Original Article

Insights into Initial Demyelinating Episodes of Central Nervous System during Puerperium

Qian Wu, Bo Chen, Na Liu, Yang Hu, Chao Pan, Ping Zhang, Zhou-Ping Tang, Bi-Tao Bu

Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430030, China

Abstract

Background: Inflammatory demyelinating disease of central nervous system (CNS) is an inflammatory disease characterized by a high childbearing female predominance. Labor-related alterations for postpartum demyelinating attacks are not entirely clear. This study aimed to summarize clinical features of female patients of reproductive age with initial CNS inflammatory demyelinating attacks during puerperium.
Methods: Fourteen female patients with initial demyelinating events during puerperium between January 2013 and December 2016 were retrospectively studied. Records of clinical features, neuroimaging, serum antibodies, cerebrospinal fluid (CSF) findings, annualized relapse rate (ARR), and treatment were analyzed.
Results: Among 14 patients, 5 patients were diagnosed with multiple sclerosis (MS), four as neuromyelitis optica (NMO), two as longitudinal extensive transverse myelitis, two as clinical isolated syndrome (CIS), and one as acute brainstem syndrome. All the 14 puerperal female patients presented with more than one manifestation of hemiplegia, paraplegia, uroschesis, visual loss or dysarthria, and with mild to moderate abnormalities of CSF. Attacks occurred during the first trimester postpartum and cesarean section was the main delivery way (n = 10). Median Expanded Disability Status Scale (EDSS) scores were 5.0 (range: 2.0–9.0) at the onset and 2.5 (range: 0–7.0) at the end of follow-ups. Patients with MS and CIS had a significantly lower EDSS scores than patients with NMO spectrum disorders ($P < 0.05$). Median ARR was 0.46 (range: 0–1.16); all patients had a low ARR (0.49 ± 0.34, 95% confidence interval: 0.29–0.69) with standardized treatments.
Conclusion: Labor-related alterations in the mother's immune system might result in newly-onset demyelinating diseases of central nervous system.

Key words: Cesarean Section; Inflammatory Demyelinations; Postpartum

Introduction

Inflammatory demyelinating disease (IDD) of central nervous system (CNS) is a rare autoimmune disorder, which contains multiple sclerosis (MS), clinical isolated syndrome (CIS), neuromyelitis optica spectrum disorders (NMOSDs), and acute disseminated encephalomyelitis. This disease preferentially affects the puerperous women, usually leading to moderate or severe disabilities including blindness, paralysis, and cognitive impairment due to its recurrent CNS attacks.[1] According to retrospective studies, IDDs are prone to relapse shortly after delivery.[2,3] However, insufficient recognition of this disease could contribute to misdiagnosis, especially for those young female patients with no history. Thus, we have conducted a retrospective study in 14 female patients of childbearing age with newly-onset demyelinating attacks during puerperium and explored the possible pathogenesis.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.211542

Methods

Ethical approval

The study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Medical Ethical Committee of Tongji Hospital, Tongji Medical College of

Address for correspondence: Prof. Bi-Tao Bu, Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Avenue, Wuhan, Hubei 430030, China
E-Mail: bubitao@tjh.tjmu.edu.cn

Received: 24-03-2017 **Edited by:** Xin Chen
How to cite this article: Wu Q, Chen B, Liu N, Hu Y, Pan C, Zhang P, Tang ZP, Bu BT. Insights into Initial Demyelinating Episodes of Central Nervous System during Puerperium. Chin Med J 2017;130:1791-5.

Huazhong University of Science and Technology. Informed written consents were obtained from all patients before their enrollment in this study.

Patients

Totally, 14 puerperal women with initial CNS acute demyelinating attacks who were admitted in Tongji Hospital from January 2013 to December 2016 were enrolled into the study. All the patients were diagnosed based on the diagnostic criteria revised by consortium of MS centers[4] in 2016 or the diagnostic criteria revised by Wingerchuk *et al*.[5] in 2015. Records of clinical features, neuroimaging, serum antibodies, cerebrospinal fluid (CSF) findings, annualized relapse rate (ARR), and treatment were analyzed. The follow-up information was obtained through telephone calls and out-patient examination. All patients were assessed using Expanded Disability Status Scale (EDSS) on admission and at the end of follow-ups.

