

An Acute Evolving Flaccid Quadriparesis in an Elderly Woman

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DESCRIPTION of CASE

A 72-year-old woman was admitted with progressive lower limb weakness, such that she was unable to stand or walk. She was previously healthy, accustomed to play tennis twice a week. Five days prior to admission she had developed low back pain radiating to the legs without a history of trauma. The pain was followed by numbness in the legs, beginning distally and then ascending over two or three days. The patient also experienced weakness that became progressively worse, initially making it difficult to climb stairs and then to walk and stand. Although she had no difficulty passing urine, she did complain of impaired sensation of bladder filling. She had noted some difficulty picking up objects with her hands but had no complaint of upper limb numbness or weakness at the time of admission.

Eighteen months earlier she had been diagnosed with diabetes mellitus, which was controlled with diet and an oral hypoglycaemic agent. There was a long-standing history of hypertension controlled with valsartan and felodipine. There was no recent history of travel overseas. No similar clinical problems were known in close family or friends.

General medical examination at the time of admission was unremarkable, aside from a palpable bladder, and she was afebrile. Examination of the nervous system showed the cranial nerves to be intact. Upper limbs were normal in tone, but the lower limbs were flaccid. Weakness was evident, the pattern being more severe in the legs with greater distal than proximal involvement. Medical Research Council muscle power grade (out of 5) was 2 distally, 3–4 proximally in the arms and 1 distally, 2 proximally in the legs. Tendon reflexes were absent throughout. Sensory examination showed reduction in pin-prick sensation to the knees and vibration sensation to the costal margins, and impaired distal proprioception.

What Is the Differential Diagnosis?

The patient had an acute evolving neurological syndrome with largely symmetrical sensorimotor dysfunction, with greater motor involvement causing an areflexic flaccid quadriparesis, the temporal and spatial pattern of which was ascending from lower to upper and from distal to proximal in the limbs. The differential diagnosis of this picture is potentially broad (Box 1), encompassing myelopathies, polyneuropathies, neuromuscular transmission disorders, and myopathies, although many of these possibilities are rapidly excluded on the basis of the clinical features.

An acute myelopathy such as cord compression or transverse myelitis may present with quadriparesis with, at

Box 1: Differential Diagnosis of Acute Evolving Flaccid Quadriparesis

Myelopathies:

- Compressive myelopathy
- Transverse myelitis, brainstem encephalitis
- Necrotising myelopathy
- Infection: poliomyelitis, enterovirus, flaviviruses

Neuropathies: see Box 2

Neuromuscular junction transmission disorder:

- Myasthenia gravis
- Lambert-Eaton myasthenic syndrome
- Botulism
- Venom: snake, sea urchin

Myopathies:

- Acute inflammatory myopathies

Others:

- Conversion disorder/factitious disorder
- Brainstem infarction (locked-in syndrome)

least in the acute phase, hypotonia and depressed reflexes (i.e., a lower motor neuron pattern of signs). More typically, spasticity and hyperreflexia with extensor plantar responses (i.e., upper motor neuron signs) with a sensory level and prominent sphincter involvement would be expected, especially with evolution over time. Bickerstaff brainstem encephalitis often has extensive cranial nerve involvement out of proportion to accompanying quadriparesis.

Acute polyneuropathies have a broad differential diagnosis (Box 2). They may be classified as primary, the Guillain-

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Abbreviations: CSF, cerebrospinal fluid; EMG, electromyography; GBS, Guillain-Barré syndrome; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging

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The Learning Forum discusses an important clinical problem of relevance to a general medical audience.

Barré group of disorders, or secondary, for example to metabolic disorders (e.g., diabetes, porphyria), infectious disease (e.g., AIDS, Lyme disease, hepatitis C), drugs and toxins (e.g., alcohol, vincristine, pyridoxine), or autoimmune and malignant disorders (e.g., connective tissue disorders) [1]. Guillain-Barré syndrome (GBS) has been fractionated in recent years according to clinical, neurophysiological, and pathological characteristics, as acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, and Miller Fisher syndrome. These syndromes may be associated with various anti-ganglioside antibodies [2]. Involvement of nerve roots (radiculopathies) may also contribute to symptomatology; for example, there is root involvement in GBS (polyradiculoneuropathy).

