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CASE REPORT PEER REVIEWED | OPEN ACCESS

Cognitive event-related potentials in patient with hereditary hemochromatosis: A case report

Nataša Klepac, Magdalena Krbot Skorić, Natalia Palac, Petra Nimac Kozina, Ivan Adamec

ABSTRACT

Introduction: Hereditary hemochromatosis is an autosomal recessive disorder, characterized by iron overload and accumulation in liver, pancreas, heart and brain with secondary tissue damage. Mutations in the hemochromatosis gene are commonly associated with hereditary hemochromatosis and consequently iron overload. The 2 most common hemochromatosis gene variants are C282Y and H63D. Hemochromatosis gene mutations are being investigated as genetic risks for neurodegenerative disorders since iron accumulation in the brain are consistent observations in many neurodegenerative diseases. Multiple studies discussed the association between hereditary hemochromatosis and Alzheimer's disease. Although cognitive impairment is well known feature of hereditary hemochromatosis the exact cause is unknown. Cognitive event-related potentials are method for testing higher cognitive functions. It allows completely non-invasive insight into cognitive processes, in particular through the display of the timeliness of the cognitive process, because the method has a very high temporal resolution. The changes in cognitive event-related potentials are characteristics for Alzheimer's disease. Case Report: We present for the first time results of cognitive event-related potentials in case of a patient with hereditary hemochromatosis. Patient is homozygous for the C282Y variant of hemochromatosis protein mutation gene and has positive family history for dementia. Cognitive event-related potentials showed reduced amplitude and prolonged latency of response which was similar to changes observed in Alzheimer's disease patients. Conclusion: Neuro-electrophysiological changes observed in our patient with hereditary hemochromatosis and cognitive impairment were similar to that observed Alzheimer's disease patients. Based on our findings hereditary hemochromatosis and Alzheimer's disease share the same neurophysiological characteristics indicating that impairment of iron homeostasis may be underlining cognitive impairment in both disorders.

Keywords: Alzheimer's disease, Cognitive event-related potentials, Hereditary hemochromatosis, Hemochromatosis gene

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INTRODUCTION

Hereditary hemochromatosis (HH) is autosomal recessive disorder, characterized by iron overload and accumulation with secondary tissue damage. It affects individuals of European descent and has been described as the most common genetic disorder in Caucasian populations. Hereditary hemochromatosis patients are unable to metabolize excess iron which leads to the build-up and consequently to widespread tissue damage, including liver cirrhosis, and other serious complications [1]. Hemochromatosis gene (HFE) protein is iron regulatory protein. Mutations in the HFE gene are commonly associated with the HH and consequently iron overload. Iron accumulation in the brain and increased oxidative stress are consistent observations in many neurodegenerative diseases and therefore HFE gene mutations are being investigated as genetic risks for neurodegenerative disorders [2]. Given the involvement of the HFE protein in iron regulation and oxidative stress, mutations in the HFE gene can be expected to affect Alzheimer's disease (AD) pathogenesis. Excessive iron accumulation in neuritic plaques and neurofibrillary tangles (NFT) and oxidative stress are consistent observations in the pathogenesis of AD [2].

Cognitive event related potentials (ERPs) are method for testing higher cognitive functions. The method is completely independent of cultural and educational impact. It allows rapid, non-invasive insight into cognitive processes, in particular through the display of the timeliness of the cognitive process, because the method has a very high temporal resolution. By changing of its parameters, it is possible to examine the changes that occur in the various steps of cognitive processing and thereby gain insight into which part of the system is damaged.

Results of ERPs methods are divided into three main elements: information on latency, amplitude and localization of the major component, 'P300'. In addition to these neurophysiological parameters, the paradigm in which is included the motor response to "target" stimulus, also provides information about the associated reaction time.

Latency of P300 component is related to the speed of classification and processing of stimuli and is dependent on the difficulty of the task related to the stimulus. It indicates the time taken for the cognitive processing of stimulus and is sensitive measure of neural activity associated with attention and working memory. Difficult categorization of stimulus indicates a longer time required for the processing of stimuli and generates a longer latency of 'P300' component. The amplitude of the P300 component reflects the intensity of mental activity required for cognitive processing of stimuli. It is proportional to the amount of attention attributed to a particular stimulus [3].

One of the indicators of cognitive deficits can be the change of localization of the major component. This shows that the neural structures responsible for cognitive processing of stimuli do not perform their function and their functions are taken over other structures.

