·CASE ANALYSIS· ·临床病例讨论·

A case report of atypical optic neuritis

XI Lei, LI Juan, CHEN Xiaojun, FEI Wenlei

[Department of Ophthalmology, Guangdong Provincial People's Hospital (Guangdong Academy of Medical Sciences), Southern Medical University, Guangzhou 510060, China]

ABSTRACT Optic neuritis is a severe blinding ocular disease, and identifying its etiology is crucial for selecting appropriate treatment strategies and evaluating patient prognosis. This paper reports the clinical data of a patient initially presenting with unilateral visual decline who was ultimately diagnosed with bilateral atypical optic neuritis. The patient was a 40-year-old male who presented with decreased vision in the left eye for 2 weeks. Fundus examination at admission revealed bilateral optic disc edema, leading to a diagnosis of bilateral atypical optic neuritis. Systemic examination showed a positive Treponema pallidum particle agglutination test. After a series of serological and cerebrospinal fluid examinations for syphilis, syphilitic optic neuritis was excluded. The patient showed a poor response to conventional treatment for optic neuritis. Further comprehensive brain and ocular examinations were performed. After excluding multiple possible causes of optic neuritis, mitochondrial gene testing ultimately confirmed the diagnosis of Leber hereditary optic neuropathy (LHON). For young male patients presenting with acute vision loss, bilateral involvement, and typical fundus findings, etiological investigation should be emphasized, particularly the application of genetic testing, to achieve early diagnosis and timely treatment.

KEY WORDS optic neuritis, atypical; optic disc edema; syphilis; Leber hereditary optic neuropathy

非典型视神经炎1例

席蕾，李娟，陈晓君，费文雷

[南方医科大学附属广东省人民医院(广东省医学科学院)眼科，广州 510060]

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First author: XI Lei, Email: xilei@gdph.org.cn, ORCID: 0000-0002-8403-910X

Corresponding author: XI Lei, associate chief physician, Email: xilei@gdph.org.cn, ORCID: 0000-0002-8403-910X

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[摘 要] 视神经炎作为一种严重的致盲性眼病，明确病因对于选择适当的治疗方案及评估患者预后具有重要意义。本文报告1例因单眼视力下降诊断为双眼非典型视神经炎患者的临床资料。患者为40岁男性，主诉为左眼视力下降持续2周，入院时体检发现双眼视盘水肿，被诊断为双眼非典型视神经炎。全身检查发现血清梅毒螺旋体颗粒凝集试验呈阳性。在进行一系列血清学及脑脊液的梅毒检查后，排除了梅毒性视神经炎的可能。按照常规治疗视神经炎的方法效果不佳。进一步完善脑部及眼部检查，在排除多种可能的视神经炎病因后，最终通过线粒体基因检测确诊为Leber遗传性视神经病变(Leber hereditary optic neuropathy，LHON)。对于出现急性视力下降且双眼受累、眼底表现典型的年轻男性患者，应高度重视病因学检查，尤其是基因检测的应用，以便实现早期诊断并开展早期治疗。

[关键词] 视神经炎，非典型；视盘水肿；梅毒；Leber遗传性视神经病变

Optic neuritis, one of the most common vision-threatening optic nerve disorder in young and middle-aged individuals, refers to a group of inflammatory conditions affecting the optic nerve[1]. Based on various factors such as etiology, clinical presentation, affected site, and recovery, optic neuritis can be classified into different types. Clinically, optic neuritis is divided into typical and atypical forms[1-3]. Typical optic neuritis is often self-limiting and carries a risk of developing into multiple sclerosis (MS) after an episode[4]. In contrast, atypical optic neuritis may or may not be associated with systemic diseases and is not necessarily linked to MS. Clinically, MS-related optic neuritis (MS-ON) is diagnosed and subsequently treated with appropriate preventive measures, while atypical optic neuritis requires a more comprehensive etiological workup[2]. Early identification of the underlying cause, accurate diagnosis, and personalized treatment can help reduce vision loss and improve the quality of life in patients with optic neuritis. This study reports the clinical data of a patient diagnosed with bilateral atypical optic neuritis who presented with monocular visual acuity loss, with the aim of improving clinicians' understanding of atypical optic neuritis and emphasizing the importance of timely etiological investigation and individualized management.

1 Case presentation

A 40-year-old male patient presented with a 2-week history of left-eye vision loss and a sensation of a black shadow obstructing his vision. The patient reported a sudden onset of vision loss in the left eye, accompanied by the sensation of a black shadow, but without ocular pain during eye movements. He had no significant medical, surgical, or trauma history, and had not experienced any recent infections. One week prior, he was diagnosed with left-eye optic neuritis at another facility but did not receive treatment.

Ophthalmic examination revealed: Right eye visual acuity 20/20, left eye visual acuity 20/40, normal intraocular pressure, and normal color vision in both eyes. Eye movements were normal, and anterior segment examination was unremarkable. Right eye pupils responded normally to direct light, while the left eye showed sluggish pupil light reaction with relative afferent pupillary defect (RAPD). Fundus examination revealed optic disc swelling in both eyes, with a flat retina. Mild optic disc vascular dilatation was noted, and a linear hemorrhage was seen around the left optic nerve head (Figure 1A and 1B). The initial diagnosis was bilateral optic neuritis.

