

SENSITIVITY OF COMPUTER ESTHESIOOMETRY ON DISTAL PARTS OF THE UPPER EXTREMITIES AT PATIENTS WITH HEREDITARY NEUROPATHY CHARCOT-MARIE-TOOTH

The purpose: to define the diagnostic importance of computer esthesiometry for use in diagnostics of hereditary neuropathy with primary defect of myelin sheath of peripheral nerves of the upper extremities. Materials and methods: 47 individuals in a condition of relative health (control group) from 21 to 50 years, comparable group - 40 patients from 6 to 81 years, with hereditary neuropathy Charcot-Marie-Tooth (CMT). Vibrating sensitivity was investigated by means of computer vibrometer "Vibrotester MBN" VT-02-1 (MBN, RF) in a wide strip of frequencies of vibration (8, 16, 32, 64, 125, 250, 500 Hz). Statistical data processing of research was lead by means of programs STATISTICA v. 7.0 (StatSoft, USA). Results and discussion: We compared received corridors vibrating sensitivity on the upper extremities for healthy volunteers with those at patients with CMT. Statistically significant increase of vibration sensitivity thresholds in a wide range of vibration frequencies on upper extremities and at patients with CMT versus healthy volunteers is shown. Computer esthesiometry method demonstrates high sensitivity in diagnostics of hereditary neuropathy with primary damage of myelin sheath of peripheral nerves of upper extremities on an example of CMT.

Keywords: Vibration perception, computer esthesiometry, hereditary neuropathy Charcot-Marie-Tooth (CMT).

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Introduction

Polyneuropathy is one of the most urgent problems of the modern neurology, occupying special place among other diseases of nervous system. A sign of peripheral (distal) polyneuropathy in group of myelinopathy and mixed forms (axon-myelinopathy) is infringement of vibrating sensitivity due to damage of thick myelinated fibers of type A (beta). Definition of vibrating sensitivity is an important component of early diagnostics of one of the most common forms of hereditary neuropathy - Charcot-Marie-Tooth neuropathy (1:3000 cases in the population), that allows to begin in due time treatment and preventive measures to reduce disability in young, employable population (Benstead and Grant, 2001; Shnayder, Kozulina, Glushenko, and Kantimirova, 2010). In the presence of CMT the peripheral nerves of the lower and upper extremities are involved in the pathological process.

Now clinical physicians (neurologists, neurogenetics doctors, pediatricians) use the graduated and not graduated tuning forks with vibration frequency 128 Hz for diagnostics of vibration sensitivity decrease caused by CMT or other neuropathies. However, the tuning research method might be inaccurate for diagnostics of hereditary neuropathies. Physicians use devices of computer esthesiometry in diagnostics of diabetic polyneuropathy: e.g. physicians in the U.S. use Biothesiometer (Biomedical Instruments, Newbury, OH); in UK - Neurothesiometer (Horwell, London). But the above-stated devices have an inconvenient design (the device should be held in a hand that is inconvenient both for the doctor, and for the patient). Distinction in the device of devices and parameters, and also in the price policy is observed. Besides, data on wide use of these

devices in the Russian Federation in the accessible literature poor (Kirichkova, Ustinovich, Shnayder, Petrova, Kurumchina, 2008; Shnayder, Kirichkova, and Kozulina, 2008; Shnayder, Gluschenko, Dmitrenko, and Kozulina, 2010), and their application is usually adapted only for needs of a neuroendocrinology (diabetology) (Kirichkova et al., 2008).

The economically accessible equipment of out-patient-polyclinic link of public health services in treatment-and-prophylactic establishments of the RF is the domestic device "Vibrotester - MBN BT-02-1"; it provides measuring of vibration sensitivity on distal parts of the upper extremities (distal phalanges). In view of the fact that the CMT violation of vibration sensitivity is due to the defeat of thick myelin fibers type A (beta), but not axon terminals located in the terminal phalanges, the ideal point of the study of vibration sensitivity of distal parts of upper extremity is the styloid process of radial bone. Consequently, the existing regulatory corridors of vibration sensitivity of the distal phalanges are not comparable with those of vibration sensitivity of the radial styloid process in patients with CMT. This prompted us to develop regulatory corridors of vibration sensation to the styloid process of elbow bone (distal parts of the upper extremities) for the national diagnostic equipment "Vibrotester - MBN BT-02-1" (MBN, RF).

