Optic neuritis at the nexus of peripheral autoimmunity and central nervous system demyelination: a nationwide cohort study

CURRENT STATUS: POSTED

Wei-Sheng Lin  
Taipei Veterans General Hospital  
wshenq@yahoo.com.tw  
Corresponding Author  
ORCiD: https://orcid.org/0000-0002-9016-2067

Ho-Min Chen  
National Taiwan University

Chih-Chao Yang  
National Taiwan University Hospital

Ta-Ching Chen  
National Taiwan University Hospital

Jou-Wei Lin  
National Taiwan University Hospital Yun Lin Branch

Wang-Tso Lee  
National Taiwan University Hospital

DOI:  
10.21203/rs.2.24450/v1

SUBJECT AREAS  
Neurobiology of Disease

KEYWORDS  
Optic neuritis, Multiple sclerosis, Neuromyelitis optica, Autoimmunity, Demyelination, Comorbidity
Abstract

Background

Long-term course of optic neuritis is heterogeneous and varies across populations. We aim to investigate immune-related determinants that predict conversion of optic neuritis (ON) to multiple sclerosis (MS) or neuromyelitis optica (NMO) in a nationwide cohort.

Methods

We conducted the population-based cohort study using data from Taiwan’s National Health Insurance Research Database. Incident ON cases during 2003~2014 were followed until the end of 2015. Pediatric and adult sub-cohorts were examined separately. The associations between immune-related comorbidities or treatment and outcomes were analyzed using Cox proportional hazards models.

Results

A total of 11923 adult and 1365 pediatric ON patients were enrolled. The rates of conversion to MS were 2.7% for adult and 3.1% for pediatric ON with median follow-up duration of 6.3 and 7.3 years respectively, while 1.2% of pediatric and adult ON evolved to NMO. Comorbid systemic lupus erythematosus was associated with increased risks of subsequent development of MS in adult (adjusted hazard ratio aHR, 2.80; 95% CI, 1.04-7.49) and pediatric ON patients (aHR, 21.65; 95% CI, 1.29-363.4). Adult ON patients were at increased risks of NMO if comorbid with myasthenia gravis (aHR, 9.13; 95% CI, 1.20-69.45) or Sjogren’s syndrome (aHR, 4.71; 95% CI, 1.74-12.76).

Conclusion

ON could be the sentinel event linking several peripheral autoimmune comorbidities to distinct forms of central nervous system demyelination. The clinical context in which ON occurs should be taken into account in the care and counseling of these patients.

Introduction

Optic neuritis (ON) often represents the harbinger of several neuroimmune disorders of central nervous system, most notably multiple sclerosis (MS) and neuromyelitis optica (NMO) [1, 2]. Previous studies reported variable rates of conversion to MS after ON, ranging from 8.3–75% (7-40.6% in pediatric ON) [1, 3–8]. The disparity between studies could be attributed to case definition, ethnic
background, source of patient population (community versus hospital-based), follow-up duration, and secular trend. In a landmark study of the natural history of ON spanning more than 50 years, the rate of conversion to MS proved to be a function of time and remained increasing beyond 30 years after ON [1]. Nevertheless, a significant fraction of ON patients remain event free for prolonged periods, underscoring the clinical heterogeneity of this condition. On the other hand, the interval between initial and second relapses in patients with NMO is generally shorter compared to that in MS. Therefore, it is anticipated that when ON signifies the initial event of NMO, the next clinical neuroimmune attack will happen sooner. However, this issue has seldom been specifically examined [9]. Furthermore, a common caveat in previous studies is the mixing-up of MS and NMO, in which NMO was viewed as a subset of MS [7, 10]. With the recognition that NMO and MS are clinically and immunologically distinct entities, it is prudent to study their relationships with ON respectively. The standard treatment for ON, intravenous methylprednisolone, has been established on the basis of the Optic Neuritis Treatment Trial, which showed that high-dose methylprednisolone treatment was associated with accelerated visual recovery and delayed onset of MS [11, 12]. Steroid treatment is believed to improve visual outcome in NMO-associated ON [13–15], whereas the relationship of steroid treatment and subsequent development of NMO remains to be clarified. Interferon beta agents have been used in selected ON patients to delay the progression to clinically definite MS [16], yet they may be potentially detrimental for NMO [17]. The differential treatment responses suggest that the immunological mechanisms of ON that later evolves to NMO could be distinct from that of MS-associated ON. Therefore, differentiation between various subtypes of ON are therapeutically relevant [14].

With these questions in mind, we conduct this nationwide population-based cohort study to better understand the long-term course of ON in Taiwan and the associated risk factors in relation to MS and NMO.

Methods

Data Source

This retrospective study used data retrieved from the Taiwan National Health Insurance (NHI)
Research Database (see Supplementary Methods, Additional File 1). The study protocol was approved by the National Taiwan University Hospital Research Ethics Committee (201904028RINC), and the need for informed consent was waived.

