A Meta-Analysis of Neuromyelitis Optica Epidemiology in Latin American Nations

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A META-ANALYSIS OF NEUROMYELITIS OPTICA EPIDEMIOLOGY IN LATIN AMERICAN NATIONS

by

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ABSTRACT

Neuromyelitis Optica (NMO) is a rare, autoimmune, neurodegenerative disease selectively affecting the optic nerves and spinal cord. Relapsing NMO is nine times more prevalent in women than in men and approximately one-quarter of NMO patients have symptoms of another autoimmune disorder (National Institute of Health, 2019). NMO has not been linked to any genetic mutations and the cause of the disorder is unknown beyond the general understanding that the body produces anti-aquaporin-4 antibodies (AQP4) which mistakenly attack cells in the nervous system. NMO affects roughly one percent of that of Multiple Sclerosis (4000-8000 patients total) in the United States, but prevalence rates are abnormally high in a handful of regions around the world, particularly among Latin America, where rates can reach up to 5/100,000 individuals. The results of this study predict that there is a connection between African genetics and NMO, but further studies will need to be conducted in more Latin America nations and other regions to determine prevalence rates as well as genetic analysis of affected individuals.

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CHAPTER ONE: INTRODUCTION

Neuromyelitis Optica (NMO) is a rare, autoimmune demyelinating disorder of the central nervous system, selectively affecting the optic nerves and spinal cord (Wingerchuk et al, 2007). The causative agent for symptoms has been identified as the anti-aquaporin-4 antibody (also known as NMO-IgG) (Weinshaker et al, 2006). Routine diagnostic criteria have evolved since the pathologic antibody was discovered in 2004 and the biomarker was deemed undetected in definite multiple sclerosis (MS) cases. Prior to the discovery of the biomarker, Neuromyelitis Optica was routinely misdiagnosed as MS.

The incidence of NMO has varied as physicians become knowledgeable in NMO diagnostic criteria. Internationally, the incidence of NMO has ranked less than 1/100,000 inhabitants (Ann-Marrie, 2013). In Latin American nations, prevalence for the disease has ranged from 0.5-5/100,000 inhabitants (Alvarenga, Schmidt & Alvarenga, 2017). The disease affects primarily non-Caucasian women between the ages of 30-40 years old but does not exclude men, children or the elderly. In Latin American nations, prevalence mirrors non-Caucasian roots and affects primarily women between the ages of 30-40 of African descent (including mestizo and afro-Caribbean people).

The prevalence of NMO across individual Latin American nations continues to be studied as healthcare professionals gain a better understanding of the disease. Current literature aims to statistically analyze epidemiology and points to strong African roots in affected patients. Despite this strong correlation, researchers have failed to investigate historical components of Latin American and African history that may potentially shine light on prevalence patterns across the

region. This research aims to analyze the historic African impact on various high prevalence Latin American nations in comparison to low prevalence nations and seeks to question the potential correlation between slave importation and present-day population distributions to NMO prevalence. Additionally, this paper will analyze epidemiological studies of Neuromyelitis Optica in various Latin American Nations for additional data.

CHAPTER TWO: LITERATURE REVIEW

2.1 Diagnostic Criteria

Neuromyelitis Optica (NMO) dates back to 1894, when Eugène Devic and Fernand Gault coined the disease and presented their findings to the Congrès Français de Mėdecine in Lyon (although it is believed that NMO was described earlier than this by Antoine Portal in 1804). The disease was originally characterized by monophasic attacks of optic neuritis (ON) and transverse myelitis (TM). By the 1900s, over 100 cases had been reviewed in the literature and relapsing cases gained attention (Bennett, 2006).

Before 1999, diagnostic criteria for Neuromyelitis Optica was not definitively outlined and the disease was rarely recognized as a separate entity from other neurodegenerative disorders such as Multiple Sclerosis. Wingerchuk et al conducted the first, large-scale analysis of Neuromyelitis Optica cases through imaging, clinical presentation, CSF characteristics, and epidemiology. NMO was strictly defined as bilateral ON and TM occurring within a two-year period, and NMO falling outside of this criterion included cases of unilateral ON or recurrent relapses over greater than a two-year period (Wingechuk et al, 1999). Since 1999, NMO criteria has been updated to reflect new literature and further discovery. The most recent revision of the standard international criteria was released in 2015 and has been divided to reflect the various forms of NMO that together have become known as Neuromyelitis Optica Spectrum Disorders (NMOSD).

