Article

Discovery Medicine 2024; 36(188): 1891–1901
https://doi.org/10.24976/Discov.Med.202436188.175

A Comparison between Demyelinating and Omicron Variant Infection-Associated Optic Neuritis

Jing Zhang[1,2], Lian Wang[2], Chunli Chen[1], Haitao Ren[3], Miao Jin[1], Hongjuan Liu[1], Bentao Yang[4], Zhiqin Huang[1], Libin Jiang[1,*], Fred Kuanfu Chen[5,6]

[1]Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Key Laboratory of Ophthalmology and Visual Science, 100730 Beijing, China
[2]Department of Ophthalmology, Beijing Puren Hospital, 100062 Beijing, China
[3]Department of Neurology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 100730 Beijing, China
[4]Department of Radiology, Beijing Tongren Hospital, Capital Medical University, 100730 Beijing, China
[5]Centre for Ophthalmology and Visual Science (Lions Eye Institute), The University of Western Australia, Nedlands, WA 6009, Australia
[6]Ophthalmology, Department of Surgery, University of Melbourne, East Melbourne, VIC 3002, Australia
*Correspondence: jlbjlb@sina.com (Libin Jiang)
Published: 20 September 2024

Background: The connection between viral infection and the onset of demyelination has garnered considerable attention. Omicron, the most recent prevalent strain of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has raised concerns. Optic neuritis (ON) associated with Omicron infection and spontaneous demyelinating ON may manifest distinct disease progressions. This study aims to contrast the features of these two distinct etiologies of ON.

Methods: This case-control study comprised fifteen patients (21 eyes) diagnosed with Omicron infection-related ON and fifteen patients (24 eyes) with demyelinating ON serving as the control group. Clinical characteristics, cerebrospinal fluid (CSF) analysis, treatment protocols, and outcomes were compared between the two groups.

Results: The Omicron-infected group exhibited a higher incidence of pain upon ocular movement ($p = 0.023$) and peripapillary hemorrhages ($p = 0.046$). In CSF analysis, there was an elevation in white cell counts (WCCs) ($p = 0.004$), with lymphocytes being the predominant cell type in the Omicron-related ON group. However, oligoclonal bands (OCBs), indicative of intrathecal synthesis, were significantly lower and lagged behind those of the demyelinating ON group ($p = 0.021$). SARS-CoV-2 RNA was not directly detected in the CSF of the Omicron-related ON group, and the degree of WCC elevation was closely linked with peripapillary hemorrhages (odds ratio = 0.029, $p = 0.02$). Additionally, the Omicron-related ON group displayed more pronounced ganglion cell loss following 3-month treatment ($p = 0.02$).

Conclusion: Omicron-related ON is distinguished by more pronounced clinical symptoms and distinct CSF characteristics compared to spontaneous demyelinating ON. The absence of viral RNA sequence in the CSF of Omicron-associated ON supports the use of steroid monotherapy; however, varying treatment options and prognoses should be considered for these two types of ON.

Keywords: demyelinated optic neuritis; Omicron variant infection; cerebrospinal fluid; imaging findings; pathogenesis and outcomes

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has undergone evolutionary changes from the Alpha, Beta, Gamma, and Delta to the Omicron variant. The Omicron strain is distinguished by reduced pathogenicity and increased contagiousness, differing from strains identified before 2021 [1]. In 2022, the Omicron variant emerged as the predominant strain, exhibiting strong replication capacity within the upper respiratory tract [2]. In December 2022, prevention and control policies in China were relaxed, coinciding with the Omicron outbreak, which resulted in 82% of the population being infected within two months [3]. This surge in cases led to a notable rise in para-infectious or post-infectious central nervous system (CNS) diseases, including encephalitis, encephalomyelitis, and longitudinally extensive transverse myelitis [4]. However, features of optic neuritis (ON) related to Omicron variant infection, particularly cerebrospinal fluid (CSF) analysis, were rarely reported. This has left the pathogenesis and relationship between the Omicron variant and demyelinated ON unclear.

Evidence suggests that certain viral infections can induce demyelination [5]. The Epstein-Barr virus and influenza virus, have been identified to link to multiple sclerosis (MS) [6] and may lead to ON attack by activating a variety of inflammatory cells. In an experimental model, Shindler *et al.* [7] demonstrated that infection with the

mouse hepatitis virus strain MHV-A59 could induce inflammatory demyelinating ON. In contrast, MHV-2, a non-demyelinating strain, did not trigger ON. It is well known that the Omicron strain is more infectious than previous strains. Therefore, we speculate that different strains of SARS-CoV-2 may have varying inflammatory effects on the CNS.

There is a marked surge in demyelinated ON cases during Omicron infection pandemics [8]. However, whether Omicron infection-related ON and demyelinating ON are coincidental remains unclear. Moreover, whether different treatment strategies and prognoses exist between the two groups remains confusing to physicians. This study aimed to compare the clinical presentation, CSF features, therapy, and prognosis of Omicron-related ON with a matched control group of demyelinating ON without prior viral infection, and discuss the underlying pathogenesis.

Materials and Methods

Study Participants and Clinical Presentation

This observational case-control study comprised a total of 30 individuals (45 eyes) recruited from the Neuro-Ophthalmology Department of Beijing Tongren Hospital, Capital Medical University. Fifteen cases (21 eyes) presented with Omicron-related ON between December 2022 and January 2023, among these, 9 were female, mean age was 39 $\pm$ 17 years. The average interval from the onset of Omicron infection to the first manifestation of ON was 13 days, ranging from 2–29 days. The control group comprised fifteen patients (24 eyes) with acute demyelinating ON, occurring within one month of symptom onset from January 2022 to May 2023, including 9 females, with a mean age of 44 $\pm$ 18 years and without a history of prior viral infection. Fig. 1 illustrates the patient selection process.

All enrolled patients met the definitive ON diagnosis criteria based on the latest 2022 international guidelines [9]: Clinical criteria A: Monocular, subacute vision loss associated with orbital pain worsening on eye movements, reduced contrast and color vision, and relative afferent pupillary deficit, with one positive paraclinical test (magnetic resonance imaging (MRI), optical coherence tomography (OCT) or biomarker); Clinical criteria B: Painless with all other features of (A); and clinical criteria C: Binocular vision loss with all (A) features, combined with two positive paraclinical tests of which one was MRI.

Fundus fluorescein angiography and other examinations were selected to exclude fundus diseases. Patients with neuroretinopathy or optic neuropathy resulting from ischemic, traumatic, compressive, toxic, genetic, or inorganic causes of visual loss were excluded. Furthermore, additional potential infectious causes, such as syphilis, tuberculosis, viral hepatitis B and C, Epstein-Barr virus, human immunodeficiency virus, herpes virus, cytomegalovirus, and similar conditions, were all ruled out.

