Responses to and Outcomes of Treatment of Autoimmune Cerebellar Ataxia in Adults

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IMPORTANCE Classic Purkinje cell cytoplasmic antibody type 1 (PCA-1, or anti-Yo) paraneoplastic cerebellar ataxia has a poor prognosis, yet little has been published otherwise regarding treatment responses and outcomes among patients with autoimmune cerebellar ataxia.

OBJECTIVES To investigate treatment responses and outcomes in adults with autoimmune cerebellar ataxia.

DESIGN, SETTING, AND PARTICIPANTS A cohort study conducted at Mayo Clinic, Rochester, Minnesota, included 118 patients who had ataxia, were 18 years or older, were seropositive for at least 1 neural autoantibody, had received at least 1 immunotherapy or cancer therapy, and had neurologist-reported outcomes documented from January 1, 1989, through December 31, 2013. Data were collected from May 14, 2013, through August 9, 2014, and analyzed from August 9, 2014, through April 27, 2015. Responses to immunotherapy (corticosteroids, intravenous immunoglobulin, plasma exchange, and immunosuppressants) and ambulatory outcomes were compared between different subgroups. Subgroups were classified as paraneoplastic vs nonparaneoplastic disorders; neuronal nuclear and/or cytoplasmic (NNC) antibody positivity vs plasma membrane protein (PMP) antibody positivity; and glutamic acid decarboxylase 65-kDa isoform (GAD65) antibody positivity vs PMP antibody positivity.

MAIN OUTCOMES AND MEASURES Response to therapy and ambulatory ability, with univariate logistic regression and Kaplan-Meier analyses.

RESULTS Inclusion criteria were met by 118 patients. Median age at onset of neurologic symptoms was 58 (range, 27-83) years, and 87 patients (73.7%) were women. Median duration from symptom onset to last follow-up was 25 (range, 2-223) months. Sixty-three patients had paraneoplastic and 55 patients had nonparaneoplastic ataxic disorders. Eighty-one patients were seropositive for NNC antibodies (most commonly PCA-1 [anti-Yo], antineuronal nuclear antibody type 1 [anti-Hu], and GAD65 antibody); 22 patients, for neural PMP receptor or ion channel antibodies (most commonly targeting P/Q- or N-type voltage-gated calcium channels); and 15 patients, for antibodies from both categories. Neurologic improvements occurred in 54 patients (with a robust change in ambulatory ability in 22) attributable to immunotherapy; univariate regression analysis revealed that improvements were significantly more common among patients with nonparaneoplastic disorders (P = .03) and those with exclusively PMP antibodies (P = .02). Kaplan-Meier analyses revealed that progression to wheelchair dependence occurred significantly faster among patients with NNC antibody positivity only (P = .02), although those with GAD65 autoimmunity progressed to wheelchair dependence at a rate similar to those with PMP autoimmunity (P = .92).

CONCLUSIONS AND RELEVANCE Although autoimmune ataxia is usually severe, treatment responses can be gratifying, particularly in patients with nonparaneoplastic disorders and in those harboring autoantibodies directed against GAD65 or neural PMPs.
Autoimmune cerebellar ataxia in adults is usually of rapid onset and progression and can be divided into paraneoplastic and nonparaneoplastic disorders.\(^4\) The neurologic deficits are typically disabling, including dysarthria, disorders of gait and balance, and limb ataxia.

A relentless progressive course to a wheelchair-bound state without response to immunotherapy is characteristic of classic paraneoplastic cerebellar degeneration. The prototypic example of this disorder is autoimmunity targeting Yo (CDR2) in patients seropositive for Purkinje cell cytoplasmic antibody type 1 (PCA-1, also known as anti-Yo antibody).\(^2,3\) Pathophysiologic and serologic studies\(^4,5\) have suggested that this autoimmunity targeting is mediated by cytotoxic (CD8\(^\text{+}\)) T lymphocytes rather than by PCA-1 antibody. Ninety percent of affected women develop cerebellar ataxia, and 90% have accompanying gynecologic or breast adenocarcinomas.\(^3\) Reported neurologic improvements attributable to immunotherapy (corticosteroids, intravenous immunoglobulin, plasma exchange, and immunosuppressants) are rare, and the median survival from symptom onset is just 2 years, with death due to cancer or neurologic decline.