The present-day diagnostic criteria and growing interest in Neuromyelitis Optica research skyrocketed after the Mayo Clinic identified the first biomarker associated to an inflammatory,

demyelinating disease (Lennon et al, 2004). This biomarker, the aquaporin-4 (AQP4) antibody, is present in more than 80% of Neuromyelitis Optica patients who undergo second-generation recombinant diagnostic assays for AQP4-Ab detection (Wildemann and Jarius, 2014). Discovery of the biomarker led researchers to further investigate the role of aquaporin in the brain and in subsequent Neuromyelitis Optica attacks. *In-vitro* studies conducted by several investigators found a disruption of the blood brain barrier (BBB), impairment of glutamate homeostasis, and induction of necrotic cell death by AQP4-Ab positive serum. Definitive proof of such mechanism did not exist until several animal studies demonstrated CNS lesions and disease characteristics following the transfer of AQP4-Ab positive serum to otherwise healthy mice.

2.2 Differential Diagnosis

NMO continues to be misdiagnosed due to its rarity and lack of recognition among neurologists and scientists in the greater community. Although it is becoming more well-understood as physicians and other medical professionals begin better identifying the illness in clinical settings and medical schools begin integrating it into their curricula, the disease still faces similarities to multiple sclerosis (MS) and other autoimmune, demyelinating disorders of the nervous system.

With this problem in mind, Wingerchuk et al (2007) continue to update NMO diagnostic criteria to further the understanding of NMO presentation and pathology. The current guidelines for NMO diagnosis focus on meeting core clinical characteristics and excluding alternate diagnosis. Core clinical characteristics of NMO include “optic neuritis, acute myelitis, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical MRI

lesions, and symptomatic cerebral syndrome with NMOSD-typical brain lesions." (Wingerchuk et al, 2015). In patients that are seronegative for AQP4-Ab (15-20% of all NMO cases), diagnostic criteria are stricter and two core clinical characteristics must be present, along with supporting MRI characteristics. To further differentiate NMO from its common misdiagnosis, MS, a series of MRI characteristics have been identified for the brain and spinal cord.

Brain lesions are typically more common for MS patients than NMO patients, which calls for increased attention when surveying patient MRI's as diagnostic tools. In NMO patients, lesions of the periventricular regions of the third and fourth ventricles, supratentorial and infratentorial white matter, midbrain, and cerebellum were most common (seen in 68% of NMOSD children with available MRI data). This was consistent with data that reported 45-55% of cases showing episodic cerebral symptoms (such as vomiting, hiccups, behavioral changes, narcolepsy, and ataxia, among other disorders). Asymptomatic lesions of the area surrounding the third ventricles and cerebral aqueduct have also been reported. The dorsal brain stem, including the area postrema and the nucleus tracts solitarius are also common sites for abnormalities, believed to be caused by a less restrictive blood brain barrier (BBB) in the region making it more accessible to autoimmune attack. 40% of NMOSD patients were found to have these abnormalities, without obvious neurodegeneration. Extensive hemispheric white matter lesions have been found in NMOSD patients as well, particularly in seropositive cases. These lesions cause a variety of symptoms depending on location, including hemiparesis, visual field defects, etc. Lesions involving the corticospinal tracts have also been identified in 23-44% of patients, however, their frequent expression is poorly understood due to the fact that AQP4 is not highly expressed in these regions. In contrast, MS lesions of the periventricular and callosal type

are discrete, ovoid masses perpendicular to the ventricles, unlike the extensive, “clouding” NMO lesions. (Kim et al, 2015).

