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Clinical short communication

Relevance of cerebrospinal fluid findings in patients with multiple sclerosis and seizures

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ABSTRACT

Seizures occur 2–3 times more frequently in Multiple Sclerosis (MS) patients compared to the general population. The prevalence of seizures is reported to be 1.5–7.8% in MS population. However, it is unclear if seizure is an indirect symptom of neuroinflammation in MS. In our study, we explored the relevance of cerebrospinal fluid (CSF) findings in this unique patient cohort with MS and seizures. We retrospectively reviewed the charts of 32 MS patients with subsequent seizures (MSSS) and 12 patients with seizures followed by MS (SFMS). These two study groups were compared with two control groups - MS without seizures (MSNOS) and seizures without MS (SNOMS). Clinical characteristics and CSF findings between these groups were compared using boot strapped independent *t*-test. The CSF lymphocyte percentage of the SFMS group (95.6 ± 3) was significantly higher compared to MSNOS (66.0 ± 36.9, $p = .04$) and SNOMS (81.7 ± 10.0, $p = .03$). The CSF IgG index was significantly higher in SFMS group (1.9 ± 1.2, $p = .02$) as compared to MSSS group (0.99 ± 0.4). Patients with seizures as initial symptom of MS may have higher degree of CNS inflammation. Nonspecific clinical symptoms and atypical imaging findings in patients presenting with seizures may warrant close monitoring for development of MS.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating inflammatory disease that affects the central nervous system (CNS) and is also associated with various other conditions, comorbidities and presentations [1,2]. Of those conditions, the concurrent prevalence of seizures and multiple sclerosis has been well recognized in the literature [3–9].Prevalence of seizures is higher in Multiple Sclerosis (MS) patients compared to the general population with an occurrence of 1.5% to 7.8 [1,10]. Seizures typically emerge in the first decade after diagnosis and can be the first manifestation of MS or an MS relapse can also present as a seizure [3,11]. Seizures may be an indirect indication of the inflammatory process in autoimmune conditions, and this may be reflected on imaging or cerebrospinal fluid analysis [8,12]. However, no prior study to our knowledge has investigated the inflammatory findings in MS patients with seizures. We aimed to compare the CSF findings between MS patients without seizures, MS patients who later had seizures, seizures patients who were later diagnosed with MS and seizure patients without MS.

2. Methods

This is a retrospective, cross-sectional, single center study. Institutional Review Board approval was obtained. We reviewed outpatient encounters between 2014 and 2017.

Inclusion criteria for MS with seizure groups: i) Diagnosis of MS by the 2010 revised Mc Donald criteria, ii) Known history of seizures, iii) Availability of CSF data when establishing initial MS diagnosis. For control groups, we also collected CSF analysis information of patients who had MS without seizures and patients who had seizures and an inflammatory etiology was suspected. Exclusion criteria: Patients who had seizures due to other risk factors, such as CNS infections, penetrating traumatic brain injury, stroke, intracranial hemorrhage and significant family history with childhood onset of seizures.

Demographic and clinical information on MS and seizures was extracted from the patient's electronic medical records. Our patients were divided into four groups – the first group included patients who had an established diagnosis of MS and subsequently developed seizures (MSSS), second group included patients whose seizures preceded the MS diagnosis (SFMS), third group included MS patients without history of seizures (MSNOS) and fourth group included seizure patients without

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Table 1
Patient demographics and CSF analysis information.

	MSSS	SFMS	MSNOS	SNOMS	*p*-value
N	32	12	18	12	
Current Age (years)	53.5 ± 12.3	39.3 ± 8.4	44.6 ± 11.7	38.3 ± 17.7	< 0.001
Gender	9 M, 23 F	4 M, 8 F	1 M,17F	5 M,7F	0.11
Ethnicity	17 AA, 15 CAU	9 AA, 3 CAU,	12AA,6C	9AA,3C	0.2
Duration of MS (years)	17.7 ± 8.7	6.47 ± 4.6	9.2 ± 6.8		< 0.001
Type of MS	20 RRMS, 10 SPMS, 2 PPMS	12 RRMS	18 RRMS		
Age at MS diagnosis (years)	35.7 ± 11	33 ± 9.52	47 ± 10.9		0.39
Age at seizure onset (years)	46.46 ± 11.8	25.07 ± 14.3		27 ± 14	0.001*
EDSS	5.5 ± 2	3.3 ± 2	2.8 ± 1.8		0.01
CSF cell count	27.6 ± 22	11.5 ± 10.3	4.2 ± 6.6	4.5 ± 6.1	0.3
CSF lymphocytes (%)	92.3 ± 20	95.6 ± 3	66.0 ± 36.9	81.7 ± 10.0	0.039*
CSF glucose (mg/dl)	64.7 ± 19	59.3 ± 7.67	56.6 ± 16.7	66.0 ± 23.9	0.6
CSF protein (mg/dl)	68 ± 40	48.2 ± 12.9	54.4 ± 56.7	48.1 ± 22.8	0.09
CSF oligoclonal bands	4.22 ± 4	7.8 ± 6	6 ± 3.9	1.8 ± 2.9	0.11
CSF IgG index	0.99 ± 0.4	1.9 ± 1.2	0.94 ± 0.44	0.58 ± 0.12	0.005*