Neuromuscular junction transmission disorders may produce acute flaccid quadriplegia, for example in myasthenia gravis, Lambert-Eaton myasthenic syndrome (wherein tendon reflexes may be markedly depressed, but present with facilitation), and botulism. The presence of sensory symptoms in our patient ruled out these diagnoses, likewise acute myopathies such as polymyositis that may also enter the differential diagnosis of acute flaccid quadriplegia.

Initial Investigations

Because of the rapidly progressive onset of weakness causing the patient to be “off legs”, with bladder involvement, and in the absence of preceding pyrexial or gastrointestinal illness, the initial investigation was magnetic resonance imaging (MRI) of the spinal cord, arranged acutely to exclude compressive or inflammatory disease. This proved normal. The key investigations to follow were electrodiagnostic studies and cerebrospinal fluid (CSF) analysis.

Neurophysiological studies comprising electromyography (EMG) and nerve conduction studies were performed. The latter showed slowed motor conduction velocities in motor nerves (e.g., peroneal 33 m/s, normal >40 m/s), but with normal latencies and amplitudes. F wave latencies were absent (tibial nerve) or markedly delayed (median, ulnar about 40 ms, normal <30 ms). Sensory amplitudes were reduced (e.g.,

median 3.4 mV, normal 4–20; sural 2.0 mV, normal 5–40), but with normal latencies. EMG showed no acute denervation, but discrete motor units were seen in distal muscles, with no volitional activity in proximal muscles of the lower limbs. These findings were consistent with an acute demyelinating polyneuropathy.

Lumbar puncture was undertaken for CSF analysis. CSF protein was elevated (1.49 g/l; normal range 0.1–0.45 g/l) with normal glucose (3.8 mmol/l; plasma glucose = 6.7 mmol/l). CSF cell count showed <5 red cells and 14 white cells (normal range <7). Cytology showed these cells to be lymphocytes and macrophages, but no neoplastic cells were seen. CSF oligoclonal band analysis showed a type 4 pattern with multiple matching bands, a finding consistent with systemic inflammation.

Routine blood tests showed normal haematological parameters and blood electrolytes. Liver-related enzymes (alkaline phosphatase, aspartate transaminase, gamma-glutamyltransferase) were elevated but with normal bilirubin and clotting parameters.

Initial Formulation

In light of the clinical, neurophysiological, and CSF findings, a provisional diagnosis of GBS was made, although the atypical elevated CSF cell count was noted.

Although possible earlier descriptions of acute inflammatory neuropathy by Wardrop (1834) and by Landry (1859, “acute ascending paralysis”) exist [3,4], it was the paper by Guillain, Barré, and Strohl published in 1916 that first drew attention to the CSF finding of raised protein in the absence of cellular reaction, the *dissociation albuminocytologique*, as characteristic of the condition that would subsequently immortalise the first two authors [5].

Initial Treatment

Because of the patient’s urinary retention, the bladder was catheterised. Evidence of autonomic involvement elsewhere was sought by continuous monitoring of cardiac rhythm. Although there was no complaint of breathing difficulty, forced vital capacity was monitored to pre-empt respiratory insufficiency. Because of immobility, standard prophylaxis for deep vein thrombosis was instituted (graduated compression stockings, fractionated subcutaneous heparin).

Evidence-based treatment guidelines for GBS recommend either plasma exchange or intravenous immunoglobulin (IVIg) as the initial treatment of choice [6]. Since the latter was more practical, the patient received a course of IVIg at 1 g/day for three consecutive days.

