



Section Editor
John J. Millichap, MD

Clinical Reasoning: A 71-year-old woman with subacute progressive distal weakness and paresthesia after vaccination

Simão Cruz, MD
Andrew M. Schaefer,
MRCP
Abhijit Joshi, FRCPath
Mark R. Baker, MRCP

Correspondence to
M.R. Baker:
m.r.baker@ncl.ac.uk

SECTION 1

A 71-year-old woman presented to the emergency department complaining of weakness and a dull ache in her lower limbs and symptoms of ascending paresthesia and anesthesia, which had appeared initially in the toes, but by the time of presentation 7 days later had ascended symmetrically to the shins. By the time of admission, she had begun to describe symptoms of paresthesia in both hands. There were no other symptoms in the upper limbs, trunk, or face, and she denied any sphincter disturbance. One week before the onset of symptoms, the patient had received a flu vaccine. She denied recent fever, sore throat, or diarrhea. There was no history of relevant alcohol intake, exposure to toxins, or recent foreign travel.

On examination, the lower limbs were symmetrically weak (Medical Research Council [MRC] grade 4 in all muscle groups except toe and ankle dorsiflexion where power was MRC grade 2). Deep tendon reflexes were absent at the ankles but preserved at

the knees. There was decreased pinprick sensation in a stocking distribution below the midshin and proprioception was impaired in the toes but retained at the ankle. The tone was normal and plantar responses were mute. Higher mental function was intact and cranial nerve and upper limb examination was unremarkable. General physical examination was normal.

Initial investigations including a full blood count, urea and electrolytes, and glycosylated hemoglobin were within normal limits. The erythrocyte sedimentation rate was within the normal range (28 mm/h). Estimated glomerular filtration rate was reduced (44.5 mL/min).

Questions for consideration:

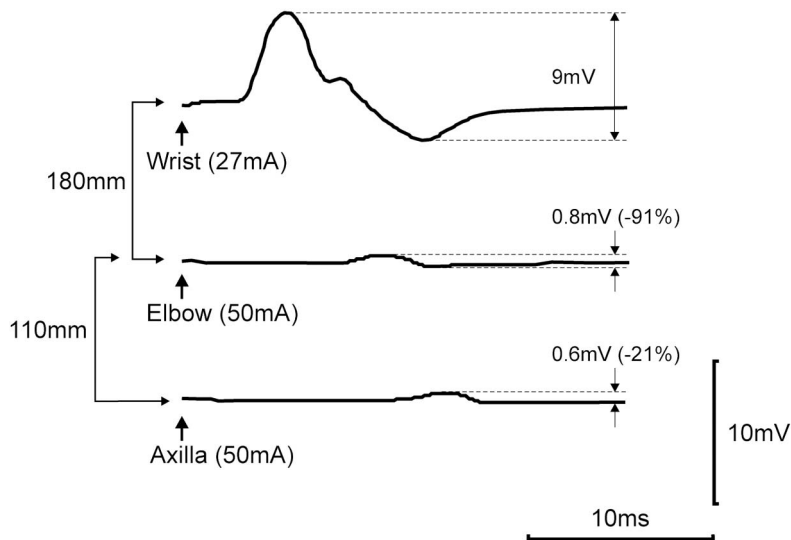
1. How would you localize the signs?
2. What clinical syndrome is being described?
3. What is the differential diagnosis?
4. How would you investigate the patient initially?

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From the Departments of Clinical Neurophysiology (S.C.) and Neurology (A.M.S., M.R.B.), Royal Victoria Infirmary, Newcastle upon Tyne, UK; Department of Neurology (S.C., M.R.B.), Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; Department of Neuropathology (A.J.), Royal Victoria Infirmary Hospitals, NHS Foundation Trust; and Institute of Neuroscience (M.R.B.), The Medical School, Newcastle University, Newcastle upon Tyne, UK.

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Figure 1 Conduction block



Abductor pollicis brevis compound muscle action potentials (CMAPs) evoked at 3 locations: wrist, antecubital fossa (elbow), and axilla. Stimulation intensities and the distances between stimulation sites are indicated. Stimulus duration was 0.5 ms. Note the diminution of CMAPs evoked at more proximal locations.

