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Characterizing the clinical, radiological and serological features of children who were diagnosed with neuromyelitis optica spectrum disorder at pediatric neurology unit

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ABSTRACT

Background: Neuromyelitis optica spectrum disorder is a rare autoimmune disease with a chronic inflammatory demyelinating characteristics that affects the central nervous. The aim of the study is to characterize the clinical, serological and radiological features of neuromyelitis optica disease in a sample of children from Iraq.

Methods: A cross-sectional descriptive study has been carried out in the period from August 2019 to September 2020, in pediatric neurology ward in Children Welfare Teaching Hospital, Baghdad. In 12 retrospectively gathered cases, the medical registration of the ward was assessed. A total of 13 patients, aged 3-16 years were included.

Results: Among the patients, girls represent 61.5% (8), and the female: male ration was (1.6:1). The patients' ages ranged from 3 to 16 years (mean 9.3 ± 4.02 years). All patients younger than 6 years were AQP-ve, in contrast to 15.3% in those older than 6 year. Negative AQP patients equally distributed between males and females. While females predominated in those with AQP positive status (5,71.4%). Weakness of the limbs and sphincteric disturbance were the first two common clinical features in both AQP positive and negative patients. The three most common brain sites insulted were deep white matter (10, 76.9%), periaqueductal area (5, 38.4%), and brainstem (4, 30.7%). All patients showed long spinal lesions, affecting predominantly the cervico-thoracic (61.53%).

Conclusion: The demographic characteristics of the present cohort were comparative to that reported in the literature. Transverse myelitis phenotype was the most common and consistent one. Vomiting was more common in AQP +ve patients.

Keywords: Neuromyelitis optica spectrum disorder, autoimmune disease, chronic inflammatory demyelination

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune disease with a chronic inflammatory demyelinating characteristics that affects the central nervous system.[1] The term NMOSD has been designed to allow incorporation of cases associated with non-AQP4 biomarkers.[2] Children with NMOSD have an annual incidence of 0.05 to 4 per 100,000, and a prevalence of 0.52 to 4.4 per 100,000.[3] Pediatric NMOSD shows a high female predominance (3:1), and it manifests before the age of 17 years.[4-6]

This study aimed to characterize variable aspects of NMOSD diagnosed in children receiving care at Children Welfare Teaching Hospital.

PATIENTS AND METHODS

A prospective / retrospective cross-sectional study has been carried out in the period from August, 2019 to September, 2020, in pediatric neurology ward in Children Welfare Teaching Hospital, which is one of the tertiary children hospitals in Iraq. One prospectively presented case was examined and diagnosed by a specialist pediatric neurologist during the period of the study and was enrolled in the study. For the retrospectively gathered cases, medical records of all patients who were labeled with the diagnosis of NMO, Devic's disease or autoimmune inflammatory nervous system disorders and were admitted and treated in Children Welfare Teaching Hospital in the period from 2016 to August 2019, were reviewed. A total number of 42 patients were labelled with the diagnosis of demyelinating diseases, of whom thirteen had diagnosis of Neuromyelitis Optica (5 males and 8 females) and were eligible to be included in the current study by showing clinical, radiological and serological criteria in compliance with the diagnostic criteria of NMO. Patients who had incomplete data, clinical and/or laboratory evidences of infectious, metabolic, vascular, or neoplastic disorders of CNS were excluded from the study. A Special forma was designed to collect data, which included the following: gender, residency and nationality, age, age of first attack, clinical presentation, neurological examination, cerebrospinal fluid (CSF) parameters including Oligoclonal band (OGB), serum AQP4

antibodies, immunoglobulin G (IgG) index, and polymerase chain reaction (PCR) of Herpes simplex virus in the CSF. Additionally, results of immunological tests that have been performed in serum like antinuclear antibody (ANA), anti–double stranded deoxyribonucleic acid (DNA) antibody, anti Ro/La, and anti-smith antibody were gathered whenever available. Furthermore, radiological data of brain, spinal and/or orbital MRI with/without gadolinium study were gathered, and those included: number, sites, size and enhancement characteristics of the lesions, and length of the lesion in the spinal cord. Treatment profile including the use of methylprednisolone, IVIG, PE, oral prednisolone, and other preventive immunomodulating medications like rituximab, cyclophosphamide, and mycophenolate mofetil were also recorded. The patients were followed over one month after admission.

