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International Journal of Physical Medicine & Rehabilitation

Case Study

A Curiously Unusual Cause for Weakness in a Geriatric Patient

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ABSTRACT

Lower extremity weakness with reversible or medical etiologies is sometimes overlooked in the elderly patient. There are various causes of increased falls and weakness in the elderly population. Some causes of increased falls vision disturbances, impaired balance due to otolith dysfunction, arthritis-related immobility and lower extremity neuropathy. Clinicians should consider rarer neurological etiologies such as Guillain-Barre and transverse myelitis as part of the differential diagnosis.

We present a complex patient case with multiple admissions for progressive weakness and falls without a clear etiology. This patient case presented a diagnostic challenge and even so no unifying diagnosis was causative. The patient had various diagnostic tests suggestive of occult infection from Lyme disease serology, tuberculosis, *Propionibacterium acnes* and stool campylobacteriosis. Patient also had a remote history of a gastrointestinal tract neuroendocrine tumor in remission following surgical resection. All these conditions were considered in the differential diagnosis and treated accordingly without symptom improvement. The patient completed Intravenous Immunoglobulin (IVIG), antibiotics, anti-inflammatory and antiviral medications without clinical response. Eventually the patient opted for hospice and palliative care rather than continuing other therapeutic options.

This complex case highlights the difficulty in establishing precipitating factors in falls within the elderly population. While many falls are triggered by weakness simply due to muscle-related-atrophy and age related inactivity, this is not always the case. There are pathologies that are reversible and treatable and it is important to identify these conditions early on and provide prompt treatment.

Keywords: Guillain-Barre syndrome; Infectious; Rehabilitation; MRI; Transverse myelitis; *Propionibacterium acnes*

INTRODUCTION

Elderly adults often present with bilateral lower extremity weakness to the emergency department associated with falling. Notably falls are a common cause of morbidity and mortality [1]. Lower extremity weakness etiologies are extensive and includes neurologic, autoimmune, infectious and traumatic conditions. Neurological causes of lower extremity weakness include Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP), spinal stenosis and Guillain-Barre syndrome. Lower extremity weakness and falls in an elderly patient require careful investigation, especially with refractory symptoms unresponsive to long-term physical rehabilitation. Soliciting caregivers' and family member's input is critical in history gathering. Clinicians should consider conditions beyond the preconceived notion that increased falls are simply an elderly patient with age-related weakness.

CASE PRESENTATION

An 82-year-old woman with a past medical history of atrial fibrillation, a surgically treated small bowel carcinoid tumor,

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Received: 06-Nov-2024, Manuscript No. JPMR-24-35008; **Editor assigned:** 08-Nov-2024, PreQC No. JPMR-24-35008 (PQ); **Reviewed:** 22-Nov-2024, QC No. JPMR-24-35008; **Revised:** 29-Nov-2024, Manuscript No. JPMR-24-35008 (R); **Published:** 06-Dec-2024, DOI: 10.35248/2329-9096.24.S26.005

Citation: Malone M, Hoffman N, Bray C, Puebla B, Rtichie D (2024). A Curiously Unusual Cause for Weakness in a Geriatric Patient. Int J Phys Med Rehabil. 12:S26.005.

latent tuberculosis, hypothyroidism and hypertension presented to our Emergency Department (ED) from an inpatient physical rehabilitation facility with worsening generalized bilateral lower extremity weakness and frequent falls. The patient had three prior hospitalizations in the preceding four months for similar presentations without a definitive diagnosis. The patient bilateral weakness progressed such that upon arrival to the ED for the fourth time, the patient had bilateral lower extremity paraparesis.

During initial hospitalization, the patient was also evaluated for seven days of diplopia. The patient had both vertical and horizontal diplopia with mild vertiginous symptoms. The patient physical examination then was remarkable for mild right eye ptosis, subjective diplopia, left-sided facial weakness (left-sided facial droop), and decreased right hemi-body sensation to light touch associated with right lower extremity weakness. Laboratory studies were non-diagnostic including thyroid hormone function, vitamin B12, folate, inflammatory markers, and creatine phosphokinase. Radiological imaging including cerebral computed tomography scan and Magnetic Resonance Imaging (MRI) were showed no acute findings (Figure 1). The patient was discharged home with ophthalmologist follow up and the latter evaluation found no abnormality explaining patient symptoms [2].

