Thenar muscles H reflex in patients with fibromyalgia: a case control study

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ACTA REUMATOL PORT. 2016;41:145-150

ABSTRACT

Objective: To delineate Hoffman reflex (H-reflex) parameters and specify the diagnostic accuracy measures of thenar muscle H-reflex in fibromyalgia (FM).

Methods: The study was a cross sectional study performed on 30 subjects with FM and 30 healthy volunteers in two major referral hospitals. We recorded the number of obtainable thenar H-reflexes and their minimum latency, threshold and amplitude in each group.

Results: There was a significantly more chance to elicit the H-reflex in patients with FM. H-reflex threshold and minimum latency were lower in FM group but no significant difference was shown for H wave amplitude. According to our study, thenar H-reflex has 46.7% sensitivity, 86.7% specificity and 66.7% diagnostic accuracy to detect FM. It also has moderate predictive values and positive likelihood ratio but low negative likelihood ratio.

Conclusion: Higher rate of thenar muscle H-reflex in FM can be interpreted as a confirmatory finding to central sensitization theory for this disorder. Obtaining H-reflex from thenar muscles could be a helpful diagnostic tool for FM that increases the confidence in diagnosis. Although it is a weak tool for screening because of low sensitivity, it has a relatively high specificity.

Keywords: Muscle H-reflex; Fibromyalgia; Diagnosis.

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INTRODUCTION

Fibromyalgia (FM) is the ringleader of the big family known as central sensitivity syndrome, manifesting with widespread pain, hyperalgia and unpleasant sensation after physical contact or thermal exposure. It is considered a multifactorial disorder for which central nervous system sensitization, infection, trauma, stress and genetics are suggested as the contributing factors[1]. Cognitive symptoms, irritable bowel syndrome, headache, unrefreshing sleep, fatigue and a number of other somatic symptoms, altered the definition from a "peripheral pain" defined disease to a "systemic symptoms" based disease[2]. It imposes a great burden to patients comparable to osteoarthritis[3] and rheumatoid arthritis[4], and affects personal relationships, physical daily activities and ability to work as well as mental health. Economic burdens are also comparable to diabetes and hypertension, and mostly influence the pre-diagnosed stage of illness[5].

FM affects 2% of the population of all ages (3.4% in women and 0.5% in men). The prevalence rate increases with age, most prominently in women compared to men (7.1% vs. 1.2%), aged 60-69[6]. The most recent estimates from United States suggest that FM involves up to 5% of all women and is the third most common rheumatic disorder after low back pain and osteoarthritis[6].

The classic criteria proposed by American College of Rheumatology (ACR)[7] emphasizes the evaluation of tender points but it has proved nonsufficient[8]. The new ACR criteria in 2010 have 83% specificity for correct diagnosis[9]. The main limitation is that they cannot be applied to patients with FM secondary to other disorders such as rheumatoid arthritis or systemic lupus erythematosus. Despite the efforts in recent years, there is no approved and optimal paraclinical tool in order to facilitate the diagnosis and follow-up of FM. Some studies have been performed in order to investigate electromyography, Magnetic Resonance Imaging (MRI) and electroencephalography responses in patients with FM[10-17]. However, a consensus about optimal diagnostic method is still lacking.

Hoffman reflex (H-reflex) is the result of sub-maximal stimulation of type Ia sensory fibers. The potential enters the posterior horn of the spinal cord and passes through the synapses with alpha-motor neurons. Finally, a compound muscle action potential is generated and is recorded as H wave. It seems that the reflex is dependent upon the balance between augmenting and inhibitory factors. H-reflex is mostly recorded from gastrocnemius-soleus complex and, sometimes, flexor carpi radialis muscles[18]. The intrinsic muscles of the foot or hand have also been reported as sites for eliciting the H-reflex[19, 20], but to our knowledge the thenar muscles have not been assessed as the site of H-reflex origin.

Despite the lack of literature on eliciting H-reflex from thenar area, due to our random findings and considering the theoretical suprasegmental facilitating effects of FM on H-reflex, the current study was performed to evaluate possible differences in H-reflex recording between patients with FM and normal population. Also we wanted to define diagnostic accuracy measures of obtainable thenar muscle H-reflex and clarify if this non-invasive tool can be used as an adjunctive measure to help diagnosis of FM.

METHODS

We carried out a matched comparative cross-sectional study with two groups of volunteers, one of FM patients and other of healthy controls. The study was conducted from September 2010 to February 2011 in outpatient clinics of physical and rehabilitation medicine at two large referral academic hospitals.

