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A woman in her fifties with progressive walking difficulties

EDUCATIONAL CASE REPORT

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A woman in her fifties developed gradually increasing unsteadiness and weakness in her legs. Clinical investigation raised suspicion of an immunological disorder. However, immunomodulatory therapy had no effect. Further investigation two and a half years after the initial contact with a doctor revealed another diagnosis, which led to a change in treatment strategy.

A woman in her fifties visited her general practitioner due to increasing walking difficulties, poor balance and numbness in her feet. She reported having had the symptoms for at least five years, with significant worsening in the previous nine months to the extent that she was no longer able to keep up with her daughter and had to use her whole leg for gear shifting when riding a motorbike. She also reported having lost some muscle mass in her calves. She had been treated with mesalazine for ulcerative colitis for the past three years, but was otherwise healthy. Her GP took an MRI of the lumbar spine and head, which detected no relevant abnormalities, and referred the patient to the neurology outpatient clinic.

At the neurology outpatient clinic, the patient was found to have symmetrical deficit in the legs with sensory ataxia, hypotonia, diminished and absent tendon reflexes, and weakness in the ankles to the point that she was almost unable to walk on her toes or heels. There were no findings of pes cavus, hammer toes or any other foot deformities. Due to progressive and symmetrical flaccid paresis, the neurologist suspected polyneuropathy. Standard blood test investigations for polyneuropathy, including TSH, free T4, HbA1c, ESR, folate, cobalamin, vitamin D, iron status, liver and kidney function tests, carbohydrate-deficient transferrin and serum electrophoresis, were normal, apart from mildly elevated IgA levels of 6.6 g/L (reference range 0.7–4.3) and CK of 550 U/L (35–210). Neurophysiological examination revealed lack of motor and sensory responses in the lower extremities. In the ulnar and median nerves bilaterally, there were prolonged motor and sensory distal latencies, decreased motor and sensory nerve conduction velocities and prolonged F-responses, as well as reduced sensory response amplitudes.

The neurophysiological examination indicated marked subacute or chronic sensorimotor polyneuropathy of mixed demyelinating and axonal type. The most common causes of subacute or chronic polyneuropathy are diabetes, excessive alcohol consumption, inflammatory disorders and genetic disorders. Less common, but important causes, include deficiencies and infection, as well as neurotoxicity and paraneoplastic disorders (1). There were no indications of

metabolic disorders, toxicity or deficiencies in our patient. We have found a couple of published case reports regarding neuropathy following initiation of treatment with mesalazine, but in both these patients the symptoms were milder with more rapid onset following the start of treatment than in our patient (2, 3).

Increased incidence of chronic inflammatory demyelinating polyneuropathy-like disorders has been reported in patients with ulcerative colitis, but it is rare (4). Her family history also did not indicate a genetic cause. Both the patient's parents were over 80 years old, and neither they, her siblings nor other known relatives had neurological symptoms.

The patient underwent further investigation with lumbar puncture, which found normal cell counts and normal levels of protein, glucose and isoelectric focusing. Additional blood tests did not detect antibodies to myelin-associated glycoprotein, gangliosides or neurons.
Paramalignant syndromes were considered to be unlikely due to the slow progression, normal cell counts in cerebrospinal fluid and absence of neuronal antibodies.

Chronic inflammatory demyelinating polyneuropathy was suspected based on the clinical findings, neurophysiological findings of demyelination and negative family history, and treatment was initiated with intravenous immunoglobulin every four weeks for six months. The patient did not experience any subjective effect from this treatment. Therefore, it was decided to try high-dose methylprednisolone pulse therapy. This was discontinued after just two courses because the patient reported many adverse reactions and that the neuropathy symptoms were progressing more rapidly than before. Therefore, intravenous immunoglobulin was resumed with different dosing intervals, from every six weeks to every other week. She received a total of 15 courses of intravenous immunoglobulin.
Classic chronic inflammatory demyelinating polyneuropathy is associated with predominantly motor involvement rather than sensory involvement. Often both proximal and distal paresis occurs, and the disorder tends have a more subacute onset with more rapid progression than in our patient. Neurophysiological examination usually reveals prolonged distal motor latency, reduced motor conduction velocity and prolonged F-responses, as in our patient (5).

However, protein levels in our patient's cerebrospinal fluid were normal, which is atypical. Neither did she have antibodies against myelin-associated glycoprotein, gangliosides or neurons, which are often, but not always, seen in chronic inflammatory demyelinating polyneuropathy. Furthermore, 70–80 % of patients with chronic inflammatory demyelinating polyneuropathy respond to treatment with glucocorticoids, intravenous immunoglobulin or plasma exchange (6, 7).

