CASE REPORT

DADS neuropathy associated with anti-TNF- α therapyRonan Niall McGinty,¹ Brian McNamara,² Helena Moore³¹Department of Neurology, Cork University Hospital, Cork, Ireland²Department of Neurophysiology, Cork University Hospital, Cork, Ireland³Bon Secours Hospital, Tralee, Ireland**Correspondence to**

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SUMMARY

A 52-year-old man with idiopathic Parkinson's disease and severe rheumatoid arthritis presented with a 1-year history of progressively worsening limb paraesthesia. Examination showed sensory loss in a glove and stocking distribution, absent reflexes and unsteady tandem gait. Nerve conduction studies suggested an acquired peripheral neuropathy with distal demyelination, which—together with the clinical phenotype—was consistent with a Distal Acquired Demyelinating Symmetric (DADS) neuropathy pattern. This was attributed to therapy with adalimumab, an antitumor necrosis factor (TNF)- α agent, which the patient had been taking for 2 years for rheumatoid arthritis. One month after discontinuing adalimumab, the limb paraesthesia had resolved completely and the patient had a normal tandem gait. Demyelinating disorders may rarely occur as complications of anti-TNF- α agents and therefore have implications for pretreatment counselling and ongoing monitoring. DADS neuropathy is a subtype of chronic inflammatory demyelinating polyradiculoneuropathy, which responds poorly to standard therapy and has not previously been described with anti-TNF- α therapy.

BACKGROUND

Antitumor necrosis factor (TNF)- α therapies, such as adalimumab, etanercept and infliximab, have significantly advanced the management of rheumatoid arthritis, ankylosing spondylitis, psoriasis and inflammatory bowel disease. Commonly recognised adverse events are infections, injection site reactions and hypersensitivity reactions.¹ Neurological adverse events such as demyelination are thought to be rare but may be under-reported,² and causality has not been established with certainty.³ Demyelination associated with anti-TNF- α agents appears to be reported more commonly as involving the central nervous system (CNS) rather than the peripheral nervous system (PNS),^{2–5} and to more often occur following use of infliximab or etanercept than adalimumab.¹

Acquired demyelinating neuropathies are a spectrum of immune-mediated disorders affecting peripheral nerves and nerve roots, including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), antimyelin-associated glycoprotein (anti-MAG) neuropathy, multifocal motor neuropathy with conduction block and POEMS syndrome.⁶ Although the different forms of acquired demyelinating neuropathies may have some overlapping clinical features, the underlying immune mechanisms and response to treatment differ. It is therefore important to establish the

correct diagnosis to ensure appropriate treatment and to prevent disease progression.

In the absence of an IgM anti-MAG antibody, the term Distal Acquired Demyelinating Symmetric (DADS) neuropathy describes a pattern of polyneuropathy that is considered a subtype of CIDP.⁷ DADS neuropathy typically presents with distal, symmetrical, sensory involvement and minimal weakness, yet shows characteristic abnormalities of motor responses on nerve conduction studies (NCS).^{7–10} Patients with DADS neuropathy often do not respond to standard CIDP therapies, such as oral steroids, intravenous immunoglobulin or plasmapheresis.^{7,8}

CASE PRESENTATION

A 52-year-old man, a farmer, presented with a 1-year history of constant and progressively worsening tingling in his hands and feet. He had a 5-year history of idiopathic Parkinson's disease (managed well with ropinirole, rasagiline, carbidopa, levodopa and entacapone) and severe rheumatoid arthritis (treated fortnightly for 2 years with adalimumab). His mother had rheumatoid arthritis and his youngest son had dysplastic kidneys and congenital heart disease.

On examination, the patient had sensory loss in a glove and stocking distribution, with absent reflexes and an unsteady tandem gait.

INVESTIGATIONS

Routine admission blood tests, including full blood count, urea and electrolytes, liver function tests, and B12 and folate, were normal. Serum immunoglobulin G, A and M, and serum protein electrophoresis were normal. Anti-MAG antibodies were negative. Cerebrospinal fluid showed a mildly elevated CSF protein level of 56 mg/dL (normal range 10–50 mg/dL) with normal cells. MRI of the brain and cervical spine was unremarkable. Motor NCS (table 1 and figure 1) showed delayed distal latencies, dispersion of compound motor action potentials (CMAP) and reduced CMAP amplitudes, but relatively preserved middle segment velocities; the calculated terminal latency indices were reduced. Sensory NCS (table 2) showed normal values for the radial nerve and an absent response from the sural nerve.