Patients infected with the Omicron variant presented with symptoms such as fever, chills, sore throat, dry cough, and altered taste or smell, with no requirement for hospitalization. Confirmation of SARS-CoV-2 infection was achieved through nucleic acid polymerase chain reaction (PCR) tests or antigen detection using nasopharyngeal/oropharyngeal swabs [10]. These infected patients had no personal or family history of demyelinating or autoimmune disorders (Fig. 1).

Treatment for all patients involved intravenous methylprednisolone pulse (IVMP) administered at 1.0 g/d for 3–5 days, followed by a gradual tapering of an oral prednisone regimen (1 mg/kg/day). Immunosuppressants were added for cases positive for aquaporin-4-immunoglobulin G (AQP4-IgG). In one case, plasma exchange was combined with this treatment. Visual acuity tests and OCT were conducted at 1 week and 3 months post-IVMP, with long-term follow-up.

Data Collection

Demographics, medical histories, symptoms, signs, chest computed tomography (CT) scans, MRI images (orbital, intracranial, and spinal cord), routine blood tests, and erythrocyte sedimentation rate (ESR) were reviewed and recorded. Serum aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) IgG tests were conducted at Guangzhou V-Medical Laboratory Co., Ltd. in Guangzhou, China using cell-based assays (CBA). Samples with titers of 1:10 underwent two separate measurements for validation. Furthermore, CSF analysis was carried out, including routine cell counts, biochemical assessments, and cytological examinations stained with the May-Grünwald-Giemsa (MGG) procedure using the natural precipitation method. Other CSF assays included tests for oligoclonal bands (OCBs), myelin basic protein (MBP), 24-hour IgG synthesis rate, and pathogen staining and culture. SARS-CoV-2 RNA detection was performed using metagenomic next-generation sequencing (mNGS) [11]. CSF results were analyzed in 11 patients in the Omicron group, 4 patients refused to undergo lumbar puncture. A total of 14 patients received serum and orbital MRI, serum results of 14 cases and 19 eyes of orbital MRI were statistically analyzed in the Omicron group. In control group, there were 15 cases in CSF and serum results, 15 cases (24 eyes) of orbital MRI were compared.

Best corrected visual acuity (BCVA) was employed to assess therapeutic effects. BCVA was converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses. LogMAR values of 2.9, 2.6, 2.3, and 2.0 were designated to correspond with no light perception (NLP), light perception (LP), hand movement (HM), and finger counting (FC), respectively [12]. Visual acuity (logMAR) $\geq$2.0 after a three-month treatment duration indicated an unfavorable visual outcome.

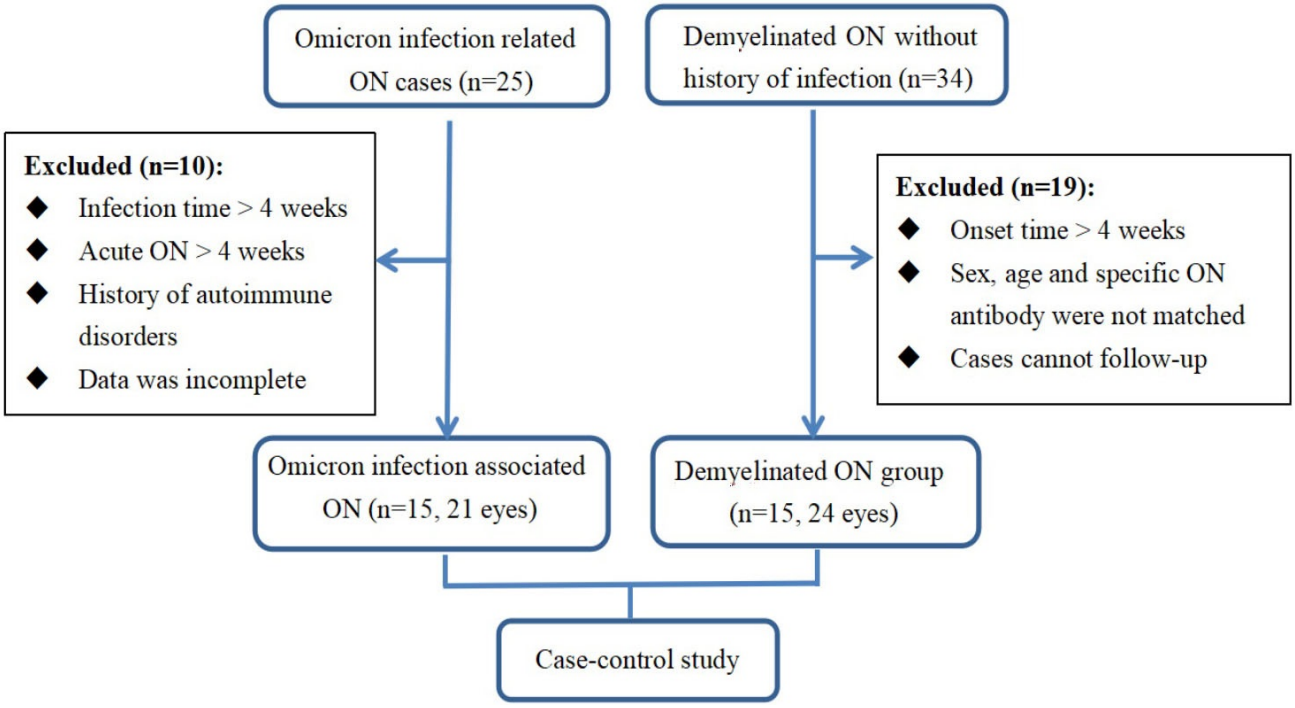

Fig. 1. Study flowchart of enrolled patients in this study. Note: Participants were recruited from the Neuro-Ophthalmology Department of Beijing Tongren Hospital, Capital Medical University.

Statistical Analysis

Statistical analysis encompassed various methods tailored to different data types. For continuous data satisfying normal distribution and equal variance assumptions, the independent *t*-test was employed. Conversely, the Mann-Whitney U test was utilized for non-normally distributed continuous data. Categorical data underwent analysis using either the Pearson chi-squared test or Fisher's exact test. Pearson's correlation and logistic regression were utilized to identify factors associated with cell counts in the CSF. Statistical significance was established with a two-tailed *p*-value threshold of <0.05. All statistical procedures were executed using SPSS software version 23.0 (IBM, Beijing, China).

Results

All enrolled patients developed ON within one month, with no significant differences observed in sex, age, and onset time between the two groups ($p > 0.05$). Cases of Omicron-related ON exhibited a higher frequency of pain during eye movement ($p = 0.023$) and peripapillary bleeding ($p = 0.046$). However, no significant differences were observed in the incidence of optic disc edema ($p = 0.565$) or the frequency of bilaterality ($p = 0.466$). Patient characteristics are summarized in Table 1, with additional details provided in Table 2 and Fig. 2A–F.

