Air-conducted cervical and ocular vestibular evoked miogenic potentials in patients with Susac's syndrome

Miogene przedsionkowe potencjały wywołane z mięśnia mostkowo-obojczykowo-sutkowego i skośnego dolnego oka u pacjentów z zespołem Susaca

ABSTRACT:
Aim: To evaluate acoustically evoked cervical and ocular vestibular miogenic potentials (AC cVEMP and oVEMP) in patients with Susac's syndrome. We did not seek for a diagnostic replacement test in those patients, but we investigated if the combined application of AC cVEMP and oVEMPs might be helpful as an additional source of information about the disease.

Material and methods: To record VEMPs, the EMG standardization method was used to continuously monitor and minimize the variability of the recordings. The stimuli were presented unilaterally one ear at a time. The waveforms were analyzed for the response, latency and amplitude. Susac's syndrome is a rare disease and two patients were analyzed in this study.

Results: In patient #1 stimulation resulted in responses on both sides with latencies within normal and symmetry limits for both c- and oVEMPs; however, the responses presented small amplitudes for cVEMPs. In patient #2, only cVEMPs were present. The P1 latencies were within normal values but amplitudes were low, in addition showing asymmetry between sides, with right side amplitude being smaller.

Conclusion: The information provided by the combined application of AC cVEMP and oVEMP might be useful in the diagnostics of Susac's syndrome revealing additional information about the affected vestibular system and be of help in the treatment and rehabilitation planning.

KEYWORDS: Susac's syndrome, branch retinal artery occlusion, cochlea, hearing loss, microangiopathy, vestibular nerve, vertigo

STRESZCZENIE:
Cel: Celem pracy była ocena miogennych przedsionkowych potencjałów wywołanych z mięśnia mostkowo-obojczykowo-sutkowego i skośnego dolnego oka (AC cVEMP i oVEMP) u pacjentów z zespołem Susaca. W prezentowanej pracy nie próbowaliśmy przedstawić badania VEMP jako testu zastępującego inne w tej jednostce chorobowej, badaliśmy jedynie, czy równoległa ocena obu rodzajów VEMP (cVEMP i oVEMP) może być pomocna jako dodatkowe źródło informacji o chorobie.


Wyniki: U pierwszego pacjenta zarejestrowano odpowiedzi dla obu rodzajów VEMP tj. cVEMP i oVEMP. Latencja falii
INTRODUCTION

Susac’s syndrome (SS) is a rare disease with a little more than 300 cases described in the literature so far [1]. The clinical triad of encephalopathy, branch retinal artery occlusion (BRAO), and sensorineural hearing loss characterizes this syndrome, however, at clinical onset they are rarely all three present at the same time [2-7]. The symptoms are a result of autoimmune microangiopathy that affects the brain, retina and inner ear (cochlea and semicircular canals) [7-9].

As mentioned at the beginning, the inner ear may be involved in the pathogenic process and in majority of cases it occurs after encephalopathic features [4,10]. The inner ear symptoms such as hearing loss (usually low and mid frequencies), tinnitus, peripheral vertigo, and nystagmus depend on the site of arteriolar microinfarction [4,7,9]. The hearing and balance problems usually develop gradually, but sometimes are very sudden.

The diagnosis of SS is mainly based on the clinical symptoms, magnetic resonance imaging (MRI) findings in the brain, and typical features detected in fluorescein angiography (FA) that documents BRAO [1,4,11]. There are also other diagnostic tools to detect brain, retina and inner ear abnormalities helping to diagnose SS. They help as well ruling out other clinical disorders since a complete clinical triad of SS is usually not present at the onset of the disease. The broad test battery is needed to better understand the disease, and to plan and monitor the treatment.

When it comes to SS and hearing and balance, to the best of our knowledge, there is not much of evoked potentials in the literature, especially when it comes to vestibular evoked myogenic potentials (VEMP). This was one of the reasons to closely look at VEMPs in this study.

