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FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures (FLAMES) unmasked by withdrawal of immunosuppression for Crohn's disease?

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Summary

A 31-year-old pregnant woman presented with headache, fever and left-sided focal motor seizures, which progressed to bilateral tonic-clonic seizures. Her medical history included Crohn's disease treated with azathioprine and adalimumab, which were discontinued when she became pregnant. Her cerebro-spinal fluid was entirely normal and viral PCR negative. Extensive testing for infectious, autoimmune or malignant causes of encephalitis were non-revealing. MRI head showed unilateral cortical FLAIR-hyperintensity which on interval scans was seen bilaterally. Anti-myelin-oligodendrocyte glycoprotein (MOG)-IgG was positive leading to a diagnosis of cortical FLAIR-hyperintense lesions in Anti-MOG-associated Encephalitis with seizures (FLAMES).

Introduction

Myelin oligodendrocyte glycoprotein (MOG) is exclusively expressed on the surface of oligodentrocytes and myelin in the central nervous system (CNS). Antibodies against MOG (MOG-IgG) have been identified in patients with a distinct demyelinating disorder of the central nervous system characterized by attacks of optic neuritis, myelitis, and/or brain/brainstem dysfunction (including acute disseminated encephalomyelitis - ADEM). A specific clinical-MRI phenotype characterized by encephalitis and seizures with cortical FLAIR abnormalities on MRI has also been described. [1, 2]

We present the case of a young woman with typical clinical and radiological features of cortical FLAIR-hyperintense lesion in anti-MOG associated encephalitis with seizures (FLAMES) whose disease onset coincided with discontinuation of long-term immunosuppression due to planned pregnancy.

Case report

A 31-year-old woman presented with headache, fever and an isolated episode of left-sided facial twitching followed by post-ictal paresis. She was 31 weeks pregnant with her second child. Her past medical history included Crohn's disease (CD), for which she had been treated with Azathioprine and Adalimumab for 17 and 10 years, respectively. Both drugs were discontinued during the first month of pregnancy. Emergency brain MRI revealed abnormal cortical hyperintensities throughout the cortex of the right hemisphere on fluid attenuated inversion recovery (FLAIR). Multiple scattered foci could also be seen on T_2 weighted and FLAIR MRI affecting the deep and subcortical white matter of the frontal and parietal lobes bilaterally, which were nonspecific. There was no associated diffusion restriction. Due to pregnancy no contrast enhanced scans were acquired (Fig 1, A). We suspected infectious encephalitis and started empiric antimicrobial therapy with antibiotic and antiviral. A lumbar puncture revealed acellular cerebro-spinal fluid (CSF), normal protein and glucose and negative viral and tuberculosis PCR. Extensive testing for infectious, autoimmune or malignant causes of encephalitis were non-revealing. Blood tests were normal or negative including full blood count, thyroid and liver function, urea and

electrolytes, as well as auto-immune indices including ANA, ANCA, ENA, immunoglobulins, antiphospholipid antibodies, lupus anticoagulant, and homocysteine. Serology for HIV, syphilis, hepatitis B and C, aquaporin-4 antibodies, antineuronal antibodies (anti-Hu, Yo, Ri, Ma2, CV2 and amphiphysin), rheumatoid factor, serum lactate and pyruvate were negative/normal. On day 2 the patient was afebrile and her neurological examination normal. Her headache was almost completely resolved, and she was discharged with a plan for an interval brain scan and subsequent outpatient follow-up. MRI head performed 18 days following symptom onset, revealed progression of the previously described findings with now bilateral cortical involvement (Fig 1, B). There was no associated diffusion restriction. On day 20 she suffered two focal to bilateral tonic-clonic seizures associated with whole body jerks, head deviation to left, tongue biting, incontinence and post-ictal confusion. We therefore started treatment with Levetiracetam. Routine EEG showed findings consistent with widespread cerebral dysfunction and additional focal right temporal cerebral dysfunction. Against the backdrop of the clinical presentations and MRI findings we suspected FLAMES. The patient was commenced on intravenous methylprednisolone 1000 mg daily for three days followed by a tapering dose of Prednisolone. Her serology for MOG-abs was reported as positive. Given she was approaching full term, and in light of the progression seen on interval MRI, a joint decision was made to deliver her baby by Caesarean section in week 36, and a healthy boy was born. Repeat MRI head with Gadolinium one week after delivery showed persistent cortical FLAIR hyperintensity within the frontal, parietal and temporal lobes bilaterally. These areas appeared slightly less conspicuous than previously. No enhancement was seen after administration of intravenous gadolinium-DTPA. Azathioprine was restarted to prevent both a flare up of inflammatory bowel disease and FLAMES.