Lumbar puncture revealed normal CSF opening pressures. Among the Omicron group, 72.7% of patients (8/11) exhibited elevated white cell counts (WCCs), ranging from 5–400 $\times$ 10^6/L. Compared to the demyelinating group, the Omicron-related ON group displayed a distinct elevation in WCCs in the cytological examination ($p = 0.004$), predominantly comprising lymphocytes (Fig. 2I). Protein levels were similarly elevated in both groups ($p = 0.407$), while glucose and chloride levels remained within the normal range. A moderate elevation in WCCs was associated with peripapillary hemorrhage (OR = 0.029, $p = 0.02$, 95% CI: 0.001–0.574). Regarding autoimmune markers, OCB positivity was significantly lower in the Omicron-related ON group compared to the demyelinating ON group ($p = 0.021$). Other markers, such as MBP (9.1%) and the 24-hour intrathecal synthesis rate (27.3%), also displayed lower values in the Omicron-related ON group, without statistical significance. However, SARS-CoV-2 RNA gene sequencing and pathogen cultures in the CSF yielded negative results even during the acute stage (Tables 1,2).

Hematological and imaging assessments revealed no differences between the two groups. ESR levels and complement components were increased to similar degrees in the serum of patients with Omicron-related ON and demyelinating ON ($p = 0.272$ and $p = 0.60$, respectively). Concurrently, serum-specific immune markers for myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG) (20.0%) and AQP4-IgG (20.0%) were identified in the serum of the Omicron-related ON group. Furthermore, 29 patients (43 eyes) underwent an MRI of the orbit, intracranial region, and spinal cord. In the Omicron-related ON group, 78.9% of affected eyes and 66.7% of eyes in

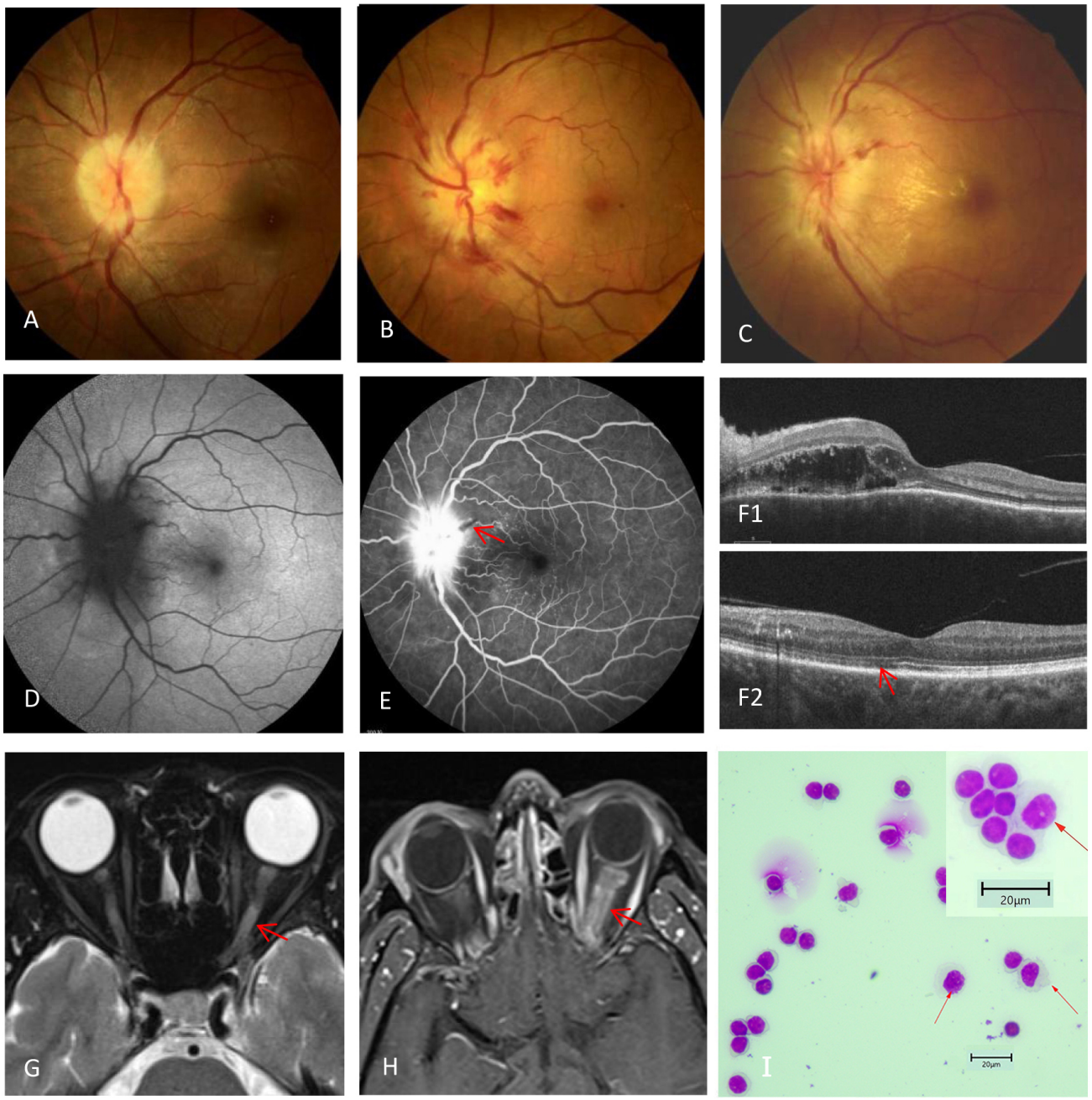

Fig. 2. Fundus and imaging images of SARS-COV-2 Omicron related-ON. (A–C) Fundus images. (A) Optic disc with obvious edema. (B) Edematous optic disc with peripapillary hemorrhage. (C) Edematous optic disc with bleeding and exudative retinal lesions. The bleeding is along the blood vessels and located on the surface of the optic disc, which is gradually absorbed after steroid therapy. (D–F) Retinal images. (D) Fundus autofluorescence image. (E) FFA image. (F) OCT image. There was no autofluorescence in the retina and hyperedema optic disc, the vascular leakage of the optic disc was obvious, and the edematous fluid affected the retina even on the nasal side of the macula (F1), the loss of the retinal outer structure in Omicron-related ON was observed after steroid treatment (F2). (G,H) Orbital MRI imaging (horizontal view). (G) T2WI imaging. (H) T1WI enhanced imaging. The intraorbital segment of the left optic nerve is thickened and significantly enhanced (red arrows in E–H). (I) Cytological microscopic photo of CSF (MGG stain, ×400): lymphocytes of different sizes distributed in clusters. Some were accompanied by activation (red arrow), the activated lymphocytes by partial zoom were shown on the top right of the photo, suggesting lymphocytic inflammation associated with Omicron variant infection. FFA, fundus fluorescence angiography image; OCT, optical coherence tomography; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; MGG, May-Grünwald-Giemsa; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; ON, optic neuritis.

