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Clinical and radiological characteristics of Neuromyelitis Optica Spectrum Disorder in the North Egyptian Nile Delta

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Abstract

Background.—Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disorder of the central nervous system that was previously thought to be a subtype of multiple sclerosis (MS). Epidemiology studies of NMOSD are rare in both Middle East and North African countries. To our knowledge, there are no such studies in Egypt. Herein, we describe a case series of NMOSD patients from North Egyptian Nile Delta region and compare them to NMOSD in other parts in the Middle East and the world.

Methods.—This is a case series study of NMOSD patients who were seen at the neuroimmunology clinic, Elhadara Hospital, University of Alexandria, Egypt, from January 2017 to January 2018. We describe their clinical, serological and radiological features.

Results.—Our study identified twenty Egyptian patients, all of who fulfilled the 2015 international NMOSD diagnostic criteria. Ten tested positive for AQP4 antibodies in the serum while the other ten were seronegative. The mean age at onset was 27.8 years with an average disease duration of 6.8 years. There was a strong female predominance with a ratio of 5.6:1. We identified clinical features of the cohort that differ from those reported in other worldwide studies.

Interpretation.—This is the first NMOSD case series in Egypt. Despite some limitation in testing and access to care, there are features of our NMOSD cases that appear to be different from other worldwide cohorts reported in the literature.

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Introduction.

Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating disorder of the central nervous system that was previously thought to be a subtype of multiple sclerosis (MS). The identification of a serological biomarker for the aquaporin-4 antibody in up to 80% of NMOSD patients with near 100% specificity separate these two disorders into distinct clinical entities. [1] Historically, NMOSD was thought to include a monophasic group with simultaneous involvement of the optic nerve and the spinal cord in a single attack.[2] Since the discovery of the aquaporin-4 antibody, however, all seropositive NMOSD patients are recognized to be at high risk for a potentially disabling relapse. It is therefore of crucial importance to accurately diagnose NMOSD and differentiate it from multiple sclerosis to allow proper management of acute exacerbations as well as prevention of further relapses.

NMOSD is rare as a percentage of all autoimmune demyelinating diseases and in total number. Its prevalence rarely exceeds 5 per 100,000.[3] In a recent review of literature,[4] the reported prevalence of NMO in different parts of the world ranged from 0.51 per 100,000 in Cuba to 4.4 in Southern Denmark and the incidence ranged from 0.053 per 100,000 per year in Cuba to 0.4 in Southern Denmark.[5] There is a strong female predominance varying from 2.27:1 in Isfahan, Iran, to 9.8:1 in French West Indies.[6–10]

The Middle East is a politically defined region of the world that stretches from northwest Africa to Pakistan. Genetically the Middle East contains a mixed population of Arabs and non-Arabs where autoimmune diseases are generally less common (or less commonly diagnosed).[11] The prevalence of MS is as low as 14.7/100,000 in Kuwait (2005)[12] with overall prevalence in the Middle East of 51.52/100,000 compared to 100/100,000 in USA and Europe.[13] Although the prevalence of MS in Egypt is reported to be the same as in Kuwait, 14.7/100,000. Egyptians and Kuwaiti were recently found to be genetically distinct. A national geographic genetic analysis of population in the Middle East revealed that less than 18% of Egyptians are of Arab genetic origin compared to 84% of Kuwaiti. Rather, more than two-thirds of Egyptian share genetic heritage with their neighboring North Africans countries.[11] In Egypt 99.4% of the population are identified as Egyptians, which reflects both ethnicity and nationality.

Epidemiology studies are rare in both Middle East and North African countries. To our knowledge, there are no such studies in Egypt. Herein, we describe a case series of NMOSD patients from North Egyptian Nile Delta region and compare them to NMOSD in other parts in the Middle East and the world.

Methods.

This is a case series of NMOSD patients who were seen at the neuroimmunology clinic, Elhadara hospital, University of Alexandria, Egypt, from January 2017 to January 2018. Our clinic serves the governorates of Alexandria, Beheira, Kafr El Sheikh and Matrouh, which constitutes approximately 14.6% of the Egyptian population. We reviewed the medical records of all cases available at the clinic during this time period (400 patients) and selected

patients who were initially diagnosed with any of the following: NMO, NMOSD, isolated or recurrent attacks of optic neuritis, isolated or recurrent attacks of transverse myelitis, or cases with atypical MS. Cases were reviewed and only those fulfilling the 2015 diagnostic criteria of NMOSD were included.

Testing for NMO-IgG was performed using ELISA technique (ElisaRSR AQP4 Ab Version2) and results were recorded as seropositive or seronegative. All patients were tested for AQP4 antibody at least a month after relapse.

After approval of IRB of the school of medicine, University of Alexandria, Egypt, the following data was gathered prospectively for all patients: complete history including onset of illness, presenting symptoms, number of attacks, family and personal past history; in addition, a complete neurological examination was performed along with routine laboratory investigations including CSF testing in selected cases and MRI brain, spinal cord and orbit with contrast administration as clinically indicated. Expanded Disability Status Scale (EDSS) scores were collected at least one month after a relapse.

Results.