All statistical analyses were carried out using the statistical packages for Social Sciences (SPSS Inc., Chicago, IL, USA) software version 23.0. Descriptive statistics were used to explore differences between AQP4-Ab positive/negative cases. Categorical data were compared using Chi square test. Two-sided P values 0.05 were considered significant.

RESULTS

The total number of children and adolescents enrolled in this study was 13. Most of the cases were diagnosed before the onset of this study (retrospective: prospective patients were 12:1). Identification of the patients was distributed annually as in figure 1.

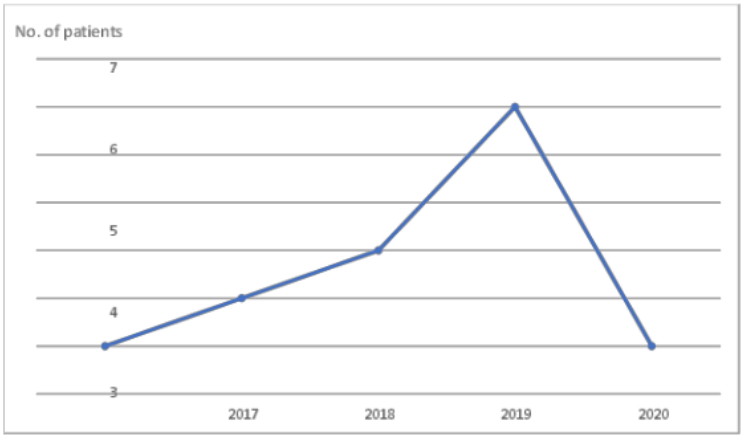

Figure 1: Distribution of patients diagnosed with NMOSD broken down by year

Girls represented 61.5% (8) and the female:male ration was (1.6:1). The patients' ages ranged from 3 to 16 years and the mean was 9.3 ± 4.02 years (±SD), as shown in figure 2. It was found that

most cases of NMO were in the school age group (66.7%), with female predominance.

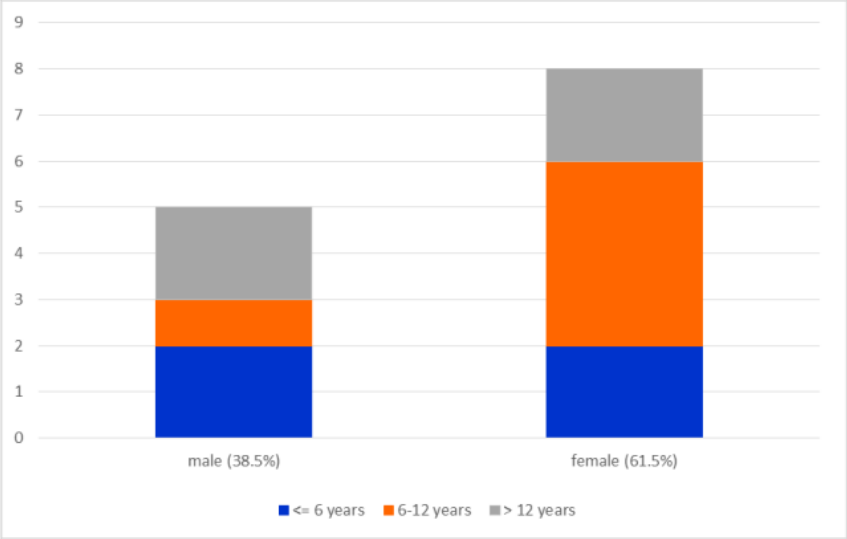

Figure 2: Age distribution of patients diagnosed with NMOSD by gender

The clinical features among the studied group is shown in figure 3. The three most common clinical features that the patients of NMO were complaining of, were weakness of limbs (13, 100%), sphinctric disturbance (11, 84.6%), and vomiting (5, 38.5%). While headache represented the least common one.

