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Original Research

Association of Sympathovagal Imbalance with Cognitive Impairment in Type 2 Diabetes

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ABSTRACT

Objective: Sympathovagal imbalance (SVI) has been reported to be associated with metabolic derangements in type 2 diabetes. We investigated the association of SVI with cognitive impairment in patients with type 2 diabetes.
Methods: Patients with a new diagnosis of type 2 diabetes (n=43) and age-matched healthy control subjects (n=43) were recruited for the study. Body mass index and blood pressure measurements were recorded. SVI was assessed by spectral analysis of heart rate variability (HRV), and cognitive function was assessed by recording the positive wave that appears in 300 milliseconds from application of stimulus in event-related potential tracing (P300). Insulin resistance was determined by the homeostatic model assessment of insulin resistance (HOMA-IR) formula using blood glucose and insulin data, and oxidative stress was assessed by estimation of malondialdehyde. Association of various factors with cognitive impairment was evaluated by Pearson correlation analysis, and independent contributions of these factors to cognitive impairment were assessed by multiple regression analysis.
Results: P300 latency was significantly prolonged in the diabetes group compared with the control group. Ratio of low-frequency to high-frequency power (LF-HF ratio) of HRV, the marker of SVI was found to be significantly correlated and linked with P300. Malondialdehyde and HOMA-IR were correlated with LF-HF ratio.
Conclusion: Treatment-naïve patients with type 2 diabetes have SVI and considerable cognitive impairment. Insulin resistance and oxidative stress contribute to cognitive impairment, and SVI could be the physiologic link to cognitive impairment in treatment-naïve patients with type 2 diabetes.

Mots clés :
trouble cognitif
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diabète de type 2
résistance à l'insuline
P300

RÉSUMÉ

Objectif : Il a été établi que le déséquilibre sympathovagal (DSV) est associé à des troubles du métabolisme lors du diabète de type 2. Nous avons examiné l'association entre le DSV et les troubles cognitifs chez les patients atteints du diabète de type 2.
Méthodes : Des patients ayant récemment reçu un diagnostic de diabète de type 2 (n=43) et des témoins en bonne santé appariés selon l'âge (n=43) ont été recrutés pour l'étude. L'indice de masse corporelle et les mesures de la pression artérielle ont été notés. Le DSV a été évalué par l'analyse spectrale de la variabilité de la fréquence cardiaque (VFC), et le fonctionnement cognitif a été évalué par l'enregistrement de l'onde positive qui apparaît 300 millisecondes après l'application du stimulus dans un enregistrement des potentiels évoqués (P300). L'insulinorésistance a été déterminée par la formule de l'évaluation du modèle d'homéostasie de l'insulinorésistance (HOMA-IR) qui utilise les données de la glycémie et de l'insuline, et le stress oxydatif a été évalué par une estimation du malondialdéhyde. L'association de divers facteurs avec les troubles cognitifs a été évaluée à l'aide de l'analyse de corrélation de Pearson, et les contributions indépendantes de ces facteurs aux troubles cognitifs ont été évaluées à l'aide de l'analyse de régression multiple.
Résultats : La latence P300 s'est prolongée de manière significative chez le groupe de diabétiques par rapport au groupe témoin. Le ratio de la puissance de basse fréquence à haute fréquence (ratio BF–HF) de la VFC,

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le marqueur du DSV, corrélait de manière significative et était lié à P300. Le malondialdéhyde et la HOMA-IR corrélaient avec le ratio BF–HF.

Conclusion : Les patients atteints du diabète de type 2 qui sont vierges de tout traitement ont un DSV et des troubles cognitifs importants. L'insulinorésistance et le stress oxydatif contribuent aux troubles cognitifs, et le DSV pourrait avoir un lien physiologique avec les troubles cognitifs chez les patients atteints du diabète de type 2 qui sont vierges de tout traitement.

Introduction

Diabetes mellitus (DM) is an established risk factor for cognitive impairment (1,2). Currently, India is considered to be the diabetes capital of the world, with more than 62 million individuals diagnosed with the disease (3). Because diabetes has been found to be quite prevalent in younger age groups in the Indian subcontinent (4), premature dementia caused by diabetes poses a serious threat to socioeconomic development. Although the pathophysiology of cognitive impairment in diabetes is not fully understood, hyperglycemia, hyperinsulinemia, insulin resistance and increased formation of advanced glycation end products (AGEs) have been proposed to be the plausible mechanisms (5,6).