DIFFERENTIAL DIAGNOSIS

The NCS findings of delayed distal latencies, reduced CMAP amplitude with dispersion and preserved middle segment velocities, are features of an acquired peripheral neuropathy with distal

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Table 1 Motor nerve conduction studies

Nerve/sites	Recording site	Onset latency (ms)	Amplitude (mV)	Distance (cm)	Velocity (m/s)	Terminal latency index
Right median—APB						0.11
Wrist	APB	11.05	3.1			
Elbow	APB	15.50	3.5	25	56.2	
Left median—APB						0.13
Wrist	APB	8.65	4.2			
Elbow	APB	13.05	3.1	26	59.1	
Right ulnar—ADM						0.16
Wrist	ADM	7.35	3.5			
Below elbow	ADM	12.30	2.7	28	56.6	
Left ulnar—ADM						0.19
Wrist	ADM	6.95	2.9			
Below elbow	ADM	12.15	2.3	26	50.0	
Right common peroneal—EDB						0.11
Ankle	EDB	18.15	0.4			
Fibular head	EDB	27.20	0.2	31	34.3	
Left common peroneal—EDB						0.09
Ankle	EDB	17.85	0.7			
Fibular head	EDB	24.65	0.6	29	42.6	
Right tibial—AH						—
Ankle	AH	21.15	0.6	—	—	
Left tibial—AH						—
Ankle	AH	23.20	0.6	—	—	

Delayed onset latency at median (normal <4.9 ms), ulnar (normal <3 ms), peroneal (normal <6 ms) and tibial nerves (normal <6 ms). Reduced amplitude at median, ulnar, peroneal and tibial nerves (normal >5 mV). Normal conduction velocity at median and ulnar nerves (normal >50 m/s). Reduced conduction velocity at common peroneal nerves (normal >45 m/s). Reduced terminal latency index (normal >0.25) at median, ulnar and common peroneal nerves. Terminal latency index calculated as distal conduction distance (mm)/(proximal conduction velocity (m/s)×distal latency (ms)),⁸ with a distal conduction distance of 65 mm for median and ulnar nerves, and 70 mm for common peroneal nerves. ADM, abductor digiti minimi; AH, abductor hallucis; APB, abductor pollicis brevis; EDB, extensor digitorum brevis.

demyelination. Together with the clinical phenotype and anti-MAG antibody negative status, the DADS neuropathy pattern was identified and attributed to adalimumab therapy.

MANAGEMENT AND OUTCOME

Adalimumab was discontinued and replaced with tocilizumab, an anti-interleukin-6 agent, for management of rheumatoid arthritis. One month later, the patient reported that his walking had improved, he felt much steadier and the limb paraesthesia had resolved completely. Repeat examination showed normal light touch, joint position sense and vibration sense, with a normal knee jerk elicited on the right and a normal tandem gait. At 18-month follow-up, the symptoms had not returned.

DISCUSSION

This appears to be the first reported case of DADS neuropathy associated with anti-TNF- α therapy. The DADS neuropathy subtype of CIDP is important to recognise early, as it tends to respond poorly to standard therapy for CIDP.

Although other forms of chronic acquired demyelinating polyneuropathies have been described following use of infliximab and etanercept,^{2 5 11 12} this appears to be the first such

Figure 1 Right median motor nerve conduction studies at wrist (upper trace) and elbow (lower trace). Waveforms represent amplitude over time. Mid-segment velocity measured between points 1 and 2.

Table 2 Sensory nerve conduction studies

Nerve/sites	Recording site	Onset latency (ms)	Peak (ms)	Amplitude (μ V)	Distance (cm)	Velocity (m/s)
Right radial nerve—thumb						
Forearm	Thumb	1.15	1.85	19.7	9	78.3
Right sural nerve—lateral malleolus						
Calf	Lateral malleolus	Absent response				

Right radial nerve showed normal onset latency (normal <3 ms), amplitude (normal >15 μ V) and conduction velocity (normal >40 m/s). Absent response from sural nerve.

case reported with the use of adalimumab alone. The immunogenicity of the different anti-TNF- α agents is not clearly understood,¹³ but this case supports considering the induction or unmasking of demyelination as a class-effect of the anti-TNF- α agents.²

While alternative explanations may exist for the development of demyelination in patients on anti-TNF- α therapy, the timing of onset and resolution of symptoms relative to drug initiation and withdrawal,^{2 5 11 12 14–17} and a positive drug rechallenge phenomenon,^{5 15} suggest that anti-TNF-therapy has a causal role.

This case emphasises that demyelination can involve the PNS as well as the CNS, so screening for symptoms or signs of demyelination should not exclusively focus on the CNS.

Given the potential role of anti-TNF- α therapies in the development of demyelinating disorders and given that demyelination may be reversed or halted on anti-TNF- α withdrawal, the increasingly widespread use of anti-TNF- α therapies has significant implications for patient selection, counselling and monitoring.

Learning points

- ▶ Central and peripheral demyelinating disorders may represent a relatively rare but potentially serious complication of all antitumor necrosis factor (TNF)- α agents, including adalimumab.
- ▶ Patients being considered for anti-TNF- α therapy should have detailed neurological assessment to screen for pre-existing demyelinating conditions or for high risk of developing a demyelinating disorder (eg, affected first-degree family members).
- ▶ Patients taking anti-TNF- α therapy require close follow-up and monitoring throughout treatment to detect any new neurological symptoms or signs early, so that anti-TNF- α therapy can be withheld pending neurological assessment.
- ▶ Reporting of suspected drug reactions should be encouraged.

Contributors HNM performed the initial clinical examination, identified and managed the case, and approved the draft for publishing. BM performed the nerve conduction studies, identified the case, approved the draft for publishing and is the guarantor. RNM performed the literature search and wrote the draft.

Competing interests None declared.

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