To further clarify the diagnosis, a comprehensive ocular examination was performed. Visual field testing (Figure 2A and 2B) revealed a temporal superior and nasal inferior para-central scotoma in the right eye and widespread visual field defects in the left eye, leaving only a tubular field in the lower part. Fluorescein fundus angiography (FFA) showed early optic disc leakage in the right eye with poorly defined borders in the late phase; in the left eye, the optic disc vessels exhibited weak filling early on with mild leakage and unclear borders in the late phase. No leakage was observed in the macula of either eye (Figure 3). Multifocal electroretinography (mfERG) revealed decreased function of the foveal cone cells in both eyes (Figure 4A and 4B). Pattern visual evoked potential (PVEP) showed normal results in the right eye but decreased amplitude and prolonged latency in the left eye (Figure 5A). Brain and optic nerve enhanced magnetic resonance imaging (MRI) scans showed no significant abnormalities in the brain or optic nerves (Figure 6A). These findings supported the diagnosis of bilateral atypical optic neuritis.

Systemic examination revealed a positive result for

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the *Treponema pallidum* particle agglutination (TPPA) test. Upon further history taking, the patient admitted to a relevant past history but had not received regular treatment. Given this, the possibility of syphilitic optic neuritis was considered. After a consultation with the neurology department, the patient was advised to undergo enhanced magnetic resonance angiography (MRA) of the brain. Additionally, to rule out an infectious etiology, lumbar puncture was performed to analyze cerebrospinal fluid (CSF).

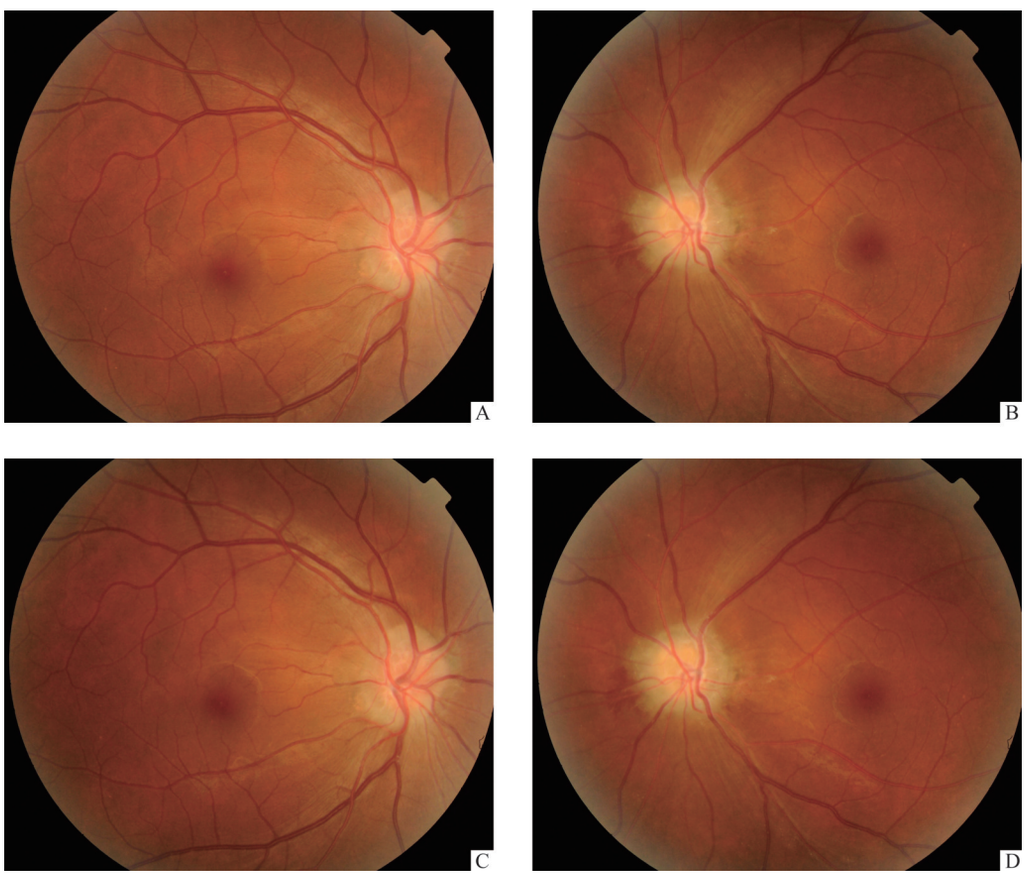


Figure 1 Fundus photography of both eyes

A: On admission, optic disc edema was observed in the right eye with unclear borders. The retina was flat at the posterior pole and no obvious abnormality was found in the macular area. B: On admission, optic disc edema was observed in the left eye with unclear borders. A small amount of hemorrhage was seen next to the optic nerve. The retina was flat at the posterior pole and no obvious abnormality was found in the macular area. C: After 1 week of treatment, the optic disc boundary of the right eye was unclear and the improvement was not obvious compared with the previous examination. D: After 1 week of treatment, the optic disc boundary of the left eye was unclear and the improvement was not obvious compared with the previous examination.

