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Differences in oligoclonal bands and visual evoked potentials in patients with radiologically and clinically isolated syndrome

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Abstract

Background: The aim of this study was to determine the prevalence of CSF and VEP abnormalities, and ANA titers in patients with either clinically or radiologically isolated syndrome (CIS and RIS).

Patients and methods: We gathered records from 330 hospitalized patients diagnosed with CIS/RIS within a three year period. Symptoms, CSF findings, VEP and ANA titers were analyzed.

Results: Incomplete transverse myelitis was the presenting symptom in 32.7%, optic neuritis in 22.7%, brainstem/cerebellar symptoms in 19.4%, hemispheral symptoms in 2.7% and multifocal symptoms in 15.2% of patients in the CIS cohort. We identified 24 (7.3%) patients with atypical or no symptoms – RIS cohort. Positive OCB were found in 75.5% patients. When we divided the patients into CIS and RIS groups the presence of OCB was 82.4% and 44% respectively. VEP was performed in 87.3% patients and prolonged latencies were found in 39.6% of them (43.8% and 14.3% in the CIS and RIS cohort, respectively). ANA were positive in 15.2% (14.7% and 16% in the CIS and RIS cohort, respectively) of patients. RIS patients had statistically significant lower percentages of positive OCB and positive VEP (p= 0,002 and 0.001, respectively).

Conclusion: Detection of OCB and VEP still has an important role for satisfying the „no better explanation for the clinical presentation“ criteria when presented with a patient with a first “radiological” demyelinating episode.

Key words: clinically isolated syndrome, radiologically isolated syndrome, oligoclonal bands, visual evoked potentials

Introduction

An acute or subacute episode of neurologic deficit which is known as a clinically isolated syndrome (CIS) is a presenting syndrome in 85% of patients who will ultimately develop multiple sclerosis (MS). Most of these patients present with optic neuritis, transverse myelitis or brainstem/cerebellar symptoms, although a substantial number have multifocal symptoms (1). Another group of patients are those who are asymptomatic or present with atypical symptoms – the radiologically isolated syndrome (RIS). The diagnostic cornerstone in the diagnosis of CIS is brain magnetic resonance imaging (MRI), the importance of which is reemphasized in the 2010 revision of McDonald's criteria (2). Nevertheless, there are other significant paraclinical investigations aiding in the diagnosis of MS that include cerebrospinal fluid analysis (CSF) and visual evoked potentials (VEP) (3). The 2010 revised McDonald criteria have altered the place of CSF analysis and VEP in relapsing cases. Despite of this, they still have an important role for satisfying the „no better explanation for the clinical presentation" criteria.

CSF analysis is an important diagnostic tool when presented with a patient displaying a CIS suggestive of MS. Presence of IgG oligoclonal bands (OCB) has been a part of the original Poser's diagnostic criteria for MS (4). Although CSF analysis is no longer necessary for establishing the diagnosis of relapsing remitting multiple sclerosis, it is of great importance in patients with an atypical clinical presentation and necessary for exclusion of infectious and inflammatory MS imitators (2,5). While the prognostic value of OCB is still a matter of debate, it remains the most useful CSF biomarker for MS (6).

VEP typically shows prolonged latencies in two thirds of patients with relapsing remitting MS but only in one third of CIS patients, although results differ between reports (7,8).

Antinuclear antibiodies (ANA) are used as a screening tool for possible "collagen vascular" MS imitators such as systemic lupus erythematosus (SLE). Nevertheless, a substantial number of CIS patients will have positive ANA without any signs of SLE (9). In MS patients on the other hand, a correlation between ANA and MS disease activity was observed in one study (10).

The aim of this study was to determine the prevalence of CSF and VEP abnormalities, and ANA titers in patients with either clinically or radiologically isolated syndrome.

Patients and methods

We gathered records from all patients who were hospitalized in our Referral Centre between 2008 to 2010 due to a suspected first demyelinating event. All patients who underwent CSF analysis for OCB, had VEP performed and ANA titers done were included in the study.

All tests were performed in the same laboratory using standardized methods suggested by the manufacturer. OCB detection was performed by isoelectric focusing followed by immunoblotting. The interpretation of findings was performed according to the Committee of the European Concerted Action for Multiple Sclerosis (Charcot Foundation) on CSF analytical standards in the diagnosis of multiple sclerosis (11). Five patterns of separation of CSF and serum proteins were identified: type 1 = no OCB in CSF and serum, type 2 = two or more OCB present in CSF but none in the serum, type 3

= two or more OCB present in CSF and irregularly spaced OCB in serum (the ″ mixed pattern ″), type 4 = irregularly spaced OCB both in CSF and serum (the ″mirror pattern″), type 5 = OCB present in both CSF and serum including several regularly spaced bands characteristic of monoclonal M protein.

