

Case Report

Primary Myelin Oligodendrocyte Glycoprotein-Immunoglobulin G-associated Optic Neuritis Presenting after a Frozen Embryo Transfer

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ABSTRACT

Myelin oligodendrocyte glycoprotein (MOG)-immunoglobulin G-associated optic neuritis (ON) is a newly recognized antibody-mediated demyelinating disease of the central nervous system, resulting in acute visual loss and pain with eye movement. The effects of pregnancy on disease pathogenesis remain incompletely understood. Herein, we present a novel association between a frozen embryo transfer (FET) and the first manifestation of MOG-ON in a previously healthy patient with unexplained infertility. The patient presented with acute bilateral visual loss 3 weeks after a single FET and was found to test positive for MOG antibodies with an otherwise unremarkable workup. The patient's vision returned to baseline with high-dose intravenous methylprednisolone and therapeutic plasma exchange. This is the first published case highlighting an association between MOG-ON and assisted reproductive technology (ART) in a patient without prior risk factors. Further studies are needed to clarify the effects of ART and pregnancy in general on disease pathogenesis.

KEYWORDS: *Assisted reproductive technology, autoimmune diseases, case report, myelin oligodendrocyte glycoprotein, optic neuritis*

INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG)-immunoglobulin G (IgG)-associated optic neuritis (ON) is a rare and distinct antibody-mediated demyelinating disease of the central nervous system with autoantibodies directed against MOG that can result in severe vision loss.^[1] While there have been several well-documented reports highlighting the association between multiple sclerosis (MS) and assisted reproductive technology (ART), there have been no reported cases of ART triggering MOG-ON.^[2-4]

Methods

The authors certify that they have obtained appropriate written informed consent from the patient described in the present case. Consent was obtained after the authors participated in the care of this patient.

CASE REPORT

A 39-year-old female with a history of unexplained primary infertility who was approximately 4 months after oocyte retrieval and 3 weeks after a single frozen embryo transfer (FET) presented to the hospital with acute bilateral vision loss, ophthalmalgia, and a positive serum pregnancy test.

When the patient arrived, she exhibited light perception in the right eye and no light perception in the left eye, which was drastically decreased from her baseline of 20/20 bilaterally. The patient also had grade one optic disc swelling of the right eye and grade two optic disc swelling of the left eye with bilateral minimally reactive pupillary responses but without an afferent pupillary defect. There was a normal anterior segment of both eyes by slit lamp exam and optical coherence tomography

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(OCT) was consistent with borderline thinning. The patient's review of systems was unremarkable, and she denied any recent illness, vaccinations, trauma, or personal or family history of autoimmune or neurological disease.

She had previously undergone controlled ovarian hyperstimulation using 150 international units (IU) of Gonal-F® (follitropin alfa; Merck and Co., Darmstadt, Germany) and 150 IU of Menopur® (menotropin; Ferring Pharmaceuticals) for 10 days with 250 mcg of the GnRH antagonist Cetrotide® (cetorelix acetate; Merck and Co., Darmstadt, Germany) initiated on day 5. A trigger shot of 1 mg Lupron® (leuprolide acetate; Abbott Laboratories, Chicago, IL) was then administered on day 10 with retrieval 35 hours afterward consisting of 11 oocytes and four resulting embryos. She then had an uncomplicated FET roughly 4 months after the retrieval with a peak estradiol level of 831 pg/mL. First, endometrial preparation was initiated using oral contraceptive pills for 12 weeks, followed by oral Estrace® 2 mg TID (estradiol; Novo Nordisk, Denmark) an estradiol patch 0.1 mg/24 h for 2 weeks and vaginal progesterone 100 mg TID (Endometrin®; Ferring Pharmaceuticals, Saint Prex, Switzerland).

On arrival, the patient's lumbar puncture was unremarkable; oligoclonal bands were absent and cerebrospinal fluid (CSF) cultures were negative. Further workup revealed T2 hyperintensity and thickening of the prechiasmatic left optic nerve and equivocal findings for the right intraorbital optic nerve [Figure 1]. Autoantibodies against aquaporin 4 were absent, while MOG antibodies were positive in a 1:40 titer. Additionally, patient had positive antibodies to JC virus and negative Sjogren's syndrome (anti SSB and anti SSA), antiphospholipid (anticardiolipin IgG, anti cardiolipin

IgM, beta 2 glycoprotein IgG, and IgM antibodies), and treponema antibodies. Furthermore, QuantiFERON tuberculosis gold, hepatitis B, hepatitis C, and human immunodeficiency virus antibodies were negative.

