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Neuromyelitis optica spectrum disorders in the Arabian Gulf: challenges and growing experience

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Abstract

Neuromyelitis optica spectrum disorders (NMOSD) have been studied in different ethnic groups, including Asians, African-Americans, and Caucasians. Demonstrating the clinical features among diverse communities is important to understand the variable disease phenotypes, which will lead to further classification and better clinical management. Testing for antibody against aquaporin-4 (AQP4), the most common target antigen in NMOSD, is not available in many countries and tests use different methods, with variable sensitivity. With negative antibody results, the diagnosis of NMOSD becomes challenging and may affect the outcomes of patients with NMOSD. There are no adequate studies that assess NMOSD cohorts in the Arabian Gulf region, despite the increasing number of diagnosed cases. It is worth assessing NMOSD cohorts in the Arabian Gulf population to study the natural history of disease and to establish an epidemiological background for future perspectives. Various challenges to implement such a mission are outlined, including disease rarity, overlapping presenting symptoms and signs, which posed the issue of mimickers in the differential diagnosis, lack of specialized clinics, absence of highly sensitive testing methods for diagnosis, and the indefinite agreement on the negative AQP4 NMOSD criteria. Collaborative efforts started to take a place among many experts in the region to establish a registry of NMOSD patients for better perception of the disease pattern.

Keywords: Neuromyelitis optica spectrum disorder, Arabian Gulf, epidemiology

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune disease that affects different areas in the central nervous system (CNS).[1] It is recognized to be an inflammatory demyelinating disease (IDD). Historically, NMO was believed to affect primarily the optic pathways and the spine either in isolation or simultaneously, as described by Devic and colleagues in 1894.[2] NMO was long considered a clinical variant of multiple sclerosis (MS). However, in the last decade, NMO has evolved from Devic's classical description to a broader disease spectrum, from a monophasic illness to a polyphasic relapsing disease. NMO is mediated mainly by an antibody targeting the astrocytic water channel protein aquaporin-4 (AQP4-IgG) that was discovered in 2004 as the first serum biomarker of any IDD.[3] Additional diverse clinical presentations were documented, such as area postrema, cerebral, and brainstem syndromes.[4] The symptoms of NMOSD are primarily related to high rich areas of AQP4 channels or through connections with same areas in the brain.[5] Wingerchuk et al. updated the NMOSD criteria with a broad clinical spectrum and divided the patients into two groups according to AQP4 sero-status.[6] Attacks are generally more severe and the recovery is often incomplete compared to other IDDs (e.g., MS); a single attack can render a patient permanently blind or paraplegic.[1] The knowledge about NMOSD has been expanding over the last few years and several studies have been conducted in different nations over the globe to describe various phenotypic and radiological lineaments.[7–9]

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Recent studies demonstrated the presence of IgG antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) in a subset of patients with seronegative NMO.[7,10–12] It was thought that anti-MOG disease primarily affects pediatric cohorts, and has a monophasic course with predilection to optic pathways.[13,14] However, with longer longitudinal follow-ups in recent studies, anti-MOG antibodies were also seen in adult cohorts, with relapsing courses and the clinical presentations included acute disseminated encephalomyelitis, bilateral optic neuritis (ON), and transverse myelitis (TM).[10,11] This article focuses on the current aspects of this disease and the challenges to establish a registry for NMOSD in the Arabian Gulf region, which is vital for allocation of resources and health care delivery.

