**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, urosepsis, 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 \( (0.49 \pm 0.34, 95\% \text{ confidence interval: } 0.29–0.69) \) with standardized treatments.

**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 Huazhong University of Science and Technology, Wuhan, Hubei 430030, China.

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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\(^2\) in 2016 or the diagnostic criteria revised by Wingerchuk \(et \, al\)^\(^3\) 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 \((n = 11)\), uroscerosis \((n = 7)\), 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].
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].

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 leukoencephalopathy syndrome 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. Next, this study summarized

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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     | 18.0 (7.0–41.0)*     |
| (days)                                               |                      |
| 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 (6.0–7.0)*       |
| 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.

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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.
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.\[^10\] 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.
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**Conflicts of interest**

There are no conflicts of interest.

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### 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             | Supertentorium and subventricular lesions | Normal                | None     | MS                 | β-interferon |
| 11             | Supertentorial and C2–C3 | ANA = 1:100             | −        | MS                 | None |
| 12             | T4–T8              | Nuclear cells = 22×10⁹/L, total protein = 511 mg/L | +        | NMOSDs (LETM)      | Oral steroid and tacrolimus |
| 13             | C3–C7              | Nuclear cells = 51×10⁹/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.