METHOD OF COMPUTER ESTHESIOMETRY ON DISTAL PARTS OF THE LOWER EXTREMITIES IN DIAGNOSTICS OF CHARCOT-MARIE-TOOTH DISEASE

The paper discusses using a computer esthesiometry method in diagnostics of hereditary neuropathy with primary damage of myelin sheath of peripheral nerves in lower extremities. Vibration sensitivity in lower extremities was examined using computer diagnostic equipment “Vibrotester - MBN” in a wide range of vibration frequencies (8, 16, 32, 63, 125, 250, 500 Hz). Statistical data processing of research was performed with the program Statistica v.7.0 (StatSoft, USA). The reference corridors of vibration sensitivity in lower extremities for persons of young and middle age are compared with those at patients with Charcot-Marie-Tooth disease (CMT). Statistically significant increase of vibration sensitivity thresholds in a wide range of vibration frequencies and in comparison with healthy volunteers is shown. Computer esthesiometry method demonstrates high sensitivity in diagnostics of hereditary neuropathy with primary damage of myelin sheath of peripheral nerves.

NATALIA SHNAYDER, ELENA GLUSHCHENKO, DIANA DMITRENKO, EKATERINA KOZULINA, ELENA KANTIMIROVA, OLGA DARSAYLIDZE, ILYA KISELEV, MARINA PILUGINA

Krasnoyarsk State Medical University, Krasnoyarsk, Russian Federation

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Introduction

Hereditary peripheral neuropathies were described in 1886 by Tooth in the United Kingdom and by Charcot and Marie in France; hence, the disorders are known as Charcot-Marie-Tooth disease (CMT). Now CMT may be the most common hereditary neurological disease (1:10 000 cases in population). This disease is caused by mutations that cause defects in neuronal proteins.

CMT has some little genetically-heterogeneous but clinically similar forms. But there is the same genetically caused myelin sheath damage of peripheral nerves (myelinopathy) in pathogenesis in majority of them. It includes thick myelinic fibers type А (beta), which provide vibration sensitivity. Damage (decrease) in vibration sensitivity can be registered at early stages of pathologic process development, much earlier than a development of again-muscular defeat (an amyotrophic syndrome), paresises and contractures of distal parts of lower extremities. That is important in inspection of clinically oligosymptomatic carriers of a mutant gene, including members of a proband’s family (patients with CMT) for working out of the personified plan of preventive and rehabilitation actions (Glushenko et al, 2009; Glushenko, 2009; Shnayer et al., 2008; Shnayder et al., 2009c).

A sign of peripheral (distal) polyneuropathy groups of myelinic pathologic and mixed forms (axon-myelinopathy) mainly is damage of vibration sensitivity due to damage of thick myelinic fibers type А (beta). Determining of vibration sensitivity is the important component of early diagnostics of CMT. That allows to begin in due time treatment-and-prophylactic establishments and to lower incapacitating injuries of young, able-bodied population (Kantimirova et al., 2008; Shnayer et al., 2009a).
Now clinical physicians (neurologists, neurogeneticians, 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 hereditary neuropathies. However, the tuning research method might be inaccurate for diagnostics of hereditary neuropathies. Physicians use devices of computer pallesthesiometry in diagnostics of peripheral polyneuropathies: e.g. physicians in the U.S. use Biothesiometer (Biomedical Instruments, Newbury, OH); in UK - Neurothesiometer (Horwell, London), in RF - Vibrotester - MBN BT-02-1 (MBN, Moscow). Economically accessible equipment for measurement of vibration sensitivity on distal parts of the upper extremities at vibration disease in outpatient-polyclinics in the RF is the domestic device Vibrotester - MBN BT-02-1 which we adapted in 2009 (the patent No83906 from 27.06.2009).

We developed standard reference corridors of vibration sensitivity for lower extremities in young and middle age persons (rationalization proposal No2489 from 18.01.2010). However, the diagnostic importance of this method of vibration sensitivity examination on distal parts of lower extremities was shown and introduced in clinical practice only for diabetic polyneuropathy (rationalization proposal No2466 from 26.02.2009). The diagnostic importance of this method for hereditary neuropathies was not studied earlier, and this diagnostic equipment was not applied in neurogenetics.