Spinal cord findings in NMOSD also follow a distinct pattern unlike that of MS. Most notably, spinal cord lesions in NMOSD tend to be longitudinal extensive (greater than three vertebral segments) and present in the cervical and upper thoracic segments. It should still be noted that longitudinally extensive transverse myelitis (LETM) is common in those with monophasic transverse myelitis and sometimes seen in multiple sclerosis, calling for a cumulative review of all symptoms and diagnostic tools, nonetheless. NMOSD patients are also less likely to develop silent MRI lesions than MS patients (Kim et al, 2015).

2.3 Treatment

Until recently, Neuromyelitis Optica had no widely applicable, FDA approved treatment plan for acute or relapsing attacks. To date, acute attacks are initially treated by a starting dose of 1000mg corticosteroid treatment (usually methyl-prednisone) over five days followed by a two to eight-week oral taper to reduce inflammation quickly and prevent subsequent neuronal damage and/or permanent disability (Kessler, Mealy, Levy, 2016). Seropositive patients who do not quickly respond to steroid treatments are offered plasmapheresis treatments over several weeks to remove circulating autoantibodies causative of attacks (Kim et al, 2013). Cost of plasmapheresis makes it a second option in most cases, except in cases of severe cervical myelitis where neurogenic respiratory failure is a high risk.

Long-term treatment of NMO includes immunosuppressive therapy and symptomatic treatment. Rituximab, mitoxantrone, and intravenous immunoglobulin are common forms of

long-term treatment, the latter being a serum-replacement instead of an immunosuppressive therapy. Similar to plasmapheresis, this treatment is also costly and is typically reserved as a last line of defense for resistant or high-risk cases (Wingerchuk et al, 2007).

Misdiagnosis of NMO as MS is common and can lead to a worsening by mistreatment. Treatments for MS tend to include interferon beta and glatiramer acetate injections that, when prescribed to NMO patients, have been found to further aggravate symptoms and lead to further disability. Recent studies by Palace et al, Kim et al, Asgari et al, and several other researchers have found interferon beta to not only be an ineffective course of treatment for NMO, but responsible for exacerbating symptoms and increasing relapse rates via autoimmune mechanisms (Asgari, 2014).

2.4 High Prevalence Populations

Recurrent NMO in black women is consistently described in the Caribbean islands as well as Rio de Janeiro, Brazil. While some regions of Latin America see prevalence rates as low as 0.37/100,000 (Volta Redonda City), the Caribbean islands see rates as high as 4.2/100,000 (Alvarenga, Schmidt, Papais-Alvarenga, 2017). In a "Nationwide Epidemiological Study of Neuromyelitis Optica in Japan," Miyamoto et al (2018) established that NMO may be more prevalent in Asia, Africa, and Latin America based on previous studies, as well as their conclusion that NMO prevalence in Japan (containing a homogenous population with Asian influence) reached 3.42/100,000. The same team conducted a comparative population-based study of NMO in Olmsted County, Minnesota, USA (82% Caucasian) and Martinique, France (90% Afro-Caribbean), and found that prevalence of Martinique reached up to 10 per 100,000.

This study, however, also noted a prevalence rate of 3.9/100,000 in Olmstead County which is unusually high for an American, Caucasian population. This may be attributed to the fact that the Rochester Mayo Clinic is located within Olmstead County, MN and is a major site of NMO treatment and research.

2.5 Current Research and Clinical Trials

Current research in NMO focuses primarily on understanding the pathogenesis of the disease as well as exploring potential treatment methods and cures. The use of monoclonal antibodies in treatment of the disease has become a major focus.

Current clinical trials utilizing monoclonal antibodies are currently being conducted by MedImmune LLC and Johns Hopkins University. The MedImmune team is investigating the usage of MEDI-551 (Cree et al., 2015), a monoclonal antibody that depletes CD19+ B-cells, one of the antibody-producing plasma cells found to be selectively increased in NMO, according to research conducted by Bennett et al (2015). Monoclonal antibody clinical trial work at Johns Hopkins University is currently focusing on the depletion of CD20+ B-cells, according to the same pattern of research that has identified it as a likely progenitor for the production of anti-AQP4 producing plasma cells (Levy, 2014).