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Data were expressed as median (range). The difference of onset age, ARR, EDSS scores between MS and CIS group and NMOSDs group were compared with the Mann-Whitney *U*-test. Statistical significance was set at $P < 0.05$.

Results

Patients' clinical manifestations

Table 1 summarizes the baseline demographic and clinical characteristics of these 14 patients. Among 14 patients, 5 patients were diagnosed with MS, four as neuromyelitis optica (NMO), two as longitudinal extensive transverse myelitis (LETM), two as CIS, and one as acute brainstem syndrome. Median onset age was 30.5 years (range: 20–37 years). Five patients suffered preceding upper respiratory tract infection. Common neurological symptoms included limb weakness (n = 13), paresthesia (n = 11), uroschesis (n = 7), mild headache and visual loss (n = 5), speech disturbance (n = 3), and vertigo (n = 2). Median EDSS scores were 5.0 (range: 2.0–9.0) at the onset and 2.5 (range: 0–7.0) at the end of follow-ups.

All the patients were divided into two groups: NMOSDs group and MS and CIS group. There was no significant difference in median age of onset between NMOSDs group and MS and CIS group (31.0 years vs. 30.0 years, $P = 0.275$; Figure 1). In comparison with patients in MS and CIS group, patients in NMOSDs group had significantly higher median EDSS scores on admission and at the end of follow-ups (on admission: 4.5 vs. 7.5, $P = 0.002$; at the end of follow-ups: 1.5 vs.3.0, $P = 0.008$; Figure 1c and 1d).

Delivery ways and breastfeeding

In this study, 8 patients were multiparas and 6 were primiparas. Except for two miscarriages, other 12 patients were successfully delivered. Nine patients insisted on breastfeeding after delivery. Median interval time between childbirth and IDD attacks was 18 days (range: 7–41 days), namely, all events assembled during the first trimester postpartum [Supplementary Material 1].