SECTION 2

While the bilateral distribution of sensory and motor features with an acute onset following vaccination might suggest an acute transverse myelitis, the absent ankle jerks, absence of upper motor neuron signs, and lack of sphincter disturbance favor a pathologic process affecting the peripheral nervous system, specifically sensory and motor nerves or roots. The clear distal predominance of the clinical features might favor a neuropathy over a radiculopathy. However, the recent onset and ascending progression suggest an ongoing process in which root involvement might evolve over time and therefore cannot be excluded. At this stage, the syndromic diagnosis is therefore that of a progressive subacute distal sensorimotor polyneuropathy.

Given the subacute onset and history of recent immunization, an inflammatory demyelinating etiology (i.e., Guillain-Barré syndrome [GBS] spectrum) would be high on the differential. There are features that could be considered atypical for GBS. These include the marked distal predominance of signs

and symptoms and the preserved knee and upper limb deep tendon reflexes 7 days after the onset of symptoms. However, in GBS, clinical progression may occur over a longer period and the possibility of preserved reflexes¹ and atypical clinical phenotypes is well-recognized.² Other etiologies to be considered include the following: infections (e.g., HIV, especially accompanying the seroconversion syndrome, borreliosis, diphtheria); other inflammatory diseases (e.g., sarcoidosis); and toxin (e.g., hexacarbons) or drug exposure (e.g., amiodarone and gold salts). In addition, a rapidly progressive confluent vasculitic mono-neuritis multiplex can mimic GBS.³

Nerve conduction studies (NCS) and needle EMG were performed on the ninth day after symptom onset. While the right median (13 μ V), radial (7.8 μ V), and sural (22 μ V) sensory nerve action potentials (SNAPs) were normal, NCS revealed a reduced right ulnar SNAP amplitude (3.6 μ V) and absent superficial peroneal SNAP.

Motor conduction studies identified conduction block in the right median nerve within the forearm (figure 1) and in the right ulnar nerve within the forearm. The right peroneal compound muscle action potential (CMAP) amplitude was also markedly reduced. Conduction velocities were moderately reduced in the median nerve (32 m/s) and reduced in the tibial nerve (36 m/s). Sensory and motor distal latencies and the remaining conduction velocities were normal. There was no clear temporal dispersion, even in the nerves with conduction block. The minimal latency of median nerve F waves was markedly prolonged (38 ms) and ulnar, tibial, and peroneal F waves were absent. Needle EMG showed decreased recruitment in several lower limb muscles without spontaneous activity or changes in motor unit action potential morphology.

Questions for consideration:

1. Based on the results of EMG/NCS, what is the most likely diagnosis?
2. What other tests might you perform to confirm the diagnosis?
3. Would you treat the patient at this stage? If so, with what?

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SECTION 3

The presence of motor conduction block in several nerves, abnormal F waves, and a sural-sparing pattern⁴ are highly suggestive of a diagnosis of acquired inflammatory demyelinating polyradiculoneuropathy (AIDP), the most common electrophysiologic GBS subtype in Europe.⁵ However, because of the short duration of the symptoms, the possibility that the conduction blocks might be caused by localized axonal lesions (i.e., partial infarction), before the development of Wallerian degeneration, could not be excluded. Furthermore, transient conduction block and minor demyelinating features are sometimes identified in axonal variants of GBS.⁶

Results of additional investigations available at this time showed a normal angiotensin-converting enzyme level, negative cryoglobulins, negative hepatitis B surface antigen, and negative anti-hepatitis B core, anti-hepatitis C, anti-HIV, and anti-*Borrelia burgdorferi* antibodies. The only positive finding was a small immunoglobulin M kappa monoclonal band on serum electrophoresis.

A lumbar puncture revealed CSF protein of 0.48 g/L without pleocytosis.

