Systematic review exploring the clinical features of optic neuritis after SARS-CoV infection and vaccination

Iliana Georganta 1,1 Despoina Chasapi,1 Charlotte Jayne Smith,1 Konstantinos Kopsidas,2 Andrew Tatham3,4

ABSTRACT

Background  This study aims to characterise the symptoms and clinical features of optic neuritis (ON) following SARS-CoV-2 infection and vaccination.

Method  A literature search was conducted in four databases (PubMed, Medline, Embase and Google Scholar) to identify relevant case reports and case series. The records were screened and articles adhering to the inclusion criteria were critically appraised.

Results  Sixty-eight studies were found to be eligible for inclusion, including 34 reporting ON following SARS-CoV-2 infection and an equal number reporting cases postvaccination. In total 93 patients and 125 eyes were included. The infection cohort included 42 patients and 56 eyes, 51.2% were female and 33.3% experienced bilateral ON. The mean visual acuity was 1.64 log of minimum angle of resolution (LogMAR), while pain was present in 77.8%. Oligoclonal bands were present in 3 patients, myelin oligodendrocyte glycoprotein (MOG) antibodies in 18 patients and AQP-4 antibodies in 4 patients. The vaccination cohort included 51 patients and 69 eyes. 60.8% were female and 35.3% had a bilateral ON. The mean visual acuity was 0.93 LogMAR. Oligoclonal bands were present in 46.7%, MOG antibodies in nine patients and AQP-4 antibodies in three patients.

Conclusion  Patients with ON post-SARS-CoV-2 infection were more likely to experience severe visual impairment than in cases following vaccination. Further research is required to outline the clinical features of ON after COVID-19 infection and vaccination, and establish causality.

INTRODUCTION

Optic neuritis (ON) is a clinical manifestation of central nervous system (CNS) inflammation that most commonly presents with pain, reduction in visual acuity (VA) and dyschromatopsia. ON is often the first indication of autoimmune demyelinating conditions; however, it can also be rarely precipitated following bacterial or viral infections.1

Cases of ON have also been reported following vaccination including rabies and influenza vaccines; however, no large cohort studies have been published on this topic.2,3

Since the SARS-CoV-2 pandemic, several cases of ON have been reported in the literature citing SARS-CoV-2 infection as the precipitating cause.4 There has also been speculation of a rare potential association between SARS-CoV-2 vaccination and ON; however, a causal association has not been established, and it is uncertain whether there is indeed any association between SARS-CoV-2 infection or vaccination and ON. Mild neurological symptoms such as headache and fatigue have been reported following SARS-CoV-2 vaccination and are also common with SARS-CoV-2 infection itself.5 Recently, a systematic review which explored the association between SARS-CoV-2 infection and vaccination and acute transverse myelitis (ATM) concluded that the incidence rate of ATM post-SARS-CoV-2 infection was as low as 0.5 per one million infections.6

The aim of this study was to characterise the symptoms and clinical features of previously reported episodes of ON following SARS-CoV-2 infection or vaccination. A narrative approach was used to compare descriptions of ON temporally associated with COVID-19 infection or vaccination with established characteristics of typical ON.

METHOD

A systematic literature search was conducted of four databases (PubMed, Medline, Embase and Google Scholar) on 20 November 2022.
Keywords used in the search strategies included but were not limited to “optic neuritis”, “MOG antibody disease”, “NMOSD” and “COVID-19” (online supplemental table 1).

All studies identified were transferred to Rayyan Software, which was used to assist with the screening process. Duplicate studies were identified automatically by the software and removed manually. Two authors (IG and DC) assessed the studies in a three-stage process by study title screening first, followed by abstract reviewing and then by full text assessment. Publications were screened by the two authors independently at every stage and carried forward to the next stage of screening if they met the predefined inclusion criteria. In cases of disagreement a third author (CJS) assisted in resolving decision disparities. Data were extracted from all studies by two independent authors (IG and DC) and was compared and confirmed by a third author (CJS). Studies including patients with a clinical or radiological diagnosis of ON of likely demyelinating or inflammatory aetiology occurring within 3 months of SARS-CoV-2 infection or vaccination were included. The 3-month interval was chosen as it reflects the sequelae of acute and subacute infection before entering the ‘chronic and postacute’ phase after 12 weeks.8 Only studies including patients with SARS-CoV-2 confirmed on a PCR/NAAT test or those who had received a SARS-CoV-2 vaccination were eligible. There was no age restriction and case reports, and case series were included in the review due to the rarity of ON following SARS-CoV-2. Only studies that were published in English were entered.

Studies including patients diagnosed with ON more than 3 months after the last vaccination date or a positive SARS-CoV-2 PCR/NAAT test were excluded, as were those including patients with an existing or suspected diagnosis of any demyelinating condition, and those where patients had synchronous infections or other ophthalmological or systemic pathology potentially contributing to their symptoms. Neuropathies that were likely to be ischaemic or granulomatous in nature were also excluded.

