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Evaluation of comorbidities and health care resource use among patients with highly active neuromyelitis optica

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ABSTRACT

Background: Neuromyelitis optica (NMO) is characterized by unpredictable attacks on the optic nerves and spinal cord, causing accumulations of neurological disability that may lead to blindness and paralysis. We examined comorbidities and health care use among patients with highly active NMO, defined as at least two relapses within 12 months of the patient's first NMO encounter in the database.

Methods: This retrospective study of a US administrative claims database compared patients with highly active NMO to matched individuals without NMO. All outcomes, including Charlson Comorbidity Index (CCI) score, hospitalizations, and emergency department visits, were measured over the 12-month period following the patient's first NMO encounter in the database.

Results: A total of 1349 patients with NMO were identified. Of these, 134 had highly active NMO (80% female, mean age 45.6 years) and were matched to 670 non-NMO controls. Patients with highly active NMO had significantly greater comorbidity burden than non-NMO controls (mean CCI score: 4.1 versus 0.6; $P < 0.0001$) and greater proportions of hospitalization (53.7% versus 4.0%; $P < 0.0001$) and emergency department visits (60.5% versus 9.7%; $P < 0.0001$).

Conclusions: High occurrence of several acute and chronic conditions and extensive health care use highlight the significant medical burden among patients with highly active NMO.

1. Introduction

Neuromyelitis optica (NMO) is a life-threatening, rare, autoimmune disease of the central nervous system. It is characterized by acute optic neuritis and longitudinally extensive transverse myelitis resulting in an accumulation of substantial, and often permanent, neurologic deficits and disability, including blindness and paralysis [1,2]. Population-based studies from a number of countries suggest worldwide prevalence rates of 0.5 to 4.4 per 100,000 individuals [3]. In the United States (US), the estimated prevalence of NMO is 4000 to 8000 patients [3]. Women are much more commonly affected than men, with a 3:1 female-to-male ratio [4]. The median age of onset is generally in the late 30s, but a wide range is reported [4,5].

The clinical presentation of NMO can be quite variable, which, when combined with the rarity of the condition, can lead to delayed diagnosis and treatment. Unilateral or bilateral optic neuritis, including central visual loss with ocular pain, is often the initial event of relapsing NMO. Clinical manifestations of myelitis may include severe paraplegia, sensory loss, bladder dysfunction, spasms, and pain. Brainstem involvement may manifest with nausea, vomiting, hiccups, vertigo, hearing loss, facial weakness, trigeminal neuralgia, diplopia, ptosis, or nystagmus [6]. Myelitis that extends into the brainstem may cause respiratory failure and death [7].

It is estimated that 80% to 90% of NMO cases follow a relapsing, rather than monophasic, disease course [4,8]. The prognosis of relapsing NMO is poor, particularly among patients with frequent relapses [9,10]. NMO relapses have been associated with long-term visual and motor disability. A prior study among 106 patients with NMO found that relapsing NMO resulted in 34% of patients with permanent motor disability, 23% patients with wheelchair dependency, and 18% with permanent blindness during the 6 years of follow-up. Moreover, 9% of patients had died by the end of follow-up [11]. Another study that used

Abbreviations: AQP4, aquaporin 4; AQP4-IgG, aquaporin 4–immunoglobulin G; CCI, Charlson Comorbidity Index; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; MS, multiple sclerosis; NMO, neuromyelitis optica; Q1, first quartile; Q3, third quartile; SD, standard deviation; Th, T-helper; US, United States.

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predictive models among patients with NMO concluded that greater relapse frequency was associated with a 20% increased risk of mortality per attack (relative risk, 1.21) [9]. Unlike multiple sclerosis (MS), where a secondary progressive phase is common later in the disease for those who initially present with relapsing remitting disease and serves as a major predictor of disability, in NMO, the disability accumulation is stepwise and directly associated with the sequelae of acute attacks [9–12]. Therefore, relapse prevention is paramount for successful treatment of relapsing NMO.

No therapies are currently approved for the treatment of NMO. High-dose intravenous corticosteroids are typically used for the treatment of acute relapses, with plasma exchange often used as rescue therapy for patients who do not respond to corticosteroids. Immunosuppressant therapies such as azathioprine, mycophenolate mofetil, and rituximab are commonly used for long-term stabilization and prevention of relapse [13]. Despite these treatments, more than half of patients will continue to experience acute attacks resulting in additional and potentially permanent neurologic disability [13–15].

In addition to the burden associated with acute relapses and the residual and accumulated disability that results from these attacks, patients with NMO also tend to have a variety of comorbid conditions. A recent systematic review of comorbid conditions associated with NMO suggests that several autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis, and myasthenia gravis co-occur with NMO [16]. Evidence also exists regarding the greater expression of AQP4 antibodies among patients with NMO and possible co-occurrence with neoplastic conditions [17]. In addition, a study conducted in the United Kingdom suggests substantial cognitive and psychiatric comorbidities among patients with NMO [18]. Although previous studies have provided evidence regarding high prevalence of comorbid conditions among patients with NMO, no prior study has comprehensively examined the prevalence using data from patients treated in real-world settings.