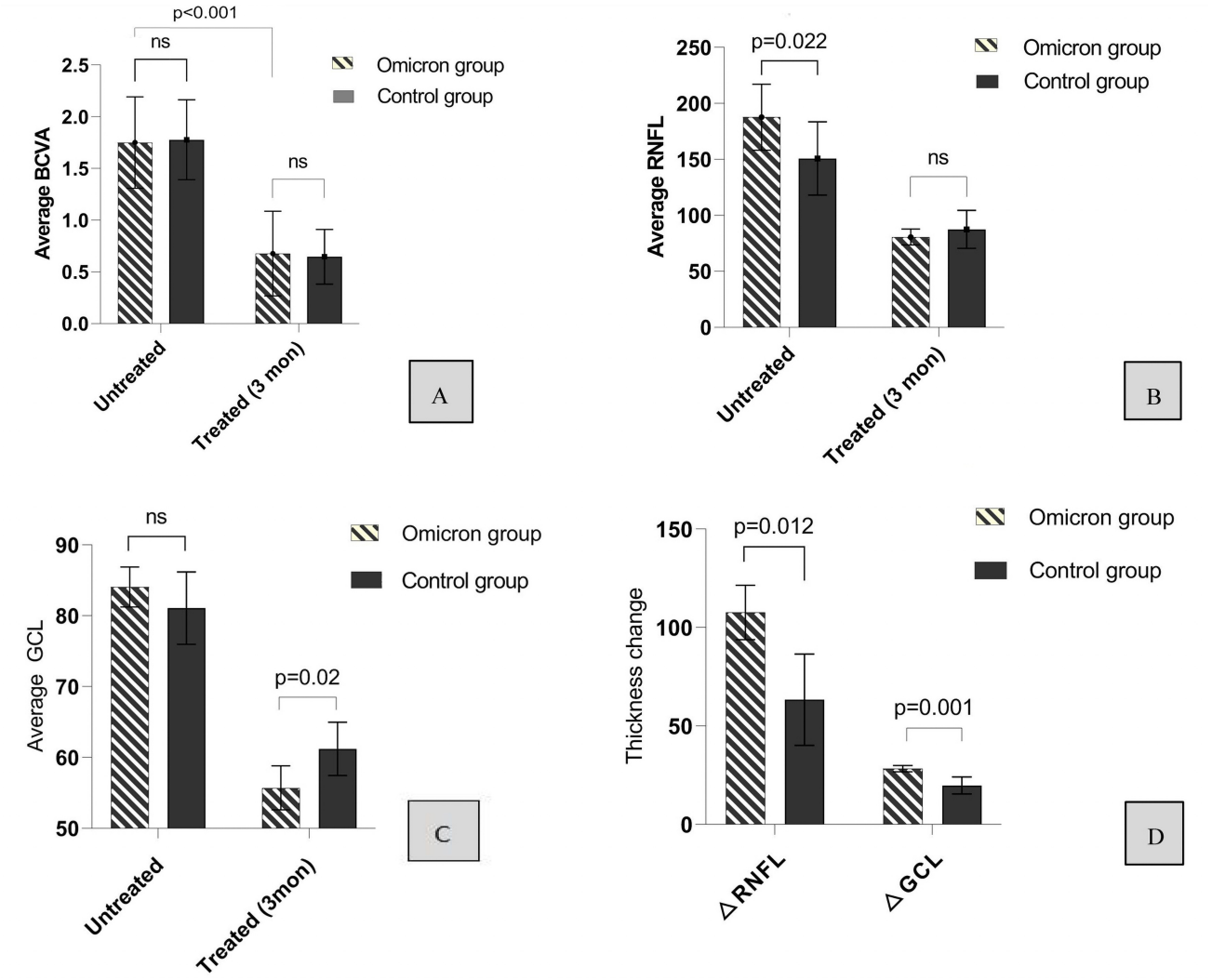

Fig. 3. Comparison of visual acuity and OCT results between the two groups before and after treatment. (A) Compared with the untreated group, visual acuity (BCVA) in the Omicron group improved significantly after 3 months of treatment ($p < 0.001$). However, there was no significant difference in visual acuity before or after treatment between the Omicron group and the control group ($p > 0.05$). (B) The onset of RNFL was significantly higher in the Omicron group ($p = 0.022$). (C) After 3 months of treatment, the thickness of GCL decreased significantly in the Omicron group ($p = 0.020$). (D) ΔRNFL ($p = 0.012$) and ΔGCL ($p = 0.001$) after 3 months of treatment were more significant in the Omicron group. Note: BCVA, best corrected visual acuity; ns, no significance; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; ΔRNFL, the thickness change of RNFL; ΔGCL, the thickness change of GCL.

the demyelinating ON group displayed thickening of the optic nerve's orbital segment with associated enhancement (Fig. 2G,H), but no difference was observed ($p = 0.373$) (Tables 1,2).

All patients received IVMP therapy without antiviral agents. In 66.7% of affected eyes, the nadir visual acuity deteriorated to counting fingers (CF) or below. Notably, compared to the nadir vision, mean visual acuity demonstrated significant improvement at both the 1-week ($p = 0.032$) and 3-month ($p < 0.001$) post-treatment intervals (Table 3). Visual outcomes did not correlate with the extent of WCC elevation in the CSF ($r = 0.422$, $p = 0.196$). The nadir vision and visual outcomes after 3 months in the Omicron-related ON group remained comparable to those in the control group ($p = 0.942$ and $p = 0.500$, respectively) (Table 4 and Fig. 3A).

In the Omicron-related ON group, the thickness of the peripapillary retinal nerve fiber layer (RNFL) at onset was greater than that in the control group ($p = 0.022$) (Fig. 3B). After 3 months of treatment, a more significant decrease in the thickness of the ganglion cell layer (GCL) was observed in the Omicron-related ON group ($p = 0.020$) (Fig. 3C). Furthermore, the changes in RNFL thickness ($p = 0.012$) and the loss of GCL ($p = 0.001$) (Fig. 3D) were more pronounced in the Omicron-related ON group (Table 4).

Table 1. Clinical features, cerebrospinal fluid results, and therapeutic outcomes of patients with Omicron variant of COVID-19-related ON (n = 15).

