Adult-Onset Opsoclonus-Myoclonus Syndrome

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Background: Little is known about adult-onset opso-
clusus-myoclonus syndrome (OMS) outside of indi-
vidual case reports.

Objective: To describe adult-onset OMS.

Design: Review of medical records (January 1, 1990, through December 31, 2011), prospective telephone sur-
veillance, and literature review (January 1, 1967, through December 31, 2011).

Setting: Department of Neurology, Mayo Clinic, Roch-
ester, Minnesota.

Patients: Twenty-one Mayo Clinic patients and 116 pre-
viously reported patients with adult-onset OMS.

Main Outcome Measures: Clinical course and lon-
titudinal outcomes.

Results: The median age at onset of the 21 OMS pa-
tients at the Mayo Clinic was 47 years (range, 27-78 years); 11 were women. Symptoms reported at the first visit in-
cluded dizziness, 14 patients; balance difficulties, 14; nau-
sea and/or vomiting, 10; vision abnormalities, 6; tremor/
tremulousness, 4; and altered speech, 2. Myoclonus
distribution was extremities, 15 patients; cranioce-
vical, 8; and trunk, 4. Cancer was detected in 3 patients
(breast adenocarcinoma, 2; and small cell lung carci-
oma, 1); a parainfectious cause was assumed in the re-
mainder of the patients. Follow-up of 1 month or more
was available for 19 patients (median, 43 months; range,
1-187 months). Treatment (median, 6 weeks) consisted
of immunotherapy and symptomatic therapy in 16 pa-
tients, immunotherapy alone for 2, and clonazepam alone
for 1. Of these 19 patients, OMS remitted in 13 and im-
proved in 3; 3 patients died (neurologic decline, 1; can-
cer, 1; and myocardial infarction, 1). The cause of death
was of paraneoplastic origin in 60 of 116 literature re-
view patients, with the most common carcinomas being
lung (33 patients) and breast (7); the most common an-
tibody was antineuronal nuclear antibody type 2 (anti-
RI. 15). Other causes were idiopathic in origin, 38 pa-
tients; parainfectious, 15 (human immunodeficiency virus,
7); toxic/metabolic, 2; and other autoimmune, 1. Both
patients with N-methyl-D-aspartate receptor antibody had
encephalopathy. Improvements were attributed to im-
munotherapy alone in 22 of 28 treated patients.

Conclusions: Adult-onset OMS is rare. Paraneoplastic
and parainfectious causes (particularly human immu-
nodeficiency virus) should be considered. Complete re-
mission achieved with immunotherapy is the most com-
mon outcome.

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Video available online at
www.archneurol.com

OPSOCLOMUS-MYOCLOMUS
syndrome (OMS) is well
described in children
(also known as Kins-
bournes syndrome3), usu-
ally occurring as a paraneoplastic neuro-
logic accompaniment of neuroblastoma1,2

with long-term neurologic, behavioral, and
developmental sequelae.3,4 The OMS lit-
erature on adults is largely confined to
cases and small case series. Most clini-
cians know that a paraneoplastic cause
should be considered (eg, antineuronal
nuclear antibody type 2 [ANNA-2, anti-
RI] and accompanying breast adenocarci-
noma or small cell carcinoma are well

known5,6). However, there are few col-
lected data to inform physicians about
which common and uncommon causes
should be considered, the clinical course,
and outcomes from treatment.7 We
describe OMS in adults consecutively
evaluated at Mayo Clinic, Rochester,
Minnesota, during a 21-year period and
prospectively evaluated for longitudinal
outcomes. We also evaluated the 40-year
cumulative literature on adult-onset OMS.

METHODS

We conducted a medical record review,
follow-up telephone interview, and serologic
evaluation of patients with adult-onset OMS
(age at onset, ≥18 years and initial examina-
tion findings predominated by opsoclonus
and myoclonus) seen at the Mayo Clinic, Roches-
MAYO CLINIC PATIENT ASCERTAINMENT

The Mayo Clinic medical records linkage system was retrospectively queried using the terms opsoclonus and Kinsbourne syndrome to identify adult patients who received a diagnosis of OMS at the Mayo Clinic between 1990 and 2011.

