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Vaccines and the association with relapses in patients with neuromyelitis optica spectrum disorder

Maureen A. Mealy[a,*], Lawrence J. Cook[b], Florence Pache[c], Diego L. Velez[d], Nadja Borisow[c], Daniel Becker[a,e], Jorge A. Jimenez Arango[d], Friedemann Paul[c], Michael Levy[a]

[a] Department of Neurology, Johns Hopkins University School of Medicine, 600N. Wolfe St. Pathology 627 Baltimore, MD 21287, USA
[b] Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, USA
[c] Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, NeuroCure Clinical Research Center and Department of Neurology, Berlin, Germany, and Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine, Berlin, Germany
[d] Department of Neurology, Neuroclinica, Medellín, CO, USA
[e] International Neurorehabilitation Institute, Lutherville, MD, USA

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ABSTRACT

Background: It is unknown if vaccines cause non-specific immune activation in patients with neuromyelitis optica spectrum disorder and no consensus on the use of vaccines exists for this population. We investigated the temporal association of vaccinations with relapses in patients with neuromyelitis optica spectrum disorder.

Methods: This is a multi-center retrospective analysis of patients with neuromyelitis optica spectrum disorder for whom immunization history and clinical records from disease onset were available. Ninety patients who met 2015 diagnostic criteria received a total of 211 vaccinations and experienced 340 relapses over a median disease course of 6.6 years. The likelihood of a relapse occurring within 30, 60, and 90 days of a vaccine was compared to the likelihood of a relapse occurring within each time point of a randomly generated date. We also compared the relapse rate between patients who received any vaccination(s) after disease onset to those who did not.

Results: We identified seven patients with neuromyelitis optica spectrum disorder who relapsed within 30 days of a vaccination, six between 31 and 60 days, and four who relapsed between 61 and 90 days. The rate of vaccine-associated relapses within 30, 60, and 90 days was significantly higher than the likelihood of a relapse spontaneously occurring within each of the given time frames (p = 0.034, 0.01, 0.016, respectively) among patients who were not on preventive immunotherapy only. Among those who were on immunotherapy to prevent relapses, there was no significant association of relapse with vaccines. Additionally, among patients on immunotherapy, the annualized relapse rate of those who received routine vaccinations was significantly lower than in unvaccinated patients.

Conclusion: The evidence suggests that there may be a risk of vaccination-associated relapses among untreated neuromyelitis optica spectrum disorder patients, however immunosuppressive therapy at time of vaccine may abort the risk; this suggests that the patients who are treated with preventive immune suppression and receive routine vaccinations for common infections may fare better. Further prospective studies are necessary to verify these findings.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a relapsing autoimmune disease that preferentially targets the spinal cord and optic nerves, leading to paralysis and blindness. Risk factors that predict a higher risk of relapse include female sex, African ancestry, positive aquaporin-4 antibody (AQP4-IgG) serostatus, and lack of preventive immunosuppression (Mealy et al., 2012, Kimbrough et al., 2014, Mealy et al., 2014, Borisow et al., 2016, Wingerchuk et al., 2007). Activation of the immune system from infections increases risk of relapse in multiple sclerosis (MS), (McKay et al., 2016) may increase the risk in NMOSD (Jarius et al., 2012), and increases morbidity and mortality in other rheumatologic diseases (Sfriso et al., 2010, Doria et al., 2008, Wolfe et al., 1994). However, vaccinations are not tightly associated with increased rates of CNS demyelination/inflammatory events in MS (Langer-Gould et al., 2014). Interestingly, the cases in MS that have

* Corresponding author.
E-mail address: mmealy1@jhmi.edu (M.A. Mealy).

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been reported in the literature tend to affect the optic nerves and/or spinal cord, and include case reports of NMOSD disease onset following vaccinations (Karussis and Petrou, 2014, Furukawa et al., 2011a, Menge et al., 2012). This raises concern that NMOSD may be more susceptible than MS, but the rate of relapses subsequent to vaccine administration has not been investigated in this disease.

