Paraneoplastic Jaw Dystonia and Laryngospasm With Antineuronal Nuclear Autoantibody Type 2 (Anti-Ri)

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Background: Opsoclonus-myoclonus syndrome and breast carcinoma were initially described as neurologic and oncologic accompaniments of antineuronal nuclear autoantibody type 2 (ANNA-2, also known as anti-Ri). However, the neurologic spectrum of ANNA-2 autoimmunity is broader, includes a syndrome of jaw dystonia and laryngospasm, and can be accompanied by lung carcinoma.

Objective: To describe clinically (with a video) ANNA-2–associated jaw dystonia and laryngospasm, its pathologic correlates, and therapeutic outcomes.

Design: Retrospective case series with prospective clinical follow-up.

Setting: Mayo Clinic’s Neuroimmunology Laboratory, Rochester, Minnesota.

Patients: Consecutive patients with ANNA-2 seropositivity identified since January 1, 1990.

Main Outcome Methods: Clinical (in 9 patients) and neuropathologic (in 2 patients) findings were reviewed.

Results: Of 48 patients with ANNA-2 seropositivity, 9 (19%) had multifocal neurologic manifestations that included jaw dystonia and laryngospasm. Among 6 patients with jaw dystonia, 5 had severely impaired nutrition, causing profound weight loss. Five patients had documented laryngospasm, which contributed to 1 patient's death. Neuropathologic examination revealed diffuse infiltration by CD8⁺ T lymphocytes, with axonal loss and gliosis in brainstem and descending spinal cord tracts. Some patients improved symptomatically after immunosuppressant or cytotoxic therapies; 1 patient improved after treatment with botulinum toxin. One patient who underwent tracheostomy because of recurrent laryngospasm was alive and well longer than 3 years after symptom onset.

Conclusions: Jaw dystonia and laryngospasm are common accompaniments of ANNA-2 autoimmunity and are associated with significant morbidity. We propose that selective damage to antigen-containing inhibitory fibers innervating bulbar motor nuclei by CD8⁺ T lymphocytes (histopathologically observed infiltrating brainstem reticular formation) is the proximal cause of this syndrome. Early and aggressive therapy offers the prospect of neurologic improvement or stabilization.

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Despite its rarity among paraneoplastic autoantibodies recognized in clinical practice, antineuronal nuclear antibody type 2 (ANNA-2, also known as anti-Ri) is one of the most common serologic tests ordered in evaluating patients suspected of having a paraneoplastic neurologic disorder.¹ Two central nervous system neuronal proteins, 53 to 61 kDa and 79 to 94 kDa, account for ANNA-2 immunoreactivity.¹ The smaller antigen, Nova, is a highly conserved RNA-binding nuclear protein,¹¹ which is expressed in brainstem and ventral spinal cord in embryonic mice and adult humans and is a marker of neurologic autoimmunity initiated by carcinoma of the breast or lung. Other cancer associations have been reported, including carcinomas of fallopian tube, ovary, bladder, and gastric neuroendocrine cells, as well as seminoma and carcinoid tumor.¹⁻¹⁰ Two central nervous system neuronal proteins, 53 to 61 kDa and 79 to 94 kDa, account for ANNA-2 immunoreactivity.¹ The smaller antigen, Nova, is a highly conserved RNA-binding nuclear protein,¹¹ which is expressed in brainstem and ventral spinal cord in embryonic mice and adult humans.

Video available online at www.archneurol.com

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Purkinje cell loss, perivascular B cells and CD4 (anti-Hu). All cases exhibited neuronal loss, reactive gliosis, involvement, and 1 case had coexisting ANNA-1 (anti-glial/neuronal nuclear antibody, collapsin response-5) and confirmed glutamic acid decarboxylase type 1, PCA-2, and PCA-Tr. Radioimmunoprecipitation assays detected antibodies specific for cation channel complexes (neuronal voltage-gated potassium and calcium channels [N-type and P/Q-type] and ganglionic and muscle acetylcholine receptor) and confirmed glutamic acid decarboxylase isofrom 65 antibody. Clinical information was obtained by medical record review and by physician contact. Patients 1 through 3 were evaluated and followed up at the Mayo Clinic. Patients 1 and 2 gave written consent for dissemination of a video. Autopsies with standard histopathologic processing were performed on patients 1 and 3. The Mayo Clinic Institutional Review Board approved the study.