INCLUSION CRITERIA

Medical records for 91 patients were reviewed by 2 of the authors (J.P.K. and A.M.). We included patients with simultaneous onset of opsoclonus and myoclonus at or after age 18 years, with OMS being the predominant clinical presentation. Seventy patients were excluded: 37 pediatric patients with symptoms persisting into adulthood, 23 patients determined to have final neurologic diagnoses other than OMS, 3 patients with only opsoclonus identified on examination, 2 patients with only myoclonus identified on examination, 4 patients for whom not enough data were available, and 1 patient with opsoclonus and myoclonus observed as part of a more widespread encephalitic disorder. The latter patient’s case has been published and is included in the current literature review.

In addition to documenting clinical information from the medical records, we attempted to contact all 21 included patients by telephone for additional longitudinal information regarding the clinical course of the disease. For patients who had died, additional information regarding the cause of death was obtained by review of the death certificate, when available.

SEROLOGIC EVALUATION

For each patient, a serum sample was evaluated, as previously described, by (1) standardized immunofluorescence criteria for IgG neural autoantibodies (ANNA-1 [also known as anti-Hu], -2, -3; amphiphysin antibody, Purkinje cell cytoplasmic antibody [PCA] type 1 [also known as anti-Yo], -2, and Tr antibodies; collapsin-response mediator-protein [CRMP] 5 IgG, antiguilal/neuronal nuclear antibody [AGNA-1], N-methyl-D-aspartate [NMDA] receptor antibody, y-aminobutyric acid B [GABA-B] receptor antibody, and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate [AMPA] receptor antibody); (2) by radioimmunoprecipitation assays for antibodies targeting neuronal voltage-gated cation channels (neuronal voltage-gated potassium channel [VGKC] complex, calcium channels [P/Q-type and N-type], muscle α-synergic and neuronal α-synergic nicotinic acetylcholine receptors) and glutamic acid decarboxylase 65-isofrom (GAD65); (3) by human embryonic kidney transfected cell-binding assays for antibodies targeting NMDA, AMPA, and GABA-B receptors and VGKC complex proteins (disintegrin and metalloproteinase 22 [ADAM22] and a soluble binding partner of ADAM22, leucine-rich, glioma-inactivated 1 [LGI1] protein) (Euroimmun); and (4) by recombinant Western blot analysis for CRMP-5-IgG, b, c

LITERATURE REVIEW PATIENTS

We searched PubMed using the terms opsoclonus and myoclonus to identify case reports and case series reporting on patients aged 18 years or older with OMS or who had opsoclonus and myoclonus as part of a more widespread disorder. We included all English-language publications identified between 1967 and 2011 with complete descriptions of individual patients.

RESULTS

We identified 21 Mayo Clinic patients (11 women and 10 men) with adult-onset OMS who met the inclusion criteria. Median follow-up was 43 months (range, 1-187 months). The median age at symptom onset was 47 years (range, 27-78 years).

A flulike prodrome before neurologic symptom onset was reported by 6 patients. The initial neurologic symptoms included dizziness, 14 patients (67%); balance difficulties (caused by myoclonus), 14 (67%); nausea and/or vomiting, 10 (48%); vision abnormalities (caused by opsoclonus), 6 (28%); tremor/tremulousness, 4 (19%); and altered speech (caused by myoclonus), 2 (10%). Symptoms progressed rapidly, and most patients were seen by a neurologist within a median of 4 weeks after symptom onset. Levels of mobility at nadir for 18 patients were wheelchair or 2-person assistance needed to mobilize, 10 patients; gait unsteadiness but able to walk independently, 6; and cane required to walk independently, 2. Other symptoms that developed included weight loss (>4.5 kg), 10 patients; mood changes, 9 (depression, 5; irritability/emotional lability, 4); dysphagia, 3 (resulting from myoclonus or nausea/vomiting); fatigue/sleep disturbance, 3; headache, 1; and falls, 1.

