OCT and VEP correlate to disability in secondary progressive multiple sclerosis

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ABSTRACT

Background: The afferent visual pathway provides a unique opportunity to monitor clinical and subclinical optic neuritis and features of neuroaxonal degeneration in secondary progressive MS.

Objective: To investigate the usefulness of visual evoked potentials (VEP) and optical coherence tomography (OCT) in evaluating SPMS, and the association between these modalities and clinical course and lesion load on the magnetic resonance imaging (MRI) in patients with SPMS with or without a history of optic neuritis (ON).

Methods: SPMS patients (n = 27) underwent clinical assessment with Expanded Disability Status Scale (EDSS) grading, visual acuity, OCT, and VEP examination. MRI of the brain and spinal cord were evaluated. Ordinal scores of VEP and MRI findings were used in the statistical analyses.

Results: The ganglion cell and inner plexiform layer (GCIPL) and retinal nerve fiber layer (RNFL) thickness correlated with VEP latency. VEP P100 score correlated with EDSS. Linear regression showed an association between GCIPL thickness and EDSS as well as VEP P100 latency and EDSS. The MRI analyses were negative.

Conclusion: VEP latency and GCIPL thickness correlated with disability measured as EDSS in patients with SPMS and are useful in monitoring SPMS patients.

Abbreviations

CNS Central nervous system
CIS Clinically isolated syndrome
DMT Disease-modifying treatments
EDSS Expanded Disability Status Scale
GCL Ganglion cell layer
IFNb Interferon-beta
IQR Interquartile range
MRI Magnetic resonance imaging
MS Multiple sclerosis
MSON Multiple sclerosis optic neuritis
MSNON Multiple sclerosis no history of ON
MSSS Multiple Sclerosis Severity Score
NEDA No evidence of disease activity
OB Oligoclonal bands
OCT Optical coherence tomography
ON Optic neuritis
RRMS Relapsing-remitting MS
RNFL Retinal nerve fiber layer
SPMS Secondary progressive multiple sclerosis
VA Visual acuity
VEPs Visual evoked potentials

1. Introduction

Multiple sclerosis (MS) is a chronic neurological disorder characterized by both inflammation and degeneration in the central nervous system (CNS) (Thompson et al., 2018). Most MS patients initially have a relapsing-remitting disease course (RRMS) characterized by attacks of...
inflammatory activity with clinical relapses or subclinical inflammation visualized by magnetic resonance imaging (MRI). Within two decades, 80% of untreated patients convert to secondary progressive multiple sclerosis (SPMS) characterized by progressively increasing neurological deficit without relapses or signs of active inflammation (Weinshenker et al., 1989).

Available treatments mainly target the inflammatory components of MS, and during the last decades, several effective disease-modifying drugs have been developed and are in practical use. In contrast, effective drugs in the progressive phase are still lacking.

Visual involvement is frequent in MS and occurs in up to 80% of patients (Fisher et al., 2006). In total, about 50% of the patients experience optic neuritis (ON) at some time point during the disease course, and it is the initial presentation of the disease in 21% (Miller et al., 2005). Postmortem examinations show both retinal atrophy and inflammation even in late-stage disease (Green et al., 2010).

The afferent visual pathway offers us a unique opportunity to study the effects of clinical and subclinical relapses and, in addition, features of neuroaxonal injury in MS patients over time.

Optical coherence tomography (OCT) is a non-invasive high-resolution, reproducible technique that uses near-infrared light to produce imaging of the retinal architecture (Oberwahrenbrock et al., 2018).

Visual evoked potentials (VEPs) have been used in clinical practice since the 1970s to assess conduction along the visual pathways with diagnostic, monitoring, and prognostic purpose (Halliday et al., 1972). VEPs provide information about the functional integrity of the visual pathway and are used to capture visual disturbances in MS (Halliday et al., 1973). A typical waveform with preserved morphology and delayed latency suggests demyelinating lesions, although not diagnostic of MS.

This study aims to compare sensitivity regarding the impact of the visual pathway by results of VEPs and OCT, respectively, and how findings correlate with the clinical history and the MRI lesion load in subjects with SPMS with or without a clinical history of ON.

