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Citation for final published version:

Saad, Toni C, Pickrell, William Owen, Payne, Gareth and Khalid, Hamandi 2019. Chronic inflammatory demyelinating polyneuropathy: a rare cause of falls. *BMJ Case Reports* 12 (12) , e231676. 10.1136/bcr-2019-231676

Publishers page: <http://dx.doi.org/10.1136/bcr-2019-231676>

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Full clinical cases submission template

TITLE OF CASE <i>Do not include "a case report"</i>
Chronic inflammatory demyelinating polyneuropathy: a rare cause of falls
SUMMARY <i>Up to 150 words summarising the case presentation and outcome (this will be freely available online)</i>
This case of chronic inflammatory demyelinating polyneuropathy (CIDP) shows that a patient's condition can evolve from the point of admission, gradually manifesting its underlying cause. Our patient's initial presentation of backpain and lower limb weakness prompted investigations which ruled out compressive myelopathy and neuropathy. As upper limb weakness developed later, along with a more proximal and symmetrical pattern of lower limb weakness, the clinical picture suggested polyneuropathy. The diagnosis of CIDP became apparent only after numerous negative tests and nerve conduction studies identified demyelination. Diagnosing CIDP enabled the commencement of definitive treatment which led to a good recovery.
BACKGROUND <i>Why you think this case is important – why did you write it up?</i>
This case illustrates the importance of paying close attention to evolving signs and symptoms, and synthesising this information with data from investigations to arrive at a reasoned diagnosis. CIDP, because it frequently mimics other conditions, sometimes requires a complex work-up to diagnose definitively. Additionally, this case shows that common symptoms sometimes have uncommon causes. Considering of these ensures a thorough initial assessment, particularly examination, and should inform the differential diagnoses. Backpain and falls are common clinical presentations which call for a systematic and reasoned assessment. This is what is required to ensure minimal diagnostic delay and error and effective therapy.
CASE PRESENTATION <i>Presenting features, medical/social/family history</i>
<p>A 71-year-old man was brought to the emergency department by ambulance after falling during an appointment with his general practitioner. He complained of five weeks of progressive leg weakness, intermittent lancinating lower back pain, and had fallen twice before attending his GP, when he had fallen for a third time. He explained that his legs had felt weak and had given out under him. He denied loss of consciousness, dizziness, palpitations, bladder or bowel disturbance and saddle anaesthesia.</p> <p>His medical background consisted of essential hypertension (medicated and controlled), recurrent inguinal hernia with previous repairs, previous non-ST elevation myocardial infarction and hypercholesterolemia. He took Amlodipine 10mg, Aspirin 75mg and Atorvastatin 80mg.</p> <p>He is a retired physics lecturer who lives with his wife. Prior to admission, he performed all activities of daily living independently. Before his complaint started, he was a regular jogger and only a few years ago was running marathons. Though he had never smoked tobacco, he admitted to drinking alcohol in excess several years ago (a maximum of two bottles of wine per day). There was no history of neurological or neuromuscular disease in the family. He denied any recent illnesses or malaise.</p>

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On admission, his general examination was unremarkable. Neurological examination demonstrated normal power and tone in both limbs (reflexes were not commented on the Emergency Department). He was admitted for observation under the medical team.

During the first two days of admission, he had several episodes of confusion and aggression towards staff, which was very much out of character, and he experienced visual hallucinations, seeing "crawly things." His fluctuating mental status was attributed to delirium caused by a urinary tract infection and was treated as such. His delirium resolved within 48 hours.

On day four of admission he was reviewed by spinal surgeons for ongoing back pain. On examination, his left lower limb was noted to be weaker than his right: Medical Research Council (MRC) 3/5 throughout versus 5/5 throughout on the right. Reflexes were thought to be normal throughout.

On day eight of admission he was reviewed by a neurologist who confirmed that his left lower limb was weaker than the right and noted that it was predominantly proximal. Some upper limb weakness was also observed, while reflexes were documented as normal.

On day 14, increased upper limb weakness was noted by the neurologists. The next day, his lower limb weakness was more clearly symmetrical and scored MRC 2/5 distally and 1/5 proximally for power. There were no sensory abnormalities and lower limb reflexes were thought to be symmetrically diminished.