Cases	Basic clinical features					Blood test		CSF test		Imaging features		Visual acuity (LogMAR) outcomes		
	Sex M/F	Age (y)	Interval time (Days)	Eye pain/affected eye	Edema/ Bleed of OD	Serum Markers, WBC, ESR, Complement	COVID-19 antibody	WCCs/0.5 mL <200), Protein, OCB, MBP, 24-hour IgG	SARS-CoV-2 RNA	Intracranial or spinal lesion	Orbital long T2WI or enhanced MRI	Nadir Vision	1 week after IVMP	3 months after IVMP
1	F	53	3	Y/Bilateral	Y/Y	ESR↑ C4 ↑	IgM +	WCC 3000 ↑, Protein ↑	(-)	(-)	Orbital (+)	R: 0.7	R: 0.22	R: 0.0
											Orbital (+)	L: 0.22	L: 0.1	L: 0.0
2	M	44	2	Y/R	Y/Y	ESR↑ C3 ↑	IgM +	Refusal to check		(-)	Orbital, canal (+)	R: 2.0	R: 1.0	R: 0.22
3	F	21	28	Y/R	Y/N	(-)	IgG +	WCC 600 ↑, OCB (+)	(-)	(-)	Orbital (+)	L: 2.6	L: 0.52	L: 0.22
4	F	75	29	Y/Bilateral	N/N	ESR↑ C4 ↑	IgG +	WCC 200 ↑, Protein ↑, 24 hours IgG (+)	(-)	(-)	Orbital (+)	R: 2.0	R: 0.92	R: 0.52
											Orbital (+)	L: 2.3	L: 2.0	L: 1.0
5	F	35	14	Y/L	N/N	C1q ↑	IgG +	(-)	(-)	(-)	Orbital, canal (+)	L: 2.0	L: 0.0	L: 0.0
6	M	65	21	Y/L	Y/N	(-)	IgM +	WCC 800 ↑, OCB (+), Protein ↑, 24-hour IgG (+)	(-)	Intracranial (+)	Orbital (+) Canal (+)	L: 2.9	L: 2.0	L: 2.0
7	F	50	25	Y/R	Y/N	(-)	IgG +	(-)	(-)	(-)	Orbital (+)	R: 0.52	R: 0.52	R: 0.4
8	F	39	8	Y/Bilateral	Y/Y	MOG-ab (1:10), ESR↑	IgG +	MBP (+)	(-)	(-)	Orbital (-)	R: 2.0	R: 0.7	R: 0.0
											Orbital (+)	L: 2.6	L: 1.0	L: 0.0
9	M	21	7	Y/Bilateral	Y/Y	MOG-ab (1:32) ESR↑ C3↑	IgG +	Refusal to check		NA	NA	R: 0.52	R: 0.5	R: 0.22
												L: 1.0	L: 0.22	L: 0.1
10	M	57	14	Y/Bilateral	N/N	MOG-ab (1:32)	IgG +	WCC 400 ↑, Protein ↑	(-)	Intracranial (+)	Orbital (-)	R: 0.0	R: 0.0	R: 0.0
											Orbital (+)	L: 2.3	L: 0.4	L: 0.22
11	F	36	24	Y/L	N/N	AQP4-ab (1:320) ESR↑	IgG +	WCC 200 ↑	(-)	(-)	Canal (+)	R: 2.3	R: 2.3	R: 0.22
12	F	21	10	N/R	N/N	AQP4-ab (1:100) WBC↑	IgG +	Refusal to check		(-)	Canal (+)	L: 2.3	L: 2.0	L: 2.0
13	M	25	2	Y/L	Y/N	AQP4-ab (1:10) WBC↑	IgM +	WCC 200 ↑	(-)	(-)	Orbital (+)	L: 0.4	L: 0.3	L: 0.22
14	M	32	3	Y/L	Y/N	NA	IgG +	Contraindications to lumbar puncture		Thoracic spinal cord (+)	Orbital (+)	R: 2.6	R: 2.6	R: 2.0
15	F	19	3	N/Bilateral	Y/Y	ESR↑	IgG +	WCC 200 ↑ 24-hour IgG ↑	(-)	Intracranial, spinal cord (+)	Orbital (+)	R: 2.9	R: 2.9	R: 2.6
											Orbital (+)	L: 2.6	L: 2.3	L: 2.3

+, positive; -, negative; ↑, elevated; ON, optic neuritis; CSF, cerebrospinal fluid; logMAR, logarithm of the minimal angle of resolution; ESR, erythrocyte sedimentation rate; WCCs, white cell counts in 0.5 mL cerebrospinal fluid measured by the natural precipitation method; OCB, oligoclonal band; MBP, myelin basic protein; IgG, immunoglobulin G; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2WI, T2 weighted image; MRI, magnetic resonance imaging; IVMP, intravenous methylprednisolone pulse; MOG, myelin oligodendrocyte glycoprotein; NA, not available; AQP4, aquaporin-4; Interval time, Interval between infection and ON onset; OD, optic disc; R, right; L, left; Y, yes; N, no; WBC, white blood cell count; 24-hour IgG, 24-hour IgG intrathecal synthesis rate.

Table 2. Comparison of clinical features, cerebrospinal fluid, serum and imaging results between the Omicron-related ON group and control group.

	Basic information				Clinical features			CSF test					Serum and image results			
Groups	Num (Eye)	Female (N.)	Age (Median)	Onset time (Days)	Bilateral rate (%)	Eye pain* (%)	Edema of OD* (%)	Bleed of OD* (%)	WCCs (%)	Protein (%)	OCB (%)	MBP (%)	24 h intrathecal synthesis rate (%)	Serum anti-AQP4/MOG	ESR Elevated (%)	Complement Elevated (%)	Orbital MRI* (%)
Omicron group	15 (21)	9	39 ± 17 (35)	14 ± 9	6/15 (40.0)	18/21 (85.7)	14/21 (66.7)	8/21 (38.1)	8/11 (72.7)	4/11 (36.4)	2/11 (18.2)	1/11 (9.1)	3/11 (27.3)	3/3	7/14 (50.0)	5/14 (35.7)	15/19 (78.9)
Control group	15 (24)	9	44 ± 18 (38)	16 ± 9	9/15 (60.0)	13/24 (54.2)	14/24 (58.3)	3/24 (12.5)	2/15 (13.3)	3/15 (20.0)	10/15 (66.7)	5/15 (33.3)	4/15 (26.7)	3/3	9/15 (60.0)	6/15 (40.0)	16/24 (66.7)
Test method			t = 0.722	t = 0.530	Fisher test	$\chi^2 = 5.201$	$\chi^2 = 0.331$	$\chi^2 = 3.973$	Fisher test	Fisher test	Fisher test	Fisher test	Fisher test		Fisher test	Fisher test	$\chi^2 = 0.795$
p -value	1.000	1.000	0.446	0.600	0.466	**0.023**	0.565	**0.046**	**0.004**	0.407	**0.021**	0.197	1.000	1.000	0.272	0.600	0.373

Note: * indicate that the number of eyes was used for statistical analysis; OD, optic disc; WCCs, white cell counts in 0.5 mL cerebrospinal fluid measured by the natural precipitation method; OCB, oligoclonal band; MBP, myelin basic protein; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging. For continuous data to meet normal distribution and Levene's test for equality of variances, the independent *t*-test was employed. Categorical data were analyzed using either Pearson's chi-squared test or Fisher's test (n <40 or T <1). Statistical significance was determined with a two-tailed *p*-value threshold of <0.05 and showed with bold font.