Methods

Between January 1, 1990, and December 31, 2008, Mayo Clinic’s Neuroimmunology Laboratory identified 48 consecutive patients who were seropositive for ANNA-2 and for whom clinical information was available. An earlier article described neurologic presentations, cancers detected, and autoantibody accompaniments for 34 of these 48 patients. Four autopsied cases of ANNA-2–associated paraneoplastic disorders have been reported, with limited neuropathologic findings, 1 case had spinal cord involvement, and 1 case had coexisting ANNA-1 (anti-Hu). All cases exhibited neuronal loss, reactive gliosis, Purkinje cell loss, perivascular B cells and CD4+ T cells, and parenchymal CD8+ T lymphocytic infiltrates, with prominent involvement of brainstem and cerebellum.

Herein, we present a more detailed report of paraneoplastic jaw dystonia and laryngospasm as an underrecognized yet common association of ANNA-2. Included are the clinical presentations of 9 patients (7 patients previously described in brief and 2 new patients), video (available at http://www.archneurol.com), and neuropathologic findings.

Results

Eight of 9 patients (89%) were female. Clinical and oncologic characteristics and accompanying autoantibodies are summarized in Table 1. The median age at neurologic symptom onset was 62 years (age range, 35–70 years). Serum ANNA-2 immunofluorescence end-point dilutions ranged from 960 to 245 760. The presentation in all cases was subacute with prominent brainstem manifestations and with evidence of limited carcinoma (new, recurrent, or documented in the past).

Jaw Dystonia

Six patients experienced intense jaw spasms that interfered with mouth opening (ie, jaw-closing dystonia [see the video]). Speech and phonation were generally unaffected. Five patients had severe nutritional complications. Three patients had consulted dentists because of an inability to remove their dentures. Patient 4 noted limitation of jaw opening 6 months after symptom onset; this prevented denture removal and led to a 9-kg weight loss due to the need to consume liquid nutrients through a straw. Patient 6 had difficulty eating and removing or inserting her dentures. Patient 9 consulted a dentist because of difficulty removing dentures, recurrent jaw clenching (≥6 times per hour), and fear of tongue biting.

Laryngospasm

Laryngospasm was documented in 5 patients. Episodes were recurrent in 4 patients and were associated with respiratory distress; 3 patients lost consciousness and needed ventilatory support. Patient 3 reported spells of difficult breathing consistent with episodic laryngospasm starting 28 months after neurologic symptom onset; 1 episode lasted several minutes and resulted in loss of consciousness. A few weeks later, the patient was found dead on the kitchen floor. Autopsy findings were consistent with asphyxiation secondary to laryngospasm. Laryngospasm was an early accompaniment of brainstem syndrome in patient 2 and caused cyanosis and loss of consciousness. Tracheostomy was performed because the episodes were increasing in frequency (several per day) and required emergency department visits. Laryngospasm subsequently continued without respiratory compromise.

