

Interhemispheric cerebral asymmetry detected by VEPS in diabetic patients with recognized depression

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Abstract

OBJECTIVES: The present study was undertaken in order to verify the hypothesis stating that patients with depression exhibit some abnormalities concerning a cerebral symmetry. For this purpose, an analysis of the relationship between the VEPs (Visual Evoked Potentials) results and the depressive symptoms intensification, as well interrelation between depressive and diabetic symptoms were performed.

MATERIAL AND METHODS: VEPs recordings were obtained from the two study groups (both aged 20–45 years), 20 healthy subjects and 32 diabetic patients with clinically documented depression. The VEPs examination was carried out using a computer system called STELLA (Stimulated Electroencephalogram on Line Analyzer).

RESULTS: VEPs examinations revealed a cerebral symmetry in the all control subjects and in 10 out of 32 diabetic patients with depressive disorders. It is noteworthy that 22 of 32 diabetic patients (68.8%) showed a hemispheric asymmetry in the VEPs recordings. Of 12 patients with a moderate depression, 10 showed the left cerebral laterality, and 2 – the right laterality. In turn, all 10 patients with major depressive disorder (MDD) demonstrated in the VEPs recordings a significant cerebral laterality with the right hemisphere dominance.

CONCLUSIONS: The obtained results suggest that interhemispheric cerebral asymmetry might be considered a specific feature of depression, and, if this is a case, it could justify a conclusion that right hemisphere dominance could be a neurophysiological marker of MDD. It should be emphasized that intensification of the depressive symptoms has an unfavorable influence on course of diabetes mellitus, its self-control and severity of following complications.

Abbreviations:

BDI	– Beck depression inventory
DM	– diabetes mellitus
HbA _{1c}	– glycated hemoglobin
ICC	– interhemispheric correlation coefficient
MDD	– major depressive disorder
VEPs	– visual evoked potentials

INTRODUCTION

Life yields a long-lasting and nearly permanent stress; sadness and frustration are the emotions which affect every human being often enough during the lifetime. Long-term stressful situations may finally result in depression. Considering quality and quantity of the psychological symptoms, depression can be recognized as mild, moderate or major. Psychological symptoms are usually combined with the numerous somatic disorders, which, in turn, aggravate the vicious circle (Lieb *et al.* 2007).

The reported results showed a three-fold more frequent incidence of depression in patients with diabetes mellitus of both type 1 and 2, as compared with general population (Lamers *et al.* 2008; Mezuk *et al.* 2008). On the other hand, it was shown that persons manifesting clinically defined depression symptoms are 2.3 times more susceptible to diabetes mellitus (DM) occurrence than normal subjects (Kawakami *et al.* 1999).

In recent years, much evidence was collected suggesting a significant clinical correlation between DM and depression. It is commonly accepted that depression is a multisystemic entity, the components of which originate from endocrinological, neurological, vascular, and immunological systems, with a crucial influence of psychosocial aspects. The treatment of chronic diseases is of eminent importance in primary care, and type 2 diabetes mellitus is one of the most common dysfunctions. Its world-wide prevalence has been increasing from year to year (Frese *et al.* 2008). Every chronic disease increases a risk of depression appearance. In case of DM, a situation is especially difficult, because of many stressful factors affecting DM patients, as an invasive self-control of blood glucose levels and insulin injections. Relations between the mentioned two diseases do not only concern psychological problems, but also comprise pathophysiological aspects, especially a connection between central nervous system (CNS) and immunologic system via cytokines (Boufidou *et al.* 2008). In patients with DM, an enhanced synthesis of some cytokines, like IL-6 and TNF- α , that are suspected to induce depression symptoms, was found. On the other hand, in patients with depression, an increased level of TNF- α was observed. Moreover, there is a proved link between lowered mood, and serum levels of IL-6, TNF- α and CRP. It is also of interest that antidepressants therapy can decrease the elevated blood cytokines concentration (Penninx *et al.* 2003; Syrenicz *et al.* 2006).

The other factor binding depression and DM is GABA, the main inhibiting neuromediator. Impairment of GABA-ergic activity is considered a significant component of neurobiology of mood disorders in depression. In serum of numerous patients with DM, there are found antibodies directed against the main enzyme responsible for GABA synthesis, which can result in GABA malfunctioning. Neuroimmunological tests revealed common pathomechanisms of those two diseases (Chan *et al.* 2008).

