

# Conversion from Clinically Isolated Syndrome to Multiple Sclerosis: What Paraclinical Tests Findings are the Most Characteristic?

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**Summary.** *Background.* Multiple sclerosis (MS) is a chronic demyelinating disease with clinical onset usually manifesting as clinically isolated syndrome (CIS). Approximately 70% of people with CIS convert to MS. Therefore, there is a pressing need to identify the most characteristic paraclinical test findings to predict CIS conversion to MS.

*Aim.* The aim of this study was to establish the most characteristic paraclinical test findings for the identification of CIS conversion to MS.

*Materials and methods.* A retrospective data analysis was performed in patients diagnosed with demyelinating encephalomyelitis according to ICD-10 (International Classification of Diseases Tenth Revision), codes G37.8 (other specified demyelinating diseases of central nervous system) and G37.9 (demyelinating disease of central nervous system, unspecified). In clinical practice, these diagnoses are called CIS. The data were obtained from medical records and included findings of paraclinical tests (magnetic resonance imaging (MRI), IgG levels and oligoclonal bands (OCBs) in cerebrospinal fluid (CSF), and brainstem auditory evoked potential (BAEP)) and final diagnosis. The patients were divided into 2 groups according to the final diagnosis (MS group and non-MS group) and into 3 age groups (18–30, 30–50, >50 years old). The prevalence and statistical difference of paraclinical tests were estimated between the groups. Chi-squared test was used to compare between categorical variables. Mann-Witney U test was used to compare between the groups. The association between two quantitative variables was determined using Spearman correlation coefficient. Results were interpreted as statistically significant when p-value <0.05.

*Results.* A total of 138 cases were included in the study. 49 patients converted to MS (35.5%), other 89 patients (64.5%) were diagnosed with other diseases than MS. Unspecified MRI lesions ( $\chi^2=4.328$ ,  $p=0.037$ ,  $n=40$ ), elevated IgG levels ( $\chi^2=10.793$ ,  $p=0.001$ ,  $n=36$ ), and positive OCBs in CSF ( $\chi^2=34.859$ ,  $p<0.001$ ,  $n=30$ ) were more prevalent in MS group compared to non-MS group. Moreover, lesions detected by the BAEP test were also more frequent among MS group ( $\chi^2=10.924$ ,  $p<0.001$ ,  $n=17$ ).

*Conclusions.* The results indicate that pathological CSF findings (positive OCBs, elevated IgG levels) and prolonged BAEP latency are characteristic in patients with CIS who later progress to MS. Unspecified brain MRI lesions are also distinctive for MS patients; however, this result should be interpreted with consideration due to methodological reasons.

**Keywords:** clinically isolated syndrome, multiple sclerosis, conversion, paraclinical tests.

## INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune inflammatory neurodegenerative disease, the precursor of which can be a clinically isolated syndrome (CIS) [1]. CIS is defined as the first clinical episode with symptoms related to neurological dysfunction suggestive of MS and when it lasts for at least 24 hours [2]. The diagnostic criteria of MS

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have been modified several times over the years – the latest 2017 McDonald Criteria for the diagnosis of multiple sclerosis is expected to speed the diagnosis of MS and reduce the chance of misdiagnosis [3]. The key changes compared to the 2011 McDonald Criteria are: positive oligoclonal bands (OCBs) in CSF can substitute for dissemination in time; both asymptomatic and symptomatic MRI lesions can be considered as dissemination in space or time; cortical lesion location was added to determining MRI criteria for dissemination in space.

CIS usually affects the optic nerve, brainstem, and spinal cord [4]. Although, approximately 70% of patients with CIS convert to MS [2, 5, 6], some patients persist with CIS within longer follow-up period. Therefore, there is a pressing need to identify paraclinical test findings characteristic of CIS conversion to MS. Some of them may be pathological findings in magnetic resonance imaging (MRI), cerebrospinal fluid (CSF), and evoked potentials (EP), that are not included in the latest 2017 McDonald Criteria. The problem is of outstanding importance since early MS diagnosis and treatment prevents long-term disability [2].

## AIM

The aim of this study was to establish the most characteristic paraclinical test findings for the identification of CIS conversion to MS.

## MATERIALS AND METHODS

This study is a retrospective analysis of medical record data collected at the Hospital of Lithuanian University of Health Sciences (LUHS) Kaunas Clinics in the Department of Neurology from January 1, 2015 to January 1, 2020. Ethical approval was obtained from the local LUHS Department of Bioethics (No. BEC-MF-30).