The patient was initially treated with 80 mg of intravenous steroids and supportive therapy, including vasodilators and neuroprotective agents. Subsequent enhanced MRI and MRA of the brain showed no significant abnormalities. No abnormalities were found in the orbit or optic nerves, and no white matter lesions or brain parenchymal changes were observed. Digital subtraction angiography (DSA) showed no significant findings (Figure 6B). Further serological testing for syphilis-specific antibodies showed TPPA positive (1: 1 280), but the rapid plasma reagin (RPR) test was negative. Lumbar puncture revealed normal intracranial pressure and no abnormalities in CSF routine, biochemical, or smear tests. Syphilis IgG, IgM, and venereal disease research laboratory (VDRL) tests were all negative, thus ruling out syphilitic optic neuritis.

Given the inability to rule out idiopathic optic neuritis, further serum testing for specific antibodies related to central nervous system demyelinating diseases was performed. Using a cell-based assay (CBA) method,

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antibodies against aquaporin-4 (AQP4), myelin oligodendrocyte glycoprotein (MOG), and myelin basic protein (MBP) were all negative (Figure 7). Finally, genetic testing revealed a mutation at the *T14484C* locus, leading to a diagnosis of Leber hereditary optic neuropathy (LHON).

After 1 week of steroid treatment, the patient reported slight improvement in left-eye vision and a reduction in the sensation of the black shadow, though it had not completely resolved. On re-examination: Right eye visual acuity 20/20, left eye visual acuity 20/25, with no significant abnormalities in the anterior segment. The left eye still exhibited a relative afferent pupillary defect. Fundus examination showed optic disc swelling and mild vascular dilatation in both eyes, with deep hemorrhage on the nasal side of the left optic nerve head. These findings had improved slightly compared to previous examinations (Figure 1C and 1D). Visual field (Figure 2C and 2D), mFERG (Figure 4C and 4D), and PVEP results (Figure 5B) showed slight improvement.

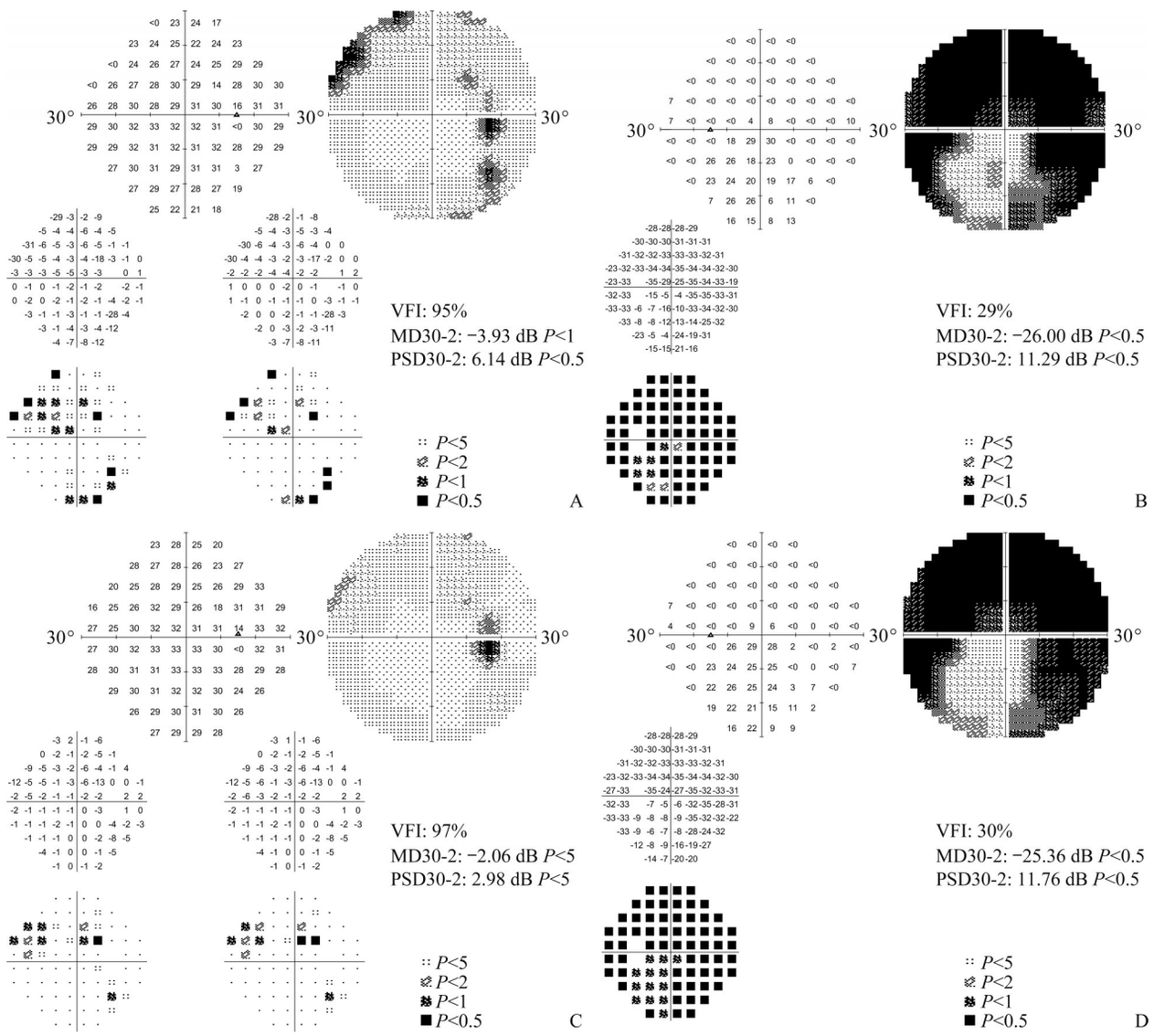


Figure 2 Visual field test of both eyes

A: On admission, the right eye has a paracentral dark spot in the upper and lower central visual field. B: On admission, the left eye has residual tubular vision in the central field of vision. C: After 1 week of treatment, the right eye has a paracentral dark spot in the upper central visual field, which is slightly improved compared with the previous examination. D: After 1 week of treatment, the left eye has residual tubular vision in the central field of vision, which is slightly improved compared with the previous examination. VFI: Visual field index; MD: Mean deviation; PSD: Pattern standard deviation

