GMR

Case Report

Dysregulation of gene expression in a patient with depressive disorder after transient ischemic attack confirmed by a neurophysiological neuromarker

M. Trystuła[1], M. Żychowska[2], M. Wilk-Frańczuk[3], J.D. Kropotov[4] and M. Pąchalska[5,6]

[1]Department of Vascular Surgery and Endovascular Interventions, John Paul II Hospital, Cracow, Poland
[2]Department of Life Sciences, Gdansk University of Physical Education and Sport, Gdańsk, Poland
[3]Cracow Rehabilitation and Orthopedics Center, Cracow, Poland
[4]Laboratory for the Neurobiology of Action Programming, Institute of the Human Brain, Russian Academy of Sciences, St. Petersburg, Russia
[5]Chair of Neuropsychology, Andrzej Frycz Modrzewski University, Cracow, Poland
[6]Center for Cognition and Communication, New York, NY, USA

Corresponding author: M. Trystuła
E-mail: m.trystula@szpitaljp2.krakow.pl

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ABSTRACT. The aim of this study was to evaluate dysregulation of gene expression associated with the cellular stress response in a patient with a post-"warning stroke" depressive disorder confirmed by

the presence of a neurophysiological neuromarker through the use of quantitative EEG and event-related potentials. The patient was tested for seven genes associated with the stress reaction: *HSPA1A*, *HSPB1*, *IL6*, *IL10*, *CRP*, and *HSF-1* along with *NF-κB*, compared to gene expression in health controls. A 54-year-old patient with a past history of schizophrenia (at the age of 20), and of transient ischemic attack (at the age of 53) and depressive disorder confirmed by functional, cognitive, emotional, and affectional diagnostics underwent additional testing for expression of the genes associated with stress response. The expression of genes coding for heat shock protein (*HSPA1A*, *HSPB1*), interleukins (*IL6*, *IL10*), and C-reactive protein was tested along with factors that regulate their expression. The results of the tests conducted on this patient were compared with 42 healthy control subjects. Diagnostic testing revealed upregulation in expression of these genes, presenting as increased expression of the target genes and of the regulatory genes. A post-"warning stroke" depressive disorder appears to be associated with overexpression of the genes coding for HSP and interleukins. Further research on larger groups of people may provide grounds for treatment modification.

Key words: Depressive disorder; Aphasia; Marker genes; HSP; Interleukins

INTRODUCTION

The post-stroke depression is both frequent in patients with established stroke (Rao, 2000; Hackett et al., 2005; Haq et al., 2010; Wu et al., 2010; Luijendijk et al., 2011; Eskes et al., 2015; Swartz et al., 2016) and minor stroke or transient ischemic attack (TIA) (Luijendijk et al., 2011; El Husseini et al., 2012; Carnes-Vendrell et al., 2016; Maaijwee et al., 2016).

Recent studies reveals that patients with stroke or TIA, a "warning stroke" not usually associated with long-lasting functional deficit, have similar frequency of depression and newly identified depression between 3 and 12 months after hospitalization (House et al., 2001; Watkins et al., 2011; El Husseini et al., 2012; Tene et al., 2016).

Researchers from North Carolina used a patient registry to identify depression and antidepressant medication use 3 and 12 months after hospitalization among 1450 individuals with ischemic stroke and 397 individuals with TIA. Three months following hospitalization for stroke or TIA, 17.9% of stroke patients had depression compared to 14.3% of TIA patients; at 12 months, the percentages were 16.4 and 12.8%, respectively (El Husseini et al., 2012). Persistent depression (diagnosis of depression at both 3 and 12 months) was present in 9.2% of those with stroke and 7.6% of those with TIA. A high proportion of patients with persistent depression was untreated with antidepressants (67.9% of those with stroke, 70% of those with TIA) (El Husseini et al., 2012). The risk of depression after even mild stroke or TIA was higher than the general population with a comparable age distribution (see also: Tene et al., 2016).