The patient was started on 5 days of high-dose intravenous methylprednisolone 1000 mg/day as well as therapeutic plasma exchange. With treatment, the patient's vision progressively improved. However, on day 3 of the plasma exchange, the patient began to have vaginal bleeding with an abnormal beta-human chorionic gonadotropin trend. She was diagnosed with an ectopic pregnancy, which was managed medically with a single dose of 105 mg methotrexate (Pfizer; New York, NY).

The patient was discharged from the hospital on a 5 day course of an oral prednisone taper along with initiation of the disease modifying treatment (DMT) rituximab with plan for 1 g twice over 2 weeks repeated at 6 months with a repeat brain magnetic resonance imaging (MRI) 3 months after starting DMT to determine the exact duration.

DISCUSSION

This is the first case report of MOG-ON associated with FET. Although definitive causation is difficult to ascertain in this limited report consisting of one patient, the timing of onset and association of ART and other neurological conditions suggest FET as a possible contributor to the inciting manifestation of MOG-ON in the present case.

MOG-ON has emerged as a unique antibody-mediated demyelinating disease of the central nervous system. It has been proposed that MOG-specific effector T-cells may be triggered if the protein escapes into the CSF and periphery, resulting in a marked activation of the classical complement cascade.^[1] In terms of MOG-ON effects on pregnancy, a single retrospective multicenter study of MOG-IgG-positive patients showed that, while roughly half of the patients with a documented pregnancy had an attack during pregnancy or postpartum, the attacks most commonly occurred in the postpartum period (57%). The cases that did occur during pregnancy were in patients with previously diagnosed recurrent disease.^[5]

Pregnancy may be protective for certain autoimmune diseases such as MS. To elaborate, there is a shift from T helper 1 (Th1) dominance to T helper 2-type cytokines and associated humoral response postulated to improve Th1-dominant cell-mediated immune diseases.^[6,7] While MS is predominantly a cell-mediated disease dominated by Th1 cytokines, CSF studies from patients with MOG-ON have shown a predominance of Th17 cell upregulation and cytokine production.^[8] Interestingly,

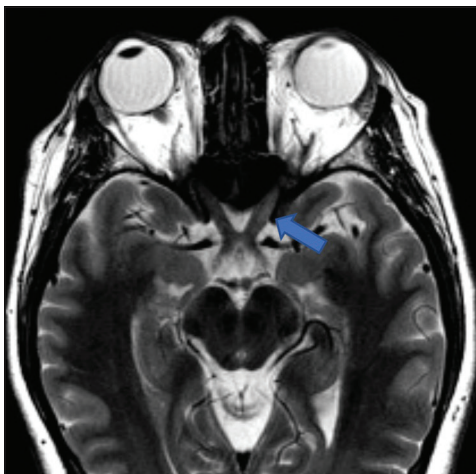


Figure 1: Focal thickening with increased T2 signal of the prechiasmatic left optic nerve in a patient with myelin oligodendrocyte glycoprotein-immunoglobulin G-associated optic neuritis (see arrow)

these Th17-related cytokines can recruit both humoral and cellular immunity with estradiol-enhancing cell-mediated immunity at low concentrations and augmenting humoral immunity at high concentrations.^[6]

A proposed mechanism of ART associated with MOG-ON points to several studies showing that ovulation induction may increase the levels of vascular endothelial growth factor, which is a protein associated with blood-brain barrier (BBB) breakdown.^[2,9] Furthermore, the estrogenic fluctuations after the use of GnRH agonists or antagonists have been shown to have a direct effect on the proliferation of B and T-cells as well as on autoantibody production and immune cell migration across the BBB.^[10] In addition, ovulation induction can significantly increase the number of MOG-IgG autoantibodies as well as B-cell survival factor B-cell-activating factor.^[2] In the present case, the initial BBB breakdown as well as the increase in MOG-IgG production may have originally occurred during the ovarian stimulation phase of her ART. However, her long-term suppressive contraceptive therapy taken from the time of stimulation to implantation may have initially inhibited her autoimmune cells until she was initiated on oral and dermal estradiol and vaginal progesterone.

This case highlights a proposed association between ART and MOG-ON though more studies are needed to validate the findings. We aim to increase the recognition of this rare manifestation so that clinicians can promptly diagnose and treat as well as counsel patients on the theoretical risk of appearance and/or relapse when undergoing ART or when planning future pregnancies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that

their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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