Commonly used paradigm to obtain ERPs is 'oddball' paradigm. In this paradigm, there are usually two different stimuli, one that occurs frequently ("non-target" stimulus) and another that occurs rarely ("target" stimulus). Respondent receives a task that is related to "target" stimulus. This task may be related to motor response - pressing buttons after the target stimuli or by checking the capability of working memory - counting "target" stimuli. In this way, it is possible to determinate the ability of discrimination of stimuli, which is one of the indicators of cognitive deficits and is associated with certain forms of dementia, and also examine the functional state of working memory and the decision-making ability [3].

In the experiment, two stimuli ("target" and "non-target") were presented to a patient using an earphone set. There were 50 "target" stimuli and 200 "non-target" stimuli for each paradigm (counting and reaction time). "Target" stimuli were tones with frequency of 2000 Hz and "non-target" stimuli were tones with frequency of 1000 Hz.

During the experiment patient was instructed to minimize blinking and body and ocular movements as much as possible. Patient's eyes were kept closed during the experiment in order to avoid unwanted blinking. In reaction time paradigm, patient was instructed to press the push button as soon as he hears the "target" stimuli. In counting paradigm, he was only instructed to count "target" stimuli with no motor reaction. A reaction time was calculated as a period from the moment the stimulus started till the moment in which the push button was pressed.

An E-Prime software (Psychology Software Tools, Inc.) was used for generation of stimuli, registration of response time and registration of false/correct responses. Event-related potentials (ERP) were recorded using a 32-channel EEG device. As a recording device, an amplifier BrainAmp with an Ag/AgCl electrode cap was used (BrainProducts GmbH, Germany). Recording software was a Brain Vision Recorder and software for analysis was Brain Vision Analyzer software (BrainProducts GmbH, Germany). The electrodes were placed according to the International 10/20 system plus additional electrodes FC5, FC1, FC2, FC6, TP9, CP5, CP1, CP2, CP6, TP10 and Oz. EEG signals were filtered with a pass band filter with a low-cutoff frequency set to 0.1 Hz and a high-cutoff frequency set to 30 Hz. All signals were digitalized by a sample rate frequency of 1000 Hz. Horizontal and vertical eye movements were recorded with HEOG (two bipolar channels) and VEOG (one channel referenced towards reference electrode).

The evoked potential analysis was performed off-line after each experiment. The analyzed interval was 100 ms before and 1000 ms after the end of the presented set. The ERP baseline was determined as the average of all samples from the first 100 ms period. Before each signal averaging, the computerized semiautomatic ocular correction and artefact rejection were made in order to reject trials in which blinks, artefacts or deviations in the eye position occurred.

CASE REPORT

We present a patient with HH that is homozygous for the C282Y variant of HFE protein mutation gene. For the past ten years he has been treated by phlebotomy because of HH.

A 57-year-old male with positive family history for cognitive impairment– his father had dementia. He was worker with eight years of education, married, right-handed. He came to our Department because of his progressive memory problems. During last two years he has been having progressive cognitive decline. First symptoms started two years ago with problems with episodic memory presented through forgetting recent events and frequent asking the same questions. Over time his symptoms progressed and he becomes disoriented in time and space, and dependent in everyday activities on help of his family members. On admission his Mini Mental State Examination (MMSE) was 16, and Clock Drawing Test 2.We performed a battery of cognitive tests to assess cognitive domains of verbal and visual memory, executive functions, speech, attention and visuoperceptives abilities. Results of neuropsychological tests are given in Table 1. Overall cognitive tests shown cognitive impairment present in all assessed domain. Activity of liver enzymes as well as level of ammonia in the blood was normal. He showed no sign of diabetes, hepatic cirrhosis and cardiomyopathy. Magnetic resonance imaging scan of the brain showed diffuse atrophy (Figure 1) and atrophy of hippocampus (Figure 2). Results of ERP-s showed reduced amplitude (4.2 μV) and prolonged latency of response (392 ms) and prolonged motor responses (756+/-177 ms) (Figures 3 and 4) for reaction time paradigm.

According to the normative values, all values of amplitude lower than 5 μV are considered reduced (related to the age of participant). Also, related to the latency, expected latency for participants from 50 to 60 years should be from 360 to 380 ms. Obtained results are in coinciding with other studies [4].

We started treatment with memantine and continued to monitored patient in our Department.

Table 1: Neuropsychological assessment.