Study Population and Selection Criteria

From the source population, all incident cases of ON between January 1, 2003 and December 31, 2014 were identified. A diagnosis of ON was defined as being documented with the following International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes: 377.3x (optic neuritis) but exclude 377.33 (nutritional optic neuropathy) and 377.34 (toxic optic neuritis). We considered the diagnosis of incident ON to be valid if (1) ON was reported at least 3 times in the records of outpatient visits or once during hospitalization within a 3-month interval, and (2) ON was not diagnosed between January 1, 2001 and December 31, 2002. The initial date of diagnosis of ON was defined as the index date. Subjects were then excluded if they had received the diagnostic codes of NMO (ICD-9-CM: 341.0) or MS (ICD-9-CM: 340) between January 1, 2001 and the index date. Pediatric ON has been distinguished from ON in adults in terms of clinical manifestations and rate of conversion to MS [13, 15]. Therefore, the pediatric (0–19 years) and adult (20 years and above) subcohorts were examined separately.

Exposures

Comorbidities, with an emphasis on immune-mediated diseases, were identified using respective ICD-9-CM codes (Supplementary Table 1, Additional File 1). Treatment with systemic steroid was identified using Anatomical Therapeutic Chemical (ATC) codes (H02AB and H02B), and it was stratified to examine whether there were dose-response relationships between systemic steroid use after ON and subsequent risk of MS or NMO. To ensure the robustness of the results, the stratification was implemented in three different ways: (1) cumulative defined daily dose (DDD), stratified into quartile; (2) duration of systemic steroid use, stratified into 1–6 days, 7–14 days, and 15 days and above; (3) methylprednisolone use or not. Subjects not treated with systemic steroid after ON were used as the reference.

Study Outcomes and Follow-up
The study outcomes were MS and NMO, respectively. The diagnosis of MS and NMO were considered to be valid if they were reported in at least 3 outpatient visits within 2 years or once during hospital admission with the respective diagnostic codes. When a patient met both the criteria for MS and NMO, the diagnosis later made and preserved was adopted; otherwise NMO was assigned if both diagnoses were kept. All patients were monitored from the index date until the earliest occurrence of MS or NMO (defined as the event date), death, withdrawal from NHI, or the end of the study (December 31, 2015), whichever came first.

Statistical Analysis

The cumulative incidences for various clinical outcomes by study groups among the overall population were plotted using Fine and Gray’s subdistribution method to estimate cumulative incidence function [18]. The Cox proportional-hazards regression model was used to investigate if comorbidities and treatment could be associated with subsequent development of MS or NMO, with adjustment for other potential confounders. A substantial fraction of subsequent MS is expected to be diagnosed within three months after the index date (i.e., the initial date of ON diagnosis) [19]. These subjects were excluded in Cox regression models in order to focus on patients presumably having clinically isolated ON, and to evaluate the longer-term predictive utility of demographic and clinical variables. The final model included age, sex, timing of diagnosis, comorbidities, systemic steroid use at baseline (defined as prescription of systemic steroid in the 3 months preceding the index date), and systemic steroid use after ON (defined as prescription of systemic steroid within one month after the index date). The relative risk of conversion to MS or NMO was expressed as a hazard ratio (HR) and 95% confidence interval (CI). Statistical tests were two-sided, and a P value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina).

Data Availability

This study was based on datasets from Taiwan’s NHI Research Database. Taiwan’s Ministry of Health and Welfare owns the database and reviews application for data use for research purposes. All aggregate data and summary statistics in this study are presented in the article or uploaded as
Results

A total of 13837 incident ON cases were identified during 2003~2014. The crude annual incidence rate ranged between 4.43 (in 2012) and 5.89 (in 2005) per 100000 persons. Among the 13837 incident cases, 549 had the diagnosis of MS or NMO prior to ON and were hence excluded from the cohort analysis. The cohort (n=13288) consisted of 11923 (89.7%) adult cases, as well as 1365 (10.3%) cases under age 20. The mean (SD) age was 51 (16.8) and 13 (4.5) years for adult and pediatric ON, and 49.8% and 50.0% were male, respectively. Details of the demographic and clinical characteristics of the cohort, including comorbidities and treatment, were presented in Table 1.

The follow-up data were presented in Table 2. The median (interquartile range, IQR) follow-up duration was 76 (40,114) and 87 (51,124) months for adult and pediatric ON, respectively. MS occurred in 321 (2.7%) adults and 42 (3.1%) pediatric patients with ON. Among them, 179 (1.5%) and 21 (1.5%) cases were diagnosed within 90 days following the index date. After excluding MS cases diagnosed within 90 days following ON, the median (IQR) duration between ON and MS diagnosis was 17 (6,31) and 26 (12,45) months for adult and pediatric patients, respectively. NMO occurred in 146 (1.2%) adults and 16 (1.2%) pediatric patients with ON, with 65 (0.5%) and 8 (0.6%) cases diagnosed within 90 days following the index date, respectively. After excluding NMO cases diagnosed within 90 days following ON, the median (IQR) duration between ON and NMO diagnosis was 16 (8,31) and 14 (6,29) months for adult and pediatric patients, respectively. The cumulative incidences of MS and NMO in pediatric and adult sub-cohorts were presented in Figure 1 and Supplementary Figure (in Additional File 1).