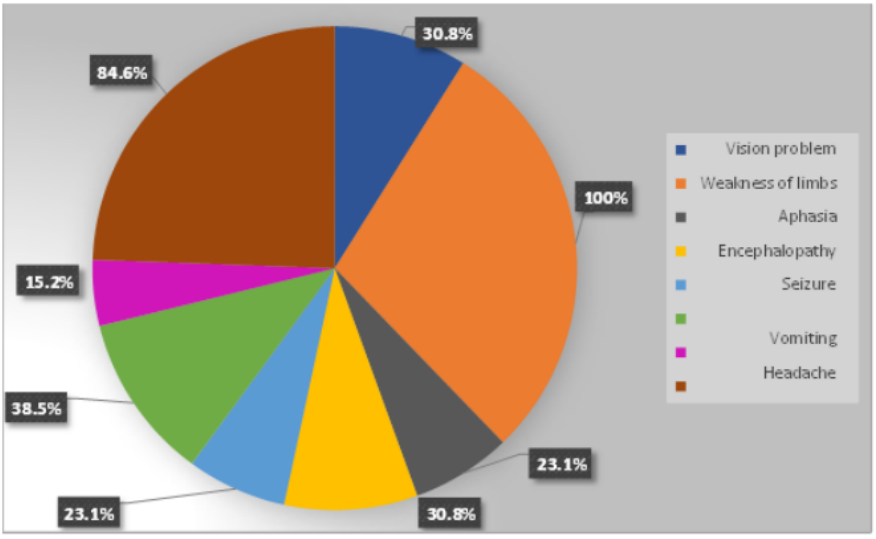

Figure 3: Clinical features of patients diagnosed with NMOSD

Table 1 shows that, all NMO patients who were younger than 6 years, were AQP-ve, while 53.8%

(77.8%) of children older than 6 year were AQP positive and 15.3% (22.22%) were AQP-ve. Negative AQP patients were equally distributed between males and females. But females predominated in those with AQP positive status. In patients with AQP positive status, the most common clinical features reported were weakness of limbs (100%), vomiting and sphinctric disturbance (71.4% for each). While sphinctric disturbance (100%) and weakness of limbs (100%) were the most common features in patients with AQP negative status. Seizure and vomiting are significantly highly prevalent in AQP -ve and +ve status, respectively (*P* value=0.033 and 0.008, respectively).

Table 1: Age, gender and clinical features of the studied group, distributed by the AQP status

Variables		AQP4 +ve (n=7) No. (%)	AQP4 -ve (n=6) No. (%)	P value*
Age (years)	< 6	0 (0)	4 (66.6)	
	6-12	4 (57.1)	1 (16.7)	
	> 12	3 (42.9)	1 (16.7)	
Gender	Male	2 (28.6)	3 (50)	
	Female	5 (71.4)	3 (50)	
Clinical presentation				
Vision loss		3 (42.9)	1 (16.7)	0.308
Weakness of limbs		7 (100)	6 (100)	0.542
Aphasia		1 (14.3)	2 (33.3)	0.416
Encephalopathy		2 (28.6)	2 (33.3)	0.853
Seizure		0 (0)	3 (50)	0.033
Vomiting		5 (71.4)	0 (0)	0.008
Headache		1 (14.3)	1 (16.7)	0.906
Sphincter disturbance		5 (71.4)	6 (100)	0.155

