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CNS Demyelination under Anti-TNF Medication: Coincidence or causal?

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Abstract

We describe the case of a 40-year-old patient with active Crohn's Disease (CD)-who developed neurological symptoms and was subsequently diagnosed with cerebral demyelination shortly after re-exposure to a therapy with Adalimumab. Based on the current state of scientific knowledge, we here discuss whether concurrent diagnosis of demyelinating disease and the Anti-Tumor-Necrosis-Factor (TNF)-alpha-therapy develop independently or whether direct causality is more likely. Basis for this purpose are the diseases´ incidence rates and the different pathophysiological hypotheses for demyelination under anti-TNF-alpha-therapy. Due to high incidence of cerebral demyelination and lack of laboratory or clinical markers to differentiate the underlying influences, a definite conclusion cannot be drawn. Based on the presented findings and state of the literature, we finally deduce recommendations for clinical practice and research gaps.

Keywords

Anti-Tumor-Necrosis-Factor (TNF)-Alpha • Demyelination • Adverse event • Multiple sclerosis

Learning points

- Anti-TNF-alpha therapy can presumably cause demyelinating lesion of the central nervous system (CNS).
- An MRI examination appears sensible approximately 6 months after initiation or reuptake of an anti-TNF-alpha-medication to exclude demyelination.
- Physicians should evaluate the neurological status in time to recognize symptoms of a possible demyelinating process in a proactive manner.

Case Description

A 40-year-old male patient with Crohn´s disease was admitted to our hospital for evaluation of an acute onset of neurological symptoms. Because of a fistulising process, between 2007 and 2015 the Crohn's disease was treated with the TNF-alpha-blocker Adalimumab. After approximately 4 years of clinical remission without medication, re-challenge of the Adalimumab-therapy was initiated in April 2019 due to new fistulae. In May 2019 the patient developed back pain radiating into his left leg. After an initial orthopedic consultation, a neurological cause was assumed. The physical examination detected streaky hypoesthesia of both arms (corresponding to dermatome C8) and the left leg (corresponding to dermatome S1). Further work-up by MRI revealed multiple cerebral demyelinating lesions with periventricular, juxtacortical and cerebellar localization as well as one spinal lesion in the region of C1. Two of the cerebral lesions showed a signal enhancement in diffusion weighting and contrast enhancement as a sign of an active neurological disease. Results of a lumbar puncture revealed positive oligoclonal bands and a cell count of 10/µl. Microbiological analyses remained negative. Visual evoked potentials showed a prolonged P100 latency due to a bilateral lesion of the visual pathway. Based on McDonald criteria, a relapsing multiple sclerosis was diagnosed.

A bolus administration of 1 g Methylprednisolone i.v. per day was started. Due to lack of improvement the daily dose was increased to 2 g per day after 5 days for the subsequent 5 days. In response to this treatment, neurological symptoms improved over the following weeks. The commonly used immune modulatory medication with Glatiramer acetate was initiated for the suspected multiple sclerosis but had to be discontinued due to side effects (flush). The patient did not receive any further immune-modulating medication. Since the bolus administration of corticosteroids in June 2019 the neurological status of the patient has been stable for more than a year. Follow-up MRI scans showed no progression or contrast enhancement (Figures 1 and 2).

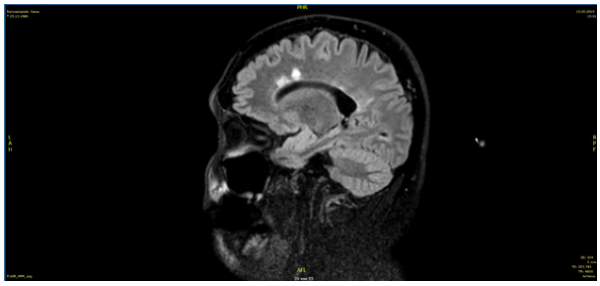

Figure 1. Periventricular demyelinating lesions (MRI-June 12, 2019).