Although depression may affect functional recovery and quality of life after TIA, the condition is often ignored (Paolucci, 2008; Sangha et al., 2015). Only a minority of patients is diagnosed properly and even fewer are treated in the common clinical practice (Mirski et

al., 2015; Trystuła et al., 2016). In recent years, diagnostic testing for depressive disorder has improved thanks to new neurotechnologies, particularly event-related potentials (ERPs) and neuromarker detection (Mirski et al., 2015; Kropotov, 2009).

Another modern direction in the diagnostics of depression is based on research on so called marker genes, which present increased or decreased expression for a particular disorder in comparison to healthy control subjects (Mehta et al., 2010). Studies on gene expression are becoming increasingly important for diagnostics and evaluation of treatment effect. These studies are difficult to perform in humans due to limited access to cells for testing. Therefore, researching gene markers in particular disorders is limited to the genes expressed in peripheral blood leukocytes, such as genes coding heat shock protein (HSP) and those associated with the immune response.

Many studies have evaluated changes in the expression of genes coding HSP and interleukins (IL) due to endogenic and exogenic stressors. It is known that heat stress (Morimoto, 1998), oxidative stress (Aguilo et al., 2004), physical exertion (Tauler et al., 2006; Jastrzębski and Żychowska, 2015), drugs and dietary supplements (Horowitz et al., 2014; Żychowska et al., 2015), and concomitant diseases along with mental disorders (Kim et al., 2008; Pae et al., 2007) impact the expression of genes associated with cellular stress response. Activity that is too low or too high for particular genes results in a homeostatic imbalance. Detection of disorders in gene expression provides the possibility of more effective treatment, but also of control of the expression imbalance itself. However, detection of so called marker genes is challenging and therefore the markers of many diseases remain unknown.

Studies on gene expression in patients suffering from depression have begun relatively recently (Kahl et al., 2004). One of the hypotheses that explains the biological background of depression suggests that it may be the result of chronic inflammatory processes (Devorak et al., 2015). According to Pace et al. (2006), overexpression of *NF-κB*, which is related to regulation of IL secretion, is characteristic of people suffering from depression and therefore effective treatment should target on impaired regulation of these genes. Horowitz et al. (2014) proved that antidepressants lower expression of *NF-κB* and pro-inflammatory cytokine expression. Searching for biomarkers and research on individual variations in patients suffering from particular conditions are still important for diagnostic purposes and control of the treatment.

The aim of the present study was to evaluate potential dysregulation of gene expression associated with the cellular stress response in a patient with a post-"warning stroke" depressive disorder confirmed by the presence of a neurophysiological neuromarker through the use of quantitative EEG (QEEG) and ERPs. The patient was tested for nine genes associated with the stress reaction: *HSPA1A*, *HSPB1*, *IL6*, *IL10*, *CRP*, and *HSF-1* along with *NF-κB*, compared to gene expression in healthy controls.

MATERIAL AND MTHODS

Ethics statement

According to the guidelines of the Helsinki Declaration in 2008, subjects participating in the experiment were informed in detail about the test procedure and provided written consent for participation in the project. The study protocols received ethical approval from the Ethical Committee of the Regional Medical Chamber (KB6/16).

Case report

A 54-year-old male patient with a past history of schizophrenia (at the age of 20), and of transient ischemic attack (at the age of 53), caused a post-"warning stroke" depressive disorder. Doppler ultrasound proved that carotid artery sclerosis did not cause the TIA. Atrial fibrillation was also ruled out. It is suspected that a vasoconstrictive reaction increased pressure and might have caused the TIA. Directly before the TIA, the patient experienced severe stress at work. As a result of the TIA, the patient developed moderate anomia, which relieved after a week. However, motion slow-down, presenting mostly during speech, remained. The patient reported a depressed mood, sleep disorders with nightmares, and fasciculation in the upper limbs and abdomen. At that time, he underwent functional brain examinations [QEEG, ERPs, standardized low resolution electromagnetic tomography (sLoreta)]. The results demonstrated functional changes related to concentration disorders, impulsiveness, and difficulties in reaction to stimuli GO/NOGO, which are characteristic manifestations of a past TIA episode. A post-"warning stroke" depressive disorder was confirmed by functional, cognitive, emotional, and affectional diagnostics, testing for a depressive disorder neuromarker through the use of QEEG and ERPs. The patient underwent twenty sessions of neurotherapy (neurofeedback), which was not effective. Therefore, we offered additional testing for expression of the genes associated with stress response. The expression of genes coding for HSP (*HSPA1A*, *HSPB1*), IL (*IL6*, *IL10*), and C-reactive protein (*CRP*) was tested along with factors that regulate their expression. The results of the tests conducted on this patient were compared with 42 healthy control subjects.