**Data analysis**

Descriptive statistics were used to explore study and patient characteristics as well as for analysing the outcomes of pain and biochemical markers. All VA data were converted to log of minimum angle of resolution (LogMAR) equivalent to assist in interpretation. A value of 2.6 LogMAR was used to represent vision of counting fingers, and it was increased by 0.1 increments to represent hand movement, light perception (LP) and no LP accordingly. The degree of visual impairment was defined as severe (<1.00 LogMar), moderate (0.48–1.00 LogMAR) or mild (0.00–0.48 LogMAR) with consideration to the WHO Criteria. Complete recovery was defined as VA LogMar 0.00 or return to the established baseline VA of the patient on the last follow-up reported. Partial recovery was defined as an improvement in vision that does not satisfy the ‘complete recovery’ criteria. Latency in the infection cohort was described as the number of days between the positive SARS-CoV-2 test and the onset of symptoms. In patients who tested positive on presentation, latency was defined as 0. To determine significance between the infection and vaccination cohorts, the χ² test was used for the dichotomous outcomes (gender, laterality, pain, oligoclonal bands, MOG antibodies, AQP-4 antibodies, complete recovery) and the unpaired t-test for continuous (age, latency, VA). P values less than 0.05 were considered statistically significant. All statistical analyses including calculating mean values, unpaired t-test results and χ² test were performed using Microsoft Excel Spreadsheet Software (Microsoft, USA). Patients with unreported data were excluded from the data analysis of the respective outcome.

**RESULTS**

**Study and patient characteristics**

In total, the search strategy identified 1464 publications, of which 68 were eligible for inclusion. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart is shown in figure 1. There were 34 studies of ON following COVID-19 infection,12–45 and an equal number of publications reported patients with ON post-COVID-19 vaccination.46–78 There were 19 case series and the remaining 49 were case reports. The minimum number of cases in a case series was 2 and the maximum 6. The 68 publications included a total of 93 patients and 125 eyes. The mean age of all the patients was 43.3 years with a range of 8–86 years and SD 17.7.

**Characteristics of infection cohort**

ON after SARS-CoV-2 infection was reported in 42 patients and 56 eyes (online supplemental table 2A). The mean age was 42.1 years (SD 19.5, median 44, range 8–74 years). There were 20 male patients (48.8%) and 21
females (51.2%). One study did not report the gender of the patient. Twenty-eight patients experienced unilateral neuritis (66.7%) and 14 bilateral (33.3%). Nineteen patients tested positive for COVID-19 at the time of ON diagnosis. The remaining 23 patients presented between 4 and 56 days after their positive test and the mean latency was 14.7 days.

**Characteristics of vaccination cohort**

ON postvaccination occurred in 51 patients and 69 eyes (online supplemental table 2B). The mean age was 44.2 years (SD 16.0, median 42.5, range 19–86 years). There was no significant difference in age between those who developed ON following SARS-CoV-2 infection or vaccination (p=0.60) (table 1). Twenty patients were male (39.2%) and 31 female (60.8%). Thirty-three (64.7%) patients presented with unilateral ON, while 18 had bilateral (35.3%). Patients had received six different types of SARS-CoV-2 vaccine. The AstraZeneca (ChAdOx1) and Pfizer-BioNTech SARS-CoV-2 Vaccine (BNT162b2) were reported in 23 and 17 patients, respectively. The Moderna vaccine (Spikevax) had been administered in four patients, the Sinopharm COVID-19 vaccine in two patients and the Johnson & Johnson (Ad26.COV2.S) in one patient. For three patients the type of vaccine was described (mRNA, Viral Vector Based); however, no further vaccine identification information was provided. No information was reported for one patient. Most cases of ON were reported after the first dose of the SARS-CoV-2. The number of patients with ON was 31 (68.9%), 12 (26.7%) and 2 (4.4%) following the first, second and third dose, respectively. Six of the publications did not specify the number of vaccine doses received. The mean latency between the vaccination and onset of symptoms was 12.3 days, the median 12 and the range 1–49.

**Differences in clinical features**

Pain was reported by 25 patients (78.1%) in the ON postvaccination cohort, whereas 7 patients (21.9%) did not experience pain. There was no documentation regarding pain for the remaining 19 patients. Similarly, in the post-infection subgroup, 21 patients (77.8%) described pain and 6 patients (22.2%) denied pain. There was no information about pain in the remaining 14 patients.

