Movement disorders in early MS and related diseases

A prospective observational study

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Abstract

Background

Little is known about the true prevalence and clinical characteristics of movement disorders in early multiple sclerosis (MS) and related demyelinating diseases. We conducted a prospective study to fill this knowledge gap.

Methods

A consecutive patient sample was recruited from the MS clinic within a 1-year-period. Patients diagnosed over 5 years before the study start date were excluded. Each eligible patient was interviewed by a movement disorder neurologist who conducted a standardized movement disorder survey and a focused examination. Each patient was followed prospectively for 1–4 follow-up visits. Movement disorders identified on examination were video-recorded and videos were independently rated by a separate blinded movement expert.

Results

Sixty patients were included (56.6% female, mean age 38.3 ± 12.7 years). Eighty percent reported one or more movement disorders on the survey and 38.3% had positive findings on examination. After excluding incidental movement disorders (e.g., essential tremor), 58.3% were thought to have demyelination-related movement disorders. The most common movement disorders in a descending order were restless legs syndrome, tremor, tonic spasms, myoclonus, focal dystonia, spontaneous clonus, fasciculations, pseudoathetosis, hyperekplexia, and hemifacial spasm. The movement disorder started 5 months following a relapse on average but in 8 patients it was the presenting symptom of a new relapse or the disease itself. The majority of movement disorders occurred secondary to spinal (85.7%) or cerebellar/brainstem lesions (34.2%). Spinal cord demyelination was the only statistically significant predictor of demyelination-related movement disorders.

Conclusion

Movement disorders are more common than previously thought even in early MS. They typically begin a few months after spinal or brainstem/cerebellar relapses but may occasionally be the presenting symptom of a relapse.

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Failure to recognize MS as a potential cause of new-onset movement disorder can lead to delays in the diagnosis and initiation of disease-modifying therapy.

Movement disorders are traditionally thought to be uncommon in multiple sclerosis (MS).¹ However, the true prevalence and incidence of movement disorders in MS is unknown as most previous reports have been retrospective or consisted of small case series or review articles.^{2,3} In addition, there is no consensus among authors on how to define movement disorders in MS, with some authors focusing on classical extrapyramidal disorders only and others including tonic spasms, cerebellar tremor, spasticity, and even ataxia. This resulted in major variability of the reported rates among different studies. Moreover, the results of previous reports could have been contaminated by non-MS-related movement disorders such as coexisting essential tremor (ET) given lack of systematic evaluation and obscure timeline in relation to disease onset. In our experience, movement disorders are not uncommon in MS even early in the disease course. In fact, some movement disorders are highly suggestive of MS and may be the presenting symptom of the disease (e.g., tonic spasms and paroxysmal focal dystonia). Failure to recognize MS as a potential cause of new-onset movement disorder can lead to delays in the diagnosis and initiation of disease-modifying therapy (DMT). We sought to study movement disorders in early MS and other central demyelinating diseases within a systematic prospective protocol.

Methods

A consecutive sample of new patients referred to the Cleveland Clinic's Mellen Center was prospectively evaluated within a 1-year period from July 2015 to June 2016. Patients who were diagnosed over 5 years before evaluation were excluded along with patients in whom a demyelinating disease was unconfirmed. Each patient who agreed to participate was interviewed by a neurologist trained in both neuroimmunology and movement disorders (H.A.) who conducted a standardized movement disorder survey and a movement disorder-focused examination based with modification on the Unified Parkinson's Disease Rating Scale. Movement disorders identified on examination were video-recorded and videos were independently rated by a separate movement disorders neurologist (X.X.Y.) blinded to the patient's clinical data. Each video reviewer was asked to designate one main phenomenology and 2 alternative possibilities for each recorded movement disorder. When there was inter-rater disagreement in the main designation, the 2 other alternative ratings were taken into account.