M – Male, F – Female, AA – African-American, CAU – Caucasian, MS – Multiple Sclerosis, MSSS – MS patients with subsequent seizures, SFMS – Seizures followed by MS, RRMS – Relapsing Remitting MS, SPMS – Secondary Progressive MS, PPMS – Primary Progressive MS. EDSS – Expanded Disability Status Scale. Data represents mean ± standard deviation and * represents significant *p*-value.

MS (SNOMS). We included seizure patients without MS and MS patients without history of seizures in the analyses for comprehensive comparison. Boxplot analysis was performed initially to assess the distribution of CSF analysis data and to identify outliers. One-way ANOVA with Bonferroni correction for multiple comparisons was applied to compare the groups and *p*-value of < 0.05 was considered statistically significant.

3. Results

We identified 32 MSSS patients, 12 SFMS patients, 18 MSNOS patients and 12 SNOMS patients. Demographic and clinical information is detailed in Table 1.

The age of seizure onset in MSSS group (46.46 ± 11.8 years) was significantly higher (cumulative *p*-value = .001) compared to SFMS group (25.07 ± 14.3 years) and SNOMS group (27 ± 14 years). Eleven out of twelve patients in SFMS group continued to have seizures while information was not available in one patient. With regards to age at MS diagnosis, the MSSS group patients were older (35.7 ± 11 years) as compared to SFMS group patients (33 ± 9.52 years, $p = .39$) but the variation was not significant. Age at lumbar puncture was the same as age at MS diagnosis in MSSS and SFMS groups.

CSF IgG index was significantly higher in SFMS group (1.9 ± 1.2) as compared to MSSS, SNOMS and MSNOS groups ($p = .012$, 0.011, and 0.001 respectively; cumulative $p = .005$). The CSF lymphocyte percentage was significantly different between the 4 groups (cumulative *p*-value – 0.039). In post-hoc analysis, SFMS group had significantly higher CSF lymphocyte percentage compared to MSNOS (*p*-value-0.04) and SNOMS (*p*-value – 0.03). Please refer to Fig. 1.

Subgroup analysis of CSF findings of RRMS patients between SFMS and MSSS groups showed similar trends in CSF lymphocyte percentage ($p = .04$) and CSF IgG index ($p = .06$) between the groups.

We analyzed the number of juxta-cortical lesions between the MSSS (2.85 ± 2.9) and SFMS (2.3 ± 2.4) groups and the variation was not significant (*p*-value = .54). Chi-square analysis showed no significance in patients with number of juxta cortical lesions between MSSS (yes 20, no 6, no MRI 6) and SFMS group (yes 9, no 2, no MRI 1).

4. Discussion

The focus of our study was to explore whether the variation in CSF findings can provide additional information on seizures as an early marker of inflammation in MS patients. We categorized our MS patients with seizures based on the age of seizure onset in relation to the age of MS diagnosis and we compared them with MSNOS and SNOMS groups. We observed higher CSF IgG index in the SFMS group compared to other groups. Likewise, we observed higher CSF lymphocyte percentage in SFMS group compared to MSNOS and SNOMS group. The age of seizure onset was considerably lower in SFMS group compared to the MSSS and MSNOS groups while the age of MS onset was not different between SFMS and MSSS groups.