Incidence of depression is high. The epidemiological data collected worldwide shows that during the whole lifetime about 21.7% of the diabetic patients is affected by depression. Nearly a half of the patients admitted by the primary care doctors, demonstrate a moderate to severe form of the disease. What makes things worse, it was found that in 50% of the patients with depression, who are under the care of general practitioners, the disease is not diagnosed properly (Anderson *et al.* 2001).

In the last years, many investigators paid attention to the right hemisphere functioning and its relationships with emotions. Those findings supported a hypothesis stating that the left hemisphere supervises positive emotions, and the right one controls negative emotions. It can be assumed that appearance of depressive reactions, resulting from a dysfunction of the left hemisphere, induces a predominance of the other, right hemisphere, which is responsible for the negative emotions (Borod *et al.* 1998; Graae *et al.* 1996; Wittling, 1990).

Considering all this evidence, the question arises to which extent a functional cerebral hemispheric asymmetry, especially with the right side dominance, can affect the incidence and intensity of the depression episodes. The authors of the present study have attempted to find the reliable neurophysiological parameters determining depressive disorders and their clinical course in the diabetic patients.

MATERIAL AND METHODS

Subjects

A group I of 32 diabetic patients (20 females and 12 males), recruited from Wrocław Center for Neurosis Treatment, was enrolled to the study. The examined group was ranging in age from 30 to 45 years, with the mean age of 38.65 ± 4.81 years. A disease history was obtained from all patients, and then every patient underwent a detailed clinical examination and basic laboratory parameters assessment. From the clinical point of view, all these patients had diabetes mellitus (DM) type 1 (14 persons) or type 2 (18 persons) detected, and all of them showed the apparent, reliably documented symptoms and signs of depression varying in degree of severity. Diabetic patients were under treatment with oral hypoglycemic agents or insulin injections; with the mean duration of DM of 6.4 ± 3.87 years. The results of the investigations in the patients group were referred to

Table 1. Characteristics of the diabetic patients in the subgroups IA – IC and the control group II

Groups	I			II
	Subgroup IA	Subgroup IB	Subgroup IC	
Beck Depression Inventory	12.6 ± 0.84 scores	15.2 ± 0.39 scores	26.8 ± 1.68 scores	6.2 ± 1.34 scores
VEPs – Interhemispheric Correlation Coefficient	0.94 ± 0.010 (0.93–0.95) (interhemispheric symmetry)	0.91 ± 0.012 (0.90–0.92) (moderate interhemispheric asymmetry *)	0.81 ± 0.013 (0.80–0.82) (significant interhemispheric asymmetry **)	0.96 ± 0.028 (0.94–0.98) (interhemispheric symmetry)
Depression symptoms	Single mild depressive episodes	Single moderate depressive episodes	Recurrent depressive episodes incl. MDD	None
Suicidal attempts	None	1 person	7 persons (in 5 cases multiple)	None
Type of diabetes mellitus	Type 1 – 8 persons Type 2 – 5 persons	Type 1 – 6 persons Type 2 – 6 persons	Type 1 – None Type 2 – 7 persons	None
Glycated hemoglobin HbA1c	6.8 ± 0.6%	7.7 ± 0.9%	12.2 ± 1.1%	4.6 ± 0.5%

* In 10 of 12 patients, the VEPs amplitudes were moderate higher on the left side (the left hemisphere dominance), and in the 2 remaining patients – moderate higher VEPs were noted over the right hemisphere.

** In all 7 patients from this subgroup, the VEPs amplitudes were significantly higher ($p < 0.001$) on the right side (the right hemisphere dominance).

the outcomes obtained from the control group (group II) comprising 20 healthy, age- and sex-matched volunteers (age range: 28–45 years; 12 females, 8 males) with no history of depression.

Methods

The self-assessment charts, like Beck Depression Inventory used in the present study, are considered to be of great usefulness in establishing a diagnosis of depression. The examined subject is requested to complete the questionnaire which consists of 22 issues; for each of the questions you can choose only one answer (yielding 0–3 scores). It is assumed that an outcome of the whole test exceeding 12 scores indicates depression.

Also a measurement of HbA_{1c}, as a most reliable index of diabetic control, was performed.