	Raw score	Standardized score
Mini Mental State Examination Test	16/30	
Memory		
California Verbal Learning Test –total recall	6	50 (7.9)
California Verbal Learning Test – immediate recall	0	11.1(2.5)
California Verbal Learning Test – delayed recall	0	7. (2.5)
Rey–Osterrieth complex figure– recall	0/36	19.5 (6.7)
Language		
The Boston Naming test	35	55.6 (3)
Token test	79/163	162
Praxis		
Rey–Osterrieth complex figure– copy	2/36	33 (1.5)
Attentional and executive functions		
Trail Making test A (seconds)	300	26
Trail Making test B (seconds)	Wasn't able to perform	65
Digit forward	6	8
Digit backward	3	6
Controlled association letters test	4	50.19 (6.43)

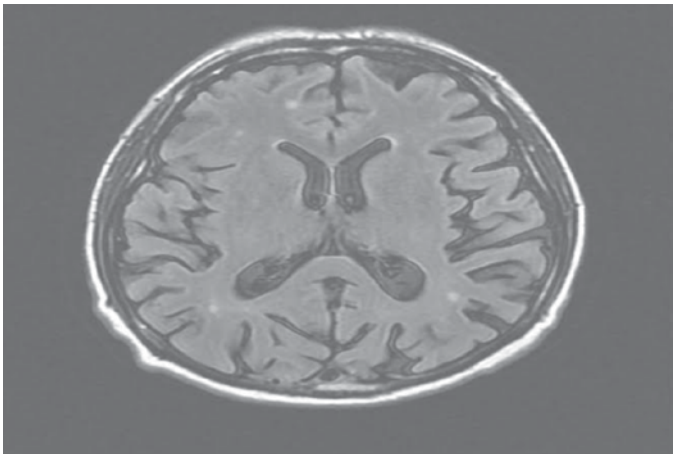

Figure 1: Magnetic resonance imaging scan of brain showing diffuse atrophy.

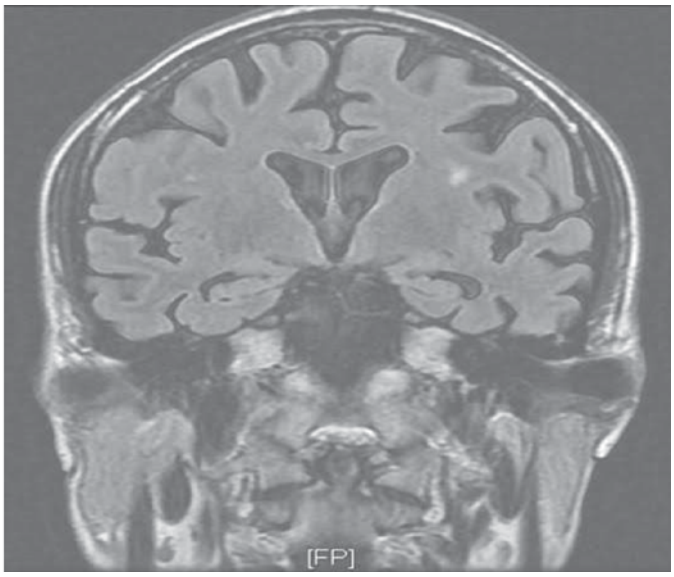

Figure 2: Magnetic resonance imaging scan of brain showing atrophy of hippocampus.

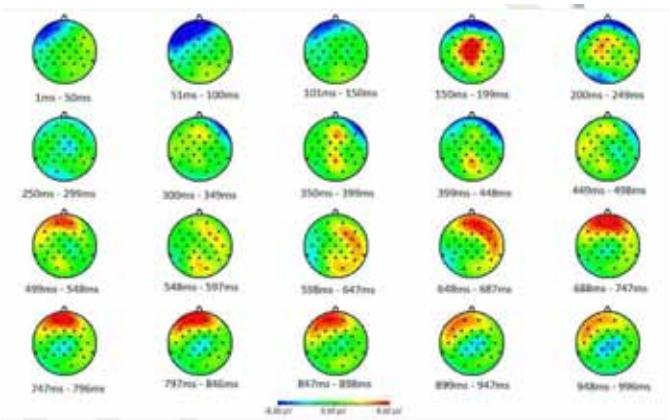

Figure 3: Spatiotemporal distribution of cognitive response. Ocular correction was preformed.