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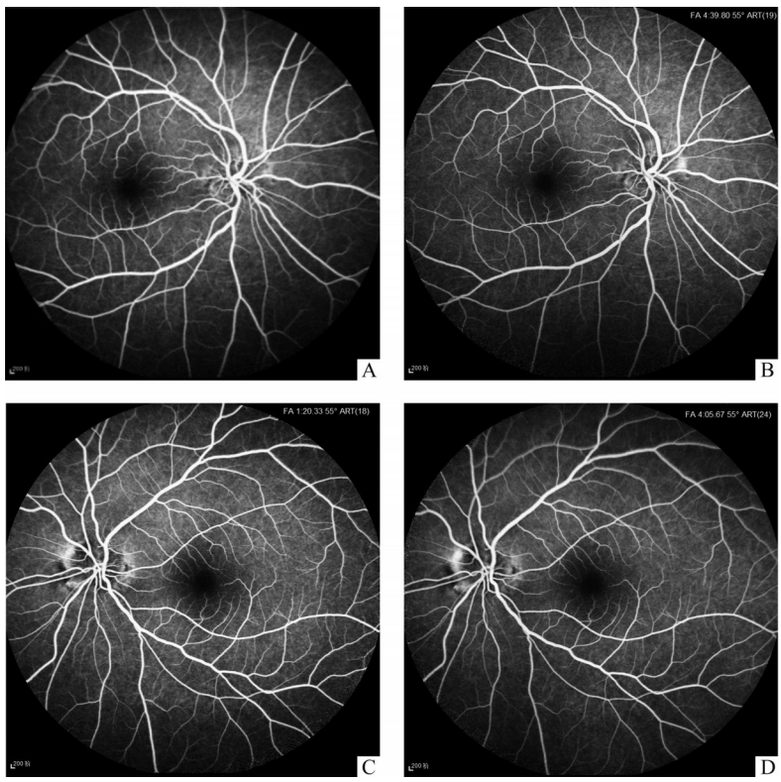


Figure 3 Fundus fluorescein angiography of both eyes at admission

A: Fundus fluorescein angiography shows fluorescence leakage from the optic disc of the right eye in the early stage. B: Fundus fluorescein angiography shows blurred optic disc border in the late stage. C: Fundus fluorescein angiography shows the blood vessels on the surface of the left optic disc are weakly filled in the early stage. D: Fundus fluorescein angiography shows mild fluorescence leakage from the optic disc of the left eye in the late stage with unclear boundaries.

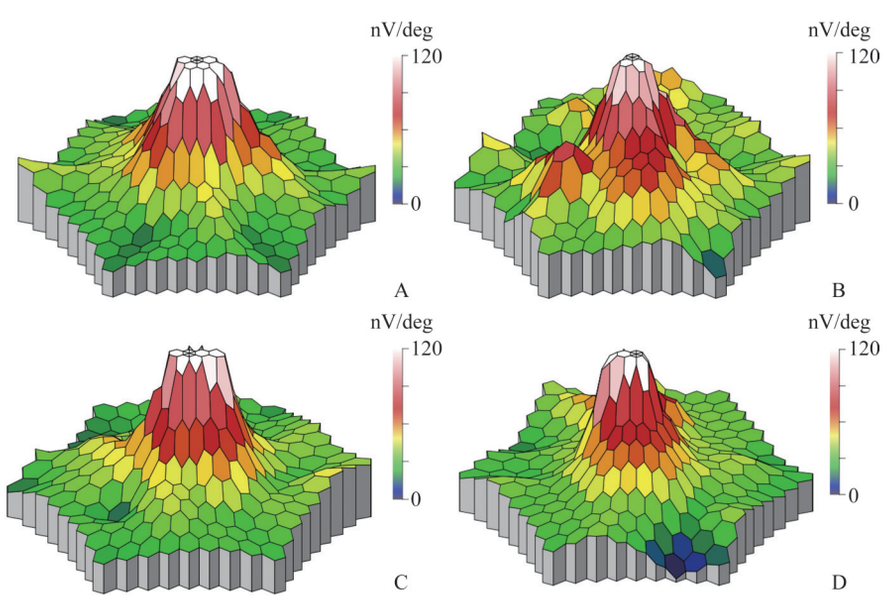
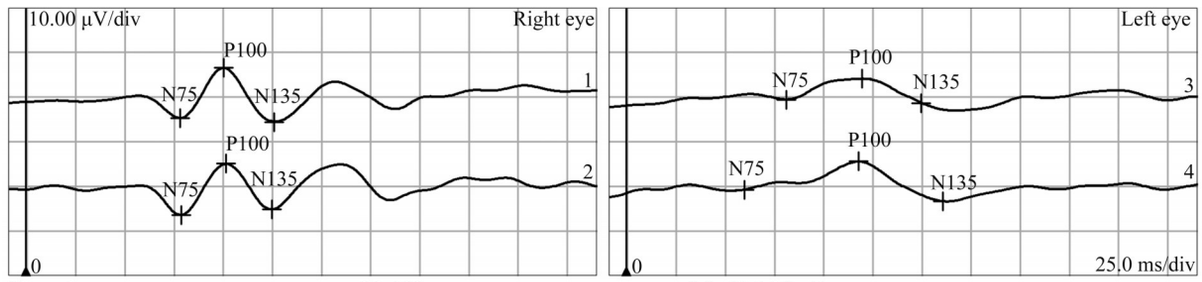