Little has been published regarding treatment responses and neurologic outcomes among patients with autoimmune cerebellar ataxia in general.\(^6\) To date, at least 17 autoantibodies have been reported as causally linked to autoimmune cerebellar ataxia.\(^7\)-\(^21\) Responses to treatment are variable. In contrast to PCA-1 and other neuronal nuclear and cytoplasmic (NNC) antibodies, IgG antibodies that target plasma membrane proteins (PMPs) (eg, voltage-gated calcium channels) might be directly pathogenic,\(^15,22-24\) and the accompanying neurologic disorders may be treatable.\(^25\) Herein, we report our treatment and outcome experience for adult patients with autoimmune cerebellar ataxia undergoing evaluation at the Mayo Clinic, Rochester, Minnesota, and include analyses of factors predicting outcomes in those patients.

Methods

To identify all relevant adult cases, we searched the medical record index system of the Mayo Clinic for the terms autoimmune, cerebellar, ataxia, paraneoplastic, and antibody from January 1, 1989, through December 31, 2013. We included all patients who were 18 years or older with cerebellar ataxia, who were seropositive for at least 1 neural antibody, who had received at least 1 immunotherapy or oncologic therapy, and who had physician-reported neurologic outcomes recorded in relation to the therapy. Patient data were not deidentified but were stored in a password-protected database by two of us (A.L.J. and A.M.). Written informed consent for medical record review for research had been obtained at the time of clinical evaluation in all patients. This study was performed with the approval of the institutional review board of the Mayo Clinic.

Serum and available cerebrospinal fluid (CSF) specimens were tested using a standardized indirect, immunofluorescence, tissue-based assay for IgG binding selectively to neuronal and glial nuclei (antineuronal nuclear antibody type 1 [ANNA-1] or anti-Hu), type 2 [ANNA-2 or anti-Ri], and type 3 [ANNA-3] and antiganglioside and/or neuronal nuclear antibody type 1 [AGNA-1]), neuronal cytoplasm (PCA [types 1 and 2], collapsin-response mediator protein 5 [CRMP-5]-IgG, and amphiphysin-IgG), or their receptors (PCA-Tr [which targets the extracellular domain of delta-notch epidermal-like growth factor-related receptor] and metabotropic glutamate receptor 1 [mGluR1]-IgG).\(^16,26,27\) The reference values for all antibodies were less than 1:240 in serum and less than 1:2 in CSF. Serum samples were tested by radioimmunoprecipitation assays for antibodies reactive with neural cation channel complexes (neuronal voltage-gated calcium channels [P/Q type and N type], voltage-gated potassium channel [VGKC] complexes, and nictinic acetylcholine receptors [AChR] of skeletal muscle type [α, subunit] and neuronal gangliocytic type [α, subunit]) and glutamic acid decarboxylase 65-kDa isoform (GAD65).\(^26\) Reference values for all antibodies were no greater than 0.02 nmol/L (with the exception of the N-type calcium channel antibody, which was ≤0.03 nmol/L). Serum samples were tested for striatal antibodies of the skeletal muscles (by enzyme-linked immunosorbent assay; the reference value was <120 nmol/L) and CRMP-5-IgG (by recombinant Western blot assay). Cell-based assays (Euroimmun) were used to confirm mGluR1-IgG positivity and to detect leucine-rich glioma inactivated 1 and contactin-associated protein-like 2 IgGs in VGKC-complex, antibody-positive sera.

The variables potentially predictive of response to treatment evaluated included age, sex, the presence of cerebellar atrophy on magnetic resonance imaging, having a nonparaneoplastic disorder, and having an elevated CSF level for protein, white blood cell count, and oligoclonal bands and seropositivity for a synaptic neural antibody. Associations among all these variables and response to treatment were assessed using univariate logistic regression. Variables associated with functional outcome with \(P < .10\) on univariate analysis were considered candidates for multivariable logistic regression analysis. We compared patients with paraneoplastic and nonparaneoplastic disorders by rates of treatment response to different immunotherapies using the Fisher exact test. For patients with nonparaneoplastic ataxia, the time from symptom onset to treatment was compared between those who responded and did not respond to treatment (as reported by the physician) using the Wilcoxon rank sum test. The time to wheelchair dependence was evaluated using the Kaplan-Meier method, and comparisons between subgroups were performed with the log rank test using JMP software (version 8.0; SAS Institute Inc). All other analyses were performed using SAS software (version 9.3). All statistical tests were 2 sided, and \(P < .05\) was considered statistically significant. Data were analyzed from August 9, 2014, through April 27, 2015.