### Patient inclusion and exclusion criteria

Eligible patients were adults (aged 18 years) diagnosed with CIS. CIS was diagnosed in accordance with the 2017 McDonald Criteria for the diagnosis of multiple sclerosis. In clinical practice, codes G37.8 (other specified demyelinating diseases of central nervous system) and G37.9 (demyelinating disease of central nervous system, unspecified) according to ICD-10 (International Classification of Diseases Tenth Revision) are considered as CIS. Patients with these ICD-10 codes were included in the study. Patients without MRI test were excluded from the study.

### Statistical analysis

Demographical data were analyzed. The number of patients with CIS diagnosis who later converted to MS diag-

nosis between January 1, 2015 and January 1, 2020 was calculated. The patients were divided into 2 groups according to the final diagnosis (MS group and non-MS group) and into 3 age groups (18–30, 30–50, >50 years old). Prevalence of CIS conversion to MS was analyzed between the groups. Prevalence and statistical difference of unspecific brain and spinal cord MRI lesions, IgG levels, positive OCBs in CSF, lesions detected by BAEP, and VEP tests were compared between the groups. MRI lesions were analyzed in accordance with their localisation (juxtacortical, periventricular, infratentorial).

All analyses were performed using SPSS (Statistical Package for the Social Sciences) version 24.0. Chi-squared test was used to compare between categorical variables. The association between two quantitative variables was determined using Spearman correlation coefficient. Mann-Whitney U test and independent-samples t-test were used to compare between the groups. The results were interpreted as statistically significant when p-value <0.05.

## RESULTS

A total of 169 CIS cases were reviewed, 31 were excluded due to insufficient data (no MRI). 138 cases were included in the study. The study enrolled 92 female (64.5%) and 46 male (35.5%) patients. Group 1 (aged 18–30) consisted of 28 (20.3%) patients with the mean age of 24.89 years ( $\pm 3.725$ ), group 2 (aged 31–50) consisted of 58 (42.0%) patients with the mean age of 40.43 years ( $\pm 6.093$ ), and group 3 (50 years and older) consisted of 52 (37.7%) patients with the mean age of 57.83 years ( $\pm 5.498$ ). The mean age of MS patients was 42.59 years ( $\pm 14.887$ ) and the mean age of non-MS patients was 44.52 years ( $\pm 12.692$ ). It was found that 49 out of 138 CIS patients converted to MS (35.5%), other 89 patients (64.5%) were diagnosed with other diseases than MS. 28 female and 21 male patients were diagnosed with MS. There was no statistically significant age difference for the conversion to MS ( $\chi^2=0.390$ ,  $p=0.823$ ).

CIS patients with unspecified brain MRI lesions more frequently converted to MS (Table 1). Moreover, patients who converted to MS were more likely to have spinal cord MRI lesions compared to patients who did not convert to MS (Table 2). Although no statistically significant differences were found between age groups among MS patients in relation to spinal MRI lesions ( $\chi^2=0.844$ ,  $p=0.656$ ). In addition, prevalence of different lesion locations in MRI did not differ between age groups (juxtacortical  $\chi^2=1.473$ ,  $p=0.479$ ; periventricular  $\chi^2=0.619$ ,  $p=0.734$ ; infratentorial  $\chi^2=0.760$ ,  $p=0.684$ ).

Positive OCBs in CSF were more prevalent in MS group ( $\chi^2=34.859$ ,  $p<0.001$ ). No significant differences of IgG levels in CSF were found between the groups: median IgG level was 43.91 mg/L (min: 8.42, max: 95.60) in the MS group and 36.51 mg/L (min: 8.82, max: 117) in non-

MS group. These results are shown in Fig. 1. Positive OCBs were more prevalent among female patients in MS group ( $\chi^2=7.088, p=0.008$ ). MS patients in the 31–50 age group had significantly lower protein levels in CSF ( $\chi^2=7.465, p=0.024$ ) compared to the other two age groups. Moderate correlation was found between IgG level in CSF and protein level in CSF ( $r_s=0.551, p=0.002$ ).

Pathological BAEP test was found to be significantly more frequent in MS group (Fig. 2). However, the relation between lesions detected by VEP test and MS diagnosis was not significant ( $\chi^2=2.210, p=0.137$ ). It was assessed that pathological VEP test results were more common among patients older than 50 years ( $\chi^2=6.089, p=0.048$ ).

### DISCUSSION

In this study, rates of conversion of CIS to MS were calculated and, compared to other publications, several contradictory results were found. The conversion rate in most publications is approximately 70%, however, we received only 35% due to a short follow-up period, so further research with longer follow-up periods is needed. As the sample of this study was relatively small, our findings are inconsistent with the literature on the averages of female conversion rates [7–9].