2. Materials and methods

The study is a quantitative descriptive study of 28 SPMS patients who underwent clinical assessment with Expanded Disability Status Scale (EDSS) grading and OCT and VEP examination. MRI scans of the CNS were re-evaluated by the same neuroradiologist (BK).

2.1. Subjects

Consecutive patients (n = 28) with an MS diagnosis according to the 2010 McDonald criteria (Polman et al., 2011) attending the Departments of Neurology at Linköping University Hospital and Ryhov County Hospital were recruited. All patients, except one that was later excluded, were classified as SPMS, which was validated against their clinical records. The patient that was excluded did not fulfill the criteria of SPMS. Fifteen patients were receiving Disease Modifying Treatments (DMTs), the most frequent treatment was rituximab (n = 9) followed by interferon-beta (IFNb) (n = 4), natalizumab (n = 1), and teriflunomide (n = 1).

The patients underwent complete neurological examination, EDSS rating (Kurtzke, 1983), and visual acuity (VA) measurements by the same investigator (AE). Clinical history of previous ON was noted. VEPs and OCT were performed in all patients. Eyes were divided into groups depending on the clinical history of ON, Multiple Sclerosis Optic Neuritis (MSON) eyes, and Multiple Sclerosis No history of Optic Neuritis (MSN0) eyes.

2.2. Defining history of optic neuritis

Clinical records since diagnosis were reviewed in the aspect of ON. ON confirmed by an ophthalmologist was noted. In the absence of an ophthalmologic examination, eye pain with vision loss followed by complete or partial recovery within weeks to months registered in clinical records was considered ON (Polman et al., 2011; Jenkins and Toosy, 2017). Other imprecise eye problems were not considered an ON unless an ophthalmologist’s examination suggested ON as a probable cause.

2.3. Healthy controls

A group of 48 healthy controls (HC), 33 women, and 15 men, mean age of 49 years, underwent OCT at the Department of Neurology at Linköping University Hospital. Both patients with a diagnosis without CNS involvement and personnel working at the Departments of Neurology and Neurosurgery volunteered.

2.4. Optical coherence tomography

OCT measurements of RNFL- and GCIPL-thickness were obtained using spectral-domain high-definition OCT system SD Cirrus HD-OCT (model 4000; Carl Zeiss Meditec, Dublin, CA, USA), as described in detail elsewhere (Nussif et al., 2004; Huang-Link et al., 2015). The OCT investigations were assessed at the Department of Neurology, Linköping University Hospital by one operator (YL). Patients were examined in a dark room without pupil dilatation. Participants underwent the Optic Disc Cube (200 × 200 scans) and Macular Cube (512 × 128) protocols with a 6 mm rim centered at the fovea. OCT scans were visually inspected immediately upon acquisition and repeated as necessary to verify that the images were focused and centered with uniform illumination and assessed for artifacts as recommended by the OSCAR-IB Consensus Criteria for Retinal OCT Quality Assessment (Tewarie et al., 2012). Only scans meeting these criteria and having a signal strength 7/10 or more were used for the analysis (Cruz-Herranz et al., 2016).

2.5. Visual evoked potentials

VEPs were assessed within six months from inclusion according to a validated procedure (American Clinical Neurophysiology S, 2006).

Electrodes were placed according to the 10–20 international system, with Oz (midline occipital electrode) as the active electrode and Fz (midline frontal electrode) as the reference. Monocular stimulation with occlusion of the other eye consisted of a checkerboard pattern with a check size of 30 min of visual angle. Contrasts were reversed at a rate of 1 Hz (1 reversal per second). At least two means of 100 noise-free sweeps were superimposed, and the total mean was considered for measurement. The latency and amplitude of the P100 component were measured. VEP amplitudes and latencies were compared with data obtained at our laboratory. Synergy Electrodiagnostic Software was used in the Nicolet® EDX apparatus (Cephalon A/S, Norresundby, Denmark).

2.6. VEP score

As in other studies, VEP abnormalities were quantified to a conventional 4-point graded ordinal score (Di Maggio et al., 2014; Pisa et al., 2017). According to local normal validated data, a P100-latency >109 ms was considered abnormal. Range 0–3 points. 0 p= normal, 1 p= increased P100 latency or morphological abnormalities, 2 p= increased P100 latency plus morphological abnormalities of P100, 3 p= absence of P100.