All 21 patients were examined by a Mayo Clinic staff neurologist. Myoclonus (sudden, brief, shock-like, involuntary movements) was identified on clinical examination in all 21 patients (Table 1). Opsoclonus, being the ocular manifestation of myoclonus, was present in all patients. The myoclonus was typically posture- or movement-induced (action myoclonus), including 3 patients with lower extremity myoclonus that was present or worse on standing, which caused unsteadiness, tremulousness, and falls. Anatomic distribution of myoclonus on examination was predominately, 15 patients (upper and lower, 13; upper only, 1; and lower only, 1); cranio cervical, 8 (hyperkinetic dysthria, 5; and head, 3); and trunk, 4. Additional neurologic findings were reported in 3 patients as brisk, deep tendon reflexes.

Evaluations

Findings from magnetic resonance imaging, performed in 20 patients, were unremarkable in all but 1 patient with small-cell lung carcinoma who had metastatic lesions in both cerebellar hemispheres and in the right caudate nucleus (patient 7). Cerebrospinal fluid (CSF) analysis was available for 18 patients (86%) (Table 1) and revealed elevated protein (>45 mg/dL) in 11 patients (median, 64 mg/dL, range, 47-137 mg/dL), elevated white blood cell count (>5/μL) in 9 patients (median, 20/μL, range, 8.9-1.64/μL; all lymphocyte predominant), elevated IgG index (>0.85) in 4 patients (median, 1.14; range, 0.88-1.64), and CSF-exclusive oligoclonal bands (>3) in 5 patients (median, 5; range, 4-8).
<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y, at Onset</th>
<th>Initial Symptoms</th>
<th>Distribution of Myoclonus</th>
<th>Additional Symptoms</th>
<th>Coexisting Autoimmune Disorder</th>
<th>CSF Findings&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/68 D, B, N U 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2/F/53 D, B</td>
<td>L 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/M/46 B, V All Fatigue/sleep issues</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/F/40 D, N All Weight loss</td>
<td>Psoriasis</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5/M/48 B, V, S Cr Weight loss, dysphagia, mood changes</td>
<td>Paraneoplastic negative</td>
<td>0</td>
<td></td>
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<tr>
<td>6/F/36 N, V, T/T All, Cr Weight loss, depression</td>
<td>0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7/M/54 D, N All, T Weight loss</td>
<td>0</td>
<td></td>
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</tr>
<tr>
<td>8/M/27 T/T All Mood changes, weight loss</td>
<td>Paraneoplastic negative</td>
<td>0</td>
<td></td>
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</tr>
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<td>9/F/70 D All Weight loss</td>
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<td>10/F/48 B, D, S Cr Fatigue/sleep issues, falls, mood changes, weight loss</td>
<td>Intraductal breast carcinoma</td>
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<td>11/M/78 B All, Cr, T Mood changes, weight loss</td>
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<td>0</td>
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</tr>
<tr>
<td>14/F/32 B, V, N Cr 0</td>
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<td></td>
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<tr>
<td>15/F/47 D, B, N, T/T All 0</td>
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<tr>
<td>16/M/44 D, B, V All Fatigue/sleep issues, weight loss</td>
<td>Paraneoplastic negative</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>17/F/30 D, B, N Cr 0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>18/M/37 19/M/52 D, B Cr, All, T</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>20/M/51 D, N All Mood changes</td>
<td>Paraneoplastic negative</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21/F/52 B, T/T All, T 0</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Abbreviations: All, all extremities; B, balance difficulties; C, white blood cell count; Cr, cranio cervical; CSF, cerebrospinal fluid; D, dizziness; L, lower limbs only; N, nausea and vomiting; NA, not available; OCBs, CSF-exclusive oligoclonal bands; P, protein; S, altered speech; T, trunk; T/T, tremor/tremulousness; U, upper limbs only; V, vision abnormalities.

<sup>a</sup>The CSF reference values were P, >45 mg/dL; C, >5/µL; IgG index, <0.85; OCBs, >3.
Of 21 patients, some follow-up data were available for 19 (Table 2). The median age at symptom onset was 50 years (range, 19-80 years); 70 patients (60%) were women. Opsoclonus-myoclonus syndrome was present in isolation in 83 patients and accompanied another neurolological or neuropsychiatric disorder in 33 patients. Coexisting disorders were mild behavioral, cognitive, and/or mood changes, 18 patients; encephalopathy, 9; cranial nerve palsies, 4; Lambert-Eaton myasthenic syndrome and ataxia, 1; and seizure disorder, 1. The 2 patients with NMDA receptor antibody had initial symptoms of prominent behavioral and/or mood change followed by encephalopathy, with opsoclonus and myoclonus additionally observed. The causes reported were paraneoplastic, 60 patients (breast and lung cancers were the most common; ANNA-2 was the most common paraneoplastic antibody detected); none identified, 38 (occurred during pregnancy in 2 women); proven parainfectious, 15 (including 7 with HIV infection); other autoimmune, 1 (GAD65 antibody seropositive); hyperosmolar nonketotic diabetic coma, 1; and cocaine ingestion, 1.