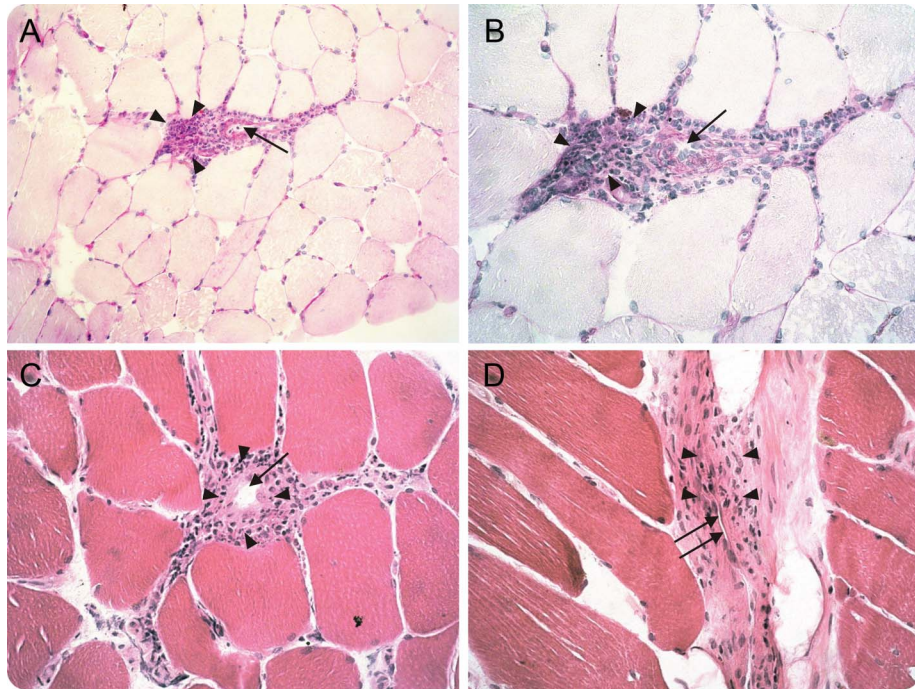
If AIDP is suspected, IV immunoglobulin or plasma exchange should be initiated within 2 weeks. Evidence has consistently shown that early intervention considerably speeds recovery and reduces disability at 4 weeks compared with supportive care.⁷ Respiratory evaluation and support, if needed, should also be provided in the emergent setting.

In the evening of day 2 of admission, the patient developed a wrist drop in her right hand, with severe weakness (MRC grade 2) of wrist and finger extension and finger abduction and decreased pinprick sensation in the right fifth digit and medial border of the fourth digit on examination.

Questions for consideration:

1. Would these new symptoms and signs lead you to revise your diagnosis?
2. What (if any) additional diagnostic investigations would be helpful at this stage?

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(A) Transverse section of skeletal muscle stained with periodic acid-Schiff-diastrase shows perivascular inflammatory infiltrates containing mononuclear and polymorphonuclear lymphocytes surrounding small vessels between muscle fascicles ($\times 10$). (B) Same inflammatory focus as in A, seen at a higher magnification ($\times 40$). (C, D) Further representative areas of perivascular and intramural inflammation seen in hematoxylin & eosin-stained sections. In each panel, arrowheads show areas of inflammation and arrows indicate the lumen of a representative arteriole ($\times 40$).

SECTION 4

These new clinical findings suggest the involvement of 2 individual nerves: right ulnar and right posterior interosseous nerve. This pattern is very suggestive of multiple mononeuropathies, which would be atypical for AIDP, and much more suggestive of mononeuritis multiplex. Although vasculitis, either primary systemic or secondary (e.g., hepatitis B or C, collagen tissue diseases), is the main diagnosis to consider with this pattern of neuropathy, other disorders should be considered, including HIV infection, leprosy, Lyme disease, lymphoma, or a paraneoplastic syndrome. To make the diagnosis of vasculitis, a sample of affected tissue is required. A percutaneous muscle biopsy was therefore performed. This showed focal inflammatory infiltrates surrounding small vessels and within vessel walls (figure 2, A–D).