In summary, in the two weeks following admission, the patient's condition developed from back pain and subjective lower limb weakness to asymmetrical and then proximal and symmetrical objective weakness. Though he did not complain of upper limb weakness on admission, proximal and symmetrical arm weakness developed subsequently. There was no sensory abnormality, and reflexes were found to be symmetrically diminished throughout.

Our patient's condition gradually worsened over the following five weeks until it reached its nadir around day 45 of admission. At this point the patient had no movement in his lower limbs and had severe bilateral upper limb weakness (MRC 1-2/5). No sensory abnormality was detected, though reflexes were symmetrically diminished.

INVESTIGATIONS *If relevant*

The initial blood tests demonstrated a leucocytosis of $18.2 \times 10^9/L$ and a neutrophilia of $13.4 \times 10^9/L$. There was a hyponatremia of 120mmol/L, and CRP was 48. No electrocardiogram or chest radiography was performed.

The MRI studies of the spine and spinal cord requested by the spinal surgeons were negative for compression of nerve roots and spinal cord, showing only degenerative bony changes, and a subtle diffuse low signal from the bony spine which the neuroradiologist's report indicated could be due to a disease process in the bone such as metastasis, myeloma or lymphoma. A month into his admission a repeat MRI with contrast confirmed the original report.

There were numerous negative/normal investigations. Blood glucose levels and haematinics were normal, which pointed away from neuropathy caused by diabetes mellitus or B12/folate deficiency. Creatinine kinase levels were measured several times, peaking at 155 units/L. The myeloma screen was normal, as were cerebrospinal fluid cytology, common cancer markers (Ca19-9, CEA, AFP) and antineuronal antibodies (anti-Yo, anti-Hu and anti-Ri). A CT thorax-abdomen-pelvis detected no malignancy. Other normal or negative tests included: ANCA, ANA, urinary porphobilinogen levels, lead levels, urinary organic acids, acetylcholine receptor antibodies (myasthenia gravis), ganglioside Q1b antibodies (Miller-Fisher syndrome), voltage-gated potassium channel antibodies (encephalitis etc.), antibodies

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against neurofascin-155, neurofascin-186/140, CASPR/contactin-1 (some subgroups of CIDP).

The only positive biochemical investigation was the CSF protein of 1.36 g/L (0.15-0.45g/L).

Finally, nerve conduction studies (NCS) confirmed a mixed motor and sensory demyelinating and axonal peripheral neuropathy. According to the European Federation of Neurological Societies/Peripheral Nerve Society diagnostic guidelines, we can say our patient has definite CIDP. Our patient's progressive symmetrical proximal and distal weakness which developed over months along with reduced tendon reflexes qualify for a diagnosis of typical CIDP. Furthermore, because he met none of the exclusion criteria (e.g. prominent sphincter disturbance, a diagnosis of multifocal motor neuropathy, etc.), but did meet the relevant nerve conduction study criteria, he qualifies for a diagnosis of definite CIDP. The specific electrophysiological criteria he meets are the absence of the F-waves in two nerves with slow median conduction velocity[1]. Some neurophysiological findings that support the diagnosis of definite CIDP are shown in Table 1.

Selected Nerve Conduction Study Data		
Sensory	Latency (ms)	Velocity (m/s)
Right median nerve	<u>3.45</u>	<u>37.7</u>
Right ulnar nerve	<u>No response</u>	
Right radial nerve	1.70	41.2
Right sural nerve	3.25	40.0
Right superior peroneal nerve	4.55	30.8
Motor		
Right median nerve (wrist)	<u>7.25</u>	
Right median nerve (elbow)	<u>13.40</u>	35.8
Right ulnar nerve (wrist)	<u>4.05</u>	
Right ulnar nerve (elbow)	<u>8.40</u>	55.2
Right tibial nerve (knee)	<u>No response</u>	
Right common peroneal (knee)	<u>19.00</u>	<u>Too low to accurately calculate</u>
F-wave		
Right ulnar nerve	<u>No response</u>	
Right tibial nerve	<u>No response</u>	