Results

Of the 239 patient medical records reviewed, those of 118 patients with autoimmune cerebellar ataxia met the inclusion criteria. These patients received 1 or more courses of immunotherapy (\(n = 102\)) or cancer therapy (\(n = 42\)). Data were collected from May 14, 2013, through August 9, 2014.

Demographic Data

Median age of neurologic symptom onset of these 118 patients was 58 (range, 27-83) years; 87 patients (73.7%) were women.
Onset was subacute (evolution ranging from days to weeks) in 111 patients (94.1%) and insidious in 7 (5.9%). All patients initially presented with 1 or more cerebellar or brainstem symptoms, including unsteadiness (n = 104), lack of coordination (n = 55), vertigo (n = 33), and diplopia (n = 30); 20 patients also presented with nausea with or without vomiting. Forty-one patients (34.7%) had extracerebellar disorders at presentation, including neuropathy (n = 16), dysphagia (n = 5), generalized weakness or fatigue (n = 5), memory loss or encephalopathy (n = 4), mood disorder (n = 3), tremor (n = 3), stiffness (n = 3), tinnitus (n = 2), headaches (n = 1), and myelopathy (n = 1). Before evaluation at the Mayo Clinic, 35 patients (29.7%) had evidence of extracerebellar disorders. These diagnoses included idiopathic demyelinating disorder (n = 8), vestibular disorder (n = 6), acute stroke (n = 4), peripheral neuropathy (n = 4), neurodegenerative diagnoses (n = 4), conversion disorder (n = 3), central nervous system infection (n = 2), alcohol abuse (n = 1), Lyme disease (n = 1), hereditary disorder (n = 1), and prion disease (n = 1). The median duration from symptom onset to last follow-up was 25 (range, 2-223) months (last follow-up, December 31, 2013).

### Neurologic Findings

All 118 patients had cerebellar signs. Evidence of additional coexisting extracerebellar disorders was documented in 63 patients (53.4%) (Table 1), the most common of which were upper motor neuron signs (n = 32). Among 14 patients with limb stiffness, 10 were seropositive for GAD65 antibodies, but only 3 had the classic stiff person syndrome phenotype in addition to ataxia. The 63 patients with paraneoplastic disorders had more severe clinical courses regardless of treatment; 17 (27.0%) became wheelchair dependent within 3 months of symptom onset compared with 4 of 55 patients with nonparaneoplastic disorders (7.3%) (P = .007).

### Serologic Findings

Of the 118 patients, 81 (68.6%) had an antibody directed against an NNC antigen, 22 (18.6%) had an antibody targeting a neural PMP receptor or an ion channel, and 15 (12.7%) had antibodies from both categories. All 118 patients had at least 1 autoantibody detected in serum samples, and 25 also had at least 1 autoantibody detected in CSF samples.

Neuronal nuclear or cytoplasmic antibodies detected in serum included GAD65 in 41 cases (median value, 245.6 [range, 0.03-3067] nmol/L), PCA-1 in 37 cases (median value, 1:15 360 [range, 1:120 to 1:983 040]), CRMP-5-IgG in 7 cases (median value, 1:3840 [range, 1:60 to 1:7680]), ANNA-1 in 4 cases (median value, 1:3840 [range, 1:1920 to 1:61 440]), PCA-2 in 3 cases (median value, 1:30 720 [range, 1:960 to 1:61 440]), ANNA-1 in 2 cases (range, 1:7680 to 1:15 360), ANNA-3 in 2 cases (range, 1:960 to 1:1920), and striatal antibody in 7 cases (median value, 1:480 [range, 1:60 to 1:3840]). Of the 45 patients who underwent autoantibody testing in the CSF, 25 had an antibody targeting NNC antigens detected, including PCA-1 in 10 cases (median value, 1:512 [range, 1:32 to 1:4096]), GAD65 in 9 cases (median value, 7.74 [range, 1:03-215] nmol/L), CRMP-5-IgG in 3 cases (median value, 1:256 [range, 1:16 to 1:1024]), ANNA-1 in 1 case (value, 1:16), ANNA-1 in 1 case (value, 1:32), and PCA-2 in 1 case (value, 1:64).