AIM

The aim of this study was to evaluate AC cVEMP and oVEMP findings in patients diagnosed with Susac’s syndrome. In this study, we did not seek for a diagnostic replacement test in those patients, but we investigated if the information from combined application of AC cVEMP and oVEMPs might be helpful as an additional source of information about the disease in patients with SS.

MATERIAL AND METHODS

Participating patients’ description

Two female patients aged 36 and 44 years old with diagnosed Susac’s syndrome.

Patient #1 (age 36 years)

The first symptoms of the disease – bilateral BRAO - occurred in March 2000 (at the age of 20 yrs.). At that time the patient was diagnosed and treated in the Department of Ophthalmology. In May 2000, she was hospitalised due to severe headache in the Department of Neurology. The MRI scans revealed small lesions in the white matter mainly supratentorially, however neuroradiological criteria for Multiple Sclerosis (MS) were not fulfilled. Visual evoked potentials were bilaterally abnormal with prolonged latency of P100 more pronounced at the right side. Brainstem auditory as well as somatosensory evoked potentials were within normal limits. The patient was discharged with the final diagnosis of MS. In January 2001, recurrent bilateral BRAO occurred. In April 2001, she was again hospitalized with severe headaches and vertigo. In neurological examination hypoaesthesia in V1-V3 branches of the right trigeminal nerve as well as pathological Romberg’s test and hearing loss were found. Another exacerbation of the disease was diagnosed as BRAO in May 2001. In July 2001, she was admitted again and Susac’s syndrome was diagnosed based on clinical symptoms and MRI results (many small lesions of vascular aetiology localized mainly supra- but also infra-tentorially as well as the typical “snowball” lesions in the central portion of the corpus callosum). Since the first clinical symptoms till December 2009 the patient experienced altogether 10 relap-
ses, which were treated with intravenous methylprednisolone and/or subcutaneous low molecular weight heparin (LMWH). Only once plasma exchange was necessary due to the intensity of relapse symptoms and no response to standard treatment. From January 2010, she was treated with repeated intravenous infusions of immunoglobulins (IVIg) with good clinical response (no exacerbation of the disease and no new lesions in MRI). In 2013, the patient decided to get pregnant and in 2014 she gave birth to a healthy baby boy. During pregnancy, the course of the disease was stable. In postpartum period, she suffered from severe exacerbation with BRAO symptoms as well as neurological progression (paresis and hypoesthesia of the right extremities) and cerebellar symptoms. After intravenous methylprednisolone and subcutaneous LMWH treatment the neurological and ophthalmological symptoms withdrew. In MRI scans, no signs of progression of the disease were found. Since 2014 the patient has been again treated with repeated IVIg with good clinical response (no clinical exacerbation of the disease and no new lesions in MRI).

Patient #2 (age 44 years)

The first symptoms of the disease – vertigo, dizziness and balance disturbances - occurred in November 2015 (at the age of 43 yrs.) and the patient was admitted to the Department of Neurology. A few months prior the hospitalization the patient noticed progressive worsening of hearing. On admission in neurological examination, some moderate pyramidal and cerebellar signs as well as bilateral hearing loss were found. After treatment with intravenous methylprednisolone almost full recovery was observed. In ophthalmological examination, all typical signs of Susac’s syndrome were found including vessel wall hyperfluorescence (increased intensity of dye staining the walls of vessels), “leakage” of dye as well as chronic changes in the periphery (capillary dropout, neovascularization, microaneurysms) in FA of the retina. MRI examination revealed numerous small lesions of vascular aetiology which were localized both supra- and infra-tentorial. Typical “snowball” lesions were found in the central portion of the corpus callosum. The evoked potential tests were found abnormal indicating the central location of the lesions. Cerebrospinal fluid analysis was normal, no oligoclonal bands were ascertained. The Susac’s syndrome was diagnosed and treatment with oral methylprednisolone (32 mg daily) was initiated. After 6 months, a relapse with BRAO and deterioration of neurological symptoms (especially cerebellar) were diagnosed. The patient was treated with intravenous methylprednisolone injections with good clinical response to treatment. From July 2016, the patient has been treated with repeated IVIg infusions with good clinical response (no clinical relapses and no new lesions in MRI).