* chi-square was used

Table 2 shows the laboratory findings in NMO patients distributed by AQP status. The mean of CSF cell was reported to be higher in AQP -ve patients (55.5 +/- 51.65 versus 30.57 ± 23.94). CSF protein was elevated in 4/13 (30.76%) patients, of which 75% were AQP -ve. All patients had normal level of CSF sugar (2/3 of blood sugar) regardless the AQP status. Eight patients (equally distributed among the two AQP status) were tested for CSF oligoclonal bands and they had negative results. Nine patients were tested for CSF IgG index, two (22.22%) showed positive results (AQP -ve test). Serological markers of vasculitis disorders (ANA, Ds-DNA, Anti - Smith, anti-Ro/La) were tested in 11/12 patients and they showed negative results. The three most common brain sites insulted were deep white matter (WM) (10, 76.9%), periaqueductal area (5, 38.4%), and brainstem (4, 30.7%), of which non-significant difference was found between AQP +ve and -ve status. All patients showed long spinal lesions (extending for more than 3 vertebral segments) in the spinal MRI, almost all were continuous and one had patchy lesion (C3-7/D2-7), and one patient exhibited extensive, whole spinal involvement with signal abnormality. The distribution of vertebral segmental lesions were as follows: cervico-thoracic involvement in 8 (61.53%); cervical in 3 (23%); thoracic in 1 (7.69%); and whole spine in 1 (7.69%), and all revealed non-significant differences between AQP +ve and – ve status (*P* value = 0.542). Contrasted orbital MRI was performed in 4 patients, of which only one AQP positive patient (25%) exhibited abnormal signals.

Table 2: Findings of CSF analysis and brain and spinal MRI, distributed by patients' AQP4 status

variables		AQP4 +ve (n=7) N. (%)	AQP4 -ve (n=6) N. (%)	P value*
CSF cells	(mean ± SD)	30.57 ± 23.94	55.5 ± 51.65	
	range	7-72	11-121	
CSF protein	< 45 mg/dl	6 (85.7)	3 (50)	
	> 45 mg/dl	1 (14.3)	3 (50)	
CSF OCB (n=8)	+ve	0 (0)	0 (0)	
	-ve	4 (100)	4 (100)	
CSF IgG (n=9)	+ve	0 (0)	2 (40)	
	-ve	4 (100)	3 (60)	
Serology marker for				

vasculitis (ANA,Anti dsDNA,Anti smith,Anti Ro/La)	+ve	0 (0)	0 (0)	
	-ve	6 (100)	6 (100)	
Brain MRI (Abnormal in 10 patients)	deep white matter	5 (71.4)	5 (83.3)	0.308
	Periventricular	0 (0)	1 (16.7)	0.261
	Brainstem	1 (14.3)	3 (50)	0.164
	Periaqueductal	4 (57.1)	1 (16.7)	0.135
	Cerebellar	1 (14.3)	2 (33.3)	0.416
	Thalamic/basal ganglia	1 (14.3)	0 (0)	0.261
Spine MRI (LETM) (Abnormal in 13 patients)		7 (100)	6 (100)	0.542
Optic MRI (done in 4 patients)		1 (14.3)	0 (0)	0.629

* chi-square was used

Table 3 shows that all patients received Methyl Prednisolone (1st line treatment) in their first admission. All AQP positive patients received IVIG during their first admission, in contrast to two patients (33.3%) in AQP – ve group. Rituximab (first cycle which is part of maintenance treatment) was administered in the first admission in 4/7 (57.1%) AQP +ve patients, while most of (5/6, 83.4%) AQP- ve patients received it in the subsequent admissions.

