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ORIGINAL ARTICLE

The frequency of paroxysmal tonic spasm in multiple sclerosis

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Background

Multiple sclerosis (MS) is one of the most important neurological diseases with autoimmune pathogenesis characterized by demyelination of the central nervous system (CNS) with various spectrum of neurological manifestations. The most common form which is the relapsing-remitting type can be presented with visual, sensory, motor, cerebellar, and sphincteric disturbances lasting for days or even months.

Objectives

To determine the frequency of paroxysmal tonic spasms in a group of Iraqi multiple sclerosis patients and to determine possible disease characteristics associated with increased risk of paroxysmal tonic spasms.

Method

A cross-sectional study included 110 patients that have been diagnosed with MS based on 2017 McDonald criteria and visited regularly the MS clinic at Ibn-Sina specialized hospital (period, 01.09.2022-01.02.2023). These patients were diagnosed with TS clinically and evaluated radiologically and by electroencephalography to exclude conditions other than Tonic spasm.

Results

A total of 16 MS patients (14.5%) had paroxysmal TS. Older age patients and those with long disease courses and high EDSS scores were found to be correlated with the occurrence of tonic spasms. Moreover, pyramidal and sensory system impairments were significant risk factors for paroxysmal Tonic spasms.

Conclusions

Tonic spasm is significantly associated with Multiple sclerosis with a frequency of 14.5%. Motor system impairment and higher EDSS score were the most remarkable predictor risk factors to have a tonic spasm.

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Multiple sclerosis (MS) is recognized as one of the most common disabling neurological disease that can affect young to middle age people with a peak incidence between 20-40 years of age. It is an autoimmune disease of the central nervous system manifested by chronic inflammation with prominent myelin loss and subsequent gliosis and nerve axons loss, while more advanced cases are characterized by less inflammation and more neurodegeneration representing the progressive stage of the disease.[1,2]

MS can result in loss of the myelin sheath surrounding axons in the brain and spinal cord including the optic nerves and with time this will damage the myelin and the axons to variable severity causing various neurological symptoms and signs that can impair the quality of life of these patients.[3,4]

Although MS is known primarily to affect the subcortical white matter of the brain including the optic nerves and spinal cord, high-resolution MRI can show evidence of inflammation involving even normally appearing white and grey matter, in the cerebral cortex and basal ganglia.[5]

Paroxysmal tonic spasms (TS) can be recognized by multiple, acute onset, short lasting and stereotyped events which might take short time ranging from a few seconds to a few minutes, with an episodic presentation that may last for days to months after their start.[6,7] In the episodes that continue for longer than 24 hours, they can be identified as a disease recurrence. These symptoms may manifest either as MS initial symptoms or later on in the course of the condition.[8]

The reported incidence of paroxysmal tonic spasms ranges between 1.6% and 17% in patients with MS during the course of their disease, of which 24% occur as the initial presentation of the disease.[6,7,9–11] Although the relapsing-remitting form of the disease is the most common pattern linked to the occurrence of tonic spasms, it has also been described in the setting of progressive MS.[11] Despite paroxysmal tonic spasms are commonly associated with many neurological diseases like multiple sclerosis, they remain underdiagnosed and pose a diagnostic challenge These must be distinguished from MS-related events such localized fits and sleep problems. Additionally, tonic spasms might be misdiagnosed as the temporary worsening of a pre-existing neurological impairment brought on by numerous circumstances such as fever and infections.[12,13]

Paroxysmal tonic spasms may be categorized on the basis of several characteristics such as painful or painless, kinetic or non-kinetic, and generalized or localized.[12–16] An episode of unilateral upper extremity flexion and lower extremity extension with a chance of spreading to the face or neck is known as a generalized tonic spasm.[16–18]

AIM OF THE STUDY

To establish the frequency of paroxysmal tonic spasms in a group of Iraqi multiple sclerosis patients and to determine possible disease characteristics that can be associated with increased risk of paroxysmal tonic spasms.

METHODOLOGY

One hundred ten patients were included in this cross-sectional study, these patients were chosen sequentially to represent our MS population in Iraq when they visited our specialized MS clinic of Ibn-Sina teaching hospital from September 2022 to February 2023. Demographic parameters (age, sex, and disease duration) were recorded and patients were diagnosed with MS based on 2017 revised criteria established by McDonald.[19]

The neurological study was done on all patients with MS and the following factors were determined for MS patients: age, gender, MS disease prognosis, the longevity of disease, and the Expanded Disability Status Score (EDSS scores)[20] were used clinically to assess the functional systems involvement and patient disability in this study. The time of occurrence of paroxysmal tonic spasm in relation to disease onset was noted if TS was reported.

Patients were diagnosed with TS if they reported multiple, short-lasting, sudden onset, and stereotyped attacks of dystonic posturing that could last seconds to minutes.[6,7] All patients were evaluated by MRI and EEG to exclude alternative conditions like seizures or sleep disorders which had been excluded from this study.

