Original Article

Differential Diagnosis for Multiple Sclerosis-related Optic Neuritis

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Abstract

Purpose: To analyze clinical features and main causes of multiple sclerosis-related optic neuritis (MS-ON), providing evidence for the differential diagnosis of MS-ON.

Methods: Clinical data were collected from 527 patients, 123 males and 404 females, diagnosed with MS-ON between June 2008 and June 2013. Visual acuity, optometry, visual field, slit-lamp microscopy, indirect ophthalmoscopy (20D), optical coherence tomography (OCT) and magnetic resonance imaging (MRI) were performed. Venous blood was sampled for detection of autoimmune antibodies and Aquaporin (AQP-4).

Results: Fifty nine cases were diagnosed with neuromyelitis optica-related optic neuritis (NMO-ON), 27 Sjogren's syndrome-related optic neuropathy, 22 tumors, 21 anterior ischemic optic neuropathy, 15 radiation-induced optic neuropathy, 14 optic neuropathy-related infection, 17 genetic eye diseases and 10 open angle glaucoma. Among168 MS-ON patients undergoing optic nerve MRI, 90 cases (53.57%) had a lesion < 15 mm in size, 15-30 mm in 76 (45.24%) and > 30 mm in two (1.19%).

Conclusion: MS-ON is more commonly misdiagnosed with NMO-ON and Sjogren's syndrome, when compared to optic neuropathy, tumors and ischemic optic neuropathy. (***Eye Science 2015; 30:23-28***)

Keywords: multiple sclerosis related optic neuritis; misdiagnosis; differential diagnosis; magnetic resonance imaging

Introduction

Optic neuritis (ON) is related to multiple sclerosis[1]. Most multiple sclerosis-related optic neuritis (MS-ON) is idiopathic. ON should be differentially diagnosed from alternative diseases. Meantime, ON is regarded as initial symptom of multiple sclerosis, neuromyelitis optica (NMO), and acute disseminated encephalomyelitis (ADEM), which significantly differ in terms of treatment and prognosis[2]. Wingerchuk's et al. found that AQP-4 could be used as specific antibodies in the diagnosis of NMO via AQP4 antibody. NMO spectrum disorder (NMOSD) has been further understood, and recurrent optic neuritis and binocular optic neuritis belong to the NMOSD[3].

ON results from ocular infection and the causes of ON infection include syphilis[4], AIDS[5] and Lyme disease[6]. ON is also related to systemic immune diseases such as Sjogren's syndrome[7], systemic lupus erythematosus[8], sarcoidosis[9] and Behcet's disease.

Along with the development of ON, differential diagnosis between ON and other eye diseases have been far from satisfaction. ON could be classified into MS-ON, neuromyelitis optica-related neuritis (NMO-ON), infection-related ON and immune-related ON[10]. Treatment and prognosis of ON caused by different etiological factors significantly differ. Hence, early differential diagnosis plays a pivotal role in clinical practice. The purpose of this retrospective study is to determine the causes of MS-ON misdiagnosis.

Materials and methods

Epidemiological data

Data were collected from 527 patients (123 males and 404 females) diagnosed MS-ON between June 2008 and June 2013 in the Department of Ophthalmology, PLA General Hospital. All patients were first diagnosed with ON. Patients presenting with systemic symptoms were excluded from this study.

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AQP4 antibody served as an antibody distinguishing idiopathic demyelinating optic neuritis (IDON) from NMO-ON. In this study, ON patients with positive AQP4 antibody were allocated into the NMO-ON group.

Neuro-ophthalmic examination

Routine ophthalmic examinations included visual acuity, optometry, visual field, slit-lamp microscopy, and indirect ophthalmoscopy (20 D). All ophthalmic examinations and records were conducted by the same associate chief ophthalmologist. MRI scanning was performed using GE 3.0T, T2WI TR 2000-3000ms, TE 80-100ms; T1WI TR 300-400 ms, and TE 10-15 ms. The paramagnetic contrast agent Gd-DTPA (0.1 mm/Kg) was used to enhance the scanning. Optical coherence tomography (OCT) examination was conducted using the Cirrus HD-OCT (Carl Zeiss Meditec Inc. Dublin, CA). Macular scanning was performed at 512×128 resolution and peripapillary nerve fiber layer thickness was measured at 200×200 resolution.