Several genetically heterogeneous but clinically similar forms of CMT are spread nowadays; but the pathogenesis of most of them causes genetic damage of the myelin sheath of peripheral nerves (myelinopathy), including the thick myelin fibers of type A (beta) such as vibration sensitivity. Violation (decrease) in vibration sensitivity can be detected at early stages of pathological process, far outpacing the development of secondary muscle damage (amyotrophic syndrome), paresis, and contractures distal parts of extremities, which is important when examining clinically asymptomatic carriers of the mutant gene, including family members probands (patients with CMT) to develop a personalized plan for preventive and rehabilitative measures (Auer-Grumbach, Wagner, Strasser-Fuchs et al., 2000; Benstead and Grant, 2001; Shnayder et al., 2008, 2010).

Due to the fact that the method of computer esthesiometry by diagnostic equipment "Vibrotester - MBN BT-02-1", using a wide band of vibration (from 8 to 500 Hz), has a higher sensitivity compared to tuning forks method in the lower extremities with CMT, we have put forward a scientific hypothesis about the potentially high sensitivity and diagnostic value of this method of functional diagnostics in the upper limbs at CMT.

Materials and methods

Research was made during 2007-2010 years in Neurophysiology Laboratory of Department of Medical Genetics and Clinical Neurophysiology performing in Krasnoyarsk State Medical University named after Prof. V.F. Vojno-Jasenetsky (Krasnoyarsk). Molecular-genetic testing of gene mutations was made in Laboratory of Medical Genetics of Scientific Research Institute of Therapy (Novosibirsk).

Careful selection and survey by neurologist and therapist were made before analysis to exclude current neurologic and somatic pathology which could be other reason of development of polyneuropathies of upper extremities with decrease in indicators of vibration sensitivity. Selection of the surveyed was carried out by a method of the stratified randomization with criteria of inclusion and an exception, developed according to the purpose and problems of the present research.

Criteria of inclusion in control group: men and women, age from 21 till 50 years old, inhabitants of Krasnoyarsk and Krasnoyarsk Region, condition of relative health. Criteria of an exception: inhabitants of other regions RF, the patients, not wishing to carry out the research or procedure report.

Criteria of inclusion in comparable group: men and women, age from 18 till 57 years old, inhabitants of Krasnoyarsk and Krasnoyarsk region, suffer from CMT. Criteria of an exception: inhabitants of other RF regions, the patients, not wishing to carry out the research or procedure report, suffer from hereditary or another genesis of polyneuropathies (paraneoplastic, dysmetabolic, inflammatory and others), alcoholism

(including the daily use more than 30 ml of alcohol within last 3 months), drug dependence, professional intoxications.

During working out of a way of research, we typed control group (47 persons) - healthy volunteers of young age from 21 till 50 years old, mean age - 26.96 ± 6.32 [95% CI: 22-29] years old, including: men - 46.7%, age - from 21 to 33 years old, mean age - 25.57 ± 5.07 [95% CI: 21-33] years old; women - 53.3%, age - from 21 till 50 years old, mean age - 28.18 ± 7.17 [95% CI: 25-29] years old.

Investigated (comparable) group made 40 patients with the developed CMT clinical pattern. The investigated group included the patients being on hospitalization in neurological department and patients being on the dispensary account on CMT in advisory polyclinic of Clinical Hospital No.51 FMBA (Zheleznogorsk city, RF), the patients passing hospitalization in neurologic department of Urban Hospital No.5 (Krasnoyarsk city, RF), and also the patients actively revealed by us in the Neurologic Centre of Epileptology, Neurogenetic and Brain Researches of University Clinic. The age of patients varied from 6 till 81 years old, median age - 30.5 [25:47] years, including the men - 22 years, median age - 25.5 [19:41] years, the women - 18 years, median age - 30.0 [26:51] years. Before research of vibration sensitivity on distal parts of upper extremities (styloid process of elbow bone) by computer esthesiometry method we defined decrease of vibration sensitivity by a tuning research method (C 128 Hz).

Vibration sensitivity examination was performed in control and comparable groups on distal parts of the upper extremities consistently to the right and left (fig. 1). During carrying out esthesiometry investigated were sitting on a chair, facing the medical couch with his eyes closed. Certain conditions were met: an ambient temperature from +20 till +22°C, exception (minimization) external exciters (noise, loud sounds, bright light). For gauge fastening of vibration sensor our original support (the patent RF No. 83906 from 27.06.09) was used.