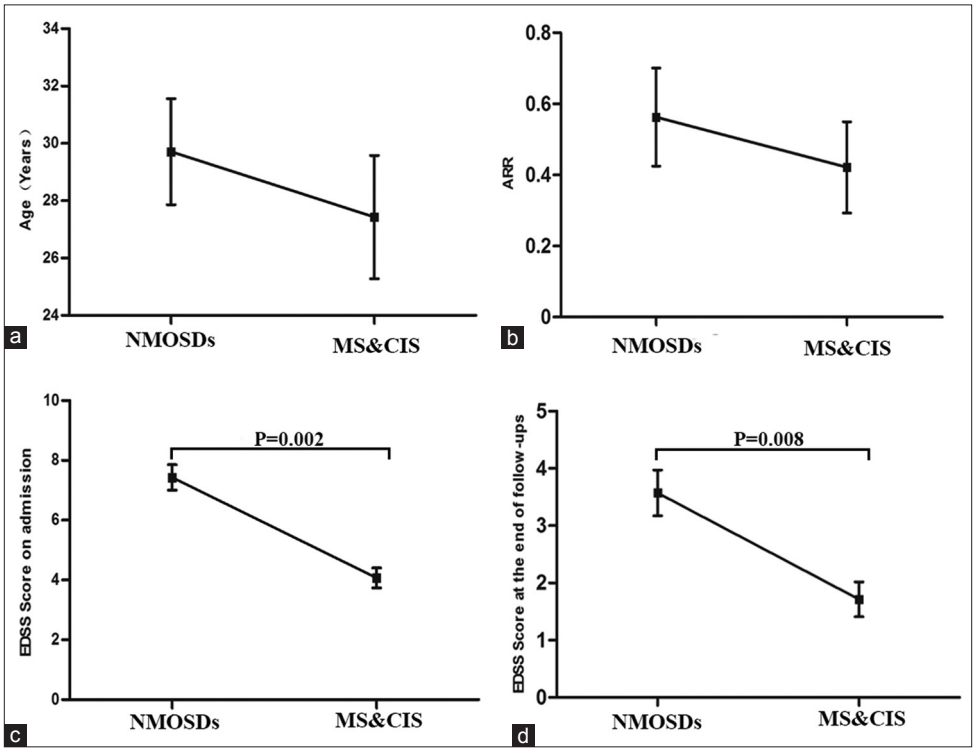

Figure 1: Comparisons of onset age (a), ARR (b) and EDSS scores (c and d) between MS and CIS group and NMOSDs group (n = 7 in each group). EDSS scores revealed that patients in MS and CIS group had relatively mild clinical symptoms and better prognosis compared with patients in NMOSDs group. EDSS: Expanded Disability Status Scale; ARR: Annualized relapse rate; MS: Multiple sclerosis; CIS: Clinical isolated syndrome; NMOSDs: Neuromyelitis optica spectrum disorders.

Serum and cerebrospinal fluid findings

The expression of anti-double-stranded DNA antibodies, antinuclear antibodies, anti-SSA antibodies, and anti-aquaporin 4 antibodies were examined by indirect immunofluorescence. Four patients, including 2 NMO and 2 MS, had serum immunological abnormalities. One NMO patient also had Sjögren syndrome. CSF tests revealed slight increases in nuclear cell count and total protein level in 2 LETM patients. High IgG index and positive oligoclonal band which indicated intrathecal IgG synthesis were found in one MS patient [Supplementary Material 2].

Lesion locations and neuroimaging features

Magnetic resonance imaging showed scattered multifocal, irregular, or atypical wedge-shaped lesions of long T1/T2 without enhancement, which involved cortical and subcortical area in MS and CIS patients [Figure 2]. In NMO and LETM patients, the maculate enhancement lesions mainly located in the central of cervical and thoracic spinal cord [Figure 3]. Case no. 6 diagnosed as acute optical neuritis had bilateral papilledema. Optical coherence tomography showed a decrease in retinal nerve fiber layer thickness [Figure 4].

Table 1: The baseline demographic and clinical characteristics of 14 patients

Characteristics	Values
Onset of age (years)	30.5 (20.0–37.0)*
Delivery ways, *n*	
Natural labor	2
Cesarean section	10
Artificial abortion	1
Spontaneous abortion	1
Interval time between childbirth and IDD attacks (days)	18.0 (7.0–41.0)*
EDSS score on admission	5.0 (2.0–9.0)*
Follow-up times (months)	32.5 (27.0–57.0)*
EDSS score at the end of follow-ups	2.5 (0–7.0)*
Positive AQP4-IgG, *n*/*N*	5/11

Data was presented by n or median (range). *: median (range). IDD: Inflammatory demyelinating disease; EDSS: Expanded Disability Status Scale; AQP4: Aquaporin 4; IgG: Immunoglobulin G.

Treatment and follow-ups

Median follow-up time was 32.5 months (range: 27–57 months). All the patients received methylprednisolone treatment intravenously at acute phase. Individualized therapy was considered in remission time. NMO patients were prescribed small doses of prednisone combined with immunosuppressants as their maintenance treatment and 4 MS patients received subcutaneous β-interferon injections as immunomodulatory therapy. Eleven patients had relapsing-remitting course and the remaining 3 patients presented with the monophasic course. Median ARR was 0.46 (range: 0–1.16); all patients had low ARR (95% confidence interval: 0.29–0.69) with standardized treatments. Median ARRs were 0.48 in NMOSDs group and 0.45 in MS and CIS group. ARR of MS and CIS patients seemed to be lower than that of NMOSDs patients, but there was no statistical difference between two groups [$P = 0.564$; Figure 1].