Epidemiological data

Based on the available literature data, NMOSD is represented at higher proportions in African, East-Asian, and Latin American populations. For rare diseases such as NMOSD, population-based studies are preferable to assess the prevalence and incidence rates; yet such studies may not be easy to conduct given the difficulty in unifying the diagnostic criteria and standardizing the laboratory antibody testing. Several prevalence and incidence were reported across the world, which are summarized in Table 1.[15–24]

NMOSD has a strong female predominance in all published studies, as the female to male ratios ranged from 1.2:1 in India, 2.8:1 in Denmark, 7.3:1 in Cuba, and all female affection in Japan and French West Indies.[16,19,21–23]

Based on the longitudinal reports published by multi-center and hospital-based studies, the mean age at onset ranged from 32.6 to 45.7 years.[7] An older age of onset was significantly associated with motor disability, while younger patients were more prone to have ON and remained ambulatory despite the visual impairment.[25] In most studies, TM was the initial presenting feature, followed by ON and simultaneous TM/ON, while other areas affected to a lesser extent.[15,16,19,21,26] Reports of brainstem, area postrema, and cerebral manifestation have been increasing in the last few years given the appreciation of a larger spectrum of the disorder. It was shown that Expanded Disability Status Scale (EDSS) at presentation was predictive of the future disability in patients with long extensive transverse myelitis (LETM) and brainstem lesion.[27] Mortality ranged from 2.9% to 25% and was disease related in the majority of cases.[7]

With respect to the anti-MOG phenotype, it was relatively rare compared to NMOSD and few studies had long observational follow-ups. In one of the largest NMOSD cohorts, four patients were tested positive for anti-MOG out of 153 NMOSD patients (47 patients were negative for AQP4 antibodies).[28] Van Pelt et al. analyzed samples of 61 AQP4-IgG seronegative patients using cell-based assay (CBA). Twenty (33%) patients were tested positive for anti-MOG-IgG and they were more frequently males, Caucasians, presented with coincident ON and TM, and had monophasic courses in contrast to AQP4-IgG seropositive patients. AQP4-IgG seropositive patients were 2.4 times more likely to suffer from relapses, and had a higher EDSS scores compared with MOG-IgG seropositive patients.[14] In a multi-center retrospective study that included 50

Table 1. Published prevalence and incidence rates from different parts of the world.

Population	Prevalence* (95% CI)	Incidence* (95% CI)	Reference
Austria	0.71 (0.17–0.96)	0.054 (0.01–0.31)	Aboul-Enein et al.[15]
Denmark	4.4 (0.30–0.54)	0.4 (3.1–5.7).	Asgari et al.[16]
Merseyside, UK	0.08 (0.03–0.16)	0.72 (0.31-1.42)	Jacob et al.[17]
Wales	1.96 (1.22–2.97)	–	Cossburn et al.[18]
French West Indies	–	0.19 (0.15–0.23)	Cabre[19]
Tehran, Iran	0.86 (0.76–0.91)		Eskandarieh et al.[20]
Mangalore, India	2.6	–	Pandit and Kundapur[21]
Japan	0.9 (0.2–2.5)	–	Houzen et al.[22]
Cuba	0.053 (0.04–0.07)	0.54 (0.39–0.69)	Cabrera-Gomez et al.[23]
New Zealand & Australia	0.70 (0.61–0.78)	0.037 (0.035–0.039)	Bukhari et al.[24]

*Per 100,000 population; CI: confidence interval.

anti-MOG Caucasian patients with a mean follow-up of 75 months, Jarius et al. reported a female predominance (M:F = 1:2.8), a median age of onset of 31 years, and a multiphasic course in 80% of patients with a median time-to-first-relapse of 5 months resulting in significant disabilities in visual and motor functions.[10]

The Arabian Gulf region refers to the six member states of the Gulf Cooperation Council (GCC) countries, namely Saudi Arabia, Kuwait, Bahrain, United Arab Emirates, Qatar, and Oman, with an estimated total population of approximately 52 million. These countries share lots of common features beyond geographic area, climate, and potential risk factors for chronic diseases. They also have similar genetic background, and high consanguinity percentage. In the Arabian Gulf, there are no national registries for MS and other demyelinating disorders except in Kuwait. Most of the databases in other countries are scattered in different cities or hospitals on either local or institutional levels. A recent cross-sectional study was conducted in Kuwait to assess demographics and clinical characteristics of patients with NMOSD using the 2015 international consensus diagnostic criteria for NMOSDs.[29] Thirty-two patients were identified with NMOSD, of whom 81.3% were women. The mean age of the cohort was 35.6±11.9 years while the mean disease duration was 6.9±6.6 years; 56.3% were AQP4 seropositive and one patient tested positive for anti-MOG. Most of the patient (50%) presented initially with ON, followed by myelitis (37.5%) while 6.3% and 3.1% presented with brainstem and area postrema syndromes, respectively. The mean EDSS score was 3.7±2.2 at last follow-up visit. The most commonly used disease modifying therapies were rituximab (59%), azathioprine (30.8%), and mycophenolate mofetil (10.3%).[29] The clinical features in Kuwait's cohort were similar to the reported figures from Western countries; however, a lower EDSS score was observed in Kuwait, which could be the result of the early use of rituximab.

