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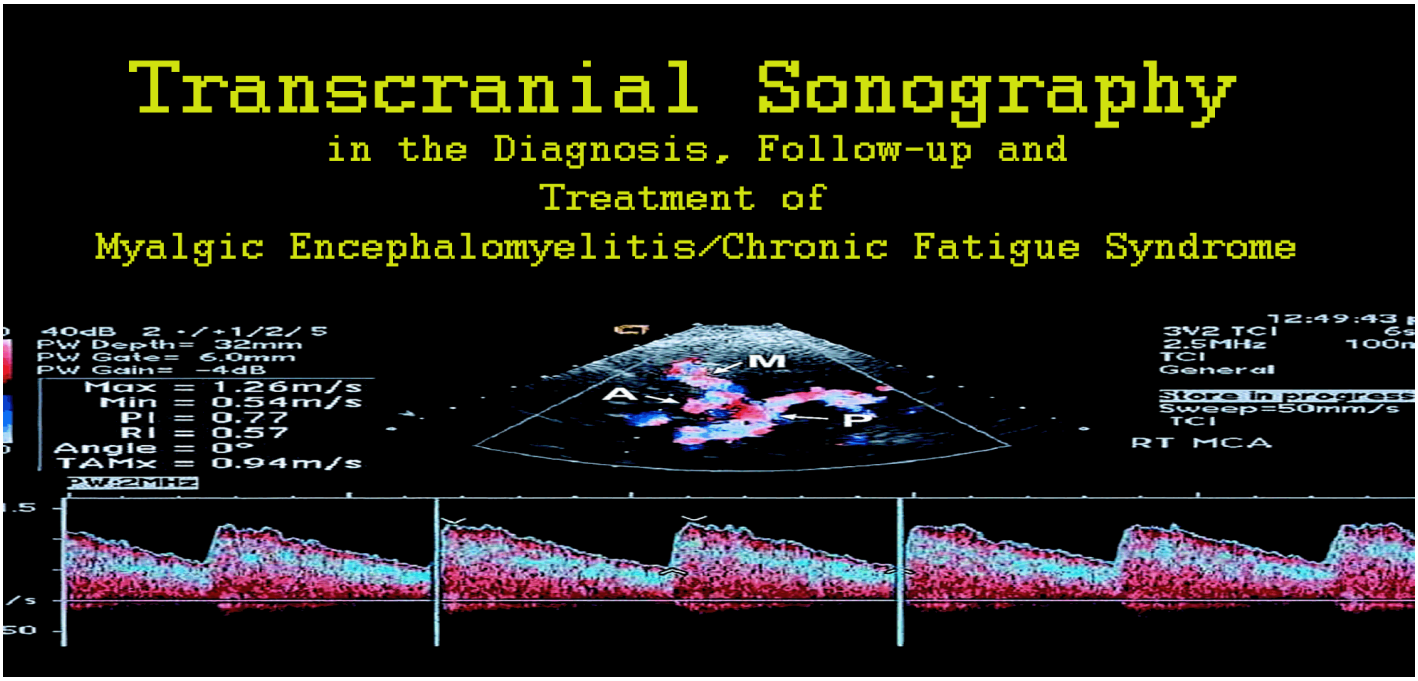

Transcranial sonography in the diagnosis, follow-up and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

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Abstract

We used a modified transcranial sonography technique to study the cortex of the temporal lobe, a brain region involved in the processing of functions that are often compromised in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) patients. We studied the meninges, the subarachnoidal space and the cortex. The spatial resolution and the ability to visualize structures of 200-300 µm size, led us to hypothesize that the linear structures parallel to the subarachnoidal space could be referred to the neuronal layers of the cortex. In real-time mode, we could observe pulsation of the meninges and the cortex synchronous with the heart beat and independent of blood flow. This pulsation was more evident at the level of the meninges, but it was also appreciable at the level of the layers of the cortex and it was not accompanied by any type of flow. In addition to these findings, we observed that the subject undergoing the procedure experienced a series of changes that might prove potentially useful in the treatment of ME/CFS. In particular, we observed a decrease of tachycardia accompanied by an increase in systolic blood pressure and by a significant increase in muscle strength measured by the degree of muscle fibre shortening at the level of the biceps brachii. These findings, together with the low cost and simplicity of the procedure, suggest that modified transcranial sonography has a significant potential in the study and treatment of ME/CFS.

Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) designates a clinical condition characterized by a complex simptomatology that includes, but is not limited to, long-lasting disabling fatigue. According to the most recent classification, it is considered a neurological disease in the World Health Organization's International Classification of Diseases (ICD G93.3) and it is characterized by widespread inflammation and multisystemic neuropathology (1). As of today, the aetiology of ME/CFS is unknown and, just like in any syndrome, it is quite likely that there may be multiple causes leading to a shared clinical picture. Several events may act as triggers, from external environmental or microbiological triggers, such as chemical exposure or infections, to psychological and social factors that may be critical in perpetuating the symptoms (2). It is worth noting that from the point of view of evolution of the human brain, ME/CFS may be defined as a "phylogenic disease" (3-7), according to principle of "integrated phylogeny" of the primate brain (8), because of its possible relation to evolution.

For patients as well as for health care professionals, the issue of treatment of ME/CFS is a truly dramatic and controversial one. In fact, proposed treatments are as diverse as cognitive behavioral interventions (9), coiling dragon needling and moving cupping on back (10), treatment with Lactobacillus acidophilus (11), or with antipsychotics (12), just to name a few of the most recent studies.

Oddly enough, among the variety of proposed treatments for ME/CFS, the application of transcranial ultrasounds by means of a common ultrasound imaging machine has not been evaluated so far. A search of the literature revealed that transcranial sonography had been used as a diagnostic tool only in one study describing cerebral and systemic hemodynamic changes during upright tilt in CFS (13). However, in that study, the Authors were focussed on observation of the middle cerebral artery using transcranial doppler monitoring, and did not use probes and techniques able to study in detail the cerebral cortex with particular reference to the gray matter of the temporal lobe. Based on our background in clinical radiology and anatomy, we were interested in studying the cerebral cortex of the temporal lobe because of the well known involvement of the temporal lobe in the processing of functions, such as semantics and memory, that are often compromised in ME/CFS patients (14). To this end, we modified the conventional procedure for transcranial sonography and we used a linear probe that is normally used for muscle-skeletal ultrasound imaging. To our surprise, we observed that not only such a procedure allowed detailed visualization of the cortex of the temporal lobe, a finding potentially important for the diagnosis and follow-up of ME/CFS patients, but also affected brain function in such a way that it could be proposed as a safe and easy treatment for a variety of diseases including ME/CFS.

Materials and Methods

The ultrasounds used for imaging, also known as sub-thermal ultrasounds, are is considered safe and have been used for foetal imaging in utero, and virtually every part of the body, including brains of newborn babies through fontanelles. For transcranial sonography we used an Esaote MyLabFive ultrasound imaging machine approved for many applications including cephalic (brain) imaging. We used the default settings for adult transcranial imaging, but instead of a transcranial probe, we used a conventional linear probe for muscle-skeletal examination and we selected 7.5 MHz frequency. Acoustic power was set to 1.0. The length of the probe was about 4 cm, *i.e*. much less than the size of the temporal cortex that we examined that is 7-8 cm. The procedure was performed at the Laboratory for Exercise Sciences Applied to Medicine of the University of Firenze (LSMAM, Director, Prof. M. Gulisano).

The volunteer healthy subject, a certified clinical radiologist (M.R.), sat in front of the imaging machine in the position he normally uses to perform an examination, and positioned the probe on his right temporal region in correspondence of the acoustic window of the temporal squama (Fig. 1). An improvised support to his right arm was provided to ensure stability. In this position, the subject was able to look at his own brain while performing the examination. Heart rate was recorded 10 min prior to the transcranial sonography procedure, immediately before, during the procedure at intervals of 30 s, at the end of the procedure that lasted 10 min, and 10 min after the end of the procedure. Systolic and

diastolic blood pressure were recorded 10 min prior to the procedure, immediately before, at the end of the procedure, and 10 min after the end of the procedure. Thickness of the biceps brachii was measured with the same probe, but this time with the conventional setting for muscle-skeletal examination.

