

# Multiple sclerosis in rheumatic patients treated with tumor necrosis factor alpha inhibitors: a single-center retrospective case series and literature review

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## ABSTRACT

Tumor necrosis factor alpha inhibitors (TNFi) are basic treatments in a number of inflammatory rheumatic conditions and autoimmune phenomena such as de novo neuroinflammatory events were already described in these populations under TNFi.

We conducted a single-center retrospective study in a cohort of rheumatic patients treated with TNFi to characterize neurological demyelinating/inflammatory disease in these patients. We report 3 cases (n= 744): all of them had spondyloarthritis, the onset of neurological manifestations occurred between 37 and 58 years old and all of them initially presented with an optic neuritis. The neurological symptoms emerged between 13 and 26 months after starting TNFi. All patients discontinued treatment with TNFi, but one resumed therapy with symptomatic worsening, having to interrupt treatment again. All patients, latter on, fulfilled multiple sclerosis (MS) McDonald criteria 1 and were diagnosed with relapsing-remitting MS. Our study support the prior view of a risk, disease-dependent or agent-dependent, although a causal relationship is yet to be enlightened.

**Keywords:** Anti-tumor necrosis factor-alpha therapy; Demyelinating disease.

## INTRODUCTION

Tumor necrosis factor alpha inhibitors (TNFi) are basic treatments in a number of inflammatory rheumatic conditions, including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA). Multi-

ple adverse effects have been identified through both clinical trials and post-marketing surveillance and a potential link between neuroinflammatory events and the use of TNFi has been suggested<sup>2</sup>. In fact, signs and symptoms of demyelination, including optic neuritis, hemiparesis, transverse myelitis and magnetic resonance imaging depicting demyelinating lesions were already described in these populations under TNFi<sup>2</sup>. A great difficulty in evaluating the true incidence of demyelination in TNFi users is that the demyelinating events can be clinically silent and therefore under-reported.

The aim of our study is to characterize cases of neurological demyelinating/inflammatory disease in a cohort of patients treated with TNFi and to review the available literature on this topic.

## METHODS

We conducted a single-center retrospective cohort study. Adult patients with RA, PsA and SpA diagnosis, who were ever treated with TNFi in a Portuguese rheumatology department and registered at the Rheumatic Diseases Portuguese Register (Reuma.pt)<sup>3</sup> until December 2020 were included and information on neuroinflammatory disease was collected.

## RESULTS

Among 744 TNFi-exposed rheumatic patients (290 RA, 127 PsA and 327 SpA), with a mean exposure time of 3.9 years ( $\pm$  1.03), we identified three cases with central nervous system demyelinating events.

## CASE 1

A 39-year-old male with ankylosing spondylitis (AS) since he was 19 years old, treated with acemetacin 90

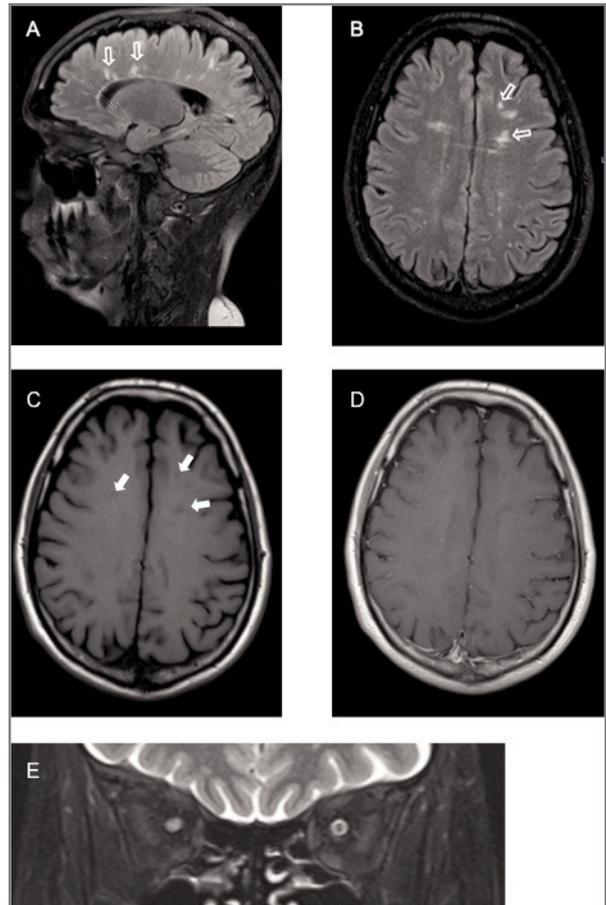
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mg/day and adalimumab 40mg fortnightly for 3 years; was admitted to the emergency room (ER) of our hospital in October 2018. He complained of right eye retro-orbital pain and ipsilateral blurred vision (specially, on the upper right hemicampus). The neurological examination revealed right eye afferent pupillary defect and severe upper hemifield visual loss. No remarkable findings were found in his blood tests: normal inflammatory markers, negative viral serologies and negative immunological studies. Cerebrospinal (CSF) study was performed: no findings suggestive of infection/inflammation were present; oligoclonal bands were negative. The brain magnetic resonance imaging (MRI) revealed hyperintensity of the right optic nerve, which was accompanied by a slight increase in caliber, consistent with optic neuritis (Figure 1. E). Furthermore, multiple supratentorial white matter lesions were present, many of which aligned perpendicular to largest axis of the lateral ventricles and involved the corpus callosum, describing a configuration of “dawson’s fingers” (Figure 1. A, B, C, D). Visual evoked potentials (VEP) showed demyelinating right eye lesion. Once the diagnosis of ON was assumed and probably attributable to TNFi, adalimumab was suspended and pulses of methylprednisolone (1g/day, for 5 days) were started, followed by prednisolone (PDN) 0.5 mg/kg/day in a reduction scheme, with clinical improvement.

