Hyperesthesia: An Early Manifestation of Diabetic Polyneuropathy

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Diabetic polyneuropathy is a specific form of peripheral nerve disorder, in which distal nerve axons degenerate insidiously under hyperglycemia of diabetes mellitus. Although all types of peripheral nerve fibers are involved, it is usually sensory dominant with eventual involvement of autonomic and motor nerve fibers. Its manifestation ranges from subclinical changes in nerve conduction to painful and severe motor and autonomic disabilities. Once established, it is irreversible. Early identification is, therefore, of clinical importance.

Among variety of sensory symptoms, numbness and diminution of sensation in the distal limbs appears first. Decrease in density of sensory nerve fibers due to destruction of the peripheral nerve inevitably leads to loss of sensation of the distal limbs. Hypoesthesia and anesthesia of the skin are therefore understood as 'the negative sensory phenomenon' in a Jacksonian sense, since it is a defect of normal function. On the other hand, tingling sensation, "pins and needle sensation", and painful paresthesia are something different from loss of function, since they seem to be due to over-activity of the surviving structure. Such 'positive sensory phenomenon' or manifestation of an excess of sensory activity is physiologically due to generation of ectopic impulses at various levels in sensory nerve fibers (1). Although the precise mechanism is still obscure, both chemical and morphological abnormalities may be involved. Hypersensitivity and cross-talk of the surviving and regenerating axonal membrane, sensitization of receptors, and central hyperexcitability are important candidates for the positive phenomenon.

In patients with established diabetic polyneuropathy, positive and negative symptoms often are intermingled. In fact, many physicians have been confused with such complex combination of paresthesia, dysesthesia, hypoesthesia, hyperpathia, allodynia, and even pain, to various sensory testing stimuli. How should we understand such mixed clinical picture? It is still obscure how the positive and negative symptoms develop and regress, and influence each other during the natural course of diabetes mellitus, since there are many limitations in a hospital-based approach, even if it is of large scale. Careful longitudinal community-based study using a large cohort with mild glucose impairment will be necessary. Since development of diabetic neuropathy is an extremely slow process, longitudinal follow-up study is necessary for many years and years. Furthermore, other causes of neurological symptoms and signs should be properly diagnosed and strictly ruled out during the study. It may not be an easy task. In this issue, Takemura et al (2) report an interesting cross-sectional community-based study on sensory changes in a glucose-intolerant cohort, which was carried out as a part of large longitudinal study on aging.

A tool the authors employed for the detection of sensory change was a current perception threshold (CPT) measurement. During the test, subjects report threshold perception to sinusoidal electric test current delivered to the skin with 5 Hz, 200 Hz, and 2,000 Hz, which are said to specifically stimulate C-, Aδ-, and Aβ-fibers, respectively. Although CPT measurement itself still has some physiological uncertainty in receptor selectivity, fiber selectivity, and pathological correlation, their results are quite informative. They confirmed the presence of early hyperesthesia to electric current, and have found a prevalence of hyperesthesia of about 20% in the diabetic population. It seems a bit lower than a previous hospital-based study using a similar technique (3), however, this community-based study clearly demonstrated the fact that hyperesthesia is common not only in the diabetic population but also in the non-diabetic insulin-resistant group. Takemura et al (2) actually found that hyperglycemic hyperesthesia is more frequent in 2,000 Hz and 250 Hz rather than in 5 Hz. A question is that then raised: if the CPT frequency theory is right, clinical hyperesthesia should be detected as large-fiber hyperesthesia of vibratory or pressure touch sense as well as smaller fiber hyperesthesia of pain-temperature sensation.

Hyperesthesia and hyperalgesia associated with diabetes have long attracted the attention of many careful investigators. It is well known that patients with newly diagnosed diabetes frequently show numbness and reduced nerve conduction velocity that improves rapidly with the establishment of euglycemia (4). Alteration in fast potassium current has been shown in experimental hyperglycemic hypoxia (5), which may cause instability of the resting membrane potential. Morley et al (6) revealed hyperalgesia in diabetic patients by applying simple square wave electric stimuli with duration of 0.6 ms. They even found that a 50 g glucose
infusion resulted in a significant decrease in the threshold level of pain even in normal subjects. Changes in pain threshold may be thus functionally altered by plasma glucose level (7). Hyperexcitability of C-fiber is also a convincing finding in streptozotocin-induced hyperglycemic rats (8).

On the other hand, Dyck et al (9) reported that hyperesthesia in diabetic polyneuropathy was found only for heat-pain threshold and not for vibratory sense. Since they found more neuropathic impairment and symptoms in hyperesthetic patients by using a sophisticated quantitative sensory testing system (QST), they concluded that hyperesthesia is a manifestation of hyperalgesia in diabetic patients. According to them, diabetic hyperesthesia is not an excess of touch sensory activity, but a result of changes in pain sensation. It is of great interest that they found hyperesthesia/hyperalgesia only in the mildest spectrum of diabetic neuropathy. In addition, in the mildest group hypoesthesia to vibratory sense was simultaneously demonstrated. In more severe cases all modalities of sensation were hypoesthetic.

In conclusion, early hyperesthesia in diabetes is still a confusing issue. What kind of fiber is responsible for it? Is it a kind of hyperalgesia? Isn’t it merely functional? Nevertheless, some investigators have begun to quantitatively study subclinical skin hyperesthesia and hyperalgesia in peripheral neuropathy by using quantitative thermotest (10) and QST (9). CPT measurement (11) appears to be another unique tool to detect ‘subclinical positive phenomenon’, although more pathophysiological validation of the test will be needed. Most conventional methods of sensory testing such as sensory nerve conduction studies merely reveal normality or negative phenomenon.

Masayuki Baba, MD, PhD
Department of Neurological Science, Hirosaki University School of Medicine, 5 Zaifu-cho, Hirosaki, Aomori 036-8562

References

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