Further Formulation and Investigations

Current diagnostic criteria for GBS are based on clinical and neurophysiological features [7,8]. Typical CSF findings support the diagnosis, although it is recognised that protein elevation may not be seen, especially if lumbar puncture is performed in the early stages of the disease. Contrary to the original findings of Guillain and his colleagues [5], criteria do permit cells in the CSF, with a cut-off of 10 mononuclear lymphocytes/ml. Increased CSF cell count is recognised as occurring if GBS is superimposed on an infection such as HIV or Lyme disease. Clinical and investigative features of GBS do not seem to differ in young and elderly patients [9]. Hence the finding of 14 cells/ml in our patient’s CSF was deemed atypical. Furthermore, the type 4 CSF banding

Box 2: Differential Diagnosis of Acute Neuropathies

Primary—Guillain-Barré syndrome variants:

- Acute inflammatory demyelinating polyneuropathy
- Acute motor axonal neuropathy
- Acute motor and sensory axonal neuropathy
- Miller Fisher syndrome

Secondary:

- Metabolic: diabetes, uraemia, porphyria
- Infection: Lyme disease, diphtheria, HIV, hepatitis C
- Drugs/toxins: alcohol, organophosphates, hexacarbons, heavy metals (arsenic, thallium, gold)
- Autoimmune: vasculitic neuropathy, with or without connective tissue disorder
- Malignant: paraneoplasia
- Other: critical illness polyneuropathy

Key Learning Points

- Acute evolving flaccid quadriplegia has a broad differential diagnosis, encompassing spinal cord, peripheral nerve, neuromuscular junction, and muscle disorders.
- After causes of myelopathy are excluded by structural imaging (MRI), the key diagnostic investigations of acute evolving flaccid quadriplegia are neurophysiology (EMG, nerve conduction studies) and CSF analysis.
- GBS is the most common cause of acute polyneuropathy; this diagnosis may be sub-classified based on clinical and neurophysiological findings, and presence of anti-ganglioside antibodies.
- Features “atypical” for GBS, such as elevated CSF cell count or abnormal liver-related blood tests, should prompt consideration of other concurrent diagnoses, including underlying malignancy.

pattern, also termed the “mirror pattern”, which occurs when the oligoclonal pattern in the CSF and serum is essentially the same, reflects primarily a systemic disease; or if there is infection in the central nervous system such as meningitis, the systemic response plays a predominant part. This pattern would be unusual for typical GBS.

MRI of the spinal cord is not required in all suspected cases of GBS, but may be indicated to exclude myelopathy if there are atypical features, as in this case, since the penalty for delayed diagnosis of cord compression may be permanent neurological disability.

Further investigations in our patient included testing for a panel of anti-ganglioside antibodies associated with acute neuropathies [2]; these proved negative. Serology for infection with *Campylobacter jejuni* was negative, as were investigations for other possible acute infections (cytomegalovirus, Epstein-Barr virus, mycoplasma).

Because of the CSF findings and the abnormalities in liver-related blood tests, further investigations were deemed appropriate. A panel of onconeural antibodies (Hu, Yo, Ri, Ma2, amphiphysin, CV2, Tr) was negative. Of tumour markers, α -foetoprotein, carcinoembryonic antigen, and total human chorionic gonadotropin were normal, but both CA125 (45 U/ml; normal 0–21 U/ml), and CA19-9 (521.0 U/ml; normal 0–25 U/ml), were above the normal range.

The elevated tumour markers prompted further investigation to search for an underlying tumour. Computed tomographic scanning of the abdomen and pelvis was normal, with no lymphadenopathy or organomegaly observed. The patient then proceeded to endoscopic retrograde

cholangiopancreatography, which showed a filling defect in the pancreatic duct indicative of pancreatic cancer.

Progress

No neurological improvement was observed following treatment with IVIg. The patient developed a chest infection and died two weeks later. Permission for autopsy was not granted. The family gave consent for the publication of this case report.

DISCUSSION

GBS has on occasion been reported in association with occult cancer. This might be a chance concurrence of two aetiologically distinct disorders, but might also reflect a paraneoplastic process. In the current classification of paraneoplastic disorders, GBS is regarded as a “non-classic syndrome”, since it is not associated with known onconeural antibodies. The more typical paraneoplastic syndrome of the peripheral nervous system is a subacute sensory neuronopathy, often associated with anti-Hu antibodies [10]. Nonetheless, one study of a large number of cases of typical GBS found the incidence of carcinoma occurring with short latency to be 1.7% [11]. GBS has on occasion been reported in association with pancreatic cancer [12]. ■

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