

Correspondence: Neuromyelitis optica is associated with elevated interferon- α

Interferon- α is used to treat a spectrum of immunological, oncological and infectious diseases¹. A range of serious side effects have been associated with the therapeutic use of recombinant interferon- α , but neuroinflammatory disease is not listed among these. NMOSD is a rare optico-spinal neuroinflammatory disease associated with autoantibodies against the glial water channel aquaporin-4 (AQP4). Here, we describe the development of neuromyelitis optica spectrum disorder (NMOSD) following the clinical administration of interferon- α and in other states of elevated interferon- α .

The index case, a 65 year-old woman (Patient 1, Figure), was referred to our Scottish NMOSD clinic after developing longitudinally extensive thoracic transverse myelitis (LETM) 10 years after starting interferon- α treatment for systemic mastocytosis. AQP4-antibodies were positive. She experienced relapsing opticospinal inflammation, requiring escalation to treatment with rituximab.

In light of the potential association with interferon- α , we reviewed the records of 14 consecutive AQP4-antibody positive NMOSD cases referred to our clinic. From these cases we identified a second patient, a 59 year-old man who developed relapsing NMOSD following interferon- α treatment for hepatitis C infection (Patient 2, Figure). Also, we identified two further cases of NMOSD associated with “interferonopathic” disease states. Interferon- α is not normally elevated in healthy individuals but can be constitutively produced in rare genetic disease of interferon activation in children², as well as systemic lupus erythematosus (SLE) in adults³. We identified a three year-old patient with a genetic interferonopathy due to an activating mutation in *IFIH1*⁴ (Patient 3, Figure) and an adult patient with SLE (Patient 4, Figure). Both patients developed longitudinally extensive cervical spinal cord lesions associated with AQP4-antibodies. We confirmed the elevation of serum interferon- α in both patients using single molecule ELISA, and showed these levels were 100x higher than the upper limit of normal (Appendix).

NMOSD is not currently recognised as a side effect of recombinant interferon- α therapy in the *Summary of Product Characteristics*. Therefore, we submitted requests to spontaneous reporting schemes (MHRA *Yellow Card* reporting and *Vigibase*, the WHO global database of individual case safety reports) and reviewed published drug safety reports. This identified a further nine cases of interferon- α associated NMOSD (Appendix). Taken together, we propose that this represents a significant safety signal between interferon- α and NMOSD. This link is biologically plausible, given the dose-dependent relationship between serum interferon- α levels and autoantibody formation⁵.

Prompt and accurate recognition of interferon- α associated NMOSD is essential. Lack of awareness of this adverse event had serious consequences in the index patient, where diagnosis was delayed (Appendix), an important determinant of outcome in NMOSD.^{Kleiter:2018bt} Given the potential for risk mitigation, we encourage physicians prescribing interferon- α therapy to be vigilant for early manifestations of NMOSD, and suggest that recombinant interferon- α therapies should carry a specific warning for this rare but devastating side effect.

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Recombinant interferon- α



Patient 1

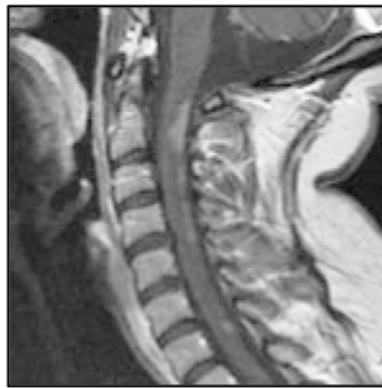


Patient 2

Raised endogenous interferon- α



Patient 3



Patient 4

Figure. Neuromyelitis optica and elevated interferon- α .

Upper panel: NMOSD with elevated exogenous interferon-alpha. Patient 1 and 2 developed AQP4+ NMOSD in the context of interferon-alpha treatment for haematological and infectious disease (see text). Case 1: Axial MRI of cervical cord showing cord oedema. Case 2: Sagittal T2-weighted MRI of the cervical cord showing a lesion expanding over 4 segments. **Lower panel:** NMOSD with elevated endogenous interferon-alpha. Case 3: MRI cervical spine in paediatric with genetic interferonopathy and activating *IFIH1* mutation. Case 4: Gd-enhanced cervical cord lesions extending over 4 vertebral segments in a patient with SLE.

Appendix: Neuromyelitis optica in states of elevated interferon- α

	Exogenous interferon- α		Endogenous interferon- α	
	Patient 1	Patient 2	Patient 3	Patient 4
Underlying disease	Systemic Mastocytosis	Hepatitis C	Monogenic interferonopathy	SLE
Interferon (duration of use)	IFN- α (10 years)	IFN- α (1 year)	872 fg/ml (normal 0-8 fg/ml)	842 fg/ml (normal 0-8 fg/ml)
MRI	LETM Low thoracic	LETM Low thoracic	LETM High cervical	LETM High cervical
Aquaporin-4 antibodies by cell based assay	Positive	Positive	Positive	Positive
Diagnostic criteria for NMOSD met⁶	Yes	Yes	Yes	Yes
Subsequent treatment	Corticosteroids Azathioprine Rituximab	Corticosteroids Azathioprine	Corticosteroids Ruxolitinib	Corticosteroids Azathioprine Rituximab
Subsequent clinical course	Relapsing transverse myelitis	Relapsing transverse myelitis	Single LETM	Single LETM

Supplementary Table 1. Clinical details of 4 patients with NMO in association with elevated interferon- α