2.7. MRI measurements of tissue damage

The patients underwent MRI in hospitals with a slightly different protocol. Axial T2 and FLAIR sequences and axial T1 sequence after gadolinium administration was always part of the examination. It varied from patient to patient if the series were performed with 3D technique or not. Synthetic MR sequence for evaluation of brain atrophy was
performed only in one of the hospitals.

MRI scans from all patients were reviewed by the same examiners (BK, YL) to evaluate the burden of supra- and infratentorial white matter lesions. Lesions periventricular, juxtacortical, near corpus callosum, optic radiation, brain stem, spinal cord, and cerebellum were registered. One Gadolinium-enhanced lesion was noted in a single patient. Gray matter atrophy on MRI was estimated either by measuring corpus callosum or noting other signs like prominent Sylvian fissure. In a minority of the patients, brain parenchymal fraction (BPF) was used to estimate brain atrophy (Vågberg et al., 2013). 20 of 27 patients had an MRI scan within one year from inclusion. The other patients had MRI scans 2–7 years old.

2.8. MRI sum score

MRI investigations were audited, and separate areas of the CNS were reviewed and judged by points according to lesion burden and summarized to an MRI sum score. (Supplementary TABLE 1, 2.)

3. Ethics

The study was conducted by the principles of the Declaration of Helsinki, and all subjects were informed of the nature and the purpose of the study and gave informed consent to participate. The investigation was made in a clinical setting as a part of routine follow-up. The study was approved by the Ethical Committee of the Linköping University, Sweden 2013/1411–31.

4. Statistics

All analyses were performed in SPSS version 24 (IBM Corp., Armonk, NY, USA). The data from MS and HC groups, as well as from subgroups MSNON and MSON, were normally distributed. Significance was computed with non-parametric tests. Correlation analysis was performed using Pearson’s coefficient (r) in continuous parameters. Analyses of ordinal scores were performed using a non-parametric Mann-Whitney U test. The correlation of ordinal scores was performed using Spearman’s coefficient (p). Linear regression was performed to investigate the association of EDSS with parameters of OCT and VEP. ANOVA followed Bonferroni Post Hoc test was applied to analyze OCT parameters between HC and MSNON. Significance was set at <0.05.

Table 1a

Demographic and clinical characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Patients/ Controls N</th>
<th>Eyes</th>
<th>Female/ Male</th>
<th>Age years mean (range)</th>
<th>EDSS median (range)</th>
<th>Disease duration at baseline mean (range)</th>
<th>OB in CSFN</th>
<th>DMT N</th>
<th>VA mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPMS all</td>
<td>N = 27</td>
<td>54</td>
<td>18/9</td>
<td>53.3* (32-76)</td>
<td>5.0 (2.0-7.5)</td>
<td>24 (8-42)</td>
<td>26/27</td>
<td>15</td>
<td>0.8 (0.3-1.6)</td>
</tr>
<tr>
<td>HC</td>
<td>N = 48</td>
<td>96</td>
<td>33/15</td>
<td>48.8 (26-72)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 1b

Demographic and clinical characteristics of MSON and MSNON.

<table>
<thead>
<tr>
<th></th>
<th>Eyes Women/ Men</th>
<th>Age years mean (range)</th>
<th>EDSS median (range)</th>
<th>Disease duration at baseline mean (range)</th>
<th>OB in CSFN</th>
<th>DMT N</th>
<th>VA mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSON</td>
<td>25 17/8</td>
<td>54.5 (40-76)</td>
<td>5.0 (3.5-7.5)</td>
<td>26.2 (11-42)</td>
<td>25/25</td>
<td>13/25</td>
<td>0.7 (0.3-1.6)</td>
</tr>
<tr>
<td>MSNON</td>
<td>29 19/10</td>
<td>52.3 (32-76)</td>
<td>5.0 (2.0-7.5)</td>
<td>22.1 (8-41)</td>
<td>27/29</td>
<td>17/29</td>
<td>0.9 (0.4-1.6)</td>
</tr>
</tbody>
</table>

Table 2

Comparison of OCT- and VEP measurements and visual acuity between the study groups.