The research aimed to define the diagnostic importance of a computer pallesthesiometry method for using in diagnostics of hereditary neuropathy with primary damage of myelin layer peripheral nerves in lower extremities.

**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. 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 polyneuropathies of lower 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 19 till 65 years old, inhabitants of Krasnoyarsk and Krasnoyarsk Region, a condition of relative health. Criteria of an exception: inhabitants of other regions RF, the patients, doing not wish to carry out the research or procedure report. Criteria of inclusion in comparable group: men and women, age from 19 till 65 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 (dysmetabolic, inflammatory, etc.), alcoholism (including the daily use more than 30 ml of alcohol within last 3 months), a drug dependence, professional intoxications.

Control group (82 persons) was divided into 2 subgroups of supervision. Group 1 - 47 (57%) persons: healthy volunteers of young age from 19 till 31 years old, mean age - 21.55±3.07 [95 % CI: 19-23] years old. This group included: men - 62% (29), age - from 19 to 31 years old, mean age - 22.41±3.46 [95% CI: 19-24] years; women - 38% (18), age - from 19 till 24 years old, mean age - 20.17±1.58 [95% CI: 19-20] years. Group 2 - 35 (43%) persons: healthy volunteers of an average and advanced age - from 40 till 65 years old, mean age - 47.2±6.85 [95% CI: 41-49] years old. This group involved: men - 43% (15), age - from 40 till 60 years old, mean age - 46.2±5.41 [95% CI: 41-48] years; women - 57% (20), age - from 40 till 64 years old, mean age - 47.95±7.81 [95% CI: 41.5-54.5] years;
The examined (comparable) group made 31 patients of young and middle age with the developed CMT clinical pattern. The group included the patients who were on hospitalization in neurological department and patients registered on the dispensary account on CMT in advisory polyclinic of Clinical Hospital No51 FMBA (Zheleznogorsk, RF), the patients passing hospitalization in neurologic department of Urban Hospital No5 (Krasnoyarsk, RF), and also the patients found in the Neurologic Centre of Epileptology, Neurogenetic and Brain Researches of University Clinic. The age of patients varied from 19 till 64 years old, mean age - 39.5±15.9 [95% CI: 20-64] years old. Of them 21 (68%) were men with mean age 36.4±16.49 [95% CI: 20-64] years old; 10 (32%) - women with mean age 47.5±13.22 [95% CI: 28-57] years old. Decrease of vibration sensitivity by 128 Hz was defined through tuning research method, before using the computer pallesthesiometry method (Vibrotester MBN ВТ-02-1, RF)

Vibration sensitivity examination was performed in control and comparable groups on distal parts of the lower extremities. During carrying out pallesthesiometry investigated were in a prone position on a medical couch, blindly. Certain conditions were met: an ambient temperature from +20 till +22ºС, an exception (minimization) external exciter (noise, loud sounds, bright light). For gauge fastening of vibration sensor our original support (the patent RF No83906 from 27.06.09) was used.

Automatic submode of the stimulations was used, including frequencies - 8, 16, 32, 63, 125, 250 and 500 Hz. Research was begun 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 appeared, 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 pallesthesiometry) on the research termination. Computer vibration record represented graphic display of the data about sensitivity level surveyed on various vibration frequencies on lower extremities. Processing of the received results was done with an applied package, the statistical programs Statistica 7.0 (StatSoft, USA). Statistical data processing was performed with use of the standard parametrical and nonparametric methods of comparison. The parametrical data were represented in the form of mean values with standard deviations and 95% of the confidence interval (CI). Distinctions were statistically significant at $p \leq 0.05$.

**Results of research**

We defined the referent intervals for healthy volunteers of young and middle age in examination of vibration sensitivity in distal parts of lower extremities. They were comparable to results of computer pallesthesiometry at suffer from CMT. Borders of vibration sensitivity in healthy volunteers were much lower ($p <0.01$) than in patients with CMT on all vibration frequencies of Vibrotester MBN (8, 16, 32, 64, 128, 250, 500 Hz) on 3 σ and more ($1 \sigma = 10\%$) (Table 1).