Results

During 10 min transcranial sonography, no side effect was reported. The parameters adopted for visualization of the temporal cortex allowed to distinguish the meninges, the subarachnoidal space and the cortex (Fig. 2). The meninges appeared as a well organized array of layers of about 5 mm thickness. The thickness of the cortex (3.8 mm) led us to hypothesize that we were observing the temporal areas designated as TG and TE, *i.e.* those areas involved in the control of eye movements and balance in standing position (area TE), social behaviour, mood and decision making (area TG). It is worth remembering that most of these functions are altered to various degrees in ME/CFS patients' symptoms (2). The spatial resolution and the ability to visualize structures of 200-300 µm size, led us to hypothesize that the linear structures (alternate gray-white stripes) parallel to the sub-arachnoidal space could be referred to the well known neuronal layers of the cortex (15). Considering the role of neuronal layer architecture alterations in neurodegenerative diseases (16), detailed study of these layers in ME/CFS might prove instrumental in diagnosis, prognosis and follow-up. With this type of setting and using Doppler technique, we could also observe arterial vascularisation of the meninges and pulsating arteries of less that one mm diameter could be easily visualized (Fig. 3). During transcranial sonography, we could also observe a peculiar pulsation of the meninges and of the cortex that was synchronous with the heart beat, but was not accompanied by any type of flow. This pulsation was more evident at the level of the meninges, but was also appreciable at the level of the layers of the cortex. A similar type of pulsation was described in 1987 by Klose et al. who used Magnetic Resonance Imaging to study the oscillation of the cerebrospinal fluid within the cardiac cycle (17). We have no evidence, as yet, that the observed pattern of brain pulsation may be altered in ME/CFS patients nor that this observation may contribute to diagnosis or follow-up. However, the easy reproducibility of the procedure as well as the absence of any discomfort, render this type of approach worth of further investigation. In fact, it was proposed that alteration of the so-called cranial rhythmic impulse might have a role in the pathogenesis of ME/CFS (18), and spinal fluid abnormalities are common in ME/CFS patients (19).

Although the primary goal of our research was to set up a technique to study brain morphology and function in ME/CFS patients, while performing transcranial sonography with the indicated setting, we noticed that some notable changes happened in the subject who was at the same time the operator of the echo machine and the object of observation. In fact, an ill-defined feeling of strength and well-being that had been reported during the first measures prompted us to further investigate whether the ultrasounds used for imaging could somehow affect brain function. The use of transcranial ultrasounds in both military and civilian settings to stimulate the central nervous system has been recently proposed (http://www.darpa.mil/Opportunities/Universities/Young_Faculty_Award_Recipients.aspx) (20), and a preliminary study performed at the University of Arizona demonstrated that transcranial ultrasound stimulation improved mood and increased heart rate, systolic and diastolic pressure and decreased oxygen saturation (http://www.quantumconsciousness.org/documents/ATUS201101634A.pdf). In the study reported above, however, transcranial ultrasound application was performed by an operator and the subject being investigated did not look at his own brain while performing the procedure. This difference might be significant because of the ensuing bio-feedback, an effect that has proven effective in a variety of conditions from neurological disorders to cancer (21, 22).

In our study, we observed that heart rate significantly decreased from 81 beats per minute (bpm) at the beginning of the procedure to 71 bpm at the end of the procedure, to 70 bpm 10 min after the end of the procedure. Systolic blood pressure increased from 115 mm/Hg (10 min before the procedure) to 125 mm/Hg (10 min after the end of the procedure). Unlike the study quoted above, diastolic pressure did not change and remained constant at 75 mm/Hg before and after the procedure. It is well assessed that cardiovascular symptoms and hypotension are

common in ME/CFS patients (23), and it has been suggested that hypotension associated with orthostatic stress may impair neurocognitive functioning in ME/CFS patients with postural tachycardia syndrome (24). Therefore, our results as well as those presented by Hameroff et al. (http://www.quantumconsciousness.org/documents/ATUS201101634A.pdf) may lead to interventional applications of transcranial sonography in the treatment of orthostatic intolerance, one of the major symptoms of ME/CFS.

The observed increase in systolic blood pressure in the absence of a concomitant increase in heart rate or diastolic pressure, is of particular significance for ME/CFS, and it can be interpreted as if transcranial sonography was associated with increased cardiac output; in particular, as if it increased the stroke volume, an index that is frequently decreased in ME/CFS patients and is associated with the most common symptoms reported in ME/CFS, *i.e*. shortness of breath, dyspnea on effort, rapid heartbeat, chest pain, fainting, orthostatic dizziness and coldness of feet (23). The observed decrease in heart rate might also prove useful in those ME/CFS where tachycardia is a symptom associated with neurocognitive defects (25).

