Clinical Reasoning: An 82-Year-Old Woman With Subacute Ophthalmoparesis and Ataxia

Marc Rodrigo-Gisbert, MD, Arnau Llaurado, MD, Andres Baucells, MD, Cristina Auger, MD, and Victoria González, MD

Correspondence
Dr. González
m.gonzalez.7@vhebron.net

Neurology® 2023;101:e570-e575. doi:10.1212/WNL.0000000000207246

Abstract

We present the case of an 82-year-old woman with subacute altered mental status, oculomotor disturbances, and ataxia. On examination, she exhibited bilateral ptosis, complete horizontal ophthalmoplegia, and limited vertical eye movements during upgaze associated with prominent truncal ataxia. Cerebral MRI showed a mild hyperintensity on T2 and fluid-attenuated inversion recovery sequences in the posterior brainstem extending to the upper cervical cord, without gadolinium enhancement. Clinical and radiologic features suggested an encephalomyelitis with prominent brainstem involvement. We summarize the comprehensive differential diagnosis in patients with subacute brainstem encephalitis, which includes infectious paraneoplastic syndromes and inflammatory disorders. This case highlights the relevance of performing a wide methodical screening for malignancy in case of negative initial workup.

From the Department of Neurology (M.R.-G., A.L., V.G.), Department of Immunology (A.B.), and Department of Neuroradiology (C.A.), University Hospital Vall d'Hebron, Barcelona.
Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Section 1

An 82-year-old woman presented with 2 months of progressively worsening altered mental status, bilateral ophthalmoparesis, and ataxia. After subacute onset, initial unsteadiness associated with horizontal diplopia and dizziness had worsened till she was unable to walk unassisted.

Medical history was positive for malignant endometrial neoplasm, treated with surgery and radiotherapy with a complete clinical response 18 years earlier. Relatives reported no prior cognitive or functional impairment.

Vital signs were normal except for mild fever (37.1°C) on admission, which was attributed to urinary tract infection and resolved with empirical antibiotic therapy. Neurologic examination showed a confused mental state with inattention, disorientation, and mental slowness. The patient exhibited bilateral ptosis, complete horizontal ophthalmoplegia, and limited vertical eye movements in upgaze. Oculocephalic reflex was absent indicating brainstem dysfunction. No facial palsy was observed, but she had dysarthria and dysphagia. Motor system examination was normal, except for absent muscle stretch reflexes in the bilateral lower limbs. These signs were associated with right upper limb dysmetria and prominent truncal ataxia. Further deterioration occurred in the following 3–4 weeks with the development of rigidity and exaggerated startle responses triggered by tactile stimulation.

Questions for Consideration:

