Published Ahead of Print on March 29, 2023 as 10.1212/WNL.0000000000207246

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI:10.1212/WNL.0000000000207246

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

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Figure Count:

2

Table Count:

0

Search Terms:

[120] MRI, [221] Paraneoplastic syndrome, Anti-Ri antibody, Brainstem encephalitis, Rhombencephalitis

Acknowledgment:

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

Study Funding:

The authors report no targeted funding

Disclosures:

The authors report no disclosures relevant to the manuscript.

Preprint DOI:

Received Date:

2022-07-13

Accepted Date:

2023-02-16

Handling Editor Statement:

Submitted and externally peer reviewed. The handling editor was Resident and Fellow Deputy Editor Ariel Lyons-Warren, MD, PhD.

Abstract

We present a case of an 82-year-old female 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 radiological features suggested an encephalomyelitis with prominent brainstem involvement. We summarize the comprehensive differential diagnosis in patients with subacute brainstem encephalitis, that 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 work-up.

Section 1

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

Past medical history was positive for malignant endometrial neoplasm, treated with surgery and radiotherapy with complete clinical response 18 years prior. Relatives reported no prior cognitive nor functional impairment.

Vital signs were normal except for mild fever (37.1ºC) upon admission, which was attributed to urinary tract infection and resolved with empirical antibiotic therapy. Neurological 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 development of rigidity and exaggerated startle responses triggered by tactile stimulation.

Questions for consideration:

- What is the differential diagnosis?

- What investigations should be performed?

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 Miller-Fisher syndrome and Bickerstaff's encephalitis (anti-GQ1b IgG 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's encephalopathy, intra-axial glioma or lymphoma. The clinical reasoning guiding neuroimage, electrophysiologic and laboratory work-up is summarized in Figure 1.

We performed additional serum testing to exclude potentially treatable conditions of adult-onset acquired cerebellar ataxia such us autoimmune disorders, vitamin deficiency states, hepatic encephalopathy, acute toxin exposure, neurosyphilis. Laboratory tests including renal/liver function tests, erythrocyte sedimentation rates, thyroid, vitamin levels (B1-6-12, E, A), folate, and serum protein electrophoresis with immunofixation were normal. Infectious serologies (HIV, Lyme disease, Treponema pallidum) and Interferon-gamma test were negative. Antinuclear antibodies were positive (1:160), but anti-DNA and anti-ENA antibodies were negative. Rheumatoid factor, Acetylcholine receptor, antiganglioside, GAD65 and anti-aquaporine-4 antibodies were also negative.

Nerve Conduction Study/EMG to evaluate neurophysiological 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 CSF showed mild lymphocytic pleocytosis (20WBCs/mm3). Biochemical and immunological analysis showed hyperproteinorrachia (83mg/dL), normal glucose and Adenosine Deaminase, elevated IgG-index (1.992) with CSF-specific oligoclonal bands. CSF cultures were negative. CSF-PCR for Herpes simplex, Varicella zoster virus, Cytomegalovirus, Enterovirus, Listeria monocytogenes and Treponema pallidum were negative. CSF-PCR for Epstein-Barr virus (EBV) was positive with a low viral load 168UI/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 (non-diluted) and serum (1:100) were positive for antineuronal nuclear autoantibody type 2 (ANNA-2 or anti-Ri) with immunoblot [EUROLINE Paraneoplastic Neurologic Syndromes (Euroimmun, Germany)]. We performed indirect immunofluorescence with serum (1:10) on monkey cerebellum (Euroimmun, Germany) that corroborated the results, confirming the diagnosis of anti-Ri paraneoplastic brainstem encephalitis.

Questions for consideration:

- What are the tumors more frequently associated with anti-Ri antibody? What kind of screening should be undertaken?

- What is the management and prognosis of paraneoplastic neurological symptoms?

Section 3

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

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

18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) showed asymmetry of 18F-FDG uptake in the bladder with hypermetabolic mesenteric adenopathy. Urinary tract ultrasound and abdominopelvic CT scan showed a polylobed bladder thickening (3.6x2.6cm). 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 1g/day for 5 days), followed by intravenous immunoglobulins (0.4g/Kg/day for 5 days). Unfortunately, no improvement in neurological manifestations was observed. Two months later, the patient passed away due to aspiration pneumonia in the setting of neurological progression.