Identified Neoplasms

Neurologic symptoms preceded the diagnosis of malignant neoplasm in patients 1, 2, 7, and 8 (Table 1) by a median of 4 months (range, 1-36 months). In 5 patients, a history of malignant neoplasm preceded the onset of neurologic symptoms. Patient 3 had been treated at age 32 years for breast adenocarcinoma (grade 3 ductal). Neurologic symptoms began at age 43 years. Biopsy of an enlarged supraclavicular lymph node 10 months later, following ANNA-2 detection, revealed a grade 3 adenocarcinoma consistent with recurrent breast neoplasm. Patient 4 had had breast carcinoma 8 years
before neurologic presentation. No recurrent or new neoplasm was found. Patient 5 had been treated for 2 unrelated cancers (buttock sweat gland angiosarcoma at age 4 years and uterine cervical carcinoma at age 30 years) before neurologic symptom onset. Twenty-four months later, biopsy of an enlarged inguinal lymph node revealed poorly differentiated squamous cell carcinoma. Recurrent cervical carcinoma with metastatic spread was presumed on the basis of positive Papanicolaou cytologic results. Patient 6 had had breast carcinoma 9 years earlier and had recurrence 4 years before neurologic presentation. Patient 9 had had breast carcinoma 26 months before neurologic symptom onset; no recurrent or new cancer was found.

### Table 1. Characteristics of 9 Patients With Antineuronal Nuclear Autoantibody Type 2 (ANNA-2, Also Known as Anti-Ri)–Associated Jaw Dystonia or Laryngospasm

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>ANNA-2 Titer</th>
<th>Location of Carcinoma</th>
<th>Opsoconus</th>
<th>Jaw Dystonia</th>
<th>Laryngospasm</th>
<th>Other Neurologic Findings</th>
<th>Magnetic Resonance Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/58&lt;sup&gt;b&lt;/sup&gt;</td>
<td>960</td>
<td>Breast</td>
<td>No</td>
<td>Yes, mouth could open only partially; 1st finger's breadth at peak attack</td>
<td>Possible</td>
<td>Ataxia, dysphagia, postural instability, axial and neck rigidity, horizontal gaze paresis, bilateral ptosis, startle myoclonus, and diplopia</td>
<td>Normal</td>
</tr>
<tr>
<td>2/F/68</td>
<td>7680</td>
<td>Breast</td>
<td>No</td>
<td>Yes, could open mouth only partially; recurrent tongue biting</td>
<td>Yes, episodic, with occasional respiratory distress; required tracheostomy</td>
<td>Ataxia, dysphagia, postural instability, axial and neck rigidity or dystonia, horizontal gaze paresis, startle myoclonus, tremor, and loss of smell and taste</td>
<td>Normal</td>
</tr>
<tr>
<td>3/F/44&lt;sup&gt;b&lt;/sup&gt;</td>
<td>122 880</td>
<td>Breast</td>
<td>Possible</td>
<td>Yes, difficulty opening mouth; recurrent jaw spasms; tongue biting; and lost 22.7 kg</td>
<td>Yes, episodic; once caused loss of consciousness; subsequent fatal episode</td>
<td>Ataxia, generalized rigidity, horizontal gaze paresis, oscillopsia, leg spasms, tinnitus, and incontinence</td>
<td>Normal</td>
</tr>
<tr>
<td>4/F/62&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7680</td>
<td>Breast</td>
<td>Yes, transient</td>
<td>Yes, inability to open mouth; lost 9 kg</td>
<td>No</td>
<td>Ataxia, horizontal gaze paresis, oculopatalal myoclonus, rigidity of the lower extremity, and spasticity</td>
<td>Unavailable</td>
</tr>
<tr>
<td>5/F/70&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3840</td>
<td>Cervix</td>
<td>No</td>
<td>Yes, acute, requiring intubation</td>
<td>No</td>
<td>Ataxia, rigidity, vertigo, dysphagia, and quadriplegia</td>
<td>Gadolinium enhancement in mesiotemporal lobes, uncs, hemispheric white matter, and pons (by radiology report)</td>
</tr>
<tr>
<td>6/F/65&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 720</td>
<td>Breast</td>
<td>Yes</td>
<td>Yes, mouth could open only partially; jaw spasms; tongue biting</td>
<td>No</td>
<td>Ataxia, dysphagia, generalized rigidity, hyperreflexia, bilateral Babinski sign, clonus, difficulty opening eyes, horizontal gaze paresis, tremor, and neck dystonia</td>
<td>Normal</td>
</tr>
<tr>
<td>7/M/66&lt;sup&gt;b&lt;/sup&gt;</td>
<td>245 760</td>
<td>Lung, non–small cell</td>
<td>Yes</td>
<td>No</td>
<td>Yes, episodic</td>
<td>Ataxia, nystagmus, myoclonus</td>
<td>Normal</td>
</tr>
<tr>
<td>8/F/35&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>15 360</td>
<td>Breast</td>
<td>No</td>
<td>Possible</td>
<td>Yes, episodic; required ICU admission (3 times); tracheostomy considered</td>
<td>Seizures, tetanic contraction left trapezius, generalized hyperreflexia, bilateral Babinski sign, and dysphagia</td>
<td>Transient nonenhancing T2-weighted signal in right insular cortex</td>
</tr>
<tr>
<td>9/F/55</td>
<td>15 360</td>
<td>Breast</td>
<td>No</td>
<td>Yes, jaw clenching (6 times per hour); tongue biting; trismus; required gastrojejunal feeding tube</td>
<td>Not documented but required tracheostomy at ICU admission with respiratory failure</td>
<td>Ataxia, oscillopsia, dizziness, downbeat rotatory nystagmus, horizontal gaze paresis, central facial numbness, and dysphagia</td>
<td>Increased T2-weighted and FLAIR signal in dorsal pons</td>
</tr>
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</table>