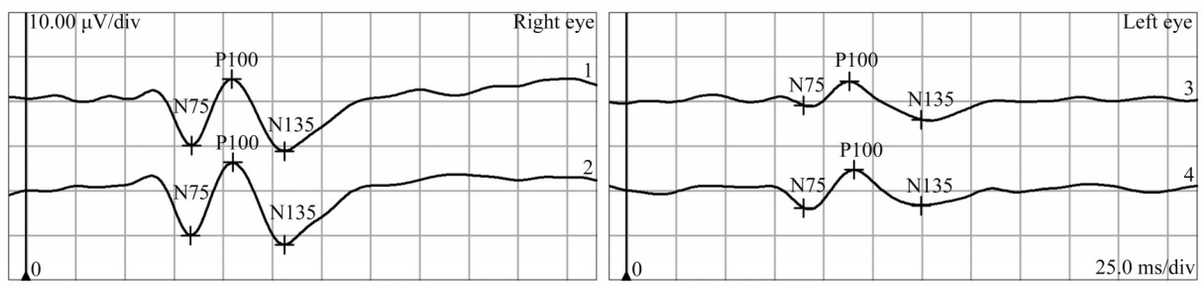
Figure 4 mfERG of both eyes

A: mfERG shows decreased cone function of the fovea in the right eye at admission. B: mfERG shows decreased cone function of the fovea in the left eye at admission. C: After 1 week of treatment, mfERG shows no obvious improvement in cone function of the fovea in the right eye. D: After 1 week of treatment, mfERG shows no obvious improvement in cone function of the fovea in the left eye. mfERG: Multifocal electroretinogram.

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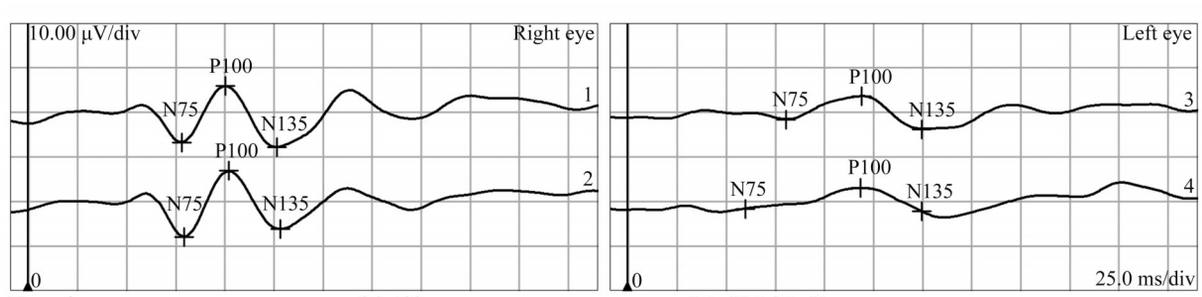


Normals	-	96−109	-	7.7 μV−16.7 μV	
Channel	N75 [ms]	P100 [ms]	N135 [ms]	N75-P100	P100-N135
1 R1 1, 0 deg	78.7	101.0	126.8	11.4 μV	12.1 μV
2 R1 1, 0 deg	79.3	102.2	125.6	11.5 μV	10.3 μV
3 L1 1, 0 deg	81.6	120.4 (!)	150.3	4.8 μV (!)	5.5 μV
4 L1 1, 0 deg	60.5	118.6 (!)	161.4	6.4 μV (!)	9 μV

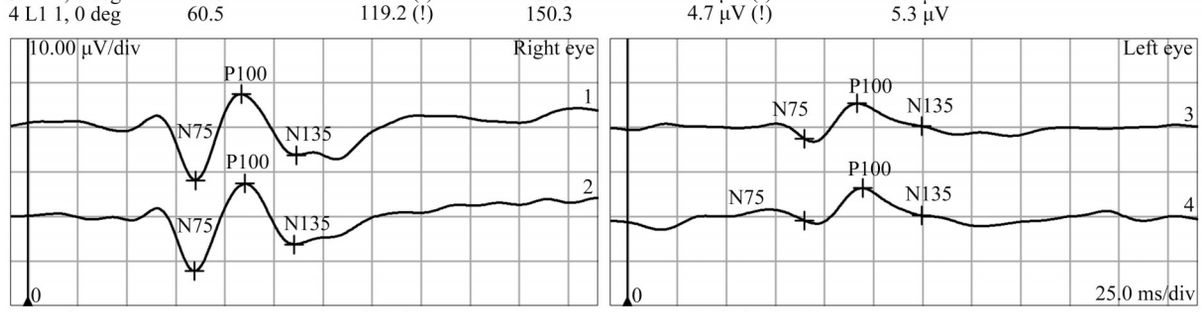


Normals	-	105−121	-	7 μV−42.6 μV	
Channel	N75 [ms]	P100 [ms]	N135 [ms]	N75-P100	P100-N135
1 R1 15 min	84.5	105.1	132.1	14.9 μV	16.2 μV
2 R1 15 min	84.0	105.7	132.1	16.3 μV	18.4 μV
3 L1 15 min	90.4	113.9	150.3	5.4 μV (!)	8.6 μV
4 L1 15 min	90.4	116.2	150.3	8.5 μV	8 μV