Among the reviewed cases, 330 were diagnosed as multiple sclerosis, 50 were classified as other demyelinating diseases and 20 fulfilled the 2015 criteria for NMOSD.[14] Ten tested positive for AQP4 antibodies in the serum while the other ten were seronegative. The mean age of the cohort was 34.4 years, while the mean age at onset was 27.8 years with an average disease duration of 80 months, range (3 –216 months). There was a strong female predominance with a ratio of 5.6:1. Optic neuritis was the most frequent initial presentation among patients, followed by transverse myelitis. Most relapses were transverse myelitis, and the average relapse rate was 1.6 attacks per year.

In our cohort, the most common presenting symptom at disease onset was optic neuritis, followed by transverse myelitis (40% and 35% respectively). Area postrema was the initial presentation in 5 patients (25%), two of who were AQP4 seropositive and 3 were seronegative. Brain stem was involved at onset in 5 patients (25%). During the disease course, simultaneous optic neuritis and transverse myelitis was reported in four patients and optic neuritis was presented bilaterally in five patients.

Aquaporin-4 was tested for all patients. Ten had a positive test result with an average titer of 19.6 U/L (4.9 – 36.9 U/L) and a median of 16 U/L. Despite the fact that 4 patients had a titer less than 3 times the cutoff level which might be considered as false positive, all except one fulfilled the 2015 criteria for the negative or unknown serostatus NMOSD. That one patient presented with an isolated attack of transverse myelitis which was longitudinal extensive from C7 to T7, central in location with mild cord expansion.

When accounting for the AQP4 serostatus, the mean age at onset was significantly higher in the seropositive group 34.9 vs 20.7 years old. Transverse myelitis was the most common presenting attack in the AQP4 seropositive group, observed in 6 patients. Simultaneous optic neuritis and transverse myelitis was only observed among our seropositive patients, finally brainstem attacks, including area postrema was the most frequent presentation among AQP4

seronegative patients. There were no significant differences in the disability status or brain involvement between AQP4 seropositive and seronegative patients in our cohort.

Patients' EDSS scores showed a wide variation ranging from 0–9 with an average of 4.6. 13 patients (65%) had an EDSS score of 4 or more at time of evaluation. The average disease duration for those patients was 91.4 months with a median of 84 months.

All relapses were treated with intravenous methylprednisolone for 5–7 days, with some patients receiving oral prednisone taper after discharge from the hospital. Regarding preventive treatment, 8 patients were on azathioprine, two on methotrexate, one on cyclophosphamide and one on oral corticosteroids in addition to hydroquinone, one on mycophenolate mofetil, two patients on interferon beta (misdiagnosed as MS), and 5 patients were not treated (due to poor medical access).

Regarding personal and family history, six patients (30%) had a past history of concomitant autoimmune disorders with two having a history of rheumatoid arthritis, two with hypothyroidism, one with lupus and one with myasthenia gravis. Three of those patients also had a family history of other autoimmune disorders including one patient with a sister also diagnosed with NMOSD.

Anti-nuclear antibody test results were available for 6 patients, and was positive in two, both of whom were also seropositive for AQP4 antibody, while 7 patients were tested for anti-ds-DNA with only one weak positive result. CSF testing was available for 7 patients, two of whom showed lymphocyte predominant lymphocytosis (76, 133 cells/pL) and 3 of whom showed elevated protein level (99–186 mg/dl). Oligoclonal bands were available for two patients and were negative.

Spinal cord and brain MRI studies were available for 19 patients. Longitudinally extensive transverse myelitis (LETM) was the abnormal finding on spinal cord MRI reported in 12 patients, with cervical involvement in three patients, thoracic cord involvement in one patient, both cervical and thoracic involvement in 6 patients and cervicomedullary involvement in two patients. One adequate orbital MRI study was available, which showed long segment unilateral T2 hyperintensity involving the intracanalicular, pre-chiasmal and chiasmal portions of the nerve. Brain MRI was abnormal in 12 patients at some point along the course of the disease with non-specific white matter changes being the most common - observed in 8 patients, followed by area postrema involvement in four patients. One patient showed an ADEM-like (acute disseminated encephalomyelitis) picture on initial brain MRI. Table 1 summarize these important findings.

Discussion.

We characterized the clinical and radiological features of NMOSD in a cohort of Egyptian patients living in Alexandria and nearby governorates (Beheira, Kafr ElSheikh and Matrouh). To our knowledge, this is the first case series of NMOSD from Egypt.