Neuronal autoantibodies targeting PMP antigens (ion channels or receptors) that were detected in serum included N-type calcium channel antibody in 14 cases (median value, 28.5 [range, 0.05-150] nmol/L), P/Q-type calcium channel antibody in 14 cases (median value, 0.16 [range, 0.03-4.16] nmol/L), neuronal VGKC complex antibodies in 7 cases (median value, 0.14 [range, 0.08-5.79] nmol/L), muscle AChR-binding antibody in 5 cases (median value, 0.12 [range, 0.04-5.43] nmol/L), neuronal gangionic AChR antibody in 3 cases (median value, 0.06 [range, 0.04-0.07] nmol/L), PCA-Tr in 1 case (value, 1:5360), and mGluR1-IgG in 1 case (value, 1:61440). Results of testing for VGKC complex antibody subtypes (leucine-rich, glioma inactivated 1 and also contactin-associated protein-like 2 IgGs) were negative in all 7 patients in whom VGKC complex antibodies were detected.

### Oncologic Findings

Sixty-three patients (53.4%) had a paraneoplastic disorder. In 54 patients, the basis was detection of a cancer contemporaneous with the onset of neurologic symptoms (Table 2); in 53 patients, detection of an antibody with a high predictive value for cancer, including PCA-1, PCA-2, PCA-Tr, CRMP-5-IgG, ANNA-1, ANNA-3, or AGNA-1; and in 44 patients, both. Among those 44 patients, cancer diagnoses occurred after paraneoplastic autoantibody detection in 29 patients (median duration to cancer diagnosis, 3 [range, 1-132] months) or before in 15 patients (median duration to neurologic diagnosis, 13 [range, 1-144] months). The remaining 35 patients (46.6%) were considered to have a nonparaneoplastic autoimmune disorder.

### Pretreatment Characteristics

We found complete data pertaining to ataxia duration and ambulatory status at treatment initiation in 98 patients. Compared
Table 2. List of Antibodies and Cancers in 63 Patients With Paraneoplastic Ataxic Disorders

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Cancer Type Detected (No. With Coexisting Antibodies or Cancer)</th>
<th>Of Those With 1 Antibody Only: No. With Immunotherapy Response/No. Receiving Immunotherapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AChR muscle binding</td>
<td>Ovarian adenocarcinoma (1*)</td>
<td>NA</td>
</tr>
<tr>
<td>AChR neuronal ganglionic</td>
<td>Pancreatic adenocarcinoma (1*)</td>
<td>1/2 (50.0)</td>
</tr>
<tr>
<td>ANNA-1</td>
<td>Small cell lung carcinoma (2*–3*), prostate carcinoma (1*)</td>
<td>NA</td>
</tr>
<tr>
<td>CRMP-5–IgG</td>
<td>Small cell lung carcinoma (2*)</td>
<td>0/4</td>
</tr>
<tr>
<td>GAD65</td>
<td>Testicular seminoma and germ cell neoplasia (1), renal cell carcinoma (1), small cell lung carcinoma (1*), uterine adenocarcinoma (1*), colon adenocarcinoma (2*), lymphoma (1), pancreatic cancer (1*)</td>
<td>9/17 (52.9)</td>
</tr>
<tr>
<td>P/Q-type CC</td>
<td>Small cell lung carcinoma (5*–7*)</td>
<td>10/12 (83.3), P/Q and N types together</td>
</tr>
<tr>
<td>N-type CC</td>
<td>Pancreatic cancer (1*), small cell lung carcinoma (2*–3*), ovarian cancer (1*)</td>
<td>10/12 (83.3), P/Q and N types together</td>
</tr>
<tr>
<td>PCA-1</td>
<td>Adenocarcinomas, ovarian cancer (20*–4*), breast (9*)</td>
<td>10/29 (34.5)</td>
</tr>
<tr>
<td>PCA-Tr</td>
<td>Small cell lung cancer (2*), prostate cancer (1*)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Striational</td>
<td>MALT lymphoma (1*), marginal zone lymphoma (1*)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>VGKC complex</td>
<td>Breast cancer (1*)</td>
<td>1/4 (25.0)</td>
</tr>
</tbody>
</table>