Three of the 49 eyes with ON post-SARS-CoV-2 vaccination were reported to have a vision of 0 LogMAR (6.1%) and 19 eyes had a severe visual impairment (38.7%) with acuity ranging from 1.00 LogMAR to NPL. Twenty-seven eyes had a mild visual impairment as their acuity was reported between 0.04 and 0.48 LogMAR (55%). The VA for 15 eyes was reported as ‘reduced’ or ‘blurry’, while the VA was not reported for five eyes and, therefore, excluded from the analysis.

Twenty five of 39 eyes with ON following SARS-CoV-2 infection had a severe visual impairment with VA of 1.00 LogMAR or worse (64%). The VA of the remaining 14 eyes was between 0.10 and 0.70 LogMAR (36%). Vision was described as reduced or blurry for 10 eyes while no data were reported for 7 eyes, which were excluded from this analysis. The average VA was 0.93 LogMAR in the vaccination cohort and 1.64 LogMAR in the infection cohort which was significantly worse (p=0.0025).

In the cohort of patients with ON post-SARS-CoV-2 infection, oligoclonal bands were only detected in 3 patients (16.7%), while they were absent in 15 (83.3%). There was no reported information for the remaining 24 patients. MOG antibodies were more commonly detected, as 18 patients tested positive and 10 negative. Similarly with the postvaccination cohort, AQP-4 antibodies were detected in a small proportion of patients, as only four were reported as positive. Titre levels were reported for two

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**Table 1** $\chi^2$ and t-test p values for outcomes explored

<table>
<thead>
<tr>
<th></th>
<th>Infection</th>
<th>Vaccination</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of eyes</td>
<td>56</td>
<td>69</td>
<td>–</td>
</tr>
<tr>
<td>Females (%)</td>
<td>51.2</td>
<td>60.8</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean age±SD (years)</td>
<td>42.1±19.5</td>
<td>44.2±16.0</td>
<td>0.60</td>
</tr>
<tr>
<td>Bilateral (%)</td>
<td>33.3</td>
<td>35.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Mean latency (days)</td>
<td>14.8</td>
<td>12.3</td>
<td>0.38</td>
</tr>
<tr>
<td>Presence of pain (%)</td>
<td>77.8</td>
<td>78.1</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean visual acuity (LogMAR)</td>
<td>1.64</td>
<td>0.93</td>
<td>0.0025</td>
</tr>
<tr>
<td>Oligoclonal bands (CSF Findings)</td>
<td>3 positive</td>
<td>7 positive</td>
<td>0.062</td>
</tr>
<tr>
<td>MOG antibodies</td>
<td>18 positive</td>
<td>9 positive</td>
<td>0.054</td>
</tr>
<tr>
<td>AQP-4 antibodies</td>
<td>4 positive</td>
<td>3 positive</td>
<td>0.97</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>17/37</td>
<td>20/38</td>
<td>0.74</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; LogMAR, log of minimum angle of resolution; MOG, myelin oligodendrocyte glycoprotein.
patients, and both were 1:1000. Oligoclonal bands in the cerebrospinal fluid (CSF) were detected in seven patients after SARS-CoV-2 vaccination (46.7%) and were absent in eight (53.3%). There was no information regarding oligoclonal bands in the remaining 36 patients. Nine patients tested positive for MOG antibodies and 15 were negative. Specific titre levels were only reported for 2 of the positive patients (1:32 and 1:2500). Three patients tested positive for AQP-4 antibodies and 17 tested negative.

Thirty-seven patients in the vaccination cohort underwent radiological investigations. The majority of the patients had MRI scans, and in a few cases, they had CT scans instead. Twenty-three of these patients were reported to have radiological changes consistent with ON such as swelling, gadolinium enhancement and hyperintensity of the optic nerve. The remaining 15 patients did not have any evidence of ON on neuroimaging, whereas no information was available about the other 14. In the infection cohort, 31 patients had radiological features of ON and 8 did not appear to have any features suggesting an active ON. Radiological results were not available for three patients.

**Prognosis**

Full recovery was observed in 20 eyes and 15 eyes were reported to meet a degree of VA improvement in the infection cohort. No improvement was noted for one patient with bilateral blindness, one eye had further deterioration in vision, while one patient with unilateral ON deceased. No recovery VA outcomes were reported for the remaining 17 eyes.

Complete recovery was reported in 17 eyes, while unspecified partial recovery was noted in 18 eyes in the vaccination cohort and 1 eye did not have any improvement. There was no documentation for the VA recovery for 33 eyes in this group. Across all the publications, the preferred treatment of choice was intravenous steroids frequently followed by a course of oral steroids or oral steroids only.

**Discussion**

Several hypotheses suggesting possible mechanisms regarding the development of autoimmune phenomena following vaccinations have been reported in the literature. One of the reported theories is that of molecular mimicry, according to which, the structural homology between pathogens and self-proteins may be responsible for inducing an autoimmune response. More specifically, this mechanism was considered relevant in the cases of demyelination following hepatitis B virus vaccines. One study published in 2005, suggested that aminoacid similarities between the small hepatitis B virus surface antigen, myelin basic protein, and myelin oligodendrocyte glycoprotein (MOG), serve as targets of immunological cross-reactivity.