Demyelinating lesions occur in the CNS and some specific location tendencies are observed – periventricular, juxtacortical, and infratentorial [10]. These lesion locations are considered as specific MS lesions. Our results differed from other reports that found specific MRI lesions related to later conversion to MS [11–15]. The authors speculate that the short follow-up period had an impact on these results. Instead, some controversial results were found. Non-specific brain MRI lesions (other locations not mentioned above) were found to be four times more frequent in MS patients than specific MRI lesions. There may be several reasons why these results do not comply with other publications. One of them could be the limitation of a retrospective study method (only the description of MRI was

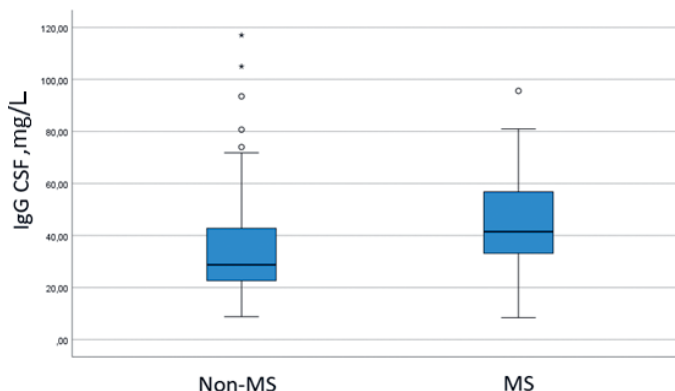


Fig. 1. IgG levels and conversion to MS ( $p=0.020$ ; the dots above the graph are the outlier values)

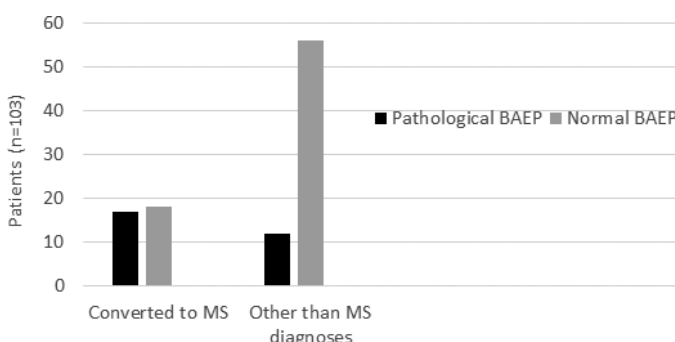


Fig. 2. Brainstem auditory evoked potential (BAEP) test and conversion to MS ( $\chi^2=10.924, p<0.001$ )

obtained). Another reason may be the subjective interpretation of MRI data by the authors. Lastly, there is no clinical protocol for the interpretation of brain MRI lesions, making it difficult to evaluate the description of MRI scans. Lithuania does not have an MRI brain lesion protocol, but countries such as the United Kingdom and the United States of America have this protocol for the reasons mentioned [16]. MRI spinal cord lesions are also considered to be specific for MS [15]. This study confirmed the findings of other publications that spinal cord lesions in MRI are characteristic in patients whose diagnosis converted from CIS to MS [12, 15]. Other authors have found that MRI spinal cord lesions have a prognostic value – patients with CIS who developed MRI spinal cord lesions at

Table 1. Brain MRI findings and MS development

	Number of patients (%)	Converted to MS (% of the number of patients)	$\chi^2$	p
MRI lesions specific to MS	40 (29.2%)	9 (22.5%)	18.367	<0.0001
MRI lesions non-specific to MS	97 (70.8%)	40 (41.2%)		
Total	137 (100%)	49 (35.7% of the total number of patients)		

Table 2. Spinal cord MRI findings and MS development

	Number of patients (%)	Converted to MS (% of the number of patients)	$\chi^2$	p
MRI spinal cord lesions	28 (57.1%)	16 (57.1%)	7.209	0.007
No MRI spinal cord lesions	21 (42.9%)	4 (19%)		
Total	49 (100%)	20 (40.8% of the total number of patients)		

baseline are more likely to progress to clinically definite MS, and a worse clinical outcome is predicted as well as a higher number of relapses [15].

OCBs in cerebrospinal fluid is a common finding in patients with MS, therefore our results did not differ from other publications [5, 7, 17, 18]. However, ten patients with positive OCBs were diagnosed with other diagnoses (or MS was not yet diagnosed), so this may be an indication that OCBs is not a specific paraclinical test. OCBs is a characteristic finding in other diseases, for example, chronic infectious encephalitis, paraneoplastic syndromes, and Behcet Disease [19]. Additionally, higher IgG levels were more common in MS group. This result also complies with other publications [20]. It was found that female patients with positive OCBs were more likely to convert to MS. The results were in compliance with the findings of other authors [7].