PARTICIPANTS AND SAMPLING

We recruited patients and healthy subjects between 20 to 60 years of age. First we recruited 5 FM patients. H-reflex could be obtained in 2 of them. Assuming power of 80%, alpha of 0.05 and confidence interval of 95%, we calculated the sample size of 30 for each arm. So, 30 subjects with FM and 30 age and sex frequency matched healthy subjects entered the study. We recruited the subjects using the convenient sampling method. Overall, 13 pairs of patients with their matched controls were examined in one hospital, and 17 were examined in the other hospital. All researchers who performed physical examination and the investigators who carried out electrodiagnostic studies were expert and qualified.

At the beginning of the session, the subjects were briefed. A trained general practitioner asked for the medical history of the patient, performed a general examination and evaluated laboratory findings including Complete Blood Count (CBC), Thyroid Function Tests (TFT), Erythrocye Sedimentation Rate (ESR), C-Reactive Protein (CRP), Creatine Phosphokinase (CPK) and Lactate Dehydrogenase (LDH). Then a physical and rehabilitation medicine specialist completed the medical history and physical examination looking for symptoms and signs of FM based on the ACR criteria. Because of the admissibility and popularity of classic ACR criteria that numerous previous studies were done based on, we applied it in our study. After the diagnosis of FM based on the first general and second specific history taking and physical examination according to ACR criteria and also ensuring of normal blood tests, the participants were led to Electromyography (EMG) laboratory to complete the investigation.

INCLUSION AND EXCLUSION CRITERIA

All the subjects signed the provided informed consent before the first physician visit. Exclusion criteria were pain due to disorders other than FM, other rheumatologic, immunologic, inflammatory and hormonal disorders interfering with diagnosis of FM, any condition that made relaxing of the upper limb impossible such as spasticity, conditions potentially affecting the assessment of H-reflex such as radiculopathies, upper motor neuron diseases, compressive neuropathies, especially Carpal Tunnel Syndrome (CTS), and peripheral neuropathies. Besides, patients with limited range of motion in upper limb and muscular weakness did not enter the study. Recruited participants were screened to ensure that they have not used medications, which increase serum serotonin level within the last one-month before the study. We excluded individuals if they could not tolerate the procedure of H-reflex measurement.

RANDOMIZATION AND BLINDING

The investigators who performed EMG studies were blinded to the study question and to patient's medical history. The clinical assessors were unaware of the results of the previous hospital visits. We used a block design to randomize the patients to observers. There was no need to blind the subjects because the H-reflex is an objective measure and the subjects could not interfere with the results.

PROTOCOLS AND PROCEDURES

In the beginning of the session a general practitioner asked for medical history including baseline demographic characteristics, features and duration of pain, sleep disturbances, fatigue, absence from work, symptoms of co-morbidities, and alternative diagnoses. The physical and rehabilitation medicine specialist performed physical examination according to the classic ACR criteria. The tender points were examined over the occipital, low cervical, trapezius, supraspinatus, second rib, lateral epicondyle, gluteus, greater trochanter and at the medial fat pad of the knee; bilaterally. The Physician considered each point as positive if patient reported the point as painful by applying less than 4kg pressure with a pressure algometer device.

We elicited H-reflex in a quiet environment with convenient temperature and after 5 minutes of rest. We instructed the participants to lie in a semi-reclined position with the head and arms supported on a firm surface to reduce variability of the H-reflex and to provide comfort throughout the testing. A Medelec EMG device with the following settings was used to stimulate the median nerve: stimulation duration (1 milliseconds), frequency (0.1 Hz), sweep speed (5 ms/division), sensitivity (500 microvolts/division), and filter setting (2 Hz to 10 KHz). Stimuli were applied 10 seconds apart to reduce the effects of post-activation depression. E1 recording electrode was put over the belly of thenar muscle area and the E2 on 1st metacarpo-phalangeal joint area.

We stimulated the median nerve above the wrist, 10 cm proximal to the site of recording. We also put a ground electrode just proximal to E1 recording electrode. In order to measure the H-wave, first we set the stimulation intensity to zero and then gradually increased the intensity until we found the lowest stimulation intensity with highest H-wave amplitude. We repeated H-wave measurement with this intensity several times to be sure of reproducibility and steady onset latency. H-wave was defined as triphasic wave with onset roughly between 20 and 30 milliseconds which comes after an initial compound muscle action potential and its amplitude becomes maximum at a submaximal stimulation intensity. The amplitude shortens with increasing the intensity.