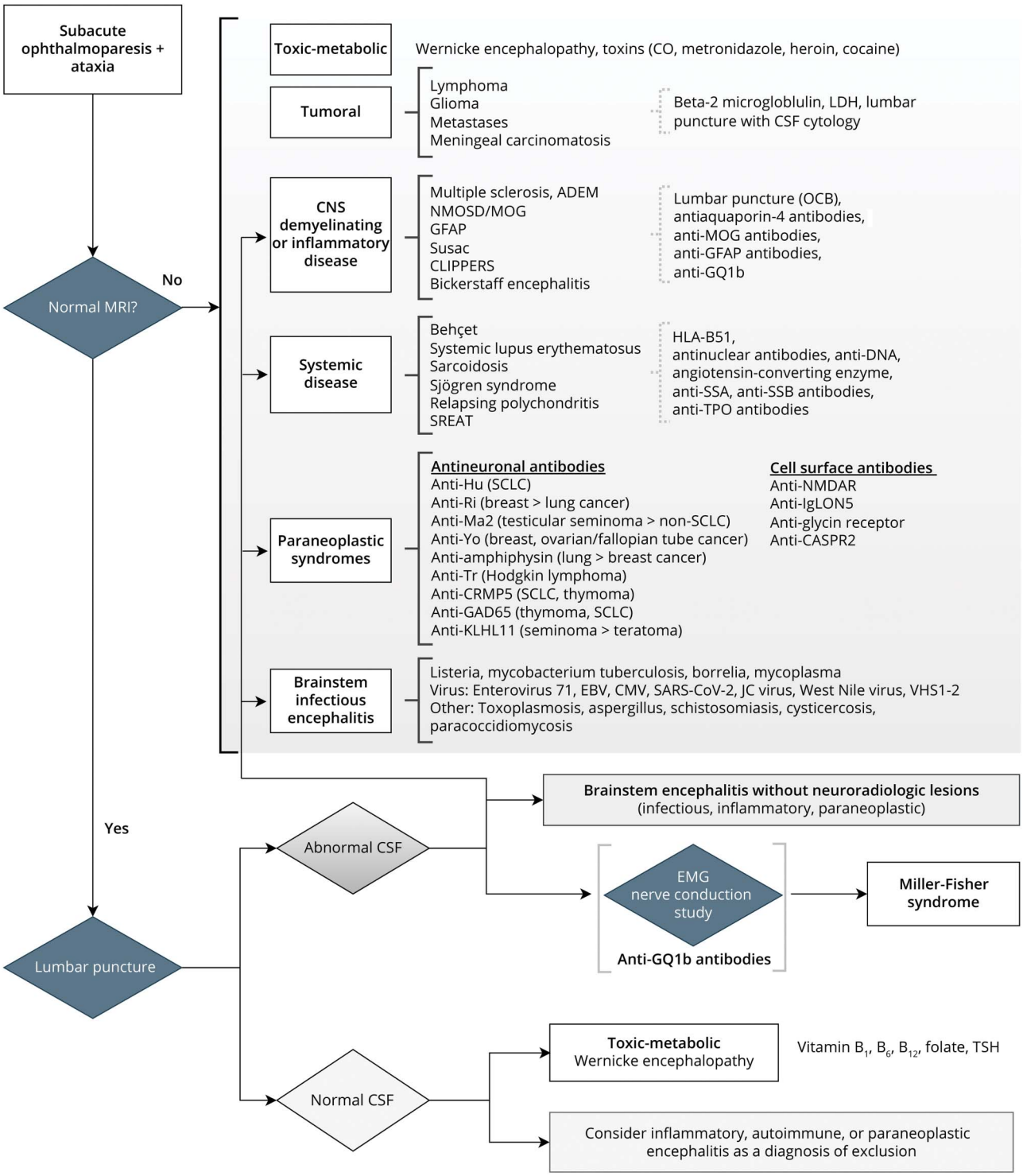
1. What is the differential diagnosis?
2. What investigations should be performed?

GO TO SECTION 2

Section 2

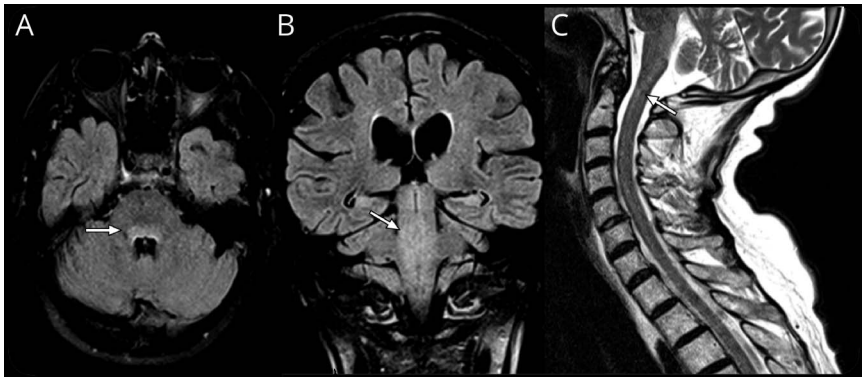
The presentation of subacute and rapidly progressive altered mental status, ophthalmoparesis, ataxia, and bulbar signs is suggestive of brainstem dysfunction with cerebellar (or cerebellar pathway) involvement. Absent muscle stretch reflexes, ophtalmoparesis, and ataxia can also suggest an overlap syndrome within the spectrum of the Miller-Fisher syndrome and