Seizures have been reported to have a higher prevalence in MS patients as compared to general population, and the reasons were attributed to the presence of extensive demyelinating lesions in gray matter. However, EEG results were mostly normal and not consistent with lesion location and type of seizures [12,13]. One study had reported the involvement of brainstem in MS-related seizures using evoked responses [14]. Given the difficulty in understanding the seizure

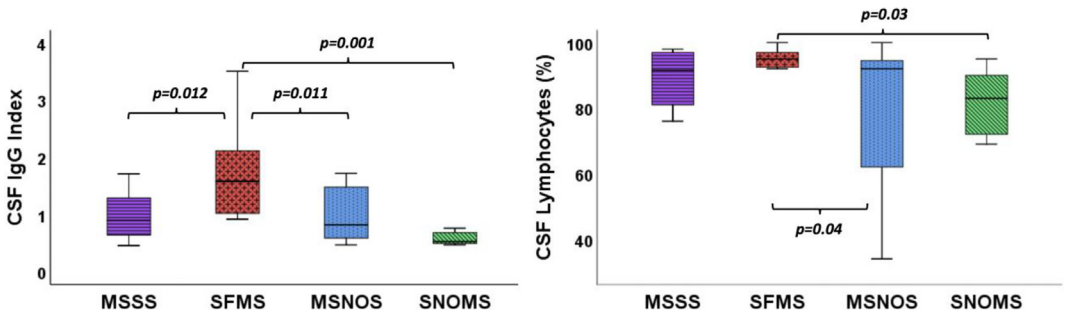

Fig. 1. Box plots showing the range, median, upper and lower quartile ranges for distribution of CSF Lymphocytes (%) (Fig. 1a) and CSF IgG Index (Fig. 1b) between Multiple Sclerosis patients with subsequent seizures (MSSS) group, seizures followed by Multiple Sclerosis (SFMS) group, MS patients with no history of seizures (MSNOS) group and seizure patients with no MS (SNOMS) group.

pathophysiology in MS, we tried to determine the contribution of neuroinflammation and humoral response in MS related seizures. Therefore, we explored the CSF indices in our unique cohorts.

Our findings suggest that SFMS patients may have prominent inflammatory process, which may be indirectly related to the early manifestation of seizures before MS diagnosis. After MS diagnosis, we speculate if this may result in higher number of relapses and worse prognosis, necessitating a different therapeutic approach in this unique cohort. In our MSSS group, only 56% of patients had seizures over the first decade of MS diagnosis. However, few studies have reported that seizures occur typically during the first decade of MS diagnosis [3,4]. These observations indicate that seizures could be due to hyperintense lesions accumulated over the course of disease in MSSS group. Longitudinal measurement of lesion load and their location might explain their correlation with seizures.

Oligoclonal bands were higher in SFMS group compared to MSSS group although the variation didn't attain significance. However, the variation was approximately two-fold higher in SFMS indicating some underlying form of ongoing inflammation compared to MSSS. In addition, it may reflect a non-clonal intrathecal response in the SFMS group. The lack of significance between the groups may be due to variability in measurement techniques and timing between seizure and CSF sample collection, since some patients underwent lumbar puncture at different institutions. However, as the interval between seizure and lumbar puncture is > 6 months when performed to evaluate suspicious plaque on MRI, the false positive chance of higher CSF inflammatory markers due to seizures is less likely in SFMS group.

The SFMS group had a higher level of inflammatory markers, which may be related to seizures. As per revised 2017 McDonald criteria, CSF analysis was a major criterion for MS diagnosis [15,16] As the elevated lymphocytes and IgG index in the CSF are signs of CNS inflammation in MS, we hypothesize that CSF analysis before the MS diagnosis might provide early insight into the underlying active inflammatory process in patients who had atypical presentations like seizures [17]. Furthermore, we speculate that in patients with subtle symptoms, non-specific MRI changes and without other risk factors for seizures, CSF analysis may facilitate diagnosis and shed light on the underlying pathology.

In our patient cohorts, the progressive forms of MS, such as SPMS and PPMS, were only found in the MSSS group. This could be secondary to this cohort being overall older and hence many patients with RRMS had progressed to SPMS. As expected, the EDSS in MSSS group was higher (5.5 vs. 3.3, $p = .011$) correlating with longer duration of MS which has also been noted in another study by Burman et al. [18]. Interestingly, no PPMS patients were in SFMS group, but this might be due to small sample size, younger age of the cohort and early age of MS diagnosis.

Strengths of our study include our unique patient cohort and available CSF analysis. A major limitation is the timing and delay between seizure and lumbar puncture due to the retrospective nature of the study. Other limitations include a small sample size although consistent with prior studies in seizures and MS literature, the assumption that seizures are secondary to MS when no other obvious etiology was detected, a single center study, a non- homogenous MSSS group, and lack of standardized CSF analysis.

5. Conclusion

Our study demonstrates the need for awareness among neurologists about the relationship between seizures and multiple sclerosis. A high index of suspicion for MS should be maintained in patients presenting with new onset seizures without apparent risk factors and having subtle and non-specific neurological symptoms and imaging findings. Validation of our results with prospective, larger scale studies may impact prognosis and direct a more aggressive therapeutic approach in the SFMS patients.

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