Discussion

This study summarizes the clinical features of puerperal female patients with initial CNS inflammatory demyelinating attacks and suggests that pathophysiological state of puerperium may not only increase the relapse rate of IDD but also be related to newly-onset IDD. In this study, 14 patients had their CNS demyelinating events during puerperium. To diagnose newly-onset IDD during puerperium, a combination of acute neurological function impairment, typical neuroimaging changes, evidence of positive serum antibodies is needed. Furthermore, it is essential to rule out reversible posterior leukoencephalopahy syndrome[6,7] and other intracranial multifocal diseases. Although previous reports confirmed that epidural anesthesia and cesarean delivery were innocuous, cesarean section was the main delivery way in this study.[8,9] Next, this study summarized

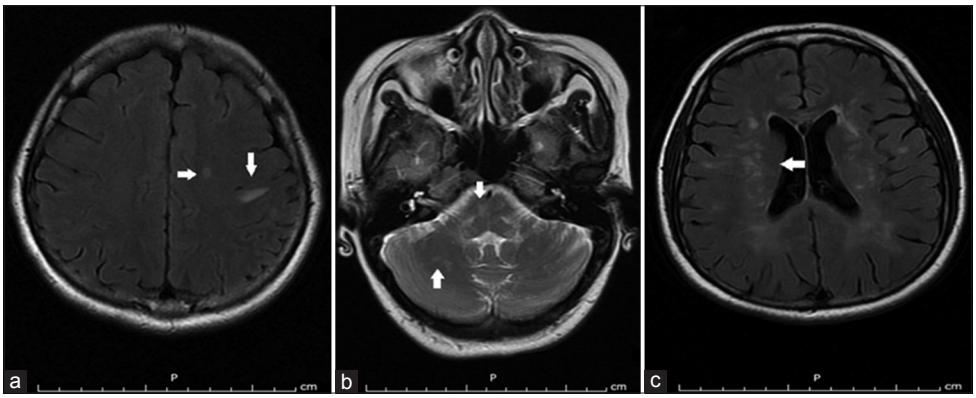

Figure 2: Head MRI images showed lesion distributions in patients with MS and CIS. (a) T2 fluid-attenuated inversion recovery of patient no. 5 showed atypical wedge-shaped high signal focus in left parietal subcortical area (arrows). (b) T2-weighted MRI of patient No. 8 showed a relatively long T2 mass-like lesion in the brainstem and cerebellum (arrows). (c) T2 fluid-attenuated inversion recovery of patient No. 10 showed some small circular lesions that vertical to lateral ventricles (arrows). MS: Multiple sclerosis; CIS: Clinical isolated syndrome; MRI: Magnetic resonance imaging.