Currently, there is no consensus on the use of vaccines for routine prevention of infectious diseases in NMOSD, though many physicians recommend vaccines for their patients because the benefits of avoiding infections are believed to outweigh the risks of triggering a relapse. However, the concern with vaccines involves the potential risk of non-specific immune activation in patients with immune-mediated diseases (Loebermann et al., 2012). In this study, we investigated the association of a relapse occurring within 30, 60, and 90 days of a vaccination and compared it with the association of a relapse occurring within randomly selected dates. The goal was to determine if vaccines may increase the risk of an NMOSD relapse.

2. Material and methods

We conducted a retrospective analysis of relapses among patients with NMOSD to investigate the association with vaccines at three NMOSD centers world-wide: the Johns Hopkins NMO Clinic (Baltimore, USA), NeuroCure Clinical Research Center at Charité University Hospital (Berlin, Germany) and Neuroclinica (Medellín, Colombia). Diagnosis was based on the 2015 international consensus diagnostic criteria for NMOSD (Wingerchuk, 2015). Local review boards at each site approved the use of human subjects for this analysis, as required. The study was approved by Johns Hopkins Institutional Review Board (NA_00041032), and shared data were de-identified. All patients with known immunization records from the time of disease onset were eligible for inclusion in this analysis, to include those who received no vaccines in order to enable a comparison group. Only patients with comprehensive health records related to their NMOSD, including treatment and relapse history, from onset of disease were included. Patients needed to have been followed up for at least 90 days following their most recent vaccination. Relapse history and vaccine history were independently extracted from each patient's health record. Vaccine-associated relapses were defined as those relapses that occurred within 30, 60 or 90 days following an immunization. Relapses were defined across all centers as a new or worsening acute neurologic symptom lasting at least 24 h, associated with a change in exam localizing to the CNS and not explainable by fever, infection or metabolic condition. MRI was used for relapse confirmation as needed. Relapse severity was characterized by net change in the Expanded Disability Status Scale (EDSS) from baseline to nadir. Preventive immunotherapy included immunosuppressive medications for which there is evidence of effectiveness in NMOSD (Kessler et al., 2016). Because interferon beta has been shown to worsen NMOSD disease (Kimbrough et al., 2012) and use of glatiramer acetate has not been shown to affect disease severity (Ayzenberg et al., 2016), patients on these medications were not considered to be treated for their disease. Proximity of relapse to pregnancy was examined in female participants because third trimester and postpartum periods have been associated with relapses (Klawiter et al., 2017).

For the purpose of our analysis in a rare disease, relapses were considered to be independent events. A permutation test was conducted to determine the probability of observing a given number of relapses within 30, 60 or 90 days of a vaccination (Good, 1994; Scott, 2008). The 30-day time point was chosen as the primary analysis based on a large study that suggested there was no increased association of any CNS demyelination beyond 30 days from time of vaccine administration (Langer-Gould et al., 2014), and the analysis was extended in this study to 60- and 90-day time points based on case reports of temporality of vaccination to relapse in NMOSD beyond 30 days (Menge et al., 2012). The test was conducted by fixing relapse dates at the observed times and then generating random vaccination dates for each patient vaccination combination and counting the number of relapses within 30, 60, or 90 days respectively. This process was repeated 2000 times to generate a sampling distribution for the test statistic. A *p*-value was estimated by comparing the observed number of vaccine-associated relapses to the sampling distribution for two groups: 1) patients who are on a preventive immunotherapy for which evidence supports use in NMOSD, including rituximab, mycophenolate mofetil, azathioprine, methotrexate or prednisone (Kessler et al., 2016), and 2) patients who are not on preventive immunotherapy, including those on glatiramer acetate and interferon beta. A comparison of annualized relapse rates (ARR) between patients who continued to receive vaccines with patients who did not was conducted by Student's *t*-test. Mann-Whitney, Fisher's exact, and *t*-tests were conducted, as appropriate, to assess differences between the vaccinated and unvaccinated groups. Statistical significance was considered for *p*-values less than 0.05.