The Cox regression analysis (Table 3) revealed that systemic steroid use at baseline and male sex were associated with decreased risks of conversion to MS in adult ON patients. The aHR (95% CI) for steroid use at baseline and male sex were 0.62 (0.38-1.00) and 0.33 (0.23-0.49), respectively. Systemic steroid use after ON and comorbid systemic lupus erythematosus (SLE) were associated with increased risks of conversion to MS in adult ON patients. The aHR (95% CI) for comorbid SLE were 2.80 (1.04-7.49). The aHR (95% CI) for systemic steroid use after ON, from lowest to highest
quartiles, were 1.06 (0.43-2.65), 3.13 (1.64-6.00), 7.38 (4.34-12.54), 8.22 (4.88-13.86). Different strategies of stratification, based on either cumulative drug day of systemic steroid use or whether methylprednisolone was used, yielded similar results with dose-response relationships (Supplementary Table 2, Additional File 1), attesting to the robustness of this finding. No significant interaction between systemic steroid use at baseline and after ON was found with regard to subsequent development of MS (see footnotes of Table 3 and Supplementary Table 2 in Additional File 1). Therefore, this interaction term was not incorporated into the final model.

Regarding conversion of adult ON to NMO, similar analysis showed that male sex was associated with a much decreased risk (aHR, 0.16; 95% CI, 0.08-0.32) (Table 3). Comorbid myasthenia gravis (MG) and Sjogren syndrome were associated with increased risks of conversion of adult ON to NMO, with aHR (95% CI) being 9.13 (1.20-69.45) and 4.71 (1.74-12.76), respectively. Systemic steroid use after ON was associated with an increased risk of conversion to NMO in adult ON patients, with the aHR (95% CI) from lowest to highest quartiles being 0.95 (0.20-4.58), 5.12 (1.93-13.54), 11.09 (4.81-25.59), 14.16 (6.23-32.18). Different strategies of stratification again yielded similar results with dose-response relationships, and replicated the significant findings described above (Supplementary Table 2, Additional File 1). No significant interaction between systemic steroid use at baseline and after ON was found with regard to subsequent development of NMO (see footnotes of Table 3 and Supplementary Table 2 in Additional File 1). Therefore, this interaction term was not incorporated into the final model.

Regarding pediatric ON, Cox regression analysis (Table 4, and Supplementary Table 3 in Additional File 1) revealed that male sex was associated with much decreased risks of MS (aHR, 0.15; 95% CI, 0.04-0.52) and NMO (aHR, 0.10; 95% CI, 0.01-0.83). Higher cumulative dosage of steroid use after ON was associated with an increased risk of conversion to MS, with the aHR (95% CI) of the third and the highest quartiles being 13.28 (3.56-49.54) and 6.91 (1.42-33.69), respectively. Comorbid SLE was also associated with an increased risk of conversion to MS in pediatric patients with ON (aHR, 21.65; 95% CI, 1.29-363.4).

Discussion
To our knowledge, this is the first large-scale cohort studies of ON in Asia. In this retrospective cohort of 11923 adult and 1365 pediatric ON patients with a median follow-up duration of 6.3 and 7.3 years respectively, MS occurred in 2.7% of adults and 3.1% of pediatric patients, and NMO occurred in 1.2% of adult and 1.2% of pediatric patients with ON. The incidence of ON in our study was comparable to other populations [1, 19], while the rate of conversion to MS was much lower compared with that reported from Caucasian populations. Together these findings were consistent with the low incidence rate of MS in Taiwan [20].