Automatic submode stimulation of "Vibrotester - MBN BT-02-1" was used, including frequencies - 8, 16, 32, 64, 125, 250 and 500 Hz. Research was began with an ascending number, in the absence of the patient's answer. The feedback with the surveyed was carried out by pressing the registration button at the first appearance of subjective vibration sense in an investigated part of a body on each of offered frequencies. When the sense appears the surveyed pressed the button and kept it in such condition till the moment of disappearance of vibration sense. The received indicators were entered in the research report of vibration sensitivity (computer esthesiometry) on the research termination. Computer vibration record represented graphic display of the data about sensitivity level surveyed on various vibration frequencies on upper extremities.

Processing of the received results was done with an applied package, the statistical programs STATISTICA v. 7.0 (StatSoft, USA). Statistical data processing was performed with use of the standard parametrical and nonparametric methods of comparison. Data for variation numbers with nonparametric distribution are described in the form of a median (Me) and percentiles [P₂₅:P₇₅]. The parametrical data represented in the form of mean values with standard deviations (SD) and 95% of the confidence interval (CI). Distinctions statistically significant at $p \leq 0.05$.

Results of research

During the research we have defined the reference intervals for healthy volunteers in the study of vibrator sensitivity in distal parts of upper extremities, which were comparable to the results of computer esthesiometry in patients with CMT. Borders of vibration sensitivity at healthy volunteers were much lower ($p < 0.01$) than at patients with CMT on all vibration frequencies of "Vibrotester - MBN BT-02-1" (8, 16, 32, 64, 128, 250, 500 Hz) on 3σ and more ($1\sigma = 10\%$) (Table 1, Figure 2).

Clinically significant violations of the vibration sensitivity of distal parts of upper extremities (styloid process of radial bone) were identified by computer esthesiometry in all patients with CMT (100%) on the expanded disease stage, in 66% of cases on the initial stage of the disease, while the using classical method tuning forks method (frequency 128 Hz) of vibration sensitivity violation have been identified and deployed the initial stages of the disease in 80% and 60% accordingly (Table 2). It should also be noted that only by using a computer pallesthesiometry identified expressed disturbances vibration sensitivity as on initial (53%) and on developed (15%) stages of the disease (Table 2).

Discussion

The vibration sensitivity level decrease on distal parts of upper extremities correlated with developed clinical semiology of CMT ($p < 0.05$): presence and expressiveness of sensitive ataxia, frustration of painful and tactile sensitivities. At the same time, decrease of vibration sensitivity was revealed in the course of carrying out computer esthesiometry comparison with frustration of other kinds of deep (proprioceptive) and superficial (painful, tactile, temperature) sensitivities. Firstly, this could be explained with etiopathogenesis of CMT conditioning genetically determined myelin sheath damage of peripheral nerves. Thus, vibration sensitivity suffers the first, and damage of other kinds of sensitivity joins at later stages of pathological process development when damage of vibration sensitivity becomes considerable. Secondly, the research found diagnostic possibilities of computer esthesiometry method using “Vibrotestere - MBN BT-02-1” in examination of patients with CMT at early stages of disease development, including periods of planning preventive rehabilitation actions and carrying out diagnostic screening of disease among members of a proband’s family. People who are clinically symptomless or asymptomatic carriers of a mutant gene can be endured to such screening also.

Taking into account, difficult access to DNA typing in various forms of CMT for most people living in remote regions of the Russian Federation, the computing esthesiometry method could be the method of choice for screening diagnostic of families burdened by CMT, and will appoint a timely methods of drug and non-pharmacological treatment in the early stages of the disease, to slow the progression of the pathological process and the degree of disability of patients of working age.

Conclusion

The computer esthesiometry method using the diagnostic equipment “Vibrotestere - MBN BT-02-1” (RF) has high sensitivity in diagnostics of myelin sheath damage in patients with CMT. It reflects first of all degree damage of the thick myelin fibers of type A (beta) caused by pathology of myelin fibers.

The computer esthesiometry method could be widely used in clinical practice for diagnostics of hereditary neuropathies with genetically determined pathology of myelin sheath (myelinopathy), including CMT, hereditary neuropathy with liability to pressure palsies, Dejerine-Sottas disease.