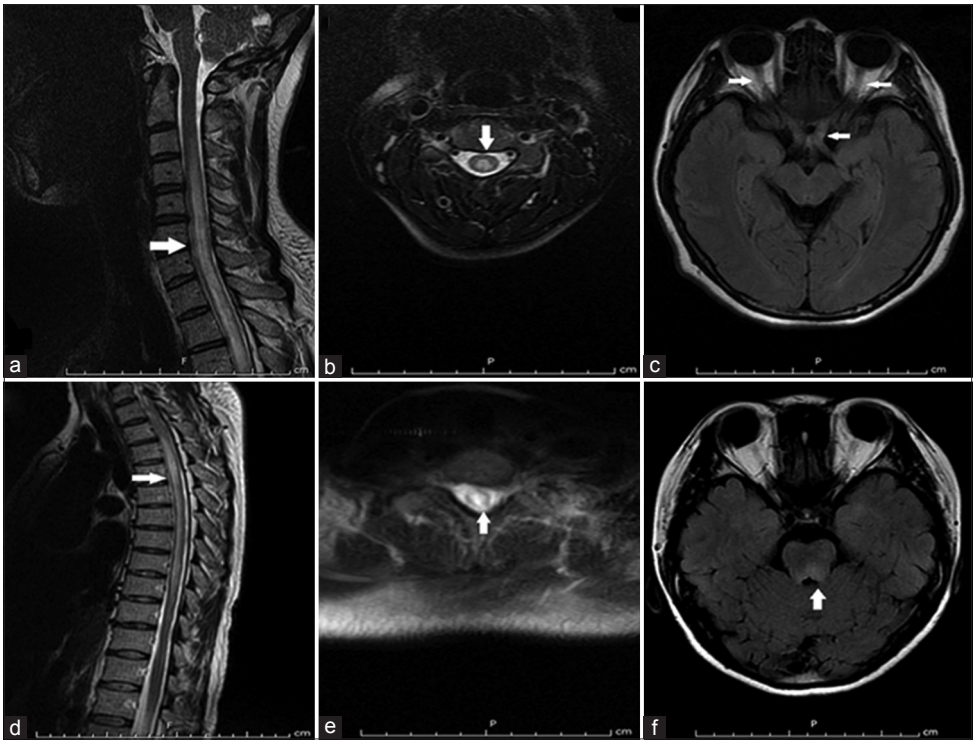

Figure 3: Neuroimaging features of NMO and other NMOSDs. (a-c) T2-weighted MRI of patient No. 1 showed long T2 lesion in the cervical spinal cord and T2 fluid-attenuated inversion recovery showed high signal lesions of optic nerve (arrows). (d and e) T2-weighted MRI of patient No. 4 showed long T2 lesion in the thoracic spinal cord (arrows). (f) T2 fluid-attenuated inversion recovery of patient No. 14 showed high signal medulla lesions around the fourth ventricle (arrow). NMOSDs: Neuromyelitis optica spectrum disorders; NMO: Neuromyelitis optica; MRI: Magnetic resonance imaging.

the sharp hormonal changes before and after childbirth that may cause newly-onset IDD during puerperium.[2,10]

While clinical evidence is insufficient regarding the benefit of estrogen at risk for IDDs exacerbations, the data of animal experiment demonstrated that estrogen and progesterone potentiated neuroprotective effects. Pregnancy-related hormones can affect lymphocyte differentiation. During pregnancy, levels of estrogen, progesterone, glucocorticoids, h-human chorionic gonadotropin (h-HCG), and thyroid hormones were increased to some degrees.[11-13] High level of serum HCG may drive an expansion of interleukin-10 (IL-10)-producing regulatory B-cells, a subtype of B lymphocytes with strong immunosuppressive functions, during pregnancy.[14] Th2 cells mainly secrete IL-6, IL-4 which can stimulate the activation of B lymphocytes. Secreted by corpus luteum and placenta, estrogen can enhance the humoral immunity by the way of prompting differentiation of Th0 lymphocytes into Th2 cells and inhibiting the function of Th1.[15] After delivery, pregnancy-related hormones decrease sharply, and inhibited immune response begin to be active. Pregnancy-related hormones could adjust the levels of immune response.[14] It has been reported that estrogen receptors (ER) existed in almost all the tissues, and the physiological effects of estrogen strongly depended on its serum level and the number of ER in the target cells. The physiological effects of estrogen depended strongly on the level of estrogen and the number of ER in the target cells.[3] Estrogen participated in the regulation of immune response to protect CNS from autoimmune attacks. Experimental allergic encephalomyelitis animal experiment has proved that estrogen has mediates neuroprotective and anti-inflammatory effects through ER signal and toll-like receptors on astrocytes and oligodendrocytes.[16] Progesterone can also protect neuron by thickening myelin sheath and enhancing the fibril connection.[11,17,18]

Methylprednisolone therapy has high blood drug concentration and short half-life which is helpful to control illness aggravation. All patients received methylprednisolone in priority during the acute stage while patients who were refractory to methylprednisolone could be treated with immunoglobulin or plasma exchange as a rescue treatment.[19] During remission stage, individualized therapy should be performed. Although there has been no evidence supporting that oral estrogen could be used as a prophylaxis treatment, estrogen supplementation therapy in the first trimester postpartum was likely to be a promising treatment to reduce IDD relapse during the postpartum period, which was corresponded with previous studies.[20,21]

In conclusion, this study showed that IDD female patients of childbearing age might suffer initial attacks in the first trimester postpartum. Labor-associated IDD attacks might be associated with sharply decreased progesterone/estrogen levels after childbirth. Prospective multicenter clinical studies are needed to verify absolute risk of newly-onset IDD during puerprium period.