During follow-up, in April 2019, the control MRI revealed new demyelinating lesions in the spinal cord at C6, C7, D7 and D8 levels. The diagnosis of a relapsing-remitting MS (RR MS) form was made and treatment with dimethyl fumarate 240 mg/day was initiated. Currently, the patient remains stable, from a rheumatological point of view, under acemetacin 150 mg/day and secukinumab 300 mg monthly.

## CASE 2

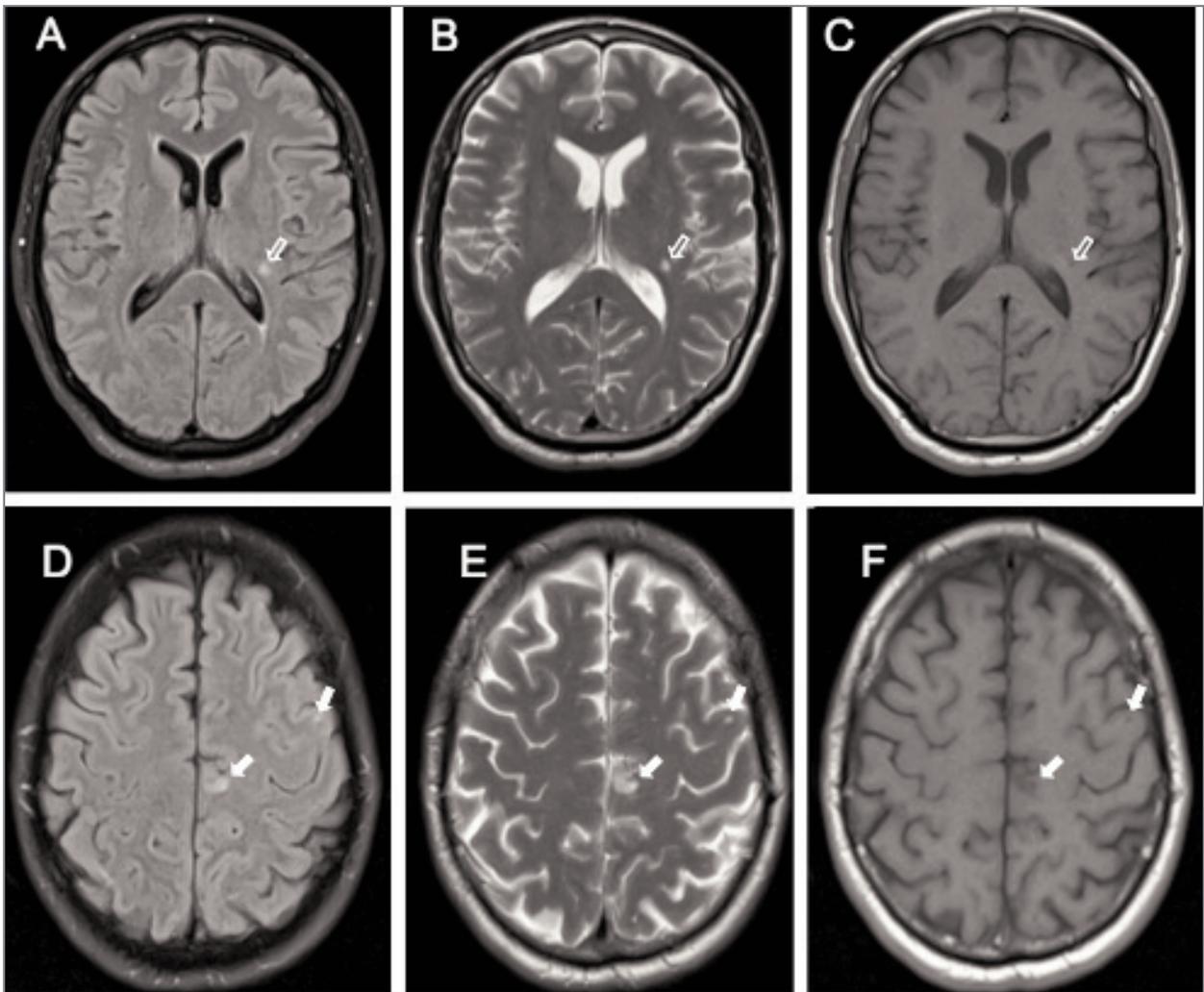
A 51-year-old man diagnosed with axial and peripheral SpA associated with Crohn's disease since he was 18 years old, under sulfasalazine 1g/day and infliximab (IFX) 5mg/kg every 8 weeks for 11 months, was observed in our hospital ER in August 2015, due to complaints of paraesthesias in the left hemiface. He also presented neurological sequelae of a past frontal sinusitis, complicated by right frontal cellulitis - numbness in the territory of the 1st branch of the right trigeminal nerve and sixth cranial pair paresis. The neurological examination excluded an objective presence of sensitivity anomalies in the left hemiface and