A



Normals	-	96−109	-	7.7 μV−16.7 μV	
Channel	N75 [ms]	P100 [ms]	N135 [ms]	N75-P100	P100-N135
1 R1 1, 0 deg	78.7	101.0	127.4	12.7 μV	13.8 μV
2 R1 1, 0 deg	79.8	102.7	129.2	14.8 μV	13.1 μV
3 L1 1, 0 deg	81.0	119.8 (!)	150.3	5.3 μV (!)	7.4 μV
4 L1 1, 0 deg	60.5	119.2 (!)	150.3	4.7 μV (!)	5.3 μV



Normals	-	105−121	-	7 μV−42.6 μV	
Channel	N75 [ms]	P100 [ms]	N135 [ms]	N75-P100	P100-N135
1 R1 15 min	85.7	109.2	137.4	19.4 μV	13.8 μV
2 R1 15 min	85.1	111.0	136.2	19.7 μV	13.7 μV
3 L1 15 min	90.4	117.4	150.3	8 μV	5.1 μV
4 L1 15 min	90.4	120.4	150.3	7.4 μV	6.2 μV

B

Figure 5 PVEP of both eyes

A: PVEP shows normal results in the right eye, P100 amplitude is reduced and the latency is prolonged in the left eye at admission. B: After 1 week of treatment, the PVEP of the right eye is normal, and the decreased amplitude and prolonged latency of the P100 in the left eye are improved compared with the previous examination. PVEP: Pattern visual evoked potential.

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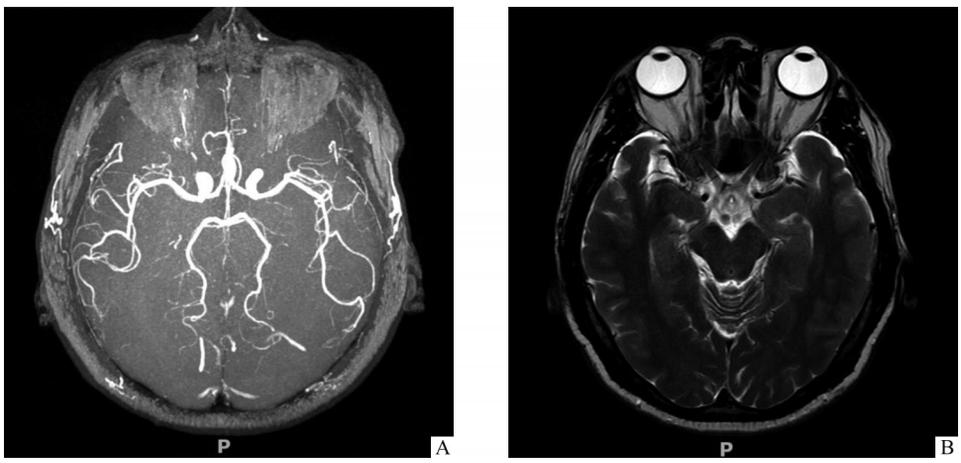


Figure 6 Enhanced MRI and MRA scan of the head and optic nerves

A: No significant result is observed in head and optic nerves enhanced MRI. B: No significant result is observed in head MRA. MRI: Magnetic resonance imaging; MRA: Magnetic resonance angiography.

