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BENTHAM SCIENCE

Topiramate: A Novel Therapeutic Candidate for Diabetes and Aggression? Positron Emission Tomography (PET) Findings

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Abstract: ***Background***: There is still limited knowledge regarding the role of impaired brain glucose metabolism in the generation of aggression during diabetes. Additionally, there are rapidly replicating piece of evidence suggesting that topiramate may exert significant mood stabilizing effect. In this respect, we aimed to evaluate the neurometabolic correlates of the therapeutic effect of topiramate in a patient with diabetes and Intermittent explosive disorder (IED).

Methods: We measured regional cerebral glucose metabolism using 2-[18F]-fluoro-2-deoxy-D-glucose and positron emission tomography (FDG-PET) in a diabetic patient with aggressive outbursts before and after treatment with topiramate. In order to reveal a defined information underlying the improvement of the aggressive symptoms we also combined the PET with Modified Overt Aggression Scale.

Results: We have found that topiramate leads to the improvement in Modified Overt Aggression Scale that was well correlated with the increase in cortical brain metabolism.

Discussion: The therapeutic role of topiramate may not only suggest secondary deficits due to diminished functions of the cortical part of emotional circuits but also indicate that diabetic individuals may be vulnerable to lower cerebral glucose metabolism in cortical regions. Further clinical trials that include well-conducted randomized controlled trials and cohort studies by using other methods (i.e., magnetic resonance spectroscopy and quantitative EEG analysis) are necessary to confirm our preliminary findings.

Keywords: Topiramate, Intermittent explosive disorder, 2-[18F]-fluoro-2-deoxy-D-glucose and positron emission tomography.

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INTRODUCTION

It has been recently shown that increased insulin resistance and higher fasting glucose levels may lead to the impairment of glucose metabolism in specific brain regions which have been shown to play a major role in cognitive function [1-3]. However, it is still unclear whether impaired brain glucose metabolism during diabetes has a direct effect on the development of psychiatric disorders. In this respect, it has been very recently shown that intermittent explosive disorder (IED) is significantly associated with diabetes [4]. Moreover, recent studies evaluating the neurometabolic correlates of IED have already shown that intermittent explosive disorder and borderline personality are associated with an increase in glucose metabolism in the limbic system and a decrease in prefrontal regions [5]. These findings may support the role of dynamically interacting central networks in the generation of aggressive outbursts during diabetes.

Topiramate (TPM) is a broad-spectrum anticonvulsant. In addition to its therapeutic effect by reducing depressive symptoms in acute bipolar depression, recent reports have also suggested the therapeutic role of topiramate in IED. To the best of our knowledge, there is very limited human data showing the therapeutic effect of topiramate on cortical brain metabolism [6].

Here we describe a 32-year-old man with newly diagnosed diabetes who experienced severe physical and verbal violence precipitated by little provocation. The patient reported no additional psychiatric symptoms and during that time he received no medical treatment. On psychiatric examination, he displayed an inappropriate emotional display with aggressive verbal outbursts. Mini-Mental State Examination revealed no abnormality. Detailed blood tests including complete blood count, renal, hepatic, thyroid function tests, erythrocyte sedimentation rate, electrolytes, and

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C-reactive protein were within normal limits except significantly elevated HbA1c levels (12.42 %) and fasting glucose levels of 230 mg/dl. The patient reported no history of genetic disease in his family history, and we have detected no coexisting vascular or lipid abnormalities.

MATERIAL AND METHODS

Cranial MRI was taken using an imager operating at 1.5 Tesla (Philips Gyroscan ACS-NT) with an eight-channel head coil. Spin-echo axial T1-weighted, axial and coronal turbo spin-echo T2-weighted and sagittal FLAIR (Fluid Attenuated Inversion Recovery) slices were obtained. Brain (F18) FDG PET-CT images were taken using Philips Gemini TF PET/CT equipped with 16 slice CT. All patients had a glucose level below 160 mg/dl and ^{18}F FDG was administered intravenously at a dose of 0.1 mCi (3.7 MBq)/kg. After injection, patients were allowed to rest quietly in a dimly lit room for at least 30 minutes during the uptake phase. At 60 min after the injection, data were acquired and PET images were reconstructed with CT data for PET attenuation correction.

The raw FDG-PET data was processed using NeuroQ software (Version 3,5. Syntermed, Inc Atlanta. USA) as described previously [7] by Akdemir *et al*. We have not included an additional control group since the NeuroQ software includes a normal brain ^{18}F-FDG PET database consisting of 50 healthy adults without neuropsychiatric disorders. Brain ^{18}F-FDG PET images in axial, coronal, and sagittal slices and the quantitative results of NeuroQ analysis were visually evaluated by 2 blinded nuclear medicine physicians. The NeuroQ program calculated the average pixel values in standardized regions of interest (ROI) as mean counts and statistically compared these counts with the control database following spatial normalization of PET images. As a result, significantly hypometabolic brain regions were automatically defined as a decrease of more than 2 SDs of regional brain metabolism. The patient received 25 mg of oral Topiramate (TPM) once daily for 15 days between two FDG-PET scanning periods.