Vaccinations have been previously associated with conditions that are presumed to interfere with myelin membranes. For example, Guillain-Barré syndrome is a well-recognised complication that may arise following a vaccination and is supported by evidence in the literature. The pathophysiological mechanism is thought to be secondary to the generation of antibodies/T-cells that could cross-react with epitopes on myelin due to generation of vaccine-associated products.

Cases of CNS demyelination following vaccine administration have also been previously published in the literature. A PubMed search between 1979 and 2013 identified 71 cases of demyelination after various vaccines, with isolated ON being the most frequent manifestation. Despite these findings, a recent systematic review which examined the association between multiple sclerosis and several vaccines did not identify significant findings to establish causation.

In this study, it was found that the majority of demyelinating episodes occurred after the administration of the first dose. One study following 1736 patients after SARS-CoV-2 vaccinations, reported that adverse events were more likely to be observed following the second dose. Furthermore, a large self-controlled case series study of people aged 13 years or older in England examined the association between myocarditis and COVID-19 vaccination. It is reported that occurrence of myocarditis was higher after the second dose. Similarly, a systematic review and meta-analysis with global data, reported that 82.1% of the included patients developed myocarditis after the second dose. It is suggested that the condition may be precipitated by cross-reactivity; however, no pathophysiological mechanism addressing increasing incidence with the second administration is reported. The CNS has been documented to be susceptible to several neuroinvasive and neurotropic viruses. A number of those viruses have also demonstrated neurovirulent properties as they have been associated with neurological disease. The viruses can penetrate the CNS via the blood-brain barrier, the blood-cerebrospinal fluid barrier as well as peripheral nerves and other routes.

Respiratory viruses, such as RSV, have demonstrated capacity to infect the CNS and induce neurological sequelae after intranasal inoculation in murine studies. Similarly, human coronaviruses (HCoV), even though they are traditionally associated with respiratory pathology they can also invade the CNS causing a range of neurological symptoms including but not limited to anosmia, ageusia, headache, seizures and encephalopathy. Association of HCoV with MS and demyelination has been previously reported; autopsy samples in patients with MS have shown statistically significant higher prevalence in OC43 coronavirus strain compared with neurologically intact controls. Therefore, there is a putative mechanism suggested in the literature and a sizeable number of case reports were identified in this study. However, in order to demonstrate causality, a putative correlation between COVID-19 infection and ON should also be established, with consideration to potential confounding factors. Due to the nature of the publications identified, the cohort...
studied may be affected by selection bias as identifying a patient for a case report is an author dependant decision. The clinical features of ON in the cases identified in this study are interesting but show considerable overlap with the known features of ON due to other factors. One of the findings of this review was that 56.4% of the patients were female, in contrast with the Optic Neuritis Treatment Trial (ONTT), a multicentre collaborative study in the USA, in which the females comprised 77% of patients. Female predominance is observed for MS and other autoimmune diseases, while a further rise in the female to male ratio has been reported for the past decades. Potentially, the 1.3:1 female to male ratio in the female to male ratio has been reported for the past decades. 

A feature of typical ON is the presence of pain, particularly on eye movement. We found that 78% of the participants experienced pain which is lower than the previously quoted 92% in typical ON. Data from more recent studies show variable rates of ocular pain ranging between 46% and 77% depending on the presence of antibodies in serum and in a small Malaysian study the presence of pain was even found to be as low as 31.7%. These findings may suggest that the higher incidence of bilateral ON in this study could be attributed to atypical aetiology.

The presence of IgG oligoclonal bands has been described as the immunological hallmark of multiple sclerosis, as they can be found in the CSF of 95% of patients with multiple sclerosis. Contrary to this finding, only 16.7% of patients with reported CSF findings in the infection cohort and 46.7% in the vaccination cohort tested positive for oligoclonal bands.

One of the significant findings of the current study was that most of the patients with ON after a COVID-19 infection presented with severe visual impairment, with 64% presenting with a VA of 1.00 LogMAR (Snellen 6/60) or worse. In the vaccination cohort, 39% of patients had a severe visual impairment, similarly with 36% of the patients in the ONTT. In conclusion, patients with ON post-SARS-CoV-2 infection experienced more severe visual impairment compared with patients after a SARS-CoV vaccination. In addition, the proportion of patients suffering from bilateral ON was higher compared with typical ON.

Beyond the case reports summarised in this review, there is no current evidence to support causation between SARS-CoV-2 infection or vaccination and ON. To establish causation, further research is needed, in particular collection of longitudinal data to determine potential progression to MS, MOGAD or NMOSD in those affected.

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