We defined movement disorders based on phenomenology then sought to identify anatomical generators of the different movement disorders based on MRI results and time in relation to relapse or disease onset. The spectrum of movement disorders is vast and following an all-inclusive approach could inflate prevalence in MS. Although spasticity and cerebellar ataxia are both considered movement disorders in some sense, we elected to include only patients with phasic tonic spasms and those with ataxic tremor instead of including all forms of spasticity and all forms of ataxia to limit the evaluation to what is considered a movement disorder from the practical standpoint and avoid inflation of movement disorder prevalence in the studied cohort. Although fasciculation is not formally considered a movement disorder, this form of involuntary movement was included in the study based on the observation that muscle twitching is a relatively frequent complaint in patients with MS. The movement disorder survey included questions on lifetime occurrence of tremor, tonic spasms, dystonia, chorea, ballism, athetosis/pseudoathetosis, myoclonus, tics, spontaneous clonus, parkinsonism, restless legs syndrome (RLS), hyperekplexia, hemifacial spasm, and fasciculations. Each medical term was defined in layperson verbiage in the survey. When needed, the movement disorder in question was described and demonstrated to the patient by the examining neurologist. The survey included questions concerning the onset of each movement disorder in relation to disease onset and in relation to relapse in relapsing subtypes. Each patient was followed prospectively for at least 1 and up to 4 follow-up visits within the following year. A repeat survey and movement disorder examination was conducted during each follow-up. We targeted patients with early disease to reduce the chances of contamination by spasticity-related movement disorders or the development of coincidental neurodegenerative movement disorders.

We classified movement disorders as spinal if they occur following an MRI-positive spinal relapse in absence of cortical, ganglionic, or infratentorial lesions that can generate similar phenomenology. The following phenomenologies were excluded from the spinal classification: hemifacial spasm, chorea, ballism, tics, and parkinsonism.

We classified movement disorders as infratentorial if they occur following an MRI-positive cerebellar or a brainstem relapse in absence of cortical, ganglionic, or spinal lesions that can generate similar phenomenology. RLS and tics were excluded from the infratentorial classification.

In patients who had both spinal and infratentorial lesions, tremor was considered infratentorial, while tonic spasms and paroxysmal dystonia were considered spinal. All other movements were considered mixed.

To determine whether the movement disorder is demyelination-related or incidental, we developed preset criteria for classification. In order to consider the movement disorder demyelination-related, the following criteria had to be fulfilled:

1. The movement disorder started after the probable clinical onset of the disease and within an identifiable time period from a definite relapse (in relapsing disorders).
2. The movement disorder can be attributed to a visible demyelinating lesion on brain or spinal cord MRI.
3. No other competing possibilities exist to explain the abnormal movement; for example, action tremors were considered incidental if it occurred transiently during steroid treatment or if the patient had a strong family history of ET.

Standard protocol approvals, registrations, and patient consents

This study was approved by the Cleveland Clinic's institutional review board (IRB). Each eligible patient was given an IRB-approved patient information sheet detailing the purpose of the study with options to opt in or out of participation. Written informed consent was obtained from each patient before video recording along with authorization for disclosure of videos for publication.

Statistical analysis

Pertinent data were compared between the cohorts using the χ^2 for categorical variables, the Student *t* test for normally distributed continuous variables, and the Wilcoxon signed-rank test for continuous variables that were not normally distributed. *p* Value of ≤ 0.05 was used to indicate significance. A multivariable logistic regression model was used to determine if there were independent predictors of having demyelination-related movement disorders. Statistical analyses were performed using R (version 3.4.3).⁴

Data, methods, and materials have been carefully described. Any data not published within the article are available in a public repository and include accession numbers to the dataset.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

Out of 198 patients screened, 60 patients met inclusion criteria and agreed to participate in the study. The demographics and clinical characteristics of the patients are summarized in table 1.

Of the entire cohort, 80% reported one or more movement disorders in their lifetime on the survey and 61.6% indicated that the movement disorder started after the probable clinical onset of their demyelinating disease. The onset of the abnormal movement in relation to disease onset was unknown in 6.2%. After excluding patients in whom all movement disorders were determined to be incidental, there were 35 patients with probable demyelination-related movement disorders (58.3% of the entire cohort). Of those, 83% indicated that the