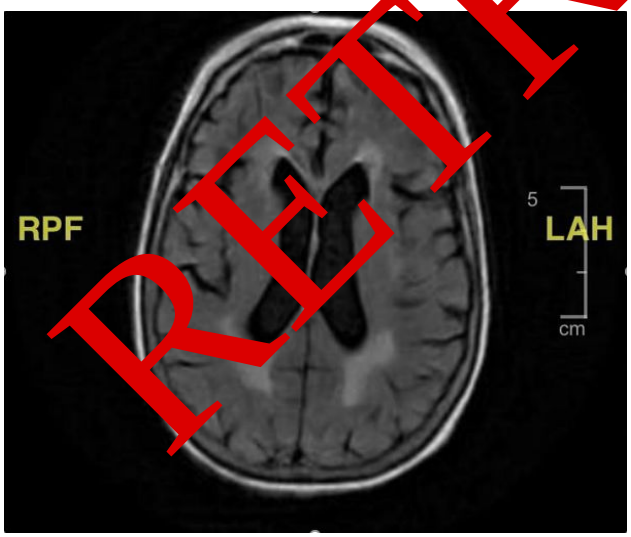

Figure 1: Brain Magnetic Resonance Imaging (MRI): There is no mass effect, hemorrhage, edema, midline shift or extra cerebral fluid collection. The ventricles and subarachnoid spaces are appropriate in size for patient's age.

The patient second hospital admission was precipitated by repeated ground level falls from severe bilateral leg weakness. On this occasion patient described worsening back pain with ambulation. The patient also developed a left facial droop during the second admission. Extensive imaging another MRI and CT scan showed no ischemic changes in the head and neck or acute stroke. Repeat cerebral MRI with and without contrast was negative (Figure 2). Lumbar spine MRI showed advanced degenerative disk disease but no significant pathology explaining patient bilateral lower extremity weakness (Figure 3). CT lumbar spine showed moderate spinal stenosis at the two lowest vertebrae of the lumbar spine and a 2 mm anterolisthesis. The patient did not exhibit urinary or fecal incontinence.

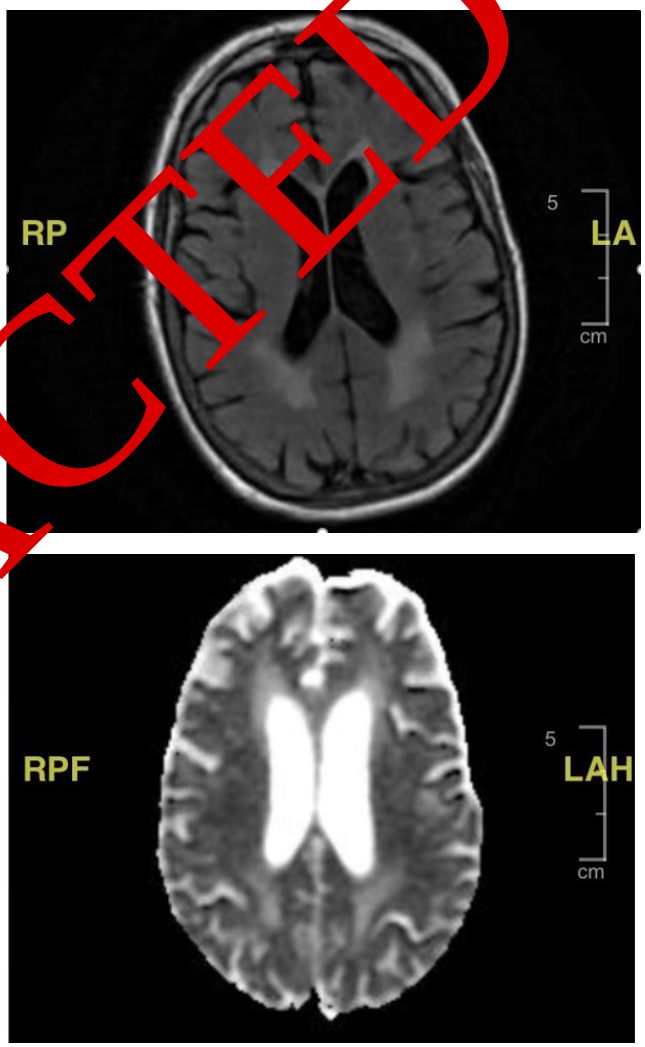

Figure 2: MRI of Brain with and without Contrast. White matter disease and volume loss indicating chronic micro-angiopathic changes. No abnormal parenchymal mass or extra-axial collection identified

The patient was admitted the third time from home following another fall associated with a pre-syncopal episode when rising from a chair. The patient reported during the prior three months patient had frequent falls without head trauma or loss of consciousness. During a one-day period, patient fell five times requiring a walker to ambulate. Radiological imaging showed no acute musculoskeletal injury. Upon reviewing the patient's medication list, all sedating medications were discontinued since the previous admission and yet the frequent falls continued.