Although Sjogren syndrome and MG were uncommon (< 2% each) in ON patients in our study, they were significantly associated with subsequent development of NMO in adult patients with ON. Indeed, the association of Sjogren syndrome and NMO has been established [21, 22]. Coexistence of MG and NMO was also recognized to be more than chance, and MG usually preceded NMO [23]. Our study corroborates these observations by providing population-level evidence of the associations. To date, cancer was the only comorbidity formally listed as one of the “red flag” features in patients with ON [14, 24]. Together with prior knowledge, our findings suggest that comorbid Sjogren syndrome or MG are also worth consideration as red flags that prompt further investigations such as aquaporin-4 serostatus in these patients. On the other hand, although SLE is also a common comorbidity of NMO, we found that it is associated with an increased risk of MS, rather than NMO, in both pediatric and adult ON. Another study in Taiwan revealed that female first-degree relatives of SLE patients are at higher risk for MS [25]. Shared genetic predisposition (such as HLA-DRB1*1501) may partly account for the association between SLE and MS [26, 27], whereas their coexistence was rarely reported [28]. SLE per se may also present with ON [6, 29], which is considered mechanistically different from MS-associated ON. Therefore, ON in patients with SLE could be either a manifestation of lupus or the forme fruste of MS. Nevertheless, the double dissociation of autoimmune comorbidity patterns between MS-associated and NMO-associated ON strongly hints at distinct immunological mechanisms underlying these two types of ON. The role of immune-related comorbidities, in combination with brain MRI and serum and CSF biomarkers [30–32], could be further explored in research concerning predictive modeling and risk-adapted management of ON patients [4].
Despite that high-dose methylprednisolone has been established as the standard treatment for ON, variations in real-world practice continue to be noted [33]. This also appeared to be the case in our population, in which more than 20% of ON patients were given only corticosteroids other than methylprednisolone (Table 1). Our pharmacoepidemiological analysis showed that systemic steroid use after ON was associated with an increased risk of conversion to MS and NMO in a dose-dependent manner in adult population. At first sight this suggests that systemic steroid treatment for ON is detrimental in the long term, yet this interpretation incurs the risk of reverse causation, and it apparently contradicts existing knowledge [12]. The more plausible explanation is that prescription of systemic steroid reflects the judgment of clinicians about the immune-mediated nature of ON in the particular patient, presumably based on clinical or paraclinical features. The association of immunomodulatory medication with subsequent MS was also observed in other retrospective studies of pediatric and adult ON [4, 7], which could be similarly explicated.

It is intriguing to note that use of systemic steroid during the 3 months preceding ON was associated with a modestly decreased risk of MS in adults. This phenomenon has not been reported, and the reason is open to speculation. One possibility is that ON developing in the immunological milieu sculpted by corticosteroid has a different pathogenesis, or MS-associated ON might have been more readily ameliorated by the fortuitous use of systemic steroid. More research is needed to clarify this issue.

Previous studies showed that pediatric ON has been distinguished from ON in adults in terms of sex ratio, laterality, associated diseases and rate of conversion to MS [13, 15]. We found that female patients in this population was associated with much increased risks of MS and NMO. Besides, comorbid SLE and higher cumulative dosage of systemic steroid use after ON were independently associated with increased risks of conversion of pediatric ON to MS. All of these findings were qualitatively similar to that in adults. In contrary to general notion, the rate of conversion to MS or NMO in pediatric ON was not lower than that in adults in our study. This could be partly accounted for by the age cutoff (20 years) used here, since adolescent ON may be more akin to adult as opposed to prepubertal ON [34], while they were included in the pediatric group in our study. On the other hand,
if the prepubertal ON is specifically examined, analytical results would be less robust given the much smaller sample size.

The strength of this study lies in its national representativeness and unprecedented size of the cohort, making statistical modeling feasible. Although the findings are not directly generalizable to other populations, the clinical relevance herein deserves further research, as discussed above. Several limitations of this study should be considered. First, the diagnosis of individual case cannot be ascertained given the nature of datasets and the policy of the database provider. Second, although the temporal scale (spanning 15 years, median follow-up duration 6–7 years) is acceptable, it is insufficient to capture all cases of MS because some patients could run a more indolent course [1]. Third, certain features of ON, such as laterality and ophthalmologic findings, were associated with differential risks of MS or NMO [24, 35], and these features could affect clinicians’ decision regarding steroid use. In other words, they were the potential sources of confounding-by-indication. However, these information were not available for this study. Similarly, relevant serologic data and neuroimaging findings were also unavailable. Therefore, caution should be exercised in the interpretation of treatment effects with regard to subsequent risks of MS or NMO. Fourth, recurrent ON is associated with an increased likelihood of developing MS or NMO in children and adults [1, 31, 35, 36]. However, we were unable to address this issue because previous diagnosis code was often retained in subsequent visits in our electronic health information systems, making differentiation between inactive and relapsing ON difficult. Fifth, the awareness of NMO as a distinct clinical entity was relatively recent, and NMO could be underdiagnosed in the earlier years of our study period. Therefore, the association of timing of ON diagnosis with subsequent development of NMO in adults (Table 3) was likely artifactual.

Conclusions
This nationwide cohort study showed that the rate of conversion to MS was much lower in Taiwanese ON patients compared with that in Caucasian populations. Adult ON patients with comorbid MG or Sjogren’s syndrome were at increased risks of NMO, while those with comorbid SLE were associated with an increased risk of MS. Physicians’ discretion to prescribe systemic steroid for ON patients
matched quite well with future probability of MS or NMO. Collectively, our findings suggest that ON could represent the converging point of different immunopathogenetic pathways, and the immune context in which ON develops may provide hints that could be helpful in risk stratification, therapeutic decision making, and prognostication for these patients.