Table 3. Comparison of post-treatment vision with baseline vision in the Omicron-related ON group.

	Time	BCVA (mean ± SD, LogMAR)	Mann-Whitney U test *Z*-value	*p*-value
Pre-treatment	Nadir baseline vision	1.75 ± 0.21		
Post-treatment	1-week vision	1.07 ± 0.21	–2.163	**0.032**
	3-month vision	0.68 ± 0.20	–3.489	<**0.001**

Note: BCVA, best corrected visual acuity; the data of the two groups do not fit normal distribution or Levene's test for equality of variances, the Mann-Whitney U test was used for statistical analysis. Statistical significance was determined with a two-tailed *p*-value threshold of <0.05 and showed with bold font.

Table 4. Comparison of vision and OCT outcomes between the Omicron-related ON and control group.

	Visual acuity		OCT (RNFL)			OCT (GCL)		
Groups	Nadir BCVA (Untreated)	3 mon BCVA (Treated)	Onset RNFL (Untreated)	3 mon RNFL (Treated)	ΔRNFL	Onset GCL (Untreated)	3 mon GCL (Treated)	ΔGCL
Omicron ON (Mean ± SD)	1.75 ± 0.21	0.67 ± 0.20	187.76 ± 64.72	80.04 ± 15.71	107.72 ± 63.06	84.08 ± 6.20	51.72 ± 6.82	28.36 ± 7.18
Control group (Mean ± SD)	1.76 ± 0.97	0.64 ± 0.90	150.82 ± 39.19	87.45 ± 0.21	63.36 ± 53.67	81.09 ± 1.82	69.23 ± 8.69	16.86 ± 9.99
Mann-Whitney U test *Z*-value	–0.073	–0.674	–2.283	–0.245	–2.527	–1.305	–2.333	–3.330
p-value	0.942	0.500	**0.022**	0.806	**0.012**	0.192	**0.020**	**0.001**

Note: OCT, optical coherence tomography; RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; ΔRNFL, the thickness change of RNFL; ΔGCL, the thickness change of GCL. These data of two groups do not fit normal distribution or Levene's test for equality of variances, the Mann-Whitney U test was used for statistical analysis. Statistical significance was determined with a two-tailed *p*-value threshold of <0.05 and showed with bold font.

Discussion

SARS-CoV-2 has undergone numerous mutations, with the Omicron variant emerging as the predominant pathogenic strain by 2024. Our study primarily focused on newly diagnosed ON cases during the acute phase of Omicron infection, with a mean interval of 13 days (ranging from 2–29 days). Importantly, this interval was much shorter than the commonly cited six-week threshold, beyond which the association between infection and ON tends to weaken [13]. Clinical features of COVID-19-associated ON have been previously documented. Unlike previous mutation reports, which primarily affected females and often included prominent retinal lesions, especially in hospitalized severe COVID-19 patients [14,15], Omicron variant-related ON showed a female-to-male ratio of 3:2 and infrequent retinal lesions. Moreover, a high incidence of pain during eye movement (86%) and peripapillary hemorrhage (38%) was observed, with 79% of eyes displaying thickening of the intraorbital segment of the optic nerve, mostly in mild infectious cases. These findings highlight the unique clinical characteristics of Omicron-related ON.

CSF analysis is pivotal for assessing infection-associated CNS lesions, yet there are limited CSF reports concerning Omicron-related ON. When the Alpha and Delta variants of COVID-19 were predominant [16–20], seventeen CSF results of ON cases were documented, with only one recording elevated WCCs. In our CSF analysis of Omicron-related ON, an unusual elevation in WCCs was observed in nearly 73% of patients, with elevated protein levels documented in 36.4% of cases. Why do different variants have variable CSF characteristics? The Omicron variants are widely acknowledged to exhibit a higher replication rate and transmissibility compared to previously identified variants. This increased virulence and altered pathogenicity may influence the immune response and inflammatory processes within the central nervous system, resulting in distinct CSF profiles. Li *et al*. [21] reported that the Omicron subvariant contains at least 30 mutations on the spike protein (S-protein) when interacting with the surface of the angiotensin-converting enzyme 2 (ACE2) receptor. These mutations give rise to various conformational preferences of the S-protein, believed to be linked to their varied transmissibility characteristics. Differences within the receptor binding domain of the S-protein and non-structural protein between the Delta and Omicron mutations have also been identified recently [22]. These differences in how the S-protein interacts with its receptor might explain the distinctive CSF characteristics of Omicron-related ON, distinguishing it from earlier mutations. The exceptional contagiousness of the Omicron strain may occur via the transneuronal pathway through the olfactory epithelium, potentially leading to rapid CNS inflammatory reactions.

Various forms of retinal microangiopathy have been reported following COVID-19 infection. In our study, a higher incidence of peripapillary hemorrhage (p = 0.046) was observed compared to spontaneous demyelinating ON. Notably, the hemorrhage manifested as a linear or flake-shaped pattern along the optic nerve fibers and blood vessels and was located in the superficial layer of the retina. Unlike the hemorrhages observed in other viral infections, such as Human Immunodeficiency Virus (HIV) disease, these patients had no preexisting systemic diseases, and the hemorrhage was not associated with vein occlusion or microvascular disease; anterior ischemic optic neuropathy (AION) was also excluded. Additionally, we found a correlation between peripapillary hemorrhage and elevated WCCs in the CSF (OR = 0.029, p = 0.02). Landecho *et al*. [23] suggested that Omicron S-protein could interact with ACE2 receptors expressed in capillary endothelial cells, potentially damaging the blood-retinal barrier (BRB), leading to hemorrhage and edema of the optic disc and retina (Fig. 2F1). The presence of peripapillary hemorrhage may serve as an indication of the Omicron virus spread via the hematogenic pathway. Some researchers [24] proposed that capillary endothelial inflammation causing thrombus formation or platelet activation may be another crucial mechanism underlying the occurrence of hemorrhages. Further investigation is needed to determine if patients with signs of peripapillary hemorrhage could benefit from the administration of antiaggregation drugs.