Outcome information was available for 115 patients (Table 3). For 41 patients, reported outcomes for a single treatment type (immunotherapy, oncologic therapy, symptomatic therapy, or other therapy) could be interpreted. Improvements were attributed to immunotherapy alone in 22 of 28 patients treated; median duration of treatment was 6 weeks (range, 1-112 weeks). These treatments were corticosteroids, 8 patients; IVIG, 6; corticosteroids and IVIG, 4; corticosteroids and plasmapheresis, 1; and other combinations, 3. Improvements were attributed to oncologic therapy in all 10 treated patients (±1 of surgery, chemotherapy, and radiotherapy); symptomatic therapy in 8 of 9 patients treated (benzodiazepines alone, 7; benzodiazepines with valproic acid, 1); ceftriaxone sodium, 2 (both patients had neuroborreliosis and improved); combination antiretroviral therapy (neurolological symptoms in 1 HIV-positive patient resolved); and insulin, 1 (resolved on treatment of diabetic coma). Fifty-three other patients received combinations of 1 or more of the treatment types listed. Of the 21 remaining patients who received no treatment, 18 were reported to have spontaneous remission (15 patients) or improvement (3).

This study represents a large single-institution case series of consecutively evaluated patients with adult-onset OMS. We observed that many patients had an idiopathic (presumed parainfectious) disorder of short duration, with full recovery after 4 to 6 weeks of treatment, usually immunotherapy and clonazepam combined. Nonetheless, in the Mayo Clinic patients, cancer was an important cause (14%), and a few patients also had a relapsing course or a poor outcome. Findings from CSF analysis helped to confirm an autoimmune cause, but neutral autoantibodies (including paraneoplastic antibodies) were not detected in any of our patients despite comprehensive serologic evaluations. Paraneoplastic autoantibody detection was similarly uncommon (2 of 24 patients with opsoclonus or OMS) in a multi-
institutional Spanish study. Our interpretation of individual treatments (immunotherapeutic vs symptomatic) was limited because most patients received both immunologic and symptomatic therapies simultaneously. We expanded on our data with a systematic review of the literature. Several patients reported in the literature had mild coexisting neurologic or neuropsychiatric symptoms, but outright encephalopathy was uncommon except in paraneoplastic cases. It was informative that both patients with NMDA receptor antibodies