Autonomic imbalance has been implicated in the pathophysiology of diabetes (7–9) and has been reported to predict the cardiovascular risk and mortality in diabetes (10). Cardiac autonomic imbalance has also been found to be associated with markers of adipose tissue inflammation in newly diagnosed and established diabetes (11). However, to date, no study has been conducted to determine the role of autonomic imbalance in the pathophysiology of cognitive impairment in diabetes.

Recent reports have suggested the involvement of cardiac autonomic regulation, including modulation of baroreflex sensitivity, in cognitive function (12,13). Earlier, it was observed that epinephrine, acting through nonselective beta receptors, enhances long-term memory consolidation (14). It has been demonstrated that children with higher resting heart rate variability (HRV), representing higher cardiac vagal modulation, have better working memory and faster reaction times (15,16). Furthermore, cognitive impairment has been reported in patients with spinal cord injury who have an alteration in sympathovagal balance (17). Autonomic dysregulation, sympathovagal imbalance and decreased HRV have been reported in patients with type 2 diabetes. However, to date, no study has been conducted to assess the link between sympathovagal imbalance (SVI) and cognitive impairment in patients with type 2 diabetes. Therefore in the present study, we have assessed the association of SVI with cognitive impairment in patients with type 2 diabetes. Because hyperinsulinemia, insulin resistance and oxidative stress have been found to be involved in the pathophysiology of cognitive impairment in diabetes (5,18), we have also assessed the contribution of these factors to SVI and cognitive impairment in patients with type 2 diabetes.

Event-related potentials (ERPs) are important clinical and research measurements in neurophysiology and neuropsychiatry, particularly because of their strategic role in the investigation of brain function (19). ERPs are noninvasive measurements that directly reflect cortical neuronal activity. ERPs are the only measurements with a sufficiently high time resolution for analysis of the dynamic patterns of neuronal brain activity, which are crucial for a deeper understanding of functional (neurophysiologic) correlates of cognitive, emotional and behavioral disturbances in patients with neuropsychiatric disorders (20). In particular, the positive wave that appears in 300 milliseconds from application of stimulus in event-related potential tracing (P300) brain potential provides information about cognition that is quantitatively comparable to other clinically used biomedical assays. The causes of P300 variability with respect to task and biologic determinants have been well characterized (20). Elaboration of P300 reflects neuropsychologic processes that increase its clinical relevance as a reliable neuroelectric measure of mental function and its application in the assessment of cognitive disorders (20). Recently, P300 has been used as a marker of cognitive impairment in patients with subclinical hypothyroidism (21) and patients with diabetes treated with metformin (22). Therefore in the present study we have used P300 as the measure of cognitive impairment in patients with type 2 diabetes.

Methods

The present study was conducted as a research project by the first author, funded by the Undergraduate Golden Jubilee Strauss Research Grant of Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, India. After approval was obtained from the Undergraduate Research Monitoring Committee and Institutional Ethics Committee of JIPMER, 86 subjects (43 control subjects and 43 patients with diabetes) were recruited from the medicine outpatient department, the diabetes clinic and the staff of JIPMER.

Sample size calculation

Total sample size was calculated to be 86 with 43 subjects in each group. The primary objective of this study was to measure and compare the ratio of low-frequency to high-frequency power of HRV (LF-HF ratio) with P300. Therefore in accordance with the method of Pal et al (23), considering the mean and standard deviation values of LF-HF ratio, accepting power as 80% and keeping the level of significance at 5%, we calculated that the total sample size required was 86 by using Open Epi software.

Grouping of subjects and estimation of biochemical parameters

Written informed consent was obtained from all the subjects before commencement of the clinical and laboratory investigations.

A 5 mL blood sample was obtained from each subject, and fasting blood glucose (FBG) and malondialdehyde (MDA) levels were estimated with an autoanalyzer (AU400, Olympus, Orlando, Florida, United States). Plasma insulin was assayed by the chemiluminescence method using kits obtained from Siemens Healthcare Diagnostics Inc. (Tarrytown, New York, United States). For determination of insulin resistance, homeostatic model assessment of insulin resistance (HOMA-IR) was calculated by using the formula, HOMA-IR=FBG (mmol/L)×Insulin (μIU/L)/22.5.

Based on the FBG level, subjects were classified into 2 groups according to American Diabetes Association criteria (24): the control group (n=43) — healthy subjects having an FBG level of 3.3 to 5.4 mmol/L and the diabetes group (n=43) — newly diagnosed, treatment-naïve, otherwise healthy patients with diabetes having an FBG level of 6.9 mmol/L or greater.

The ages of the subjects in both the groups were between 18 and 44 years, and both men and women were included in each group.

Exclusion criteria were as follows:

- Subjects with any acute illness
- Subjects receiving any medications for any kind of health problem