Neurophysiological testing

QEEG

Nineteen channel EEG have been recorded in resting state with eyes open (3 minutes), eye closed (3 minutes) and during performing of the cued GO/NOGO task described in detail in Kropotov (2009). Behavioral parameters such as Commission and Omission errors, reaction time (RT) were found within the normal limits but the variance of response was significantly ($P < 0.02$) higher in the subject in comparison to HC group (data taken from the Human Brain Institute) (Table 1).

Table 1. Behavioral data in the cued GO/NOGO task in comparison with the data obtained in a group of healthy controls of the corresponding age (N = 53).

Data	Ignorance (Commission)	No deceleration (Ommission)	RT1	Var(RT1)
Patient	9%	4%	405 ms	14.1 ms
Normal value	2.6%	0.7%	400 ms	7.6 ms
P value	0.15	0.11	0.95	0.02

According to the subject's anamnesis two working hypotheses were tested: 1) the subject will show neuromarkers of anxiety, and 2) the subject will show neuromarkers of schizophrenia. The first hypothesis was proven: indeed the subject had low voltage fast EEG subtype with excessive high beta activity at the vertex (Figure 1a). According to literature this QEEG endophenotype is often seen in subjects with anxiety (Enoch et al., 1999). The second

hypothesis was not proven: no decrease of NOGO-GO difference wave in the cued GO/NOGO task, a hallmark of schizophrenia (Kropotov, 2016), was found in this subject (Figure 1b).

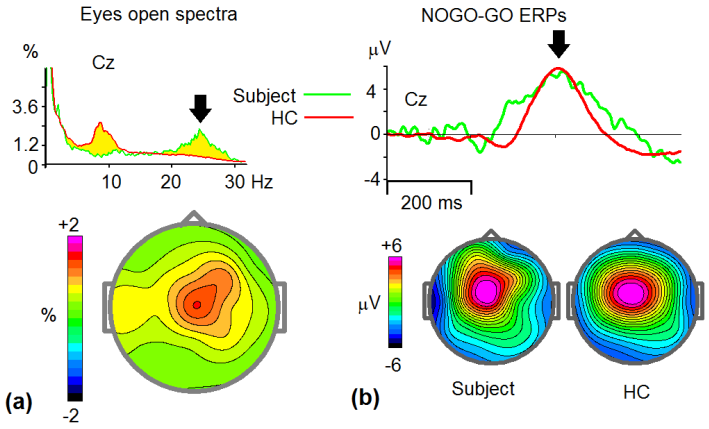

Figure 1. Testing functional neuromarkers of anxiety and schizophrenia in the subject. **a.** Top: relative EEG spectra in resting state with eyes open at Cz for the subject (green) and for the group of healthy controls of the corresponding age (N = 53). Note significant (P < 0.01) increase of the relative high beta activity with maximum indicated by arrows. Bottom: map of the difference spectra (Subject-HC) at frequency indicated by arrow. **b.** Top: ERP GONOGO wave at Cz for the subject (green) and the group of healthy controls of the corresponding age (N = 53). Note no difference between the waves at maximum indicated by arrow. Bottom: maps for the subject and healthy controls at the time indicated by arrows (at the top of the figure).

Neuropsychological testing

Neuropsychological examination was performed using the Cracow Neurolinguistics Tool for Aphasia Diagnostics (Pąchalska, 2011). In the first examination, conducted three days after the onset, the patient was diagnosed with moderate amnestic aphasia. Other linguistic functions, such as understanding, writing, and reading, were not impaired or remained within the normal limit (Figure 2). Follow-up examinations performed after one week showed normalized profile of language functions. The patient not present anomia anymore (Figure 2).