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Cause</th>
<th>Duration Before Immunotherapy, wk</th>
<th>Symptom Duration Before Immunotherapy, wk</th>
<th>Immunotherapy</th>
<th>Duration of Immunotherapy, wk</th>
<th>Symptomatic Therapy for Myoclonus</th>
<th>Initial Outcome, ≤1 mo</th>
<th>Final Outcome</th>
<th>Total Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unknown</td>
<td>1</td>
<td>PLEX, 3 times; prednisone, unknown dose</td>
<td>4</td>
<td>Clonazepam, unknown dose</td>
<td>Progressive neurologic decline, died 1 mo after symptom onset</td>
<td>Died</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Paraneoplastic</td>
<td>No immunotherapy</td>
<td>NA</td>
<td>NA</td>
<td>Clonazepam</td>
<td>Only minimal opoclonus</td>
<td>Neurologic remission</td>
<td>Neurologic remission</td>
<td>145</td>
</tr>
<tr>
<td>3</td>
<td>Unknown</td>
<td>2</td>
<td>IV methylprednisolone, 1 g, 5 doses; IVIG, 5 doses</td>
<td>2</td>
<td>Clonazepam, 0.5 mg, 2 times/d</td>
<td>Neurologic remission, apart from brief, infrequent attacks of opoclonus</td>
<td>Neurologic remission</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Unknown</td>
<td>4</td>
<td>IV methylprednisolone, 1 g, 5 doses; IVIG, 5 doses</td>
<td>2</td>
<td>None</td>
<td>Improvement</td>
<td>Neurologic remission</td>
<td>59</td>
<td></td>
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<tr>
<td>5</td>
<td>Unknown</td>
<td>NA</td>
<td>Unknown</td>
<td>0</td>
<td>Clonazepam</td>
<td>Unknown</td>
<td>Neurologic remission</td>
<td>Unknown</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Unknown</td>
<td>8</td>
<td>IV methylprednisolone, 1 g, 5 doses; IVIG, 5 doses</td>
<td>2</td>
<td>Clonazepam, 1-2 mg, 3 times/d</td>
<td>Unknown</td>
<td>Neurologic remission</td>
<td>187</td>
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<tr>
<td>7</td>
<td>Paraneoplastic</td>
<td>4</td>
<td>IVIG, 3 doses; IV methylprednisolone, 1 g, 5 doses</td>
<td>2</td>
<td>Clonazepam</td>
<td>Significant improvement but still required gait assistance</td>
<td>Died</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Unknown</td>
<td>54</td>
<td>IV methylprednisolone, 1 g, 5 doses</td>
<td>1</td>
<td>Valproic acid, 750 mg, morning; 500 mg, evening</td>
<td>Occasional myoclonus</td>
<td>Neurologic remission</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Unknown</td>
<td>12</td>
<td>IV methylprednisolone, unknown duration or dose; PLEX, 7 times</td>
<td>2</td>
<td>Clonazepam</td>
<td>Marked improvement, continued improvement at final follow-up</td>
<td>Death from myocardial infarction 1 y after symptom onset with neurologic symptoms at time of death</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Paraneoplastic</td>
<td>32</td>
<td>IVIG, 3 doses/wk for 3 wk; IVIG, 2 doses/wk for 2 wk; IVIG, 8 doses during 3 mo; total, 21 doses</td>
<td>26</td>
<td>None</td>
<td>Improved balance, clearer speech</td>
<td>Improved, but mild dysarthria persisted; required walker/scooter for ambulation</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Unknown</td>
<td>2</td>
<td>IV methylprednisolone, 1 g, 5 doses; IVIG, 3 doses</td>
<td>2</td>
<td>Clonazepam (too sedated); divalprox sodium, 500 mg, 2 times/d</td>
<td>Improvement</td>
<td>Unknown</td>
<td>1.5</td>
<td></td>
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<tr>
<td>12</td>
<td>Unknown</td>
<td>4</td>
<td>IV methylprednisolone, 1 g, 3 doses; IVIG, 5 doses</td>
<td>2</td>
<td>Clonazepam</td>
<td>Symptoms persisted, required inpatient rehabilitation</td>
<td>Neurologic remission</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Unknown</td>
<td>2</td>
<td>Prednisone, unknown dose or duration; IVIG, 3 doses</td>
<td>3</td>
<td>Clonazepam, 1.5 mg, 3 times/d; gabapentin, 300 mg, 3 times/d</td>
<td>Improvement</td>
<td>Neurologic remission</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Unknown</td>
<td>2</td>
<td>IV methylprednisolone, 1 g, 3 doses; IVIG, 7 doses</td>
<td>2</td>
<td>Clonazepam, 1 mg, 3 times/d</td>
<td>Symptoms resolved, except opoclonus</td>
<td>Neurologic remission</td>
<td>99</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
had coexisting neuropsychiatric symptoms followed by encephalopathy.8,71

Among both the Mayo Clinic patients and those reported in the literature, lung and breast carcinomas were the most common cancers identified, and ANNA-2 was the most commonly reported paraneoplastic antibody.

