (83.6%) were excluded according to the exclusion criteria and additional duplicated articles not detected initially by COVIDENCE but later on by our review of citations. Our independent raters had good initial agreement on inclusion of full-text review (kappa=0.65, SE=0.06, p=0.54–0.76). After resolving initial disagreements, 11/26 (42.3%) studies were considered eligible (figure 1), representing 6.9% of the total search (11/159). The reasons for excluding 15/26 article were in the order of high to low percentage to as follows: studies only on IDCA cases without HA cases or controls (n=6, 40%); 23 26 27 30 32 studies on cases of ataxia with or without coeliac disease instead of ataxia cases versus controls (n=3, 20%); 31 33 34 studies that defined IDCA distinctively from the general consensus (ie, non-genetic ataxias caused by acquired conditions and sporadic neurodegenerative disorders) (n=2, 13.3%); 15 34 a study that only tested for anti-deamidated gliadin peptide (DGP) antibody without testing for AGA (n=1, 6.7%); 23 a study that only tested for anti-TTG2 antibody without testing for AGA (n=1, 6.7%); 29 a study that did not include IDCA cases (n=1, 6.7%); and a duplicated study with same patient groups but under different titles (n=1, 6.7%). 36 These 11 studies included in the meta-analysis were all rated as 7 stars or above on Newcastle-Ottawa Quality Assessment Scale Adapted for Cross-Sectional Studies and thus included for meta-analysis. A total of 847 patients with IDCA, 443 HA cases and 1654 controls were included.

Our review showed that the percentage of AGA seropositivity in IDCA, HA and controls greatly vary across the studies (table 1). Our primary analysis showed that IDCA cases have fourfold higher odds than controls of being found as seropositive for AGA (overall OR_{I/C}=4.28, 95% CI 3.10 to 5.90, p<0.001, seven studies9 12–14 18–20; I^2=38.5%, p=0.135) (figure 2A). We also found that IDCA cases have twofold higher odds than HA cases of being found as seropositive for AGA (OR_{I/H}=2.23, 95% CI 1.45 to 3.44, nine studies9 11 13 14 17–20; I^2=32.4%, p=0.159) after excluding one study23 of infinite OR due to no AGA seropositivity in patients with HA (figure 2B). Visual examination of the funnel plot of the OR_{I/C} (see online supplementary figure 1A) and OR_{I/H} (see online supplementary figure 1B) showed no deviation of the funnel shape with the studies evenly spread on
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For the six studies that included HA cases and controls,\(^9\)\(^\text{13}\)\(^\text{14}\)\(^\text{18}\)\(^\text{–}^\text{20}\) the odds of AGA seropositivity for HA cases was not significantly higher than controls (OR\(_{\text{I/C}}\)=1.41, 95% CI 0.82 to 2.44, \(p=0.215\)). We found that the pooled OR\(_{\text{I/C}}\) was primarily driven by one particular study with a large sample size,\(^9\) which contributed to 69% of the total weight. Thus, we performed further sensitivity analysis to exclude this study and the odds of AGA seropositivity was still threefold higher in IDCA cases than controls (OR\(_{\text{I/C}}\)=3.18, 95% CI 1.79 to 5.67, \(p<0.001\); \(I^2=39.8\), \(p=0.140\)). Similarly, IDCA cases still had close to twofold higher odds of being found as seropositive for AGA than HA cases after excluding the most weighted study (OR\(_{\text{I/H}}\)=1.72, 95% CI 1.03 to 2.86, \(p=0.04\), eight studies\(^{11}\)\(^\text{13}\)\(^\text{14}\)\(^\text{17}\)\(^\text{–}^\text{20}\)\(^\text{22}\); \(I^2=14.4\), \(p=0.317\)).

We next investigated the factors that could influence the association between AGA and IDCA cases. We first conducted the geographic region-specific subgroup analysis. The pooled OR\(_{\text{I/C}}\) for the East Asian subgroup (three studies from Taiwan, Japan\(^\text{12}\) and China\(^\text{15}\)) was 3.41 (95% CI 1.67 to 6.97, \(p=0.001\); \(I^2=73.2\), \(p=0.024\)) and the pooled OR\(_{\text{I/C}}\) for the rest of the studies (four studies from the UK,\(^8\)\(^\text{20}\) Germany,\(^19\) and Canada\(^\text{14}\)) was 4.53 (95% CI 3.16 to 6.49, \(p<0.001\); \(I^2=0.0\), \(p=0.509\)) (figure 3A). We further compared odds of AGA between IDCA cases and HA cases. Two Asian studies\(^{13}\)\(^\text{18}\) had a pooled OR\(_{\text{I/H}}\)=3.08 (95% CI 1.41 to 6.72, \(p=0.005\); \(I^2=49.4\), \(p=0.013\))), whereas seven non-Asian studies\(^{9}\)\(^\text{11}\)\(^\text{14}\)\(^\text{17}\)\(^\text{20}^\text{19}^\text{20}\)\(^\text{22}\) had a slightly lower pooled OR\(_{\text{I/H}}\) of 1.94 (95% CI 1.15 to 3.26, \(p=0.013\); \(I^2=32.7\), \(p=0.178\)) (figure 3B). In summary, the association between AGA seropositivity and IDCA cases could be similarly observed across different geographic regions.

