Central Processing of Gut Pain in Diabetes Patients with Gastrointestinal Symptoms

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Objective: To evaluate the brain responses to painful visceral and somatic stimuli in diabetic patients with gastrointestinal symptoms.

Design and methods: The sensitivity to electrical esophageal and median nerve stimulations were assessed in 15 healthy volunteers and 14 type-1 diabetic patients with autonomic neuropathy and gastrointestinal symptoms using an euglycemic hyperinsulinemic clamp. Evoked brain potentials were recorded.

Results: Patients had reduced sensitivity to esophageal (48%; \(P<0.001\)) and median nerve (80%; \(P<0.001\)) stimulations. They also had increased 8.8% \((P=0.007)\) and non-reproducible \((P=0.006)\) latencies of evoked potentials to esophageal stimulations with 26% reduction in amplitude \((P=0.011)\). No potential differences were seen to median nerve stimulations. In diabetics the topographic location of the first peak in potentials was more centrally \((P<0.001)\) and gastrointestinal symptoms were correlated to characteristics of brain potentials \((P=0.049)\).

Conclusions: This study supports that diabetes induces changes in peripheral visceral nerves as well as in the central nervous system.
Gastrointestinal (GI) symptoms are more prevalent in diabetes mellitus (DM) than in the general population (1,2). The pathogenesis is undoubtedly multi-factorial including motor dysfunction, glycemic control, psychological factors, etc. (3,4). However, diabetic autonomic neuropathy (DAN) seems to play a central role (1,3,5). The aims were in healthy controls and patients with long-standing DM and GI symptoms to describe 1) the sensory thresholds to electrical esophageal and median nerve stimulation and 2) the evoked brain potentials (EPs) recorded with a high resolution electroencephalogram (EEG) system.

RESEARCH DESIGN AND METHODS
Fourteen type-1 diabetes patients (12 females, mean 34.4 years, range 20-51 years) and 15 healthy controls (10 females, mean 33.5 years, range 21-50 years) participated. Primary GI or other diseases were ruled out including endoscopy where appropriate. The diabetes lasted 14 to 40 years (mean 22 years) and they were managed with multiple injection insulin regimen or insulin pump. Mean glycated hemoglobin (HbA1c) level was 9.6% (range 7.1-14.1%). DAN was verified by abnormal gastric emptying breath test, heart rate variability (HRV), and modified Ewing tests (6,7). A HRV index was calculated based on mean of RR intervals, SDNN, SDNNi, SDANN and RMSSD (6), and an autonomic score was calculated as the sum of orthostatic blood pressure changes, RR variability upon deep respiration and QTc (7). All patients had one or more GI symptoms and a GI symptom score was calculated based on the sum of: Nausea, vomiting, early satiety, bloating, abdominal pain, diarrhea and constipation, all ranging from no(=0), moderate(=1) to severe symptoms(=2). No medication (except insulin) was allowed 24 hours before the study.

After 6 hours fasting the blood glucose level was adjusted in all subjects to 6mM using a hyperinsulinemic hyperglycemic clamp technique (8). A 64 surface electrode EEG cap was mounted (10-20 system). A 3mm catheter was swallowed with the ring electrodes positioned in the distal esophagus. Electrical stimulations were applied as single stimuli consisting of a series of 5 short 1ms square pulses at 200Hz. The sensations were rated at a 0-10 visual analogue scale (VAS) with 0=no perception; 3=vague perception of moderate sensation; 5=pain detection threshold. Afterwards, right median nerve stimulation was performed with identical protocol settings. The electrocardiogram was monitored during all stimulations.

Fifty identical esophageal and 30 median nerve stimulations were applied twice at 0.2Hz with 5 minutes break. The EEG signals were recorded with a sampling rate of 1000Hz (SynAmp, Neuroscan, El Paso, TX). The EPs were processed offline and the mean of the two stimulation runs were computed (Neuroscan software v 4.3.1, Neuroscan, El Paso, TX), figure 1a. On topographic maps the primary topographic location of each component was identified. The latencies and amplitudes of each component (N1-P1-N2-P2-N3) at Cz (vertex) were identified blindly using topographic brain maps as guidance. For correlation analysis a total EEG index was calculated based on the average of the N1, P1 and N2 latencies (mean 100) divided by the average of the N1, P1 and N2 amplitudes (mean 100).