Table 1 Demographics and clinical data

Demographics	Values
Age at study enrollment, y	38.3 $\pm$ 12.7
Duration since diagnosis, mo	11.4 $\pm$ 18.2
Duration since probable clinical onset of disease, mo	32.3 $\pm$ 37.3
Newly diagnosed at the time of enrollment	38.3
On DMT at the time of enrollment	33.3
Female	56.6
White	85
Clinical diagnosis	
RRMS	63.3
CIS	10
NMOSD	9
ITM	6.6
PPMS	6.6
SPMS	3.3
RIS	3.3
ADEM	1.6

Abbreviations: ADEM = acute disseminated encephalomyelitis; CIS = clinically isolated syndrome; DMT = disease-modifying therapy; ITM = idiopathic transverse myelitis; NMOSD = neuromyelitis optica spectrum disorder; PPMS = primary progressive multiple sclerosis; RIS = radiologically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis. Values are mean $\pm$ SD or %.

movement disorder occurred within a well-defined period (average 5 months) in relation to a clinical relapse. In 13% of the entire cohort, the abnormal movement was the presenting symptom of a relapse, including 4 patients in whom it was the first symptom of the disease (6.6%). Only 38.3% of the entire cohort had positive findings on the focused movement disorder examination during the study period. The main phenomenology agreement rate between the examining neurologist and the blinded rater was 80%. There were no cases of interrater disagreement in all 3 possible ratings for any given video. The incidence of new movement disorders that were not present during the initial evaluation but appeared within the following year was 5% for the entire cohort. The frequencies of the different movement disorder subtypes are summarized in table 2.

Of the entire cohort, 22% had one or more movement disorders that were determined to be incidental, including physiologic benign fasciculations (10), ET (6), idiopathic tic disorder (6), idiopathic RLS (5), physiologic hypnic myoclonus (5), steroid-related tremor (2), psychogenic tremor (2), idiopathic hemifacial spasm (1), primary hyperekplexia (1), and coexisting idiopathic Parkinson disease in a patient with idiopathic transverse myelitis (1).

Table 2 Frequency of movement disorders in the study cohort

Movement disorders reported on survey (n)	Incidental movement disorders (n)	Demyelination-related movement disorders (n)	Movement disorders present on exam (n)	Movement disorders at relapse presentation (n)
Tremor (31)	Fasciculations (10)	RLS (23)	Tremor (19)	Tremor (3)
RLS (28)	Tremor (10)	Tremor (21)	Tonic spasms (5)	Tonic spasms (2)
			Pseudoathetosis (3)	
Myoclonus (21)	Tics (6)	Tonic spasms (16)	RLS/akathisia (3)	Acute RLS (1)
Fasciculations (19)	RLS (5)	Myoclonus (16)	Focal dystonia (2)	Focal dystonia (1)
Tonic spasms (17)	Myoclonus (5)	Focal dystonia (11)	Myoclonus (2)	Pseudoathetosis (1)
Focal dystonia (10)	Hemifacial spasms (1)	Spontaneous clonus (10)	Spontaneous clonus (1)	
Spontaneous clonus (10)	Hyperekplexia (1)	Fasciculations (9)	Hemifacial spasm (1)	
Pseudoathetosis (8)	Parkinson disease (1)	Pseudoathetosis (8)	Parkinsonism (1)	
Hyperekplexia (8)		Hyperekplexia (7)	Motor tics (1)	
Tics (6)		Hemifacial spasm (2)		
Hemifacial spasm (3)				

Abbreviation: RLS = restless legs syndrome.

The majority of demyelination-related movement disorders occurred secondary to spinal (85.7%) or infratentorial lesions (34.2%). Only 17% of patients with presumed spinal movement disorders had concomitant infratentorial lesions. Movement disorders secondary to basal ganglia lesions occurred in only 1 patient.

Restless legs syndrome

Secondary RLS was the most common demyelination-related movement disorder in the study cohort (38.3%). All patients developed typical RLS symptoms acutely or subacutely following a spinal relapse and met the published International RLS Study Group diagnostic criteria for RLS except for the idiopathic etiology requirement.⁵

Tremor

Twenty-five patients had action hand tremor, of which 19 were determined to be demyelination-related (15 with infratentorial lesions and 4 with spinal lesions without infratentorial involvement). Two patients had combined resting/action/intentional tremor with prominent proximal component consistent with rubral tremor (video 1). One patient developed task-specific tremor when attempting to hold the computer mouse (video 2). One patient had resting tremor without any other parkinsonian features (video 3). One patient had transient orthostatic tremor following a spinal attack. Combining demyelination-related tremor of any phenomenology yielded a total of 21 patients (35% of the entire cohort).