3. Results

We identified 90 patients meeting inclusion criteria who received a total of 211 vaccinations over a median disease course of 6.6 years (IQR 3.1–10.8; mean 8.0) in which 340 relapses occurred (Table 1). Ninety-one percent of our sample was female, 67% was Caucasian, and 89% was AQP4-IgG seropositive. Ninety-five percent of relapses were characterized as myelitis and/or optic neuritis and 61% of the vaccines received were intramuscular influenza (Table 1). Seven patients with NMOSD were identified who relapsed within 30 days of a vaccination, 6 more who relapsed 31–60 days and 3 more who relapsed 61–90 days after vaccination (Table 2). Those patients who had a vaccine-associated relapse had a median disease duration of 8.5 years, 100% were female, 81% were Caucasian and 75% were AQP4-IgG seropositive. None of the female patients with a vaccine-associated relapse were pregnant or within 6 weeks of delivery. One patient was in receipt of two vaccines on different dates within 90 days of a relapse, and only the vaccine that was within 30 days of the relapse was considered for this analysis, so as to avoid double-counting of events. Five of the attacks were at the disease onset and eleven occurred later in the disease course. Eleven events involved myelitis only, three with optic neuritis only and two with both simultaneously (Table 2). Tetanus/diphtheria accounted for the highest proportion of vaccination-associated relapses where 15% of patients receiving this vaccination experienced a relapse within 90 days. The sampling distribution for the number of relapses among all patients with NMOSD within 30, 60, and 90 days of randomly generated vaccination dates is displayed in Fig. 1. Seven relapses were observed in the total cohort of patients within 30 days of vaccination, which corresponds to a *p*-value of 0.215. When extending the analysis to within 60 and 90 days of a vaccination, 13 and 16 NMOSD relapsing patients were identified, respectively. The probability of observing 13 or 16 or more relapses among the total group within 60 or 90 days of a vaccination is also not significant, corresponding to *p*-values of 0.153 and 0.332, respectively.

Among the 211 vaccinations, 118 were administered while patients were on preventive immunosuppressive therapy. Of the 16 vaccine-associated relapses, 13 occurred among patients who were not on immunotherapy, with one additional on glatiramer acetate. Two patients were on immunosuppressive treatment for a mean time of 47 months. Median net change in EDSS from baseline to nadir among all relapses was 3.0 (IQR 1.8–4.5; mean 3.3). A permutation test performed only among NMOSD patients who were not using preventive immunotherapy revealed a strong association between vaccines and relapses. *P*-values for these tests were 0.034, 0.01, and 0.016 for 30-day, 60-day, and 90-day relapses, respectively. Vaccines were not associated with relapses among patients on preventive immunotherapy. In fact, among patients who were using preventive immunotherapy, routine vaccination was associated with an 81% lower risk of relapse compared to patients who were not vaccinated after disease onset (95% CI 0.056,

Table 1
Demographic and clinical profile of patients.

Demographics & clinical characteristics	USA	Germany	Colombia	Total cohort
Number of patients	44	27	19	90
Vaccinations				
Number	160	46	5	211
Median (IQR)	2	1	0	1 (0–3)
Mean (SD)	3.6	1.6	0.3	2.3 (3.83)
Relapses				
Number	149	118	73	340
Median (IQR)	3	4	3	3 (2–5)
Mean (SD)	3.4	4.1	3.8	3.7 (2.21)
Mean Per Year	0.65	0.74	0.68	0.68
Sex – female (%)				91
Anti-aquaporin-4 seropositivity (%)				89
Current age, median (IQR)				52.2 years (38.4–60.0)
Race (%)				
Caucasian				67
Latin American				19
African Descent				13
Asian				1
Duration of disease, median (IQR)				6.6 years (3.1–10.8)
Types of relapses (%)				
Transverse myelitis				55
Optic neuritis				36
Optic neuritis + Transverse myelitis				4
Brainstem				4
Diencephalic lesion				1
Type of immunotherapy at time of vaccination (%)				
None				36
Rituximab				33
Mycophenolate mofetil				15
Glatiramer acetate				5
Azathioprine				4
Interferon beta				3
Prednisone				3
Methotrexate				1
Types of vaccinations (%)				
Influenza (intramuscular); *inactivated*				61
H1N1 Flu (intramuscular); *inactivated*				2
Tdap (tetanus, diphtheria, and pertussis); *inactivated*				8
Td (tetanus, diphtheria); *inactivated*				4
Pneumococcal; *conjugate*				7
Hepatitis B; *subunit*				5
Hepatitis A; *inactivated*				2
Human papillomavirus; *subunit*				2
Other				9

0.642). The ARR of those who were vaccinated ($n = 53$) was 0.40 compared with 0.59 in those unvaccinated ($n = 37$), which was significantly different ($p < 0.05$).