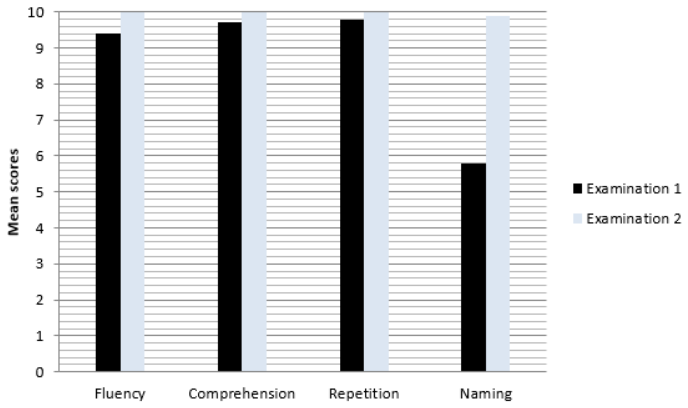

Figure 2. Results obtained with Cracow Neurolinguistic Tool for Aphasia Diagnostics.

The patient scored 28 of 30 on the Beck Depression Inventory, which indicates a severe a post-"warning stroke" depressive disorder. Neurofeedback was recommended, using bipolar electrodes in the Cz-Fz points. The primary goal of therapy was to lower high beta activity of 20-30 Hz.

Follow-up functional examinations of the brain (QEEG, ERPs, sLoreta) performed to assess neurofeedback therapy effectiveness suggested improvement in all examined neuropsychological parameters. Post-stroke depressive disorder also decreased, although the improvement was insignificant. Application of the new neurotechnologies enabled detection of depression neuromarker through the use of QEEG and ERPs and confirmed the post-stroke depressive disorder. Due to the fact that neurofeedback was not fully effective in treatment of depression, the patient underwent genetic testing, which might suggest additional therapeutic options for improving the patient's quality of life.

Genetic testing

The patient's peripheral blood leukocytes were used for gene expression testing. Testing included genes coding HSP, ILs, *HSF-1*, and *NF-κB*. Blood samples were taken from the ulnar vein to assess relative expression of tested genes in leukocytes via quantitative reverse transcription polymerase chain reaction (qRT-PCR). Gene expression testing demonstrated downregulation of transcriptional factors and dramatic upregulation of genes encoding heat shock protein and selected interleukins in the patient with depression compared to expression in the control group. It is possible that dysregulation in the expression of transcriptional factors and genes associated with the cellular stress response is associated with depression.

Participants and sample collection

A 2-mL sample of venous blood was obtained from the treated patient and 42 healthy control subjects in order to test for gene expression. The blood was sampled in the afternoon (approximately 4:00 pm). The control group consisted of healthy men ranging in age from 40 to 60 years (mean 53.4 years), who did not recently receive any drugs. Blood was collected in the afternoon, between 4:00 and 5:00 pm. All procedures for genetic testing were performed in exactly the same way for the patient and controls.

RNA isolation and RT

Whole blood was lysed by TRIZOL (Lifetechnology, Poland). Isolation of RNA was performed as described by Chomczynski and Sacchi (1987). Isolated RNA was purified with DNase I (Initrogen, LifeTechnologies, Poland) in order to remove the DNA. Purity and concentration of obtained RNA was determined spectrophotometrically (Eppendorf BioPhotometer Plus, Germany). RT was performed from 2 µL RNA using Transcript Me RNA kit (DNA, Gdańsk, Poland). Remnant RNA was purified by RNAse H. After RT, cDNA was stored at -20^{o}C.

Quantitative reverse transcription polymerase chain reaction (qRT-PCR)

qRT-PCR was performed in three technical replicates using a Light Cycler 480II (Roche, Poland). The reaction mixture contained: 5 µL LightCycler polymerase (Roche,

Poland), 0.25 µL of each reverse and forward primers, 2 µL cDNA, and water to a final volume of 10 µL. The thermal profile of the PCR was consistent with the manufacturer's instructions.