During the third admission, the patient had diarrhea of one-week duration. Stool studies showed campylobacteriosis treated with azithromycin. During this hospitalization, the patient once more developed a left sided facial droop. Again, extensive imaging including another head and CT Angiography (CTA)

showed no acute head and neck vascular ischemic changes. There were no spinal MRI findings (Figure 3) explaining patient lower extremity weakness. During this third admission, the patient had The patient first lumbar puncture with results displayed in Table 1. Ultimately, the patient was diagnosed with Bell's palsy and completed 7 days of prednisone and 5 days of acyclovir. By now, the patient had an immense fear of falling and patient was discharged to a rehabilitation facility for mobility and activities of daily living therapy.

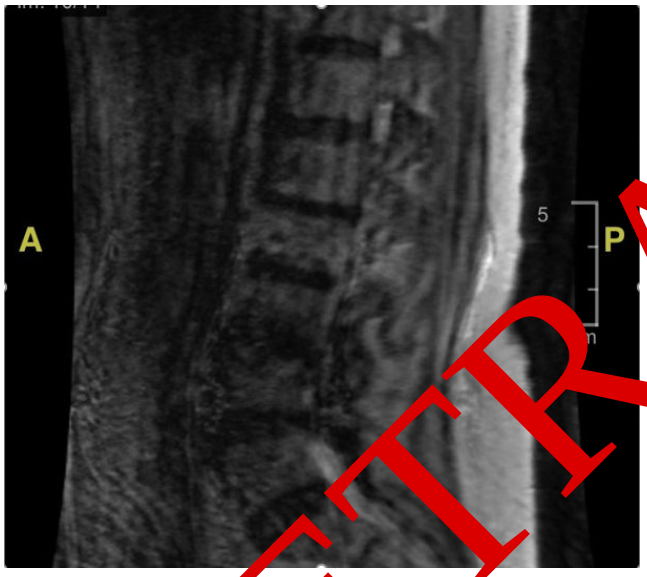

Figure 3: Lumbar spi MRI without contrast: The bracket encloses the area where re appear to be degenerative changes that most pro unced at lumbar vertebral levels of L3-L4 and L4-L5. Th e is also some degree of spinal can steno at least moderate at L3-L4. Based upon the MR ere are no acute fracture or subluxation.

The patient presente from the above rehabilitation facility, the patient fourth admission with bilateral lower extremity asymmetric motor and sensory deficits. During this admission, the patient exam showed asymmetric lower extremity weakness with full strength in patient bilateral upper extremities. The patient right leg had adequate quadriceps and hamstring strength but poor dorsiflexion. The patient left lower extremity showed poor hamstring strength 1/5 in severity but adequate distal lower extremity strength. The patient had weak bilateral hip flexion.

Thus, this patient had persistent progressively worsening bilateral leg weakness over five months without a definitive diagnosis. This admission the lumbar puncture was repeated. The cerebrospinal fluid analyses from both lumbar punctures are in Table 1. The results were significant for profound hypoglycorrhachia with elevated protein and lymphocytic pleocytosis. The CSF showed no myelin basic protein, oligo clonal banding or epithelial malignancy. The patient spinal fluid culture grew *propionibacterium acne* for which the patient received two weeks of ampicillin without improvement and the patient also had a third lumbar puncture as seen in Table 1.

Lumbar puncture results			
	Third lumbar puncture	Se d lumbar	tial first mbar puncture
CSF appearance and colour	Cloud colorless	Yellow Clo / hazy	Xanthochromia
CSF WBC	4	263	157
CSF RBC	3	29	18
CS LUCOSE	46	19 mg/dl	6
F Total ein	66	>460 mg/dl	460

Table 1: Lumbar Puncture Results: The table illustrates the sults of the patient's lumbar puncture and the resulted inf ation found from CSF analysis.

Given the CSF findings, there were concerns for a possible fungal or viral infection. The patient had a positive QuantiFERON-TB Gold (QFT) test and an elevated 1,3-β-d-glucan level of 285 (60–79 mg/mL as the indeterminate). However, CSF polymerase chain reaction for herpes virus simplex I and II, varicella, West Nile virus, and tuberculosis were all negative. This was consistent with the previous two separate lumbar punctures distanced by time post antibiotics culture and staining were negative for fungus, Acid-Fast Bacillus (AFB) and Venereal Disease Research Laboratories (VDRL). Cerebrospinal fluid Cryptococcus antigen and Brucella titers were negative. Full serum infectious diagnostics were all negative or non-reactive including *Brucella*, coxsackie, and HIV antibodies.