No correlation was found between ARR per person and number of vaccines per person. Confounding factors included duration of disease, which was a median 8.1 years in vaccinated patients versus 4.3 years in unvaccinated, and race in which more patients of African descent were vaccinated. Age at disease onset, sex, and treatment status were similar between groups. There were additionally no differences among sites in sex, AQP4 antibody status, age at onset, current age, and disease duration. Race and number of unvaccinated patients were significantly different among sites. Multivariable analyses were not conducted due to sample size.

4. Discussion

In this analysis, vaccines are associated with relapses in patients with NMOSD who are not on preventive immunotherapy. The highest association is during the first 30 days after a vaccine, but the risk significantly persists for at least 90 days after vaccination. Notably, the association of vaccines to relapses is not present among patients who are using preventive immunotherapy. Moreover, in the immune-treated patients, routine vaccines are associated with lower annualized relapse rates indicating a disease benefit from vaccines, without the risk. Extrapolating from the McKay review that suggests activation of the immune system from infections increases the risk of relapse in MS (McKay et al., 2016), a possible explanation for this difference is that the prevention of infections by vaccines allows for less immune activation, and subsequently, fewer relapses. The severity of relapses among those associated with vaccines was similar to previous reports in NMOSD (Abboud et al., 2016). Our study suggests that the patients who fared best were those treated with preventive immune suppression for NMOSD who received routine vaccinations for common infections.

A recent systematic review of the impact of vaccinations on MS by Mailand and Frederiksen found no association between relapse rates and vaccination against hepatitis B virus, human papillomavirus vaccine (HPV), seasonal influenza, H1N1 influenza, typhoid, tetanus, diphtheria, pertussis, and several others (Mailand and Frederiksen, 2016, Chang et al., 2016). While the number of patients available in our cohort of a rare disease does not enable us to make any conclusions about specific vaccines, the data in MS largely mirror that in NMOSD, such that, overall, there appears to be no increased risk of relapses associated with vaccinations. However, the MS literature does not separately analyze the impact that disease modifying therapy may have on this association. Interestingly, most studies examining the

Table 2
Clinical characteristics of relapses temporally associated with vaccinations.

Type of vaccine	Date of vaccine	Type of event	EDSS change (baseline to nadir)	Vaccine-to-event (days)	AQP-4 serostatus	Background immunosuppression
1. Tdap (inactivated)	5/12/2014	Myelitis	1.0	10	positive	MMF (recurrence)
2. Hepatitis A (inactivated) & typhoid (live attenuated)	2/3/2012	Myelitis	0.5	13	positive	None (recurrence)
3. Td (inactivated)	11/17/2004	Myelitis	6.5	14	positive	None (initial event)
4. Influenza (IM; inactivated)	11/15/2003	Myelitis & ON	8.5	16	negative	None (initial event)
5. Influenza (IM; inactivated)	9/29/2014	Myelitis	1.5	23	positive	None (recurrence)
6. Tdap (inactivated)	12/24/2012	Myelitis	5.5	26	negative	None (initial event)
7. Influenza (IM; inactivated)	11/16/2009	Myelitis	2.0	30	positive	None (recurrence)
8. Influenza (IM; inactivated)	10/15/2014	Myelitis	2.5	32	positive	None (recurrence)
9. Influenza (IM; inactivated)	11/8/2011	Myelitis & ON	4.0	39	negative	None (recurrence)
10. Influenza (IM; inactivated)	9/30/2012	ON	3.0	40	positive	None (initial event)
11. Hepatitis B (#3 of 3; subunit)	6/1/2009	Myelitis	0.5	44	negative	GA (recurrence)
12. Influenza (IM; inactivated)	10/15/2010	ON	3.0	47	positive	AZA (recurrence)
13. Pneumococcal (conjugate)	6/1/2002	ON	3.0	54	positive	None (initial event)
14. Td (inactivated)	8/1/2013	Myelitis	5.0	62	positive	None (recurrence)
15. Influenza (IM; inactivated)	11/29/2005	Myelitis	3.0	64	positive	None (recurrence)
16. Influenza (IM; inactivated)	12/9/2011	Myelitis	unavailable	83	positive	None (recurrence)