Statistical analysis

In order to calculate the level of genes expression, the Schmittgen and Livak (2008) $\Delta\Delta C_t$ method was used. Tata box protein (*TBP)* was measured as a reference gene. For control group, mean and SD were calculated. All graphs and calculations were performed using GraphPad Prism 6.0 (graphpadprism.com). The primers used in PCRs are presented in Table 2.

Table 2. Primers used in PCRs.

Gene	Primers
TBP	F: TGGACTGTTCTTCACTCTTGGC R: TTCGGAGAGTTCTGGGATTGTA
HSPA1A	R: TTCGGAGAGTTCTGGGATTGTA F: TGGACTGTTCTTCACTCTTGGC
HSPB1	R: GAGGAAACTTGGGTGGGGTCCA F: AAGGATGGCGTGGTGGAGATCA
IL6	R: GACATCAAGGCGCATGTGAAC F: TCCACGGCCTTGCTCTTGTTT
IL10	R: AATTCGGTACATCCTCGACGG F: GAATCCAGATTGGAAGCATCC
CRP	R: TCTTGGTCTTGACCAGCCTCT F: TCGTTAACGGTGCTTTGAGG.
HSF-1	R: CAGGAGCTTGGAGTCCATGCA F: GAGCAGCTCCTTGAGAACATC
NF-kB	R: GATCCCATCCTCACAGTGTTT F: TGGACTACCTGGTGCCTCTA
HIF-1	R: TTCCATTTTTCGCTTCCTCTGAGCATTC F: ACTGCCACCACTGATGAATCAAAAACAG

RESULTS

Differences in gene expression in the patient are described in the context of the control group in Figure 3.

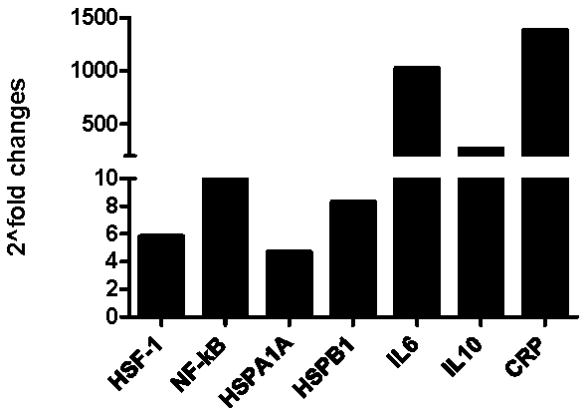

Figure 3. Fold change in expression between patient and control groups. Dark columns indicate higher expression in the patient group.

Significant differences in the expression of all tested genes between the patient and control group (N = 42) were noted. The largest differences were seen in *CRP* mRNA (12^379-fold), *IL6* mRNA (2^1022-fold), *IL10* mRNA (2^266-fold), *HSPB1* mRNA (2^8-fold), and *HSPA1A* mRNA (2^4.66-fold).

The profile of differences in *HSF-1* and *NF-κB* was also higher in the patient and amounted to 2^5.8-fold for *HSF-1* and 2^13-fold for *NF-κB*. Precise values of Qt for the tested genes and standard deviations within the control group are presented in Table 3.

Table 3. Relative expression (2^Qt) of genes in the patient and control group (N = 40) and t.

Relative expression (Qt) of genes	*HSF-1*	*NF-κB*	*HSPA1A*	*HSPB1*	*IL6*	*IL10*	*CRP*
Patient	4.2938	3.7	5.651	40.098	8.962	42.834	28.351
Control group	0.74	1.15	13.35	1.89	0.04	0.03	0.03
(Mean ± SD)	±0.2	±0.21	±2.631	±0.78	±0.021	±0.02	±0.01
P value	<0.0001		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