Investigations into the pathogenesis of NMO are plentiful throughout the United States. As previously discussed, epidemiology is consistently updated to reflect advances in our understanding of molecular mechanisms of relapse, and treatment methods are further refined in favor of new data, such as the widespread contraindication of interferon beta. Several studies

also aim to uncover genetic predispositions to the disease, such as those conducted by Matiello et al (2010) and Alonso et al (2018).

Outside of the United States, various nations contribute to Neuromyelitis Optica research, large contributors being China, Canada, and the United Kingdom. International studies of Neuromyelitis Optica follow similar investigations in pathogenesis and potential treatment methods. Regional and international conferences are held in the name of NMO research to present findings and invite patients to participate and sample collection and clinical trial research, such as the Guthy-Jackson Charitable Foundation annual NMO Patient Day and Conference.

CHAPTER THREE: METHODOLOGY

3.1 Experimental Approach

Our approach for this study was to begin by identifying the number of African slaves that were imported into various Latin American nations, compile this data with present-day African population proportions in such nations, and compare this information to present day NMO prevalence rates. From the review of literature, it was apparent that Afro-Caribbean populations in Latin America faced higher rates of NMO than other groups, and so a comprehensive comparison of these data sets were the main focus. The Trans-Atlantic Slave Database was consulted to acquire embarkation and disembarkation data of the nations used in this study, while nations that had an abundant and conclusive level of NMO literature were also chosen to be included. Studies without a conclusive prevalence estimate but with useful epidemiological data were also found. Many nations in Latin America did not have applicable epidemiological data and so these were not discussed in this study.

CHAPTER FOUR: RESEARCH FINDINGS

4.1 Cuba

Neuromyelitis Optica rates among the Cuban multiethnic population were on the lower end of the spectrum compared to other Latin American nations. Black patients were older with a greater rate of relapse and more severe motor impairment (Gomez, Quevedo & Rodriguez, 2009). The percentage of mulattos/mestizos and black Cubans was identified by the Library of Congress' Country Profile on Cuba, which reflected the most recent 2002 census (Library of Congress, 2006). African slave importation skyrocketed after 1750 through 1875, bringing the estimated total number of slaves that survived and successful disembarked in Cuba to over 778,000.

Table 1

Table 1: African slaves disembarked in Cuba between 1651 and 1875.

	Disembarked
1651-1675	336
1701-1725	2417
1726-1750	991
1751-1775	8386
1776-1800	56239
1801-1825	228516
1826-1850	317709
1851-1875	163947
Totals	**778541**

4.2 Mexico

Mexico's prevalence rate was determined by a retrospective study of hospital case records, which identified 34 patients who met NMO diagnostic criteria. All 34 patients identified as Mexican Mestizo which represents 79% of the Mexican population (Rivera, Kurtzke, Booth & Corona, 2008). It should be noted that the Mexican census did not identify Afro-Mexican individuals outside of mestizo and so Afro-Mexican individuals typically identify as Mexican mestizos.

The African impact on Mexico is a relatively mysterious field of study demonstrated by 1) the lack of African identification in national censuses and 2) the lack of accurate data describing the population breakdown of the nation. Although the most data found counted imported African slaves to Mexico at roughly 200,000, this data does not account for children born to slaves (who subsequently became slaves) or the reproduction of African men and women with indigenous and Europeans, resulting in an additional African-rooted Mestizo and Afro-Mexican population (Africa's Legacy in Mexico, n.d.).

4.3 French West Indies

The French West Indies notably expressed one of the highest rates of NMO in Latin America at 3.1/100,000 individuals. Additionally, the French West Indies had the highest Afro-Caribbean population demographics at just over 90% (Cabrera et al, 2009). Out of the nations studied, they also had the highest total number of imported slaves at over 1.1 million.

Table 2

Table 2: African slaves disembarked in Saint Domingue between 1676 and 1825.

	Disembarked
1676-1700	4924
1701-1725	43373
1726-1750	140559
1751-1775	244193
1776-1800	339686
1801-1825	808
Totals	**773543**

Table 3

Table 3: African slaves disembarked in Guadeloupe between 1651 and 1850.