Questions for consideration:

- What are paraneoplastic neurological syndromes?

- Which paraneoplastic neurological syndromes manifest with brainstem symptoms?

- What are the key clinical and radiological features of anti-Ri paraneoplastic syndrome?

Discussion

Paraneoplastic neurological syndromes (PNS) are immune-mediated effects of a remote cancer, that 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 anti-amphiphysin, anti-Tr, anti-GAD65 and cell-surface antibodies such as anti-NMDAR, anti-IgLON5, anti-glycine receptor and anti-DPPX.

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: (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 the majority of cases, previous case reports have described possible neuroradiologic abnormalities. The characteristic MRI finding is the presence of T2-weighted and FLAIR hyperintensities in the

posterior brainstem with uncommon gadolinium enhancement. The involvement of upper cervical cord, basal ganglia, 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 females (79% of female patients), while lung cancer is most common in males (25% of male patients)(4). Atypical cancer types were more prevalent in males, 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-CKB (Brain-type Creatine Kinase), anti-Ri, anti-VGKC and anti-Yo antibodies (12, 13). To our knowledge, there is only one case report of a 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, as the neurologic syndrome frequently precedes the discovery of cancer (4). Mammography and breast ultrasound in female, and whole-body CT scan in male are the first steps to rule out an occult cancer. Failure to identify gynecological 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.

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Name	Location	Contribution
Marc Rodrigo-Gisbert, MD	Department of Neurology. University Hospital Vall d'Hebron, Barcelona	Design and conceptualized study, Major role in the acquisition of data. Drafted the manuscript for intellectual content
Arnau Llauradó, MD	Department of Neurology. University Hospital Vall d'Hebron, Barcelona	Drafting/revising the manuscript for content. Major role in the acquisition of data

Andrés Baucells, MD	Department of Immunology. University Hospital Vall d'Hebron, Barcelona	Design and conceptualized study. Analysis and interpretation of data
Cristina Auger, MD	Department of Neuroradiology. University Hospital Vall d'Hebron, Barcelona	Analysis and interpretation of data
Victoria González, MD	Department of Neurology. University Hospital Vall d'Hebron, Barcelona	Design and conceptualized study; analyzed the data. Revised/supervised the manuscript for intellectual content

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.

Abbreviations: MRI, magnetic resonance imaging; CO, carbon monoxide; CNS, central nervous system; ADEM, Acute disseminated encephalomyelitis; NMOSD, neuromyelitis optica spectrum disorders; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; GFAP, glial Fibrillary Acidic Protein; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; OCB, oligoclonal bands; SREAT, steroid-responsive encephalopathy and associated autoimmune

thyroiditis; TPO; thyroid peroxidase; SCLC, small cell lung cancer; EBV, Epstein-Barr virus; CMV, Cytomegalovirus; HSV, Herpes simplex virus; CSF, cerebrospinal fluid; EMG, electromyography; TSH, thyroid-stimulating hormone.