Abbreviations: FLAIR, fluid-attenuated inversion recovery; ICU, intensive care unit.

<sup>a</sup> Patient 3 had coexisting voltage-gated calcium channel antibody (P/Q type [0.45 nmol/L in serum]). Patients 5 and 8 had coexisting glutamic acid decarboxylase antibodies (0.31 and 0.19 nmol/L, respectively, in serum).

<sup>b</sup> Described previously in brief by Pittock et al.<sup>3</sup>

<sup>c</sup> African American race/ethnicity. All other patients were of white race/ethnicity.
TREATMENT RESPONSES

Table 2 summarizes available information regarding treatment modalities. It also gives outcomes for jaw dystonia and laryngospasm.

**NEUROPATHOLOGIC FINDINGS**

**Patient 1**

In patient 1, the brain weighed 1185 g. Extensive artifactual disruption of both cerebral hemispheres (separated at the corpus callosum) and the brainstem (midbrain level) limited gross evaluation. Microscopic examination of the cerebral cortex, hippocampal formation, basal ganglia, and cerebellum revealed acute ischemic changes consistent with antemortem hypoxia in widespread cortical and subcortical neurons, scattered hippocampal pyramidal cells, and cerebellar Purkinje cells. There was moderate gliosis (Figure, A) and scant perivascular lymphocytic infiltration through all levels of brainstem tegmentum and ventral spinal cord. Immunohistochemistry identified T lymphocytes (CD3⁺/CD8⁺) and some B lymphocytes (CD20⁺). Microglial ag-
ggregates were numerous in pons, and scattered microglia were observed close to neurons (Figure, F). Foamy macrophages observed in medullary nuclei were in striking bilateral infiltrates that appeared to be tract specific (Figure, E). Mild and patchy cerebellar Purkinje cell loss with accompanying Bergmann gliosis (not shown) was consistent with a chronic process.

**Patient 3**

In patient 3, the brain weighed 1170 g. Brainstem and spinal cord were atrophic, the fourth ventricle was enlarged, and the cerebellum was preserved. No histopathologic abnormalities were found in the cerebral cortex, hippocampal formation, basal ganglia, or cerebellum. Gliosis was intense throughout brainstem gray matter (not shown but similar to that in patient 1 [Figure, A]), particularly in periaqueductal gray and subpial areas. Meninges were thickened, and occasional inflammatory cells were seen. Diffuse but sparse microglial activation was evident in gray matter of the mesencephalon, pontine tegmentum, medullary nuclei, and reticular formation.