RESULTS
The blood glucose level was adjusted to a mean of 6.0±0.1mM for the controls and 6.2±0.2mM for the patients.
Combining all three sensory levels, the diabetes patients had reduced sensitivity to esophageal \( (F=16, P<0.001; \text{post-hoc: VAS}=1: P=0.03; \text{VAS}=3: P=0.01; \text{VAS}=5: P=0.03) \) and median nerve \( (F=26, P<0.001; \text{post-hoc: VAS}=1: P=0.15; \text{VAS}=3: P=0.048; \text{VAS}=5: P<0.001) \) stimulation. There were no significant correlations between esophageal and median nerve thresholds in both groups \( (all P>0.3) \).

Comparing the two stimulation runs for EPs in controls they were reproducible \( (\text{latencies: } F=3.3, P=0.11; \text{amplitudes: } F=0.3, P=0.62) \). The EPs were more variable in the diabetes patients with longer latencies in the second run \( (F=11, P=0.006) \).

Analyzed combined \( (N1-P1-N2-P2) \) patients had increased latencies \( (F=7.6, P=0.007) \) and reduced amplitudes \( (F=6.7, P=0.01) \) of the EPs, figure 1b+c. For median nerve stimulation neither the latencies \( (F=0.7, P=0.4) \) nor amplitudes \( (F=0.5, P=0.5) \) were different from healthy controls. In patients the location of the first positive deflection of the EP was shifted more centrally compared to the frontal location in healthy controls \( (\chi^2=17, P<0.001) \), while no differences in the topographic distribution of the other peaks were found \( (all P>0.5) \).

The GI symptom score only correlated to the total EEG index \( (r=0.55; P=0.049) \); increasingly abnormal esophageal EP correlated positively to symptom. The total EEG index did not correlate to the diabetes duration \( (P=0.3) \), HbA1c level \( (P=0.6) \), HRV index \( (P=0.8) \) or autonomic score \( (P=0.5) \).

**DISCUSSION**

Diabetes patients had reduced esophageal sensitivity with reduced quality and non-reproducible EPs having increased latencies and reduced amplitudes. The EEG findings correlated with GI symptoms.

Our results are comparable to previous findings in small samples of patients \( (9-11) \). The observed decrease in sensation and increase in latencies of EPs is an indicator of altered sensory processing. DAN induces a decrease in conduction velocity of both peripheral and spinal nerve fibers contributing to an increase in latency \( (10) \). However, the visceral sensory system is not hard-wired, and neuroplastic changes could be expected in diabetes involving spinal and supraspinal reorganization with activation of latent ascending pathways as well as descending inhibitory or facilitatory control mechanisms \( (12) \). A combination of all these mechanisms is probably involved resulting in the final configuration of the EPs. Structural cerebral changes could also explain the findings. Reduced density of cortical grey matter, cortical atrophy and deep white matter lesions are seen in patients with long-lasting diabetes \( (13) \). Aging has shown to increase sensory thresholds, reduce amplitude and increase latencies of somatic EPs \( (14) \) and similar aging-like changes may be present in long-lasting diabetes.

The reduced upper GI sensitivity with altered and delayed brain response seems somehow surprising since diabetes patients have an increased prevalence of GI symptoms \( (1,2) \). However, the topographic findings indicates changes in the primary pain processing of visceral pain and such central changes may result in GI events being perceived in an abnormal way \( (15) \). This theory is supported by GI symptoms being correlated to the degree of abnormal EPs. Hence, viscerosensory EPs may be a useful biomarker of diabetes induced neuropathic-like mechanisms, which are not assessed using traditional cardiovascular tests.

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Figure 1: Evoked brain potentials at vertex (Cz) to painful esophageal electrical stimulation (a). The grand mean and typical examples are illustrated for both healthy controls (top) and diabetic patients (bottom) with verified autonomic neuropathy and related gastrointestinal symptoms. The latencies (b) and amplitudes (c) of the evoked brain potentials at Cz are illustrated. Including the first four components (N1-P2), the latencies were increased and the amplitudes reduced in the diabetic patients. Error bars indicate standard error of mean and (*) indicates significant results of the post-hoc test.