**Abbreviations**

aHR, adjusted hazard ratio; ATC, Anatomical Therapeutic Chemical; CI, confidence interval; DDD, defined daily dose; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; IQR, interquartile range; MG, myasthenia gravis; MS, multiple sclerosis; NHI, National Health Insurance; NMO, neuromyelitis optica; ON, optic neuritis; SLE, systemic lupus erythematosus.

**Declarations**

Ethics approval and consent to participate: The study was approved by the National Taiwan University Hospital Research Ethics Committee (Ref. No. 201904028RINC), and the need for informed consent was waived.

Consent for publication: Not applicable.

Availability of data and materials: This study is based on datasets from Taiwan’s National Health Insurance Research Database. Taiwan’s Ministry of Health and Welfare owns the database and reviews application for data use for research purposes. All analytical data relevant to the study are included in the article and its supplementary information (Additional File 1).

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by grants from the Ministry of Science and Technology, Taiwan (MOST 107-2314-B-002-165-), and National Taiwan University Hospital Yunlin Branch (NTUH106.A001 and NTUH108.F004). Taiwan Ministry of Science and Technology and National Taiwan University Hospital Yunlin Branch had no role in each of the following: design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; decision to submit the manuscript for publication.

Authors' contributions: WSL, JWL, and WTL conceived the study. HMC acquired the relevant datasets. WSL and HMC analyzed and interpreted the data. WSL drafted the initial manuscript. All authors
critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Acknowledgements: Not applicable.

Additional File
File name: Additional file 1.pdf

Title of data:
Supplementary Methods

Supplementary Table 1. Diagnosis codes used in this study

Supplementary Table 2-1. Adjusted hazard ratio of incidence of NMO and MS for patients with age >=20 (steroid use stratified by whether methylprednisolone was used)

Supplementary Table 2-2. Adjusted hazard ratio of incidence of NMO and MS for patients with age >=20 (steroid use stratified by cumulative duration)

Supplementary Table 3-1. Adjusted hazard ratio of incidence of NMO and MS for patients with age 0-19 (steroid use stratified by whether methylprednisolone was used)

Supplementary Table 3-2. Adjusted hazard ratio of incidence of NMO and MS for patients with age 0-19 (steroid use stratified by cumulative duration)

Supplementary Figure. Cumulative incidence rate of NMO and MS (excluding MS and NMO diagnosed within 90 days after the index date) (A) age 0-19 (B) age 20 and above.

References
1. Rodriguez M, Siva A, Cross SA, O'Brien PC, Kurland LT: **Optic neuritis: a population-based study in Olmsted County, Minnesota.** *Neurology* 1995, **45**(2):244-250.

2. Toosy AT, Mason DF, Miller DH: **Optic neuritis.** *The Lancet Neurology* 2014, **13**(1):83-99.

3. **Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up.** *Archives of neurology* 2008, **65**(6):727-732.

4. Heussinger N, Kontopantelis E, Gburek-Augustat J, Jenke A, Vollrath G, Korinthenberg
5. Isayama Y, Takahashi T, Shimoyoma T, Yamadori A: Acute optic neuritis and multiple sclerosis. Neurology 1982, 32(1):73-76.

6. Kim YM, Kim HY, Cho MJ, Kwak MJ, Park KH, Yeon GM, Lee Y, Nam SO: Optic Neuritis in Korean Children: Low Risk of Subsequent Multiple Sclerosis. Pediatric neurology 2015, 53(3):221-225.

7. Lin YC, Yen MY, Hsu WM, Lee HC, Wang AG: Low conversion rate to multiple sclerosis in idiopathic optic neuritis patients in Taiwan. Japanese journal of ophthalmology 2006, 50(2):170-175.

8. Francis DA, Compston DA, Batchelor JR, McDonald WI: A reassessment of the risk of multiple sclerosis developing in patients with optic neuritis after extended follow-up. Journal of neurology, neurosurgery, and psychiatry 1987, 50(6):758-765.

9. Pirko I, Bluwet LA, Lesnick TG, Weinshenker BG: The natural history of recurrent optic neuritis. Archives of neurology 2004, 61(9):1401-1405.

10. Phillips PH, Newman NJ, Lynn MJ: Optic neuritis in African Americans. Archives of neurology 1998, 55(2):186-192.

11. Beck RW, Cleary PA, Anderson MM, Jr., Keltner JL, Shults WT, Kaufman DI, Buckley EG, Corbett JJ, Kupersmith MJ, Miller NR et al: A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. The New England journal of medicine 1992, 326(9):581-588.
development of multiple sclerosis. The Optic Neuritis Study Group. *The New England journal of medicine* 1993, **329**(24):1764-1769.

13. Borchert M, Liu GT, Pineles S, Waldman AT: *Pediatric Optic Neuritis: What Is New*. *Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society* 2017, **37 Suppl 1**:S14-s22.

14. Jenkins TM, Toosy AT: *Optic neuritis: the eye as a window to the brain*. *Current opinion in neurology* 2017, **30**(1):61-66.