We decided that H-reflex is not obtainable in a particular subject if after 3 trials and gradually increasing the intensity to supramaximal intensity performed on both hands, no H-reflex could be observed. In order to avoid tester bias all measurements achieved and recorded by digital device.

ETHICAL CONSIDERATIONS

Ethics approval was obtained from common institutional review boards of the two centres and the study protocol was carried out in accordance with the Declaration of Helsinki. The rationale of the study was explained to all participants. Patients were informed that they were free to withdraw from the study at any time. A trained study nurse accompanied patients and provided verbal information, if needed, and a leaflet on the diagnostic procedures to eligible participants. Patients gave written informed consent at the screening visit and did not pay for the diagnostic procedures. They were referred to other departments for appropriate treatment if needed.

STATISTICAL ANALYSIS

The collected data were analyzed using SPSS-20 software**.** We used Kolmogorov-Smirnov test to evaluate the normality of variable distribution. Then we used Chi Square test to compare the frequency of obtainable H-reflex in FM and control group. Distribution of amplitude, threshold and minimum latency were not normal so we used Mann-Whitney test to compare these variables between groups. Finally we drew a 2 by 2 table showing the frequency of obtainable and unobtainable H-reflexes in FM and control groups to calculate the diagnostic accuracy measures.

RESULTS

DESCRIBING THE SAMPLE

The sample was composed of 30 sex and age matched pairs. Nineteen (63%) of these pairs were female. Mean age was 40 ± 11.2 and 40 ± 11.3 years for the FM and control groups, respectively, with no statistically significant difference (P = 0.95). The upper limb length was 62 ± 6.5 cm in FM group and 62 ± 6.3 cm in control group, which did not differ significantly (P = 0.86).

H-REFLEX MEASURES

The chance of eliciting an H-reflex was significantly higher in FM group (P=0.005). Table I shows the frequency of success in eliciting the H-reflex in FM and

TABLE I. FREQUENCIES (%) OF OBTAINABLE H-REFLEX FOR FM AND CONTROL GROUPS

	FM	Control	Total
H-reflex positive	14 (23)	4 (7)	18 (30)
H-reflex negative	16 (27)	26 (43)	42 (70)
Total	30 (50)	30 (50)	60 (100)

TABLE II. PARAMETERS OF ELICITED H-REFLEX FOR FM AND CONTROL GROUPS

	Study group (mean ± SD)		
	FM	Control	P-value*
Minimum stimulation intensity (mA)	15.1±3.9	19.6±3.6	0.04
Amplitude (mV)	9.7±1.2	8.7±1.1	0.79
Onset latency (ms)	24.2±1.4	28.6±4.4	0.01

*The level of significance is 0.05

TABLE III. STATISTICAL MEASURES OF VALIDITY FOR H-REFLEX TEST IN FIBROMYALGIA

Sensitivity	46.7%
Specificity	86.7%
Diagnostic accuracy	66.7%
Positive predictive value	77.8%
Negative predictive value	61.9%
Positive likelihood ratio	3.5
Negative likelihood ratio	0.62

control groups. Minimum stimulation intensity for eliciting H-reflex was 15.1 ± 3.9 millivolts in FM group, which was lower than 19.6 ± 3.6 millivolts in control group (P=0.04). Minimum onset latency was also lower in FM group (24.2 ± 1.4 ms) compared with 28.6 ± 4.4 ms in control group (P=0.01). There was no statistically significant difference between the H-reflex amplitudes of the two groups (P=0.79). Table II summarizes the H-reflex parameters in the study population.

DIAGNOSTIC ACCURACY MEASURES

Using the values of Table I, we calculated important statistical measures of validity for thenar muscle H-reflex in patients with FM. The proportion of individuals with elicited H-reflex out of all individuals with FM (sensitivity) was 46.7% while the proportion of individuals without elicited H-reflex out of all normal subjects (specificity) was 86.7%. The likelihood that a person with positive thenar H-reflex actually has FM (positive predictive value) is 77.8% and the likelihood that a person who has negative thenar H-reflex actually has not FM (negative predictive value) is 61.9%. To investigate how much more likely it is that a person has FM after the H-reflex test is done (post-test probability), we calculated positive and negative likelihood ratios which were 3.5 and 0.62, respectively. For easier understanding and comparison, we have summarized the measures of validity in Table III.