The VEPs examination was carried out using a computer system called STELLA (Stimulated Electroencephalogram on Line Analyzer) designed and constructed in our laboratory. The control subjects and the patients underwent a VEPs procedure using monocular stimulation with a full-field checkerboard pattern. A size of the checkerboard pattern displayed on the TV screen size was of 23 × 23 degrees of visual angle, whereas each check subtended 138 minutes. The visual pattern reversed at a rate of 0.5 Hz (one alteration per 2 sec). The red fixation point was placed in the centre of the TV screen. The averaged evoked response was registered following 64 repetitions of the pattern stimulus. The VEPs were registered over the scalp from two recording electrodes O₁ and O₂. The analysis concerned the VEPs waveforms for each cerebral hemisphere. It comprised the analysis assessing a difference between maximum and minimum amplitude through the entire VEPs waveforms, likewise a correlation coefficient,

reflecting the interhemispheric symmetry, calculated for the individual VEPs tracing in the time interval of 101–200 ms from the stimulation onset.

Statistical analysis

Standard statistical Student t-test was applied for comparison of the two variables. The values are presented as the mean ± SD, and a level of statistical significance was set at $p < 0.05$. Non-parametric data was given as the absolute numbers or percentages.

RESULTS

The analysis of the BDI outcomes was a base for dividing the patients into the three subgroups depending on the BDI scores obtained: IA subgroup (13 patients) – 12.6 ± 0.84 scores; IB subgroup (12 patients) – 15.2 ± 0.39 scores; IC subgroup (7 patients) – 26.8 ± 1.68 scores. A BDI scores difference turned out to be statistically significant between the three patient subgroups ($p < 0.001$). The psychological examinations were performed also in the 20 control subjects. The results of the BDI obtained in this group let us exclude a diagnosis of depression. The group-mean BDI score was 6.2 ± 1.34 and differed significantly ($p < 0.001$) from the outcomes obtained in each of the three patient subgroup. None of the control subjects reported any depressive episode in the past, likewise all of them denied whatever suicidal attempts or even such thoughts.

After this preliminary classification, the patients from every depression subgroup were subjected to the VEPs examinations. Evaluation of the VEPs waveforms was focused on correlation coefficient for the VEPs recorded from the right and the left hemisphere for the

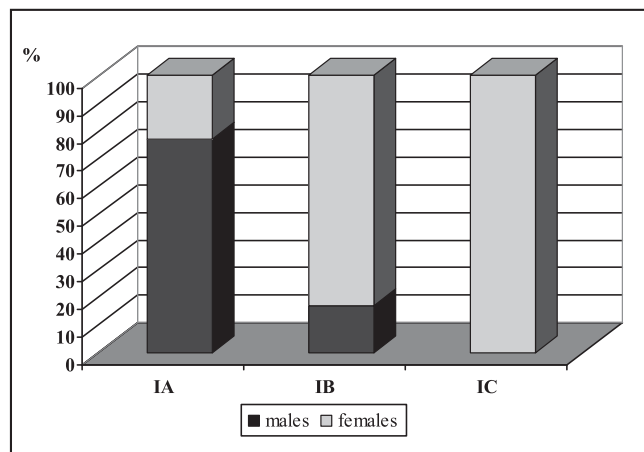


Figure 1. A percentage contribution of females and males in the IA – IC patients subgroups.

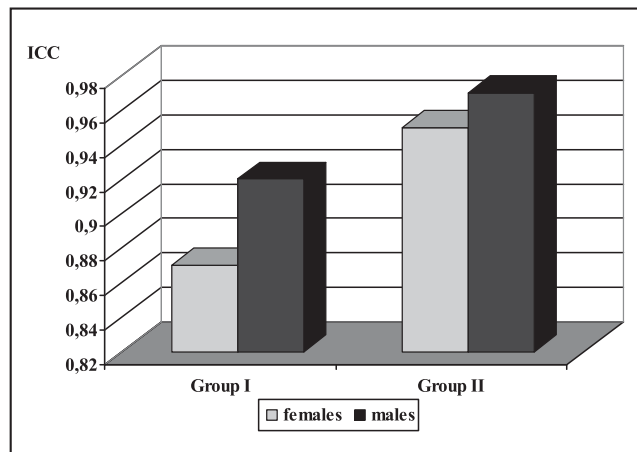


Figure 2. Comparison of mean value of ICC (Interhemispheric Correlation Coefficient) with a gender contribution in the group I and group II.

