OBSERVATIONS

# Severity of Autonomic and Sensory Neuropathy and the Impairment of Visual- and Auditory-Evoked Potentials in Type 1 Diabetes

## Is there a relationship?

It became clear in the last decades that neuropathy is not a separate clinical entity, but a component of several related complications (1). Although the functional consequences of neuropathy are well defined in various organ systems, the relationship of the alterations in the networks of the neuronal system is still poorly documented. Assessment of the potential common alterations of the different neuronal functions in patients with diabetic neuropathy may provide new pathogenetic and diagnostic considerations. Previously, we observed correlations between the delay of certain auditory-evoked potentials and the severity of autonomic and peripheral sensory neuropathy in patients with type 1 diabetes (2). In addition, we found a relationship between the latency of visual-evoked potentials and the peripheral neuronal function (3). The aims of this study were to analyze the possible correlations between the central auditory and visual afferentations and the severity of autonomic and sensory neuropathy in patients with long-standing type 1 diabetes.

A total of 10 middle-aged type 1 diabetic patients with long-standing diabetes were included in the study (4 male and 6 female subjects aged 43.8 ± 15.2 years [mean ± SD], duration of diabetes 23.1 ± 9.3 years, BMI 27.9 ± 3.9 kg/m$^2$). Patients with abnormal hearing, proliferative retinopathy, impaired visual acuity, or neuropathy of origin other than diabetes were excluded. The quantitative characteristics of the brainstem function were evaluated by the detection of auditory-evoked potentials after the delivery of an audible click of short duration via an earphone (4). The latencies of the first five waves (I–V) were analyzed in this study. The central afferent visual function was evaluated via the delay of the major positive component (P100) of the visual-evoked potentials that was generated following a pattern-reversal checkboard stimulation (5). Cardiovascular autonomic function was assessed by means of the five standard cardiovascular reflex tests (2,3,6). The heart rate tests (the heart rate response to deep breathing, the 30:15 ratio, and the Valsalva ratio) mainly reflect the parasympathethic function, whereas the systolic blood pressure response to standing up and the diastolic pressure change to a sustained handgrip predominantly characterize the sympathetic integrity. Detection of current perception thresholds (CPTs) with a neuroselective transcutaneous stimulator, the Neurometer (Neurotron, Baltimore, MD), allowed for the assessment of the sensory function at three different frequencies on the median and peroneal nerves (6). The analysis of the auditory-evoked potentials revealed negative relationships between the heart rate tests and the prolongation of the latencies of waves III and V (heart rate response to breathing–wave III, $r = -0.586$, $P < 0.01$; 30:15 ratio–wave III, $r = -0.588$, $P < 0.01$; heart rate response to breathing–wave V, $r = -0.498$, $P < 0.05$; Valsalva ratio–wave V, $r = -0.463$, $P < 0.05$; and 30:15 ratio–wave V, $r = -0.599$, $P < 0.01$). The statistical procedure demonstrated positive correlations between higher CPT values obtained at 2,000 and 250 Hz at the peroneal nerve and the latencies of wave V (CPT at 2,000 Hz–wave V, $r = 0.527$, $P < 0.01$; and CPT at 250 Hz–wave V, $r = 0.547$, $P < 0.01$). The delayed visual afferent function correlated negatively with the heart rate tests, similar to the finding of the auditory-evoked potentials (heart rate response to breathing–P100, $r = -0.51$, $P < 0.05$; Valsalva ratio–P100, $r = -0.552$, $P < 0.01$; and 30:15 ratio–P100, $r = -0.438$, $P < 0.05$). Positive associations were proven between the degree of the peripheral sensory dysfunction on the peroneal nerve and the latency of the P100 potentials (CPT at 2,000 Hz–P100, $r = 0.461$, $P < 0.05$; CPT at 250 Hz–P100, $r = 0.521$, $P < 0.05$; and CPT at 5 Hz–P100, $r = 0.561$, $P < 0.01$). The final evaluation of the results demonstrated a correlation between the latencies of the auditory- and visual-evoked potentials in this group of patients (wave V–P100, $r = 0.571$, $P < 0.01$).

In this study, the severity of the parasympathetic impairment and the lower-limb sensory neuropathy was consequently associated with the latencies of both the auditory- and the visual-evoked potentials. These findings validate our previous data that central afferent dysfunction is associated with the most common forms of diabetic neuropathy. Moreover, as a novel observation, a correlation was found between the impairment of the auditory- and visual-evoked potentials, suggesting that different central manifestations are related to each other. The regions responsible for the generation of the waves III and V of the auditory-evoked potentials and the P100 potentials in the central nervous system may be similarly sensitive to the pathogenetic process, resulting in neuropathy in the peripheral nerves. Our findings also suggest that the abnormal central afferentation might play an important role in the development of the parasympathetic efferent dysfunctions. The assessment of these characteristic alterations of the central conduction may provide an additional diagnostic approach for a more precise detection of the central manifestations of diabetic neuropathy.

