LABORATORY ASSESSMENT OF DIABETIC PERIPHERAL NEUROPATHY

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Peripheral sensory neuropathy is one of the most challenging problems of diabetes mellitus. The incidence varies between 5—50%, 8% of diabetics have this at the time of diagnosis and 50% developed is with 25 years of duration. Its clinical presentation is highly variable[1] Evaluation of diabetic neuropathy is customarily performed by motor nerve conduction study. This can be very well documented but correlates very poorly with clinical findings in a diabetic*. This is owing to the fact that diabetic neuropathy is predominantly sensory. Therefore a precise sensory evaluation is of paramount importance in the diagnosis, objective quantification and monitoring the natural evoluation or effects of therapy[3].

The time honoured way of testing with tuning fork or test tubes with hot and cold water cannot accurately quantify the vibration perception threshold (VPT) or thermal discrimination threshold (TDT). Recent years have witnessed a surge of renewed interest in instrumentation for accurately quantifying the sensory perceptions.

Diabetic peripheral neuropathy can involve either small or large nerve fibre population or both, and can produce specific symptom patterns. Currently laboratory assessment of diabetic peripheral neuropathy consists of assessing the small and large fibre functions separately and specifically. Clinically predominant large myelinated fibre dysfunction causes abnormalities of two point discriminations, touch and pressure and vibration sense. The vibration perception threshold is usally assessed by (i) biothesiometer (Biomedical Instruments, Newbury, Ohio, USA) (ii) Vibrameter (Somdic AB, Stockholm, Sweden)[4].

Loss of function in thinly myelinated (A) and unmelinated (C) fibres produces disturbance of temperature and pain sensation. The laboratory assessment, of this small fibre function is carried out by estimation of the thermal discrimination threshold (TDT). This is carried out by (i) Marstock stimulator (Somedic, Stockholm, Sweden)[5] and (ii) Automated Thermal Threshold Tester[6].

The details of these instruments, the methodology, advantages and disadvantages are described below.

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1. Biothesiometer

This instrument existed for about half a century. However currently there is renewed interest in using this instrument for determining VPT following publication of an article in British Medical Journal in 1984'. This hand held biothesiometer has a rubber tractor which vibrates at 100 Hz when operating on 50 Hz mains. There is a linear scale which directly depicts the applied voltage. The operation of this instrument is very simple. The subject is seated in comfortable and relaxed position and is made to feel the vibration sense by testing over the forehead. Then the VPT is measured on the palmar aspect of the distal phalanx of the dominant index finger and the tip of the dominant big toe. The biothesiometer is held steadily over the testing site in such a way that the weight of the vibrator exerts a standard pressure. The amplitude of the vibration is gradually increased. The subject is asked to concentrate his attention on the test and to report the first appearance of the vibration sensation by saying 'Now'. The VPT is taken as the mean of three recordings.

The values can be expressed in the arbitrary scale of volts or as amplitude of vibration which is proportional to the square of the applied voltage. However the former is simple and gives adequate quantification. The accepted ranges of the normal subjects and their relationship to age and sex has been described in the literature[8]. Standards for normal subjects, their satisfactory reproducibility and relationship to age has been described by various authors[9].

2. Vibrameter

This consists of an electromagnetic vibrator with a 13mm diameter probe that vibrates at right angles to the skin at a frequency of 100 Hz. The amplitude of the skin displacement (the vibration amplitude) is measured and can be displayed on a digital displayer. The apparatus can deliver two standardised rates of increase in vibrational intensity. It may be either slow or fast. The subject is instructed to indicate when the stimulus is felt in either rate of increase or stimulus intensity. The average of three trials is taken as VPT.

Between the above two instruments, Biothesiometer is more suitable in the Indian national context. The biothesiometer is cheap easy to perform and has a greater patient compliance. In contradistinction, the vibrameter is costly, the skin temperature has to be maintained at 34±1°C with a thermostatically controlled heat source and takes at least 5 minutes for each APT determination[10].

Thermal Discrimination Threshold (TDT) Assessment

1. Marstock Stimulator: It is is an instrument for quantifying the cutaneous warm and cold threshold. Additionally cold pain and heat pain threshold also can be determined.