Discussion:

To the best of our knowledge, this is the first case of FLAMES in a pregnant woman. Cortical encephalitis is a recently described phenotype in MOG-IgG-associated disorder.[3] MOG-abs positive cortical

encephalitis is characterized by a combination of epileptic seizures, headache, fever, focal cortical symptoms and uni- or bilateral cortical FLAIR hyperintensity. Among the clinical MOG-IgG-associated disorders, encephalitis restricted to the cerebral cortex may perhaps be the most under-recognized syndrome. The clinical and MRI findings are rather distinct from MOG-abs associated demyelination.[3,4,5]

We suspect FLAMES in our case was unmasked by the withdrawal of immunosuppression using azathioprine, prescribed for a different condition - CD. The main reason why we favour this over other potential triggers, is the timing of drug withdrawal and manifestation of the syndrome. However, a combination of this and other causes (see below) is entirely possible. Few patients with MOG-IgG-associated disorders have a coexisting autoimmune disorder, rendering an association between CD and MOG-IgG-associated disease a rare occurrence. A first case of CD in a patient with MOG-associated demyelination has only recently been reported.[6] However, co-morbidity involving these conditions has important implications. Firstly, evaluation for MOG-antibodies should be considered in CD patients presenting with a clinical and radiological phenotype atypical of multiple sclerosis (MS). Secondly, rituximab, a monoclonal anti-CD20 antibody found to be effective in MOG autoimmunity, should be avoided since it may induce or exacerbate CD (Fraser et al., 2016; Varma et al., 2017). And thirdly, antitumor necrosis factor (TNF) alpha therapies should be avoided since their role in induction or exacerbation of CNS demyelinating disorders is well established.

Alternative causative explanations need to be considered, including (i) anti-tumor necrosis factor (TNF) alpha therapy and (ii) pregnancy itself. Anti-TNF alpha therapies have a well-established role in induction or exacerbation of demyelinating disorders of the CNS.[7] However, in our case FLAMES developed only after adalimumab had been suspended for about seven months. Given a half-life of adalimumab of up to 20 days, a causative effect appears unlikely. A moderately increased risk of CNS demyelination due to pregnancy itself has been described in NMOSD.[8,9] It can only be speculated whether women developing MOG-abs associated disorders, including FLAMES, share such an increase in risk. Of note, our patient

had a previous uncomplicated pregnancy.

Our patient presented with unilateral cortical FLAIR-hyperintense lesions, which on follow-up MRI progressed to a bilateral manifestation without leptomeningeal enhancement. The lesions were steroid responsive, as described previously in the literature; the patient has meanwhile resumed treatment with azathioprine and remains free of seizures or other symptoms related to FLAMES. [4]

Due to the rarity of FLAMES no treatment guidelines based on controlled clinical studies are available, including pregnant women. The recommendations found in the current literature largely rely on case reports, retrospective and prospective observational studies. A personalized treatment regimen is therefore required, especially in the case of pregnant patients. Spontaneous improvement in patients with FLAMES has been reported.[10] However, corticosteroids were administered due to the presence of convulsive seizures in pregnancy and a diagnosis early after presentation. Improved awareness of this distinct clinico-radiographic syndrome is critical to ensure correct diagnosis and prompt consideration of immunotherapy, particularly in more severe cases.

