Clinical Reasoning: A 68-Year-Old Man With Proximal Weakness and Seizures

Author(s):
Tychicus Chen, MD, FRCPC

Corresponding Author:
Tychicus Chen
tychicus@mail.ubc.ca

Affiliation Information for All Authors: Tychicus Chen, Division of Neurology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada.

Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Contributions:  
Tychicus Chen: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Number of characters in title: 73

Abstract Word count:

Word count of main text: 1699

References: 11

Figures: 2

Tables: 0


Acknowledgements: The author wishes to thank: Dr. Jennifer Percy, Division of Neurology, Department of Medicine, University of British Columbia, for provision of EEG images; as well as the patient and his family.

Study Funding: The authors report no targeted funding

Disclosures: T. Chen reports no disclosures.
A 68-year-old retired carpenter developed progressive weakness over 4 weeks. He had difficulty rising from low position, climbing stairs, and raising his arms overhead, particularly toward evenings. He had no pain, sensory, bowel or bladder symptoms, and denied ptosis, diplopia, dysphagia, or dyspnea. He had mild unintentional weight loss but no fevers. Past medical history revealed eczema and active smoking (50-pack-years). There was no family history of neuromuscular disorders.

On examination, vital signs were normal; he was alert, oriented, attentive, and fluent with no memory disturbance. Cranial nerves revealed symmetric, reactive pupils, full extraocular movements, facial strength, and no fatigable ptosis. Muscle bulk and tone were normal without fasciculations. Neck strength was full, with variable moderate weakness in shoulder and hip girdles, slightly worse with repetition. Deep tendon reflexes were absent except biceps and patella which were reduced but present. Sensation and coordination were unremarkable.

What is the differential diagnosis for progressive weakness without sensory loss?

What clinical tests and investigations would you consider?
SECTION 2

This patient presents with subacute painless, proximal, symmetric weakness over 4 weeks, with possible fatigability, importantly without craniobulbar or sensory abnormalities, and reflexes are reduced or absent. Main considerations include muscle or neuromuscular junction disorders. Motor neuropathy including acute motor axonal neuropathy and multifocal motor neuropathy with conduction block, as well as motor neuron disease such as primary muscular atrophy, are unlikely without reduced tone or fasciculations. Amyotrophic lateral sclerosis is unlikely without bulbar or upper motor neuron signs. Lack of sensory symptoms make polyradiculopathy and peripheral neuropathy unlikely, as well as spinal cord disease without sphincter dysfunction or upper motor neuron signs—noteable exceptions include acute flaccid myelitis from poliovirus, nonpolio enteroviruses, and West Nile virus. This patient had no recent travel or infectious prodrome. There were no corticobulbar signs or encephalopathy to suggest other central processes.

Muscle disorders may be inflammatory or noninflammatory, congenital or acquired. Inflammatory and toxic myopathies may present with myalgias—this patient had no pain or exposures. His age and subacute presentation are atypical for most muscular dystrophies or genetic myopathies, with no relevant family history, although some genetic conditions demonstrate low penetrance or anticipation, including certain limb-girdle muscular dystrophies or Pompe disease. Myopathies may include systemic involvement: cardiac dysfunction, rashes (dermatomyositis), myoclonus (mitochondrial myopathies) or myoglobinuria from muscle damage—which were not present. Acquired neuromuscular junction conditions can be divided into postsynaptic disorders like myasthenia gravis (MG), associated with thymoma; or presynaptic disorders such as Lambert-Eaton Myasthenic syndrome (LEMS), associated with smoking and small cell lung cancer (SCLC) but much less common than MG or botulism—although unlikely without pupillary involvement. While both MG and LEMS may present with proximal weakness, the clinical phenotype is more typical for LEMS. Ocular involvement, diurnal variation and fatigability are characteristic of MG, whereas patients with LEMS may have improvement with repetition or the days
progression, as well as autonomic symptoms. Electrodiagnostics and serum creatine kinase levels can help distinguish the above.

On further history, he denied erectile dysfunction but complained of increasingly dry mouth. Repeat examination revealed post-exercise facilitation of deep tendon reflexes. Serum biochemistry and creatine kinase were normal. Spinal imaging demonstrated no abnormalities. Nerve conduction studies confirmed normal sensory potentials and low compound muscle action potentials without motor conduction block which improved with exercise (Figure 1A-B). Slow repetitive nerve stimulation (RNS) showed decrement (Figure 1B), while fast RNS showed increment (Figure 1C). Chest radiograph and CT showed minimal mediastinal and hilar lymphadenopathy with no suspicious pulmonary masses or thymoma. Serum voltage-gated calcium channel (VGCC) antibodies returned highly positive (387.1 pmol/L).