The study was done in conformity with the Declaration of Helsinki's principles and informed approval was taken from all the participants. The protocol of the study was approved by the Department of Medicine, College of Medicine, University of Mosul (approval date: November 29, 2022, no: MDSC-4).

Statistical analysis

In case of parametric data, the Anderson Darling test was used to test the continuous data for normal

distribution using. Normally distributed data were represented in tables or graphically plotted as mean±SD. Non-normally distributed variables were plotted in boxplot and whisker as the median and interquartile range (percentile range, 25% to 75%) was used to represent the data. Non-parametric data were represented as the number of cases (and %). Statistics analysis was conducted using the Chi-square test or Fisher exact test (total sample <20 and if 2 or more with expected frequency less than 5), the differences in the median of the two groups were assessed by the Mann- Whitney U test (when data do not follow a normal distribution).

Odds-ratio (with 95% confidence intervals) was assessed by binary logistic regression analysis when the outcome can be categorized into 2 binary levels, and if possible, the probability plot was used to present the relationship. Minitab version 17.0, SPSS version 20 and medcalc version 14.8 software package were used to perform the statistical analysis, with a p-value of <0.05 being regarded as significant.

RESULTS

Paroxysmal tonic spasms were found in 16 patients with MS patients (14.5), while the remaining 94 patients (85.5%) did not have TS as demonstrated in Figure 1.

Demographic characteristics and its association with TS

Out of 110 patients in the study group, 73 (66.3%) were females, 37 (33.7%) were males, and the median age was 28 years.[22-39] Age was found to be significant as higher age was reported in patients with TS compared with patients who did not report any episodes of TS (mean age in patients with TS: 40 years vs mean age in patients without TS: 24 years, p <0.001). Regarding gender, we found that among the 16 patients who had TS; 13 patients (81.2%) were females while the remaining 3 patients (18.8%) were males. On the other hand, 60 patients out of 94 (63.8%) who did not have TS were females while 34 patients (36.2%) were males. The difference was not statistically significant (Table 1).

MS course and TS

The association between the MS subtype and RLS is demonstrated in Table 2, where 88 patients (80.0%) had RRMS, 16 patients (14.5%) had SPMS and 6 patients (5.5%) had PPMS. Among the 16 patients with MS/TS+ 13 patients (81.2%) had RRMS, 2 patients (12.5%) had SPMS and 1 patient (6.2%) had PPMS. On the other hand among the 94 patients with MS/TS- 75 of them (79.7%) had RRMS, 14 patients (14.8%) had SPMS and 5 patients (5.3%) had PPMS. There is no significant association between MS subtypes and RLS.

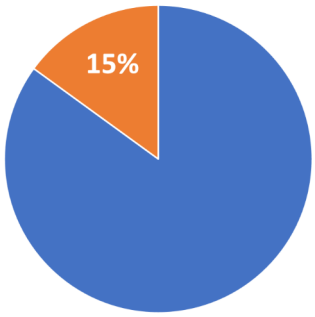

Figure 1 *The frequency of paroxysmal tonic spasm in multiple sclerosis*

Table 1 *Demographic characteristics of MS patients and their association with tonic spasm*

		No. TS	TS	Total	*p*-value
Number	**-**	94	16	110	-
Age (years)	***Median (IQR)***	24 (21 – 34)	40 (35 – 45)	28 (22 – 39)	<0.001
	Range	16 – 56	28 – 55	17 – 56	
Sex	***Female***	60	13	73	0.233
		63.8%	81.2%	66.3%	
	Male	34	3	37	
		36.2%	18.8%	33.7%	

Table 2 *Association between MS subtype and TS*

	Not	RLS	Total	*p* value
RRMS	75	13	88	0.857
	79.7%	81.2%	80.0%	
SPMS	14	2	16	
	14.8%	12.5%	14.5%	
PPMS	5	1	6	
	5.3%	6.2%	5.5%	

Duration of MS and TS

The occurrence of paroxysmal tonic spasms was associated by the duration of MS, with an odds ratio

Table 3 *Functional system involvement distribution by tonic spasm*

		No TS	TS	Total	p value
Number		94	16	110	-
Sensory	No	24	9	33	*0.006*
	%	25.5%	56.2%	30.0%	
Pyramidal	No	21	12	33	*<0.001*
	%	22.3%	73.7%	30.0%	
Cerebellar	No	14	2	16	0.575
	%	14.8%	12.5%	14.5%	
Visual	No	22	3	25	0.428
	%	23.4%	18.8%	22.7%	
Brain stem	No	19	2	21	0.587
	%	20.2%	12.5%	19.1%	

of 1.47 for each year in disease duration (95%CI: 1.254-1.733, p<0.001).