Tonic spasms

Seventeen patients had tonic spasms involving the lower extremity (13), upper extremity (4), or truncal muscles (4). The most frequent tonic spasm subtypes in descending order

were extensor, isometric, and flexor spasms; 41% of patients had combined patterns. In 16 patients (26.6%), tonic spasms occurred with or following a spinal relapse. The tonic spasms were painful in 65% of cases, kinesogenic in 70%, and stimulus-sensitive (often to touch) in 23.5% (video 4).

Myoclonus

Sixteen patients (26.6%) were determined to have demyelination-related myoclonus, of which 44% were mixed brainstem/spinal myoclonus, 37.5% were spinal myoclonus (proprio-spinal or focal), 12.5% were brainstem myoclonus, and 6.25% were presumed cortical myoclonus (due to absence of demyelinating lesions in the brainstem and cord).

Focal dystonia

Per our previously reported definition,⁶ 11 patients (18.3%) had focal paroxysmal dystonia of the upper or lower extremity following a well-defined spinal (8) or brainstem relapse (1). One patient with primary progressive MS had focal dystonia from a right thalamic lesion and in one patient the origin was undetermined. In one patient with neuromyelitis optica spectrum disorder (NMOSD), the paroxysmal dystonia was the first symptom of the disease and followed an unusual pattern in which one hand would become dystonic for a few days at a time separated by prolonged dystonia-free periods (video 5). The paroxysmal dystonia was painful in 27% of cases, kinesogenic in 73%, and stimulus-sensitive in 36%.

Other demyelination-related movement disorders

Of the 10 patients with spontaneous ankle clonus, 8 had spinal lesions. All cases were kinesogenic, painless, and occasionally stimulus-sensitive. Nine patients developed new subjective

sense of body fasciculations following a spinal relapse but there were no objective fasciculations on examination in any of them. Eight patients developed finger pseudoathetosis following a sensory relapse of spinal (4), infratentorial (1), or mixed (3) origin (video 6). Seven patients developed new hyperekplexia following disease onset of whom 3 had spinal lesions, 2 had infratentorial lesions, 2 had both spinal and infratentorial lesions, and 1 had supratentorial lesions only. There were 2 patients with hemifacial spasm secondary to pontine demyelination. There were no demyelination-related or incidental cases of chorea or ballism in this cohort.

Results of the statistical analysis

Patients with demyelination-related movement disorders were more likely to have spinal lesions than patients without (84.4% vs 56.5%, $p = 0.048$) (table 3). Though there were more patients in the movement disorder cohort with

infratentorial demyelination (55.9% vs 36%), this difference was not significant ($p = 0.3$).

In the adjusted analysis (table 4), the presence of spinal lesions remained the only significant predictor of having a demyelination-related movement disorder (odds ratio 4.95, 95% confidence interval 1.32–21.8).

Discussion

Unlike most previous work, we followed a prospective systematic protocol to study movement disorders in demyelinating diseases. We specifically evaluated movement disorders in early disease in order to reduce contamination by spasticity-related movement disorders or the development of coincidental neurodegenerative conditions. Our results are substantially different from previous retrospective studies, revealing a very high prevalence of

Table 3 Demographic and diagnostic differences between patients with multiple sclerosis (MS) with demyelination-related movement disorders and patients with MS without a related movement disorder