Autoimmune antibody test

Fasting serum extraction was performed to test rheumatoid immune antibody without glucocorticoid administration. Serum anti-AQP-4 antibody was tested by cytological detection. All subjects underwent serum sampling measurement for at least two times. The titer of detection was at least 1:100. All patients enrolled in this study were followed up for > one year in the Neuro-ophthalmology Department of PLA General Hospital.

Results

Etiology misdiagnosis

The highest rate of misdiagnosis for IDON was 25.49%, mainly misdiagnosed as Sjogren's syndrome-related optic neuritis (17.65%). The second most com mon misdiagnosis was vascular lesion (15.03%), with the most important type being non-arteritic anterior ischemic optic neuropathy (NAION) (13.73%). Tumor lesions (22/14.38%) were confirmed as malignant by biopsy, including 6 craniopharyngioma, 5 pituitary adenoma, 2 metastases (Figure 3), 3 optic nerve glioma(Figure 4), 4 optic nerve sheath meningioma(Figure 5), 1 inflammatory pseudotumor (Figure 6) and 1 lymphoma. Genetic testing confirmed 17 cases of hereditary disease including 15 Leber's hereditary optic atrophy(Figure 7), 2 autosomal dominant optic atrophy, 15 radiation optic neuropathy, 14 optic neuropathy-related infection, 3 poisoning and malnutrition optic neuropathy and 20 other eye diseases.

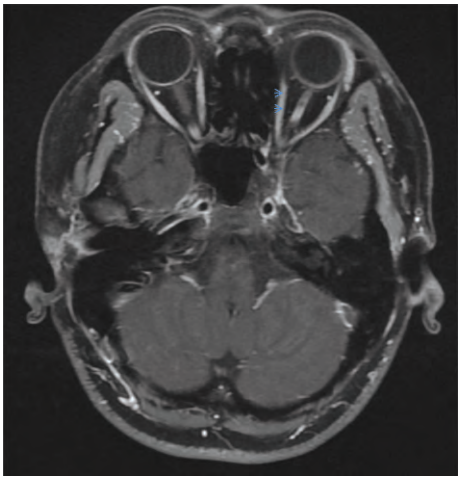

Figure 1 Orbital axial image of typical IDON patients: Segmental thickening with intensity of the optic nerve in the left eye

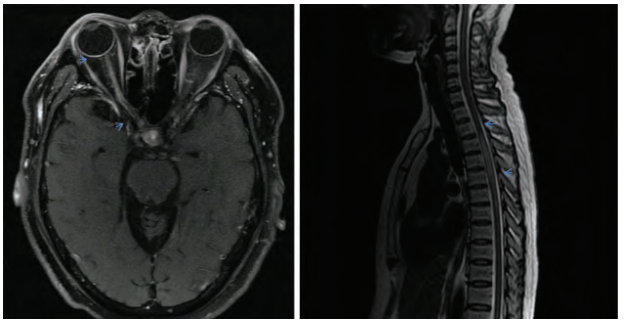

Figure 2 Patient diagnosed with NMO: long segmental imaging enhancement of the optic nerve, the emergence of long segmental T2 images of the thoracic spine after six months' follow-up

Imaging findings

Orbital MRI scanning was conducted in 168 MS-ON patients, and 159 (94.64%) showed high signal on T2WI. In total, 100 (59.52%) cases were found high signaling by Gad enhancement scanning, 0 (0%) in the intraocular segment, 166 (98.81%) in the orbit, 1 in the tubular segment (0.60%) and 1 (0.60%) in the intracranial segment. The size of the lesion was <15 mm in 90 cases (53.57%), 15-30 mm in 76 (45.24%) and >30 mm in 2 (1.19%), as illus-