Table 3: Treatment of NMO patients, distributed by AQP status

Variables		AQP4 +ve (n=7) N. (%)	AQP4 -ve (n=6) N. (%)
methylprednisolone		7 (100)	6 (100)
IVIG	1st admission	7 (100)	2 (33.3)
	Subsequent admission	0 (0)	4 (66.7)
Rituximab	1st admission	4 (57.1)	1 (16.7)
	Subsequent admission	3 (42.8)	5 (83.4)

DISCUSSION

Potential involvement of autoimmunity in the pathogenesis of NMOSD is suggested by the overlap with other autoimmune diseases, the specific NMO antibody, the various infections that may precede NMO neurological symptoms, the immune-histological findings of prominent infiltration with neutrophils, eosinophils, and IgM deposition in the lesions [7], and the good clinical response to immune-modulatory treatments. Two important clinical presentations of NMOSD are ON and TM. [8,9] Other presenting attacks have been described and were considered as core criteria of NMOSD presentation. [10-15] Treatment for NMOSD includes treatment of acute attacks, preventative therapy, and symptomatic management. [1] All patients with NMO should be considered at risk of disabling relapses in order to initiate early therapy and emphasize the importance of relapse prevention treatment. [16]

There was a sharp rise in the frequency rate of NMO during 2019 (6 patients), which may reflect the increasing identification of variable NMO spectrum disorders. This was followed by sharp reduction during 2020 (one patient till the time of writing this thesis) which might be explained by the local health (COVID-19 crisis) and political situations that impede patients' transportation and resulted in delay of their management.

The identification of all patients in the present cohort was achieved by fulfilling NMO, 2015 [2] diagnostic criteria, by collecting either two core clinical features or one core clinical feature and positive AQP antibodies.

The study showed equal gender distribution in the preschool age group. When all ages are included, it was found that female predominated (F:M 1.6:1), a fact that is pronounced in children older than 6 yr (2:1). This ratio is in line with results of other studies, by Huppke et al. [17] in Germany, 2010 (2.5:1), by Fragoso et al. [18] Brazil, 2013 (2.6:1), by Collongues et al. [19] France, 2010 (3:1), and by Chitnis et al. [6] USA, 2015 (2.1:1). Pronouncement of female predominance in older children and older fertile-aged females was also seen in other studies. [6,20] Other authors reported higher ratios, like 8-9:1 by Tillema et al. [21] in USA, 2012, and 5:1 by Pena et al. [22] in Venezuela, 2010. This disparity may be due to difference of samples' size or may be the ratio in both latter studies were calculated in the AQP positive patients. In the present study, female predominance was also found to be pronounced in AQP positive patients (2.5:1 versus 1:1), a result that is in line with studies by Pena et al. [22] Collongues et al. [19] and Tillema et al [21]. However, female predominance was found in AQP negative cases in a study that was conducted by Absoud et al. [23] in UK, 2014.

Generally, this sex difference is explained by variable factors like: hormonal changes; differences of immunocompetence and immune reactivity; differences of major histocompatibility complex risk alleles; differences of genetic imprinting; differences of the transcription of inflammation – related genes; and differences of the responsiveness to environmental factors like infections. [20]

The mean age of presentation was 9.3 ± 4.02 years (±SD) (median 10 year, range: 3-16 year). This was in agreement with studies conducted by Absoud et al. [23] (median years, range: 2.9-16.8 years), Lechner et at. [24] (2020) (median 11 year, range: 3-17 year), and Chitnis et al. [6] (2015) (mean: 10.2±4.7), with the youngest reported age was 16 months old. While it was comparatively lower than studies conducted by Boesen et al. [25] 2019, (11.4 years (range = 5–14 years), and Fragoso et al. [18] (mean 13 ± 3.4 year, range: 5-17 years), Collongues [19], 2010 (median 14.5 year, range: 4.1-17.9), Pena et al. [22] 2010 (mean 11 year, range: 5-13), and Huppke et al. [17] (median 12 year, range: 3- 17 year).

The clinical features of NMOSD is variable, caused by involvement of various areas of the central nervous system (spinal cord, optic nerve, brainstem, area postrema, etc). [26] In the present study, weakness (paraplegia/paraparesis, quadriplegia) (13, 100%) and sphincter disturbance (11, 84.6%) were the two most common features reported. Lotze et al. [27] reported weakness in 100% of his cohort, while Kim et al. [28] found lower frequency of that feature (1/4), which might be explained by very small sample size. Considering transverse myelitis as the phenotype for both features, our result is again consistent with Lotze et al. [27] but disagreed with Pena et al. [22] (50%), Absoud et al. [23] (6/20), Collongues et al. [19] (6/12).