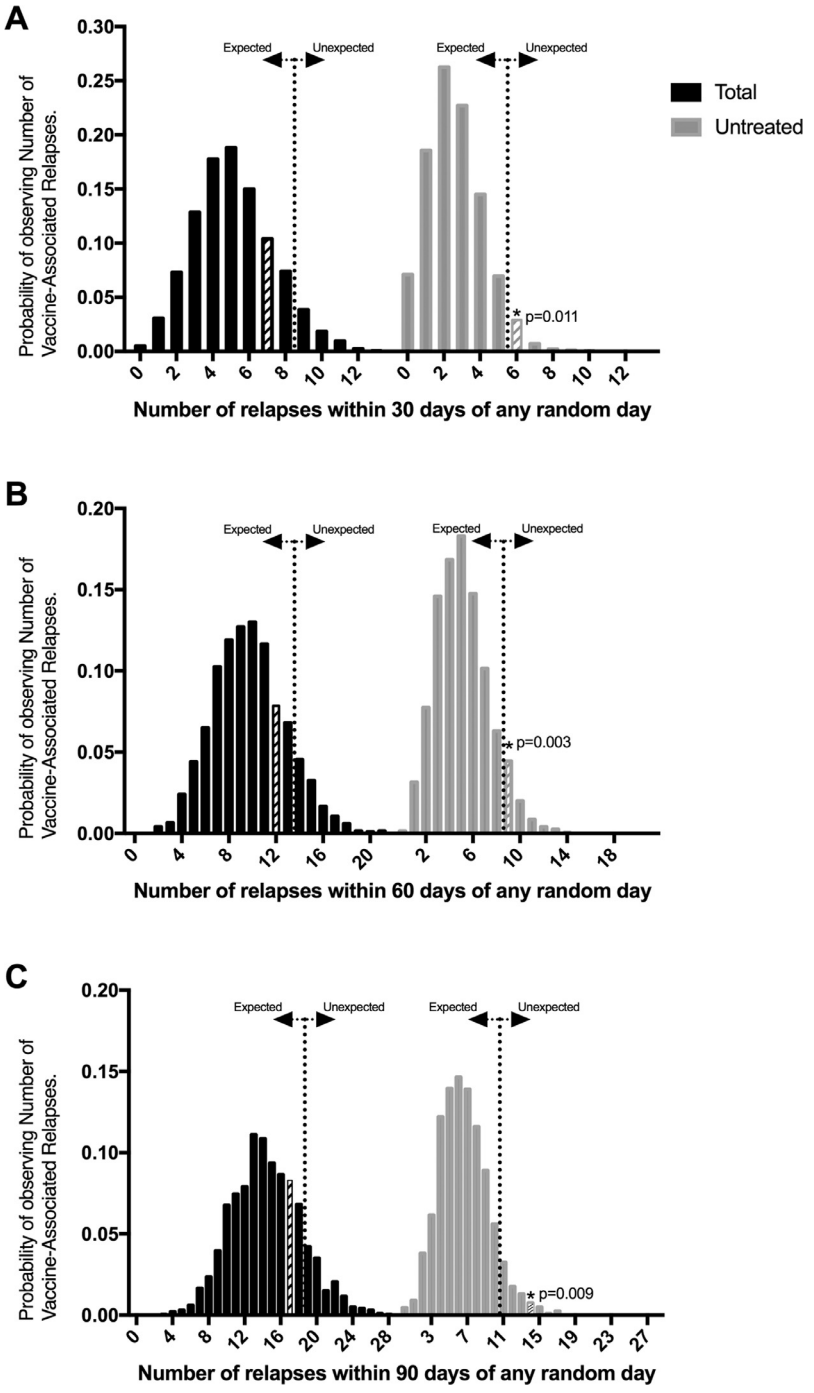

Fig. 1. Probability of observing a given number of vaccine-associated events. **A.** Within 30 days of any random day, 8 or fewer relapses are expected in the total NMOSD population. In the total group (black bars), 7 relapses were observed within 30 days of a vaccine which is within the range of expectation ($p = 0.215$). Among the untreated NMOSD population (gray bars), 5 or fewer relapses are expected to occur within 30 days of any random day but 6 were observed. The number of observed relapses occurring within 30 days of a vaccine in the untreated NMOSD study population is outside the range of expectation ($p = 0.034$). **B.** Within 60 days of any random day, 13 or fewer relapses are expected in the total NMOSD population. In the total group (black bars), 13 relapses were observed which is within the range of expectation ($p = 0.153$). Among the untreated NMOSD population (gray bars), 8 or fewer relapses are expected to occur within 60 days of any random day but 11 were observed. The number of observed relapses occurring within 60 days of a vaccine in the untreated NMOSD study population is outside the range of expectation ($p = 0.01$). **C.** Within 90 days of any random day, 18 or fewer relapses are expected in the total NMOSD population. In the total group (black bars), 17 relapses were observed which is within the range of expectation ($p = 0.332$). Among the untreated NMOSD population (gray bars), 10 or fewer relapses are expected to occur within 90 days of any random day but 14 were observed. The number of observed relapses occurring within 90 days of a vaccine in the untreated NMOSD study population is outside the range of expectation ($p = 0.016$).

relationship between MS onset and tetanus vaccination administration suggest that the vaccine may play a preventive role in MS development, and while less evidence supports this, some data suggest the same of the diphtheria vaccine (Mailand and Frederiksen, 2016). This contrasts with our findings of a disproportionate relationship between the tetanus +/− diphtheria vaccine and a subsequent relapse. Given the low number of patients receiving this vaccine in our cohort, more investigation is warranted, but this may be a result of the differing immunopathogenic mechanisms that distinguish MS from NMOSD.

