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Clinical and radiological characteristics of neuromyelitis optica spectrum disorder in the North Egyptian Nile Delta

Sara Salama[a,b,*], Hazem Marouf[a], M. Ihab Reda[c], Amal R. Mansour[d], Osama ELKholy[a], Michael Levy[b]

[a] Department of Neurology and Psychiatry, University of Alexandria, Alexandria, Egypt
[b] Department of Neurology, Johns Hopkins University, Baltimore, MD, USA
[c] Department of Radiology, University of Alexandria, Alexandria, Egypt
[d] Department of Clinical Pathology, University of Alexandria, Alexandria, Egypt

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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.

1. 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 (Zekeridou and Lennon, 2015). Historically, NMOSD was thought to include a monophasic group with simultaneous involvement of the optic nerve and the spinal cord in a single attack (Jarius and Wildemann, 2013). 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 (Mori et al., 2018). In a recent review of literature (Pandit et al., 2015), 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 (Etemadifar et al., 2015). There is a strong female predominance varying from 2.27:1 in Isfahan, Iran, to 9.8:1 in French West Indies (Asgari et al., 2011; Cossburn et al., 2012; Etemadifar et al., 2014; Jacob et al., 2013; Cabre et al., 2009).

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

* Corresponding author at: 600 N. Wolfe St., Pathology 509, Baltimore, MD 21287, USA.
E-mail address: ssalamafouad@gmail.com (S. Salama).

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autoimmune diseases are generally less common (or less commonly diagnosed) (Cooper et al., 2009). The prevalence of MS is as low as 14.7/100,000 in Kuwait (2005) (Alshubaili et al., 2005) with overall prevalence in the Middle East of 51.52/100,000 compared to 100/100,000 in USA and Europe (Heydarpour et al., 2015). 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 < 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 (Cooper et al., 2009). 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.

2. 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.

3. 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 (Wingerchuk et al., 2015). 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 81.8 months, range (3–300 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 < 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 to 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/μL) 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 summarizes these important findings.

4. 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