A recent retrospective chart review was conducted in Abu-Dhabi, the capital of UAE in 2018, which included four major governmental hospitals.[30] Although the study included 46 patients, only 10 patients were positive for AQP4-IgG or satisfied the NMOSD criteria,[6] resulting in prevalence and incidence rates of 1.76 and 0.17 per 100,000 persons, respectively in Emirati population aged $\geq$ 20 years. The remaining patients were classified as either monophasic TM ($n = 29$) or untested/seronegative relapsing TM ($n = 7$) not satisfying the diagnostic criteria. Cerebral spinal fluid (CSF) test was performed in 30 patients; 19 patients had documentations of being tested for oligoclonal bands (OCB)/IgG index and only four had positive results. It worth mentioning that CSF analysis was mainly performed to exclude infections and to look for other inflammatory causes in TM patients rather than suspicion of demyelinating disorders. There were no descriptive data of the relapse rates or the disability scores. A comparative summary between this study and the one conducted in Kuwait is outlined in Table 2.

Misdiagnosis is common

Due to the similarity in the clinical presentation between NMOSD and MS, many of NMOSD cases might be labeled as MS, especially if the clinical suspicion in patients with red flags and atypical presentations were not raised. In addition, short-segment myelitis contributed to 12% of NMOSD, which could be mistaken for MS while positive OCB might be present in 20% of NMOSD patients.[10,31] Over-reliance on magnetic resonance imaging to establish the dissemination in time and space of McDonald criteria was one of the most

Table 2. Summary of the comparative data in the studies conducted in Kuwait and Abu-Dhabi, UAE.

	Kuwait ($n = 32$) Mean ± SD; *n* (%)	Abu-Dhabi (n = 10) Mean ± SD; *n* (%)
Gender:		
• Female	26 (81.3)	7 (70)
• Male	6 (18.7)	3 (30)
Mean age at onset	28.9 ± 9.8	43 ± 18.7
Anti-AQP4-IgG	18 (56.3)	8 (17.3)
OCB in CSF	10 (31.3)	4/19 (21)

AQP4: aquaporin-4; OCB: oligoclonal bands; CSF: cerebral spinal fluid.

common contributors to the misdiagnosis. MS remains a diagnosis of no better explanation and the dissemination in time and space is not specific to MS and may be seen with various disorders including NMO.[32] In one of the largest studies assessing misdiagnosed cases in two referral centers in Kuwait and Lebanon that included 431 patients referred for diagnostic opinion, 26% of the patients were misdiagnosed as MS, of which 8.5% had NMOSD.[33] In another study conducted in three US academic centers, 29.4% of the analyzed patients were initially misdiagnosed with MS.[26] The association between NMOSD and other inflammatory diseases, Sjogren's disease, and systemic lupus erythematosus adds to the diagnostic challenge of this disease and may mask the necessity for AQP4-IgG testing.[34,35] Twenty percent of NMOSD are monophasic, and can be misdiagnosed as a clinical isolated syndrome.[1] Patients with aggressive MS who sustained severe disabling relapses with poor recovery may resemble the presentation of NMOSD which is often severe.[36] Therefore, confirming the diagnosis of NMOSD may be difficult in the early course of the disease.