Perivascular collections of mononuclear cells were rare and small (Figure, B). Immunophenotyping revealed that many were CD3+ (T lymphocytes). CD68+ macrophages and CD20+ B lymphocytes were less frequent. CD8+ T lymphocytes were identified in pontine tegmentum and diffusely throughout brainstem parenchyma and midcerebellar peduncle (Figure, C and D). Neuron loss was diffuse but was especially marked in areas with prominent microglial activation (tectum, inferolateral nucleus, and lateral vestibular nucleus) and in medullary and pontine reticular formation. Many neurons in medullary tegmentum were swollen and hypochromatic. As already noted, microscopic architecture of cerebellar cortex was preserved. There was no evidence of Purkinje neuron loss or Bergmann gliosis.

Spinal cord had a distinctive pattern of degeneration (Figure, G and H). Myelin pallor, gliosis, and axonal loss were marked in anterior funiculi. Axonal loss was confirmed by Bielschowsky staining. Glial fibrillary acidic protein immunoreactivity was increased in gray matter of dorsal root entry zone and in degenerated tracts. Degeneration was severe in reticulospinal, vestibulospinal, tectospinal, and propriospinal tracts. Anterocorticospinal, laterospinothalamic, and spinocerebellar tracts were affected partially in an asymmetric distribution. Dorsal funiculi were preserved; lateral funiculi were partially affected, more prominently in lumbar spinal cord, with fibers preserved in rubrospinal and laterocorticospinal tracts. Rare perivascular infiltrates of inflammatory cells were identified by CD68 immunoreactivity of macrophages. Activated microglia were frequent in gray matter. Ventral horn motor neurons and thoracic nuclei were readily identified.

**COMMENT**

Paraneoplastic neurologic dysfunction associated with ANNA-2 is multifocal but predominantly affects brainstem, cerebellum, and spinal cord. The occurrence of jaw dystonia and laryngospasm as neurologic manifestations of ANNA-2 autoimmunity in 9 of 48 seropositive cases (19%) herein warrants emphasis because of its potential for severe morbidity and mortality if unrecognized. Eating was severely impaired in 5 of 6 patients who had jaw dystonia; 3 had marked weight loss. Laryngospasm contributed to the death of at least 1 patient.
The predominance of women in this study (8 of 9 patients) and the frequent association of breast carcinoma (7 of 9 patients) concur with previous descriptions of ANNA-2 autoimmunity.1,3 Because the neurologic signs and symptoms associated with ANNA-2 often antedate the diagnosis of primary or recurrent neoplasm, detection of ANNA-2 mandates a focused search for occult carcinoma in the breast or lung or for less common cancers such as cervical carcinoma (as in patient 5 herein).

Early and aggressive therapy with immunosuppressant or cytotoxic agents offers the prospect of neurologic improvement. Five of 7 patients herein who received tumor or immunosuppressive treatment had physician-reported amelioration of jaw dystonia and laryngospasm. Improvement after botulinum toxin injection into jaw-closing muscles was modest and short-lived in patient 2. In formulating a plan for the clinical care of patients with similar presentation, the potential for fatal acute airway obstruction must be considered. Two of 9 patients died suddenly at home. Frequent attacks of laryngospasm with respiratory compromise requiring emergency department visits necessitated prophylactic tracheostomy in patient 2.