What is the etiology of LEMS?

What is the treatment for LEMS?
LEMS is a presynaptic neuromuscular junction disorder characterized by inhibition of P/Q-type VGCC that mediate calcium influx which normally respond to membrane depolarization, leading to proximal weakness and autonomic dysfunction. Antibodies against VGCC are present in 85-95% of cases, higher in paraneoplastic LEMS which is highly associated with SCLC, found in 60% of cases, with smoking a strong risk factor. SCLC must be considered when LEMS is diagnosed, found on initial screening in most patients. However, tumor may begin small with undetectable parenchymal lung mass and only lymphadenopathy as in this case. Immunotherapy with corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange (PLEX) are used, however as with all paraneoplastic syndromes, management relies on treatment of the underlying malignancy.

Similar to how maximum voluntary contraction transiently increases intracellular calcium concentration, leading to post-exercise facilitation and increment, symptomatic treatment targets augmentation of synaptic calcium which increases release of acetylcholine quanta. 3,4-diaminopyridine (DAP) blocks presynaptic potassium-channels which prolong depolarization, leading to increased calcium influx and intracellular calcium accumulation, which improve the ability of vesicles to fuse and release acetylcholine. Acetylcholinesterase inhibitors like pyridostigmine have modest benefit and are no longer first line. Guanidine increases intracellular calcium but is not widely available due to bone marrow suppression and nephrotoxicity.

The patient was treated with IVIG and 3,4-DAP with improvement in strength. Although no pulmonary mass was seen, given strong suspicion endobronchial ultrasound was pursued, and lymph node biopsy confirmed SCLC. Staging PET and MRI brain showed limited disease confined to the lungs without brain involvement. He started chemotherapy with carboplatin and etoposide with planned radiotherapy. Unfortunately, he developed neutropenia delaying chemotherapy, followed by confusion and seizures, and was brought to hospital and intubated for status epilepticus.
What are potential causes of seizures in this patient?

What is your next step in management?
SECTION 4

Infectious meningoencephalitis must be considered with neutropenia and chemotherapy. Seizures are a rare side effect of 3,4-DAP from potentiation of synaptic action potentials, although reported with higher doses as CNS penetration is less than with 4-aminopyridine, however side effects may still occur\(^4\). New seizures in a patient with malignancy should prompt consideration for brain metastases. Limbic encephalitis would also be a strong consideration with SCLC.

EEG demonstrated frequent periodic independent epileptiform discharges in the temporal regions bilaterally (Figure 2, top), with recurrent electrographic seizures which continued despite prompt discontinuation of 3,4-DAP and addition of escalating antiepileptic drugs. Broad antimicrobial coverage was started however cerebrospinal fluid (CSF) showed normal protein, no cells, negative viral studies, and sent for paraneoplastic antibodies. Contrast MRI showed no abnormalities to suggest metastases or encephalitis (Figure 2, bottom).

Plasma exchange was initiated for presumed limbic encephalitis, however seizures remained refractory without anesthetic infusions despite multiple antiepileptics. Although limbic encephalitis associated with SCLC should not be a reason to withdraw treatment, the family ultimately wished to withdraw care in respect of previous advance care directives following extensive counselling. A few days after he died, cell-based assay for gamma-aminobutyric acid-B receptor (GABA\(_B\)R) antibodies returned highly positive from CSF.

What is the significance of this result?
DISCUSSION

This case, although unfortunate, highlights several important points. LEMS was clinically suspected early based on history and physical exam, highlighting the importance of clinical reasoning and signs such as post-exercise facilitation. This was confirmed which led to an aggressive search for underlying SCLC, despite initial chest imaging interpreted as insignificant, leading to earlier tissue diagnosis and treatment. The most important prognostic factor for SCLC is cancer stage at diagnosis, with median survival ranging 4-11 months. Some studies have shown longer survival in SCLC with paraneoplastic LEMS, likely from earlier diagnosis and treatment or from other immune-mediated effects.

Clinicians should be aware of side effects for medications prescribed, especially less commonly used medications like 3,4-DAP. In this case, although it was prudent to stop the drug immediately when the patient presented with seizures, cognitive bias should be avoided in assuming this as the sole cause. It is always important to consider a broad differential diagnosis, especially when patients with a typical presentation develop atypical symptoms, as the diagnosis of anti-GABA\textsubscript{B}R encephalitis was unexpected. GABA\textsubscript{B}R are guanine nucleotide-binding protein-coupled metabotropic receptors for the inhibitory neurotransmitter GABA and are expressed broadly throughout the nervous system. Anti-GABA\textsubscript{B}R antibodies have been implicated in paraneoplastic limbic encephalitis, although only around 100 cases have been reported since 2010, and are also associated with SCLC in up to 50%. In the largest cohort to date of 32 patients, seizures occurred in 90%, while 42% developed super refractory status epilepticus. MRI showed mesial temporal changes in only 44%, whereas EEG was abnormal in 84% with epileptic and encephalopathic findings in 44%. One patient also had LEMS, with proximal weakness preceding encephalitis by 9 months.