Two years after initiating treatment, the patient attended a check-up at the neurology outpatient clinic to evaluate starting treatment with rituximab or other second-line treatment. She reported having noticed a gradual deterioration despite continual treatment with intravenous immunoglobulin. She mentioned difficulties walking on trails, but still had no symptoms in her

arms apart from mild tingling in her fingers. Clinical examination revealed increased deficit with atrophy of the left anterior calf and marked weakness in the ankles bilaterally, as well as decreased sensation distal to the knees and absent tendon reflexes. The diagnosis was re-evaluated based on normal cerebrospinal fluid and absence of autoantibodies, as well as a lack of efficacy of first-line treatment. Since a positive family history is not always present in genetic disorders, blood samples were sent for genetic testing. The analysis identified Charcot-Marie-Tooth disease type 1A (CMT1A) caused by duplication of the PMP22 *gene. Following this finding, no further genetic testing was performed, and immunomodulatory therapy was stopped. The patient was provided with a foot drop splint and orthopaedic footwear, as well as information about inheritance, prognosis and the option of genetic counselling and presymptomatic testing of her adult children. Six months after the end of treatment with intravenous immunoglobulin, the patient reported that she had not noticed an increased rate of progression.*

Discussion

Correct diagnostic investigation is a prerequisite for ensuring that patients with inflammatory polyneuropathy receive immunomodulatory therapy and that patients with hereditary disease avoid futile, expensive and potentially harmful treatment. A genetic diagnosis also allows the opportunity for genetic counselling.

Although clinical findings in inflammatory and hereditary polyneuropathy may overlap, certain features point more towards one or the other (Table 1). No cause is found in 50 % of patients with sensory-predominant chronic polyneuropathy, despite thorough investigation. The likelihood of finding a cause is greater in patients with motor-predominant symptoms (8, 11). Hereditary neuropathy with no known family history and with demyelinating pattern on neurography can be misdiagnosed as chronic inflammatory demyelinating polyneuropathy (9, 12). Both clinical experience and retrospective studies suggest that overdiagnosis of the disease is common (13). Factors that frequently lead to this are misinterpretation of neurophysiological findings and transient efficacy of immunomodulatory therapy (13, 14). A retrospective study at 16 European university hospitals revealed that 35 (3.2 %) of 1104 patients diagnosed with chronic inflammatory demyelinating polyneuropathy had Charcot-Marie-Tooth disease. The mean duration of immunomodulatory therapy in misdiagnosed patients was 17 months (10).

Table 1

Clinical and investigational features of Charcot-Marie-Tooth disease and chronic inflammatory demyelinating polyneuropathy. The table is based on the authors' clinical experience, international recommendations and review articles (5, 8– 10).

Feature	Charcot-Marie-Tooth disease	Chronic inflammatory demyelinating polyneuropathy
Age at onset	Often early	All
Family history	Often positive	Negative
Course	Slow progression	Progressive or relapsing
Muscles involved	Distal more than proximal	Proximal and distal
Skeletal deformities	Common	Rare
Nerve conduction abnormalities	Diffuse and homogenous motor conduction slowing without conduction block	Heterogeneous motor conduction slowing and conduction block
Cerebrospinal fluid	Normal	Often elevated protein levels
Efficacy of immunomodulatory therapy	No	Yes

In our patient, the main focus was on family history and neurography findings. However, there is a large amount of overlap in the neurography findings in acquired and hereditary demyelinating polyneuropathy. Prolonged distal motor latencies, reduced motor nerve conduction velocities and prolonged F-responses occur in both cases. Furthermore, negative family history is not unheard of in hereditary polyneuropathy. A relatively recent study revealed a pathogenic genetic variant in 30 out of 200 patients with neuropathy of unclear aetiology. In 6 of these 30 positive results, hereditary neuropathy had not been suspected based on the family history and clinical findings (14). Another study revealed *PMP22* mutations in 10 out of 111 patients diagnosed with chronic inflammatory demyelinating polyneuropathy (12).

Hereditary neuropathies are classified on the basis of clinical findings (sensory or motor), inheritance, neurography findings and genetics (Table 2). Charcot-Marie-Tooth disease is the most common type. A population-based study in the former Akershus county found a prevalence of 1 case per 1214 people (20). Severity varies considerably, and this can lead to false negative family history since family members with few symptoms are often not diagnosed. Some patients have a de novo mutation or recessive inheritance and therefore no known family history (15). Around 10 % of patients with *PMP22* duplication (Charcot-Marie-Tooth disease type 1A) have a de novo mutation and milder clinical symptoms (21).