DISCUSSION

Significantly increased rates of seropositivity for serum antibody to gluten proteins were previously found in some patients with IDCA in the absence of coeliac disease, some of whom were also found to have a clinical response to a gluten-free diet.\(^\text{10}^\text{17}\) Therefore, cerebellar ataxia has been suggested as one of the presentations of gluten sensitivity.\(^{30}\) Since gluten ataxia is a relatively rare disorder, meta-analysis presents as a useful tool to study the prevalence of such disorder across different geographic regions, and this method could also be applied to other immune-mediated

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Figure 1  Study selection flow diagram. \(^a\)MEDLINE and Embase were searched via Ovid. Scopus was searched via Scopus.com. \(^b\)Hand search of citation lists from Google Scholar, selected studies and investigators further identified five additional published articles for review. Abstracts marked as yes or maybe on COVIDENCE by one or two reviewers were included in the full-text review. Different opinions between the two reviewers (C-YL and S-HK) in screening and eligibility were resolved by discussion and adjudication by a third, independent reviewer (WT). AGA, antigliadin antibody; CD, coeliac disease; DGP, deamidated gliadin peptide; TTG, tissue transglutaminase.
cerebellar ataxias. Our meta-analysis of available studies supports the notion that AGA seropositivity is associated with cerebellar ataxias. In our analysis, the main pooled ORc and ORhs are driven by the study conducted by Hadjivassiliou et al based on its large sample size. After excluding this study that accounts for nearly 70% of the total weight, the pooled ORc and ORhs in the rest of the included studies were similar, which further corroborates the association between AGA seropositivity and cerebellar ataxias. To our knowledge, this is the first systematic review and meta-analysis exploring the association between gluten sensitivity and cerebellar ataxia. The overall odds of having cerebellar ataxias are over fourfold higher in patients with gluten sensitivity. There are significant differences in the prevalence of cerebellar ataxic disorders between Western and Asian populations, such as multiple sclerosis (neuromyelitis optica), and multiple system atrophy-cerebellar type (degenerative causes).38 39 Interestingly, we found that the association between AGA seropositivity and cerebellar ataxias is similar across different geographic regions in our meta-analysis. On the other hand, cerebellar disease is much rare in most Asian countries such as Japan,40 making a clear distinction between gluten ataxia and coeliac disease. None of the studies indicated the coexistence of coeliac disease in cases with cerebellar ataxia associated with gluten sensitivity, which deserve further investigation.

One of the major confounding factors among the included studies is the different cut-off values, and different manufacturers (table 1) using different antigens and standards for AGA seropositivity, which might account for some inconsistency between the absolute prevalence of AGA in different studies. Thus, the systematic review of our study also highlights the importance of unifying the analytic methods to detect the presence of AGA and to define the titre threshold for AGA ‘seropositivity’. A uniform protocol is required to adequately compare and to further define the disease prevalence, the response rate of gluten-free diet and/or immunomodulatory therapy in patients with the aforementioned predefined threshold for AGA seropositivity.

Anti-DGP antibody is considered a sensitive and specific marker for coeliac disease and follows closely with the antibodies to TTG2. AGA is considered neither sensitive nor specific for coeliac disease41 while the presence of anti-TTG2 or anti-DGP seropositivity indicates coeliac disease,5 separating from (non-coeliac) gluten sensitivity. In other words, all/most patients with coeliac disease have AGA as well as anti-TTG/DGP seropositivity are considered (non-coeliac) gluten sensitive.41 42 While AGA is the most commonly studied antibody to be associated with cerebellar ataxia, the antitransglutaminase 6 (TG6) antibody has been proposed to be more specific to the gluten sensitivity associated with