Compared to studies in other parts of the world, there are a few clinical features among NMOSD patients in Egypt that are different. For example, the mean age at onset of NMOSD

patients in our cohort was 27.8 years which was lower than that found in other studies (range 30–39.5),[4, 6–10, 15-18] capped on the other end of the age spectrum by an epidemiology study in USA which reported a mean age of onset of 41.1 years.[19] In other worldwide studies, pediatric onset is rare, with less than 5% of cases presenting prior to the age of 18. [20, 21] In contrast, among our 20 subjects in the study, 7 (35% of cases) had disease onset at age 18 or less. Late onset NMOSD, defined as onset age >50 years, was found less often in our cohort (10%) as compared to 25% (108/430) in a large multicenter cohort study.[22] The two late onset patients were both seropositive females with the ages of 57 and 58 years which, despite the small number, is consistent with that reported in the literature where 80% were females and 85% were AQP4 seropositive.[23] Although a very late onset NMOSD (above 75 years) is reported in the literature,[24] none were found in our cohort. Our much younger age of onset could potentially be explained by the fact that the mean age of the Egyptian population is 24.7 years compared to 37.3 years in USA[25] or it could be explained by the small number of patients included in our study. Alternatively, there may be a genetic component that predisposes susceptible patients to earlier onset of NMOSD that is different from other populations worldwide. This is particularly interesting because it has been suggested that the prevalence of NMOSD is similar in all studied areas around the world, which led to the conclusion that neither the genetic and ethnic background, nor a clear latitude gradient, play a significant role in the development of NMOSD.[3] But since no prevalence studies were carried in Egypt, this conclusion is yet to be generalized.

When comparing the pediatric onset with the adult onset NMOSD, the pediatric onset patients tended to be AQP4 seronegative. While younger patients tended to present initially with optic neuritis, subsequent relapses favored the spinal cord, similar to adult onset patients. The only seropositive pediatric case experienced only optic neuritis relapses. Brain involvement and disability status were not significantly different between the two age groups. NMOSD has a strong female predominance, which is also evident in our study with a female: male ratio of 5.6:1. This is consistent with the literature which reported a ratio ranging from 2.2 up to 9.8.[8, 10, 19] Among the AQP4 seropositive patients in our cohort, 90% were females, which reflects a similar study of an Austrian cohort where females represented 87% of all seropositive patients.[26] The higher prevalence of AQP4 seropositivity in females was also reported in a UK cohort where 86% of the seropositive LETM were females.[27] A recent study in 2017 reported that female predominance in NMOSD is more evident in the fertile age group and they tend to be AQP4 seropositive.[28]

The only available test for AQP4 antibodies in Egypt _to our knowledge _is the ELISA assay, which has a sensitivity of 65%.[29] In contrast, the cell based assay (CBA) for AQP4 antibodies has a sensitivity of 76%, which is clearly superior.[29, 30] In accordance with that fact, Pittock et al stressed on the superiority of CBA when testing AQP4 antibody, along with the higher frequency of false positive results with ELISA (0.5% vs 0.1% for CBA), which calls for caution when interpreting the low positive results.[31] Despite the fact that ELISA was the technique used in our cohort, those who tested low positive (except for one patient) already fulfilled the 2015 NMOSD criteria for the negative or unknown serostatus NMOSD (as previously stated in the results). The lack of access to a cell-based assay in our study (which is not available in Egypt neither experimental nor commercial) might have led to missed seropositive cases due to its superior specifcity.[30]

When accounting for the AQP4 serostatus, we observed several differences between the seropositive and seronegative patients in our cohort. First, the mean age at onset was significantly higher in the seropositive group. Second, transverse myelitis was the most common presenting attack in the AQP4 seropositive group. Third, simultaneous optic neuritis and transverse myelitis was only observed among our seropositive patients, which is different from the report by Jarius et al, where simultaneous optic neuritis and transverse myelitis was more common in AQP4 seronegative patients.[32] Fourth, brainstem attacks, including area postrema was the most frequent presentation among AQP4 seronegative patients, unlike the Danish study where brainstem involvement was more common in the AQP4 seropositive group.[33] There were no significant differences in the disability status or brain involvement between AQP4 seropositive and seronegative patients in our cohort.

Conclusions.

In conclusion, this is the first NMOSD case series study in Egypt. Despite some limitations in testing and access to care, there are features of our NMOSD population that appear to be different from other worldwide cohorts reported in literature. These differences include younger age at onset, higher proportion of pediatric-onset presentation, and more frequent brainstem presentation among AQP4 seronegative patients. Further multicenter studies with a larger cohort and CBA for AQP4 antibody testing need to be conducted to confirm our results.

Acknowledgments

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Table 1.

Demographic and clinic features of the cohort.

Characteristic	Number (%)
Total Cohort	20
Sex	
Female	17 (85)
Current Age (years)	
Range	15–59
Mean ± SD	34.40 ± 11.3
Median	32.0
Age at onset (years)	
18	7(35)
Range	8.0–58.0
Mean	27.80±13.71
Median	25.5
EDSS	
Range	0.0–9.0
Mean ± SD	4.63±2.79
Median	4.25
Antibody serostatus	
AQP4 seropositive	10 (50)
AQP4 low positive	4 (20)
AQP4 seronegative	10 (50)
Duration of disease (years)	
Range	0.25–25.0
Mean	6.82±7.43
Median	3.50
Number of relapses	
2	6
>2	14
Range	1.0–15.0
Mean	4.55±3.62
Median	3.2
Presenting symptom	
Optic neuritis	8 (40)
Transverse myelitis	7(35)
Brainstem	5(25)
Area postrema	5(25)

Characteristic	Number (%)
A DEM-like	1(5)
Optic neuritis + Transverse myelitis	1(5)

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