Visual symptoms (blurred vision, orbital pain, reduced visual activity, blindness, and reduced color) was reported in 4/13 (30.8%) patients. This result is in contrast to that reported in the literature (Pena et al. [22] (5/6), Absoud et al. [23] (12/20), Lotze et al. [27] (7/9), and Collongues et al. [19] (6/12)). This might be presumed due to underestimation of orbital insult by the local practice, by misinterpretation or discounting of clinical/laboratory findings including eye examination, VEP and orbital MRI. Orbital MRI was performed in 4/13 patients. This diagnostic service was not available consistently locally, thus impeded completing the diagnostic work up of NMOSD patients. There is a local trend not to use VEP as a diagnostic tool for optic neuritis, which was justified by the presence of age-related technical limitations and misinterpretation of the results. Both practices might cause underestimation of orbital involvement in NMOSD patients, particularly in the clinically silent cases and non-communicative patients.

Vomiting was reported in the initial presentation in 5/13 patients, who were AQP seropositive. Vomiting was reported in the initial presentation of NMO patients by Apiwattanakul et al. [29] (3/12 AQP +ve patients), Pena et al. [22] (1/6 patient, who presented with vomiting, headache and vertigo), and Lee et al. [30] 2016 (3/10 patients). Prevalence of this clinical presentation in AQP +ve patients could be explained by the possibility that the area postrema is a circumventricular organ in the brain that is AQP4-rich, chemosensitive and vomiting center. It is one of the main targeting sites in NMOSD. [30]

Seizure and encephalopathy were initial presentation in 3 and 4 patients, respectively (23.07%, 30.7%). Both features were reported in higher percentages by: McKeon et al. [15] USA, 2008 (45% of his cohort had symptoms such as encephalopathy, seizures, ophthalmoparesis, ataxia, or area postrema syndrome), Kim et al. [28] who found seizure and encephalopathy in 2/4 and 3/4 patients, respectively, and Lotze et al. [27] who reported seizures and encephalopathy in 2/4 patients, for each. The current study reported the clinical features as general phenotypes as the following: transverse myelitis (6, 46.1%), optic neuritis and transverse myelitis (3, 23.07%), ADEM-like with transverse myelitis (4, 30.7%). Other studies reported these phenotypes as the following; Pena et al. [22] reported TM (1/6, 16.7%), ON (3/6, 50%), ON and TM (2/6, 33.3%); Absoud et al. [23] found TM (3/20, 15%), ON (12/20, 60%), ON and TM (3/20, 15%) and ADEM-like (2/20, 10%); and Lechner et al. [24] who found TM (6/18, 33.3%), ON (1/18, 5.6%), ON and TM (6/18, 33.3%) and brainstem (3/18, 16.7%). CSF oligoclonal band was investigated in (8/13) and found negative, a result that is in agreement with Banwell et al. [31] Canada, 2007 (0/13), Huppke et al. [17] (0/6), and Pena et al. [22] (0/5). It was found positive in small percentages of patients in studies conducted by Collongues et al. [19] (3/12, 27.3%), Mckeon et al. [15] (2/34), and Absoud et al. [23] (2/17, 12%). In the current study, we found elevated CSF IgG index in 2/9 (22.2%), which was in agreement to studies like Chitnis et al. [6] (7/23, 30%).

Brain MRI showed abnormal signals in 10/13 patients, all of whom had abnormalities in the deep white matter. While periaqueductal area was involved in 50% and brainstem in 40%. That was in agreement with results concluded by studies like: Absoud et al. [23] who found abnormal signals in deep white matter (8/15, 53.3%), periaqueductal area (5/15, 33.3%) and brainstem (5/15, 33.3%); Kim et al. [28] who found abnormal signals in white matter (3/3, 100%), periventricular area (2/3, 66.6%) and brainstem (2/3, 66.6%); and Lotze et al. [27] who reported abnormal MRI signals in deep white matter in nearly all patients and 7/9 patients (77.7%) have brainstem lesions.