MS diagnostic tools are not unidimensional, so in addition to MRI lesions and pathological CSF findings, the EP test is another useful method for diagnosing MS [21]. EP tests are used for evaluation of electrophysiological responses to external stimuli, some of the EP tests are BAEP and VEP [21]. This study revealed that pathological BAEP findings were more common among patients converted to MS. However, the BAEP test is not used as a diagnostic tool for MS as it lacks specificity [22]. The authors hypothesize that pathological BAEP results may also be of non-demyelinating origin, as the mean age of the patients included was 43 years, and may be the result of cerebrovascular diseases [23]. According to the 2017 McDonald Criteria, prolonged VEP latency is considered as an indicative criterion for MS diagnosis [24]. Conversely, no relation was found between the prolonged VEP latency and the conversion to MS. Our study could be limited by the relatively small sample size as prolonged VEP latency was found in only ~25% of MS patients [22].

## CONCLUSIONS

The results indicate that pathological CSF findings (positive OCBs, elevated IgG levels) and prolonged BAEP latency are characteristic factors of MS in patients diagnosed with CIS. Unspecified brain MRI lesions are also distinctive for MS patients; however, this result should be interpreted with consideration due to methodological reasons.

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#### **NUO KLINIŠKAI IZOLIUOTO SINDROMO IKI IŠSĖTINĖS SKLEROZĖS: KOKIE PARAKLINIKINIŲ TYRIMŲ RADINIAI YRA BŪDINGIAUSI?**

##### **Santrauka**

*Ivadas.* Išsėtinė sklerozė (IS) – tai lėtinė neurodegeneracinė liga, kuri dažniausiai prasideda kaip kliniškai izoliuotas sindromas (KIS). Apie 70 % pacientų, sergančių KIS, jis progresuoja į IS. Dėl šios priežasties turėtų būti nustatyti KIS progresavimui į IS būdingi paraklinikinių tyrimų radiniai.

*Tikslas.* Nustatyti, kurie paraklinikinių tyrimų radiniai yra būdingi KIS progresavimui į IS.

*Tiriamieji ir tyrimo metodai.* Buvo atlikta retrospektyvinė duomenų analizė, tiriant pacientus, hospitalizuotus su TLK-10 (tarptautinė ligų klasifikacija) diagnozėmis: G37.8 (kitos patikslintos demielinizuojančios nervų sistemos ligos) ir G37.9 (demielinizuojančios centrinės nervų sistemos ligos, nepatikslintos). Klinikinėje praktikoje šios diagnozės yra vadinamos KIS. Galvos ir nugaros smegenų specifiniai ir nespecifiniai IS MRT židiniai, IgG ir oligokloninės juostos likvoro, klausos sukeltų smegenų kamieno potencialų tyrimo (BERA) patologinių radinių dažniai buvo palyginti grupėse, kur KIS progresavo į IS, ir grupėse, kur KIS neprogresavo į IS. Chi-kvadrato testas naudotas kategoriniams kintamiesiems palyginti. Dviejų grupių palyginimams naudotas Mano-Vitnio U testas. Asociacija tarp dviejų kiekybinių kintamųjų apskaičiuota naudojant Spirmeno koreliacijos koeficientą. Rezultatai laikomi statistiškai reikšmingais, kai  $p < 0,05$ .

*Rezultatai.* Į tyrimą buvo įtraukti 138 pacientai. Nustatyta, kad 49 pacientams KIS progresavo į IS (35,5 %), o kitiems 89 pacientams (64,5 %) buvo nustatyta kitos ligos arba palikta KIS diagnozė. Pacientams, kuriems KIS progresavo į IS, dažniau buvo rasti nespecifiniai IS MRT galvos smegenų židiniai ( $\chi^2 = 4,328$ ,  $p = 0,037$ ,  $n = 40$ ), padidėjusi IgG koncentracija ir teigiamos oligokloninės juostos likvoro ( $\chi^2 = 10,793$ ,  $p = 0,001$ ,  $n = 36$ ;  $\chi^2 = 34,859$ ,  $p < 0,001$ ,  $n = 30$ ). Taip pat buvo nustatyta, kad pacientams, kuriems KIS progresavo į IS, dažniau buvo pailgėjęs latentiskumas sukeltųjų potencialų tyrime (BERA) ( $\chi^2 = 10,924$ ,  $p < 0,001$ ,  $n = 17$ ).

*Išvados.* Šio tyrimo rezultatai rodo, kad patologiniai likvoro (padidėjusi IgG koncentracija ir teigiamos oligokloninės juostos) ir BERA tyrimo radiniai yra būdingesni pacientams, kuriems KIS progresuoja į IS. Taip pat nustatyta, kad nespecifiniai galvos smegenų MRT židiniai yra dažnesni IS grupėje, tačiau šis rezultatas turėtų būti vertinamas atsargiai dėl galimų metodologinių trūkumų.

**Raktažodžiai:** kliniškai izoliuotas sindromas, išsėtinė sklerozė, konversija, paraklinikiniai tyrimai.

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