Kenshalo introduced this thermo electric method employing the Peltier principle[11]. The heating and cooling of a metal thermode is dependent on the direction of current flow through it. The amount of current passed gives an accurate measure of the amplitude of the stimulus. The technique was the first to apply the thermal stimulus without tactile cues. Later modifications included continuous water circulation through the element to maintain background skin temperature. Marstock stimulator, the temperature interval between the perception of thresholds for warm and cold stimuli are determined. They are defined as the most sensitive index of neural abnormality[12].

Operation: The subject sits comfortably in a chair and the thermode is held in position of the test site without pressure. The subject is given a reversing switch in the hand and is asked to press it as soon as the threnode is felt to be warm or cool. On pressing the switch the direction of current and therefore the direction of temperature change is reversed. The temperature is measured by a thermocouple and displayed on a chart recorder. To test diabetic neuropathy, the TDT is usually tested on the palmar aspect of the index finger, thenar eminence and lateral border of foot beneath the lateral melleolus. The difference between warm and cold thresholds of five readings are averaged to give the mean difference of thermal discrimination.

Similarly the cold-pain and heat-pain threshold is documented by asking the subjects to press the switch when the thermode begins to get painfully hot or painfully cold.

This sensory measurement are simple and reproducible and provide quantitative assessment of small nerve fibre function. The hand is found to be more sensitive then the foot and with advancing age there is reduction in the sensitivity. There is no difference between the dominant and nondominant sides. The TDT is always significantly abnormal in feet of diabetic subjects with neuropathic ulcerations and Charcot joints. The normal values in the best sites of measurements (Thenar eminence of the hand and lateral aspect of the foot) and their variations in diabetic peripheral neuropathy has been described in the literature[13].

2. Automated Thermal Threshold Tester (Glasgow system)

Dyck et al [14] were the first to use an automated forced-choice method for measurement of thermal thresholds. Recently Jamal et al[15] have used the Glasgow System for determination of hot threshold (HT) and cold threshold (CT) and indicated that this technique provides an accurate and reproducible index of function in small A and C groups of nerve fibres.

The methods of examination is a "psychophysical" one and it uses "forced choice technique". The instrument comprises of a thermode assembly consisting

of a thermode, a thermode interface unit with a digital thermometer and visual display unit and water bath with a thermostat. Further it has a microprocessor unit and a subject response box communicating with the computer. The microprocessor in conjuction with the computer controls the temperature of thermode and duration of stimulus. It randomly delivers this stimulus (hot or cold) over two separate time periods indicated by 2 lights (1 and 2) in the subject response box. The microprocessor, processes the return signals from the patient response box, controls the up and down transformation of the temperature and gives the computerised valve of hot threshold and cold threshold.

Das et al[16] conducted a comparative evaluation of automated thermal threshold tester and the Marstock stimulator in the assessment diabetic neuroparhy at British Diabetic Association foot centre, London.

It was evident that delineation of diabetic neuropathy from normal was achieved by either instrument. However in the Marstock stimulator the amount of stimulus applied being large this delineation was much better. Many subjects found Marstock easy to perform as the difference in temperature was clearly much more delineated. In the automated thermal tester a greater degree of concentration and patient cooperation was called for. The Marstock stimulator measures the TDT whereas the automated thermal tester measures the hot threshold. They in fact are not the same but possibly compliment each other.

Clinical applications of sensory testing in Diabetic Neuropathy

Neuropathy: The main applications are for documenting, diagnosing and quantifying the sensory deficit in diabetics. The simplicity, reproducibility and safety of this test has led to utilisation in monitoring the effect of many new drugs for the treatment of diabetic neuropathy.

The diabetic foot syndrome is usually a combination of neuropathy, peripheral is chaemia and infection and this test enables one to distinguish neuropathic foot from ischemic as a guideline for further investigations.

Comparison of TDT with VPT suggest that small fibres are more susceptible to damage than the large fibres in a diabetic neuropathic foot[13]. In contradistinction Das et al[17] have shown abnormal peripheral nerve function in the diabetic ischemic limb. There was a predominantly large fibre effect whereas the small fibre function were normal. Thus this sensory testing might throw light upon the. pathogenesis of diabetic peripheral neuropathy.

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