Early Diabetic Neuropathy: A Diagnostic Challenge

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Diabetic peripheral neuropathy is one of the major complications in type-1 and type-2 diabetic patients. This is the most common and earliest complication which may occur much earlier in type-1 than in type-2 diabetes. Fifty percent of patients with peripheral neuropathy are asymptomatic [1].

Regarding its diagnosis, the American Academy of Neurology considered that symptoms alone have a poor diagnostic accuracy in predicting the presence of neuropathy. Signs are better predictors than symptoms, and multiple signs, even better than single signs [2,3].

The American Diabetes Association recommends all patients should be assessed for peripheral neuropathy at diagnosis of type-2 diabetes; after 5 years to be performed a diagnosis of type-1 diabetes, and as from then, on an yearly basis. This screening should include a careful history and assessment of either temperature or pinprick sensation, and vibration sensation using a 128-tuning fork; as well as annual 10-g monofilament testing. Electrophysiological testing is rarely needed [4]. However, the impairment of nerves starts early in glycemic dysregulation prior to over hyperglycemia, included in patients with "near impaired glucose tolerance" [5]: insulin resistance [6], and metabolic syndrome other than impaired glucose tolerance may represent independent risk factors for peripheral neuropathy [7].

The staging of diabetic neuropathy is crucial [8]. The diagnosis of asymptomatic or preclinical neuropathy is essential in order to stop progression to advanced or irreversible stages, and to prevent further complications. Once symptoms appear, there are few effective therapeutic strategies [9].

The Michigan Neuropathy Screening Instrument has a high sensitivity and specificity for the early diagnosis of diabetic neuropathy [10]. The Utah Early Neuropathy Scale was developed and it is able to quantify early small-fiber sensory neuropathy [11].

Standard nerve conduction studies are the methods of choice for detecting neuropathy. Special techniques, such as sural/radial ratio [12] and late responses should be included [9,13] therein. These techniques only assess large-fiber function. For the assessment of small fibers, which may be damaged in the early stage of diabetes, other methods ought to be used: the cutaneous silent period (a cutaneous spinal reflex: its afferents are A-delta fibers) [14], and the sympathetic skin responses (SSR, which assess sudomotor sympathetic function) [15] which can be evaluated with any EMG equipment. Imaging techniques, such as ultrasonography or magnetic resonance imaging have been tested with promising results [16,17].

The Quantitative Sudomotor Axon Reflex Test (QSART) has been found to evaluate early neuropathy more precisely than SSR [18]. Neuropad is an easy-to-use patch that assesses plantar sweat production through a color change from blue to pink, encouraging, thus, patients to perform self-examination and promoting education about foot care [19]. Confocal Corneal Microscopy (CMM) quantifies early

small nerve fiber damage, and may detect subclinical prediabetic nerve injury [14]. SUDOSCAN measures electrochemical skin conductance: it tests sweat gland function in a non-invasive form. This test has a potential to screen early small fiber neuropathy, and to assess response to therapeutic interventions in diabetic patients [20]. QSART, Neuropad, SUDOSCAN and CCM are not available in many centers.

Skin biopsy is currently the gold standard to quantify small fibers. However, it is invasive, expensive and requires a special histological technique to quantify intraepidermal nerve fiber density [21].

Cardiovascular Autonomic dysfunction (CAN) may occur early, during the initiation of metabolic syndrome. The prevalence is 7.7% at diagnosis of type-1 diabetes mellitus, and 5% at diagnosis of type-2 diabetes mellitus.

Patients may be asymptomatic for decades. Earlier diagnosis is needed before CAN becomes symptomatic, since it is an independent risk factor for cardiovascular mortality [22]. The Survey of Autonomic symptoms can be an aid in the early detection of CAN [23], but the combination of cardiovascular reflex tests (which are gold standard in autonomic testing) with tests of sudomotor function may allow a more accurate diagnosis of autonomic neuropathy [24].

In conclusion, the diagnosis of early or subclinical neuropathy is challenging. Efforts to detect small-fiber (both sudomotor function and cardiac autonomic tests) and large-fiber dysfunction should be made in order to allow therapeutic interventions to prevent impaired quality of life and life threatening complications of diabetic patients.

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