RESULTS

A magnetic resonance imaging scan of the brain performed on the admission day showed no abnormality. In contrast, FDG-PET scanning revealed reduced glucose uptake in the left temporoparietal, left posterior visual cortical, right posterior cingulate and right anterior temporal region (more than two standard deviations below the mean of the asymptomatic control group, NeuroQ, Syntermed) (Table **1**, Fig. **1**). The optimum control of aggression occurred taking 25 mg of TPM once daily after 15 days. We have shown that the improvement in the aggressive symptoms was associated with significant reduction of three points on the Modified Overt Aggression Scale score which was positively correlated with increased brain metabolism in respective brain regions

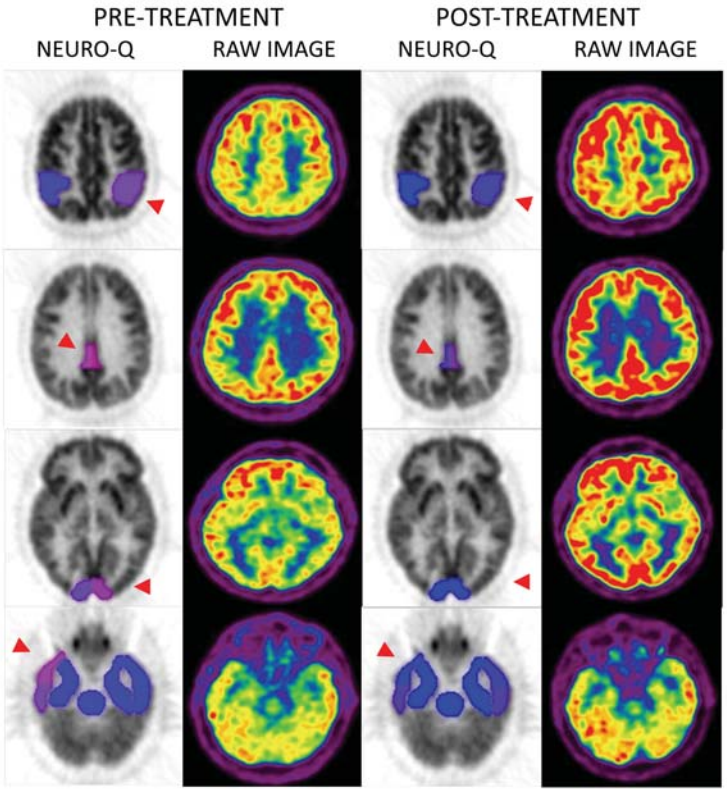

Fig. (1). The raw FDG-PET data was processed using NeuroQ software (Version 3,5. Syntermed, Inc Atlanta. USA) and the average pixel values in standardized regions of interest (ROI) were automatically calculated. Area/whole brain ratios were compared to the normal values in the database. Please see that topiramate improved reduced glucose uptake (>2 standart deviations (2 SD's) below normal mean) on the left temporoparietal, right posterior cingulate, right anterior temporal and left posterior visual cortical region.

Table 1. NeuroQ quantified the pretreatment metabolism of left temporoparietal, right posterior cingulate, right anterior temporal and left posterior visual cortical region as falling more than 2 standart deviations (2 SD's) below normal mean. Please see that topiramate normalized reduced glucose uptake in respective brain regions (within 2 SD's of normal).

	Pretreatment standard deviation value (>2 SD's)	Post treatment standard deviation value (within 2 SD's)
Visual cortical metabolism (Left)	2.17	0.36
Parietotemporal metabolism (Left)	2.04	0.95
Cingulate metabolism (Right)	2.49	1.11
Temporal metabolism (Right)	2.40	0.38

after15 days of TPM treatment (within two standard deviations of normal) (Table **1**).

DISCUSSION

In our case, functional abnormalities did not entirely parallel morphological changes and were found mainly in cortical regions. Interestingly, we have found that the improvement of aggressive symptoms correlated well with the normalized brain metabolism. Our pretreatment findings showing reduced cortical glucose uptake may indicate to secondary diminished functions of the cortical part of emotional circuits which have been already shown to play a significant role in the generation of aggression [8, 9]. Recent studies suggested the importance of this type of quantitative neurometabolic analysis and indicated that low cerebral glucose metabolism may predict the severity of vascular and degenerative Parkinson's Disease (PD). These findings are in line with another recent study showing that SPECT/PET applications may help to make an early and accurate diagnosis of the premotor stage of PD that is preceding the motor abnormalities of PD [10, 11].

In agreement with previous findings showing that hyperglycemia may secondary lead to the impairment of glucose metabolism in specific brain areas [1-3], our results indicate that diabetic individuals may be vulnerable to lower cerebral glucose metabolism in cortical regions and suggest that topiramate may be a well suitable agent with its therapeutic effect on the impairment in cortical metabolism. This is in line with our previous study showing that the antidepressant efficacy of topiramate was correlated with the normalized metabolism in the right temporal cortical area [6].

It has been already known that diabetes mellitus is associated with significant damage to the microvasculature of the brain which may result in impaired cerebral metabolism [3, 12, 13]. Additionally, recent studies demonstrated that topiramate exerts significant pericyte protective effect against glucotoxicity related mitochondrial oxidative stress during diabetes that was associated with improved neurobehavioural tests in mice [14-16]. These findings together suggest that topiramate may also be a well suitable agent with its cellular and microvascular protective actions in slowing the diabetic complications in CNS. As a conclusion, this case helps us to increase our understanding of the roles of cerebral glucose metabolism in the pathogenesis of diabetes and intermittent explosive disorder and indicate to the multimodal therapeutic role of topiramate in neuropsychiatric diseases that are associated with diabetes. Further well-conducted randomized controlled trials to evaluate the therapeutic effects of topiramate (also in bipolar/diabetic patients) via additional quantitative methods (i.e., magnetic resonance spectroscopy and quantitative EEG analysis) would be the logical future steps to be taken in the field of psycho-endocrinology research.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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