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Efficacy of mycophenolate mofetil for AQP4 antibody positive optic neuritis immunotherapy

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麦考酚酸酯治疗 AQP4 抗体阳性视神经炎疗效观察

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摘要

目的:评价麦考酚酸酯(MMF)对 AQP4 抗体阳性视神经脊髓炎谱系障碍(NMOSD)患者预防复发和视力预后的作用。

方法:回顾性病例研究。收集 2017-01/2019-12 收治的 AQP4 抗体阳性 NMOSD 患者 11 例,其中男 3 例,女 8 例。NMOSD 特有的重要临床表现为视神经炎。发病平均年龄 36.3±6.0(27~47)岁,平均病程 3.4±1.4(2.2~6.8)a。在 NMOSD 缓解期加用 MMF 1a 或 1a 以上。记录应用 MMF 患者的年复发率(ARR)、最佳矫正视力(BCVA)和不良反应。

结果:MMF 治疗的中位时间为 18(12,36)mo。ARR 在基线时为 0.66/a,治疗后为 0.16/a。91%的患者 ARR 下降,82%的患者无临床复发。MMF 治疗后 ARR 明显改善($P<0.05$)。治疗后平均 BCVA 与治疗前比较无显著差异($P>0.05$)。11 例患者中,3 例(27%)出现不良反应,其中 1 例(9%)出现转氨酶升高,2 例(18%)出现轻度胃肠道反应。没有因不良反应而停用 MMF 的情况。

结论:MMF 治疗 AQP4 抗体阳性 NMOSD 患者能在一定程度上降低其视神经炎的 ARR,保护患者的视功能。

关键词:视神经脊髓炎谱系障碍;视神经炎;麦考酚酸酯;复发;视力

Abstract

• AIM: To evaluate the efficacy of mycophenolate mofetil (MMF) on the prevention of relapse and visual prognosis of patients in neuromyelitis optica spectrum disorders (NMOSD) with AQP4 antibody positive optic neuritis.

• METHODS: We retrospectively reviewed 11 patients with initial diagnosis of NMOSD and AQP4 antibody positive optic neuritis from January 2017 to December 2019. Among the 11 patients, 3 were male and 8 were female. The unique core clinical manifestation of NMOSD was optic neuritis. The onset age was 36.3±6.0 (27-47) years old. Duration of the disease was 3.4±1.4 (2.2-6.8) a. MMF was added in the relieving period of NMOSD for 1a or over 1a. Annualized relapsing rate (ARR), best corrected vision activity (BCVA) and adverse reactions of MMF were recorded.

• RESULTS: The median time of MMF treatment was 18 (12, 36) mo. The ARR was 0.66/a at baseline and 0.16/a after the treatment. There were 91% of the patients had decreased ARR and 82% of them had no clinical relapse. The patients had significant improvement on ARR after MMF treatment ($P<0.05$). In total, there was no significant difference between the mean BCVA after treatment and that at baseline ($P>0.05$). Of the 11 patients, 3 patients had side effects (27%), including 1 patient with elevated liver transaminase (9%), and 2 patients with mild gastrointestinal reaction (18%) during follow-up period. None of them discontinued MMF due to adverse events.

• CONCLUSION: MMF treatment for AQP4 antibody positive NMOSD can reduce the ARR of optic neuritis to a certain extent and protect the visual function of patients.

• KEYWORDS: neuromyelitis optica spectrum disorders; optical neuritis; mycophenolate mofetil; relapse; visual acuity

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INTRODUCTION

Multiple sclerosis and neuromyelitis optica spectrum disorders (NMOSD) have a high recurrence rate and idiopathic optic neuritis can be seen in their early stage as the only coreclinical manifestation. It has been found that more and more idiopathic optic neuritis was proved to be NMOSD in China[1]. Compared with multiple sclerosis associated optic neuritis, NMOSD has higher rate of recurrence and more serious disability[2]. In patients with AQP4 antibody positive NMOSD, the severe visual impairment is much more common[3]. Therefore, early and correct diagnosis of NMOSD, early identification and appropriate intervention are of great significance to prevent disease recurrence and reduce the progress of neurological disability especially in patients of NMOSD being with optic neuritis as the initial core manifestation.