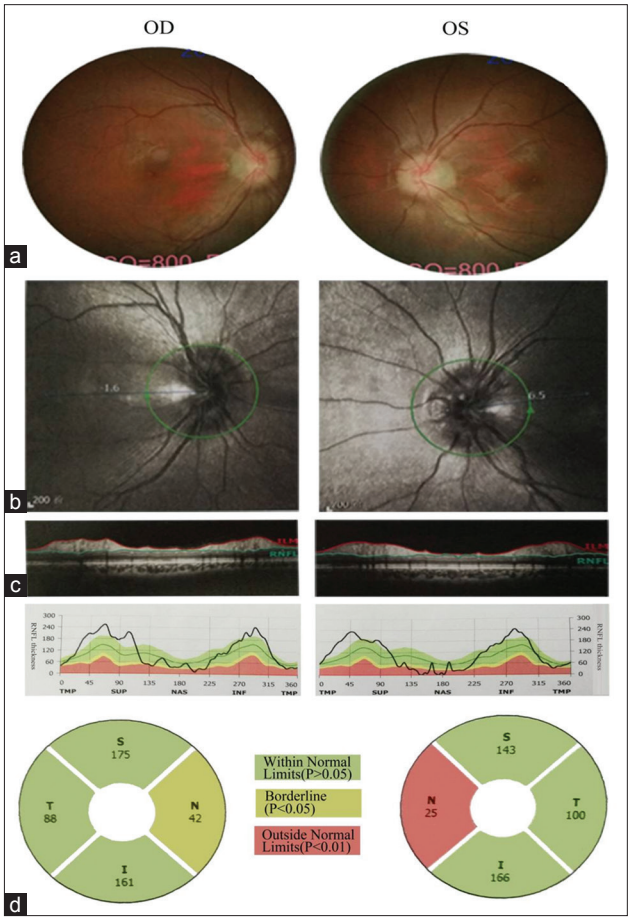

Figure 4: Examinations and changes of optic nerve at acute optic neuritis onset. (a) Bilateral fundus of patient No. 6 showed edematous papillary. (b) Fudus fluroscence angiography showed normal vessels without fluorescent leakage. (c and d) Optical coherence tomography showed thinning thickness of nasal retinal nerve fiber layer in left eye.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Ramien C, Taenzer A, Lupu A, Heckmann N, Engler JB, Patas K, *et al.* Sex effects on inflammatory and neurodegenerative processes in multiple sclerosis. Neurosci Biobehav Rev 2016;67:137-46. doi: 10.1016/j.neubiorev.2015.12.015.
2. Zare-Shahabadi A, Langroodi HG, Azimi AR, Sahraian MA, Harirchian MH, Baghbanian SM. Neuromyelitis optica and pregnancy. Acta Neurol Belg 2016;116:431-8. doi: 10.1007/s13760-016-0654-x.
3. Fong A, Chau CT, Quant C, Duffy J, Pan D, Ogunyemi DA. Multiple sclerosis in pregnancy: Prevalence, sociodemographic features, and obstetrical outcomes. J Matern Fetal Neonatal Med 2017;10:1-6. doi: 10.1080/14767058.2017.1286314.
4. Traboulsee A, Simon JH, Stone L, Fisher E, Jones DE, Malhotra A, *et al.* Revised recommendations of the consortium of MS centers task force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. AJNR Am J Neuroradiol 2016;37:394-401. doi: 10.3174/ajnr.A4539.
5. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, *et al.* International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177-89. doi: 10.1212/WNL.0000000000001729.
6. Kraemer M, Weber R, Herold M, Berlit P. Reversible cerebral vasoconstriction syndrome associated with fingolimod treatment in relapsing-remitting multiple sclerosis three months after childbirth. Mult Scler 2015;21:1473-5. doi: 10.1177/1352458515600249.
7. Igel C, Garretto D, Robbins MS, Swerdlow M, Judge N, Dayal A. Neuromyelitis optica in pregnancy complicated by posterior reversible encephalopathy syndrome, eclampsia and fetal death. J Clin Med Res 2015;7:193-5. doi: 10.14740/jocmr2031w.
8. Lu E, Zhao Y, Dahlgren L, Preston R, van der Kop M, Synnes A, *et al.* Obstetrical epidural and spinal anesthesia in multiple sclerosis. J Neurol 2013;260:2620-8. doi: 10.1007/s00415-013-7035-7.
9. Drake E, Drake M, Bird J, Russell R. Obstetric regional blocks for women with multiple sclerosis: A survey of UK experience. Int J Obstet Anesth 2006;15:115-23. doi: 10.1016/j.ijoa.2005.10.010.
10. Shimizu Y, Fujihara K, Ohashi T, Nakashima I, Yokoyama K, Ikeguch R, *et al.* Pregnancy-related relapse risk factors in women with anti-AQP4 antibody positivity and neuromyelitis optica spectrum disorder. Mult Scler 2016;22:1413-20. doi: 10.1177/1352458513519181.