Of note, CSF Lyme antibodies were positive for elevated IgG and IgM levels of 2.12 (reference range 0.000.09) and 0.28 (0.00-0.06) respectfully. Other negative results for the following antibody testing included anticardiolipin, voltage gated calcium channel antibody, chromatin antibody, double stranded DNA antibody, SCL-70 RNP antibody, Smith, SS-B/SS-A/Ro and Antinuclear Antibodies (ANA). Complement C3 and C4 levels were normal. The patient had normal Erythrocyte Sedimentation Rate (ESR) in two of the patient admissions, although a C-Reactive Protein (CRP) was never tested. The patient had a thyroid peroxidase antibody level of 49.1 IU/mL (reference range 0.0-35.0 IU/mL) consistent with hypothyroidism, although patient's known hypothyroidism was well-controlled with levothyroxine given the patient free T4 were normal and the patient TSH level remained below 10 uIU/mL (reference range 0.358-3.740).

As stated above, the patient had a history of pathologic T2 stage A3b small bowel carcinoid diagnosed 15 years previously. The patient underwent partial small bowel resection without any tumor identified in the bowel. The patient was monitored for remission with 24-hour urine tests for 5-Hydroxyindoleacetic Acid (5-HIAA), serum serotonin and chromogranin A, and showed no disease recurrence. The patient had no carcinoid symptoms such as flushing, abdominal pain or weight loss. We evaluated the patient for carcinoid tumor small bowel

recurrence by screening for gastrin, vasoactive intestinal peptide, and 24-hour urine 5-hydroxytryptamine levels, these were all within normal limits.

The patient completed a multitude of broad-spectrum antibiotics and underwent penicillin desensitization due to a penicillin allergy to ensure adequate CSF penetrance given that patient CSF grew *propionibacterium acne*. Following desensitization, the patient tolerated a course of penicillin. The patient also completed an Intravenous Immunoglobulin (IVIG) course for possible Guillain-Barre syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. There was no response to either of these treatments. Neurosurgery recommended leptomeningeal biopsy to assess for the presence of possible malignancy. However, the patient declined this as it would not alter further treatment. Ultimately, the patient and family opted for comfort measures and pursued hospice care.

DISCUSSION

The differential diagnosis for lower extremity weakness is broad and complicated by various overlapping conditions, particularly in the elderly. Older adults often have aging related visual, auditory, vestibular, sensory and motor impairments contributing to falls. Yet when evaluating lower extremity weakness and falls it is imperative to consider atypical etiologies such as malignancy and infectious and autoimmune disorders. Our patient was a complex case without clear etiology explaining the patient's progressive weakness of oculomotor, facial and lower extremity musculature despite repeated and extensive laboratory testing and imaging exams.

There are certain autoimmune conditions that can lead to progressively worsening extremity weakness such as inflammatory myopathies, myasthenia gravis or Lambert-Eaton syndrome. However, most of these autoimmune conditions tend to affect all limbs equally and symmetrically. The patient in this case had isolated bilateral lower extremity weakness with sparing of patient upper extremity. The patient appeared to have been susceptible to auto-immune conditions given a history of hypothyroidism with elevated thyroid peroxidase positive antibodies of 49.1 and thyroglobulin antibody level of 208 (levels below 20 IU/mL are typically considered normal). However, studies have shown that the presence of these two antibodies does not necessarily correlate with autoimmune disease and elevated levels are seen in normal individuals [3]. Additionally, the patient thyroxine T4 thyroid hormone and creatine kinase levels remained consistently within normal limits throughout the patient multiple admissions, therefore hypothyroid-related-myopathy was also deemed unlikely.

The CSF findings were consistent with hypoglycorrhachia and elevated protein. This is indicative of either chronic inflammation disrupting the blood-brain barrier, an infectious process, or an autoimmune illness such as Guillain-Barre syndrome or Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) [4]. If there was an infectious etiology for the patient's symptoms, given the chronicity and lack of neutrophil elevation, it would likely have been viral, fungal, or tuberculosis as opposed to bacterial. Further testing including an autoimmune panel, complement levels and immunoglobulin levels were all negative, decreasing the likelihood of patient condition being rheumatological in origin. Testing was negative for anti-voltage gated antibody and anti-acetylcholine receptor antibody decreasing the likelihood of disorders such as myasthenia gravis: A disorder with similar presentation.