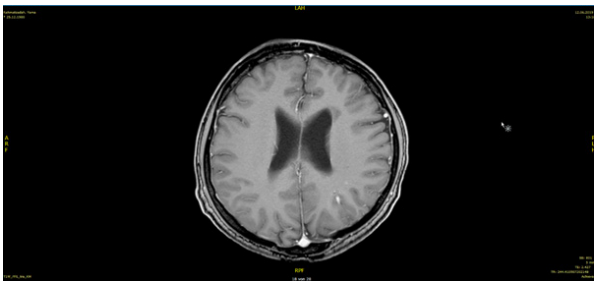

Figure 2. Juxtacortical demyelinating lesions (MRI-June 12, 2019).

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Results and Discussion

The temporal induction of the neurological problems shortly after re-exposure of Adalimumab raised the question of a causal association between the induction of demyelination and anti-TNF-alpha therapy.

In support of this hypothesis, similar cases demonstrating an association of demyelinating disease and anti-TNF-alpha-therapy are described in different studies [1].

Approximately 8 of 100,000 people in western countries develop a multiple sclerosis each year [2]. In patients with Crohn's disease, it is well recognized that incidence of MS is increased by a factor of 1.5 [3]. Different studies estimate the incidence of cerebral demyelinating lesions after an anti-TNF-alpha-therapy as between 20 and 200 of 100,000 patients without a coherent period of observation [1]. Therefore, it is virtually impossible to conclusively judge if a causal relationship is applicable in our patient.

However, there are different hypotheses concerning the pathophysiology of direct demyelination induced by anti-TNF-alpha-therapy [4]. One of these postulates that the different types of TNF-alpha-receptors (TNF-R1 and TNF-R2) might be a crucial factor. This hypothesis is supported by results from animal models demonstrating that cerebral inflammation and demyelination are maintained and triggered via TNF-R1 whereas protective properties such as regeneration of oligodendrocytes causing remyelination and elimination of auto reactive CD4+-T-cells and macrophages are ascribed to TNF-R2 [5]. Accordingly, selective TNF-R1-inhibition might be an interesting approach to prevent this potentially severe side effect in the future.

Other hypotheses suggest a lack of action of TNF-alpha blockers in the CNS by the Blood-Brain Barrier (BBB) as the key factor in a potential causality between anti-TNF-alpha-agents and cerebral demyelination: One of them is based on the observation of an increased pro-inflammatory effect on cerebral demyelination through increased invasion of peripheral auto-reactive T-cells into the CNS while the anti-inflammatory effects of TNF-alpha-blockers are not operative in the CNS due to the BBB [6].

Despite the scarcity of studies, there are different lessons to be drawn for further research targets based on result from these pre-clinical studies and clinical observations: Firstly, clinical features as well as predictive laboratory or clinical surrogate markers for cerebral demyelination after anti-TNF-therapy should be identified. Secondly, it is of particular importance to study the course of demyelination in the context of classical MS to clarify the question whether the neurological symptoms are completely reversible after discontinuing the anti-TNF-alpha-medication or whether a chronic disease is induced. Additionally, long term studies are needed to evaluate a meaningful strategy how to best treat patients presenting with this clinical constellation. Moreover, the development of TNF-R1-selective drugs might be beneficial.

Despite a lack of definitive evidence for a causal association, the here presented case report constitutes a note of caution. In clinical practice, development of neurological symptoms in patients receiving anti-TNF-alpha-therapy should be thoroughly evaluated and prompt discontinuation, especially during the first year after induction or re-exposition. Furthermore, the current evidence raises the question whether a multiple sclerosis should be considered as a contraindication for anti-TNF-alpha-agents.

Conclusion

In summary, current scientific knowledge supports the notion that a causal association of anti-TNF-alpha-medication on the multifactorial genesis of cerebral demyelination is possible. Nevertheless, to provide definite proof in individual cases remains challenging due to the high incidence of cerebral demyelination in the whole population of industrialized countries and missing predictive laboratory or clinical markers to differentiate the underlying influences.

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