EDSS score and TS

Regarding the association between EDSS score and the presence of TS, the median EDSS score for patients with TS was 3.5 (IQR:2.5-5) while for patients without TS, it was 1 (IQR:1-2). There was a significant association between high EDSS with TS risk, with an odds ratio of 12.95 (95%CI: 3.803 – 44.083, p<0.00).

Function system status

Only motor and sensory systems involvement were significant in association with TS as illustrated in Table 3. Nine patients, out of 33 MS patients with sensory system impairment, had a paroxysmal tonic spasm, this difference was significant with P value of 0.006 and from 33 MS patients who had motor functional system impairment, 12 had paroxysmal tonic spasms, the difference is much significant with *p* value <0.001.

Treatment of MS in our locality is mainly based on using the standard international protocols, These 110 patients with multiple sclerosis are on disease-modifying treatment provided by the Iraqi ministry of health for free as shown in Table 4.

Table 4 *The disease-modifying group used in Iraqi MS patients*

Treatment	No.(%)
Interferon Beta-1B (Injections)	88 (80%)
Fingolimod (Oral)	12(11%)
Natalizumab (Infusion)	10 (9%)

DISCUSSION

The present study has identified that there is a significant association between MS and TS with a prevalence of TS in MS patients of 14.5%, this rate is in the line with the general frequency of abnormal movement that has been reported in MS including paroxysmal tonic spasm which shows a frequency between 1.6% to 17%.[12] Although the exact cause is still not clearly understood, several pathophysiological mechanisms have been proposed to explain the association between MS and the occurrence of various abnormal movements including paroxysmal TS. The most accepted theory was proposed by Osterman et al whereby paroxysmal events caused by the signal generation and spread of ectopic and spontaneous nerve motifs by the demyelinated axons and these waves transversely transmitted (ephaptic transmission) to other normal axons within the nerve fibre tracts and ultimately appeared as paroxysmal TS.[21]

The strength of this theory is based on the fact that proprioceptive and tactile stimuli are well known to trigger many types of tonic spasms. Moreover, an alternative theory is based on the effect of "inflammatory irritation" that characterizes inflammatory demyelinating diseases like MS also has been suggested based on the remarkable response of these TS to corticosteroids in many documented cases.[22] Yet, a third possible theory is that partially demyelinated nerve fibres are known to have ion channel dysfunction.[23] Such configuration in ion channels will make minor physiological stimuli cause a great nerve stimulation, such as in hyperventilation when low ionized calcium is known to trigger TS. This theory can be supported by the remarkable effect of antiepileptic drugs and the carbonic anhydrase inhibitor acetazolamide on the frequency and severity of attacks.

Analysis of the results concerning the demographic characteristics has revealed that the older the age, the more significant chance for developing TS, This reciprocal association could be critically related to the fact that older MS patients have a greater tendency for developing more inflammation, demyelination and plaque formation due to advancement of disease pathogenicity, such demyelination in neuronal axons and their connections with other tracts in the brain and spinal

cord will cause greater sensory and motor disease burden which is also found to be significant in the current study.

The association between MS subtypes and the risk of developing TS has been negatively confirmed in this study, perhaps because all MS subtypes have the same pathological effect on the CNS with inflammation, demyelination gliosis and neurodegeneration.[1,2]

The present research has demonstrated that increasing disease duration correlates directly with the prevalence of TS (the risk of developing TS increased by a rate of 1.5 folds per year). This association could be explained perhaps in the context of the fact that the longer MS disease duration, the longer ongoing inflammation and plaque formation and the higher tendency to indulge motor and sensory system deficits which in turn has been greatly linked with the risk of complaining from TS.

The significant reciprocity between the decline in the functional system and developing TS was identified in the study, this was unusually true for sensory and pyramidal system involvement, However, the deficits in the impairment of brainstem, cerebellar and visual functional systems have negatively conjoined with the risk of having TS. This association perhaps could be illustrated in the context of the fact that corticospinal tracts and spinothalamic tracts which control motor and sensory perception are the main structures involved in MS.[24] It's also worthy to mention that the paroxysmal symptoms including TS have been claimed to be linked with the deficits of ascending spinothalamic sensory tracts relative to central somatosensory processing deficits due to abnormal peripheral afferent input, taking into consideration that this aforementioned explanation is only weakly supported by scientific evidence.[25-27]

This study shows a significant correlation between a higher Expanded Disability Status Score and the risk of developing TS. This can also be explained by the fact that the disability measured by EDSS score depends mainly on the pyramidal weakness which in turn is considered a significant risk for developing TS.

CONCLUSION

Paroxysmal tonic spasm is significantly associated with MS. Predictor risk factors include older age patients, longer MS duration, patients with motor and sensory system disability and patients with higher global EDSS scores, results strengthen the idea that the inflammatory d amage correlated with MS may induce paroxysmal TS. The prompt identification of TS is important, especially in MS patients as proper treatment can result in dramatic improvement of patient quality of life.

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