15. Yeh EA, Graves JS, Benson LA, Wassmer E, Waldman A: *Pediatric optic neuritis*. *Neurology* 2016, **87**(9 Suppl 2):S53-58.

16. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW: *Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group*. *The New England journal of medicine* 2000, **343**(13):898-904.

17. Shimizu J, Hatanaka Y, Hasegawa M, Iwata A, Sugimoto I, Date H, Goto J, Shimizu T, Takatsu M, Sakurai Y et al: *IFNbeta-1b may severely exacerbate Japanese optic-spinal MS in neuromyelitis optica spectrum*. *Neurology* 2010, **75**(16):1423-1427.

18. Fine JP, Gray RJ: *A Proportional Hazards Model for the Subdistribution of a Competing Risk*. *Journal of the American Statistical Association* 1999, **94**(446):496-509.

19. Soelberg K, Jarius S, Skejoe H, Engberg H, Mehlsen JJ, Nilsson AC, Madsen JS, Reindl M, Wildemann B, Grauslund J et al: *A population-based prospective study of optic neuritis*. *Multiple sclerosis (Houndmills, Basingstoke, England)* 2017, **23**(14):1893-1901.

20. Lai CH, Tseng HF: *Population-based epidemiological study of neurological diseases in Taiwan: I. Creutzfeldt-Jakob disease and multiple sclerosis*. 

14
Neuroepidemiology 2009, 33(3):247-253.

21. Iyer A, Elsone L, Appleton R, Jacob A: A review of the current literature and a
guide to the early diagnosis of autoimmune disorders associated with
neuromyelitis optica. Autoimmunity 2014, 47(3):154-161.

22. Min JH, Kim HJ, Kim BJ, Lee KW, Sunwoo IN, Kim SM, Kim BJ, Kim SH, Park MS, Waters
P et al: Brain abnormalities in Sjogren syndrome with recurrent CNS
manifestations: association with neuromyelitis optica. Multiple sclerosis
(Houndmills, Basingstoke, England) 2009, 15(9):1069-1076.

23. Leite MI, Coutinho E, Lana-Peixoto M, Apostolos S, Waters P, Sato D, Melamud L,
Marta M, Graham A, Spillane J et al: Myasthenia gravis and neuromyelitis optica
spectrum disorder: a multicenter study of 16 patients. Neurology 2012,
78(20):1601-1607.

24. Petzold A, Wattjes MP, Costello F, Flores-Rivera J, Fraser CL, Fujihara K, Leavitt J,
Marignier R, Paul F, Schippling S et al: The investigation of acute optic neuritis:
a review and proposed protocol. Nature reviews Neurology 2014, 10(8):447-458.

25. Kuo CF, Grainge MJ, Valdes AM, See LC, Luo SF, Yu KH, Zhang W, Doherty M: Familial
Aggregation of Systemic Lupus Erythematosus and Coaggregation of
Autoimmune Diseases in Affected Families. JAMA internal medicine 2015,
175(9):1518-1526.

26. Waubant E, Ponsonby AL, Pugliatti M, Hanwell H, Mowry EM, Hintzen RQ:
Environmental and genetic factors in pediatric inflammatory demyelinating
diseases. Neurology 2016, 87(9 Suppl 2):S20-27.

27. Barcellos LF, May SL, Ramsay PP, Quach HL, Lane JA, Nititham J, Noble JA, Taylor KE,
Quach DL, Chung SA et al: High-density SNP screening of the major
histocompatibility complex in systemic lupus erythematosus demonstrates
strong evidence for independent susceptibility regions. *PLoS Genet* 2009, 5(10):e1000696.

28. Fanouriakis A, Mastorodemos V, Pamfil C, Papadaki E, Sidiropoulos P, Plaitakis A, Amoiridis G, Bertsias G, Boumpas DT: **Coexistence of systemic lupus erythematosus and multiple sclerosis: prevalence, clinical characteristics, and natural history.** *Seminars in arthritis and rheumatism* 2014, 43(6):751-758.

29. Lin YC, Wang AG, Yen MY: **Systemic lupus erythematosus-associated optic neuritis: clinical experience and literature review.** *Acta ophthalmologica* 2009, 87(2):204-210.

30. Olesen MN, Soelberg K, Debrabant B, Nilsson AC, Lillevang ST, Graaslund J, Brandslund I, Madsen JS, Paul F, Smith TJ et al: **Cerebrospinal fluid biomarkers for predicting development of multiple sclerosis in acute optic neuritis: a population-based prospective cohort study.** *Journal of neuroinflammation* 2019, 16(1):59.

31. Zhou H, Zhao S, Yin D, Chen X, Xu Q, Chen T, Li X, Wang J, Li H, Peng C et al: **Optic neuritis: a 5-year follow-up study of Chinese patients based on aquaporin-4 antibody status and ages.** *Journal of neurology* 2016, 263(7):1382-1389.

32. Berger T, Rubner P, Schautzer F, Egg R, Ulmer H, Mayringer I, Dilitz E, Deisenhammer F, Reindl M: **Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event.** *The New England journal of medicine* 2003, 349(2):139-145.