We have performed statistical analysis to identify the percentage of patients with pathological CSF cell counts, CSF protein levels, presence of OCBs, prolonged latencies on VEP, and ANA positivity within each group of patients (Table 2). Groups were composed of patients with their presenting symptoms as follows: group 1 – transverse myelitis, group 2 – optic neuritis, group 3 - brainstem/cerebellar lesions, group 4 - hemispheral symptoms, group 5 - RIS, group 6 - multifocal. The significance of the differences between the groups was analyzed by one way analysis of variance (ANOVA). If the difference between groups was significant, post hoc analysis using Tukey HSD for homogenous distribution and Games-Howell test for non homogenous distribution were used. P levels of <0.05 were considered as significant. Statistical analysis was performed using SPSS 19.0 (Chicago, IL) statistical software.

Results

In the three year period we identified 330 patients who were admitted because of the first demyelinating event. All studied patients had at least two demyelinating lesions on the MRI which were suggestive of MS.

Transverse myelitis (TM) was the presenting symptom in 108 (32.7%) patients, 75 (22.7%) patients presented with optic neuritis (ON) and 64 (19.4%) with brainstem lesions. Hemispheral symptoms were the presenting symptom in 9 (2.7%) patients. We

identified 24 (7.3%) patients who were either asymptomatic at presentation or presented with symptoms atypical for MS but had typical demyelinating lesions on MRI. They were diagnosed as CIS type 5 – RIS. Detailed clinical presentation, CSF and VEP findings are presented in Table 1. The rest of the patients (50 or 15.2%) had multifocal deficits.

Positive OCB were found in 249 (75.5%) patients. CSF pattern type 1 was found in 71 patients (21.5%), type 2 in 219 patients (66.4%), type 3 in 30 patients (9.1%), type 4 in 8 (2.4%) and in 2 (0.6%) patients type 5. Pleocytosis in CSF (defined as more than 5 cells per cubic milliliter) was found in 129 (39.1%) of patients, ranging from 6 to 130 cells per cubic milliter. Elevated levels of CSF proteins from 0.38 to 1.35 grams per liter (g/l) were found in 194 (58.8%) patients, with the normal range being 0.17 – 0.37 g/l.

When we divided the patients into CIS and RIS groups the presence of OCB was 82.4% and 44% respectively.

VEP was performed in 87.3% patients and prolonged latencies were found in 39.6% of them (43.8% and 14.3% in the CIS and RIS cohort, respectively). ANA were positive in 15.2% (14.7% and 16% in the CIS and RIS cohort, respectively) of patients.

Difference between groups regarding CSF cell count, CSF protein level, presence of OCB, prolonged latencies on VEP and ANA positivity are presented in Table 2.

Discussion

This study has shown that RIS patients have statistically significant lower percentage of positive OCB and positive VEP compared to patients with CIS. Most of the patients in our cohort (74.8%) presented with symptoms from the classical triad of CIS – optic neuritis, incomplete transverse myelitis and brainstem/cerebellar lesion, making our

results concurrent with other reports (1). In patients presenting with such symptoms suspicion of MS should be high and the diagnosis more straightforward. Another issue is with patients who present as RIS. Such patients pose a greater diagnostic challenge as data on the value of OCB detection and VEP analysis in RIS patients are still lacking. OCB detection is a valuable diagnostic aid for corroborating MRI findings and substantiates clinical suspicion of MS. On the other hand, VEP is useful, not only as a diagnostic tool for optic neuritis, but also as a detection method for subclinical lesions of the optic nerves. These two paraclinical methods combined with MRI contribute to assessment of the risk of CIS patients to develope MS.

Presence of OCB in patients with CIS varies between groups with reports ranging from 59 to over 80% (12,13). We have found positive OCB (type 2 and 3) in 75.5 % of all patients. Patients with positive OCB are regarded to be at a higher risk of conversion to clinically definite MS (CDMS) in a shorter period of time (13,14). OCB are reported to be positive in 95% of patients of with CDMS, significantly higher than in CIS patients (15). This difference could be explained by a greater disease activity in CDMS as OCB are in fact a product of inflammation. Given this, negative OCB has been associated with a more favorable prognosis, although further studies are warranted to support these findings (5). We found statistically significant less OCB positive RIS patients (44%) than patients who presented with the typical MS group of symptoms - TM, ON, brainstem (up to 82.4%). The presence of OCB in RIS varies from 30-61.4% (16,17), which together with our results argues that RIS patients have lower chance of having positive OCB. About one third of RIS patients will go on to develop CIS and OCB have been associated with an increased risk when associated with high lesion load on MRI (18). Given the fact

that OCB represent inflammatory activity such an association is comprehensible. These findings of a growing percentage of positive OCB with the disease progression, suggest a continuum from RIS over CIS to clinically definite MS.