In the last few years, the phenotypic features of NMOSD have been broadened to diverse non-neurological symptoms, including intractable nausea, vomiting, hiccups, and prodromal cardiac symptoms such as bradycardia and arrhythmias.[37,38] The spectrum extended to enclose atypical presentations; tumor like lesions, progressive encephalopathy and hormonal disturbances like amenorrhea.[39,40] Thus, the diagnosis may be missed or delayed in patients presenting with atypical presentations or non-CNS manifestations at onset.

Suboptimal testing methods and sampling time

Most centers in the Arabian Gulf lack the ability to test for AQP4 and anti-MOG antibodies, hence, all samples are sent abroad to different laboratories. In addition to the delay in the diagnosis, getting results from several laboratories using different methodological approaches for anti-body detection may result in a standardization bias. Lower sensitivities (~63%) of enzyme-linked immunosorbent assay (ELISA) or fluorescence activated cell sorting techniques may lead to an error in the diagnostic decision. In contrast, CBA for AQP4 antibodies has a better sensitivity of 86% in detecting patients with NMOSD.[41,42] In accordance with this fact, Pittock et al. stressed the superiority of CBA when testing AQP4 antibody, especially in view of the relatively higher false positives with ELISA (0.5% vs 0.1% for CBA).[43] Beside the methodology used, the results may depend on the timing of sample collection as the detection rate is higher during a relapse while false negative may be seen after plasmapheresis or institution of disease modifying therapies.

Ambiguity of double negatives NMOSD

There is conflicting evidence around the so-called "double negative" patients (negative both AQP4-IgG and MOG IgG), using the most sensitive method. Some patients may have limited variants of NMO (e.g., recurrent ON or recurrent myelitis). Such patients are collectively being labelled as NMO spectrum disorder, although the absence of para-clinical features makes many neurologists reluctant to label these patients as seronegative NMOSD.[6]

Scant number of experts

In our region, the number of specialized centers or specialists with adequate expertise in diagnosing demyelinating disorders including NMOSD is small. The diagnosis of a demyelinating disorder is often established by a general neurologist. The patient may not be referred to a specialist unless there is a diagnostic ambiguity or failing multiple disease modifying therapies. Although MS remains the most common demyelinating disorder, NMOSD is still an under-diagnosed entity. If the diagnosis of NMOSD was not entertained during the diagnostic phase, the chance of misdiagnosis is high. In a busy neurology clinic, the chance of performing a comprehensive diagnostic approach with the notion of "no better explanation" in mind is minimal. It was suggested at one stage in our region, that suspected MS patients need to be referred to specialized clinics at least once to confirm the diagnosis or prior to the initiation of DMTs. Accurate diagnosis is, however, essential to minimize harm from inappropriate treatment as MS therapies may severely exacerbate NMOSD. The fear of prolonging the waiting time in specialized clinics was the main factor in not implementing such idea. Furthermore, most patients prefer attending clinics close to their residential areas when they suffer from a relapse or getting infusions.

Given the small number of specialized centers in the region, it is paramount to start educating the general neurologists about the MS mimickers by conducting workshop, developing a practice recommendation and encouraging the referral of patients with atypical presentation and red flags. The increasing number of diagnosed patients with NMOSD necessitates the

establishment of a registry in the Arabian Gulf in order to study the natural history of such a rare disease. This will also grasp the attention of residents and junior neurologists who may get involved in research and potentially assume further training in MS and other demyelinating disorders. MS registries are being established in most Gulf countries either at the national or institutional levels. This enables most specialists to incorporate the data of NMOSD patients into the sub-section of the registry. Most databases used in the region have sections for diagnosis where a specific diagnosis of demyelination disorder such as MS or NMO can be entered. At several regional meetings, most neurologists expressed their interests to participate in those registries given the ease in following patients longitudinally. A collaborative work among specialists was established at the regional level to collect the data of NMOSD patients and to extract the data from the respected registries in the near future to analyze the epidemiology of the disorder and to study the natural history of NMO in the region.

Conflict of Interests

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