TAMÁS T. VÁRKONYI, MD, PHD[1]
ÉVA BÖRCSÖK, MD[1]
FERENC TÓTH[2]
ZSUZSANNA FÜLÖP, MD[3]
RÓBERT TAKÁCS, MD[1]
LÁSZLÓ ROVÓ, MD, PHD[2]
CSABA LENGYEL, MD, PHD[1]
JÓZSEF GÉZA KISS, PHD[2]
MÁRTA JANÁKY, MD, PHD[2]
ZSOLT HERMÁNYI, MD[4]
PÉTER KEMPLER, MD, PHD, DSC[4]
JÁNOS LONOVICS, MD, PHD, DSC[1]

From the [1]First Department of Medicine, University of Szeged, Szeged, Hungary; the [2]Department of Otolaryngology, University of Szeged, Szeged, Hungary; the [3]Department of Ophthalmology, University of Szeged, Szeged, Hungary; and the [4]First Department of Medicine, Semmelweis University, Budapest, Hungary.

Address correspondence to Dr. Tamás Várkonyi, University of Szeged, First Department of Medicine, H-6701, Szeged, P.O. Box 469, Hungary. E-mail: vart@in1st.szote.u-szeged.hu.

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# Higher Rate of Obesity and Hypertension in Adolescents With Type 2 Diabetes Than in Those With Type 1 Diabetes

We read with interest the article by Eppens et al. (1) concerning the prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes.

Because the study was clinic based and included a relatively small number of subjects with type 2 diabetes ($n = 68$), we present our findings from a nationwide screening program, which was conducted between 1992 and 1997 for all schoolchildren aged 6–18 years (2). Diabetes was diagnosed in 381 boys and 454 girls whose fasting blood glucose exceeded 7 mmol/l. Type 1 diabetes was considered if they received insulin therapy within 6 months and if it was confirmed by their referred physicians (2). Type 2 diabetes was considered if they were under diet control or were currently receiving oral antidiabetic agents without recurrent diabetic ketoacidosis. Those who received insulin injection within 3 years were excluded due to uncertainty in the classification of diabetes. Overweight and obesity were defined by 85th to 95th and above 95th percentile of age- and sex-specific cutoffs, whereas hypertension was diagnosed if systolic or diastolic blood pressure was >95th percentile of age- and sex-specific cutoffs in our population.

There were 330 subjects with type 1 diabetes and 505 subjects with type 2 diabetes. Hypertension was more prevalent in adolescents with type 2 than type 1 diabetes (44.4 vs. 23.4%, $P < 0.001$), which is similar to the report by Eppens et al. (1). After adjusting for age and sex, subjects with type 2 diabetes also showed a higher risk of hypertension (odds ratio 2.25 [95% CI 1.59–3.20], $P < 0.001$).

Similar to the findings by Eppens et al., adolescents with type 2 diabetes had a higher rate of obesity in our population (45.4 vs. 8.8%, $P < 0.001$). However, we found a higher rate of overweight in those with type 2 diabetes (10.1 vs. 7.2%, $P < 0.001$), which was not observed by Eppens et al. When applying the same definition of overweight and obesity (3), as Eppens et al. did, adolescents with type 2 diabetes also showed a higher rate of both overweight and obesity (overweight 28.6 vs. 15.0%, $P < 0.001$; obesity 30.0 vs. 7.2%, $P < 0.001$).

The findings of our population-based study support and extend the observations by Eppens et al., showing that adolescents with type 2 diabetes were more obese and had a higher rate of hypertension than those with type 1 diabetes.

HUNG-YUAN LI, MD[1]
JUNG-NAN WEI, PHD[2]
FUNG-CHANG SUNG, PHD[3]
LEE-MING CHUANG, MD, PHD[1,4]

From the [1]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Chia Nan University of Pharmacy and Science, Tainan, Taiwan; [3]Institute of Environmental Health, China Medical University College of Public Health, Taichung, Taiwan; and the [4]Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, Taiwan.

Address correspondence to Dr. Lee-Ming Chuang, MD, PhD, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Rd., Taipei, Taiwan. E-mail: leeming@ha.mc.ntu.edu.tw.

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# Use of Repaglinide During the First Weeks of Pregnancy in Two Type 2 Diabetic Women

Repaglinide, the only glinide available in Italy, is a secretagogue developed for type 2 diabetes (1). There is no evidence about its use during human pregnancy. Studies on rats that showed its effects on long bone growth excluded any teratogenity (2). More data exist regarding the safety of metformin in pregnancy, even though it is not recommended as an oral hypoglycemic agent in diabetic pregnancy (3,4).

We report two case subjects of type 2 diabetic women who used repaglinide at conception and during the first 6–7 weeks of an unplanned pregnancy.

The first patient, L.M., was 38 years old and was diagnosed with type 2 diabetes when she was 31; since 2004, she had been treated with repaglinide (1.5 mg/day) and metformin (3 g/day). When we first visited her, she was 6 weeks and 4 days into her second pregnancy, with a pregestational BMI of 26.2 kg/m$^2$.

The second patient, N.G., was 34 years old, developed diabetes in 2001, and had been treated with repaglinide (2.5 mg/day) for 2 years. When we first visited her, she was nulliparous at the 6th gestational week, with a pregestational BMI of 21.3 kg/m$^2$.

Both gestational ages were confirmed by ultrasound. Neither patient had evidence of micro- and macrovascular complications or autonomic neuropathy. Due to the lack of data on the safety of repaglinide in pregnancy, they were both switched to insulin. Other therapies included a multivitamin and mineral supplementation.

L.M. was given alfa metildopa begin-