11. Christianson MS, Mensah VA, Shen W. Multiple sclerosis at menopause: Potential neuroprotective effects of estrogen. Maturitas 2015;80:133-9. doi: 10.1212/NXI.0000000000000288.
12. Bove R, Chitnis T. The role of gender and sex hormones in determining the onset and outcome of multiple sclerosis. Mult Scler 2014;20:520-6. doi: 10.1073/pnas.1617115114.
13. Liu SM, Zhou YZ, Wang HB, Sun ZY, Zhen JR, Shen K, *et al.* Factors associated with effectiveness of treatment and reproductive outcomes in patients with thin endometrium undergoing estrogen treatment. Chin Med J 2015;128:3173-7. doi: 10.4103/0366-6999.170258.
14. Davoudi V, Keyhanian K, Bove RM, Chitnis T. Immunology of neuromyelitis optica during pregnancy. Neurol Neuroimmunol Neuroinflamm 2016;3:e288. doi: 10.1002/jnr.20330.
15. D'hooghe MB, D'Hooghe T, De Keyser J. Female gender and reproductive factors affecting risk, relapses and progression in multiple sclerosis. Gynecol Obstet Invest 2013;75:73-84. doi: 10.1159/000346319.
16. Offner H. Neuroimmunoprotective effects of estrogen and derivatives in experimental autoimmune encephalomyelitis: Therapeutic implications for multiple sclerosis. J Neurosci Res 2004;78:603-24. doi: 10.1016/j.clineuro.2016.07.004.
17. Voumvourakis KI, Tsiodras S, Kitsos DK, Stamboulis E. Gender hormones: Role in the pathogenesis of central nervous system disease and demyelination. Curr Neurovasc Res 2008;5:224-35. doi: 10.1001/archneur.62.9.1362.
18. Xue W, Deng Y, Wang YF, Sun AJ. Effect of half-dose and standard-dose conjugated equine estrogens combined with natural progesterone or dydrogesterone on components of metabolic syndrome in healthy postmenopausal women: A randomized controlled trial. Chin Med J 2016;129:2773-9. doi: 10.4103/0366-6999.194646.
19. Rubio Tabares J, Amaya Gonzalez PF. Plasma exchange therapy for a severe relapse of Devic's disease in a pregnant woman: A case report and concise review. Clin Neurol Neurosurg 2016;148:88-90. doi: 10.1016/j.jns.2009.05.028.
20. Alonso A, Jick SS, Olek MJ, Ascherio A, Jick H, Hernán MA. Recent use of oral contraceptives and the risk of multiple sclerosis. Arch Neurol 2005;62:1362-5. doi: 10.1001/archneur.62.9.1362.
21. Itoh N, Kim R, Peng M, DiFilippo E, Johnsonbaugh H, MacKenzie-Graham A, *et al.* Bedside to bench to bedside research: Estrogen receptor beta ligand as a candidate neuroprotective treatment for multiple sclerosis. J Neuroimmunol 2017;304:63-71. doi: 10.1016/j.jneuroim.2016.09.017.