Characteristic	Data available	Demyelination-related movement disorder		<i>p</i> Value
		No (n = 25)	Yes (n = 35)	
Age, n (%)	60 (100)			
Mean ± SD		37.7 ± 13.4	38.9 ± 12.6	0.73
<30 y		8 (32)	11 (31.4)	0.92
30–49 y		11 (44)	14 (40)	
≥50 y		6 (24)	10 (28.6)	
Sex, n (%)	60 (100)			0.22
Male		17 (68)	17 (48.6)	
Female		8 (32)	18 (51.4)	
Ethnicity, n (%)	60 (100)			0.85
Caucasian		22 (88)	29 (82.9)	
African American		3 (12)	6 (17.1)	
Disease type	60 (100)			0.47
RRMS		14 (56)	24 (68.6)	
Other		11 (44)	11 (31.4)	
Months since diagnosis, n (%)				
Mean ± SD	60 (100)	9.7 ± 17.2	12.7 ± 19.2	0.69
<12		18 (72)	22 (62.9)	0.64
≥12		7 (28)	13 (37.1)	
MRI disease burden, n (%)				
Brain without infratentorial involvement	59 (98.3)	12 (48)	12 (35.3)	0.30
Brain with infratentorial involvement		9 (36)	19 (55.9)	
Spinal cord	55 (91.7)	13 (56.5)	27 (84.4)	0.048

Abbreviation: RRMS = relapsing-remitting multiple sclerosis.

Table 4 Multivariable logistic regression of factors associated with patients with multiple sclerosis (MS) having demyelination-related movement disorders

Characteristic	OR (95% CI)	p Value
Age	1.02 (0.97–1.08)	0.40
Sex		
Female	Reference	—
Male	1.83 (0.51–6.97)	0.36
Ethnicity		
Caucasian	Reference	—
African American	1.90 (0.37–12.00)	0.46
Disease type		
Relapsing-remitting MS	Reference	—
Other	1.06 (0.26–4.62)	0.93
Months since diagnosis		
<12	Reference	—
≥12	1.16 (0.33–4.26)	0.81
MRI disease burden		
No brain lesions	Reference	—
Supratentorial brain lesions only	1.41 (0.20–10.67)	0.73
Infratentorial brain lesions	2.46 (0.31–21.41)	0.39
No spinal cord lesions	Reference	—
Spinal cord lesions present	4.95 (1.32–21.78)	0.02

Abbreviations: CI = confidence interval; OR = odds ratio.

movement disorders in early demyelinating diseases of 58% and an annual incidence rate of 5%, not counting incidental movement disorders. Prior estimation in retrospective cohorts was between 0.4% and 1.6%.^{7,8} The retrospective nature of these studies and the lack of systematic evaluation by a specialist probably account for this large difference in prevalence estimates. Cross-sectional studies of tremor and RLS in MS yielded much higher prevalence rates comparable to our findings.^{9–11}

We found that most demyelination-related movement disorders occur secondary to spinal demyelination followed by cerebellar/brainstem involvement, while ganglionic movement disorders were extremely rare in this early disease cohort. Spinal demyelination was the only independent predictor of demyelination-related movement disorders. Traditional ganglionic movement disorders are probably more prevalent in longstanding and progressive forms of MS based on preliminary data from an ongoing separate study by our group (unpublished). The new onset of focal or multifocal movement disorder in a young patient should prompt a search for MS by obtaining brain and most importantly spinal MRI. In patients with established MS, the development of a new movement

Most of the movement disorders were spinal in origin except for tremor, which mainly resulted from cerebellar/brainstem involvement.

disorder can indicate a new relapse and should prompt new imaging, acute relapse management as appropriate, and consideration of DMT escalation if indicated.

Most of the movement disorders were spinal in origin except for tremor, which mainly resulted from cerebellar/brainstem involvement. However, in at least 5 patients, the tremor was spinal in origin and was largely indistinguishable from cerebellar tremor except in one patient who had leg orthostatic tremor following a spinal attack. The origin of spinal tremor comes from interruption of the spinocerebellar tracts and the phenomenology in those patients was distinct from pseudoathetosis secondary to sensory deprivation from lesions in the posterior column. Our tremor prevalence rate of 35% is intermediate to the rates previously reported by cross-sectional studies of patients with MS in all stages of the disease (26%–58%).¹⁰ In general, distal postural/action tremor of both hands was the most common tremor type in our cohort, while rubral tremor was rare (3.3%). Contrary to the general conception but in agreement with our findings, Alusi et al.¹⁰ also did not find any cases of rubral tremor in their cross-sectional study of 100 patients with MS of any duration. This has therapeutic implications since the similarity to ET may make the case for trying common tremor medications such as propranolol or primidone, or considering ventral intermedialis thalamic DBS for severe or resistant cases.¹² Only a few patients with MS will have rubral tremor that requires unconventional treatments or novel DBS targets such as the Ventralis Oral nucleus or Zona Incerta.^{13,14}

The distinction between sensory paresthesia and RLS in patients with MS has always been challenging but in our study, we found that a large number of patients will meet established criteria for RLS shortly after having a spinal relapse. Our RLS prevalence rate (38%) is higher than the prevalence rate reported in the cross-sectional study by Manconi et al.,¹¹ in which they excluded patients with recent diagnosis or relapse. This suggests that secondary RLS following spinal relapses could be transient and may resolve over time, bringing prevalence numbers down in mixed or advanced disease cohorts.