Studies [8,25] have indicated an increased morbidity risk during the peak of epidemics caused by SARS-CoV-2 variants in individuals with demyelinating ON. Serum-specific immune markers for MOG-IgG (20.0%) and AQP4-IgG (20%) were detected in the Omicron-related ON group. However, further research is required to determine whether these findings indicate a temporal coincidence or necessary causality. In our investigations of Omicron-related ON, comparison with demyelinating ON revealed a distinct inflammatory response in the CSF, characterized by significantly elevated WCCs (p = 0.004) and predominantly activated lymphocytes (Fig. 2I). Furthermore, CNS destruction and autoimmune antibody synthesis markers were identified in the CSF, including OCBs (18.2%), MBP (9.1%), and 24-hour IgG synthesis rate (27.3%), which had lower positive rates in Omicron-related ON. Positivity for OCBs in the CSF has been recognized as a sensitive indicator for MS; an increased value may reflect the recurrence rate of MS. OCBs can also be detected in certain infectious diseases, such as neurosyphilis. Interestingly, in our study, we found that the efficiency of intrathecal synthesis of OCBs in the Omicron-related ON group was very low and significantly lagged behind that of the demyelinating ON group (p = 0.021). Empirically, infection-related ON is mostly associated with a monophasic disease course [26]. The results suggest that Omicron-related ON had a lower ability than demyelinating ON to synthesize autoimmune antibodies in the CSF, although the inflammation was extremely severe in the acute phase of infection. OCBs

in CSF may potentially serve as an additional distinguishing marker between the two groups. Moreover, Omicron-related ON was associated with more pronounced ocular rotation pain ($p = 0.023$), optic disc hemorrhages ($p = 0.046$), more pronounced optic disc RNFL edema ($p = 0.022$), and serious damage to ganglion cells ($p = 0.020$) than the demyelination ON group. These results suggest that Omicron infection-related ON and demyelination ON have different disease courses but are closely related.

Evidence of direct optic nerve damage caused by COVID-19 infection remains insufficient. In 2022, Casagrande *et al*. [27] reported that SARS-CoV-2 RNA was detected in the retina and optic nerve of autopsied COVID-19 patients, but the S-protein of the virus was inactive. Stein *et al*. [28] suggested that despite the extensive distribution of SARS-CoV-2 RNA throughout the body (myocardium, lymph nodes, sciatic nerve, and ocular tissue) in autopsies of severe COVID-19 infection cases, there was little evidence of direct viral cytopathology outside the respiratory tract. Thus far, no autopsies of Omicron-infected patients have been conducted. We performed mNGS to detect the RNA sequence of the SARS-CoV-2 in the CSF. This method is sensitive for diagnosing CNS infection by viral, bacterial, or fungal agents [29]. However, in our Omicron-related ON cases, direct detection of SARS-CoV-2 RNA in the CSF was absent. Instead, activated lymphocytes were noted, suggesting ON to be primarily a secondary immune inflammation triggered by SARS-CoV-2. Plausible pathogenesis underpinning the Omicron-related ON has been postulated [30]: plenty of viral-induced proinflammatory factors (IL-2, IL-6, IL-8, TNF, etc.) pass through the blood-brain barrier, activating myelin-specific lymphocytes in the CSF. These activated lymphocytes affect macrophages, microglia, and astrocytes, mediating partial innate immune dysregulation, and thereby contributing to the growth of demyelinating lesions. Additionally, molecular mimicry between viral and self-antigens is another conceivable pathogenic pathway. These results reasonably explain why patients with Omicron-related ON achieve better visual outcomes using steroid monotherapy instead of combined antiviral therapy.

In our study, IVMP remained the principal treatment for infection-activated immune ON. Most of our cases exhibited a positive response to IVMP therapy alone, resulting in substantial visual acuity improvement. Visual outcomes did not differ significantly when compared to the demyelination group ($p > 0.05$); however, OCT findings indicated more pronounced optic disc edema and severe GCL damage in Omicron-infected cases. No relapses have occurred in the Omicron-related ON group within one year of follow-up, but one patient experienced recurrence in the demyelination group. Whether the majority of patients with virus infection-activated ON show a monophasic course and are less likely to recur, and whether the two groups should have different steroid treatment strategies, such as steroid withdrawal without the need for slow taper reduction after vision recovery, warrants further investigation through large sample studies and long-term follow-up.

This study has some limitations. Firstly, it included a limited number of cases enrolled during the initial Omicron strain outbreak in China, potentially introducing bias and limiting the generalizability of the findings. Secondly, our study exclusively focused on adults, and the results may not apply to children or other age groups. Additionally, the relatively short follow-up duration necessitates longer-term observation to determine the extended prognosis and relapse rates between the two groups. Despite these limitations, our study provides valuable insights into the close association and distinctive differences between Omicron-related ON and spontaneous demyelinating ON.

Conclusion

Omicron-related ON is characterized by more pronounced ocular rotation pain, optic disc hemorrhages, more severe optic disc edema, and the loss of ganglion cells. Obvious differences in the CSF were observed in the acute phase between both types of ON. The steroid monotherapy should be considered when viral RNA is absent in the CSF of Omicron-associated ON. ON is not a result of direct infection but a secondary immune reaction triggered by the Omicron variant. Therefore, different treatment options and prognosis should be considered when encountering either type of ON in clinical practice.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author, Libin Jiang, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China. Email: jlbjlb@sina.com. Phone: +86 13693664088. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Author Contributions

JZ: Data curation, Sample collection, Writing - original draft, Writing - review & editing. LW: Data curation, Sample collection, Writing - review & editing. CLC: Data curation, Writing - review & Editing, Supervision. HTR: Data curation and picture editing. MJ: Data curation, Sample collection, Data analysis. HJL: Investigation, Writing - review & Editing, Supervision. BTY: Investigation, Writing - review & editing, Supervision. LBJ: Methodology, Writing - original draft, Writing - review & editing, Supervision. ZQH and FKC: Investigation, Writing - review & editing. All authors have been involved in revising it critically for important intellectual content. All authors have given final approval for the version to be published. All authors have participated sufficiently in the work to take

public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

All study participants provided informed consent, and this study protocol was approved by the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (TRECKY 2020-045), and strictly adhered to the principles outlined in the Declaration of Helsinki.

Acknowledgment

Not applicable.

Funding

This work was supported by the National Natural Science Foundation of Beijing [grant number 7222028]; the Capital Health Development Scientific Research Project [grant number 2020-2-1082]; and the Health Research Program of Dong Cheng, Beijing, China [grant number (2022)-14].

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al*. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. JAMA Neurology. 2020; 77: 683–690.

[2] Liu J, Ding F, Wu Y, Jing W, Yan W, Qin C, *et al*. Trends of SARS-CoV-2 Infection in Sentinel Community-Based Surveillance After the Optimization of Prevention and Control Measures - China, December 2022-January 2023. China CDC Weekly. 2023; 5: 159–164.

[3] Fu D, He GH, Li HL, Tan HM, Ji XH, Lin ZQ, *et al*. Effectiveness of COVID-19 Vaccination Against SARS-CoV-2 Omicron Variant Infection and Symptoms-China, December 2022–February 2023. China CDC Weekly. 2023; 5: 369–373.