Testing protocol, stimulus and signal acquisition characteristic

Both patients were tested with acoustically evoked cervical and ocular vestibular miogenic potentials (AC cVEMP and oVEMP). All VEMPs were acquired using SmartEP a fully computerized two-channel evoked potential system (Smart-EP, Intelligent Hearing Systems, Miami, FL, USA).

The recordings were obtained with each subject lying comfortably on a bed with the upper body elevated at 30° from horizontal. Surface gold-cup electrodes were used.

For cervical VEMPs (cVEMPs), the patients were instructed to relax and lift their heads during recordings to provide tonic background sternocleidomastoid (SCM) muscle activity with no shoulder or abdominal muscle tension if possible. At all times a researcher was present directing the patient to increase or decrease their head lift to correct the muscle contraction level and to stay in the selected Root Means Squared (RMS) EMG activity levels using the continuous pre- and post-stimulus biofeedback EMG activity monitoring for guidance. Both patients could perform head lift without any adversity. The electrodes were placed on the skin above the SCM muscle. The non-inverting (+) electrodes were attached to the skin bilaterally in the midpoint of the SCM muscle between the mastoid and the sternum, while the inverting (-) ones were placed bilaterally on the sternum and the SCM junction. The ground electrode was positioned in the upper part of the sternum. All electrode impedances were kept at 3 kΩ or less.

For ocular VEMPs (oVEMPs), the patients were instructed to gaze up at a target located approximately 20° from the vertical line behind their head to provide the tonic activity of the inferior oblique (IO) muscle. The electrodes were placed on the skin beneath the eyes. The non-inverting (+) electrodes were attached to the skin bilaterally 0.5 cm beneath the orbital margin, the inverting (-) ones were placed bilaterally approximately 2-3 cm below them. The ground electrode was positioned in the upper part of the sternum. All electrode impedances were kept at 3 kΩ or less.

As mentioned earlier, the EMG standardization method integrated into the acquisition software was used to continuously monitor and further minimize the variability of the VEMP recordings, as described in detail in a previous study by Yavuz et al. [12].

In this study, acoustic stimuli were used. The stimuli consisted of a single 500-Hz tone bursts exact-Blackman-windowed and of 5 ms duration. They were presented unilaterally one ear at a time for ipsilateral recordings of cVEMPs, and contralateral recordings of oVEMPs. The stimuli were delivered via ER3a insert earphones (Etymotic Research, Inc. Elk Grove Village,
The recorded electrophysiological responses were then normalized per prestimulus (base) EMG RMS (Root Means Squared) calculations to minimize the variability of the VEMP recordings.

**cVEMP and oVEMP data analysis**

Both cervical and ocular VEMPs were collected by averaging three sets of 64 sweeps. For both types of recordings, a stimulation rate of 3.1/s was used.
The resulting VEMP waveforms were analyzed for the response presence in time domain. In cVEPs the first distinctive positive peak was identified as P1, followed by the distinctive negative N1. In oVEPs the first distinctive negative was identified as N1, followed by the distinctive positive peak P1.

The latencies and amplitudes of the waves were measured. Normalized values of amplitudes were used to assess the corrected asymmetry ratios (corrAR (%)) between the left and the right side recordings [16]. Responses that were not detected (absent) were assigned amplitude of zero. Latencies greater than the mean + 2SD of 13.31 ms (AC cVEMP) and 10.57 ms (AC oVEMP) were considered as abnormal (upon data collected from 20 healthy ears in subjects without any otological or neurological problems as controls).

Ethical consideration

This study is a part of a retrospective-prospective project that was approved by the Institutional Ethics Committee Review Board and both participating patients signed informed consent forms. The project conforms to The Code of Ethics of the World Medical Association (Declaration of Helsinki).

RESULTS

Table I shows AC cVEMP and oVEMP results with values for P1 and N1 latencies and amplitudes of responses along with asymmetries. Figure 1 and 2 present waveforms of VEMPs recorded from patient #1 and #2, respectively.