Additional blood tests revealed a raised rheumatoid factor ($>1,490$ IU/mL; normal range 0–19 IU/mL) and a low complement component 4 (<0.04 g/L). However, anti-DNA, anti-chromatin, anti-ribosomal P, anti-Ro-52 and 60, anti-La, anti-centromere, anti-Sm, anti-RNP, anti-Scl-70, anti-Jo-1, anti-MPO, anti-PR3, and anti-GBM antibodies were negative or normal.

EMG/NCS were repeated 9 days after admission. These now showed severely reduced CMAP amplitudes throughout, particularly in those nerves where conduction block had been identified previously. The sural SNAP was now absent.

Question for consideration:

1. Would you change your management of the patient? If so, what therapeutic changes would you make?

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SECTION 5

There is histologic evidence of vasculitis. Although the etiology is not yet fully established, the initial screening would be suggestive of a collagen tissue disease–associated vasculitis (e.g., rheumatoid arthritis or systemic lupus erythematosus).

The priority of treatment is to prevent further nerve damage and immunosuppression is therefore indicated. Treatment of noninfectious vasculitides affecting large diameter arterioles comprises initial induction therapy with corticosteroids but there is often the need to add another immunosuppressant in order to achieve a long-term response. IV methylprednisolone (1 g/d for 3–5 days) followed by oral prednisone is the most effective immediate therapy.⁸ This patient received IV methylprednisolone 1 g/d for 3 days and was subsequently started on oral prednisone 0.75 mg/kg/d. In the following weeks, there was no further progression of the symptoms. Mycophenolate mofetil (500 mg BD) was added as a steroid-sparing immunosuppressive agent and 6 months after discharge from hospital the wrist drop had resolved and the left foot drop had improved clearly to the extent that she was able to ambulate with a cane.

DISCUSSION This case illustrates a rare presentation of vasculitic neuropathy with electroclinical features mimicking AIDP.

The occurrence of early nerve conduction abnormalities meeting the criteria for conduction block in vasculitic neuropathies has been documented.^{9,10} The proposed mechanism is axonal conduction failure related to ischemic injury and thus it is not true conduction block but rather a transient phenomenon preceding full Wallerian degeneration. Therefore, within the first 10 days of symptoms and in the absence of other clear-cut signs of demyelination—particularly if the clinical presentation or the progression over the ensuing days is atypical for AIDP—it is essential to repeat electrophysiologic studies in order to help inform decisions around investigation and treatment, particularly when aggressive immunosuppression might be considered.

Interestingly, classical teaching is that pain is the sine qua non of vasculitic neuropathy but this is not strictly true. Pain occurs in about 96% of patients with nonsystemic vasculitic neuropathies¹¹ and in one series in which symptoms of pain were documented in patients with systemic vasculitis (i.e., Churg–Strauss syndrome, microscopic polyangiitis, or Wegener granulomatosis), one third of patients presented with painless mononeuropathies.¹² Thus, while vasculitic neuropathy typically presents with pain, painless presentations are recognized.¹³

Our patient was vaccinated prior to the onset of symptoms. Although there have been rare reports of the emergence of vasculitic neuropathy or systemic vasculitis after vaccination,¹⁴ larger epidemiologic surveillance studies¹⁵ have not demonstrated a clear link between vaccination and vasculitic neuropathy. In the most recent population-based study, 12 case reports of vaccine-associated neuropathy were identified; only 3 of these fulfilled Peripheral Nerve Society criteria for definite vasculitic neuropathy and 5 for clinically probable vasculitic neuropathy.¹⁵ In the setting of recent vaccination, GBS seems to be a more frequent complication than vasculitic neuropathy.¹⁴

AUTHOR CONTRIBUTIONS

Dr. Cruz: design/conceptualization of the study, analysis/interpretation of neurophysiology data, drafting/revising the manuscript. Dr. Schaefer: design/conceptualization of the study, drafting/revising the manuscript. Dr. Joshi: analysis/interpretation of histologic data, drafting/revising the manuscript. Dr. Baker: design/conceptualization of the study, analysis/interpretation of neurophysiology data, drafting/revising the manuscript.

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DISCLOSURE

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