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Effectiveness and safety of immunosuppressive therapy in neuromyelitis optica spectrum disorder during pregnancy☆

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ABSTRACT

Objective: To evaluate the effectiveness and safety of immunosuppressive therapy in neuromyelitis optica spectrum disorder (NMOSD) during pregnancy.
Methods: Sixteen NMOSD patients who had at least one pregnancy after NMOSD onset were enrolled. The patients were divided into two groups according to whether they received immunosuppressive therapy during pregnancy. The annual relapse rate (ARR) before pregnancy (BP); during the first (DP1), second (DP2), and third trimesters (DP3); first trimester postpartum (PP1); and second trimester postpartum (PP2) were calculated. The Expanded Disability Status Scale (EDSS) was used to evaluate the degree of disability. Pregnancy outcomes were recorded and the children were followed up and their health condition was evaluated.
Results: In the group taking prednisone alone or in combination with azathioprine as immunosuppressive therapies, there was no difference among ARRs of each period (DP1, DP2, DP3, PP1, PP2) and BP. Compared with EDSS BP, EDSS increased slightly 6 months postpartum with no statistical significance ($p = 0.102$). In the group without immunosuppressive therapy, ARR increased during PP1 ($p = 0.014$) and EDSS increased 6 months postpartum as compared to BP ($p = 0.017$). Moreover, the added EDSS value was higher in the group without immunosuppressive therapy than in the group with therapy ($p = 0.038$). In 22 pregnancies from 16 patients, 16 pregnancies ended in live births and 6 pregnancies ended in abortions, including 2 spontaneous and 4 induced abortions. None of the children had congenital diseases or malformations. There were no records of abnormal growth among the children during 6 months to 12 years of follow-up.
Conclusion: Untreated women showed a propensity for disease relapse in PP1 and increased degree of disability postpartum. Immunosuppressive therapy during pregnancy and postpartum period can reduce the risk of relapse and degree of disability. Immunosuppressive therapy with low-dose prednisone was relatively safe. However, the safety of azathioprine during pregnancy remains unclear and needs future reevaluation.

1. Introduction

Neuromyelitis optic (NMO) is an autoimmune disorder of the central nervous system characterized by recurrent optic neuritis and longitudinal extensive transverse myelitis [1]. In 2004, the discovery of a highly specific serum biomarker, which was named aquaporin-4 (AQP-4), made NMO a distinctive disease compared to multiple sclerosis. In 2007, a definition of neuromyelitis optic spectrum disease (NMOSD) was proposed by Wingerchuk [2]. In 2015, the diagnostic criteria of NMOSD were revised by the International Panel for NMO diagnosis (IPDN) [3]. In this new nomenclature, the individual definition of NMO was disregarded, and it was classified into a unified term: NMOSD.

NMOSD is more common in women of childbearing age. With the development of diagnosis and treatment of NMOSD, our goal was not only to reduce patients' relapse rate and their degree of disability, but also to improve the quality of life of patients and to meet their childbearing requirements. NMOSD is a rare disease, and pregnancy complicated with NMOSD is even rarer. Most doctors agreed that the relapse rate is not different from that before pregnancy, but it increases significantly after delivery, especially during the first postpartum trimester. Therefore, it seems reasonable to administer immunosuppressive therapy during pregnancy and postpartum period, but studies of the effectiveness and safety of immunosuppressive therapy for NMOSD during pregnancy are scarce.

In order to explore the role of immunosuppressive therapy in NMOSD during pregnancy and the postpartum period, 16 patients

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who had pregnancies after the onset of NMOSD were enrolled in our study.

2. Patients and methods

2.1. Patient selection

Sixteen NMOSD patients who had pregnancies after the onset of NMOSD and were being treated at the Department of Neurology, Tsinghua Yuquan Hospital from June 2004 to June 2015 were enrolled. All of the patients met the diagnostic criteria proposed by IPND in 2015 [3]. Onset of NMOSD was before pregnancy in all patients. Each patient had at least one delivery. Patients who had initial manifestation of NMOSD during pregnancy or postpartum period were excluded. This research was approved by the Hospital Ethics Committee and written informed consent was obtained from all subjects.

2.2. Methods

All of the patients were divided into two groups according to whether they received immunosuppressive therapy during pregnancy and postpartum period. Eight patients accepted immunosuppressive therapy and the other 8 patients did not. Any attack that occurred during pregnancy or within 6 months postpartum was defined as a pregnancy-related attack [4]. High-dose intravenous methylprednisolone and/or immunoglobulin were used as acute phase regimens and prednisone 10 mg daily was used as immunosuppressive therapy during pregnancy. Prednisone 10 mg combined with azathioprine 50 or 100 mg daily was used in some severe cases.