The lack of acute inflammatory lesions found in the 2 autopsied cases herein (55 months after symptom onset in patient 1 and 30 months after symptom onset in patient 3) likely reflected their slowly progressive clinical courses and long survival. The lesions found were typical of chronic encephalomyelitis. Neurologic deficits correlated well with brainstem and spinal cord pathologic findings, especially sparing of corticospinal and dorsal column pathways. We attributed ataxia and spasticity resembling cerebellar and pyramidal tract dysfunction to loss of postural motor pathways in those patients with minimal “upper motor neuron” weakness. Selective pathologic involvement of brainstem tegmentum, proprionspinal connections, and postural motor descending systems (bulbospinal upper motor neurons) can cause signs of disinhibition or excitatory phenomena other than opsendynosis (such as trismus, myoclonus, laryngospasm, limb or back spasm, and “spasticity” without the Babinski sign). Lesions of ventral funiculus can cause spasticity without weakness.18 A novel brainstem syndrome consisting of jaw and face spasms with horizontal spasticity without weakness.18 A novel brainstem syndrome consisting of jaw and face spasms with horizontal spasticity without weakness. In both cases, pathologic evaluation was limited to pons and medulla and revealed perivascular cuffs of chronic inflammatory cells, microglial proliferation, and diffuse astroglisis. Similar to one of our cases, the motor nuclei of the fifth cranial nerves were normal. In 2000, jaw dystonia was described in a patient with infarction of pontine reticular formation20 and in a patient with neuro–Belçet syndrome affecting brainstem, basal ganglia, and deep white matter.21 None of the 4 previous case reports8,15-17 of ANNA-2–related neuropathologic findings described jaw dystonia or laryngospasm. Prestigiacomo et al7 described diffuse perivascular and interstitial “lymphoplasmacellular” infiltration and gliosis, especially in basal ganglia, amygdala, frontal cortex, and white matter, in a patient who died 3 years after onset of opsendynosis-myoclonus syn-
drome associated with bladder carcinoma. Similar to our 2 pathologic cases, the cord exhibited “marked neuronal loss in the spinal gray matter along with an intense astroglisis and chronic inflammatory infiltration.”78,1426 This was the sole previous study to report histopathologic spinal cord findings. Hormigo et al described a patient with “perivascular and interstitial inflammatory infiltrates, particularly involving brainstem.”16,1483 B cells and CD4+ T cells predominated in perivascular spaces, and parenchymal infiltrates contained CD8+ T cells. Unlike our 2 pathologic cases, their patient had ataxia and severe Purkinje cell loss. In the patient described in their case report, Brieva-Ruiz et al noted severe Purkinje loss with prominent Bergmann gliosis, and they observed perivascular infiltrates in the mesencephalon and pons. The immunophenotype of perivascular and parenchymal lymphocytic infiltrates was similar to that described by Hormigo et al14 and to what we found. The case reported by Vigliani et al17 was complicated by the coexistence of ANNA–IgG (anti–Hu), but the findings were similar to those of patients 1 and 3 herein. There was diffuse neuronal loss and gliosis throughout brainstem and involving cranial nerve nuclei. In their patient, Vigliani et al17 noted lymphocytic infiltration, predominantly B cells, in perivascular spaces and T cells in brainstem parenchyma.

The distribution of pathologic lesions in patients 1 and 3 herein plausibly accounts for loss of voluntary horizontal gaze movements by involvement of parame-dian pontine reticular formation. Neurons that inhibit bulbar motor nuclei are scattered throughout brainstem reticular formation. Immunologic effectors of neuronal injury and inflammation associated with ANNA-2 seropositivity have not been defined to date. ANNA-2 antibodies bind in vitro to antigens that are restricted to central nervous system neurons, including the highly conserved RNA-binding protein Nova, which is expressed in ventral brainstem and spinal cord.11,12 Pathologic findings in our cases accord with the anatomical distribution of Nova protein. It is doubtful that IgG directed at antigens confined to the cytoplasm and nucleus would have access to antigens in living cells. However, circulating and locally synthesized IgGs rapidly access intracellular antigens after death. Synthesis of ANNA-2–IgG reflects concomitantly activated helper T cells specific for the same protein. CD8+ T lymphocytes among parenchymal inflammatory cells in central nervous system lesions of the patients we describe herein are conceivably targeting neurons that manifest Nova-derived peptides in the context of upregulated major histocompatibility complex class 1. Jaw dystonia and laryngospasm may be the outcomes of a specific neuronal peptide–directed attack enabled by a local cytokine environment favoring neuronal surface upregulation of major histocompatibility complex class 1 molecules bearing pertinent ANNA-2 peptide fragments.

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