DISCUSSION

Many studies regarding changes in the expression of genes coding HSPs and ILs due to endogenic and exogenic stressors have been published (Góral-Półrola et al., 2015). Studies focusing on changes in gene expression in psychiatric patients most often regard diseases such as schizophrenia (Freudenreich et al., 2010; Chase et al., 2015), depression (Horowitz et al., 2014), and anorexia (Kahl et al., 2004). According to Arion et al. (2007) overexpression of *HSPA1A* and *HSPB1* during the developmental process might be related to occurrence of schizophrenia, whereas Freudenreich et al. (2010) reported immune response disorders in patients suffering from this illness. Experiences gained during research conducted on people with various dysfunctions indicate that gene expression might be increased or decreased in comparison to healthy control subjects. However, it is not easy to find a biological marker specific to the particular condition, especially because of concomitant diseases. In the presented case, the patient was diagnosed with a post "warning stroke" depressive disorder. According to Devorak et al. (2015) an inflammation theory is one of the basic explanations for biological mechanisms triggering depression. High expression of pro-inflammatory factors might be a result of this disorder. The patient described here was tested for pleiotropic cytokine IL6 and anti-inflammatory cytokine IL10. The expression level for the gene encoding IL6 was significantly elevated, as was the expression of the gene coding CRP, which often indicates intensity of inflammation. In addition to the aforementioned genes, the expression of HSP genes was tested along with transcription factors of the pathways associated with cellular stress responses (*HSF-1* and *NF-κB*).

The patient diagnosed with a post-"warning stroke" depressive disorder had also increase in expression of the genes for transcription factors *HSH-1* and *NF-kB* (2^5.8 and 2^13.2-fold) and increased expression of genes for *IL6*, *IL10*, and *CRP* (2^1022-, 286-, and 1379-fold, respectively). Higher transcription was also detected for the genes encoding *HSPA1A* and *HSPB1*. Based on the fact that the main function of HSP 70 and HSP 27 is to protect cells from apoptosis and support degradation of denatured proteins, it can be assumed that the stress level in this patient is high. However, interpretation of changes in HSP gene expression is difficult because its high level on one hand indicates that stress has already exceeded the critical level, and on the other, low expression suggests that there is no sufficient protection against stressors (Morton et al., 2009). It cannot be excluded that prolonged

overexpression may exacerbate a post-"warning stroke" depressive disorder, similar to its influence on occurrence of schizophrenia (Arion et al., 2007).

The expression of the gene encoding *NF-κB*, which is known to be associated with production of pro-inflammatory ILs, was surprisingly low (Tak and Firestein, 2001). Furthermore, Pace et al. (2006) proved that its expression is upregulated in depressive disorders. It is possible that its increased expression was related to very high expression of the gene for *IL6*. In addition, increased expression of the second transcription factor might have been caused in increased *HSPA1A* expression. According to Ferat-Osorio et al. (2014), increased HSP expression results in a decrease in expression of *HSF-1* and pro-inflammatory cytokines. In our Patient genes encoding HSP increased lower than genes encoding interleukin and *NF-kB*.

In summary, the patient diagnosed with a post-"warning stroke" depressive disorder confirmed by the presence of a neurophysiological neuromarker through the use of QEEG and ERPs, also cognitive, emotional, and behavioral disorders characteristic of depression, had apparent dysregulation of tested genes, including a stress response characterized by overexpression of all tested genes, especially *IL6* and *CPR* mRNA. These data correspond with the inflammation theory as an underlying biologic mechanism in depression. Based on the expression results, increased cellular stress might be concluded. Although low expression of transcription factors in this patient is surprising and does not correspond with reports of Pace et al. (2006).

CONCLUSION

It was found that in a patient with a post-"warning stroke" depressive disorder confirmed by the presence of a neurophysiological neuromarker through the use of QEEG and ERPs, the HSF and NF-kB dependent pathways appear to be upregulated. Overexpression of genes associated with HSP and interleukins might suggest that the patient should receive a therapy that will lower such expression. It might be helpful to control the expression of these genes during treatment in order to choose the best therapeutic option. The obtained results should be confirmed by studies conducted on a larger number of people suffering from a post "warning stroke" depressive disorder.

Conflicts of interest

The authors declare no conflict of interest.

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