A stronger affinity is found between abnormal VEP findings and clinical conversion of RIS patients (18). Abnormal VEP was found in 14.3% of our RIS group. A recent study indicated that VEP shows prolonged latencies proportionally more in CDMS and even more in secondary progressive MS (8). As the disease progresses in time, it also progresses in space, affecting various sites in the central nervous system and frequently impairing the brainstem. Although VEP is not specific for MS it is very useful in affirming the diagnosis in CIS patients and identifying RIS patients that are at higher risk for clinical conversion.

This study has several limitations; this was observational, retrospective study with a referral bias, because all patients came from tertiary center specialized in MS. CIS patients are often stratified for risk for MS based on imaging findings. All patients in this study had demyelinating lesions on the brain MRI; however we did not correlate the MRI results with CSF, VEP and ANA titers. Other two shortcomings are that the study relied on the documentation of clinical symptoms in the patients' charts and the lack of follow-up data.

However our study gives a direct comparison between CIS and RIS patients on a large cohort.

Conclusion

In conclusion, we have found that RIS patients have lower chance of having positive paraclinical MS criteria (CSF and VEP findings) comparing to patients with CIS. Never the less, detection of OCB and VEP still has an important role for satisfying the „no better explanation for the clinical presentation“ criteria when presented with a patient with a first “radiological” demyelinating episode.

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Tables

Table 1. Overview of RIS patients - their age, sex, symptoms and CSF, VEP and ANA findings.

Pt. No	Sex	Age	Symptoms	CSF			VEP	ANA
				Cell count	Protein	OCB		
1	F	25	Headache	2	0.26	N	N	N
2	F	29	Headache	3	0.60	P	ND	N
3	F	41	Headache	7	0.72	N	N	N
4	M	42	Headache	7	0.56	N	N	P
5	M	40	Panic attacks	6	0.51	N	N	N
6	F	38	Headache, Panick attacks	3	0.50	P	ND	N
7	F	44	Headache	11	0.49	P	N	N

8	M	17	Uveitis	10	0.47	P	ND	N
9	F	17	Headache	10	0.45	N	N	N
10	F	46	Headache, transient blurring of vision	4	0.43	N	N	N
11	F	44	Jaw pain	1	0.43	N	N	N
12	F	52	Fatigue	4	0.41	N	N	N
13	M	29	Pain in the right temple	24	0.40	P	N	N
14	F	51	Fatigue, pain in the neck	1	0.40	N	N	N
15	F	22	Transitory ischemic attack	7	0.53	P	N	N
16	M	28	Headache	3	0.24	N	N	N
17	F	36	Epilepsy	12	0.38	P	P	N
18	F	50	Cognitive symptoms	5	0.38	P	N	N
19	F	37	Paresthesie in the tongue during neck retroflexion	10	0.37	P	N	N
20	F	45	Headache, Arthralgiae	1	0.36	N	N	N
21	F	35	Conjuctivitis, Fatigue	5	0.43	P	P	N
22	F	30	Seizures	1	0.33	N	N	N
23	F	29	Aphthae	12	0.31	N	N	N
24	F	45	Headache, Insomnia	1	0.29	N	N	N

Pt. No – patient number, F – female, M – male, CSF – cerebrospinal fluid, OCB – oligoclonal bands, VEP – visual evoked potentials, ANA – antinuclear antibodies, N – negative, P – positive, ND – not done. CSF cell count /mm^3; CSF proteins g/l.

Table 2. Results presented as % of patients with pathological results.

	CIS	TN	ON	BS/C	H	M	RIS	p value	Post hoc analysis*
CSF cell count	40.9	37	46.7	45.3	11.1	24.5	16	0.031	NS
CSF proteins	56.9	59.3	56	50	55.6	68.2	68	0.447	NS
OCB	82.4	82.4	72	81.3	66.7	77.3	44	0.002	RIS *vs.* TN, ON, BS/C
VEP	43.8	41.2	67.8	43.3	62.5	53.8	14,3	0.001	ON *vs.* TN, RIS RIS *vs.* ON, M
ANA	14.7	17.6	13.3	17.2	0	11.4	16	0.701	NS

TN – transverse myelitis, ON – optic neuritis, BS/C - brainstem/cerebellar lesion, H - hemispheral symptoms, M – multifocal, RIS – radiologically isolated syndrome; CSF – cerebrospinal fluid, OCB – oligoclonal bands, VEP – visual evoked potentials, ANA – antinuclear antibodies.

*significance calculated in post hoc analysis; NS – not significant