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### Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Type of study</th>
<th>Country</th>
<th>IDCA (n)</th>
<th>HA (n)</th>
<th>Healthy control (n)</th>
<th>Other diseases (n)</th>
<th>AGA seropositivity (n/percentage)</th>
<th>ELISA kit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abele et al (2002)17</td>
<td>Cross-sectional</td>
<td>Germany</td>
<td>65</td>
<td>15</td>
<td>–</td>
<td>MSA: 32</td>
<td>IDCA (10/15%); HA (1/7%)</td>
<td>Pharmacia, Erlangen, Germany</td>
</tr>
<tr>
<td>Abele et al (2003)19</td>
<td>Cross-sectional</td>
<td>Germany</td>
<td>32</td>
<td>63</td>
<td>73</td>
<td>–</td>
<td>IDCA (4/13%); HA (6/10%); control (4/6%)</td>
<td>UniCap Giadim IgG/IgA Immunocap, Pharmacia Diagnostics, Germany</td>
</tr>
<tr>
<td>Bushara et al (2001)43</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>26</td>
<td>24</td>
<td>–</td>
<td>–</td>
<td>IDCA (7/27%); HA (9/38%)</td>
<td>SCIMEDX, Denville, New Jersey, USA</td>
</tr>
<tr>
<td>Guan et al (2013)44</td>
<td>Cross-sectional</td>
<td>China</td>
<td>100</td>
<td>25</td>
<td>51</td>
<td>–</td>
<td>IDCA (24/24%); HA (4/16%); control (8/16%)</td>
<td>Cusabio Biotech, Newark, Delaware, USA</td>
</tr>
<tr>
<td>Hadjivassiliou et al (2003)39</td>
<td>Cross-sectional</td>
<td>UK</td>
<td>132*</td>
<td>59</td>
<td>1200</td>
<td>MSA-C: 33</td>
<td>IDCA (54/41%); HA (8/14%); control (149/12%)</td>
<td>Cogent Diagnostics, Edinburgh, UK</td>
</tr>
<tr>
<td>Liu et al (2010)13</td>
<td>Cross-sectional</td>
<td>Taiwan</td>
<td>361</td>
<td>207</td>
<td>194</td>
<td>–</td>
<td>IDCA (33/9%); HA (3/1%); control (2/1%)</td>
<td>IBL-Hamburg GmbH, Germany</td>
</tr>
<tr>
<td>Lock et al (2006)46</td>
<td>Cross-sectional</td>
<td>UK</td>
<td>20</td>
<td>7</td>
<td>30</td>
<td>Idiopathic peripheral neuropathy: 32</td>
<td>IDCA (8/40%); HA (3/43%); control (5/17%)</td>
<td>Orgentec Diagnostika, Mainz, Germany</td>
</tr>
<tr>
<td>Pellecchia et al (1999)47</td>
<td>Cross-sectional</td>
<td>Italy</td>
<td>24</td>
<td>23</td>
<td>–</td>
<td>–</td>
<td>IDCA (3/13%); HA (0/0%); control (1/7%)</td>
<td>Alfa-Gliatess, Eurosprint, Trieste, Italy</td>
</tr>
<tr>
<td>Sivera et al (2012)42</td>
<td>Cross-sectional</td>
<td>Spain</td>
<td>44</td>
<td>43</td>
<td>–</td>
<td>Paraneoplastic cerebellar ataxia: 6</td>
<td>IDCA (6/14%); HA (3/7%)</td>
<td>Not described</td>
</tr>
<tr>
<td>Wong et al (2007)44</td>
<td>Cross-sectional</td>
<td>Canada</td>
<td>29</td>
<td>18</td>
<td>59</td>
<td>MSA-C: 9</td>
<td>IDCA (27%); HA (1/6%); control (3/5%)</td>
<td></td>
</tr>
</tbody>
</table>

*Additional 44 patients with IDCA from the other research group in London was recruited for AGA testing in addition to the original 132 patients with IDCA. These 44 are not included for meta-analysis because there was no HA and controls recruited at the same time.

AGA (+), positive antigliadin antibody; ALS, amyotrophic lateral sclerosis; EIA, enzyme immune-assay; HA, hereditary ataxia; IDCA, idiopathic, sporadic ataxia; MSA, multiple system atrophy; MSA-C, multiple system atrophy cerebellar type; PD, Parkinson’s disease.
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A. Idiopathic cerebellar ataxias vs. controls

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guan (2013)</td>
<td>1.70 (0.70, 4.11)</td>
<td>13.25</td>
</tr>
<tr>
<td>Hadjivassiliou (2003)</td>
<td>4.88 (3.32, 7.19)</td>
<td>66.98</td>
</tr>
<tr>
<td>Ihara (2006)</td>
<td>25.56 (2.68, 245.59)</td>
<td>2.02</td>
</tr>
<tr>
<td>Liu (2010)</td>
<td>9.66 (2.29, 40.70)</td>
<td>5.00</td>
</tr>
<tr>
<td>Lock (2005)</td>
<td>3.33 (0.90, 12.38)</td>
<td>6.00</td>
</tr>
<tr>
<td>Aboie (2003)</td>
<td>4.80 (0.42, 54.96)</td>
<td>1.74</td>
</tr>
<tr>
<td>Wong (2007)</td>
<td>1.44 (0.23, 9.17)</td>
<td>3.02</td>
</tr>
<tr>
<td>Overall (I^2 = 38.5%, p = 0.135)</td>
<td>4.28 (3.10, 5.90)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