Abbreviations: AChR, acetylcholine receptor; AGNA, antiglial and/or nuclear antibody; ANNA, antineuronal nuclear antibody; CC, calcium channel; CRMP-5, collapsin-response mediator protein 5; GAD65, glutamic acid decarboxylase 65-kDa isoform; MALT, mucosa-associated lymphoid tissue; NA, not applicable; PCA, Purkinje cell cytoplasmic antibody; PCA-Tr, PCA receptor; VGKC, voltage-gated potassium channel.

with patients with nonparaneoplastic disorders, patients with paraneoplastic disorders were more likely to be wheelchair bound before treatment began (22 of 51 patients [43.1%] vs 6 of 47 [12.8%]; P = .003) but also received treatment more quickly (mean [SD], 9.6 [20.6] vs 15.4 [29.4] months; P = .002).

Physician-Reported Treatment Responses
Overall, 54 of 118 patients (45.8%) had physician-reported neurologic improvement with immunotherapy (n = 51) or cancer therapy (n = 3), including chemotherapy in 3 patients and radiotherapy in 1 patient. Improvement was reported with treatment consisting of corticosteroids (33 of 84 patients [39.3%]), including 8 of 39 in the paraneoplastic group [20.5%] and 25 of 45 in the nonparaneoplastic group [55.6%]), intravenous immunoglobulin (11 of 44 [25.0%], including 2 of 17 in the paraneoplastic group [11.8%] and 9 of 27 in the nonparaneoplastic group [33.3%], plasma exchange (9 of 28 [32.1%], including 6 of 20 in the paraneoplastic group [30.0%] and 3 of 8 in the nonparaneoplastic group [37.5%]), and cyclophosphamide (5 of 25 [20.0%], including 5 of 19 in the paraneoplastic group [26.3%] and 0 of 6 in the nonparaneoplastic group), but not with rituximab therapy in 3 treated patients. The difference in treatment responses between paraneoplastic and nonparaneoplastic disorders was statistically significant only for corticosteroid therapy (8 of 39 patients [20.5%] vs 25 of 45 patients [55.6%]; P = .002). Neurologic improvements were not predicted by abnormal CSF findings, as evidenced by improvement in 10 of 18 patients (55.6%) with an elevated white blood cell count, 32 of 60 (53.3%) with an elevated protein level, and 12 of 23 (52.2%) with an elevated CSF-exclusive oligoclonal band number.

Results of the univariate logistic regression analysis are shown in eTable 1 in the Supplement. The following variables were associated with a response to immunotherapy: male sex (P = .04), having a nonparaneoplastic disorder (P = .03), and seropositivity for synaptic autoantibodies (P = .02). For multi-variable analysis (eTable 2 in the Supplement), a model that included a nonparaneoplastic diagnosis and being older at onset had an area under the curve of 0.649. The area under the curve is a measure of the model’s ability to discriminate between individuals who responded to immunotherapy vs those who did not; an estimate of 0.7 or higher is regarded as acceptable.

Findings were nonsignificant for the suggestion that earlier immunotherapy might favor improvement among patients with nonparaneoplastic disorders. The median interval from symptom onset to immunotherapy was 6 months for those with a response to treatment vs 12 months among those without a response (P = .05).

Twenty-two patients (18.6%) were judged to have robust responses to immunotherapy trials documented. A robust response was defined as a sustained improvement from one of 5 ambulatory categories to another. The 5 ambulatory categories included bed bound or wheelchair dependent, walker dependent, cane dependent, abnormal gait but ambulatory without gait aid, and normal gait (Table 3). Those patients included
who improved only with a second treatment trial after initial treatment with a different immunotherapy modality had failed (eTable 3 in the Supplement). Patients in the nonparaneoplastic group more commonly had robust responses to short-term immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) than those in the paraneoplastic group (18 of 52 patients [34.6%] vs 4 of 51 [7.8%]; P = .002). The robust responses in the 4 patients with paraneoplastic disorders (sustained in 3) were all attributed to plasma exchange.

One or more maintenance treatments were required to sustain improvements in 16 patients, including mycophenolate mofetil (7 patients), azathioprine sodium (3 patients), prednisone (3 patients), cyclophosphamide (3 patients), and intravenous immunoglobulin (1 patient). Of the remaining 6 patients, no additional immunotherapy was required to sustain the response in 3, whereas the response was short lived in 3 patients and no further immunotherapy was documented.