Vibration sensitivity decrease was revealed by means of computer pallesthesiometry in all patients with CMT (100% of all cases) both on developed and on initial disease stages. While the use of classical tuning research method (frequency 128 Hz only) found the vibration sensitivity decrease in 74% of cases on initial stage, in 94% of cases - on developed stage (Table 2).

Computer pallesthesiometry revealed the expressed decrease of vibration sensitivity 3 times more often than at use of classical tuning research method: 39% vs. 13% on initial stage, and 55% vs. 18% - on developed stages of disease (Table 2).
**Table 1. Borders of Vibration Sensitivity at Healthy Individuals (Control Group) and at Patients with CMT (Comparable Group) on Distal Parts of the Lower Extremities for Vibrotester-MBN (RF)**

<table>
<thead>
<tr>
<th>Vibration frequency (Hz)</th>
<th>Mean value of vibration sensitivity in a wide strip of vibration (Db)</th>
<th>N1 M ± m</th>
<th>N2 M ± m</th>
<th>N3 M ± m</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>-3.98 ± 7.92</td>
<td>1.96 ± 12.33</td>
<td>16.12 ± 7.84</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>-5.4 ± 7.57</td>
<td>-0.39 ± 11.22</td>
<td>15.56 ± 8.13</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>-1.71 ± 8.56</td>
<td>2.04 ± 11.99</td>
<td>17.5 ± 11.48</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>128</td>
<td>-4.28 ± 7.98</td>
<td>1.74 ± 10.89</td>
<td>17.93 ± 10.85</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>250</td>
<td>-1.59 ± 9.92</td>
<td>1.57 ± 12.11</td>
<td>17.59 ± 10.76</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>5.53 ± 13.28</td>
<td>6.94 ± 15.6</td>
<td>18.84 ± 7.97</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

Note: M - mean value of a threshold of vibration sensitivity on each frequency of vibration of gauge Vibrotester-MBN in Db; m - a standard deviation from mean value (Db); N1 - control group 1; N2 - control group 2; N3 - comparable group; P1 - statistical importance of distinctions of vibration sensitivity at individuals of control group 1 and patients of investigated group; P2 - statistical importance of distinctions of vibration sensitivity at individuals of control group 2 and patients of investigated group.

**Table 2. Comparative Estimation of Vibration Sensitivity Decrease Level of Lower Extremities in Patients with CMT**

<table>
<thead>
<tr>
<th>Vibration sensitivity decrease level</th>
<th>CMT stages</th>
<th>Initial stage (n1 = 15)</th>
<th>Developed stage (n2 = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tuning research method (N; %)</td>
<td>Computer pallesthesiometry (N; %)</td>
<td>Tuning research method (N; %)</td>
</tr>
<tr>
<td>Norm</td>
<td>4; 26%</td>
<td>-</td>
<td>1; 6%</td>
</tr>
<tr>
<td>Mild</td>
<td>4; 26%</td>
<td>3; 22%</td>
<td>7; 43%</td>
</tr>
<tr>
<td>Moderate</td>
<td>3; 22%</td>
<td>4; 26%</td>
<td>1; 6%</td>
</tr>
<tr>
<td>Expressed</td>
<td>2; 13%</td>
<td>6; 38%</td>
<td>3; 18%</td>
</tr>
<tr>
<td>Loss of sensitivity</td>
<td>2; 13%</td>
<td>2; 13%</td>
<td>4; 27%</td>
</tr>
</tbody>
</table>

**Discussion**

The vibration sensitivity level decrease on distal parts of lower 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 computer pallesthesiometry comparison with frustration of other types 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 revealed diagnostic possibilities of computer pallesthesiometry method done with Vibrotester MBN 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 oligosymptomatic carriers of a mutant gene can be endured to such screening also.
Conclusion

1. The computer pallesthesiometry method using the diagnostic equipment Vibrotester MBN (RF), have high sensitivity in diagnostics of myelin sheath damage in patients with CMT. It reflects first of all degree the thick myelinic fibers type А (beta) damage at the expense of genetically caused pathology of myelin fibers.

2. The computer pallesthesiometry method can 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, Déjerine-Sottas disease.

References