	Disembarked
1651-1675	3082
1676-1700	268
1701-1725	1223
1726-1750	885
1751-1775	28694
1776-1800	12980
1801-1825	22270
1826-1850	3469
Totals	**72871**

Table 4

Table 4: African slaves disembarked in Martinique between 1626 and 1850.

	Disembarked
1626-1650	545

1651-1675	7677
1676-1700	10317
1701-1725	32639
1726-1750	67557
1751-1775	29966
1776-1800	30135
1801-1825	24279
1826-1850	13796
Totals	**216911**

Table 5

Table 5: African slaves disembarked in French Guiana between 1651 and 1850.

	Disembarked
1651-1675	1121
1676-1700	1425
1701-1725	1317
1726-1750	2550
1751-1775	3535
1776-1800	6262
1801-1825	10031
1826-1850	4358
Totals	**30599**

Table 6

Table 6: African slaves disembarked in French Caribbean, unspecified between 1651 and 1850.

	Disembarked
1651-1675	1121
1676-1700	1425
1701-1725	1317
1726-1750	2550
1751-1775	3535
1776-1800	6262
1801-1825	10031

1826-1850	4358
Totals	30599

4.4 Additional Studies

A South African study investigating the cause behind recurrent, multiphasic, demyelinating disease of the central nervous system was clinically identified as Neuromyelitis Optica with features of acute disseminated encephalomyelopathy. Some MRI imaging found lesions typical to multiple sclerosis, however, the patients were all determined to originate from a population with little MS prevalence. These patients were notable cases in the sense that they were not seropositive for NMO-IgG. Like NMO presentation, they were sensitive to anti-inflammatory steroid therapies. (Mod, Mochan, Saffer, 2001).

In a cross-sectional study conducted among multiple cities in South America and Brazil, a total of 226 patients meeting the 2006 NMO criteria were identified. The recurrent group made up 188 of those patients and was predominantly occupied by women and people of African descent. The monophasic group was predominantly occupied by women and whites and included pediatric forms of the disease. In a separate group of Neuromyelitis Optica Spectrum Disorders (NMOSD), 86 patients were identified and again dominated by women and those of African heritage (Alvarenga et al, 2015).

CHAPTER FIVE: CONCLUSION AND DISCUSSION OF RESULTS

5.1 Discussion

Various regions in Latin America have failed to provide adequate data regarding NMO prevalence as well as population demographics, making many nations unfit for the study. These results suggest that in general, Latin American nations with a higher African demographic and higher embarkation level see higher rates of NMO prevalence, as demonstrated in the French West Indies with an extremely skewed demographic and 3.1/100,000 rate, more than triple the international average.

Table 7

Table 7: A comparison of slaves imported, population distribution, and NMO prevalence in Latin American Nations with published data.

Nation	**Estimated Total Number of African Slaves Imported Between (1501-1866)**	**Percentage of the present population identified as Afro-Latinx/Mestizo**	**NMO Prevalence Rate (per 100,000)**
Cuba	778,541	62%	0.52
Mexico	~200,000	79%	~1
French West Indies	1,120,215	90%	3.1

All of the following tables were created using data extracted from the Trans-Atlantic Slave Trade database (Emory University, 2013).

The connection between genetics and NMO is not well-understood or described otherwise in the literature. While nations such as the French West Indies fell into the expected results, Mexico saw a slightly elevated NMO prevalence rate with a very low African importation count.

5.2 Conclusions and Further Directions

The results of this study predict that there is a connection between African genetics and NMO, but further studies will need to be conducted in more Latin America nations and other regions to determine prevalence rates as well as genetic analysis of affected individuals. This study paves way for further investigation in prevalence rates of surrounding nations in Latin America, a genetic investigation into African heritage and its role in the development of NMO, and an analysis of symptom severity among different ethnic groups, to further investigate the cause for more severe motor impairments in black NMO patients in Cuba (Gomez, Quevedo & Rodriguez, 2009).

Additionally, future research should expand this work to other nations beyond Latin America, such as Japan and Russia, to better determine how NMO is distributed across the globe and to also collect more samples for genetic analysis in the non-Afro-rooted populations.

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