Ambulatory Outcomes
Final ambulatory outcomes were tabulated regarding the use of gait aids (regardless of response to immunotherapy), including a wheelchair in 56 patients (47.5%), a walker in 26 (22.0%), and a cane in 7 (5.9%). Among the 29 remaining patients (24.6%), 25 required no gait aid but had an abnormal gait and 4 had a normal gait. Patients in the nonparaneoplastic group were more likely to be ambulatory with or without gait aids.

Table 3. Robust Neurologic Improvements in 22 Patients

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Antibody Specificity</th>
<th>Cancer Diagnosis</th>
<th>Neurologic Nadir</th>
<th>Therapy to Which Improvement Attributed</th>
<th>Neurologic Zenith</th>
<th>Maintenance Treatment</th>
<th>Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>63/M/58</td>
<td>AChR ganglionic</td>
<td>None</td>
<td>Use of cane</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>Azathioprine sodium</td>
<td>36</td>
</tr>
<tr>
<td>43/M/54</td>
<td>GAD65</td>
<td>None</td>
<td>Use of walker</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>Mycophenolate mofetil</td>
<td>220</td>
</tr>
<tr>
<td>17/F/46</td>
<td>GAD65</td>
<td>None</td>
<td>Use of walker</td>
<td>Methylprednisolone</td>
<td>Abnormal but independent</td>
<td>Mycophenolate mofetil</td>
<td>19</td>
</tr>
<tr>
<td>97/M/67</td>
<td>GAD65</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>Methylprednisolone</td>
<td>Use of cane</td>
<td>Prednisone</td>
<td>120</td>
</tr>
<tr>
<td>22/F/47</td>
<td>GAD65</td>
<td>None</td>
<td>Use of cane</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>None required</td>
<td>8</td>
</tr>
<tr>
<td>123/F/72</td>
<td>GAD65, striational</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>Mycophenolate mofetil</td>
<td>87</td>
</tr>
<tr>
<td>141/F/78</td>
<td>VGKC complex, P/Q-type CC</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>Mycophenolate mofetil</td>
<td>10</td>
</tr>
<tr>
<td>110/F/69</td>
<td>N-type CC</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>Methylprednisolone</td>
<td>Use of walker</td>
<td>Azathioprine</td>
<td>119</td>
</tr>
<tr>
<td>27/F/48</td>
<td>P/Q-type CC</td>
<td>None</td>
<td>Use of cane</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>Mycophenolate mofetil</td>
<td>4</td>
</tr>
<tr>
<td>53/F/56</td>
<td>P/Q-type CC</td>
<td>None</td>
<td>Use of walker</td>
<td>Methylprednisolone, IVIg</td>
<td>Abnormal gait but independent</td>
<td>Prednisone</td>
<td>1</td>
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<tr>
<td>76/F/62</td>
<td>P/Q-type CC</td>
<td>None</td>
<td>Use of cane</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>Methylprednisolone</td>
<td>4</td>
</tr>
<tr>
<td>5/M/34</td>
<td>P/Q-type C, N-type CC</td>
<td>None</td>
<td>Use of cane</td>
<td>Methylprednisolone</td>
<td>Normal gait</td>
<td>Mycophenolate mofetil</td>
<td>34</td>
</tr>
<tr>
<td>139/M/78</td>
<td>P/Q-type CC, N-type CC</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>Prednisone</td>
<td>Use of walker</td>
<td>Prednisone</td>
<td>21</td>
</tr>
<tr>
<td>82/F/64</td>
<td>GAD65</td>
<td>History of diagnoses of breast and thyroid cancer</td>
<td>Use of wheelchair</td>
<td>IVIg</td>
<td>Use of cane</td>
<td>IVIg</td>
<td>1</td>
</tr>
<tr>
<td>19/M/46</td>
<td>GAD65</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>IVIg</td>
<td>Use of walker</td>
<td>Mycophenolate mofetil, cyclophosphamide</td>
<td>52</td>
</tr>
<tr>
<td>16/F/46</td>
<td>AChR binding, PCA-1</td>
<td>Ovarian adenocarcinoma</td>
<td>Use of wheelchair</td>
<td>Plasma exchange</td>
<td>Use of walker</td>
<td>None required</td>
<td>29</td>
</tr>
<tr>
<td>132/F/75</td>
<td>PCA-1</td>
<td>Fallopian tubal adenocarcinoma</td>
<td>Use of wheelchair</td>
<td>Plasma exchange</td>
<td>Use of walker</td>
<td>Cyclophosphamide</td>
<td>5</td>
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<tr>
<td>48/F/55</td>
<td>PCA-1</td>
<td>Ovarian adenocarcinoma</td>
<td>Use of wheelchair</td>
<td>Plasma exchange</td>
<td>Abnormal gait but independent</td>
<td>Cyclophosphamide</td>
<td>9</td>
</tr>
<tr>
<td>24/F/47</td>
<td>P/Q-type CC, N-type CC</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>Plasma exchange</td>
<td>Use of cane</td>
<td>None required</td>
<td>68</td>
</tr>
<tr>
<td>99/F/67</td>
<td>PCA-1</td>
<td>Breast and fallopian tubal adenocarcinomas</td>
<td>Bedbound</td>
<td>Plasma exchange</td>
<td>Use of walker</td>
<td>Cyclophosphamide</td>
<td>5</td>
</tr>
<tr>
<td>117/M/70</td>
<td>VGKC complex</td>
<td>History of prostate adenocarcinoma</td>
<td>Bedbound</td>
<td>Plasma exchange</td>
<td>Use of walker</td>
<td>Azathioprine</td>
<td>1</td>
</tr>
<tr>
<td>33/F/50</td>
<td>AChR binding</td>
<td>None</td>
<td>Use of wheelchair</td>
<td>Plasma exchange</td>
<td>Abnormal gait but independent</td>
<td>Not undertaken</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: IVIg, intravenous immunoglobulin. See Table 2 for other abbreviations.

