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There is still a role for the blink reflex in the diagnosis and follow-up of multiple sclerosis

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HIGHLIGHTS

- At present, the diagnostic criteria for multiple sclerosis (MS) do not include neurophysiological testing.
- The blink reflex is a sensitive test for MS and abnormalities are related to disease duration, disability, and lesions in the brainstem.
- Neurophysiological methods should be included for diagnosis and follow-up of patients with MS.

ABSTRACT

Objective: The evolution of the diagnostic criteria for multiple sclerosis (MS) has essentially evolved to clinical manifestations and magnetic resonance imaging. Inexpensive, quick to apply, non-invasive, quantitative and reliable neurophysiological tests are rare in daily practice and absent in clinical trials.
Method: The blink reflex was assessed in 50 patients with remitting-relapsing MS (RRMS) and 100 matched controls.
Results: Patients with RRMS had abnormalities in the blink reflex waves in relation to controls. If only RRMS patients were considered, these abnormalities were more pronounced in patients with longer disease duration, higher disability and for those with clinical or image lesions in the brainstem.
Conclusion: Neurophysiological tests, such as the blink reflex, can be used for helping the diagnosis and follow-up of patients with RRMS, since the reflex can identify dissemination in time and in space in a clear and quantitative manner.
Significance: Potential good methods for diagnosis and follow-up of MS should be considered for clinical trials and daily practice.

1. Introduction

The dissemination of encephalic and/or spinal cord lesions in time (DIT) and in space (DIS) is the cornerstone for the diagnosis of multiple sclerosis (MS) in patients presenting typical signs and symptoms of the disease. The evolution of the criteria has provided more sensitivity and more specificity for the diagnosis of MS, which is now typically based upon clinical manifestations and magnetic resonance imaging (MRI) (Polman et al., 2010). The follow-up on such patients, including determination of disease evolution, includes new signs or symptoms of neurological dysfunction and/or identification of new lesions through MRI.

Other parameters have appeared as potential indicators of neurological impairment in MS. Thickness of the nervous layer of the retina measured by optical coherence tomography (OCT) is now a well-accepted measurement for assessing neuronal loss (Fjeldstad et al., 2012). Maintenance of cognitive function is now considered to be an important parameter for assessing disease control in MS Reuter et al., 2011; Lovera and Kovner, 2012). Glial fibrillary acid

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protein is now considered to be a potential indicator of disease progression (Axelsson et al., 2011). However, while MRI, OCT, clinical parameters and biomarkers continue to establish their role in evaluating DIT and DIS in MS, electroneurophysiological methods seem to have lost all value for such evaluations.

The P100 visual evoked potential (VEP) is scarcely mentioned nowadays in the literature and it is even more rarely assessed in clinical trials, despite its strong correlation with neurological disability (Tuqcu et al., 2013). Multimodal evoked potentials show stronger correlation to MS prognosis than does T2 lesion load seen on MRI (Ramanathan et al., 2013), and the combination of integrated facial reflexes may suggest previously unidentified brainstem lesions (Habek, 2013). Visual pathways of patients with MS show a variety of definite abnormalities, independently of a history of optical neuritis (Castro et al., 2013). However, doctors attending patients with MS and drug companies evaluating MS treatments in clinical trials seem to have forgotten these possibilities.

Electrophysiological methods for assessment of MS are typically non-invasive, quickly applied and inexpensive tools that provide clear numerical values for confirmation of DIT and DIS. One of these electrophysiological responses, known as the "blink reflex", forms the topic of the present paper.

The blink reflex, also known as the orbicularis oculi reflex test, was described in 1896 by Overend (1986) and may be indicative of lesions or dysfunctions of the brainstem, affecting the trigeminal-facial arch. This reflex is elicited by stimulation of the supraorbital nerve on one side of the face, leading to two ipsilateral responses (*R*1 and *R*2) and one contralateral response (*R*2c). *R*1 represents an oligosynaptic pathway involving the main sensory nucleus of the trigeminal nerve and the intermediate subnucleus of the facial nerve. The second response, *R*2, involves a pathway of descent to the spinal trigeminal tract. The contralateral response, *R*2c, reflects the crossing of the brainstem in the medulla and progresses through the reticular formation to elicit a response at the contralateral facial nucleus. The present study is a reappraisal of the blink reflex method as a tool to diagnose and follow up lesions of the central nervous system. Following a study on a large number of controls subjects (Brooks et al., 2014) and on patients with headache (Brooks and Fragoso, 2013), the present work focus on the blink reflex in patients with MS.

