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Aquaporin-4 IgG neuromyelitis optica spectrum disorder onset after Covid-19 vaccination: Systematic review

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is rarely reported following Coronavirus disease 2019 (COVID-19) vaccination. We identified 16 cases of new onset NMOSD with positive aquaporin-4 IgG (AQP4-IgG) following COVID-19 vaccination. Transverse myelitis was the most common clinical presentation (75%). Most patients received high dose steroids for acute treatment and maintenance therapy was started in 12 patients (75%). Twelve patients (75%) had improvement of their symptoms at the time of discharge or follow-up. The included cases share similar epidemiology and natural course to non-vaccine related cases. Clinicians should be aware of possible post-vaccination NMOSD to help with earlier diagnosis and treatment.

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory demyelinating disease of the central nervous system associated with episodes of optic neuritis, transverse myelitis and other neurological manifestations including area postrema syndrome. The discovery of aquaporin- 4 (AQP4) antibodies as a specific biomarker for NMOSD allowed for better understanding of the disease pathogenesis as an astrocytopathy and its distinction from other inflammatory disorders, especially multiple sclerosis (Lennon et al., 2005). AQP4-IgG antibodies are found in about 80% of NMOSD cases, and through their binding with AQP4 antigen and activation of complement-mediated and antibody-dependent cell-mediated cytotoxicity, they lead to astrocyte cell injury and subsequent demyelination (Waters et al., 2012; Nytrova et al., 2014). Though we currently understand more about the disease pathogenesis, factors responsible for disease onset are not well understood.

Vaccinations have been implicated as a potential trigger for multiple central and peripheral nervous system inflammatory syndromes, including demyelinating diseases (Langer-Gould et al., 2014). The relationship between vaccination and NMOSD has been studied in prior case reports and systematic reviews showing that NMOSD can either relapse or arise de-novo following vaccinations (Vanood and Wingerchuk, 2019; Anamnart et al., 2022; Paybast et al., 2022). However, due to the small number of reported cases, including multiple seronegative cases, it is difficult to assess for any causal relationship.

With the ongoing COVID-19 pandemic, COVID-19 infection has been associated with various neurological disorders including, autoimmune neurological disorders like NMOSD (Guerrero et al., 2022; Mirmosayyeb et al., 2022). As massive worldwide vaccination programs against COVID-19 occurred in response to the pandemic, multiple cases with potential post-vaccination neurological complications have been reported including NMOSD (Sriwastava et al., 2022; Toljan et al., 2022; Chen et al., 2021). Herein, we describe one case of AQP4-IgG positive NMOSD following the third dose of mRNA COVID-19 vaccine and conduct a systematic review on the existing data regarding the relationship between COVID-19 vaccines and the development of new onset AQP4-IgG positive NMOSD cases.

A 67-year-old male with no previous history of autoimmune disorders received the third dose of mRNA COVID-19 vaccine and 2 weeks later developed pain involving the left eye. One week later, he had progressively worsening headache with intractable nausea, vomiting, and hiccups for which he presented to an outside emergency department and discharged without clear diagnosis. Few days later, the patient developed left-side weakness and numbness and was admitted to an outside facility. Magnetic resonance imaging (MRI) of the spine showed findings consistent with longitudinally extensive transverse myelitis (LETM) involving the cervical spine. Serum and cerebrospinal fluid (CSF) testing were positive for AQP4-IgG by fluorescence-activated cell sorting (FACS) assay (titer serum 1:1000, CSF 1:128). There were no evidence of other neural antibodies. The patient was diagnosed with AQP4-IgG NMOSD and was treated with intravenous methylprednisolone (IVMP)

and plasma exchange (PLEX) with initial improvement in his symptoms. He was discharged home with a pending referral to outpatient neurology; no maintenance treatment was initiated. Two weeks later, the patient presented to our facility due to worsening of his left-sided weakness and decreased vision in the left eye. MRI of the orbits, brain and spine revealed findings consistent with left optic neuritis (ON) extending into the optic chiasm, and LETM involving the cervical spine (Fig. 1). Repeat serum testing for AQP-4 IgG was positive. Despite treatment of the acute attack with IVMP and PLEX, the patient had persistent severe neurological deficits with Expanded Disability Status Scale (EDSS) of 8 at the time of discharge 60 days after onset of symptoms. He was started on eculizumab for NMOSD attack prevention. (Fig. 2).

Section snippets

Literature search methodology

EMBASE and Ovid MEDLINE databases were searched using the following terms “Neuromyelitis optica, NMOSD, Devic disease, demyelinating disease, vaccines, immunization, COVID-19 vaccines and SARS-CoV2 vaccine”. Articles published in languages other than English were excluded during the review process. The search methodology is outlined in Supplementary data 1....

Case selection

Two authors (E.H. and D.G.) independently searched the databases, screened the articles' titles and abstracts, and subsequently reviewed the ...

Study identification and selection

Using the search methodology described in Supplementary data1, 2065 articles were initially obtained from EMBASE and 420 from Ovid MEDLINE. After screening the articles' titles and abstracts, 2464 irrelevant articles were excluded. The full text of the remaining 21 articles were then reviewed, and 10 of these were excluded as they included duplicate cases. From the remaining 11 articles, we identified 15 cases of newly diagnosed AQP4-IgG seropositive NMOSD following COVID-19 vaccines (Anamnart...

Discussion

Our systematic review represents the highest number of AQP4-IgG seropositive NMOSD cases reported so far in the literature following COVID-19 vaccination. This high number could be in part due to the massive worldwide vaccination campaigns that were started in response to the COVID-19 pandemic as millions of people received vaccination within a short-time period, and this has not been the case for other types of vaccines. In contrast to prior reviews, we included only AQP4-IgG seropositive...

Conclusions

Though no causality could be established, our systematic review shows that new AQP-IgG seropositive NMOSD cases following COVID-19 vaccines share similar natural history to non-vaccine related cases. Clinicians should be aware of possible post-vaccination autoimmune neurological disorders including NMOSD to help with earlier diagnosis and treatment to minimize long-term deficits....

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