101–200 ms interval from the stimulation onset. In the patients with depression, the correlation coefficients, reflecting the VEPs interhemispheric symmetry, were less than in the control subjects (range: 0.94–0.98) and showed a clear tendency to decrease gradually within the subgroups IA – IC (0.93–0.95; 0.90–0.92; 0.80–0.82, respectively). Difference between the three patient subgroups and the control group was statistically significant ($p < 0.001$).

A percentage contribution of HbA_{1c} showed a clear tendency to increase gradually within the subgroups IA – IC ($6.8 \pm 0.6\%$; $7.7 \pm 0.9\%$; $12.2 \pm 1.1\%$, respectively). This results were referred to the control group, where HbA_{1c} equals $4.6 \pm 0.5\%$. Difference between the three patient subgroups and control group was statistically significant ($p < 0.001$).

The values of the VEPs interhemispheric correlation coefficient (ICC) coupled with the results of BDI, depressive symptoms, type of DM and blood concentration of glyated hemoglobin observed in the examined patients and control group are compiled in Table 1.

Totally, the VEPs interhemispheric asymmetry was observed in 19 of 32 diabetic patients with depression (59.37%), of whom the 9 demonstrated a right cerebral laterality. In the control group VEPs interhemispheric asymmetry was observed in 7 of 20 persons (35.0%), but all of them demonstrated a left cerebral laterality.

It seemed also interesting to assess a gender contribution in the assigned three subgroups of the diabetic patients suffering from depressive symptoms (Fig. 1).

It was striking that the subgroup IC – with a severe form of depression – was constituted exclusively by the female patients. With regard to the VEPs parameters the patient subgroups presented, as follows: IA – 10 males and 3 females showed interhemispheric symmetry; IB – 10 females showed a moderate left hemisphere dominance and 2 males – a moderate right hemisphere dominance; IC – 7 females showed a considerable right hemisphere prevalence.

The VEPs parameters in the control group proved to have the values significantly different from those observed in the depressive patients.

The VEPs results in the controls, like in the patients, revealed also a gender dependence. In the 12 control females, the mean correlation coefficient for the VEPs hemispheric recordings was 0.95 ± 0.02 , and 7 of them showed a moderate left hemisphere dominance. Conversely, in the 8 normal males, the mean correlation coefficient was higher, as compared with the normal females, 0.97 ± 0.01 , and the VEPs amplitudes showed the interhemispheric symmetry in the all recordings. Comparison of mean value of ICC with a gender contribution in the patients group and control group is seen in Fig. 2.

DISCUSSION

There is no doubt that depression, like diabetes mellitus can be considered a disease of the XXI century; it occurs more and more often, and its symptoms are becoming more annoying. A simultaneous occurrence of DM and depression increases a risk of premature death. Research on 10.000 adult American patients suffering both from DM and depression showed a 2.5-fold higher mortality as compared with the patients with only one of the two diseases (Lin *et al.* 2004).

Our patients with DM demonstrated significantly higher BDI index, which is getting larger, as the DM complications became more severe (Tab. 1). This observation could be elucidated by a stress accompanying the chronic diseases. In turn, depression is thought to be related to a worse patients' compliance as to secondary prevention concerning physical activity, healthy nutrition, smoking cessation, regular medication taking and doctors visiting. We have obtained results supporting that thesis: in the examined patients, the more severe depression symptoms in the successive subgroups were

correlated with the increasing HbA_{1c} level. At the very efficient self-control and treatment, a level of HbA_{1c} should not exceed 6%. In IA subgroup, HbA_{1c} level was $6.8 \pm 0.6\%$; it means that both self-control and treatment must be improved. In IB subgroup, HbA_{1c} level was $7.7 \pm 0.9\%$, so DM was not monitored properly. Finally, HbA_{1c} level over 12% noted in the patients of IIC subgroup was absolutely unacceptable; those patients were more obese than those from IA and IB subgroups, more frequently suffered from severe complications, and, in consequence, were compelled to be referred to the specialized medical centers. The comparable results were reported by Lin and co-workers (Lin *et al.* 2004).