* Additional details are given in eTable 3 in the Supplement.

a Indicates immunotherapy used to maintain neurologic improvement.

b Response not sustained despite long-term immunotherapy.

c Response not sustained, but no further immunotherapy tried.
Fifty-seven patients (50%) were expected to be wheelchair dependent by 25.5 months. Progression to wheelchair dependence was faster among patients with paraneoplastic compared with nonparaneoplastic autoimmune ataxia and among those with positivity for neuronal nuclear and cytoplasmic antibodies (NNC Abs+) only (vs positivity for plasma membrane protein Abs [PMP Abs+] only).

The time from symptom onset to the final ambulatory outcome was available for 114 patients and was analyzed using the Kaplan-Meier method (Figure 1 and Figure 2). Fifty-seven patients (50.0%) became wheelchair dependent by 25.5 months by Kaplan-Meier analysis (Figure 1, A). Patients with paraneoplastic autoimmune ataxia progressed to wheelchair depen-
Progression to wheelchair dependence was faster among patients with Purkinje cell cytoplasmic antibody type 1 (PCA-1) seropositivity and glutamic acid decarboxylase 65-kDa autoantibody (GAD65) seronegativity. Patients with GAD65 seropositivity and patients with plasma membrane protein (PMP) seropositivity progressed to wheelchair dependence at similar rates.

Abs indicates antibodies; superscript minus sign, seronegativity; and superscript plus sign, seropositivity.
Discussion

In our large series of treated patients with outcome data, autoimmune cerebellar ataxia often led to severe disability. However, 45.8% of our patients had neurologic improvement with immunotherapy, which was robust in 18.6%; 62 of 118 (52.5%) remained ambulatory.

The subgroup with paraneoplastic disorders accounted for about half of the cases and had substantially less responsiveness to immunotherapy (7.8% had robust responses) and a worse overall prognosis (43 of 63 patients [68.3%] were wheelchair bound by the last follow-up). This group of 63 patients was dominated by 58.7% with PCA-1 (anti-Yo) autoimmunity, which likely explains our finding of male sex as a predictor of response to immunotherapy. However, a small group of those patients with paraneoplastic disorders (4 patients, all with PCA-1, representing 10.8% of those with that antibody) experienced substantial benefit with plasma exchange. Those patients also may harbor an unidentified IgG whose pathogenicity was abrogated by removal. In contrast, more than half of the cases with nonparaneoplastic autoimmune cerebellar ataxia improved with immunotherapy. Having a nonparaneoplastic disorder was the single strongest predictor of a response to immunotherapy. At last follow-up, 76.4% remained ambulatory.