Figure 1 Algorithm for the Diagnosis of Subacute Ophthalomoparesis and Ataxia



Categories of differential diagnosis show in white boxes with specific examples to the right and recommended confirmatory testing shown in italics. ADEM = acute disseminated encephalomyelitis; CLIPPERS = chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CMV = cytomegalovirus; CO = carbon monoxide; EBV = Epstein-Barr virus; GFAP = glial fibrillary acidic protein; HSV = herpes simplex virus; MOGAD = myelin oligodendrocyte glycoprotein antibody–associated disease; NMOSD = neuromyelitis optica spectrum disorders; OCB = oligoclonal bands; SCLC = small cell lung cancer; SREAT = steroid-responsive encephalopathy and associated autoimmune thyroiditis; TPO = thyroid peroxidase; TSH = thyroid-stimulating hormone.

Figure 2 Brain MRI



Fluid-attenuated inversion recovery MRI brain in the axial (A) and coronal (B) planes. Arrow indicates the presence of a periependymal hyperintensity and swelling ventral to the fourth ventricle of the medulla. Sagittal plane of a T2-weighted sequence (C) showing the extension of the hyperintensity from the brainstem to the cervical spine (C1-2 levels, arrow).

Bickerstaff encephalitis (anti-GQ1b immunoglobulin [Ig] G antibody syndrome).

The differential diagnosis of a subacute brainstem encephalitis includes infectious, inflammatory, and paraneoplastic brainstem encephalitis together with other subacute-onset brainstem disorders such as Wernicke encephalopathy, intra-axial glioma, or lymphoma. The clinical reasoning guiding neuroimage, electrophysiologic, and laboratory workup is presented in Figure 1.

We performed additional serum testing to exclude potentially treatable conditions of adult-onset acquired cerebellar ataxia such as autoimmune disorders, vitamin deficiency states, hepatic encephalopathy, acute toxin exposure, and neurosyphilis. Laboratory tests including renal/liver function tests, erythrocyte sedimentation rates, thyroid, vitamin levels (B_1, B_6, B_{12}, E, and A), folate, and serum protein electrophoresis with immunofixation were normal. Infectious serologies (HIV, Lyme disease, and *Treponema pallidum*) and interferon gamma test showed negative results. Antinuclear antibodies were positive (1:160), but anti-DNA and anti-ENA antibodies were negative. Rheumatoid factor, acetylcholine receptor, antiganglioside, GAD65, and antiaquaporine-4 antibodies were also negative.

Nerve conduction study/EMG to evaluate neurophysiologic signs of anti-GQ1b antibody syndrome ruled out an acute polyradiculoneuropathy. No findings of neuromuscular junction disorders were observed.

Cerebral MRI revealed hyperintensity in T2-weighted sequences in the posterior brainstem spreading caudally through the pons, the medullary junction, and the upper cervical cord (Figure 2). In addition, slight cerebellar vermis atrophy was observed in T1 sequence (image not shown). There was no restriction on diffusion-weighted sequence nor gadolinium enhancement in T1-weighted sequence (image not shown). These findings supported the diagnosis of brainstem encephalitis.

Cytologic examination of the CSF showed mild lymphocytic pleocytosis (20 white blood cells/mm^3). Biochemical and immunologic analyses showed hyperproteinorrachia (83 mg/dL), normal glucose and adenosine deaminase, and elevated IgG index (1.992) with CSF-specific oligoclonal bands. CSF cultures showed negative results. CSF-PCR for herpes simplex, varicella zoster virus, cytomegalovirus, enterovirus, listeria monocytogenes, and *Treponema pallidum* showed negative results. CSF-PCR for Epstein-Barr virus (EBV) showed positive results with a low viral load of 168 UI/mL (logarithm 2.23). This finding was considered of no clinical significance due to negative serum EBV serologies (IgM negative, IgG positive). Thus, infectious etiology was excluded.