Mycophenolate mofetil (MMF) is an immunosuppressant commonly used in organ transplantation and rheumatic immune diseases. In recent years, MMF has been gradually used in the treatment of neuroimmune diseases. Several small case series have shown that MMF was benefit for the treatment of NMOSD[4-6] and its efficacy was better than azathioprine[7-8]. Currently there is no unified standard for the treatment of NMOSD especially for NMOSD with only optic neuritis and without other neurology symptoms. In order to evaluate the effectiveness, safety and visual prognosis of MMF for NMOSD with optic neuritis as the unique core manifestation, 11 cases of AQP4 antibody positive NMOSD patients who were first diagnosed in the clinic of ophthalmology from January 2017 to December 2019 and treated by MMF were reported in current study.

SUBJECTS AND METHODS

Demographic of Patients From January 2017 to December 2019, 11 patients of NMOSD (3 males and 8 females) with idiopathic optic neuritis and MMF immunotherapy were enrolled in this study. The unique core symptom was optic neuritis, and AQP4 IgG antibody was positive in all patients. The average age of onset was from 36.3±6.0 (27-47) years. Duration of the disease was an average of 3.4±1.4 (2.2-6.8)a. The preoperative visual acuity was from hand motion to 20/20. Inclusive criteria: 1) Age≧18 years old, NMOSD diagnosis met the 2015 Wingerchuk criteria[2]. In this criteria, MRI were tested for all patients to rule out NMOSD from multiple sclerosis; 2) MMF attacked more than 2 times before MMF treatment, and the course of disease was more than 1a; 3) No other immunosuppressant was used before treatment; 4) Informed consent was signed voluntarily. Exclusion criteria: 1) Combined with uveitis, scleritis, glaucoma, retinal disease, other optic neuropathy and ocular diseases; 2) Patients were with other immune system diseases; 3) Chronic infectious diseases such as hepatitis and tuberculosis; 4) Severe liver and kidney damage and hematological and malignant tumors; 5) With any other neuropsychiatric diseases; 6) Pregnancy or preparing for pregnancy. The study was reviewed and approved by the hospital's Ethics Committee, in accordance with the Declaration of Helsinki, and informed consent was obtained from all patients prior to inclusion (Table 1).

All patients underwent medical history collection, ophthalmic examinations, serological tests, imaging examinations and neurology examinations before MMF initiation. Ophthalmic examinations included best corrected visual acuity (BCVA), pupil light reflex test, fundus examination, optic nerve optical coherence tomography (OCT), visual field examination and electrophysiological examination. Snellen visual acuity chart was used for visual acuity examination, and the results were converted into the minimum resolution angular logarithm (LogMAR) visual acuity. Imaging and neurology examination were evaluated by neuroimmunologists in our hospital. The serological tests included the detection of autoimmune antibodies, including rheumatoid factor, antinuclear antibody, anti-dsDNA, soluble nuclear antigen peptide antibody, immunoglobulin IgG/IgA/IgM, complement C3 and C4, C-reactive protein and AQP4 IgG antibody.

The systemic diseases included arrhythmia in 1 case (9%) and hypertension in 2 cases (18%). The diseases were under control. Among the 11 patients, 4 eyes (18%) were with moderate myopia. No other systemic or ocular disease history was reported.

Immunotherapy The patients were given glucocorticoid pulse therapy according to the standard treatment plan of acute stage before admission. Methylprednisolone 1g daily intravenously was given for 3-5d. Then the patients were changed to oral prednisone for sequential reduction[7]. The initial oral dose of prednisone was 1 mg/kg, and the oral sequential treatment was reduced by 5-10 mg every 1-2wk to the maintenance dose (prednisone ≦ 10 mg) till 6mo. MMF treatment was started when oral prednisone dosage was maintained for 1mo (Saikeping, 0.25 g/tablet); MMF and pulse glucocorticoid were used simultaneously in patients with NMOSD relapse during MMF monotheray.