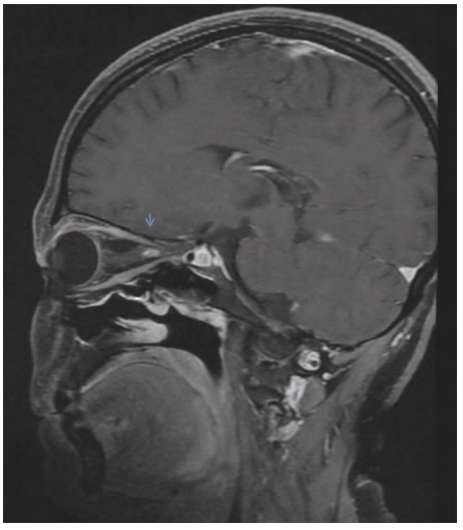

Figure 3 Orbital metastasis of small cell lung cancer: orbital sagittal near the orbital apex, metastatic lesions with visible clear boundary, evident enhanced images.

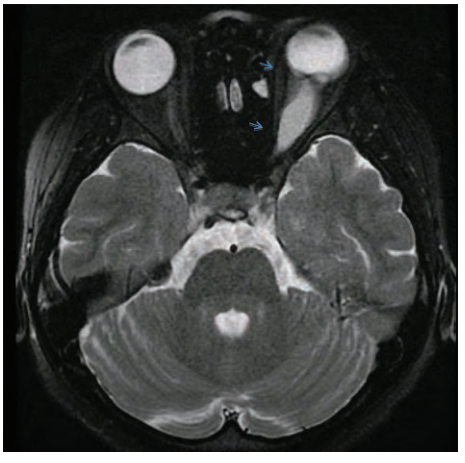

Figure 4 Optic nerve glioma: orbital axial imaging, fusiform thickening of the optic nerve; long T2 signal imaging is visible on T2WI in the SPIR–FLAIR.

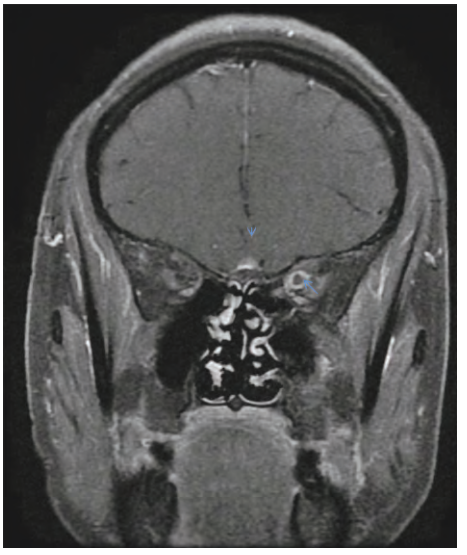

Figure 5 Optic nerve sheath meningioma: occurring in the orbital apex, involved with the canal section; a coronal "sleeve" sign and abnormal enhancement in the left eye are visible.

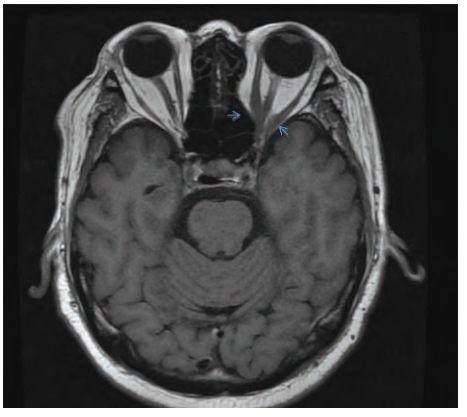

Figure 6 Myositis pseudo tumors, showing the steroid-dependent decline of visual function, due to optic nerve backlogged by the segmental muscle at the orbital apex.

trated in Figure 1 and Table 2.