The diversity of reported paraneoplastic autoantibodies, including those with specificity for other neuronal nuclear antigens,7,35 neuronal calcium channels,69,77 and NMDA receptors,8,71 serves to emphasize the importance of comprehensive paraneoplastic serologic evaluations (rather than syndrome-specific physician-selected antibody testing) in these patients. Rarer oncologic associations that merit exclusion include melanoma41,53,55 and neoplasms of the gynecologic,34,37,40,42,55,70 urologic,6,43 hematologic,51 and gastrointestinal systems.7

Comparison of paraneoplastic and idiopathic cases was not possible within our own cohort given the low number of patients with cancer. Bataller et al7 reported that older age, higher frequency of encephalopathy, and a more severe clinical course are more common among paraneoplastic cases. Patients from our cohort were similar in age and sex profile as well as clinical presentation to patients reported in the literature. In contrast, the proportion of patients in the collated literature with an established cause (62%) was much higher than in our series. Since individual reported cases usually have rare or unique characteristics prompting description, this higher proportion of paraneoplastic cases in the literature compared with our clinical practice may represent a reporting bias. Other myoclonic presentations that ought to be recognized as possibly paraneoplastic include opsoclonus only,30 progressive encephalomyelitis with rigidity and myoclonus,79 and isolated generalized small-amplitude limb and axial myoclonus.80 This latter group has myoclonus but no opsoclonus as an additional

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**Table 2. Treatment and Outcome Data for 21 Adults With Opsoclonus-Myoclonus Syndrome (continued)**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Cause</th>
<th>Symptom Duration Before Immunotherapy, wk</th>
<th>Duration of Immunotherapy, wk</th>
<th>Duration of Therapy for Myoclonus</th>
<th>Initial Outcome, ≤1 mo</th>
<th>Final Outcome</th>
<th>Total Follow-up, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>Unknown</td>
<td>4</td>
<td>IV methylprednisolone, 125 mg, unknown duration; IVIG, 5 doses; PLEX, 7 times plus IV methylprednisolone, 1 g, on alternate days</td>
<td>3</td>
<td>Clonazepam, 1 mg, 3 times/d; gabapentin, 400 mg, 3 times/d</td>
<td>Symptoms resolved, except opsoclonus</td>
<td>Neurologic remission</td>
</tr>
<tr>
<td>16</td>
<td>Unknown</td>
<td>6</td>
<td>IV methylprednisolone, 1 g, unknown duration; IVIG, 9 doses</td>
<td>8</td>
<td>Clonazepam, 2 mg, 2 times/d</td>
<td>Improvement, but relapse</td>
<td>Mild symptoms</td>
</tr>
<tr>
<td>17</td>
<td>Unknown</td>
<td>2</td>
<td>IV methylprednisolone, 1 g, for 5 d; IVIG for 3 d; then weekly IVIG alternating with IV methylprednisolone, 1 g, for 6 wk; then IV methylprednisolone, 1 g, every other week for 4 wk; every 3 wk, 3 doses; monthly for 6 mo; every 6 wk, 4 doses; total IV methylprednisolone, 1 g, 25 doses; mycophenolate mofetil, 1500 mg, 2 times/d for 16 mo</td>
<td>112</td>
<td>Clonazepam, 0.5 mg, 3 times/d</td>
<td>Improvement, but relapse</td>
<td>Neurologic remission</td>
</tr>
<tr>
<td>18</td>
<td>Unknown</td>
<td>2</td>
<td>Unknown</td>
<td>1</td>
<td>Clonazepam, 1 mg, 3 times/d</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>19</td>
<td>Unknown</td>
<td>3</td>
<td>IV methylprednisolone, 1 g, 5 doses</td>
<td>1</td>
<td>Clonazepam, 1 mg, 4 times/d</td>
<td>Neurologic remission</td>
<td>Unknown</td>
</tr>
<tr>
<td>20</td>
<td>Unknown</td>
<td>8</td>
<td>IVIG plus IV methylprednisolone, 1 g, for 3 d; weekly for 6 wk; every other wk for 6 wk</td>
<td>16</td>
<td>Baclofen, 15 mg, 3 times/d</td>
<td>Improvement</td>
<td>Neurologic remission</td>
</tr>
<tr>
<td>21</td>
<td>Unknown</td>
<td>12</td>
<td>IVIG for 3 d; IVIG plus IV methylprednisolone, 1 g/wk for 6 wk; every other week for 6 wk</td>
<td>12</td>
<td>Levetiracetam, 1500 mg, 2 times/d</td>
<td>Improvement</td>
<td>Neurologic remission</td>
</tr>
</tbody>
</table>

Abbreviations: IV, intravenous; IVIG, IV immune globulin; NA, not available; PLEX, plasma exchange.