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Appendix

FIGURE 1. COMPUTER ESTHESIOMETRY METHOD FROM THE STYLOID PROCESS OF ELBOW BONE AT PATIENT WITH CMT ("VIBROTETER - MBN BT-02-1")



TABLE 1. BORDERS OF VIBRATION SENSITIVITY AT HEALTHY INDIVIDUALS (CONTROL GROUP) AND PATIENTS WITH CMT (COMPARABLE GROUP) ON DISTAL PARTS OF THE UPPER EXTREMITIES FOR "VIBROTETER - MBN" BT-02-1 (MBN, MOSCOW)

Vibration frequency (Hz)	N ₁ =47		N ₂ =40		Mann Whitney test
	Me	[P ₂₅ : P ₇₅]	Me	[P ₂₅ : P ₇₅]	
8	-1	-4: 7	5	-3: 14,5	<i>p</i> <0,01
16	0	-7: 6	6	-2: 17	<i>p</i> <0,01
32	0	-4: 8	5,5	-2: 21	<i>p</i> <0,01
64	5	-4: 12	14	-1: 22	<i>p</i> <0,01
128	1	-3: 7	10,5	1: 21	<i>p</i> <0,01
250	6	-9: 12	14,5	3: 24	<i>p</i> <0,01
500	9	4: 18	16	3: 24	<i>p</i> <0,05

Notes: Me - median value of a threshold of vibration sensitivity on each frequency of vibration of gauge Vibroteter-MBN in Db, [P₂₅: P₇₅] - 25 and 75 percentile from median value (Db). N₁ - control group; N₂ - comparable group

FIGURE 2. THE REFERENT INTERVALS OF VIBRATION SENSITIVITY IN DISTAL PARTS OF UPPER EXTREMITIES AT HEALTHY INDIVIDUALS AND PATIENTS WITH CMT FOR "VIBROTESTER - MBN BT-02-1" (MBN, RF): RED SOLID LINE - THE VIBRATION SENSITIVITY IN PATIENTS WITH CMT (COMPARABLE GROUP); BLUE DOTTED LINE - THE VIBRATION SENSITIVITY IN HEALTHY VOLUNTEERS (CONTROL GROUP)

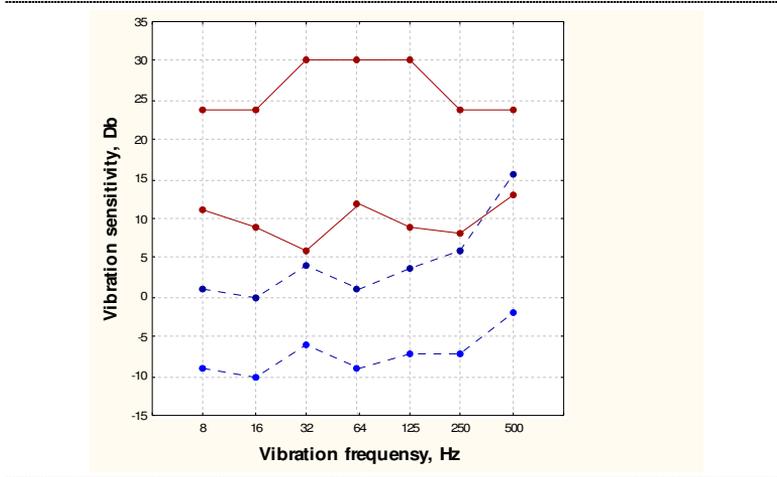


Table 2. COMPARATIVE EVALUATION OF THE DEGREE OF VIOLATION OF VIBRATION SENSITIVITY IN THE UPPER EXTREMITIES IN PATIENTS WITH CMT IN THE INITIAL AND DEVELOPED STAGES OF THE DISEASE WITH METHOD OF COMPUTER PALLESTHESIOMETRIA AND CLASSIC TUNING RESEARCH METHOD

Vibration sensitivity decrease level	CMT stages			
	Initial stage (n ₁ = 15)		Developed stage (n ₂ = 15)	
	Tuning research method (number of cases; %)	Computer pallesthesiometria (number of cases; %)	Tuning research method (number of cases; %)	Computer pallesthesiometria (number of cases; %)
Norm	6 (40%)	5(34%)	3 (20%)	--
Mild	9 (60%)	2 (13%)	12(80%)	--
Moderate	--	--	--	--
Expressed	--	2 (13%)	--	6 (40%)
Loss of sensitivity	--	6 (40%)	--	9 (60%)