Clinical Reasoning:

A middle-aged woman with progressive symmetric weakness and a CSF pleocytosis

Douglas Marks, BS
Adelene Jann, MD
Teresa DeAngelis, MD

Correspondence & reprint
requests to Dr. Jann:
aejann@gmail.com

SECTION 1

A 54-year-old Ecuadorian American woman presented with 4 days of progressive bilateral extremity weakness, which began in the upper extremities but quickly spread to the lower extremities. The patient also reported reduced gait stability, bilateral distal paresthesias, and patchy decreased sensation with pain over her lower abdomen and pelvis. At presentation, she denied symptoms of dysautonomia or bulbar dysfunction. Past medical history included longstanding rheumatoid arthritis treated with chronic methylprednisolone, hypertension, left sciatic radiculopathy, scoliosis, uterine prolapse, and thyroid disease.

On examination, the patient's vitals were stable. Mental status and cranial nerves were normal. Motor strength was decreased symmetrically in the upper and lower extremities (4/5) with areflexia and absent plantar reflexes. The patient had decreased pinprick sensation over the T6–T8 dermatomes and diminished vibratory sense distally. Joint position sense was preserved bilaterally. The patient demonstrated a paraparetic slow gait with assistance.

Questions for consideration:

1. What is the differential diagnosis? How does the presence of both sensory deficits and motor involvement narrow the differential?
2. What is the next step in management for this patient? What additional testing would you order?

GO TO SECTION 2

From the Department of Neurology, Mount Sinai School of Medicine, New York, NY.

Disclosure: Author disclosures are provided at the end of the article.

Table	Diagnostic testing		
Studies	Data		
CSF studies			
Basic studies	WBC: 139 (poly 19%, lymphocytes 43%), glucose: 57, protein: 246		
Negative studies	Cryptococcus Ag, VDRL, Lyme disease PCR, AFB culture and smear, bacterial culture, Mycoplasma IgM and IgG, Whipplei PCR, West Nile PCR, VZV PCR, HSV1 PCR, oligoclonal bands		
Positive studies	HSV-2 PCR 1,200 copies/mL		
Serum studies			
Negative or normal studies	Anti-GM1, anti-GD1b, anti-GQ1b, EBV Ab IgM, Lyme Ab, hepatitis A and B, HIV, M-spike and protein electrophoresis, ESR, anti-SSA, anti-SSB, anti-dsDNA, anti-Jo1, heavy metals, thallium, ACE		
Positive or abnormal studies	Diphtheria Ab, ANA, rheumatoid factor 27, TSH 0.14, T4 1.00, T3 reverse 71, T3 Total 49, TPO-Ab 6.3, West Nile Virus IgM 0.11, CMV IgG Ab, EBV VCA Ab IgG, HSV1 and HSV2 IgM 1:20, HSV1 IgG, Mycoplasma IgM		
Site	Latency, ms	Amplitude, mV	Conduction velocity, m/s
Hospital day 2: nerve conduction studies (NCS), EMG			
NCS (right median)			
Wrist	4.5	4.2	—
Elbow	9	3	47
NCS (right peroneal)			
Ankle	4.4	3.6	—
Fibular head	10.8	2.5	45
Popliteal fossa	12.8	2.5	45
Tibialis anterior-fibular head	5.5	4.2	—
Fibular head-popliteal fossa	7.4	4.2	47
EMG	Reduced recruitment in deltoid, biceps, pronator teres, extensor indicis proprius, first dorsal interosseous, peroneus longus, gastrocnemius		
Hospital day 11: NCS, EMG			
NCS (right median)			
Wrist	7.8	1.4	—
Elbow	14.2	1.2	31
NCS (right peroneal)			
Ankle	6.1	2.7	—
Fibular head	13.5	0.9	34
Popliteal fossa	15.6	0.7	38
Tibialis anterior-fibular head	6.2	2.5	—
Fibular head-popliteal fossa	9.3	1.7	29
EMG	Reduced recruitment in deltoid, biceps, first dorsal interosseous, vastus medialis		

Abbreviations: Ab = antibody; ACE = angiotensin-converting enzyme; AFB = acid-fast bacilli; ANA = antinuclear antibody; CMV = cytomegalovirus; EBV = Epstein-Barr virus; ESR = erythrocyte sedimentation rate; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; TPO-Ab = thyroid peroxidase antibody; TSH = thyroid-stimulating hormone; VDRL = Venereal Disease Research Laboratory; VZV = varicella zoster virus.

SECTION 2

An acute inflammatory neuropathy or cervical myelopathy were top on the differential diagnosis. Neuromuscular junction disorders and myopathies were considered less likely due to the patient's sensory involvement. Infectious etiologies, such as Lyme disease and HIV, were also considered and tested in the serum and CSF.