*When IV methylprednisolone was administered, methylprednisolone acetate was used.

References 3-7, 36, 40, 45, 48, 50, 61, 62.
Table 3. Literature Review Patients: Summary of Findings Among 116 Reported Patients With OMS

<table>
<thead>
<tr>
<th>Presenting Symptom (n = 93)</th>
<th>Myoclonus Distribution (n = 87)</th>
<th>Coexisting Neurologic Disorder (n = 33)</th>
<th>Paraneoplastic Cause With Corresponding Cancer (n = 21)—a</th>
<th>Infectious Causes (n = 15)</th>
<th>Other Causes (n = 5)</th>
<th>Outcomes (n = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness, 44 G, 44</td>
<td>Behavior changes, 19b</td>
<td></td>
<td>ANNA-2, anti-Ri, 14; breast adenocarcinoma, 4; none found, 3; non-small cell lung carcinoma, 5; small cell lung carcinoma, 2; ovarian, 1; bladder carcinoma, 1</td>
<td>HIV, 7; 2 of these had TB meningitis, 1 had pulmonary TB, 1 had EBV</td>
<td>Other autoimmune, 1; GAD65 Ab, 1</td>
<td>Remission, 51; 18 of these were spontaneous</td>
</tr>
<tr>
<td>Imbalance, 35 AE, 15</td>
<td>Non–small cell lung carcinoma, 7</td>
<td></td>
<td>Borrelia burgdorferi, 2</td>
<td>Streptococcal throat infection, 1</td>
<td>During pregnancy (presumed autoimmune), 2</td>
<td>Mild symptoms, 33</td>
</tr>
<tr>
<td>Nausea, 32 T only, 9</td>
<td>Encephalopathy, 9</td>
<td>Breast adenocarcinoma, 7</td>
<td>Calcium channel, P/Q or N-type, 2; small cell lung carcinoma, 2</td>
<td>CMV, 1</td>
<td>Hyperosmolar nonketotic diabetic coma, 1</td>
<td>Rapid deterioration and death, 12</td>
</tr>
<tr>
<td>Tremor, 20 CC, 4</td>
<td>Melanoma, 3</td>
<td></td>
<td>EBV, 1</td>
<td></td>
<td>Improved but residual significant disability, 12</td>
<td>No improvement, 7</td>
</tr>
<tr>
<td>Vision disturbed, 15</td>
<td>CC and T, 4</td>
<td>CN palsy, 4</td>
<td>Ovarian carcinoma, 3</td>
<td></td>
<td></td>
<td>Total deaths, 28; cancer, 10; neurologic disorder, 8; sepsis, 1; pulmonary embolism, 1; unknown/not documented, 8</td>
</tr>
<tr>
<td>Seizure disorder, 3</td>
<td>HD, 4</td>
<td>Renal cell carcinoma, 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever, 2 UE only, 3</td>
<td>SZ, 1</td>
<td>Medullary carcinoma thyroid, 1</td>
<td>ANNA-1; anti-Hu, 2; small cell lung carcinoma, 2</td>
<td>Coxsackie virus, 1</td>
<td>Cocaine, 1</td>
<td></td>
</tr>
<tr>
<td>Headache, 2 LE, 3</td>
<td></td>
<td>Ovarian teratoma, 1</td>
<td>Ovarian carcinoma, 2</td>
<td></td>
<td>West Nile virus, 1</td>
<td></td>
</tr>
<tr>
<td>Hearing loss, 1 T and UE, 2</td>
<td>LEMS and cerebellar degeneration, 1</td>
<td>Esthesioneuroblastoma, 1</td>
<td>Amphiphysin IgG, 1; small cell lung carcinoma, 1 (same patient ANNA-1 seropositive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety, 1 T and LE, 2</td>
<td></td>
<td>B-cell lymphoma, 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AE, all extremities; ANNA-2, antineuronal nuclear antibody type 2; CC, cranio cervical; CMV, cytomegalovirus; CN, cranial nerve; EBV, Epstein-Barr virus; G, generalized; GAD65 Ab, glutamic acid decarboxylase 65 kDa isform antibody; HD, hyperkinetic dysarthria; HIV, human immunodeficiency virus; LE, lower extremities; LEMS, Lambert-Eaton myasthenic syndrome and cerebellar degeneration; NMDA Ab, N-methyl-d-aspartate receptor antibody; OMS, opsoclonus-myoclonus syndrome; RUE, right upper extremity; SZ, seizure disorder; T, trunk; TB, tuberculosis; UE, upper extremities.