The improvements noted in many of our patients with antibodies targeting calcium channels and other ion channels and receptors were consistent with those of previous reports. Similarly, patients with antibodies targeting PMP ion channels, water channels, or receptors (such as N-methyl-D-aspartate receptors and aquaporin 4) often have robust clinical improvement after receiving antibody-depleting treatments, such as plasma exchange and rituximab.

Consistent with previous studies, variable immunotherapy responses were notable among patients seropositive for GAD65 antibodies, and a shorter interval from symptom onset to treatment predicted a greater likelihood of improvement. Response rates and ambulatory outcomes of the patients who were seropositive for GAD65 antibodies (the nonparaneoplastic group) were similar to those of the patients seropositive for PMP antibodies. GAD65 is a synaptic antigen that is cytoplasmic facing and thought to be inaccessible to antibody in vivo. However, patients with another disorder in the GAD65 autoimmune neurologic spectrum, stiff person syndrome, are reported to have coexisting IgG that is reactive with cell surface antigens in many instances, including glycome receptor antibodies. Thus, some patients with immunotherapy-responsive GAD65 in our series may have had 1 or more coexisting (but yet uncharacterized) cell surface antigen–directed antibodies.

Robust responses to immunotherapy (defined as a clear change in ambulatory status) occurred during only the second treatment trial in 8 of 22 patients with a robust treatment response. A similar effect was reported in patients with autoimmune epilepsy. For example, if corticosteroids did not induce early improvement, a trial of plasma exchange could be beneficial. Short courses of immunotherapy brought about improvements but rarely responses that were sustained; hence, maintenance immunotherapy was required. Although the duration of therapy could not be determined from our data set, general recommendations are available. Treatment for 3 to 6 months with a slow taper of immunotherapy is more effective in general than short courses for a duration ranging from days to a few weeks. Plasma exchange could be considered in paraneoplastic disorders when other immunotherapies have not produced improvement and the cancer is treatable.

This study was limited by the necessity of a retrospective design because these disorders are rare, which limited the interpretations of the treatment results. In particular, in the absence of established treatment protocols, the duration and combination of immunotherapies varied. We conclude that although detection of a paraneoplastic disorder or NNC antibody may portend a worse prognosis, this finding should not deter physicians from trials of immunotherapy in these patients because some may improve. Sequential trials of corticosteroids, plasma exchange, and intravenous immunoglobulin could be undertaken in any patient with autoimmune ataxia, including those with paraneoplastic disorders, although these patients are less likely to respond overall. Data from validated disability scales were not recorded making it impossible to rate changes in pertinent neurologic domains, apart from ambulation (such as speech, limb coordination, and cognition). Although these patients all had ataxia–predominant disorders, half had a variety of coexisting extracerebellar signs. These mixed phenotypes are common in autoimmune neurologic practice, and a multifocal neurologic presentation may serve as a diagnostic clue. For example, patients with paraneoplastic chorea frequently have accompanying peripheral neuropathy. Of additional note, we included patients who were seronegative for neural antibodies, and we did not reevaluate stored serum and CSF specimens of patients with seronegative ataxia for more recently reported neuronal autoantibodies pertinent to autoimmune ataxia, although these autoantibodies are comparatively rare in our laboratory experience.

Conclusions

Autoimmune cerebellar ataxia is a potentially treatable disorder. Factors that may predict better immunotherapy response and neurologic outcomes include a nonparaneoplastic disorder, the detection of 1 or more PMP antibodies, or the detection of GAD65 antibodies.
ARTICLE INFORMATION
Accepted for Publication: July 28, 2015.
Published Online: September 28, 2015.

Author Contributions: Dr McKeon had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: McKeon.
Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Jones, McKeon.
Critical revision of the manuscript for important intellectual content: Flanagan, Pittock, Mandrekar, Eggers, Ahlskog, McKeon.
Statistical analysis: Flanagan, Mandrekar, McKeon.

Study supervision: McKeon.

Conflict of Interest Disclosures: Dr Pittock reports receiving no royalties to date but may accrue revenue for patients relating to aquaporin 4 (AQP4) antibodies for diagnosis of neuromyelitis optica and AQP4 autoantibody as a cancer marker; he also reports receiving research support from the Guthy-Jackson Charitable Foundation, Alexion Pharmaceuticals, Inc, and grant RO1 NS065829 from the National Institutes of Health. No other disclosures were reported.

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