To exclude a myelopathic process, x-rays of the cervical and lumbar spine were initially performed and showed no evidence of subluxation or fracture. An MRI spinal survey was significant for compound scoliosis of the lower thoracic and lumbar spine, multilevel disc bulges, and mild enhancement of the cauda equina. However, neither intramedullary lesions nor spinal cord compression were observed.

To evaluate for acute neuropathy, nerve conduction studies (NCS) and EMG were performed. As seen in the table, the study on hospital day 2 demonstrated prolonged distal latencies, decreased amplitudes, prolonged F-responses, and reduced recruitment, consistent with early acute inflammatory demyelinating polyradiculoneuropathy (AIDP).

Questions for consideration:

1. What are commonly employed treatments for AIDP?
2. What is the expected CSF finding in AIDP?

GO TO SECTION 3

SECTION 3

Following electrophysiology results, we empirically began a 5-day IV immunoglobulin (IVIg) treatment. When CSF studies were obtained, elevated protein was present, as would be expected with AIDP. However, an unanticipated lymphocytic pleocytosis was also identified.

Clinically, the patient was deteriorating. By hospital day 4, the patient had increased proximal weakness (2/5), unilateral vocal cord paralysis, and a left-sided lower motor neuron facial palsy. In addition, the patient began demonstrating dysautonomia, with refractory constipation, and hypo-

natremia (120 mEq/L). A low serum osmolality confirmed the syndrome of inappropriate antidiuretic hormone (SIADH) vs a pseudohyponatremia secondary to IVIg.

Of note, by hospital day 3, the patient had developed an outbreak of genital herpes and oral thrush. She reported similar episodes of genital herpes outbreaks in the past.

Questions for consideration:

1. What etiologic triggers are classically associated with AIDP?
2. What additional testing might be helpful?

GO TO SECTION 4

SECTION 4

Investigations for common etiologic triggers in the serum and CSF were, for the most part, nonrevealing: *Campylobacter* stool testing was negative, as were acute antibodies to cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Borrelia burgdorferi*. Anti-*Mycoplasma* immunoglobulin M was detected in the serum, which prompted a brief course of azithromycin; however, the antibiotic was subsequently discontinued when additional serologic studies were negative. Anti-glycan antibodies were not detected (GM1, GD1b, GQ1b). HIV testing was negative. The complete diagnostic workup is outlined in the table.

On hospital day 11, the patient's CSF PCR studies returned positive for herpes simplex virus (HSV)-2. The patient was treated with IV acyclovir and then converted to oral valacyclovir 1 g 3 times a day. Within 2 days of administration, the patient substantially improved with increased proximal muscle strength, partial resolution of left facial weakness, and reduction in genital blisters. A repeat EMG and NCS were performed which was consistent with advanced AIDP with diffuse prolonged distal latency, reduced CMAP amplitudes, and conduction block. The EMG showed no fibrillations or positive waves. She was transferred to acute rehabilitation after 5 days of valacyclovir with continued improvement in her examination.

DISCUSSION Guillain-Barré syndrome (GBS) is a diverse group of inflammatory neuropathies, which includes AIDP, initially described among French soldiers who developed a rapidly progressing paralysis that resolved spontaneously. CSF studies showed elevated protein without pleocytosis (dissociation albumino-cytologique).¹ With the development of the polio vaccine, GBS has become the most common cause of flaccid paralysis worldwide.² Patient age, rate of progression, extent of peak deficit, and subtype are helpful prognostic indicators. IVIg and plasmapheresis have been shown in multiple studies to reduce the duration and the severity of illness.^{2,3} While full recovery is common, 20% of patients are still unable to walk without assistance at 6 months.¹

Classically, GBS is considered a postinfectious autoimmune syndrome that is most often seen as a rare sequela of *Campylobacter*, *Mycoplasma*, CMV, or EBV infection.^{3,4} Observing GBS in the context of an active infection is less frequent, but reported.^{5,6} CSF pleocytosis is rare in GBS, seen only in approximately 2% of patients and often in the context of underlying HIV infection.⁴ For these reasons, we were initially skeptical of GBS as the diagnosis.

Major clinical criteria for the diagnosis of GBS include acute onset of symmetric progressive muscle

weakness, areflexia, mild sensory deficits, and facial and oropharyngeal weakness. The development of inappropriate secretion of ADH (SIADH) has also been well described; "excess" ADH may be secondary to dysfunction of peripheral autonomic fibers, in particular the vagal nerve and reflex pathways from the left atrium, carotid sinus, and aortic arch.⁷ Electrophysiology findings characteristic for AIDP include multiple nerves demonstrating conduction velocity <70% of the lower limit of normal and distal latency >150%.^{4,8,9} Retrospective studies have shown this criterion to have near 100% specificity for AIDP.⁸ Of note, the patient described above had a classic clinical presentation for GBS as well as electrophysiology findings characteristic for AIDP even by the strictest criteria.