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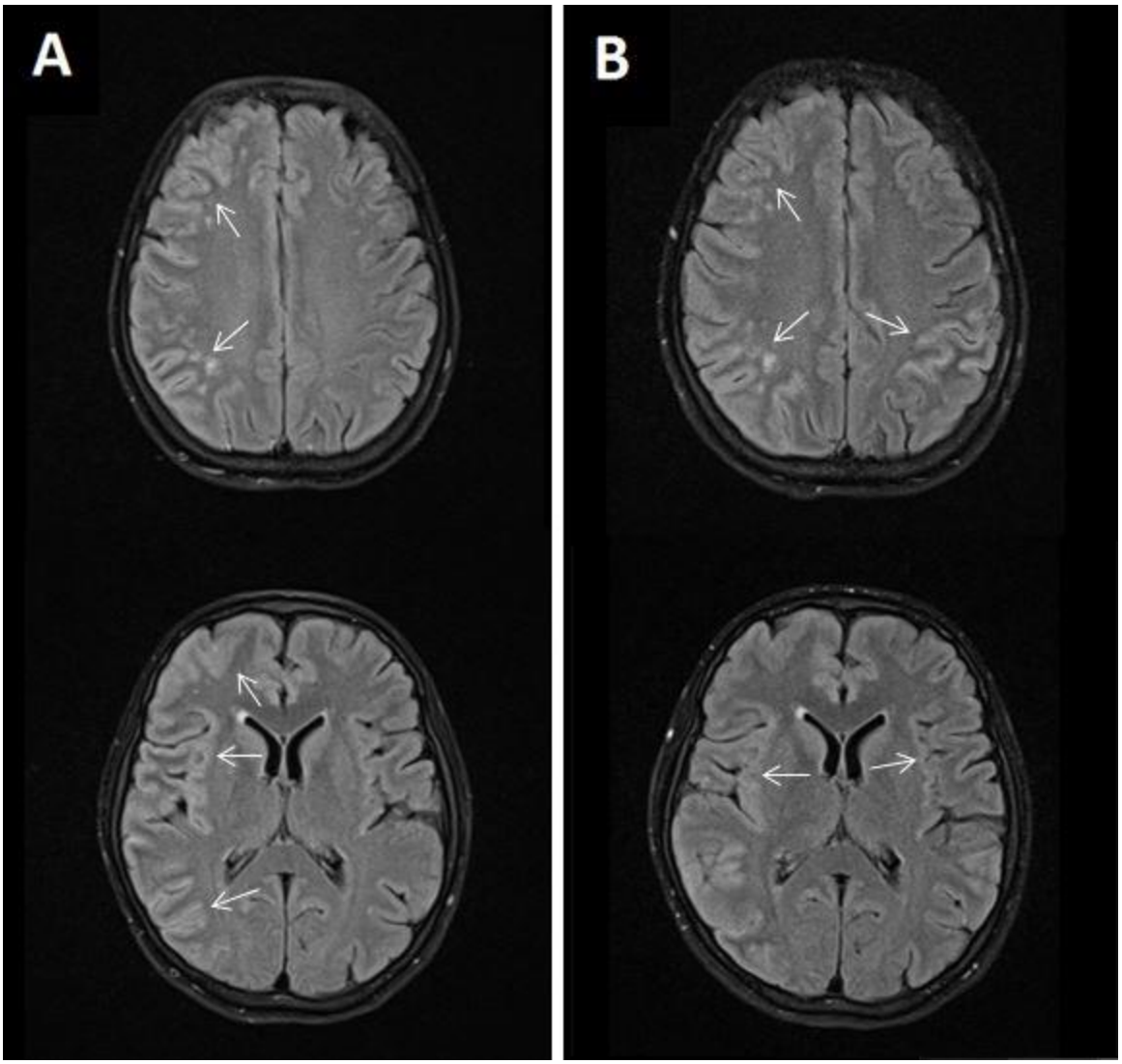

FIGURE LEGENDS

Figure 1: Brain magnetic resonance imaging (MRI) of a 31-year-old woman with cortical FLAIR-hyperintense Lesion in Anti-MOG-associated Encephalitis with Seizures (FLAMES). On axial T_2-weighted fluid attenuated inversion recovery (T_2-FLAIR) images, cortical hyperintensity can be seen throughout the cortex of the right cerebral hemisphere (white arrows) (A). On follow-up brain MRI acquired 3 weeks after first presentation (B) there is progression with bilateral cortical involvement

(white arrows). FLAIR hyperintensity now also extends to the left superior parietal lobule and postcentral gyrus.