DISCUSSION

H-REFLEX PARAMETERS

The results of our study showed that the chance of obtaining H-reflex from thenar muscles is significantly higher in patients with FM compared to normal subjects. This confirms the theory of increased central sensitivity in FM. H-reflex displays the late response of A fibers (large myelinated nerve fibers) and since in patients with FM central hypersensitivity may occurs in all kinds of nerve fibers including A fibers, higher rate of H-reflex in FM could be justifiable and interpreted.

Minimum stimulation intensity and onset latency of H-reflex were lower in patients with FM. Lower stimulation intensity also is consistent with central sensitivity theory suggesting lower threshold of intraspinal synapses due to increased excitatory or decreased inhibitory factors. Smaller onset latency in patients with FM suggests that this condition possibly affects fast fiber terminals more than the slow fiber terminals, so the overall latency will be reduced. This finding could help us for better understanding the nature of this multifactorial condition.

The unexpected finding of our study was similar amplitude of H waves in FM and control subjects. Changes in H-reflex amplitude after applying a conditioning stimulus have been used to evaluate post-synaptic events or to assess changes in the amount of the presynaptic inhibition acting on Ia afferent terminals. It has been suggested that the amplitude of the test reflex depends on the motor neuron excitability and the existing pre-synaptic inhibition of Ia fibers[18]. Our finding suggests that factors other than motor neuron pool excitability may contribute to form the H wave amplitude. Another explanation lies in the H wave amplitude itself as it is the most variable parameter of H-reflex. It is possible that equal H wave amplitude in FM and normal subjects is due to technical issues. For example, if we increased the number of attempts to detect a typical H wave, we could record the waves with higher amplitudes in FM group.

DIAGNOSTIC ACCURACY MEASURES

Several studies have been performed in order to evaluate electromyography and nerve conduction study (EMG & NCS) parameters in FM. Some of them failed to show any differences, while others found dissimilarities in EMG & NCS parameters[10-14]. Among the various measures, surface and needle EMG are the most widely investigated parameters. These studies are very heterogeneous regarding the target investigated muscles and the target EMG & NCS parameters. This can partially explain why the results are not consistent.

Our results show that thenar muscle H-reflex has a low sensitivity (46.7%) and a relatively high specificity (86.7%). This means that the probability of obtaining an H-reflex in patients with FM is not very high, so it is not a useful test for screening. On the other hand, the probability that H-reflex cannot be obtained in persons without FM is high, so the false positive results are low for this test.

The results also show that obtaining H-reflex from thenar muscles has 77.8% positive predictive value and 61.9% negative predictive value. Both positive and negative predictive values for thenar H-reflex are within intermediate range. This shows that this test cannot be used as a single tool for detecting FM, but it might be helpful as an adjunct to increase the accuracy of other tools.

Eventually, to see if obtaining H-reflex can be used by clinicians to revise their pre-test estimates of the disease (post-test probabilities), we calculated the likelihood ratios. Regarding to the estimated 3.5 for positive likelihood ratio and 0.62 for negative likelihood ratio, we can say that ability to obtain thenar H--reflex may help to improve our confidence that a patient actually has FM, but negative thenar H-reflex does not have any important information and it will not increase our confidence that the patient has not FM. The likelihood ratios have advantage over sensitivity, specificity and predictive values because they are independent of disease prevalence and, therefore, can be applied across settings and patients.

STUDY LIMITATIONS

As a preliminary investigation, our results suggested that H-reflex could be useful to help diagnosis of FM. Meanwhile, the procedure has an inherent limitation. The procedure for obtaining H-reflex has not been fully standardized and clinicians may use slightly different techniques for this purpose. As a result inter-rater bias could be high if no standard procedure is used. Some studies have described the appropriate methods to elicit the H-reflex and examined the reliability of this measurement in different muscles. However, when using the H-reflex as a measurement tool, it is necessary to describe certain details regarding how the reflex has been elicited and the responses recorded, so that conclusions can be drawn with more confidence

CONCLUSION

Our results are partly confirming the central sensitivity theory for FM. Higher rate of thenar muscle H-reflex in FM can be interpreted as a confirmatory finding to central sensitization theory for this disorder. Obtaining H-reflex from thenar muscles area could be a helpful diagnostic tool for FM that increases the confidence in diagnosis. Although it is a weak tool for screening because of low sensitivity, it has a relatively high specificity. It also may be that H-reflex be used for monitoring of treatments too. These hypotheses require testing in future research.

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