Few studies have concentrated on the blink reflex in MS despite its overall sensitivity of 90.8% (Mikropoulos et al., 2010) and the possibility of identifying previously undiagnosed lesions (Hopf et al., 1991; Kumaran et al., 2000; Klissurski et al., 2009). Furthermore, when the economic conditions of the health system are unfavorable, electrophysiological techniques should be preferred, rather than MRI, for the follow-up of patients with MS (Nazniel et al., 2002).

Due to the relative complexity of the arch-reflex integration in the brainstem, it is the contralateral wave (*R*2c) that correlates better with lesions in MS (D'Aleo et al., 1999; Degirmenci et al., 2013).

2. Methods

This study was approved by the Ethics Committee of Universidade Metropolitana de Santos under the number 020/2011, CAAE 0017.0.161.000-11. All participants gave their informed consent prior to enrollment and were aware of the experimental nature of this study. The patient group consisted of 50 patients with relapsing-remitting MS. The control group consisted of 100 subjects matched for gender and age who were attending the EMG laboratory for nonspecific complaints, as well as volunteers who were enrolled in the project. Control subjects who did not sign the test agreement statement, or those previously diagnosed with central or peripheral nerve diseases, earlier cranial nerve lesions, autonomic disturbances or diabetes mellitus, or those using drugs with anticholinergic properties, were excluded.

The patient was in a relaxed state, lying supine on the examining table, with the eyes either open or gently closed. For the blink

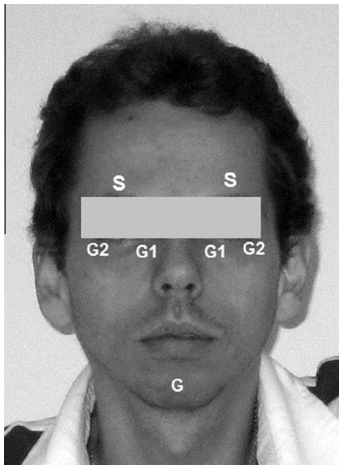

Fig. 1. Electrode placement for the recording of facial nerve responses. G1 and G2 are the electrodes. S is the stimulation point. G is the ground electrode.

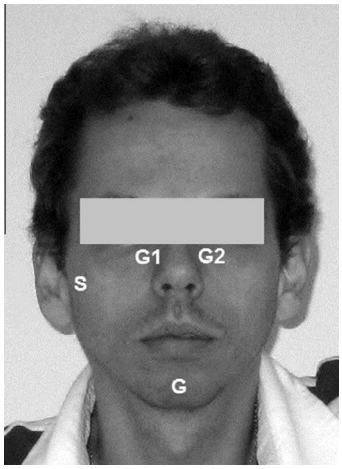

Fig. 2. Electrode placement for the recording of the blink reflex responses. G1 and G2 are the electrodes. S is the stimulation point. G is the ground electrode.

Table 1
Demographic data for the controls group and for patients with relapsing-remitting multiple sclerosis (RRMS). No significant differences were observed between the two groups.

	Controls (n = 100)	Patients with RRMS (n = 50)
Age	37.0 ± 14.5 (M = 36.8 ± 14.7) (F = 38.4 ± 14.9)	37.7 ± 14.8 (M = 35.6 ± 16.1) (F = 37.8 ± 13.7)
<50 years old ⩾50 years old	n = 70 n = 30	n = 37 n = 13
Gender	M = 40 (40%) F = 60 (60%)	M = 18 (36%) F = 32 (64%)
Ethnic background	Caucasians = 55 (55%) (Age = 37.6 ± 15.2) Non-caucasians = 45 (45%) (Age = 37.8 ± 14.5)	Caucasians = 33 (66%) (Age = 36.5 ± 14.3) Non-caucasians = 17 (34%) (Age = 38.0 ± 14.7)