**FIGURE 1.** A and B. Sagittal/axial fluid attenuated inversion recovery (FLAIR) scans showing multifocal ovoid hyperintense lesions in the deep periventricular white matter (“dawson’s fingers”) – open arrows; C.: T1W signal hypointensities in corresponding loci (“black holes”) – white arrows; D.: No evidence of gadolinium enhancement was noted; E.: Coronal T2W scan with hyperintensity of the right optic nerve.

there were no oculomotor deficits. Brain MRI revealed T2WI hyperintense lesions, namely in the juxtacortical white matter of the left precentral gyrus and in the ipsilateral posterior arm of the internal capsule. In both locations, corresponding T1WI hypointensities are noted (“black holes”) (Figure 2).

Although these findings apparently had no relation with the clinical picture, they were considered as a possible occurrence of demyelinating lesions of the central and peripheral nervous system due to the use of IFX. Therefore, therapy with IFX was suspended and treatment with pregabalin 150 mg/day was started. A lumbar puncture was not performed due to technical



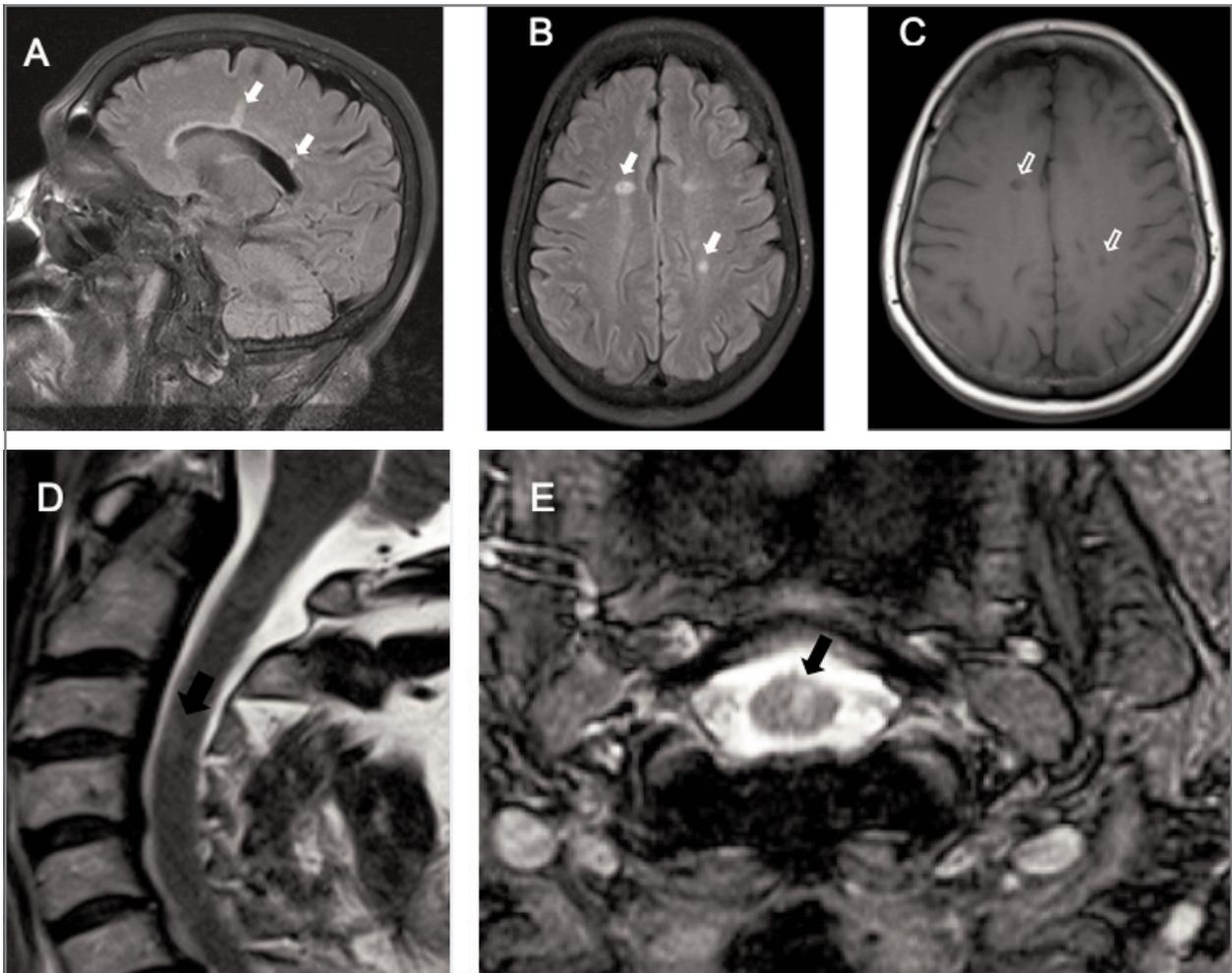
**FIGURE 2.** A, B and C. Axial T2WI and FLAIR scans showing hyperintense lesion with corresponding T1WI hypointensity in the posterior arm of the left internal capsule – open arrows; C., D. and E: Axial T2WI and FLAIR scans demonstrating multifocal hyperintense lesions with corresponding T1WI hypointensities in the left precentral gyrus and left frontal parassagittal juxtacortical/cortical white matter – white arrows.

difficulties. VEP were normal. Taking into account the overlapping findings in the reevaluation MRI, the clinical improvement and the worsening of the joint complaints, we decided to resume IFX treatment in April 2016. Nevertheless, one month later, the patient complained of retro-orbital pain and central/paracentral visual loss of left eye (LE). A probable