<table>
<thead>
<tr>
<th></th>
<th>MS all</th>
<th>HC</th>
<th>MS all vs HC</th>
<th>MSNON</th>
<th>MSNON vs MSNON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes N</td>
<td>54</td>
<td>96</td>
<td>p&lt;0.01</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>RNFL µm mean</td>
<td>75.9 (13.4)</td>
<td>89.5 (8.9)</td>
<td>p&lt;0.01</td>
<td>68.6</td>
<td>82.1</td>
</tr>
<tr>
<td>GCIPL µm mean</td>
<td>66.3 (10.7)</td>
<td>79.7 (5.0)</td>
<td>p&lt;0.01</td>
<td>61.4</td>
<td>70.5</td>
</tr>
<tr>
<td>VEP ms</td>
<td>51.2 (23.3)</td>
<td>131.1 (24.2)</td>
<td>p&lt;0.01</td>
<td>112.4</td>
<td>112.4</td>
</tr>
<tr>
<td>VEP µV (SD)</td>
<td>7.9 (5.8)</td>
<td>6.9 (5.8)</td>
<td>p = 0.26</td>
<td>8.7 (5.8)</td>
<td>8.7 (5.8)</td>
</tr>
<tr>
<td>VA mean (SD)</td>
<td>0.83 (0.27)</td>
<td>0.74 (0.29)</td>
<td>p = 0.03</td>
<td>0.9 (0.22)</td>
<td>0.9 (0.22)</td>
</tr>
</tbody>
</table>

score. One SPMS patient did not undergo a VEP examination. Thus, in total, three eyes were missing in correlation analyses of VEP.

Visual acuity was significantly lower in the MSON group (Tables 1b, 2).

MRI scores did not differ in the two groups (Supplementary Table 1). In three cases (eyes), the laboratory tests with VEP and OCT suggested a history of ON, but since it was not noted in the clinical records, and the patients did not recognize it, those three eyes were considered not to have a history of ON although they could have undergone a subclinical ON (Talman et al., 2010).

5.2. Correlations

Considering all 54 MS eyes examined GCIPL correlated to EDSS, VA, VEP latency, and VEP amplitude, and the correlation between GCIPL and VEP latency was significant in both MSON and MSNON eyes. MSON GCIPL correlated with VEP amplitude. RNFL significantly correlated with VEP P100 latency in all MS eyes as well as in MSON. RNFL and GCIPL thickness correlated with VEP score (Table 3a).

VEP latency and VEP score correlated with EDSS and VEP amplitude correlated with the MRI score (Table 3b).

5.3. Regression analyses

Simple linear regression showed a significant association between GCIPL and EDSS (Fig. 3a) but not between RFNL and EDSS (Fig. 3b). There was also a significant association between VEP-latency and EDSS (Fig. 4a) but not between VEP-amplitude and EDSS (Fig. 4b).

5.4. MRI evaluation

MR sum score summaries are presented in Supplementary Table 2. MRI sum score did not differ between MSON and MSNON eyes. There was no correlation between MRI parameters and OCT or VEP data.

6. Discussion

The included patients represent a typical spectrum of SPMS with progressive disease, high EDSS (median 5, range 2.0–7.5), and MRI without contrast enhancement and with black holes. Although considered SPMS, 50% of the patients were on DMT. It is a well-known challenge to terminate treatment in progressive MS.

Almost equally occurring were anamnestic or verified ON on one

Fig. 1. (a) RNFL thickness in MSON and MSNON (b) GCIPL thickness in MSON and MSNON.
hand and the absence of these parameters on the other. Although we found significant differences between MSON and MSNON eyes with prolonged VEP latency and thinner thickness of RFNL and GCIPL in MSON, many MSNON eyes showed structural loss of retinal axonal fibers in accordance with others (Waldman et al., 2017). Some report a higher sensitivity for VEP compared to OCT in a subacute phase of ON (Di Maggio et al., 2014) or MSNON patients (Grecescu, 2014).

There is a dispute of the pathophysiological reason for the thinning of the RNFL and GCIPL layers in eyes without a history of ON (Britze and Frederiksen, 2018). The patients with SPMS could have had mild, subclinical optic neuritis. The measurements could also be affected by primary degeneration of neurons in the GCIPL with anterograde (Wallerian) degeneration of axons with thinning of RNFL reflecting global degeneration. Retrograde neuroaxonal degeneration from

Fig. 2. (a) VEP P100 latency in MSON and MSNON (b) VEP amplitude in MSON and MSNON.