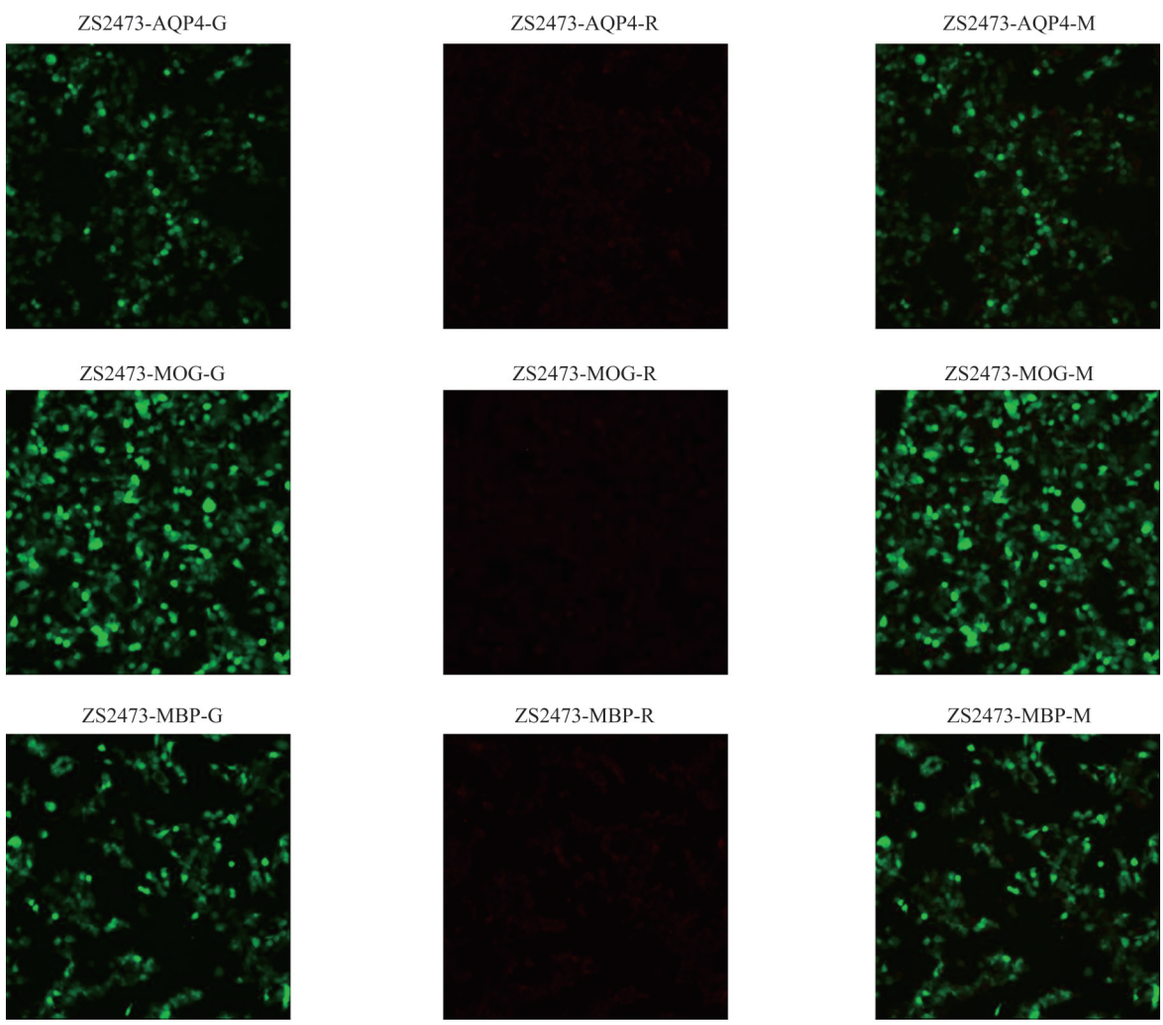


Figure 7 Detection of antibodies to demyelinating diseases of the central nervous system (×400)

AQP4: Anti-aquaporin 4; MOG: Anti-myelin oligodendrocyte glycoprotein; MBP: Anti-myelin basic protein.

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2 Discussion

Optic neuritis, a condition characterized by inflammation of the optic nerve, typically presents as subacute, unilateral, painful vision loss[3]. It can be classified into various types. According to the Chinese expert consensus on the diagnosis and treatment of optic neuritis (2014)[5], optic neuritis can be categorized into four types based on etiology: Idiopathic, infectious and infectious-related, autoimmune, and unclassified optic neuritis. The etiological diagnosis of optic neuritis determines the treatment regimen, duration, and prognosis for the patient. However, the clinical manifestations of different types of optic neuritis are often similar and can be confusing, especially in the case of atypical optic neuritis, where treatment and prognosis are closely tied to the underlying cause[3, 6-8]. Therefore, a comprehensive diagnostic approach is required for differential diagnosis.

Among the various types, syphilitic optic neuritis (SON) has been increasing in incidence in recent years. It presents with highly variable clinical manifestations, often insidiously, and can mimic various infectious and autoimmune optic neuritis conditions. This makes it prone to misdiagnosis and missed diagnosis, warranting attention. According to the 2022 Expert Consensus on the Diagnosis and Treatment of Syphilitic Optic Neuritis in China[7], the diagnosis of syphilitic optic neuritis requires the inclusion of non-treponemal tests (NTT) such as the VDRL slide test, RPR test, and the toluidine red unheated serum test (TRUST). Additionally, positive results in treponemal tests such as the fluorescent treponemal antibody absorption test (FTA-ABS), TPPA, treponemal particle agglutination test (TPHA), enzyme-linked immunosorbent assay (ELISA), and chemiluminescent immunoassay (CLIA) are required. Finally, syphilitic serology test of CSF must also be positive. However, it is important to note that in a small number of late-stage cases, NTT may yield negative results. Furthermore, given the diverse imaging findings in SON patients, both CT and MRI cannot provide direct diagnostic evidence. Therefore, if SON is suspected, comprehensive syphilis serological testing should be performed, and the diagnosis should ultimately be confirmed through CSF analysis.

In the case of our patient, after completing the necessary tests, we found a positive result in the treponemal test (TT), a negative result in the NTT, and no abnormalities in the CSF, thus excluding syphilitic optic neuritis. However, since the patient's brain MRI showed no obvious demyelinating changes, and anti-demyelinating optic neuritis antibodies were negative, we did not consider demyelinating optic neuritis (DON). Given the patient's normal systemic infection markers, infectious optic neuritis was also unlikely. Furthermore, the ocular examination did not show findings consistent with ischemic optic neuropathy.