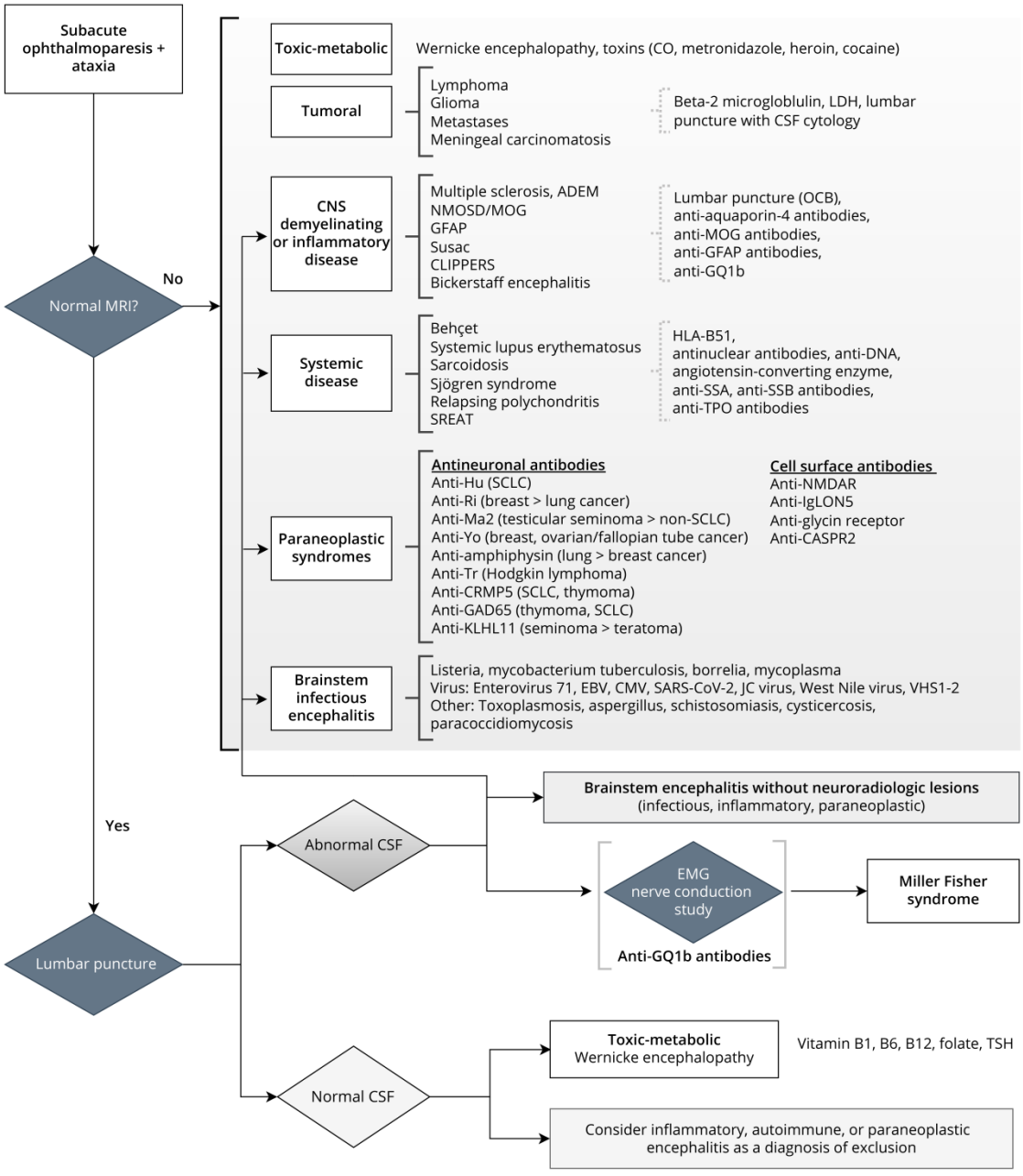
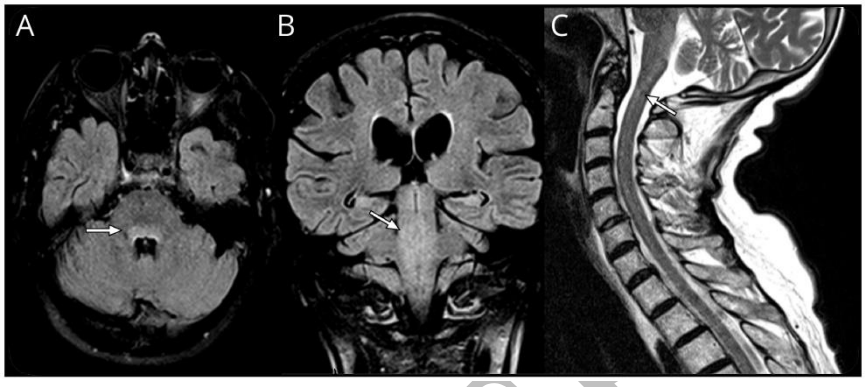


Figure 2. Brain Magnetic Resonance Imaging

FLAIR (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 4th 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).



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Neurology published online March 29, 2023
DOI 10.1212/WNL.0000000000207246