Ultimately, CSF (nondiluted) and serum (1:100) were positive for antineuronal nuclear autoantibody type 2 (ANNA-2 or anti-Ri) with immunoblot (EUROLINE Paraneoplastic Neurologic Syndromes [Euroimmun, Lübeck, Germany]). We performed indirect immunofluorescence with serum (1:10) on monkey cerebellum (Euroimmun) that corroborated the results, confirming the diagnosis of anti-Ri paraneoplastic brainstem encephalitis.

Questions for Consideration:

1. What are the tumors more frequently associated with anti-Ri antibody? What kind of screening should be undertaken?
2. What is the management and prognosis of paraneoplastic neurologic symptoms?

GO TO SECTION 3

Section 3

Anti-Ri–associated paraneoplastic neurologic syndrome (Ri-PNS) is characterized by brainstem and cerebellar neurologic manifestations and commonly associated with breast and small cell lung cancers.

Gynecologic neoplasm screening (including physical examination, mammography, and transvaginal ultrasound) detected no findings suggestive of breast or ovarian cancer nor relapse of endometrial neoplasia in this patient.

^{18}F-fluorodeoxyglucose (FDG) PET showed asymmetry of ^{18}F-FDG uptake in the bladder with hypermetabolic mesenteric adenopathy. Urinary tract ultrasound and abdominopelvic CT scan showed a polylobed bladder thickening (3.6 × 2.6 cm). The biopsy performed through urethrocystoscopy confirmed the diagnosis of a high-grade urothelial carcinoma (cT3N1) with neuroendocrine differentiation (Ki67 70%, synaptophysin, CD56).

Surgery indication was excluded, given the presence of lymph node involvement and the age of the patient. Given the low/moderate sensitivity of this tumor to chemotherapy, its potential toxicity, and the functional disability of the patient (Eastern Cooperative Oncology Group Performance Status 4), it was decided not to administer chemotherapy.

In parallel with these studies, first-line immunotherapy was started: corticosteroid therapy (pulsed IV methylprednisolone 1 g/d for 5 days), followed by intravenous immunoglobulins (0.4 g/kg/d for 5 days). Unfortunately, no improvement in neurologic manifestations was observed. Two months later, the patient died of aspiration pneumonia in the setting of neurologic progression.

Questions for Consideration:

1. What are paraneoplastic neurologic syndromes?
2. Which paraneoplastic neurologic syndromes manifest with brainstem symptoms?
3. What are the key clinical and radiologic features of anti-Ri paraneoplastic syndrome?

Discussion

PNSs are immune-mediated effects of a remote cancer, which can affect any part of the nervous system, often presenting with stereotyped clinical manifestations. Two types of antibodies have been associated with PNS: "onconeuronal antibodies" targeting intracellular antigens and antibodies targeting cell surface–targeted antigens. The onconeuronal antibodies are more often paraneoplastic and commonly respond poorly to immunotherapy.[1]

Recently, updated criteria for PNS have been proposed to improve accurate diagnosis.[2] The PNS-Care Score combines clinical phenotype, antibody type, and the presence or absence of cancer to classify the level of evidence for PNS. Brainstem encephalitis has been mainly associated with antibodies targeting intracellular antigens including anti-Hu, anti-Ri, anti-Ma2, anti-Yo, and novel anti-Kelch–like protein-11. Other antibodies less frequently identified are antiamphiphysin, anti-Tr, anti–glutamic acid decarboxylase-65, and cell surface antibodies such as anti-NMDA receptor, anti-IgLON5, antiglycine receptor, and anti–dipeptidyl peptidase-like protein-6.