The same authors, as well the other ones emphasized that MDD appears mainly in patients with DM type 2, which can be a result of various level of emotional acceptance of the disease. Patients with DM type 1 experience the disease mostly in the childhood, therefore such a state for them is a sort of norm. In contrast, DM type 2 starts in adults, often in subjects earlier otherwise healthy, therefore DM, as a long-term, incurable disease, with its all restrictions, difficulties and consequences lasting to the end of the life, is accepted less eagerly. Therefore so important is participation in diabetes education programmes (Mezuk *et al.* 2008; Lin *et al.* 2004).

Depression is a serious burden for the whole community and deteriorates life quality. Disease is a reason of untimely deaths, caused not only by suicides, but by accidents, resulting from attenuated concentration and incoherence, as well.

The main purpose of our investigation was to search the criteria of a predictive value with regard to this dangerous disease. The examination carried out in the patient group using BDI revealed that the scores clearly exceeded 12, meaning that a condition of diagnosing depression was fulfilled.

VEPs examinations performed in the patients and control subjects rendered very interesting observations as for cerebral symmetry – correlation coefficient was significantly higher at male than at female in both groups. They supported our previous findings that the female brain, concerning a visual perception, has a tendency to be asymmetric, whereas the male brain showed the interhemispheric symmetry. The VEPs results obtained in our study from the patients with depression formed a quite distant pattern, although, it is noteworthy that the subgroup IA, in which the all VEPs recordings showed the interhemispheric symmetry, was constituted in 77% by men. In turn, the subgroup IC, interestingly, consisted exclusively of women, who showed significant prevalence of the right cerebral hemisphere.

The analysis of the VEPs parameters in the individual patient subgroup rendered a lot of interesting information. Together with a successive increase of the BDI score numbers in the subgroups IA – IC, the values of correlation coefficient decreased, respectively, which

reflected an extent of the interhemispheric asymmetry. It is of interest that in the subgroup IA – IC, together with an increasing dominance of the right hemisphere and increasing concentration of glycated hemoglobin in a blood, depressive symptoms got more intensified, and suicidal attempts incidence was higher. Considering the commonly known fact that the right cerebral hemisphere is responsible for emotional feelings, the obtained VEPs results seem to have a logical justification. It is interesting that the all suicidal attempts observed in our patient group concerned the persons showing in the VEPs recordings a dominance of the right hemisphere, which is corroborative for the findings of the other authors (Graae *et al.* 1996; Wittling, 1990). In our material, among 8 patients who reported suicidal attempt (of whom in 5 the attempts were multiple), there was only 1 man from the subgroup IB and 7 women assigned to the subgroup IC.

A very interesting report published by authors from the Northwestern University (Chicago, Ill, USA) showed that chronic depression, worsening with time, can lead to DM type 2 development (Carnethon *et al.* 2007). A connection between the long-term (of 10 years) depression symptoms and the risk of DM type 2 occurrence was analyzed in 4681 elderly patients. The authors found that chronic depression increased a probability of DM type 2 incidence regardless of the other risk factors, as overweight or CRP level. The suggested cause of this phenomenon was to be high level of cortisol, stress hormone, observed in patients with depression. A high discharge of cortisol probably leads to tissue insulin-resistance, increasing a risk of clinically evident DM. Moreover, cortisol facilitates a visceral obesity development, and reduces glucose uptake by the muscles, which are the two other DM risk factors. The quoted authors stated that high levels of cortisol is probable to put on risk of DM both elderly and young persons with depression (Carnethon *et al.* 2007).

Stebelova *et al.* (2007) notified that experimentally induced DM resulted in lower melatonin levels and the daily pattern of melatonin levels was without a characteristic night-time increase of hormone concentration. The lower amplitude of melatonin rhythm induced by experimental diabetes can contribute to desynchronization of daily rhythms – so characteristic for depression.

Coming to the conclusion, in the light of the results presented above, it seems reasonable to consider application of VEPs, a non-invasive and simple examination, as a useful tool in predicting a possible depressive episode, likewise as a marker of clinical course of depression. A special care should be given to diabetic patients with right cerebral laterality, because of more frequent occurrence of MDD and tendency to autodestruction in this patient population. Thus, these patients should be qualified to active counseling.

Worsening of depression symptoms was shown to have an unfavorable influence on DM course, therefore,

all patients with DM should be examined by a psychiatrist at least once a year. The BDI test could render a possibility of making an early diagnosis of depression, which would result in the better self-control and treatment, and in consequence, could reduce many serious DM complications.

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