In addition to tremor and RLS, other movement disorders, specifically tonic spasms, paroxysmal focal dystonia, and pseudoathetosis, were all encountered at the onset of a new relapse or the disease itself and may be valuable in the clinical evaluation of patients with MS. MS literature has several case reports of MS or NMOSD presenting with tonic spasms or paroxysmal dystonia.^{15–18} We also found frequent movement disorders that

were not previously associated with MS, such as subjective fasciculations, pseudoathetosis, and hyperekplexia. We are currently conducting a separate study focusing on spinal movement disorders and the distinction between their different subtypes. Nearly half the patients (40%) with demyelination-related movement disorders required symptomatic management but 42% of those treated were not satisfied with treatment response. Accurate identification of the proper phenomenology is the first step towards improved, phenomenology-directed, symptomatic treatment. It will also facilitate proper enrollment in symptomatic and restorative trials.

Our study does not capture the general prevalence of movement disorders in MS since patients with longstanding disease were excluded. This was intentional to increase the confidence in the demyelinating origin of these abnormal movements. However, this expectedly led to very small numbers of patients with primary progressive MS and secondary progressive MS in the study and therefore we cannot make conclusions regarding movement disorders in progressive MS. Many patients with progressive disease experience spasticity-related or traditional ganglionic movement disorders, which are the subject of a separate study we are currently conducting. Our findings cannot be confidently generalized to patients with NMOSD, acute disseminated encephalomyelitis, or transverse myelitis given their limited representation in our cohort. Other limitations include the short follow-up duration and the fact that the interrater phenomenology agreement was under 100% for first rating. Because many of the movement disorders were transient or episodic, only a small percentage of the movement disorders listed on the surveys could be verified objectively on examination during the study period; however, every effort was made to discuss the semiology with each patient in detail, including obtaining collateral information and details about timing in relation to disease onset and relapse. We developed preset criteria in an effort to differentiate demyelination-related from incidental movement disorders and avoid inflating movement disorder prevalence in the study cohort. We recognize that our criteria are not immune to classification bias and that some degree of misclassification might have occurred inadvertently. However, our rate of incidental movement disorders was low (22%) and all of them were carefully analyzed as detailed in the Results. This category included movement disorders that started in childhood (e.g., benign fasciculation, idiopathic tics, primary hyperekplexia) as well as patients with tremor in the setting of steroids or a strong family history of ET. Since our study did not include any patients with pediatric-onset MS, it is unlikely that any of these longstanding movement disorders were early signs of demyelination. A degree of selection bias might have occurred as well since patients with movement disorders are more likely to opt in to a movement disorder study; however, in most cases, exclusion from the study was based on not meeting inclusion criteria, while the rate of opting out was very low. This study was also purely clinical without any supportive electrophysiologic data.

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Disclosure

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Appendix 1 Author contributions

Name	Contribution
Hesham Abboud, MD, PhD	Study concept and design, data collection, data analysis, writing the first draft, accepts responsibility and final approval of the manuscript
Xin Xin Yu, MD	blinded video rater, data analysis, review and critique
Konrad Knusel, MS	statistical analysis, co-writing results, review and critique
Hubert H. Fernandez, MD	overseeing movement disorders content, review and critique, final approval of the manuscript
Jeffrey A. Cohen, MD	overseeing neuroimmunology content, review and critique, final approval of the manuscript.

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Practical Implications

Neurology® Clinical Practice is committed to providing clinical insights helpful to neurologists in everyday practice. Each Full Case includes a “Practical Implications” statement, a pearl of wisdom for the practicing clinician.