Ri-PNS was first described in 1988 by Budde Steffen et al. in the clinical context of opsoclonus with or without myoclonus syndrome (OMS).[3] Ri-PNS clinical spectrum has been associated with a progressive multiphasic evolution characterized by the following: (1) cerebellar syndrome (gait ataxia, action tremor); (2) brainstem involvement with oculomotor disturbances (ophthalmoplegia, internuclear ophthalmoplegia, ptosis, OMS, and/or cranial nerve palsies); and (3) pyramidal and/or extrapyramidal signs (parkinsonism, oromandibular dystonia, or stiff person syndrome). Other atypical clinical features were limbic encephalitis, neuropathy, syndrome of inappropriate antidiuretic hormone secretion, dysautonomia, and central hypoventilation.[4]

Although cerebral MRI is normal in most cases, previous case reports have described possible neuroradiologic abnormalities. The characteristic MRI finding is the presence of T2-weighted and fluid-attenuated inversion recovery hyperintensities in the posterior brainstem with uncommon gadolinium enhancement. The involvement of upper cervical cord, basal ganglia, and insular and/or limbic region is a rare finding.[4,5]

Anti-Ri antibody is strongly associated with malignancy (high-risk antibody). Breast cancer is the most frequent cancer in female individuals (79% of female patients), while lung cancer is most common in male individuals (25% of male patients).[4] Atypical cancer types were more prevalent in male patients, including bladder neoplasm,[6] neuroendocrine tumors,[7-10] and mediastinal seminoma.[11]

PNS associated with urothelial carcinoma is uncommon and has been reported in high-grade tumors with squamous differentiation. Several antibodies have been identified in this context: anti-Hu, anti–brain-type creatine kinase, anti-Ri, anti–voltage-gated potassium channel, and anti-Yo antibodies.[12,13] In the current scientific literature, there is only 1 case report of an Ri-PNS associated with bladder carcinoma with neuroendocrine differentiation in a male patient.[14] The level of diagnostic certainty for PNS in this case is definite based on the PNS-Care Score.[2]

The most effective treatment for PNS is tumor-specific treatment such as surgery or chemotherapy. Unlike PNS associated with cell surface antibodies, isolated immunotherapy has a poor prognosis and overall unsatisfactory effect in PNS associated with onconeuronal antibodies (e.g., anti-Ri antibodies), if underlying cancer is not treated.[4] It is recommended to start first-line immunotherapy with corticosteroids or immunoglobulins as early as possible. The efficiency of second-line immunotherapy (cyclophosphamide, rituximab) to prevent relapses is currently under investigation.[15]

In case of anti-Ri antibody detection, screening for malignancy is mandatory because the neurologic syndrome frequently precedes the discovery of cancer.[4] Mammography and breast ultrasound in female individuals, and whole-body CT scan in male individuals are the first steps to rule out an occult cancer. Failure to identify gynecologic or lung malignancies should prompt further investigations including urethrocystoscopy with urinary cytology to rule out bladder neoplasm. FDG PET/TC may not be the imaging method of choice for bladder cancer due to diffuse bladder binding with urinary isotope excretion, which could interfere the detection of small lesions.

This case highlights the importance of systematic malignancy screening in Ri-PNS and describes an uncommon association with bladder neuroendocrine carcinoma.

Acknowledgment

The authors acknowledge Josep Dalmau who provided insight and expertise that greatly assisted the therapeutic management of this patient.

Study Funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 13, 2022. Accepted in final form February 16, 2023. Submitted and externally peer reviewed. The handling editor was Resident and Fellow Deputy Editor Ariel Lyons-Warren, MD, PhD.

Appendix Authors

Name	Location	Contribution
Marc Rodrigo-Gisbert, MD	Department of Neurology, University Hospital Vall d'Hebron, Barcelona	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Arnau Llaurado, MD	Department of Neurology, University Hospital Vall d'Hebron, Barcelona	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and analysis or interpretation of data
Andres Baucells, MD	Department of Immunology, University Hospital Vall d'Hebron, Barcelona	Study concept or design; analysis or interpretation of data
Cristina Auger, MD	Department of Neuroradiology, University Hospital Vall d'Hebron, Barcelona	Major role in the acquisition of data; analysis or interpretation of data
Victoria González, MD	Department of Neurology, University Hospital Vall d'Hebron, Barcelona	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