In order to determine the anatomical correlate of the subjectively perceived increase in muscle strength, we measured by ultrasonography the thickness of the biceps brachii in relaxation and maximal contraction, before and after transcranial sonography (Fig. 4).Ten min before transcranial sonography, the thickness of the biceps increased from 24.9 mm (Fig. 4, panel A) to 38.3 mm during maximal contraction (Fig. 4, panel B). Ten min after the end of the procedure, the thickness of the biceps increased from 24.9 mm (Fig. 4, panel C) to 43.2 mm (Fig. 4, panel B). The increase in thickness was accompanied by a concomitant increase in the angle between the muscle fibres and the muscle aponeurosis. These results demonstrate that the subjectively perceived increase in muscle strength was indeed associated with a measurable increase in the capacity of the muscle to contract with significant increase in muscle fibre shortening.

Discussion

The results presented in this study raise the possibility of using transcranial sonography as a tool for the diagnosis, follow-up and treatment of ME/CFS patients. In recent years the cost of ultrasound imaging machines is significantly decreased and a good quality apparatus is now sold (in the year 2012) for about 20.000,00 Euros. In the hands of properly trained health care professionals the procedure of transcranial sonography described here can be used for the study of brain pulsations and/or rhythmic impulses and for the study of vascularisation of the meninges. Furthermore, considering that significant neuroanatomical changes occur in ME/CFS, and that these changes are consistent with impaired memory (26), transcranial sonography may prove a simple and inexpensive tool to assess these changes and monitor progression of the disease as well as improvements associated with treatments. The inherent safety of the technique as well as the absence of discomfort make this procedure quite acceptable by patients and this characteristics may prompt extensive studies on a significant number of patients.

In addition to its use a tool contributing to diagnosis and follow-up, our results suggest that transcranial sonography may also prove useful in controlling some of the most disturbing symptoms of ME/CFS, *i.e*. chronic pain and mood alterations as demonstrated by Hameroff et al. ((http://www.quantumconsciousness.org/documents/ATUS201101634A.pdf), hypotension, tachycardia and muscle weakness.

Figure legends

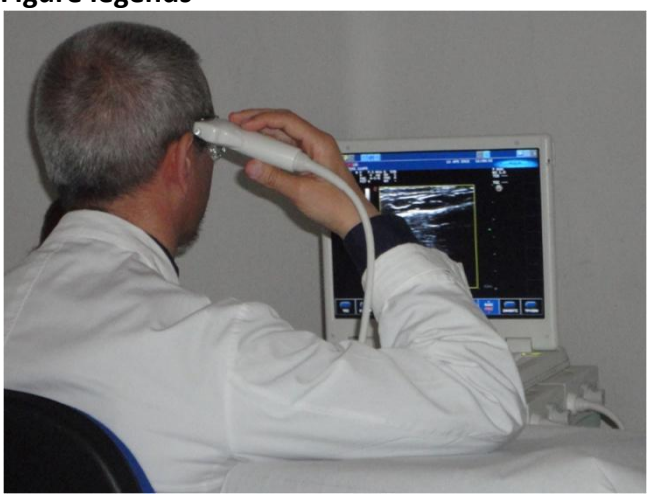

Figure 1. The operator (M.R.) applying the probe to his right temporal region. Sitting in front of the ultrasound imaging machine, the operator is able

to observe his own brain in real time. In this way it is possible to observe brain pulsations as well as blood flow through meningeal arteries. We hypothesize that direct observation of the brain triggers a bio-feedback effect.