Table 2

Affected genes, inheritance and clinical and neurophysiological features of the most common hereditary neuropathies. The table is based on the authors' experience with clinical and genetic diagnostic investigation of people with neuropathy, and international databases and review articles (15–19).

Neuropathy	Most commonly affected genes	Inheritance	Clinical and neurophysiological features
Charcot-Marie-Tooth disease, type 1 (CMT1)	*PMP22* (duplication), *MPZ*, *SH3TC2*	Usually autosomal dominant, more rarely recessive	Demyelinating, low nerve conduction velocities. Most commonly hereditary neuropathy. Predominantly motor. Foot drop, pes cavus and hammer toes.
Charcot-Marie-Tooth disease, type 2 (CMT2)	*AARS1, GARS1, HSPB1, LRSAM1, MFN2, MME, MPZ, SORD*	Autosomal dominant or recessive	Axonal, almost normal nerve conduction velocities. Less pronounced foot deformities than in CMT1.
Charcot-Marie-Tooth disease, type X (CMTX)	*GJB1*	X-linked dominant or recessive	Demyelinating or axonal. Second most common form of CMT. Affects males more severely. Hearing loss, optic neuropathy, transient hemiparesis, monoparesis or quadriparesis can occur in younger patients.
Hereditary motor neuropathy (HMN)	*BSCL2, HSPB1, GARS1*	Autosomal dominant/ recessive or X-linked	Slow progression. Exclusively motor.
Hereditary sensory and autonomic neuropathy	*SPTLC1, SPTLC2, ATL1, DNMT1*	Autosomal dominant or recessive	Hearing loss, development of dementia and loss of sensation. Open painless sores occur. Autonomic involvement with orthostatic hypotension.
Hereditary neuropathy with liability to pressure palsies	*PMP22* (deletion)	Autosomal dominant	Triggered by compression of peripheral nerves. Recurrent, transient focal mononeuropathies. Cranial nerve involvement and loss of hearing may occur. Foot drop common.

The symptoms of Charcot-Marie-Tooth disease type 1 often present before the age of 25 years, while symptoms generally present later in type 2. Many patients report symptoms of weakness in the lower legs, ankles or soles of the feet, and are not able to run as fast as their peers. Some patients have mild symptoms that are not noticed for several years, and it is often difficult to say when the symptoms began. Sensory symptoms are often subtle. Walking difficulties gradually become predominant and are due to a combination of paresis and sensory ataxia. Neuropathic pain is uncommon, but pain on

exertion occurs frequently. Some people eventually also develop symptoms in their hands. Examination often reveals foot drop and pes cavus. Hammer toes and thickened palpable nerves occur. Disease progression is usually slow, and few patients require a wheelchair.

Neurography plays an important role in diagnostic investigation and grading of severity. Neurography often reveals more serious pathology than expected from clinical examinations. Charcot-Marie-Tooth disease type 1 is demyelinating and characterised by considerably reduced nerve conduction velocity (<38 m/s). Secondary axonal degeneration with reduced amplitudes occurs (22).

A Norwegian study analysed 52 neuropathy genes and identified a genetic cause in one-third of patients with unexplained polyneuropathy (23). The first step in genetic testing for neuropathies is usually *PMP22* duplication and deletion analysis. If this is normal, more than 100 known neuropathy genes are analysed with deep sequencing. Good information about clinical findings, inheritance and neurography findings is useful in assessing whether the variants detected are likely to be pathogenic or not. Gene panels for peripheral neuropathies are available at Haukeland University Hospital, Telemark Hospital, the University Hospital of North Norway and Oslo University Hospital (24).

There is as yet no specific treatment for Charcot-Marie-Tooth disease. A combination of baclofen, naltrexone and sorbitol is currently being trialled in phase 3 studies. Personalised treatment with allele-specific RNA interference has shown promising results in an animal model (25).

Many patients benefit from physical activity and orthopaedic devices, and some patients benefit from surgery for foot deformities. To prevent worsening of the neuropathy, it is recommended that patients limit alcohol consumption and avoid neurotoxic medications. Pregnant women with Charcot-Marie-Tooth disease have been found to have a higher rate of placenta previa, abnormal presentations and preterm deliveries (26).

Our patient had no family history or typical findings such as pes cavus and hammer toes. However, in retrospect, we can see that the combination of slowly progressive demyelinating polyneuropathy and normal cerebrospinal fluid should have raised suspicion of a genetic cause much sooner. Genetic testing should have been performed before initiation of immunoglobulin treatment, and certainly after there was no effect after six months of treatment.

The patient has given consent for the article to be published.

The article has been peer-reviewed.

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