To gain a fuller appreciation of the medical burden of NMO, particularly among patients with frequent relapses and for whom the need for effective treatment is most urgent, we sought to measure the prevalence of comorbidities and proportions of clinical event-driven health care resource use in the US using a large, administrative insurance claims database.

2. Methods

2.1. Study design

We conducted a retrospective case-control study designed to examine incremental comorbidity and health care resource use burden among patients with highly active NMO, defined as at least two relapses within 12 months of the patient's first NMO encounter in the database, compared with the overall NMO population and with age- and sex-matched individuals without NMO.

2.2. Data source

For the purposes of this study, we used multiple years (2009–2014) of the MarketScan Commercial Claims and Encounters database and the MarketScan Medicare Supplemental database. In the US, insurance providers include government-sponsored plans such as Medicare (covering elderly individuals aged 65 years or older and disabled beneficiaries), Medicaid (covering individuals below a certain threshold of the poverty line), and nongovernment commercial plans that are generally provided by employers. These databases contain employer- and health-plan–sourced information on medical and drug utilization of beneficiaries enrolled in privately insured fee-for-service plans, such as preferred and exclusive provider organizations, point-of-service plans, indemnity plans, health maintenance organizations, consumer-directed health plans, and capitated health plans [19]. Complete payment and charge information, dates and place of service (e.g., inpatient, outpatient, emergency), diagnoses, procedures, and detailed information on hospitalizations, including admission and discharge dates, can be retrieved from medical claims within these databases. Pharmacy claims in these databases include complete outpatient prescription drug information, which consists of patient co-payments, mail-order drugs, injectables, drugs from specialty pharmacies, and all standardized prescription-level fields collected on a typical pharmacy claim (e.g., date of fill/refill, drug name and class, strength, quantity, days' supply).

These databases also contain medical (i.e., inpatient, outpatient, physician office, and ancillary services) and pharmacy claims for Medicare-eligible retirees with employer-sponsored Medicare supplemental plans. Since de-identified unique patient numbers were used to tracked patients longitudinally and no patient consent forms were required, the institutional review board at RTI International determined this study to be exempt.

2.3. Eligibility criteria

2.3.1. Patients with NMO

Enrollees were identified as having NMO if they met either of the following criteria between January 1, 2009, and June 30, 2013: (1) had at least one inpatient or two outpatient visits for an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis of NMO (ICD-9-CM code 341.0), or (2) had at least two visits ($\geq$ 6 months apart) for a diagnosis of transverse myelitis (ICD-9-CM code 341.2x or 323.82) in combination with at least one visit for an inflammatory optic-related condition (most commonly ICD-9-CM code 377.3). Due to the lack of laboratory data, and unavailability of aquaporin 4–immunoglobulin G (AQP4-IgG) test to identify patients with NMO, we relied on ICD-9-CM diagnostic codes to identify patients with NMO. Although, these tests may have lower accuracy than biomarker tests, we included ICD-9-CM codes for NMO and allied conditions (transverse myelitis and optic-related conditions) to obtain a pool of patients with possible NMO. To avoid classifying patients with MS with certain similar symptoms as having NMO, we excluded enrollees who had been treated with beta-interferon therapy or other MS-related treatments (i.e., glatiramer acetate, natalizumab, dimethyl fumarate, teriflunomide, and fingolimod). Finally, individuals with a diagnosis of MS after the initial NMO, transverse myelitis, or optic neuritis diagnosis were excluded from the study population. The first date of an NMO, transverse myelitis, or optic neuritis event was considered to be the *index date*.

2.3.2. Patients with highly active NMO

To identify the highly active relapsing NMO population, we further restricted our NMO population to those with at least two relapses in the 12 months following the index date. A relapse event was defined as either (1) an inpatient visit with a principal discharge diagnosis of NMO, transverse myelitis, optic neuritis, or other associated neurological condition (identified by clinical expert); (2) an inpatient/outpatient visit for intravenous methylprednisolone (five administrations); or (3) an inpatient/outpatient visit for plasma exchange or intravenous immunoglobulin. Relapse events occurring within 28 days of each other were part of a single relapse.

For all patients with NMO, the first month (i.e., first 30 days) following the index date was not used for assessment of outcome measures in order to eliminate the bias of counting the health care encounter that led to their identification. Thus the 12-month follow-up period for cases was month 2 through month 13 after their index date. Patients with NMO with $<$ 13 months of continuous enrollment after their index date were excluded from the study.

2.3.3. Non-NMO controls

We obtained a 5% random sample of the MarketScan databases for the purposes of analyzing non-NMO enrollees (control cohort). Patients