B. Idiopathic cerebellar ataxias vs. hereditary ataxias

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboie (2002)</td>
<td>2.73 (0.32, 23.03)</td>
<td>4.12</td>
</tr>
<tr>
<td>Bushara (2001)</td>
<td>0.61 (0.19, 2.03)</td>
<td>13.09</td>
</tr>
<tr>
<td>Guan (2013)</td>
<td>1.86 (0.52, 6.31)</td>
<td>13.86</td>
</tr>
<tr>
<td>Hadjivassiliou (2003)</td>
<td>4.41 (1.94, 10.04)</td>
<td>27.77</td>
</tr>
<tr>
<td>Liu (2010)</td>
<td>5.11 (1.78, 14.63)</td>
<td>16.95</td>
</tr>
<tr>
<td>Lock (2005)</td>
<td>0.89 (0.16, 5.08)</td>
<td>6.17</td>
</tr>
<tr>
<td>Sivera (2012)</td>
<td>2.11 (0.49, 9.02)</td>
<td>8.66</td>
</tr>
<tr>
<td>Aboie (2003)</td>
<td>0.98 (0.17, 6.68)</td>
<td>6.11</td>
</tr>
<tr>
<td>Wong (2007)</td>
<td>1.38 (0.11, 16.21)</td>
<td>3.06</td>
</tr>
<tr>
<td>Overall (I^2 = 32.4%, p = 0.159)</td>
<td>2.23 (1.46, 3.44)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 2  Pooled OR for antigliadin antibody seropositivity in idiopathic cerebellar ataxias vs controls (A) and idiopathic cerebellar ataxias vs hereditary ataxias (B) are represented by the diamonds. The grey solid squares indicate the OR of the individual study result. The size of the squares refers to the weight that each study contributes to the overall meta-analysis. The 95% CI for the individual and the pooled OR is specified.

The limitation of this systematic review and meta-analysis is that all studies included were cross-sectional and the sample size is relatively small; however, this does not mean the finding is not applicable to the population level across different geographic regions. At the individual patient level, it is still debatable whether AGA is pathognomonic of immune-mediated cerebellar ataxias given a significant portion of HA cases and controls also have AGA seropositivity. The prevalence of AGA seropositivity in healthy subjects carries the implicit warning that finding AGA seropositivity…

cerebellar ataxia—a phenomenon that is especially true given that AGA seropositivity could be found in about 10% of healthy subjects, AGA thus may sometimes be considered as an epiphenomenon and the search for more specific antibody as the disease marker is needed. However, there are no widely standardised and commercially available methods to detect anti-TG6 antibodies. There is only one study in our meta-analysis that measured anti-TG6, which yields the OR of 9.31. Further systematic study of anti-TG6 and gluten ataxia is needed.

seropositivity in an ataxic patient should not necessarily result in diagnostic closure. In addition, not every patient with ataxia with AGA seropositivity responds to gluten-free diet or intravenous immunoglobulin; therefore, other causes of ataxia might also sometimes be considered. Therefore, the recognition of gluten sensitivity in patients with ataxia may be highly important to initiate gluten-free diet. Future research should focus on standardised methods with a consensus of cut-off values of AGA seropositivity, which will serve as a starting point to further clearly define gluten ataxia as a disease entity. In addition,
identifying the disease-specific antibodies such as anti-TG6 will also be important for elucidating the immune-mediated causes of the cerebellar ataxias.

Contributors C-YL: study concept, data acquisition, analysis and interpretation, manuscript draft and revision; M-JW: conducting meta-analysis, data analysis and interpretation and revision of the manuscript; WT: data acquisition and interpretation; M: manuscript draft and revision; M-JW: conducting meta-analysis, data analysis and interpretation of the manuscript; WT: data acquisition and interpretation and critical revision of the manuscript for important intellectual content; RP: guidance and oversight on search strategy design and execution, preparation of results for screening and study selection processes, critical revision of the Methods section of the manuscript; AA: study concept, analysis and interpretation, critical revision of the manuscript for important intellectual content; PHRG: study concept, analysis and interpretation, critical revision of the manuscript for important intellectual content; S-HK: study concept, data acquisition, analysis and interpretation, critical revision of the manuscript for important intellectual content and study supervision.

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