Before immunotherapy initiation, blood pressure, electrocardiogram, blood routine, urine routine, liver function, renal function and electrolytes were tested. After signing the informed consent of immunotherapy, the patients were given the initial dose of MMF 1g twice a day[7]. All patients underwent ophthalmic examinations and general examinations during their follow-up visit every 6-8wk. The neurological examinations were evaluated by neuroimmunology specialist. According to the patient's complaint, visual acuity, pupil light reflex, fundus examination, optical nerve OCT, visual field test and/or electrophysiological test, the disease activity of optic neuritis and myelitis were evaluated for increasing the dosage of MMF.

Criteria for Diagnosis and Recurrence The criteria for diagnosis and recurrence of NMOSD were as following: 1) Optic neuritis; 2) Acute myelitis. Neuroimmunologists completed MRI evaluation and diagnosis of myelitis. Criteria

Table 1 Demographic of patients with optic neuritis in NMOSD

Patients number	Gender	Onset age of disease (years)	Duration of disease (mo)	AQP4 antibody positive	Laterality	Time on MMF (mo)	MMF dosage at baseline (mg/d)	MMF dosage at 1a follow-up visit (mg/d)
1	F	37	26	+	Left	12	2000	2000
2	F	47	54	+	Left	12	2000	2000
3	M	36	39	+	Right	15	2000	2000
4	F	37	36	+	Both	24	2000	2500
5	F	36	26	+	Left	12	2000	2000
6	F	33	36	+	Left	36	2000	2000
7	F	34	60	+	Right	18	2000	2000
8	F	38	30	+	Both	18	2000	2000
9	M	41	30	+	Both	13	2000	2000
10	M	43	82	+	Both	18	2000	3000
11	F	27	36	+	Left	24	2000	2000

MMF: Mycophenolate mofetil.

for diagnosis and recurrence of optic neuritis: 1) Acute vision loss with or without ocular rotation pain; 2) visual field defect associated with optic tract; 3) Relative afferent pupil dysfunction and/or visual evoked potential (VEP) abnormality; 4) Excluding ischemic, compressive, invasive, traumatic, toxic, nutritional metabolic and hereditary optic neuropathy; 5) Excluding optic chiasm and subsequent optic pathway and central lesion; 6) Excluding anterior segment disease, retinopathy, macular disease, glaucoma and other uveitic diseases.

Statistical Analysis The onset time and the incidence of recurrent optic neuritis before and after MMF treatment were recorded. The annual recurrence rate (ARR) of optic neuritis was calculated. BCVA and adverse events were recorded before and after MMF initiation. SPSS 19.0 software was used for statistical analysis. Wilcoxon rank sum test was used to compare ARR, and paired t test was used to compare LogMAR corrected visual acuity before and after MMF treatment. $P<0.05$ was statistically significant.

RESULTS

Relapsing The median time of MMF treatment was 18 (12, 36) mo. The ARR was 0.66/a at baseline and 0.16/a after MMF treatment. Compared with that at baseline, the average ARR was decreased after MMF treatment, and the differences were statistically significant ($P<0.05$). After MMF initiation, 2 patients (18%) experienced relapsing and the total number of recurrence were 3. In total, 90% of patients were with decreased ARR and 81% of them were no clinical recurrence. During the follow-up period, 2 patients (18%) developed myelitis symptoms at 12mo after MMF initiation (4a after NMOSD onset) and 18mo after MMF starting (8.3a after NMOSD onset) respectively. One of them had mild neurological symptoms and did not change the original MMF treatment regimen after neurology consultation. The other patient were transferred to the department of neurology for rituximab treatment after being on MMF for 18mo. Currently the two patients were in stable condition (Table 2).

BCVA In current study, the average BCVA (LogMAR) before MMF treatment was 0.43±0.66. The average BCVA (LogMAR) was 0.06±0.08 in the better eye and was 0.84±0.79 in the fellow eye at baseline. After 12mo of immunotherapy, the average BCVA (LogMAR) was 0.40±0.59 in all eyes; and the average BCVA (LogMAR) was 0.07±0.08 in the better eye and was 0.76±0.70 in the fellow eye. After being on MMF for 12mo, there was no significant difference in the mean BCVA, BCVA of the better eye and BCVA of the fellow eye when compared with those before MMF starting ($P=0.134$, 0.341, 0.105).