Considering the patient's age, the acute vision loss in the left eye, bilateral optic disc swelling, and central visual field defects in both eyes, we proceeded with routine tests, which did not reveal clear ocular or neurological causes. Therefore, we considered the possibility of LHON and performed mitochondrial genetic testing. Ultimately, the diagnosis of LHON was confirmed through the relevant genetic testing.

LHON is a rare, genetic optic neuropathy caused by mutations in mitochondrial DNA (mtDNA)[9-10]. Due to the heterogeneity in its clinical presentation, the age of onset, type of mutation, disease progression, and prognosis can vary significantly among patients. In the early stages, the clinical manifestations are non-specific. Typically, it presents as acute or subacute vision loss in one eye in young adult males, often progressing to involve the other eye within a few weeks to months. Some patients may have mild symptoms, while others may experience rapid progression to severe vision loss. Additionally, due to its maternal inheritance pattern, many patients do not have a family history, though vision loss is common in young males. While LHON may show signs of optic disc congestion, capillary dilation, and other changes in the acute phase, these ocular and systemic findings are not specific to LHON, making diagnosis reliant on genetic testing. Consequently, LHON is difficult to identify in its early stages.

In summary, when young patients, especially males, present with acute or subacute vision loss, with bilateral involvement occurring sequentially or simultaneously, and exhibit atypical optic neuritis fundus findings, but routine examinations do not reveal obvious ocular or neurological causes, LHON should be considered regardless of family history. Genetic testing

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is recommended for early diagnosis and prompt treatment.

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Conflict of interest: The authors declare that they have no conflicts of interest to disclose.

References

[1] Spillers NJ, Luther PM, Talbot NC, et al. A comparative review of typical and atypical optic neuritis: advancements in treatments, diagnostics, and prognosis[J/OL]. Cureus, 2024, 16 (3): e56094[2024-12-02]. https://doi.org/10.7759/cureus.56094.

[2] Sarkar P, Mehtani A, Gandhi HC, et al. Atypical optic neuritis: an overview[J]. Indian J Ophthalmol, 2021, 69(1): 27-35. https://doi.org/10.4103/ijo.IJO_451_20.

[3] Jamali Dogahe S, Pakravan P, Pakravan M. Acute optic neuritis: an update on approach and management[J]. J Ophthalmic Vis Res, 2023, 18(4): 433-440. https://doi.org/10.18502/jovr.v18i4.14556.

[4] Abel A, McClelland C, Lee MS. Critical review: Typical and atypical optic neuritis[J]. Surv Ophthalmol, 2019, 64(6): 770-779. https://doi.org/10.1016/j.survophthal.2019.06.001.

[5] 中华医学会眼科学分会神经眼科学组. 视神经炎诊断和治疗专家共识(2014年)[J]. 中华眼科杂志, 2014, 50(6): 459-463. https://doi.org/10.3760/cma.j.issn.0412-4081.2014.06.013.
Neuro-Ophthalmology Group of the Chinese Ophthalmological Society. Diagnosis and treatment of optic neuritis expert consensus (2014)[J]. Chinese Journal of Ophthalmology, 2014, 6: 459-463. https://doi.org/10.3760/cma.j.issn.0412-4081.2014.06.013.

[6] Petzold A, Fraser CL, Abegg M, et al. Diagnosis and classification of optic neuritis[J]. Lancet Neurol, 2022, 21(12): 1120-1134. https://doi.org/10.1016/S1474-4422(22)00200-9.

[7] 中华医学会眼科学分会神经眼科学组. 梅毒性视神经炎诊断和治疗专家共识(2022)[J]. 中华实验眼科杂志, 2022, 40(8): 695-700. https://doi.org/10.3760/cma.j.cn511434-20221107-00589.
Neuro-Ophthalmology Group of the Chinese Ophthalmological Society. Expert consensus on diagnosis and treatment of syphilitic optic neuritis[J]. Chinese Journal of Ophthalmology, 2022, 40(8): 695-700. https://doi.org/10.3760/cma.j.cn511434-20221107-00589.

[8] 中华医学会眼科学分会神经眼科学组, 兰州大学循证医学中心/世界卫生组织指南实施与知识转化合作中心. 中国脱髓鞘性视神经炎诊断和治疗循证指南(2021年)[J]. 中华眼科杂志, 2021, 57(3): 171-186. https://doi.org/10.3760/cma.j.cn112142-20201124-00769.
Neuro-ophthalmology Group of Ophthalmology Branch of Chinese Medical Association, Evidence-based Medicine Center of Lanzhou University/World Health Organization Collaborating Centre for Guideline Implementation and Knowledge Translation. Evidence-based guidelines for diagnosis and treatment of demyelinating optic neuritis in China(2021)[J]. Chinese Journal of Ophthalmology, 2021, 57 (3): 171-186. https://doi.org/10.3760/cma.j.cn112142-20201124-00769.

[9] Morgia CL, Cascavilla ML, De Negri AM, et al. Recognizing Leber's Hereditary Optic Neuropathy to avoid delayed diagnosis and misdiagnosis[J]. Front Neurol, 2024, 15: 1466275. https://doi.org/10.3389/fneur.2024.1466275.

[10] Tăbăcaru B, Stanca HT. Further advances in the diagnosis and treatment of Leber's Hereditary Optic Neuropathy-a review[J]. Rom J Ophthalmol, 2022, 66(1): 13-16. https://doi.org/10.22336/rjo.2022.4.

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