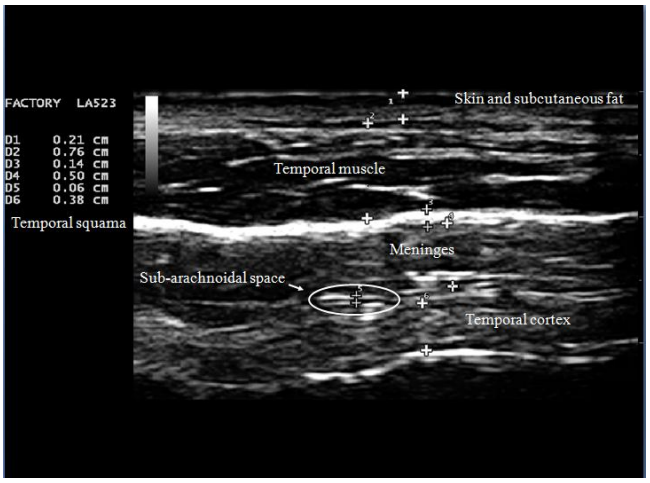

Figure 2.
Two dimension image of the temporal region. The skin layers and the temporal muscle are clearly visible. The temporal squama appears as an hyper-reflecting (white) irregular line of about 1.4 mm thickness. The meninges appear as a well organized array of layers of about 5 mm thickness. The sub-arachnoidal space (white arrow) is identified by two hyper-reflecting (white) lines sandwiching an hypo-reflecting (black) space containing liquor. The size of the sub-arachnoidal space was about 0.6 mm. The neuronal layers of the temporal cortex (3.8 mm thickness) appear as alternate layers of hyper- and hypo-reflecting structures. The thickness of the cortex corresponds to that of the TE and TG areas.

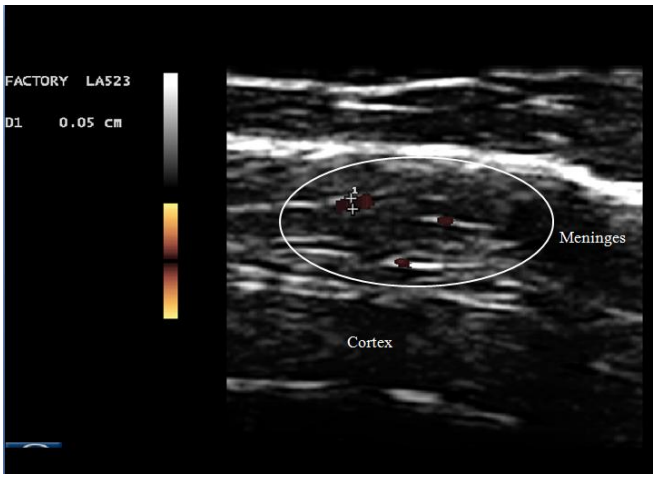

Figure 3. Pulsating arterial blood vessels in the meninges.

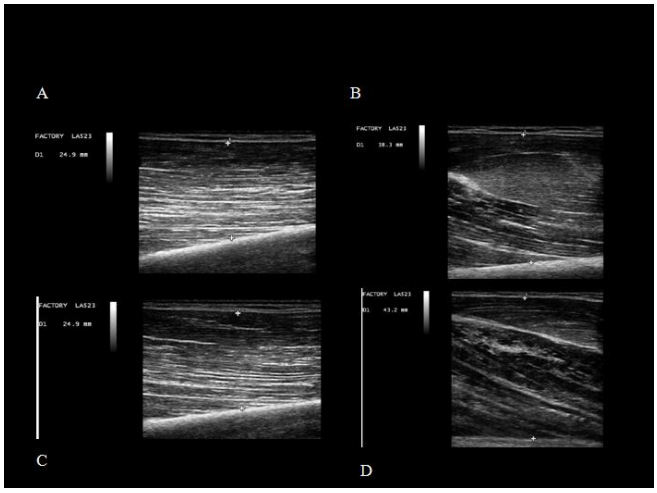

Figure 4.
Two dimension image of the left biceps brachii. Also in this case the operator applied the probe to his own biceps.
A. Thickness of the relaxed biceps 10 min before the procedure; 24.9 mm.
B. Thickness of the contracted biceps 10 min before the procedure; 38.3 mm.
C. Thickness of the relaxed biceps 10 min after the procedure; 24.9 mm. Please notice; this image is not the same shown in panel A, as clearly visible looking at the orientation of the fibres. Nevertheless, the measurement is identical, thus demonstrating the reproducibility of the procedure.
D. Thickness of the contracted biceps 10 min after the procedure; 43.2 mm.

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ME COMMENT

"Respondents found the least helpful and most harmful interventions were Graded Exercise Therapy and Cognitive Behavioural Therapy" Norfolk and Suffolk ME Patient Survey 2009 http://www.norfolkandsuffolk.me.uk/surveylink.html