Table 1: Selected nerve conduction study data showing the specific diagnostic criteria met for a definite diagnosis of CIDP. The abnormal data are underlined. The nerve conduction study shows normal amplitude median, radial, sural and superficial peroneal sensory action potentials but absent ulnar sensory action potential. Where present, the sensory nerve conduction velocities are all normal, except for the median nerve which is reduced at 37.7m/s (should be >40m/s). The motor responses show an absent tibial motor response. The median, ulnar and common peroneal distal motor latencies are significantly prolonged. The ulnar proximal conduction velocity is normal, but there is slowing of median and common peroneal conduction below the lower limit of normal in the forearm and lower leg respectively. Both the median and common peroneal compound motor action potentials are significantly reduced in amplitude, but the ulnar is within the normal range. The ulnar and tibial F-waves are absent, and these two nerves also demonstrate slowed conduction velocity, thus satisfying the electrophysiological criteria for a diagnosis of definite CIDP.

DIFFERENTIAL DIAGNOSIS *If relevant*

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The numerous differential diagnoses were narrowed down to a handful of *subacute/chronic demyelinating polyneuropathies*: subacute/chronic because of the natural history of the disease; demyelinating because of the NCS findings; polyneuropathy because clinical examination evidenced multiple nerve or nerve root involvement.

Though Guillain-Barré syndrome (GBS) is a demyelinating polyradiculopathy it was ruled out because it presents acutely. Systemic causes of demyelinating polyneuropathies (myeloma, diabetes) were also been ruled out. Multifocal motor neuropathy was considered, although the patient's symmetrical pattern of weakness did not favour this diagnosis. Motor neurone disease, because it is not a demyelinating disease, was excluded by the nerve conduction studies.

Two known syndromes fit the all the data: chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy. MADSAM neuropathy was unlikely because it often affects discrete peripheral nerves (rather than roots or plexuses) and our patient had no clinical sensory abnormality. Based on his symmetrical, predominantly proximal chronic polyneuropathy of a demyelinating character without autonomic involvement, the definitive diagnosis of CIDP was made.

TREATMENT *If relevant*

Our patient underwent two courses of intravenous immunoglobulin (IVIG) therapy. Though he recovered some strength, it was difficult to ascertain whether the improvement was merely coincidental. However, he demonstrated a clearer response to intravenous glucocorticoid therapy (methylprednisolone) and was eventually transferred to a neuro-rehabilitation hospital with a tapering dose of oral steroids.

OUTCOME AND FOLLOW-UP

Over the three months following diagnosis, the patient gradually regained strength: first self-propelling in a wheelchair, then transferring independently. Three months after discharge he was able to walk short distances with crutches, though his discharge from the rehabilitation unit was delayed several times due to further urinary tract infections and hyperglycaemia secondary to steroid therapy.

DISCUSSION *Include a very brief review of similar published cases*

CIDP is a disorder of peripheral nerves and nerve roots. It is one of several diseases and syndromes which are characterised by be chronic immune-mediated inflammation, these include: Multifocal Motor Neuropathy, MADSAM neuropathy, demyelinating syndromes with paraproteins, POEMS syndrome, and demyelinating neuropathy secondary to systemic disorders such as infection or diabetes mellitus. [1]

The underlying pathology of CIDP is poorly understood, but it is known to involve both a cellular and humoral autoimmunity. [1] Some cases of CIDP are associated with known antibodies which target isoforms of neurofascin, a neuronal cytoskeleton protein. A recent study has shown that IgG4 responses to NF155 correlate to a treatment-resistant form of CIDP which responds to Rituximab in 14% of patients with CIDP. [2] In this case, autoantibodies against neurofascin-155, -140 and -186 were negative, as were autoantibodies to contactin-1, another antibody implicated in CIDP.

On a medical take, if a patient presents with a fall or leg weakness it is imperative to consider neurological causes. Leg weakness rightly prompts immediate concern about spinal

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cord compression, but other causes should be borne in mind. As our case illustrates, a further question which is worth asking is whether the patient could be presenting with a neuroinflammatory condition, be it CIDP or perhaps multiple sclerosis. For any such patient, a complete lower limb neurological examination (including reflexes and sensation) is indispensable.