33. Biousse V, Calvetti O, Drews-Botsch CD, Atkins EJ, Sathornsumetee B, Newman NJ: **Management of optic neuritis and impact of clinical trials: an international survey.** *Journal of the neurological sciences* 2009, 276(1-2):69-74.

34. Waldman AT, Stull LB, Galetta SL, Balcer LJ, Liu GT: **Pediatric optic neuritis and**
risk of multiple sclerosis: meta-analysis of observational studies. Journal of AAP: the official publication of the American Association for Pediatric Ophthalmology and Strabismus 2011, 15(5):441-446.

35. Lucchinetti CF, Kiers L, O'Duffy A, Gomez MR, Cross S, Leavitt JA, O'Brien P, Rodriguez M: Risk factors for developing multiple sclerosis after childhood optic neuritis. Neurology 1997, 49(5):1413-1418.

36. Absoud M, Cummins C, Desai N, Gika A, McSweeney N, Munot P, Hemingway C, Lim M, Nischal KK, Wassmer E: Childhood optic neuritis clinical features and outcome. Archives of disease in childhood 2011, 96(9):860-862.

Tables

Table 1. Demographic and clinical features of incident optic neuritis patients in 2003-2014

|                          | Age 0-19 (N=1,365) | Age 20 above (N=11,923) |
|--------------------------|--------------------|-------------------------|
| Male sex (%)             | 683 (50.0)         | 5933 (49.8)             |
| Mean of age, years (SD)  | 13.0 (4.5)         | 51.0 (16.8)             |
| **Comorbidity, No. (%)** |                    |                         |
| Allergic rhinitis        | 160 (11.7)         | 742 (6.2)               |
| Asthma                   | 67 (4.9)           | 447 (3.7)               |
| Atopic dermatitis        | 22 (1.6)           | 89 (0.7)                |
| Thyrotoxicosis           | 3 (0.2)            | 405 (3.4)               |
| Diabetes mellitus        | 11 (0.8)           | 1859 (15.6)             |
| Myasthenia gravis        | 3 (0.2)            | 28 (0.2)                |
| Regional enteritis       | 5 (0.4)            | 28 (0.2)                |
| Ulcerative enterocolitis| 0                  | 4 (0.0)                 |
| Systemic lupus erythematosus | 12 (0.9)       | 107 (0.9)               |
| Systemic sclerosis       | 0                  | 8 (0.1)                 |
| Sjogren syndrome         | 0                  | 128 (1.1)               |
| Dermatomyositis          | 0                  | 9 (0.1)                 |
| Rheumatoid arthritis     | 0                  | 100 (0.8)               |
| Polymyositis             | 0                  | 4 (0.0)                 |
| Malignancy               | 39 (2.9)           | 780 (6.5)               |

Steroid use at baseline (%) | 266 (19.5) | 2792 (23.4)

Steroid use within 1 month after index date (%)
### Drug type

| Drug Type   | Mean (SD) 18 | Median (Q1,Q3) 18 |
|-------------|-------------|-------------------|
| methylprednisolone | 493 (36.1) | 14 (7,23)         |
| oral only   | 280 (20.5)  | 177 (13.0)        |
| no use      | 592 (43.4)  | 14              |

### Cumulative drug day of steroids

| Duration         | Mean (SD) 18 | Median (Q1,Q3) 18 |
|------------------|-------------|-------------------|
| 1-6 days         | 15.3 (9.1)  | 14 (7,23)         |
| 7-14 days        | 15.7 (9.2)  | 14 (7,24)         |
| 15 and above     | 15 (9.1)    | 14 (7,23)         |

### Cumulative DDD of steroids

| Duration         | Mean(SD) 18 | Median (Q1,Q3) 18 |
|------------------|-------------|-------------------|
| 1-6 days         | 158.7 (150.0) | 139 (44,223)     |
| 7-14 days        | 138.1 (133.4) | 104 (28,220)     |
| 15 and above     | 1582 (13.2)  | 1514 (13.3)       |

Abbreviation: DDD, defined daily dose.

*a* steroid use during the three months preceding the index date.