Discussion

The pathogenesis and clinical features of MS-ON have been investigated by this single-center retrospective study. Most optic neuritis is classified based on the sites of pathological changes. In 2014, neuro-ophthalmologists in China began to classify optic neuritis based on the etiology, which was of significance in the prognosis and treatment of MS-ON. At present, few detailed studies focusing upon MS-ON have been performed.

It has been proposed that specific AQP4 antibody can be used in the diagnosis of NMO[3]. The studies focusing on AQP4 and its clinical significance further widen the classification of NMO. Patients with positive AQP4 antibody can be diagnosed as either NMO or NMO-ON. ON is also associated with infection and systemic immune diseases, so current researchers have concluded that the etiology of optic neuritis might be due to syphilis[11], AIDS[5], and Lyme disease[12]. In recent years, IDON diseases, such as Sjogren's syndrome[13], systemic lupus erythematosus[14], sarcoidosis[9] and Behcet's disease[9] have captivated widespread attention.

In this study, 118 patients initially diagnosed with

Table 1 Diseases distribution misdiagnosed as optic neuritis

Group	Diagnosis	Incidence(n)	Proportion (%)	MRI abnormality
Vascular disease	Anterior ischemic optic neuropathy	21	13.73	0/21
	Giant cell arteritis	2	1.31	0/2
		23	15.03	
Poisoning/malnutrition	Tobacco and alcohol amblyopia	2	1.31	0/2
	Methylismus optic neuropathy	1	0.65	0/1
		3	1.96	
Radiation disease	Radiation optic neuropathy	15	9.8	15/15
		15	9.8	
Hereditary disease	Heritage optic neuropathy,	15	9.8	7/15
	dominant optic atrophy	2	1.31	0/2
		17	11.11	
Infectious disease	Syphilis	12	7.84	12/12
	AIDS	2	1.31	2/2
		14	9.15	
Immunological diseases	Sjogren's syndrome,	27	17.65	21/27
	Systemic lupus erythematosus,	6	3.92	3/6
	Vasculitides,	2	1.31	0/2
	Behcet's disease,	2	1.31	0/2
	Wegener's granuloma	2	1.31	2/2
		39	25.49	
Eyes related disease	Normal tension glaucoma	10	6.54	0/10
	Ametropia,	2	1.31	0/2
	Ocular cone retinal rod dystrophy,	2	1.31	0/2
	Stargardt disease,	5	3.27	0/5
	VKH disease	1	0.65	0/1
		20	13.07	
Tumor	Raniopharyngioma,	6	3.92	6/6
	Pituitary adenoma,	5	3.27	5/5
	Optic nerve fiber meningioma,	3	1.96	3/3
	Optic neurofibroma,	4	2.61	4/4
	Inflammation pseudotumor,	1	0.65	1/1
	Lymphadenoma,	1	0.65	1/1
	Metastatic tumor	2	1.31	2/2
		22	14.38	
Total		153		

Table 2 MS–ON MRI examination

MRI	Frequency (n)	Proportion (%)
T2WI high signal	159	94.64
Intension	100	59.52
Total	168	
Ball section	0	0.00
Arcula section	166	98.81
Canal section	1	0.60
Intracranial section	1	0.60
Total	168	
Size of lesions		
<15 mm	90	53.57
15–30 mm	76	45.24
>30 mm	2	1.19
Total	168	100

MS-ON were positive for AQP-4 antibody and 40 of them had a prognosis of NMO. Compared to MS-ON, NMO-ON tends to affect bilaterally and recur. Hence, abnormal autoimmune antibodies and connective tissue diseases are easily misdiagnosed. AQP-4 antibody is a highly specific biomarker for the diagnosis of NMO[15]. Positive AQP-4 antibody reaction aids in the diagnosis of NMO and plays an important role in judging ON as the initial symptom of the isolated syndrome disease[15].

NMO-ON should be mainly distinguished from MS-ON. Our study found that the complications of immune diseases should be emphasized and distinguished from MS-ON. Recent studies demonstrated that Sjogren's syndrome is associated with central

nervous system diseases, especially MS and NMO[16]. NMO correlates with autoimmune diseases, especially Sjogren's syndrome, but rarely occurs in MS patients (0-3.3%)[17,18]. In the NMO-ON group, 20 patients suffered from autoimmune diseases, which is consistent with previous studies.