Cell culture and animal model experiments indicate that AIDP is predominantly mediated by T-cell autoimmune attack on the Schwann cell as compared to other subtypes which appear to be a primarily humorally mediated process which directly damage the axon.¹⁰ These distinct mechanisms are in line with current serologic testing, with anti-glycan antibodies more closely associated with non-AIDP subtypes of GBS.¹ As would be predicted, anti-GM1, GD1b, and GQ1b were not detected in our patient's serum.

Despite the high frequency of AIDP among the GBS variants, no infectious agent is usually identified.¹ Although HSV-2 infection does not commonly precede AIDP, our patient's clinical course, CSF findings, and response to antiviral therapy are highly suggestive of HSV-2 initiating a symmetric demyelination process likely by similar mechanisms as those seen in other viremias.^{4-6,10} It can be argued that a direct viral invasion could be responsible for the acute neuropathy in our patient. The sensory changes at the thoracic level could support this, but her diffuse weakness, involvement of several peripheral and cranial nerves clinically and on NCS/EMG, and lack of intramedullary lesions on spine MRI support more of global process. In our literature review, we identified an analogous case of a patient with chronic stable HIV disease who developed AIDP in the context of active infection with HSV-2.⁶ The patient also had detectable HSV in the CSF with a lymphocytic pleocytosis and complete resolution of symptoms with valacyclovir and IVIg treatment. These case reports may implicate HSV-2 as a rare GBS trigger in immunosuppressed patients. While CSF testing for HSV-2 is not regularly performed in setting of AIDP, we agree that in the appropriate clinical context, it can reveal the underlying pathology and identify treatment options. We hope that these differences will have consequences for treat-

ment when novel pathway-specific pharmacologic agents are introduced.

AUTHOR CONTRIBUTIONS

D. Marks and Dr. Jann participated in analysis and interpretation of data and drafted and revised the manuscript. Dr. DeAngelis developed the study concept and participated in analysis and interpretation of data, revision of the manuscript, and supervision of the study.

DISCLOSURE

D. Marks and Dr. Jann report no disclosures. Dr. DeAngelis has served on scientific advisory boards for Teva Pharmaceutical Industries Ltd. and EMD Serono, Inc.

REFERENCES

1. Hughes R, Cornblath DR. Guillain-Barré syndrome. *Lancet* 2005;366:1653.
2. Winer JB. Treatment of Guillain-Barré syndrome. *QJM* 2002;95:717–721.
3. Pascuzzi R. Peripheral neuropathy. *Med Clin N Am* 2009; 93:317–342.
4. Whitesell J. Inflammatory neuropathies. *Semin Neurol* 2010;30:356–364.
5. Hart IK, Kennedy PE. Guillain-Barré syndrome associated with cytomegalovirus infection. *Q J Med* 1998;67:425–430.
6. Chen-Plotkin AS, Christopoulos KA, Venna N. Demyelinating polyneuropathy and herpes simplex lumbosacral radiculitis in a patient with chronic HIV infection. *AIDS* 2007;21:1663–1664.
7. Posner JB, Ertel NH, Kossmann RJ, Scheinberg LC. Hyponatremia in acute polyneuropathy: four cases with the syndrome of inappropriate secretion of antidiuretic hormone. *Arch Neurol* 1967;17:530–541.
8. Van den Bergh PY, Pieret F. Electrodiagnostic criteria for acute and chronic inflammatory demyelinating polyradiculoneuropathy. *Muscle Nerve* 2004;29:565–574.
9. Karagoz E, Tanridag T, Karlikaya G, Midi I, Elmaci N. The electrophysiology of diabetic neuropathy. *Internet J Neurol* 2005;5.
10. Brettschneider J, Petzold A, Sussmuth S, Tumani H. Cerebrospinal fluid biomarkers in Guillain-Barré syndrome: where do we stand? *J Neurol* 2009;256:3–12.

Neurology[®]

Clinical Reasoning: A middle-aged woman with progressive symmetric weakness and a CSF pleocytosis

Douglas Marks, Adelene Jann and Teresa DeAngelis

Neurology 2012;78:e88-e92

DOI 10.1212/WNL.0b013e31824e8f30

This information is current as of April 2, 2012

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/78/14/e88.full
References	This article cites 9 articles, 0 of which you can access for free at: http://n.neurology.org/content/78/14/e88.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Cerebrospinal Fluid http://n.neurology.org/cgi/collection/cerebrospinal_fluid Guillain-Barre syndrome http://n.neurology.org/cgi/collection/guillainbarre_syndrome Viral infections http://n.neurology.org/cgi/collection/viral_infections
Permissions & Licensing	Information about reproducing this article in parts (figures,tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright Copyright © 2012 by AAN Enterprises, Inc.. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.