Adverse Events During the immunotherapy, a total of 3 patients (27%) had adverse events. Liver transaminase increased slightly in one patient (9%). No special treatment was given after physician consultation. Liver function was closely observed and the transaminase returned to normal range 2mo later gradually. Another 2 patients (18%) had mild nausea and vomiting within 1wk after MMF initiation, and gradually improved after 2wk without special intervention. In addition, it is worth noting that one patient (9%) developed femoral head necrosis due to high-dose steroid pulse therapy for three times during past 3a, and another patient (9%) developed femoral head necrosis being on oral methylprednisolone maintenance dose. These two patients were treated conservatively in the department of orthopedics and their condition are temporarily stable. During the follow-up period, no other serious adverse events were reported and no systemic disease progression were observed. None of the patients discontinued MMF treatment due to adverse events.

DISCUSSION

NMOSD is a group of central nervous system inflammatory demyelinating diseases that most often involves the optic nerve and spinal cord. It has the characteristics of alleviating recurrence with high recurrence rate and heavy disability[2-9]. Each attack of NMOSD will bring damage to their visual function or spinal cord function. It is very important to intervene the acute onset of NMOSD patients and prevent recurrence in the chronic stage. At present, there is a consensus that patients with AQP 4 antibody positive NMOSD

Table 2 Relapse, visual outcomes and adverse events of patients with optic neuritis in NMOSD before treatment and after being on mycophenolate mofetil for 1a

patients Number	BCVA (LogMAR) at baseline		BCVA (LogMAR) at 1a follow-up visit		Relapsing time of optic neuritis	Relapsing time of myelitis	Adverse events
	OD	OS	OD	OS			
1	1.0	0.3	1.0	0.3			Elevating Transaminase
2	0.8	CF	0.8	CF			Mild nausea (Relieved in 2wk after oral MMF administration)
3	0.6	1.0	0.8	1.0			Femoral head necrosis*
4	0.8	0.3	0.8	0.3	1	1	
5	1.0	0.6	1.0	0.7			Mild nausea and diarrhea (Relieved after oral administration of MMF for 1mo)
6	1.0	1.0	1.0	1.0			
7	0.2	1.0	0.2	1.0			
8	0.6	0.1	0.6	0.1			
9	CF	0.8	0.02	0.7			Femoral head necrosis&
10	0.6	HM	0.6	CF	2	1#	
11	1.0	0.3	1.0	0.3			

BCVA: Best corrected visual acuity; OD: Right eye; OS: Left eye; MMF: Mycophenolate mofetil; CF: Counting fingers; HM: Hand motion; *: Occurred in this patient due to high-dose steroid pulse therapy for three times; &: This patient suffered with femoral head necrosis being on oral prednisone maintenance dose for 6mo; #: Patient number 10 with recurrent myelitis and optic neuritis were treated with rituximab after 18mo of MMF treatment.

should receive long-term immunotherapy as soon as they are diagnosed[2]. The classical immunosuppressive agents for preventing the recurrence of NMOSD include prednisone, azathioprine, MMF, methotrexate, and new therapeutic drugs such as rituximab, IL-6 receptor antibody, and ikuzumab. According to current experience, azathioprine, MMF and rituximab are often recommended as first-line drugs[2-9]. In recent years, rituximab has been recommended to prevent the recurrence of NMOSD. Rituximab may induce transfusion reaction, infection, and even death[10-11]. In addition, its clinical application is limited by the high price and insurance issues[4-10].