Tumor lesions are still the main cause of misdiagnosis. The rate of misdiagnosis was 14.38%, dominantly as craniopharyngiomas and pituitary tumors. Imaging test is utilized in the diagnosis of ON, especially in identifying atypical ON. Currently, it is widely accepted that IDON and multiple sclerosis share similar mechanism and pathological changes, manifested as optic nerve inflammation and demyelination. Irreversible damages to optic nerve could occur during the recovery and remission of axonal injury due to axon damage[19]. These pathological manifestations are characterized as increasing abnormal signals and optic nerve thickening on T2-weighted MRI image. SPIR-FLAIR is able to explicitly and accurately locate and measure the length of optic nerve. Gd-DTPA contrast enhancement scanning can reflect the onset of acute ON[20,21], whereas it tends to weaken or disappear in convalescence after corticosteroid use[22].

In this study, optic nerve enlargement was observed during acute stage of ON. Due to widespread application of imaging tools, the misdiagnosis rate has increased in recent years, mainly because acute optic nerve diseases showed strengthened signals and thickened optic nerves. We therefore proposed that these differences could help in the early and differential diagnosis of MS-ON. The main manifestations of NMO are ON and acute myelitis[23]. In this study, we found that NMO-ON affected a large lesion of optic neuropathy could affect bilateral eyes, mainly involved with the whole orbital nerve in the posterior segment and significantly elevated after contrast enhancement. Pula et al. demonstrated that optic nerve thickening by > 40 mm hinted the lineage diagnosis of NMO[24]. However, MS-ON patients in this study were unilaterally affected presenting with small lesions that generally did not involve with the optic nerve of entire orbit. Early and accurate imaging diagnosis of neuromyelitis optica influences the treatment and prognosis of MS-ON.

Previous studies suggested that gradual thinning of optic atrophy was detected in patients with hereditary diseases, such as Leber's hereditary optic neuropathy (LHON). However, recent research found that LHON patients showed high T2WI signal of long segment in both eyes during acute or sub-acute phases, and displayed mild to moderate enhancement after strengthening[25,26]. LHON is generally characterized as long lesions, occasionally involving with the optic chiasm. These changes in acute or sub-acute LHON are considered to be caused by damages to the blood brain barrier[27]. It is of great importance to understand typical MRI manifestations of IDON. In this study, the misdiagnosis of ON was more frequently observed in patients with tubular lesions, probably resulting from narrow space among tubular segments, optic nerve hyperemia and edema caused by compression during early stage. The lesions aggravating for > 6 months should be potentially considered as a tumor. with the presence of long lesions involving with the optic nerve of entire orbit should be considered as an indication of NMO or LHON.

Ischemic injuries to the optic nerve are more common in the elderly population compared with the young counterparts[28]. Ischemic optic neuropathy and ON share similar clinical symptoms[29], which are difficult to distinguish. Differential diagnosis requires detailed inquiry of medical history, physical and ocular examination and MRI scanning of the optic nerve. Other eye diseases show similar features to ON. For instance, open angle glaucoma is accompanied by optic nerve atrophy and some hereditary eye diseases (Leber, Stargardt disease, *etc.*) are manifested as defects in the central visual field. Decreased visual acuity caused by psychological factors should be distinguished from ON[30], probably associated with the improvement in neuro-ophthalmic examinations.

The present study has several limitations. This is a single center study with a relatively small sample size and short follow-up. A multi-center prospective study with a large sample size remains to be conducted.

In conclusion, MS-ON is likely to be misdiagnosed as NMO-ON, followed by optic nerve damage caused by autoimmune diseases, malignant tumors and ischemic optic neuropathy. Early differential di-

agnosis of MS-ON from alternative diseases contributes to the treatment and prognosis of MS-ON.

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