Table 2. Follow-up of study patients with incident optic neuritis
| Variable                                                                 | No. (%)                      | Age 0-19 (N=1,365) |
|-------------------------------------------------------------------------|------------------------------|-------------------|
| Follow-up time, months                                                  |                              | 86.2 (42.3)       |
|                                                                         | Mean (SD)                    |                   |
|                                                                         | Median (Q1,Q3)               | 87 (51,124)       |
| Death                                                                   |                              | 46 (3.4)          |
|                                                                         | No. (%)                      |                   |
| **MS as endpoint**                                                      |                              | 1277 (93.6)       |
| death                                                                   |                              | 46 (3.4)          |
| event                                                                   |                              | 42 (3.1)          |
| **MS within 90 days after index date**                                   |                              | 21 (1.5)          |
|                                                                         | No. (%)                      |                   |
| **Lag time of MS, months (excluding MS within 90 days after index date)**|                              |                   |
| Mean (SD)                                                               | 29.1 (22.6)                  |                   |
| Median (Q1,Q3)                                                          | 26 (12,45)                   |                   |
| **NMO as endpoint**                                                     |                              | 1303 (95.5)       |
| death                                                                   |                              | 46 (3.4)          |
| event                                                                   |                              | 16 (1.2)          |
| **NMO within 90 days after index date**                                  |                              | 8 (0.6)           |
|                                                                         | No. (%)                      |                   |
| **Lag time of NMO, months (excluding NMO within 90 days after index date)**|                              |                   |
| Mean (SD)                                                               | 18.6 (15.9)                  |                   |
| Median (Q1,Q3)                                                          | 14 (6,29)                    |                   |

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica.

Table 3. Adjusted hazard ratio of incidence of NMO and MS for patients with age >=20

| MS                                                                 | aHR  | 95% CI   | P value |
|-------------------------------------------------------------------|------|----------|---------|
| Steroid use at baseline\(^{a,b}\)                                | 0.62 | 0.38-1.00| 0.05    |
| Cumulative DDD of steroid used within 1 month after index date\(^{a,b}\) |      | < .001   |         |
| No use                                                            | ref  |          |         |
| <Q1                                                               | 1.06 | 0.43-2.65|         |
| Q1-Q2                                                             | 3.13 | 1.64-6.00|         |
|                             | Male vs. female |  |  |  |
|-----------------------------|-----------------|---|---|---|
| Q2-Q3                      | 0.33            | 0.23-0.49 | < .001 |
| >=Q3                       | 8.22            | 4.88-13.86 |
| Male vs. female             | 0.33            | 0.23-0.49 | < .001 |
| Age                        | 0.97            | 0.96-0.98 | < .001 |
| Allergic rhinitis          | 1.04            | 0.49-2.17 | 0.92 |
| Asthma                     | 1.96            | 0.83-4.65 | 0.13 |
| Atopic dermatitis          | 0.95            | 0.13-6.90 | 0.96 |
| Thyrotoxicosis             | 0.00            | -            | 0.97 |
| Diabetes mellitus          | 0.64            | 0.29-1.41 | 0.27 |
| Myasthenia gravis          | 0.00            | -            | 0.99 |
| Systemic lupus erythematosus | 2.80          | 1.04-7.49 | 0.04 |
| Sjogren syndrome           | 0.35            | 0.04-3.00 | 0.34 |
| Rheumatoid arthritis       | 1.77            | 0.22-14.39 | 0.59 |
| all types of cancer        | 0.52            | 0.13-2.11 | 0.36 |
| Diagnosis of ON            |                 |              | 0.37 |
| 2003-2005                  | ref             |              |     |
| 2006-2010                  | 0.89            | 0.61-1.30 |
| 2011-2015                  | 0.71            | 0.44-1.14 |

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica; DDD, defined daily dose; ON, optic neuritis.

a If we add the interaction term of steroid use at baseline and use within 1 month after index date in the model of MS analysis, the P value of interaction term is 0.2710.

b If we add the interaction term of steroid use at baseline and use within 1 month after index
date in the model of NMO analysis, the P value of interaction
term is 0.6847.

Table 4. Adjusted hazard ratio of incidence of NMO and MS for patients with age 0-19

| MS                                      | aHR  | 95% CI   | P value |
|-----------------------------------------|------|----------|---------|
| Steroid use at baseline                 | 0.09 | 0.01-1.25| 0.07    |
| Cumulative DDD of steroid used within 1 month after index date |       |          | < .001  |
| No use                                  | ref  |          |         |
| <Q1                                     | 0.83 | 0.08-8.80|         |
| Q1-Q2                                   | 3.97 | 0.79-20.01|        |
| Q2-Q3                                   | 13.28| 3.56-49.54|        |
| >=Q3                                    | 6.91 | 1.42-33.69|        |
| Male vs. female                         | 0.15 | 0.04-0.52 | 0.003  |
| Age                                     | 0.99 | 0.89-1.11 | 0.91   |
| Allergic rhinitis                       | 0.74 | 0.15-3.73 | 0.72   |
| Asthma                                  | 1.54 | 0.17-14.13| 0.70   |
| Systemic lupus erythematosus            | 21.65| 1.29-363.4| 0.03   |
| Diagnosis of ON                         |      |          | 0.37    |
| 2003-2005                               | ref  |          |         |
| 2006-2010                               | 0.97 | 0.38-2.50|         |
| 2011-2015                               | 0.34 | 0.07-1.64|         |

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica; DDD, defined daily dose; ON, optic neuritis.
Figures
Figure 1

Cumulative incidence rate of NMO and MS. (A) age 0-19 (B) age 20 and above.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Additional file 1.pdf