References

1. Bradshaw MJ, Linnoila JJ. An overview of autoimmune and paraneoplastic encephalitides. *Semin Neurol*. 2018;38(3):330-343.
2. Graus F, Vogrig A, Muniz-Castrillo S, et al. Updated diagnostic criteria for paraneoplastic neurologic syndromes. *Neurol Neuroimmunol Neuroinflamm*. 2021;8(4):e1014.
3. Budde-Steffen C, Anderson NE, Rosenblum MK, et al. An antineuronal autoantibody in paraneoplastic opsoclonus. *Ann Neurol*. 1988;23(5):528-531.
4. Simard C, Vogrig A, Joubert B, et al. Clinical spectrum and diagnostic pitfalls of neurologic syndromes with Ri antibodies. *Neurol Neuroimmunol Neuroinflamm*. 2020;7(3):e699.
5. Testud B, Brun G, Kaphan E, Stellmann JP, Girard N, Hak JF. Distinctive MRI features of paraneoplastic encephalitis with anti-Ri antibodies. *Rev Neurol (Paris)*. 2021;177(3):315-317.
6. Prestigiacomo CJ, Balmaceda C, Dalmau J. Anti-Ri-associated paraneoplastic opsoclonus-ataxia syndrome in a man with transitional cell carcinoma. *Cancer*. 2001;91(8):1423-1428.
7. Diaz AD, Garcia MH, Hernandez AG. Cerebellar dysfunction and spastic paraparesis associated to anti-Ri antibodies in a patient with a pancreatic neuroendocrine tumor. *J Neurooncol*. 2016;130(3):605-606.
8. Boch M, Rinke A, Rexin P, et al. Paraneoplastic brainstem encephalitis in a patient with exceptionally long course of a metastasized neuroendocrine rectum neoplasm. *BMC Cancer*. 2014;14(1):691.
9. Kikuchi H, Yamada T, Okayama A, et al. Anti-Ri-associated paraneoplastic cerebellar degeneration without opsoclonus in a patient with a neuroendocrine carcinoma of the stomach. *Fukuoka Igaku Zasshi*. 2000;91(4):104-109.
10. Mitchell AN, Bakhos CT, Zimmerman EA. Anti-Ri-associated paraneoplastic brainstem cerebellar syndrome with coexisting limbic encephalitis in a patient with mixed large cell neuroendocrine lung carcinoma. *J Clin Neurosci*. 2015;22(2):421-423.
11. Launay M, Bozzolo E, Venissac N, Delmont E, Fredenrich A, Thomas P. Paraneoplastic limbic encephalitis with positive anti-RI antibodies and mediastinal seminoma [in French]. *Rev Neurol (Paris)*. 2008;164(6-7):612-619.
12. Anil H, Karamik K, Ates M, et al. A rare clinical entity in bladder cancer: paraneoplastic cerebellar degeneration. *Clin Genitourin Cancer*. 2017;15(5):e863-e865.
13. Zhu Y, Chen S, Chen S, et al. An uncommon manifestation of paraneoplastic cerebellar degeneration in a patient with high grade urothelial, carcinoma with squamous differentiation: a case report and literature review. *BMC Cancer*. 2016;16(1):324.
14. Villagran-Garcia M, Muniz-Castrillo S, Ciano-Petersen NL, et al. Paraneoplastic neurological syndromes associated with renal or bladder cancer: case series and PRISMA-IPD systematic review. *J Neurol*. 2022;270;(1):283-299.
15. Abboud H, Probasco J, Irani SR, et al. Autoimmune encephalitis: proposed recommendations for symptomatic and long-term management. *J Neurol Neurosurg Psychiatry*. 2021;92(8):897-907.

Clinical Reasoning: An 82-Year-Old Woman With Subacute Ophthalmoparesis and Ataxia

Marc Rodrigo-Gisbert, Arnau Llaurado, Andres Baucells, et al.

Neurology 2023;101;e570-e575 Published Online before print March 29, 2023
DOI 10.1212/WNL.0000000000207246