a Of 76 patients tested, 20 were seropositive for at least 1 paraneoplastic antibody.
b Coexisting neurologic disorders: changes in cognition, mood, personality, and behavior.
diagnostic clue; these patients report only tremulousness and therefore may receive a misdiagnosis of tremor, and frequently have a paraneoplastic disorder.

Most patients in our cohort with an idiopathic diagnosis were assumed to have a parainfectious autoimmune cause of OMS, based on the self-limited symptoms, CSF findings, absence of cancer or paraneoplastic antibody, and response to immunotherapy; none had a specific cause identified. The findings from the literature review reinforce the importance of thorough evaluations for a parainfectious cause, including HIV.65,66,74 The cause of OMS in HIV is probably autoimmune, since autoimmune encephalitis has been described in both early HIV seroconversion illness66,74 or during immune reconstitution after initiation of antiretroviral therapy.74 The cause of OMS in HIV is probably autoimmune, since autoimmunity is common in HIV-positive patients, and OMS is also responsive to corticosteroid therapy in this context.65 For other infectious causes, successful treatments have included corticosteroids and/or IVIG alone combined with antimicrobial therapy, when appropriate.30,44,54,59,68,78 Other infectious causes reported in patients with opsinclonus but without myoclonus include psittacosis, salmonella, St Louis encephalitis, and Rickeetsia nororii.50

Rare nonparaneoplastic, nonparainfectious autoimmune cases have been reported, including a patient with GAD65 antibody.79 Another unusual reported entity is OMS developing during pregnancy, which is assumed (like chorea gravidarum81,82) to have an autoimmune cause and is similarly responsive to immunotherapy.49

Most Mayo Clinic patients were very responsive to treatment. Almost all patients received short-term immunotherapy in combination with symptomatic therapy and did not experience relapse on discontinuing therapy. Few required further immunotherapy for longer periods to maintain remission. The literature review clarified the benefits of immunotherapy; we were able to determine that 79% of patients who received only immunotherapies achieved remission or improvement regardless of the cause of OMS. Cancer was identified in some of these patients, and cancerspecific treatments (surgery, chemotherapy, and radiation) were effective either alone or in combination with other therapies.† The benefits of chemotherapy probably stem from the elimination of cancer but also the immunosuppressant effects of those drugs. Although the prognosis with OMS is worse among paraneoplastic cases than among idiopathic cases,7 long-term survival is possible for some patients.63

It was somewhat informative to find that spontaneous remissions may occur; however, because the consequences of OMS may be profound, we do not advocate a wait-and-see approach. A practical treatment guide based on our experience and that of others could include an initial short course of either intravenous methylprednisolone acetate or IVIG, administered daily for 3 to 5 days, followed by weekly treatments for 6 weeks. Combination immunotherapy and plasma exchange could be reserved for patients whose condition is refractory to IVIG or corticosteroid monotherapy. Patients could be observed for signs of relapse once therapy is completed, before considering further treatment. The rare patient requiring longer treatment may benefit from a corticosteroid/IVIG-sparing immunosuppressant, such as mycophenolate mofetil or azathioprine. As illustrated by patient 10 (diagnosis and treatment after 32 weeks of symptoms and only partial recovery) and by the pediatric literature,83,84 early initiation of immunotherapy appears to be important to ensure an optimal neurologic outcome.

Symptomatic therapy was almost universally used among the Mayo Clinic cohort, usually as an adjunct to immunotherapy, but may be effective as monotherapy in mild cases of OMS.33,39,65,66,74 Effective reported therapies include benzodiazepines,54 gabapentin,42,85 valproic acid45,30,33,43,46,53,59,70 and levetiracetam.79,80

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Conflict of Interest Disclosures: None reported.


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