The annual relapse rate (ARR) of each period was calculated during each trimester of pregnancy (first trimester: DP1; second trimester: DP2; third trimester: DP3), and the first and second trimesters postpartum (first trimester: PP1; second trimester: PP2). The Expanded Disability Status Scale (EDSS) score was used to evaluate the disability degree before pregnancy and 6 months postpartum. The elevation of EDSS score 6 months postpartum was calculated. Pregnancy outcomes were recorded and the children were followed up and their health conditions were evaluated.

Quantitative data were expressed as mean ± standard deviation, and categorical data were expressed as rate or percentage. A Wilcoxon test was used when the ARR or EDSS of different periods were compared in the same group. A Mann-Whitney test was used when the ARR or EDSS were compared between the two groups. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 20.0. Results were defined to be statistically significant when $p < 0.05$.

3. Results

3.1. Clinical data

Sixteen NMOSD patients who had 16 deliveries and 6 abortions were recruited into the study. The mean age at onset was 22.9 ± 4.3 years old and the mean age at delivery ranged from 23 to 39 years old. Thirteen of them were seropositive for AQP-4 antibodies and 3 were negative. Two patients were complicated with other autoimmune diseases, 1 patient with allergic purpura and 1 patient with Hashimoto's thyroiditis. A total of 5 patients were treated with prednisone combined with azathioprine. Two of them underwent induced abortions because of exposure to azathioprine. Two stopped the use of azathioprine and took prednisone alone after an adverse pregnancy outcome. After the pregnancies that eventually ended in delivery, only one patient continued prednisone combined with azathioprine, and the other 7 patients in the group with immunosuppressive therapy received prednisone alone (Table 1).

3.2. ARR and EDSS in different periods in 16 NMOSD patients

Sixteen patients had 21 pregnancy-related attacks; 42.9% (9/21) of relapses occurred in PP1, 28.6% (6/21) in DP2, 19.0% (4/21) in DP1, 4.8% (1/21) in DP3, and 4.8% (1/21) in PP2. The ARR was 1.00 ± 1.79 in BP, 1.00 ± 1.79 in DP1, 1.50 ± 2.00 in DP2, 0.25 ± 1.00 in DP3, 2.25 ± 2.05 in PP1, and 0.25 ± 1.00 in PP2. There was no significant difference between ARR of each period and BP. EDSS (2.72 ± 1.48) at 6 months postpartum was higher than BP (2.19 ± 1.31) ($p = 0.004$) (Fig. 2). There were no significant differences in ARR ($p = 0.442$) or EDSS ($p = 0.721$) BP between the patients with immunosuppressive therapy and patients without immunosuppressive therapy.

3.3. ARR and EDSS in different periods in patients with immunosuppressive therapy

In the group with immunosuppressive therapy, 37.5% (3/8) had no pregnancy-related attacks, and among these, 2 patients took prednisone 10 mg daily and 1 patient took prednisone 10 mg and azathioprine 100 mg daily as immunosuppressive therapy. A total of 62.5% (5/8) had 7 pregnancy-related attacks, and all 5 patients took prednisone 10 mg daily as immunosuppressive therapy. Among pregnancy-related

Table 1
Demographic and clinical data of 16 NMOSD patients.

Case	Age at onset	Age at pregnancy	AQP-4-Ab	Other autoimmune disease	Immunosuppressive therapy during pregnancy ending in delivery	Number of pregnancies	Number of miscarriage	EDSS BP	EDSS 6 months postpartum
1	26	27	+	None	P10 mg + AZA100 mg daily	2	1	6.0	6.0
2	26	29	+	None	P10 mg daily	2	1	3.0	3.5
3	28	39	+	None	P10 mg daily	1	0	1.0	2.0
4	26	32	+	None	P10 mg daily	2	1	1.5	1.5
5	19	27	−	None	P10 mg daily	1	0	1.0	1.0
6	23	29	+	None	P10 mg daily	1	1	1.5	1.5
7	15	23	+	None	P10 mg daily	1	0	2.0	2.5
8	15	23	+	None	P10 mg daily	2	1	2.0	2.0
9	17	27	–	Allergic purpura	None	1	0	2.0	3.0
10	25	31	+	None	None	1	0	4.0	5.5
11	23	30	+	None	None	2	1	2.0	3.5
12	26	28	–	None	None	1	0	2.0	2.5
13	24	26	+	None	None	1	0	1.0	1.0
14	22	24	+	None	None	1	0	3.0	4.0
15	28	29	+	Hashimoto's thyroiditis	None	1	0	2.0	2.5
16	24	26	+	None	None	1	0	1.0	1.5

AQP-4 Ab = aquaporin-4 antibody, BP = before pregnancy, P = prednisone, AZA = azathioprine.