Azathioprine should be the first choice for AQP4 antibody positive or recurrent NMOSD optic neuritis. Azathioprine can inhibit the proliferation of T and B lymphocytes by interfering with purine synthesis in cells[12-14]. Azathioprine was widely used in the treatment of NMOSD in alleviating period. A retrospective study showed that oral azathioprine 2-3 mg/(kg·d) could reduce the average ARR of patients from 2.20 to 0.52, and the effect was better when the dosage was more than 2 mg/(kg·d)[15]. Another retrospective study showed that after azathioprine treatment, the average ARR in 89% of NMOSD patients decreased from 1.5 to 0[16]. However, azathioprine takes effect slowly (3-6mo) and the recurrence rate is high after treatment. In the clinical treatment of NMOSD, more effective and safe immunomodulatory drugs are constantly explored. Although azathioprine could effectively reduce the ARR of NMOSD patients, its curative effect was inferior to rituximab and MMF[17]. In a retrospective study by Costanzi *et al*[15], 38% of patients stopped taking azathioprine because of intolerance or ineffective treatment. Mealy *et al*[17] found that the failure rate of azathioprine treatment was as high as 53%. MMF and rituximab showed better efficacy on preventing disease recurrence than azathioprine[17]. Chen *et al*[8] observed that azathioprine and MMF had no significant difference in preventing recurrence, but MMF had higher tolerance, suggesting that MMF and rituximab had more advantages than azathioprine[11,15-18].

MMF is metabolized into mycophenolic acid with active effect *in vivo*, which can inhibit lymphocyte proliferation. At present, a number of clinical studies have reported that when the dosage of MMF was 750-3000 mg/d, the ARR of 80% patients could be significantly reduced from (0-11.8)/a to (0-3.0)/a, and half of the patients had no recurrence during the follow-up[4-6,10,17-19]. Huh *et al*[5] showed that after 20mo of MMF treatment (1000-2000 mg/d), the ARR of NMOSD patients decreased from 1.5/a to 0/a, 60% of the patients did not relapse. Chen *et al*[6] observed 62 cases of neuromyelitis optica and NMOSD treated with MMF (average dose of 2000 mg/d). The ARR of the patients decreased from 1.2/a to 0/a, and most of the patients had stable conditions or improved disability status.

In current study, the ARR of optic neuritis decreases significantly from 0.66/a to 0.16/a after MMF 2000 mg/d treatment, and there is no significant decrease in average visual function, visual function in better eye or worse eye after MMF treatment. At present, the dosage of MMF in the treatment of NMOSD varies greatly. There is no unified course of treatment for AQP4 antibody positive optic neuritis. The long-term therapeutic efficacy of MMF in the treatment of AQP4 antibody positive optic neuritis, drug dosage, and when to stop immunotherapy need to be further confirmed.

The common adverse events of MMF include gastrointestinal reactions, elevated liver enzymes, leucopenia, and infection.

A few studies reported that MMF had diarrhea, elevated liver enzymes, infection, bone marrow suppression and other adverse events[5,10,17-20]. When the MMF dose was 750-3000 mg/d, 5%-41% of the patients had adverse events, and 0-39% of the patients discontinued the treatment[4-6,10,17-20]. In the study of Huang *et al*[7], 90% of the NMOSD patients received MMF treatment dose of 1000 mg/d, and the total incidence of adverse events was 39%. In the study of Chen *et al*[6], 62 patients with neuromyelitis optica and NMOSD were treated with MMF with an average dose of 2000 mg/d, 4.8% of patients had MMF adverse events and no patients stopped MMF. In our study, the dose of MMF was 2000 mg/d, and the incidence of adverse events (27%, 3/11) was similar with that of the previous studies. No patient changed or stopped MMF treatment due to adverse events in our study. Long-term follow-up in larger case series still need to be implemented in the future.

In conclusion, our study evaluated that MMF had a certain efficacy on reducing the recurrence of AQP4 antibody positive optic neuritis with good tolerance. In patients with AQP4 antibody positive NMOSD with optic neuritis as the only core symptom, MMF and rituximab may become the first choice of immunotherapy in the future. MMF is convenient for its oral administration with less adverse drug reactions and cheaper price than biological agents which make it more acceptable by NMOSD patients. Multicenter, randomized, double-blind and high-level evidence researches are still needed for this rare disease. The individualized treatment regimen and the withdrawal time of MMF still need further observation.

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