LETM was reported in all patients. Similar result was obtained in many studies. [22,23,19,31,32] But smaller percentages were observed by Huppke et al. [17] (5/7), and Lechner et al. [24] (9/20).

Only 4 patients had performed orbital MRI, of whom one AQP +ve patient showed abnormal signals of the optic nerve. Pandit et al. [32] noticed optic pathway insult in 68.8%. Other studies did not mention that radiological feature in a clearly expressed way.

All seropositive patients received IVIG in the first admission after Methylprednisolone, in contrast to 33.3% of AQP negative patients. This can be explained by the fact that illness severity is higher in AQP positive patients. [33] This observation was emphasized in the practice of administering the maintenance therapy (Rituximab) which was given in 4 (AQP +ve) versus one (AQP -ve) patients in the first admission.

Following the patients for variable durations since the time of onset of their illness revealed the following for each: Four patients achieved self-sufficient ambulation within 1 month of onset of illness; one child died during the 2nd relapse; one girl achieved normal ambulation within 1 month of the 2nd relapse and a year later she had recurrent dystonic spasm of arms and pyramidal signs (patellar clonus); one boy became wheel chair bounded; one girl has frequent urinary incontinence; a girl has visual unilateral impairment (visual acuity is 20/60) from 1st attack of ON, however, she completely recovered from another attack which caused paraplegia; a boy who is able to walk for more than 200 meters performing daily activities, has asymmetrical motor dysfunction of upper limb and is unable to run; a girl is ambulating for less than 200 meters without provision and has unilateral blurred vision; a girl achieved full ambulation with ataxia of left arm, mild craniopathy and mild cerebellar signs; and a child has moderate hemiparesis with self-sufficient ambulation.

Up to our knowledge, this is the first study addressing the epidemiological – clinical profile of pediatric NMOSD. The clinical data was available in all patients enrolled. The limitations of this study include: small sample size; single-center setting; most of the patients' data was collected retrospectively; and lack of standardized blood testing of serological markers.

We conclude that: there was a sharp rise in the frequency rate of NMOSD during 2019 whichmay reflect the increasing identification of variable NMOSD spectrum disorders; the demographic characteristics of the present cohort were comparative to that reported in the literature; that transverse myelitis phenotype was the most common and consistent one; that AQP seropositivity was highly prevalent in children who had vomiting; that brain deep white matter and spinal LETM were the most common neuro - radiological manifestations; that a large proportion of children with

NMOSD was not investigated appropriately for orbital involvement during the diagnostic work-up; and that all cases enrolled in the present study fulfilled 2015 NMOSD criteria, indicating that pediatric neurologists were familiar with the recently revised criteria. It is recommended to assess serum AQP antibody level (cell-based assays) in any patient with optic neuritis or transverse myelitis; to send patients with negative AQP antibody for anti MOG antibody; to create and distribute applicable diagnostic and therapeutic guidelines; to conduct larger, epidemiological multi-center studies for better assessment of epidemiological, diagnostic, therapeutic and prognostic issues of pediatric NMOSD.

Conflict of interest:

no conflict of interest to declare

Ethical approval: An approval by the local ethical committee of Children Welfare Teaching Hospital was obtained (IRB: no. 20, on Jul. 2019).

Source of support: no source of support

Criteria of authors' inclusions

- Hayder Kadhim Jabbar: acquisition of data or analysis and interpretation of data; statistical analysis, manuscript preparation and final approval of the version to be published.
- Nebal Waill Saadi: Concept and design of study, drafting the article or revising it critically for important intellectual content; manuscript preparation, manuscript editing and final approval of the version to be published.

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