Our findings have a significant implication in the practical treatment of NMOSD: we recommend starting preventive treatment for NMOSD prior to any future vaccinations. Although this approach may reduce the efficacy of the vaccine, our data suggests that it would reduce the risk of an NMOSD relapse. This is opposite from the current guidelines in MS that call for starting disease modifying therapy after vaccination (Ocrelizumab (Ocrevus™) 2017; Fingolimod (Gilenya™) 2010). Our data also indicate that those who are routinely vaccinated after onset of disease while on preventive therapy have the best outcomes; therefore, it is important to emphasize that avoidance of vaccinations altogether is not in the best interest of the patient.

A limitation to this study includes the low number of live attenuated vaccines administered such that a separate analysis of their temporality to relapses was not possible. Specifically, no one in our cohort received Japanese encephalitis and yellow fever vaccines, both of which are live vaccines that have been associated with unmasking NMOSD (Furukawa et al., 2011b, Schöberl et al., 2017). Further, few patients in our cohort received the HPV vaccine, for which relapse temporality has been reported in case studies involving patients with NMOSD (Menge et al.,

2012, Scott, 2008). We also do not have access to the adjuvants that were used for each of the vaccines, which can stimulate different arms of the immune system (Coffman et al., 2010). Further, this study was limited by the small number of AQP4 seronegative patients. While there was no significant difference between the proportion of seronegative patients who had a vaccine-associated relapse as in the overall cohort, a trend could emerge in larger studies that included more seronegative patients. Of note, one of the relapses in a seronegative patient occurred following administration of the third in a series of hepatitis B vaccines, which has been previously reported in another seronegative patient (Heekin et al., 2015). Finally, this study was further limited by the inherent biases that exist in retrospective data analyses, and therefore lacks rigorous controls. Selection bias was minimized through the wide inclusion of any patients for whom detailed vaccination and clinical records were available, regardless of frequency of follow-up at each participating center.

5. Conclusion

A comprehensive, well-controlled prospective analysis that assesses relapses, vaccines and infections would be warranted for future research to confirm our findings that suggest that patients who are treated with preventive immune suppression and receive routine vaccinations for common infections may fare better than those who do not.

Conflicts of interest

None

Disclosures

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