ON was assumed on the LE and IFX was once again discontinued. Initially, he was treated with pulses of methylprednisolone (1 g ev, for 3 days), followed by PDN 0.5 mg/kg/day in a reduction scheme, with total recovery of the LE hypovision. In June 2016, no new findings on brain MRI were found, although some degree of left optic nerve

(LON) atrophy was observed. The diagnosis of relapsing-remitting MS (RR MS) was made and treatment with glatiramer acetate was initiated. For the SpA associated with Crohn's disease, he is currently medicated with ustekinumab 90 mg every 8 weeks, with no axial or peripheral joint complaints.

### CASE 3

A 60-year-old female with AS, under adalimumab for 2 years, was being followed up since 2011 in a neurology outpatient clinic due to a mild stroke, exhibiting since then minor left facial paresis and right hemiparesis grade 4+ as sequelae. In July 2018, follow-up



**FIGURE 3.** A, B and C. Axial T2WI and FLAIR scans showing multifocal ovoid hyperintense lesions in the deep periventricular white matter (“dawson’s fingers”) with corresponding T1WI hypointensity – open arrows; D. and E.: Sagittal T2WI and axial T2\*WI revealing spinal cord hyperintensities in the levels C1 and C3.

MRI showed T2WI hyperintense lesions (with corresponding T1WI hypointensities) in the subcortical and periventricular white matter of the frontal and parietal regions, in the corpus callosum and in the cervical spinal cord (Figure 3).

CSF analysis showed no increased proteins, pleocytosis or oligoclonal bands. VEP revealed a demyelinating lesion of the LON. A diagnosis of RR MS was performed. The patient discontinued the TNFi and started treatment with secukinumab 300 mg monthly. Clinical and imaging monitoring since that evaluation showed no development of new symptoms or demyelinating events. Given the patient’s age and clinical stability no specific treatment was added.