Close inspection of Table 1 and the waveforms in both Figures (1 and 2) reveals that in patient #1 the stimulation resulted in responses on both sides with latencies within normal and symmetry limits for both cervical and ocular VEMPs; however, the responses presented small amplitudes for cVEMPs.

In patient #2, only cVEMPs were present. The P1 latencies were within normative values but amplitudes were low and in addition showing asymmetry between sides with right side amplitude being smaller. The oVEMPs were not detected in this patient.

DISCUSSION

In patients with Susac’s syndrome, clinical symptoms along with MRI findings in the brain, and typical features of BRAO detected in FA are essential for the diagnosis [11]. However, in most cases, all three features of the clinical triad, i.e. encephalopathy, BRAO and hearing loss, are not present at the onset, which complicates the diagnosis of Susac’s syndrome [4-7]. The understanding of this disease is still incomplete [2,3,7,17]. Many other tests and multi-disciplinary approach is therefore indicated, with otoneurological being one of them.

In Susac’s syndrome, peripheral vertigo and tinnitus often accompany the hearing loss caused by occlusion of the arteries of the cochlear and semicircular canals [7]; however, they
are not specific for the Susac’s syndrome. In today’s otoneurological clinical practice numerous tests are available to evaluate the functionality of the audio-vestibular system. The use of those tests in everyday clinical practice is limited by their selectivity, utility, and sometimes costs. In our Department, vestibular evoked miogenic potentials (VEMPs) are part of routine testing in various vestibular problems.

Based on our experience with VEMPs [12,18] and those from other studies [19,20], the VEMPs show to be a very promising test in clinical practice. Both air-conducted cervical and ocular VEMPs are noninvasive, easy to acquire and, what is nowadays important, they require short time and low instrumentation costs. VEMPs are electrical potentials from muscles in response to vestibular stimulation. Cervical VEMPs (cVEMPs) represent a short inhibition on a background tonic activity of the sternocleidomastoid (SCM) muscle [21] and represent vestibulo-colic reflex with the saccule being the predominant origin [20,22]. Ocular VEMPs (oVEMPs) are recorded as well against a background of tonic muscle activity, but in this case, it is a response of a short excitation of the inferior oblique (IO) muscle and represent vestibulo-ocular reflex with the utricle being the predominant origin [21-30].

In both presented patients with Susac’s syndrome, combined use of cervical and ocular VEMP shows to be helpful in the diagnostic process indicating abnormal responses in both cases that came along with the balance problems reported in patients’ medical history and at the time of VEMP testing. In both subjects, in cVEMPs P1 latencies were normal and amplitudes were decreased pointing out the peripheral location of pathology with the saccule and inferior vestibular nerve otolith function on both sides being affected. The oVEMPs in the first patient were present showing functional utricle and superior vestibular nerve within normal limits. On the contrary, the second patient’s oVEMP results presented no response on both sides indicating a loss of superior vestibular nerve otolith function. The absence of the electrophysiological response may indicate any pathology within the vestibulo-ocular reflex, however, knowing this patient’s history and the most recent MRI results showing no brainstem involvement, the non-functioning utricle and therefore loss of superior vestibular nerve function is the most probable one.

Acquiring AC cVEMPs and oVEMPs together may be helpful to identify the functional integrity of the inferior and superior vestibular nerve bundles and otolith saccular and utricular function [12,21,22,28]. The rapid development of VEMPs related research [21-27,29] and our experience with VEMPs [12,18], have led us to use cVEMP together with oVEMP as additional tests in diagnostic battery in various vestibular problems, now covering also patients with Susac’s syndrome.

CONCLUSIONS

The information provided by the combined application of air-conducted cervical and ocular VEMPs might be useful in diagnosis of patients with Susac’s syndrome revealing additional detailed information about the affected vestibular system. The MRI scans provide the most useful information on Susac’s syndrome that is essential for the diagnosis and treatment monitoring; however, it does not provide information about vestibular involvement in the pathological process. In our opinion, the cervical and ocular VEMPs may serve as an additional source of information about the vestibular function and be of help in the diagnosis, treatment and rehabilitation planning in patients with Susac’s syndrome.

References

Tables: 1

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