<table>
<thead>
<tr>
<th></th>
<th>VEP Amp</th>
<th>VEP 100ms</th>
<th>VEP score</th>
<th>VA</th>
<th>EDSS</th>
<th>DD</th>
<th>MRI score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RNFL MSON</strong></td>
<td>$r=0.25$</td>
<td>$-0.46$</td>
<td>$-0.47$</td>
<td>$-0.25$</td>
<td>$-0.25$</td>
<td>$-0.042$</td>
<td>$-0.34$</td>
</tr>
<tr>
<td><strong>GCIPL MSON</strong></td>
<td>$r=0.49$</td>
<td>$-0.016$</td>
<td>$-0.46$</td>
<td>$-0.25$</td>
<td>$-0.14$</td>
<td>$-0.042$</td>
<td>$-0.34$</td>
</tr>
</tbody>
</table>

**Table 3a**

Correlations OCT eyes.

GCIPL—ganglion cell inner plexiform layer, RNFL—retinal nerve fiber layer, MSON—Multiple sclerosis with history of optic neuritis (number of eyes), MSNON—Multiple sclerosis without a history of optic neuritis (number of eyes), VEPs—visual evoked potentials, VA—visual acuity, EDSS—expanded disability status scale, DD—disease duration, MRI—magnetic resonance imaging. * = significant result.
post-geniculate lesions could be a third reason for thinning of RNFL and GCIPL. Pihl-Jensen et al. (2021) have investigated the use of OCT compared to VEP in predicting CIS to convert to clinically definite MS using MSNON eyes as predictive value and found that OCT values could serve as an independent predictor of MS development.

Overall there was a good correlation between VEP latency and VEP score compared to thickness of RFNL and GCIPL in accordance with other reports (Fatehi et al., 2012; Naismith et al., 2009), showing that both VEP and OCT probably measure relevant features of SPMS.

It has previously been shown that thinning below RNFL 75 µm by time-domain OCT was associated with impaired visual function measured by automated visual field testing (Costello et al., 2006). RNFL is composed of the axons projected from retinal ganglion cells, and thinning represents axonal loss. As suggested by others atrophy rate of RNFL may be slower in SPMS than in RRMS (Balk et al., 2016; Henderson et al., 2010), claiming that atrophy of the afferent visual system is more present in the early phase of the disease.

In a study of 166 MS patients (94% RRMS) with baseline examination and a two-year follow-up (Garcia-Martin et al., 2011), Garcia-Martin et al. found RNFL atrophy in MS patients with non-visual relapses as well as in patients with progression and disease evolution. This finding supports the idea that these events are not focal but are more widespread in the central nervous system.

Even though our study was relatively small, the OCT results correlate with the VEP score (all) and VEP P100 latency, all but RNFL in the MSNON group. It has been suggested that VEP has superior sensitivity to OCT to detect clinical or subclinical ON, where VEP detected 81%, and OCT RNFL showed 60% sensitivity of detecting an ON at least six months before the investigation (Naismith et al., 2009).

In a study by Raz et al. (2013), the authors found prolonged VEP latency also in fellow eyes in patients with their first ON. VEP latencies in the fellow eyes could not be explained by demyelinating lesions along

<table>
<thead>
<tr>
<th></th>
<th>VA</th>
<th>EDSS</th>
<th>DD years</th>
<th>MRI score</th>
<th>VEP Lat, (ms)</th>
<th>VEP Amp, (µV)</th>
<th>VEPscore</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEP latency (ms)</td>
<td>r=0.16</td>
<td>p=0.40</td>
<td>r=0.11</td>
<td>p=0.012</td>
<td>x</td>
<td>r=0.31</td>
<td>p=0.82</td>
</tr>
<tr>
<td>VEP amp (µV)</td>
<td>r=0.29</td>
<td>p=0.004*</td>
<td>p=0.43</td>
<td>p=0.93</td>
<td>x</td>
<td>p=0.030*</td>
<td>p=0.001*</td>
</tr>
<tr>
<td>VEP score</td>
<td>r=0.18, p=0.22</td>
<td>p=0.10</td>
<td>r=0.063</td>
<td>p=0.29</td>
<td>r=0.31</td>
<td>x</td>
<td>p=0.40</td>
</tr>
<tr>
<td></td>
<td>p=0.47</td>
<td>p=0.66</td>
<td>p=0.037*</td>
<td>p=0.030*</td>
<td>x</td>
<td>p=0.003*</td>
<td></td>
</tr>
</tbody>
</table>
post-chiasmal pathways (assessed by diffusion tensor imaging). Delayed peaks in fellow eyes resulted from a wider waveform, which occurred with a concomitant decrease in the gap in time between VEP peaks of both eyes. These changes offered a functional advantage; synchronization of inputs highly correlated with improved time-constrained binocular perception.