## DISCUSSION

Although we cannot exclude that the described cases resulted of chance without any connection to the exposure to biological therapy, there are several signs of the presence of a true association of TNFi with central nervous system demyelinating episodes, which are supported by similar previous descriptions in the literature<sup>4-7</sup>.

Firstly, the cases we describe present a temporal relationship with the use of TNFi and, in one case, the reintroduction of the drug led to a new clinical relapse. In fact, the neuroinflammatory events described previously have, for the most part, a temporal relationship with TNFi and all tend to improve at least partially

upon discontinuation of such therapy, worsening and/or relapsing if a reintroduction is attempted<sup>8</sup>. Of note, patients with MS treated with TNFi have shown disease exacerbation<sup>9</sup>.

Secondly, the most common age of onset of neurological symptoms in patients with MS is generally earlier, between 25 and 35 years old, in contrast to what we observed in this case series, where the symptoms started at older ages (between 37 and 58 years old). This observation is also common to previously published data<sup>10</sup>.

According to recent evidence, a particular aspect of this problem is that there seems to be a preferential relationship between these adverse effects of TNFi and certain rheumatic diseases. The three cases we describe occurred in patients with SpA and a recent prospective cohort study in Denmark and Sweden, based on nationwide registries and including 175520 rheumatic patients, showed that the use of TNFi for the treatment of SpA appears to be related to an increased risk in the incidence of neuroinflammatory disease. However, this increased risk does not occur for patients with RA exposed to TNFi<sup>11</sup>. On the contrary, other authors believe that these neuroinflammatory phenomena that develop during therapy with TNFi are agent-dependent and not disease-dependent<sup>12</sup>.

Despite that, in all 3 cases here presented, there was evidence of new clinical neurological manifestations, even after TNFi discontinuation, and the diagnosis of RR MS was made. This observation raises again the question whether the demyelinating events were the result of uncovering latent MS. This is highlighted by some authors who argue that in patients who are candidates for TNFi therapy, a detailed neurological evaluation is mandatory and, when indicated, a close neurological follow-up and an appropriate monitoring with MRI and electromyography are also essential<sup>12</sup>. In most published cases, demyelination stopped after interrupting the therapy with TNFi, but progressive disease was also observed<sup>8</sup>. Furthermore, previous literature suggested a possible association between SpA and multiple sclerosis based mainly on case reports: it was a rare finding and the data of a large French case-series including 685 patients with a one year follow up concluded that this association resulted presumably from chance<sup>13</sup>. However, these data allow no definite conclusion and more robust evidence is needed.

Understanding the etiopathogenesis of these lesions is, therefore, fundamental, and could have a role in the best care of these patients.

TNFi seem to be related to the etiopathogenesis of

demyelinating lesions as high levels of TNF have been found in cerebral white matter lesions, serum and CSF of patients with MS. In addition, a genetic variant in the gene encoding TNF-receptor 1 that mimics the effect of TNFi confers susceptibility to MS<sup>14,15</sup>. Furthermore, autoimmune association is clearly identified, and admittedly more common in patients with MS, among other autoimmune diseases, indicating that MS may be part of a generalized susceptibility to autoimmunity<sup>16</sup>. Multiple autoimmune syndromes appear to be present in 4.4% patients with known autoimmune disease and, as so, there are authors who advocate testing an extended panel of auto antibodies in these patients, taking into account the prognostic and therapeutic relevance of such finding<sup>17</sup>.

However, a complete understanding of this causality is far from being achieved.

Moreover, there are no clear recommendations regarding therapy for CNS demyelinating process in patients previously treated with TNFi. Among the cases reported by three different Spanish pharmacovigilance sources, two patients also started treatment for RR MS due to disease progression and, as with our patients, most take corticosteroid regimens with a good short-term response, despite no effect in the disease course<sup>18</sup>. When the worsening of the rheumatic disease implies the reintroduction of biological therapy, a switch to a drug with a different mode of action is made. In the case of patients with SpA, blocking of IL-17 could be a good option, as some data point to a reduction of MRI lesion activity in MS<sup>19</sup>. For other pathologies, there are no specific recommendations on this regard. More insight is needed in order to adopt preventative measures.

## CONCLUSIONS

Although a causal relationship between TNFi and demyelinating disease remains uncertain, it seems clear that these drugs should be discontinued if neurological symptoms appear. Long-term follow-up of these patients is required to identify whether there will be a progression to a definitive CNS chronic demyelinating disease and to better understand and treat this group of patients.

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