The co-occurrence of LEMS and anti-GABA\textsubscript{B}R encephalitis in the setting of SCLC is rare. It has also been described in a case report where seizures occurred before initiation of 3,4-DAP and the authors suggest broad screening for paraneoplastic antibodies when treating LEMS. However, anti-GABA\textsubscript{B}R antibodies have been demonstrated in patients with SCLC without encephalitis, and one study found no
anti-GABA_bR antibodies in 116 patients with SCLC without neurologic symptoms, although this was in serum. Coexistent paraneoplastic syndromes with concurrent autoantibodies are exceptionally rare, however it is important to remain diligent for multiple paraneoplastic syndromes in a single patient.

The prognostic significance of anti-GABA_bR encephalitis coinciding with paraneoplastic LEMS is unknown given the rarity, however the few cases reported seem to show stabilization of symptoms with immunotherapy and cancer treatment. Prolonged intubation can occur as status epilepticus and neuromuscular respiratory failure are both reasons for ventilatory support. One wonders if more aggressive immunotherapy may have been successful in this case, however seizures remained refractory to multiple antiepileptics and PLEX, and patient and family wishes must be respected. However, it should be emphasized that paraneoplastic limbic encephalitis associated with SCLC can respond to treatment and should not be a reason to withhold oncotherapy. In the cohort of 32 patients above, the majority had cognitive improvement and seizure freedom; the median survival was 17 months. In another series of 28 patients with anti-GABA_bR encephalitis without LEMS, mortality was 32% and median survival 6.5 months; tumor progression was the most common cause of death and status epilepticus in one. Onset above age 45 and presence of tumor were associated with higher risk.

Finally, this case demonstrates challenging decisions clinicians may face without complete information when certain results are not immediately available, or access to specialized testing is limited. As in many cases the diagnosis becomes clear over time, and hindsight is 20/20.
References:
Figure Captions:

Figure 1: Left ulnar motor studies and repetitive nerve stimulation (RNS) recording left abductor digitii minimi. (A) Motor curves stimulating at the wrist (distal), below elbow, and above elbow: low distal amplitude (4.6 mV), normal distal latency (3.2 ms), and mild slowing across the elbow without conduction block (53 to 39 m/s). (B) Slow RNS (3 Hz, 10 stimulations): (a) before exercise, decremental response in amplitude (2.7 to 1.3 mV; 51% decrement) from stimulus 1 to 4 (blue bars); (b) following 60 seconds of maximum voluntary contraction, repair of motor amplitude (now 6.4 mV) demonstrating post-exercise facilitation, but still decremental response in amplitude (6.4 to 5.1 mV; 21% decrement) from stimulus 1 to 4 (blue bars). (C) Fast RNS (30 Hz, 90 stimulations): incremental response in amplitude (3.0 to 8.2 mV; 172% increment) between stimulus 20 and 90 (blue lines).
Figure 2: (A) EEG recorded in longitudinal bipolar montage shows frequent independent left temporal (black arrows) and right temporal (white arrows) epileptiform abnormalities. Timebase 15 mm/s, sensitivity 7 μV/mm, LF filter 0.5 Hz, HF filter 70 Hz. (B) MRI Brain, T2-FLAIR (B.a) axial and (B.b) coronal views, and T1-weighted (B.c) axial and (B.d) coronal views, showing no temporal lobe abnormalities; axial (B.e) T1-weighted post-gadolinium with (B.f) fat-saturated views, showing no abnormal enhancement.
Clinical Reasoning: A 68-Year-Old Man With Proximal Weakness and Seizures
Tychicus Chen

Neurology published online April 30, 2021
DOI 10.1212/WNL.0000000000012137

This information is current as of April 30, 2021

Updated Information & Services
including high resolution figures, can be found at:
http://n.neurology.org/content/early/2021/04/30/WNL.0000000000012137.citation.full

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Clinical neurology examination
http://n.neurology.org/cgi/collection/clinical_neurology_examination
EMG
http://n.neurology.org/cgi/collection/emg
Lambert-Eaton syndrome
http://n.neurology.org/cgi/collection/lambert_eaton_syndrome
Paraneoplastic syndrome
http://n.neurology.org/cgi/collection/paraneoplastic_syndrome
Status epilepticus
http://n.neurology.org/cgi/collection/status_epilepticus

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