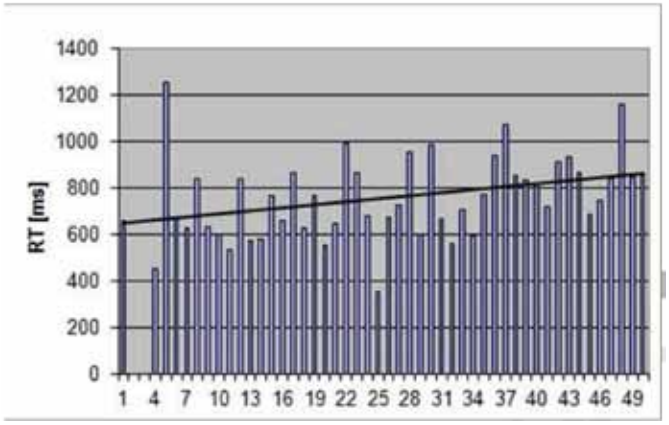

Figure 4: Prolonged reaction time required for the processing of stimuli.

DISCUSSION

Changes in brain iron status have been established in AD affecting plaque formation, amyloid processing, and expression of and response to inflammatory agents suggesting that changes of iron homeostasis can be central to the pathogenic events in AD. HH is characterized by iron overload and accumulation in organs with secondary tissue damage. During the past 10 years, multiple studies have addressed the association of the HFE gene mutations with AD. It was showed that alleles in the HFE gene accelerate the onset of AD by five years founding an association with increased oxidative stress in AD patients [5]. In contrast to the above studies, there are also studies that found no association of HFE alleles with AD [6]. So the relationship between AD and HH is still controversial. Case reports have described patients with extrapyramidal or cognitive dysfunction, confusion and psychomotor retardation, fatigue and impaired short-term memory [7]. Despite that fact there has been little investigation of the cognitive deficit that was observed in HH [8]. It was speculated that neurological symptoms results from hepatic encephalopathy rather than deposition of iron in the brain [9]. However, Williams et al. reported patient with HH and movement disorders symptoms that had just mildly raised serum alanine aminotransferase with other liver function tests that were within normal range. They verified iron accumulation in the brain by the biopsy as a cause of patient symptoms [10]. Here we report for the first time the results of neuropsychological test and ERP-s in patients with HH. ERPs have been used as a marker of cognitive function in patients with psychiatric and neurological disorders. Moreover, they showed validity as an objective tool for the demonstration of cognitive function in AD. Due to AD there are early changes in ERP such as reduction of the amplitude and increase in latency that can differentiate AD subjects from healthy elderly persons and other causes of dementia such as head injury. Moreover, there is also strong relation between ERP and other cognitive variables which are also impaired in patients with Alzheimer's, such as memory and cognition. Brain areas, such as the central-parietal cortex, frontal cortex and the hippocampus, generate the ERP, which are structures usually affected in patients with AD [11]. Changes in ERP as well results on neuropsychological test of our patient with HH were identical to AD. Based on these facts and absence of liver enzymes abnormalities we concluded that a cognitive deficit in HH is consequence of brain impairment due to iron accumulations in specific region of the brain such as central-parietal cortex, frontal cortex and hippocampus. We speculated that this fact could accentuate the role of iron homeostasis in the pathogenesis of AD. Our case report has several limitations. The possible iron accumulation in the brain as a cause of cognitive impairment was not confirmed by brain biopsy. The design of the study was case report so we did not compare results of our patient with results of AD patients.

CONCLUSION

We report detailed cognitive testing and neuro-electrophysiological evaluation of the patients with hereditary hemochromatosis (HH) and cognitive impairment. Results of cognitive evoked potentials showed reduced amplitude and prolonged latency of response and prolonged motor responses. Based on our findings we concluded that neuro-electrophysiological changes observed in patient with HH - and cognitive impairment shares many common characteristics with Alzheimer's disease (AD) patients. This could indicate that iron overload and accumulation in neuritic plaques and neurofibrillary tangles may be common cause of cognitive impairment in AD and HH patients. Further studies with follow-up should be performed to test this hypothesis.

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Author Contributions

Nataša Klepac – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Magdalena Krbot Skorić – Acquisition of data, Drafting the article, Final approval of the version to be published
Natalia Palac – Acquisition of data, Revising it critically for important intellectual content, Final approval of the version to be published
Petra Nimac Kozina – Acquisition of data, Drafting the article, Final approval of the version to be published
Ivan Adamec – Substantial contributions to conception and design, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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