Recently Piedrabuena and Bittar (2021) found a correlation between the reduced thickness of RNFL, prolonged latency, and decreased amplitude of the VEP P100 wave, which was associated with higher EDSS in RRMS, which is results in agreement with ours.

We found no correlation between MRI parameters and OCT or VEP data, indicating that VEP and OCT investigations provide complementary information. Berman et al. (2020) found a correlation of VEP latency with optic radiation lesion load in eyes without a history of ON. Others (Alonso et al., 2018) have found a correlation between OCT values and quantifying MRI techniques. Saidha et al. (2013) found that GCIPL thickness correlates with cortical gray matter and caudate atrophy, implying that OCT measurements can be used as a structural marker in MS. The same group found association between GCIPL atrophy and whole brain atrophy, gray and white matter atrophy and thalamic atrophy. The association was stronger in progressive MS than in RRMS (Saidha et al., 2015). In studies of PPMS patients Petracca et Al found GCIPL correlated with thalamic volume as well as wholebrain atrophy suggesting that GCIPL atrophy mirror whole-brain, gray matter and thalamic atrophy, especially in progressive MS (Petracca et al., 2017; Petracca et al., 2018).

We did not find any correlation to disease duration reflecting the conception that MS is a highly individual disease with both aggressive and more benign courses (Klineova and Lublin, 2018).

7. Limitations

The small size of the study population is one limitation, and the heterogeneity of the group is another. The control group did not undergo a VEP examination.

8. Future perspectives

The future holds an opportunity to treat neurodegenerative processes, and the need to monitor MS patients to study the efficacy of neuroprotective drugs will increase. VEP is a longstanding well-characterized technique that better detects traces of exposition of inflammation of the optic nerve. OCT remains a promising technique to monitor both inflammatory processes in the acute phase as well as degenerative changes of the retina, which can represent changes in the central nervous system. There is a need for further longitudinal studies to explore if there are associations between OCT measures and neurodegeneration in MS patients, including patients with SPMS. MRI modalities specifically displaying the optic radiations (ORs) or tracts as well as regional atrophy will further contribute to the knowledge of MS and map out neurodegeneration in SPMS. In MS, no evidence of disease activity (NEDA), defined as an absence of relapses, disability accumulation, or brain MRI activity, has been introduced as a treatment goal (Banwell et al., 2013). NEDA is associated with a relatively preserved

![Fig. 4. (a) Linear regression between VEP P100 and EDSS (b) Linear regression between VEP amplitude and EDSS.](image-url)
RNFL over two years, showed by Pisa et al. (2017).

9. Conclusion

There was a good correlation between OCT and VEP, whereas there was no association to MRI findings indicating that OCT and VEP provide additional information to MRI and should be included in the follow-up of patients with SPMS.

The main conclusions from our study are that VEP latency and GCIPL correlate with a progressive disease measure as EDSS. We found a strong correlation between VEP and OCT results. In summary, both VEP and OCT are, in addition to MRI, warranted in the follow-up of patients with SPMS.

CRediT authorship contribution statement

Anna Eklund: Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. Yumin Huang-Link: Conceptualization, Methodology, Validation, Formal analysis, Writing – review & editing. Beatrix Kovačević: Methodology, Resources, Validation. Charlotte Dahl: Conceptualization, Supervision. Magnus Vrethem: Conceptualization, Methodology, Validation, Resources, Supervision. Jonas Lind: Methodology, Formal analysis, Visualization.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.msard.2022.104255.

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A. Eklund et al.