If a patient's presentation suggests a neuroinflammatory condition, a further question to consider is whether the pattern of weakness is best explained by GBS or CIDP (or something else). In GBS the exact point of onset of symptoms can usually be readily identified by the patient, whereas this is not the case in CIDP. The progression of symptoms over two to four weeks suggests GBS, whereas CIDP will have a slower natural history (more than eight weeks from onset to nadir). Usually, prominent sensory signs such as ataxia and impaired sensation favour CIDP. Proximal limb weakness favours CIDP, as in the present case, whereas GBS classically produces length-dependent 'ascending paralysis' affecting the power of distal muscles first. (GBS includes acute inflammatory demyelinating polyneuropathy (the commonest GBS) but also other variants such as axonal GBS). In CIDP it is common for sensory symptoms to dominate the clinical picture. Usually, there is greater impairment in vibration and position sense than in pain and temperature sense. Occasionally, painful dysesthesias occur. Back pain is a known feature, and signs of spinal stenosis and cord compression can occur if there is enough nerve root hypertrophy. Autonomic involvement in CIDP is not usually significant, whereas it often is in GBS. [3]

It has been commented that CIDP is over-diagnosed. It is, therefore, worth being aware of the chameleons and mimics of CIDP. We have already discussed some CIDP chameleons—conditions which might at first appear to be CIDP. Mimics are conditions whose signs and symptoms suggest CIDP but are in fact due to a different disease process. [4] These mimics are associated with red flags which should prompt the formulation of alternative diagnoses to CIDP. Such red flags include: prominent pain symptoms, significant muscle aching, no or little sensory disturbance, co-morbid conditions and/or systemic features of malignancy, cranial nerve involvement (though it is possible to have cranial nerve involvement in CIDP), respiratory muscle involvement, head drop, significant autonomic involvement, and failure to respond to normal treatment. Some mimics of CIDP not already mentioned include:

- Genetic mimics e.g. CMT1X
- POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes)
- Paraprotein related neuropathy
- Amyloid
- Treatment related fluctuations in GBS
- Vasculitis

In practice it can be difficult to diagnose CIDP with certainty. Initial presentations can be diverse and vague, and there are unusual cases of CIDP which present solely with sensory neurology,[5] [6] while other cases display significant nerve root hypertrophy leading to compressive pathology. [7] While it is important to rule out spinal cord compression in cases of lower limb weakness, primary pathology of the nervous system itself should not merely be an afterthought. This favours a good outcome for patients, as there is evidence that IVIG, glucocorticoids and plasma exchange that can all provide patients a clinically significant benefit. [3]

LEARNING POINTS/TAKE HOME MESSAGES 3 to 5 bullet points – this is a required field

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- Signs and symptoms are sometimes dynamic, and need to be monitored closely from the point of admission to form an accurate diagnosis
- CIDP is a rare neurological cause of falls which should be considered in patients with proximal and symmetrical weakness and pain as part of a thorough neurological assessment
- There is no definitive autoantibody test for CIDP, though a subgroup of IVIG-resistant CIDP is associated with anti-neurofascin antibodies
- It is important to consider a broad range of differential diagnoses when the clinical picture is uncertain
- Sometimes, CIDP is a diagnosis of exclusion

REFERENCES *Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)*

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FIGURE/VIDEO CAPTIONS <i>figures should NOT be embedded in this document</i>
PATIENT'S PERSPECTIVE <i>Optional but strongly encouraged – this has to be written by the patient or next of kin</i>
<p>There is a lot I do not remember about the last few months. I remember feeling unwell and being unable to drive at Christmas time, having had backpain for months. I finally went to my GP and promptly collapsed on the floor in clinic, whereupon he called an ambulance. As I got weaker and weaker in hospital I became worried. I could not understand why it was taking so long for the doctors to figure out what was wrong with me. Every day as I was waking up I would have the same feeling: today will be just like yesterday, and tomorrow will be the same again. It was crushing boredom, and I couldn't get my head around why it was taking so long to get a diagnosis. But after a while I drew a line under it all and put my whole trust in the doctors—I really had no choice. I remember one neurologist telling me, once the diagnosis had been made, that it was a rocky road ahead. It certainly has been rocky but I take each day as it comes. I roll today's boulder out of the way and will do the same tomorrow. I've never asked 'why me?'. It's much better to just keep going. I've only now started to tell our friends about all this because it was too painful to rake it all over. But things are better now, though I know we're not out of the woods yet.</p> <p>Addendum: the patient sadly died about a year after discharge due to unrelated disease.</p>
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