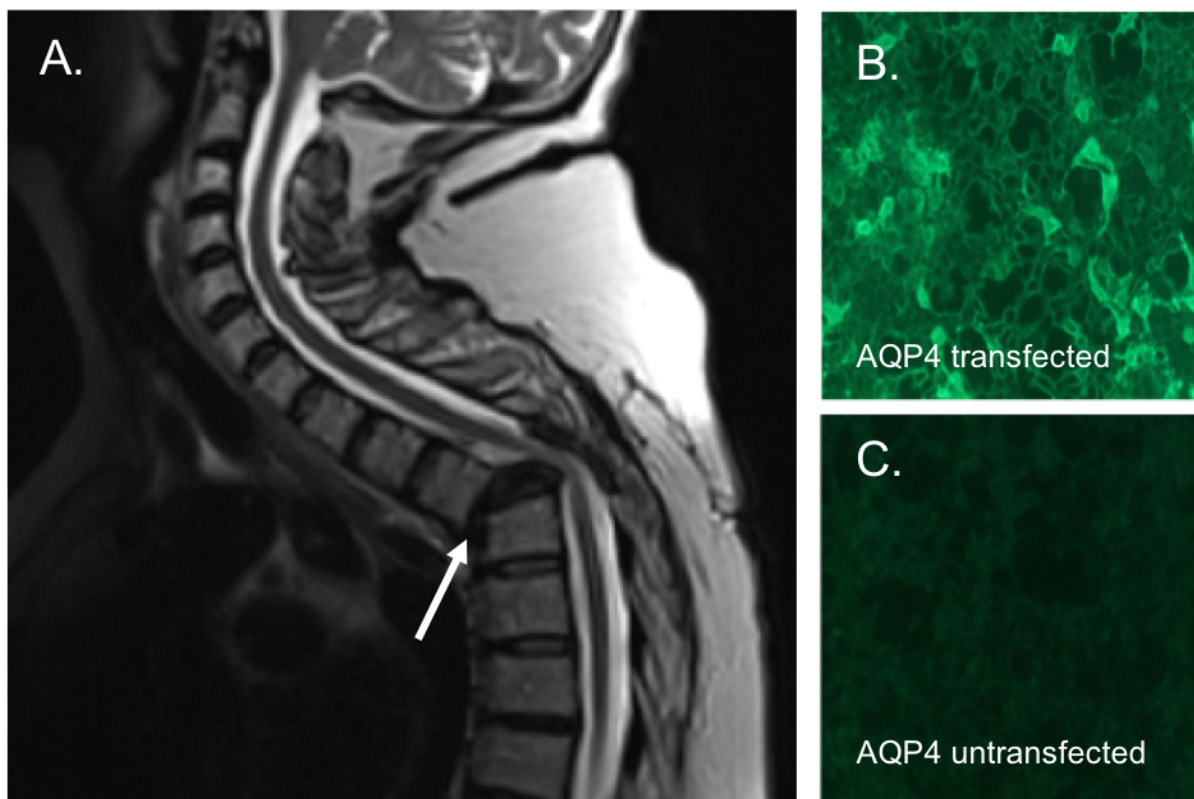
All adult patients described above met the international consensus diagnostic criteria for neuromyelitis optica spectrum disorder (NMOSD)⁶. The paediatric patient also met these criteria, noting the cautious use of the criteria in children advocated by the paediatric NMOSD working group. All IFN single molecule ELISA measurements were made using a Simoa HD-1 Analyzer (Quanterix), as previously described⁵.

Abbreviations: Cell-based assay: CBA, Interferon alpha: IFN- α , Longitudinally extensive transverse myelitis: LETM, Neuromyelitis optica spectrum disorder: NMOSD, Single molecule array: Simoa, Systemic lupus erythematosus: SLE

<i>Reporting Source</i>	<i>Drug</i>	<i>Adverse event</i>	<i>Number of cases</i>
<i>MHRA Yellow Card</i>	Interferon alpha	Neuromyelitis Optica	2
		Antibodies against Aquaporin-4	1
<i>Vigibase</i>	Interferon alpha	Neuromyelitis Optica	2
<i>Global published case reports</i>	Interferon alpha	Neuromyelitis Optica	4

Supplementary Table 2. Spontaneous reports of NMOSD following interferon- α therapy. Requests for spontaneous reports were submitted to the UK Medicines and Healthcare Products Regulatory Agency (MHRA) Yellow Card Spontaneous Reporting scheme, and also to Vigibase, the WHO global database of individual case safety reports (Lindquist M. Drug Information Journal. 2008;42(5):409-19). Search was performed using the MedDRA preferred term “Neuromyelitis optica spectrum disorder”. Data from Vigibase comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases. The information does not represent the opinion of the World Health Organization.

Global case reports: **(1)** Usmani N, et al. J Neurol. 2014 Jan;261(1):240–1 **(2)** Kawazoe T, et al. Intern Med Tokyo Jpn. 2012;51(18):2625–9 **(3)** Yamasaki M, et al. Clin Neurol. 2012;52(1):19–24 in Japanese, abstract in English **(4)** Mangioni D et al. BMC Pharmacol Toxicol. 2014 Sep 30;15:56



Supplementary Figure 1. Consequences of lack of recognition of interferon-associated NMO. (A) NMOSD is known to mimic other spinal cord pathologies such as intrinsic cord tumours and biopsy in this scenario is associated with a high rate of complications such as vertebral collapse (Ringelstein M et al. *Mult Scler.* 2014 Jun;20(7):882-8). Patient 1 initially presented with a thoracic spinal lesion mimicking an intrinsic spinal cord tumour, and underwent spinal cord biopsy which was complicated by vertebral collapse (white arrow). (B,C) A diagnosis of NMOSD can be rapidly confirmed by the presence of anti-aquaporin-4 (AQP4) antibodies, shown here in a fixed cell-based assay for patient 1, with AQP4 transfected cells (green) and AQP4 untransfected cells (negative control, Euroimmun IIFT Autoimmune Diagnostics).

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