Carcinoid tumors have been associated with a paraneoplastic disorder involving the peripheral nervous system and can present with peripheral neuropathy and cerebellar dysfunction [5]. Given the patient's history of carcinoid and one of the patient hospital admissions that included symptoms of diarrhea and abdominal pain the differential of either an infectious process or a recurrence of the patient small bowel neuroendocrine tumor recurrence were considered. However, the patient levels of gastrin, vasoactive intestinal peptide and 5-hydroxytryptamine levels from 24-hour urine assessing for recurrent carcinoid were all within normal limits. The patient abdominal imaging lacked findings suggestive of neuroendocrine tumor recurrence.

In investigating the possibility of an infectious etiology, tuberculosis testing was performed. The patient had a positive IGRA test and fungitell assay but lacked other findings suggestive of tuberculosis. Patient chest-x-ray showed no acute or chronic infiltrates. Additionally, CSF culture and PCR were negative for tuberculosis. The elevated 1,3-β-d-glucan resulting in a positive IGRA test was possibly related to multiple antibiotics administered during patient treatment. Many antimicrobial drugs cause elevation of 1,3-β-d-glucan given the reactivity between the assay used to test for 1,3-β-d-glucan and certain antibiotic [6].

The patient CSF Lyme serology was considered positive and despite completing 2 weeks of ampicillin and intravenous penicillin, the patient failed to show clinical improvement. The patient was also treated for presumed Bell's palsy with antiviral medications and steroids. Several viral agents are suggested in the etiology of Bell's palsy, specifically reactivated viruses such as the Varicella Zoster Virus (VZV) and Herpes Simplex Virus (HSV) type 1 and type 2 [7]. In this case, however, Bell's palsy was deemed unlikely given that the CSF PCR was negative for infectious agents associated with Bell's palsy.

Also, in the differential diagnosis, one should consider Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Onset is often preceded by a respiratory or gastrointestinal infection triggering a T-cell mediated autoimmune attack against peripheral nerve and root myelin. However, increased white blood cells in CSF is not typical and a CIDP diagnosis is less likely with a higher number of leukocytes [8]. Infectious etiology was considered and treated appropriately without success. Clinically, the patient did not present as a traditional CIDP patient given that the weakness spared in upper extremity.

The patient's stool testing suggested possible campylobacter infection and with associated gastroenterology symptoms Guillain-Barre syndrome (AIDP) was considered in the differential diagnosis. This disorder is due to the autoimmune correlation with this type of bacterial infection [9]. GBS treatment was initiated with IVIG. Additionally, the patient spinal fluid

culture grew *Propionibacterium acnes* and as a result, the patient received 2 weeks of ampicillin but failed to show any improvement despite multiple antibiotic agents and IVIG.

Although Transverse Myelitis (TM) was at one point considered for a differential diagnosis, there was not enough objective data substantiating this diagnosis. Transverse myelitis is commonly misdiagnosed as GBS because of the similarities of sensory loss and weakness. However, the TM is associated with symptoms corresponding to a spinal cord level and is typically symmetrical paralysis and/or paresthesia [9]. Our patient had asymmetric syndromes with waxing and waning levels of strength therefore TM was an unlikely etiology of our patient's symptoms.

The differential diagnosis for patient paresis was subsequently narrowed down to carcinomatosis meningoencephalitis. This is a rare disorder whereby cancerous cells from a primary source such as mammary gland or gastrointestinal seeds into the leptomeninges [10]. The patient had a history of neuroendocrine tumor of small bowel and although it was in remission, it still made patient more susceptible to carcinomatosis meningoencephalitis [10]. Additionally, the patient CSF lumbar puncture results showed hypoglycorrhachia and elevated protein and given infectious causes were ruled out, carcinomatosis meningoencephalitis is a likely diagnosis [10]. In most cases, the best initial diagnostic modality is MRI with gadolinium, this test is both highly sensitive and specific. However, inconclusive cases can further be evaluated with a biopsy [10]. This condition has a poor prognosis. The patient was offered a leptomeningeal biopsy to be performed by interventional neurology. Ultimately, it was decided not to proceed with the biopsy given there would be minimal change to the outcome. The patient elected for a palliative care approach.

CONCLUSION

In general, the etiology for bilateral lower extremity weakness and subsequent falls includes a broad list of etiologies and it is imperative to employ a systematic approach to an extensive list of differential diagnoses. It is important to consider rare neurological etiologies to explain the development of bilateral lower weakness and associated falls in elderly populations. One must expand the differential diagnosis beyond traditional differentials and preconceived notions that the bilateral lower extremity weakness stems from age-related inactivity and sensory motor aging changes.

CONFLICT OF INTEREST

Authors declare there is no conflict of interest.

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