[4] Paterson RW, Brown RL, Benjamin L, Nortley R, Wiethoff S, Bharucha T, *et al*. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. Brain: a Journal of Neurology. 2020; 143: 3104–3120.

[5] Bakhshi A, Eslami N, Norouzi N, Letafatkar N, Amini-Salehi E, Hassanipour S. The association between various viral infections and multiple sclerosis: An umbrella review on systematic review and meta-analysis. Reviews in Medical Virology. 2024; 34: e2494.

[6] Goetz V, Yang DD, Abid H, Roux CJ, Levy R, Kossorotoff M, *et al*. Neurological features related to influenza virus in the pediatric population: a 3-year monocentric retrospective study. European Journal of Pediatrics. 2023; 182: 2615–2624.

[7] Shindler KS, Kenyon LC, Dutt M, Hingley ST, Das Sarma J. Experimental optic neuritis induced by a demyelinating strain of mouse hepatitis virus. Journal of Virology. 2008; 82: 8882–8886.

[8] Levine KS, Leonard HL, Blauwendraat C, Iwaki H, Johnson N, Bandres-Ciga S, *et al*. Virus exposure and neurodegenerative disease risk across national biobanks. Neuron. 2023; 111: 1086–1093.e2.

[9] Petzold A, Fraser CL, Abegg M, Alroughani R, Alshowaeir D, Alvarenga R, *et al*. Diagnosis and classification of optic neuritis. The Lancet. Neurology. 2022; 21: 1120–1134.

[10] Yang ZR, Jiang YW, Li FX, Liu D, Lin TF, Zhao ZY, *et al*. Efficacy of SARS-CoV-2 vaccines and the dose-response relationship with three major antibodies: a systematic review and meta-analysis of randomised controlled trials. The Lancet. Microbe. 2023; 4: e236–e246.

[11] Qu C, Chen Y, Ouyang Y, Huang W, Liu F, Yan L, *et al*. Metagenomics next-generation sequencing for the diagnosis of central nervous system infection: A systematic review and meta-analysis. Frontiers in Neurology. 2022; 13: 989280.

[12] Liu Y, Fan H, Shao Y, Zhang J, Zuo Z, Wang J, *et al*. Gut microbiota dysbiosis associated with different types of demyelinating optic neuritis in patients. Multiple Sclerosis and Related Disorders. 2023; 72: 104619.

[13] Pattanaik A, Bhandarkar B S, Lodha L, Marate S. SARS-CoV-2 and the nervous system: current perspectives. Archives of Virology. 2023; 168: 171.

[14] Azab MA, Hasaneen SF, Hanifa H, Azzam AY. Optic neuritis post-COVID-19 infection. A case report with meta-analysis. Interdisciplinary Neurosurgery: Advanced Techniques and Case Management. 2021; 26: 101320.

[15] Lecler A, Cotton F, Lersy F, Kremer S, Héran F, SFNR's COVID study group. Abnormal MRI findings of the orbital or visual pathways in patients with severe COVID-19: Observations from the French multicenter COVID-19 cohort. Journal of Neuroradiology = Journal De Neuroradiologie. 2021; 48: 331–336.

[16] Sriwastava S, Tandon M, Podury S, Prasad A, Wen S, Guthrie G, *et al*. COVID-19 and neuroinflammation: a literature review of relevant neuroimaging and CSF markers in central nervous system inflammatory disorders from SARS-COV2. Journal of Neurology. 2021; 268: 4448–4478.

[17] Deane K, Sarfraz A, Sarfraz Z, Valentine D, Idowu AR, Sanchez V. Unilateral Optic Neuritis Associated with SARS-CoV-2 Infection: A Rare Complication. The American Journal of Case Reports. 2021; 22: e931665.

[18] Kogure C, Kikushima W, Fukuda Y, Hasebe Y, Takahashi T, Shibuya T, *et al*. Myelin oligodendrocyte glycoprotein antibody-associated optic neuritis in a COVID-19 patient: A case report. Medicine. 2021; 100: e25865.

[19] Jossy A, Jacob N, Sarkar S, Gokhale T, Kaliaperumal S, Deb AK. COVID-19-associated optic neuritis - A case series and review of literature. Indian Journal of Ophthalmology. 2022; 70: 310–316.

[20] Abdul-Salam State SE, Sfredel V, Mocanu CL, Albu CV, Bălășoiu AT. Optic neuropathies post-Covid 19 - review. Romanian Journal of Ophthalmology. 2022; 66: 289–298.

[21] Li Y, Shen Y, Zhang Y, Yan R. Structural Basis for the Enhanced Infectivity and Immune Evasion of Omicron Subvariants. Viruses. 2023; 15: 1398.

[22] Panja A, Roy J, Mazumder A, Choudhury SM. Divergent mutations of Delta and Omicron variants: key players behind differential viral attributes across the COVID-19 waves. Virusdisease. 2023; 34: 1–14.

[23] Landecho MF, Yuste JR, Gándara E, Sunsundegui P, Quiroga J, Alcaide AB, *et al*. COVID-19 retinal microangiopathy as an in vivo biomarker of systemic vascular disease? Journal of Internal Medicine. 2021; 289: 116–120.

[24] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel

coronavirus pneumonia. Journal of Thrombosis and Haemostasis: JTH. 2020; 18: 844–847.

[25] Hümmert MW, Bütow F, Tkachenko D, Ayzenberg I, Pakeerathan T, Hellwig K, *et al*. Effects of the COVID-19 Pandemic on Patients with NMO Spectrum Disorders and MOG-Antibody-Associated Diseases: COPANMO(G)-Study. Neurology(R) Neuroimmunology & Neuroinflammation. 2023; 10: e200082.

[26] Lotan I, Nishiyama S, Manzano GS, Lydston M, Levy M. COVID-19 and the risk of CNS demyelinating diseases: A systematic review. Frontiers in Neurology. 2022; 13: 970383.

[27] Casagrande M, Fitzek A, Spitzer M, Püschel K, Glatzel M, Krasemann S, *et al*. Detection of SARS-CoV-2 genomic and subgenomic RNA in retina and optic nerve of patients with COVID-19. The British Journal of Ophthalmology. 2022; 106: 1313–1317.

[28] Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, *et al*. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature. 2022; 612: 758–763.

[29] Chen YY, Guo Y, Xue XH, Pang F. Application of metagenomic next-generation sequencing in the diagnosis of infectious diseases of the central nervous system after empirical treatment. World Journal of Clinical Cases. 2022; 10: 7760–7771.

[30] Lima M, Siokas V, Aloizou AM, Liampas I, Mentis AFA, Tsouris Z, *et al*. Unraveling the Possible Routes of SARS-COV-2 Invasion into the Central Nervous System. Current Treatment Options in Neurology. 2020; 22: 37.