Supplementary Material 1: Detail clinical data of 14 patients in this study

Patient number	Onset of age (years)	Reproductive history	Delivery way	Interval times (days)	Breast feeding	EDSS score on admission	Follow-up times	EDSS score at the end of follow-up	ARR
1	24	G1P1	Cesarean section	10	Yes	9.0	33 months	4.5	0.71
2	33	G2P2	Cesarean section	15	Yes	7.5	23 months	5.0	0.47
3	31	G3P2	Cesarean section	22	Yes	7.0	27 months	4.5	0.48
4	27	G1P1	Cesarean section	39	No	8.5	34 months	3.0	1.16
5	30	G3P2	Natural birth	30	Yes	3.0	22 months	1.0	0
6	31	G2P2	Natural birth	23	Yes	3.0	31 months	1.0	0
7	31	G2P1	Spontaneous abortion	10	No	4.5	39 months	2.0	0.75
8	20	G1P0	Elective abortion	41	No	5.0	43 months	1.0	0.45
9	35	G3P2	Cesarean section	30	Yes	3.5	29 months	3.0	0.50
10	22	G1P1	Cesarean section	10	No	4.5	27 months	2.5	0.36
11	23	G1P1	Cesarean section	29	No	5.0	41 months	1.5	0.89
12	32	G2P1	Cesarean section	7	Yes	7.0	44 months	3.0	0.35
13	24	G2P1	Cesarean section	23	Yes	7.5	32 months	2.5	0.77
14	37	G3P1	Cesarean section	15	Yes	5.5	37 months	2.5	0

EDSS: Expanded Disability Status Scale; ARR: Annualized relapse rate.

Supplementary Material 2: Neuroimaging, serum antibody, diagnosis, and treatments of the 14 patients with IDDs

Patient number	Lesion locations	Serum and CSF findings	AQP4-IgG	Diagnosis	Treatments in remission time
1	Optic nerve and C3–C7 and T1–T7	Normal	+	NMO	Oral steroid and tacrolimus
2	Optic nerve and C1–C7	Normal	+	NMO	Oral steroid and tacrolimus
3	Optic nerve and C6–T5	Anti-SSA antibodies (+) and ANA = 1:1000	+	NMO and SS	Oral steroid and azathioprine
4	Optic nerve and T1–T8	ANA = 1:320	+	NMO	Oral steroid and tacrolimus
5	Isolated lesion in left frontal lobe	Normal	−	CIS	β-interferon
6	Optic nerve	Normal	−	CIS (acute optic neuritis)	Oral steroid
7	Optic nerve, supertentorial and T1–T2	Normal	None	MS	β-interferon
8	Supertentorial and subtentorial lesions	ANA = 1:100	None	MS	β-interferon
9	Optic nerve and supertentorial lesions	IgG index = 0.9, OCB (+)	−	MS	β-interferon
10	Supertentoria and subventricular lesions	Normal	None	MS	β-interferon
11	Supertentorial and C2–C3	ANA = 1:100	−	MS	None
12	T4–T8	Nuclear cells = 22×10^6/L, total protein = 511 mg/L	+	NMOSDs (LETM)	Oral steroid and tacrolimus
13	C3–C7	Nuclear cells = 51×10^6/L, total protein = 812 mg/L	+	NMOSDs (LETM)	Oral steroid and tacrolimus
14	Isolated brainstem lesions	Normal	+	NMOSDs (acute brainstem syndrome)	Azathioprine

ANA: Anti-nuclear antibodies; SSA: Sjogren syndrome antigen A; CIS: Clinical isolated syndrome; LETM: Longitudinal extensive transverse myelitis; NMOSDs: Neuromyelitis optica spectrum disorders; IDDs: Inflammatory demyelinating diseases; IgG: Immunoglobulin G; OCB: Oligoclonal band; NMO: Neuromyelitis optica; MS: Multiple sclerosis; CSF: Cerebrospinal fluid; AQP4: Aquaporin 4; SS: Sjögren syndrome; +: Positive AQP4-IgG result; –: Negative AQP4-IgG result.