Advances in Medical Sciences 61 (2016) 198–202

Contents lists available at ScienceDirect

Advances in Medical Sciences

journal homepage: www.elsevier.com/locate/advms

Original Research Article

Polymorphisms in the type I deiodinase gene and frontal function in recurrent depressive disorder

Elżbieta Gałecka [a,*], Monika Talarowska [b], Agata Orzechowska [b], Paweł Górski [a], Janusz Szemraj [c]

[a] Department of Pneumology and Allergy, Medical University of Łódź, Poland
[b] Department of Adult Psychiatry, Medical University of Łódź, Poland
[c] Department of Medical Biochemistry, Medical University of Łódź, Poland

ARTICLE INFO

Article history:
Received 10 March 2015
Received in revised form 29 October 2015
Accepted 28 December 2015
Available online 13 January 2016

Keywords:
Type I deiodinase
Polymorphism
Cognitive functions
Recurrent depressive disorder

ABSTRACT

Purpose: Significant impairment of some psychological functions, including cognitive functioning, has been characteristically found in depressed patients. Memory disturbances may be related to the levels of thyroid hormones (TH) that are under the influence of different mechanisms and molecules, including deiodinase type 1(D1) – an important determinant of circulating triiodothyronine (T3). We investigated the relationship between two functionally known polymorphisms within the *DIO1* gene, i.e. *DIO1*a-C/T and *DIO1*b-A/G, and cognitive functioning in patients diagnosed with recurrent depressive disorder (rDD). In the planned analysis we mainly concentrated on the frontal function: working memory, executive functions and verbal fluency.

Materials and methods: Genetic variants were genotyped in 128 patients using a method based on polymerase chain reaction (PCR). Cognitive functions were assessed by the Trail Making Test, the Stroop Test and the Verbal Fluency Test (VFT).

Results: No significant associations were found between *DIO1* polymorphisms and cognitive functioning in rDD. Only the CT and TT genotypes of the *DIO1*a variant were significantly related to verbal fluency. There were no significant differences between the distribution of the genotypes and demographic/medical variables.

Conclusions: Based on the study, the examined polymorphisms are not an important risk or protective factor for cognitive impairment in depressive patients. Functional variants within the *DIO1* gene that affect triiodothyronine (T3) levels seem not to be associated with cognitive functions. Nevertheless, considering the fact that the *DIO1* gene is related to the course and management of depression, further studies on a larger sample size might be suggested.

1. Introduction

Depressive disorder is one of thoroughly investigated diseases. It is widely known that the etiology of depression is heterogenic and the characteristic features observed in depressed patients are complex. Depressive disorder is characterized by changes in the levels of thyroid hormones (TH) [7]. The changes include higher levels of circulating thyroxine (T4) and low levels of triiodothyronine (T3). In addition, supplementation of an antidepressant therapy with T3 improves therapeutic effects. Cognitive impairment is common and widely recognized as an important dysfunction in patients diagnosed with depression [1–3]. The cognitive impairment, which is correlated with both the earlier onset of depressive symptoms and the prolongation of episodes, may in return contribute to the ineffectiveness of an antidepressant therapy and impede full recovery, thus leading to incomplete functional remission [4].

The aforementioned disturbances include different forms from moderate to significantly intensified [5], such as psychomotor retardation, decrease in effectiveness of memory processes, learning novel information, attention, spatial visualization, verbal fluency and executive function [4]. It is worth emphasizing that particularly frontal functions such as attention, working memory and executive function play an important role in the course of depressive disorders [6]. In addition, cognitive deficits are regarded as a sustained marker for the occurrence of depressive episodes but

* Corresponding author at: Department of Pneumology and Allergy, Medical University of Łódź, 22, Kopcińskiego St., 90-153 Łódź, Poland. Tel.: +48 42 6787505; fax: +48 42 6787505.
E-mail address: galeckaela@wp.pl (E. Gałecka).

http://dx.doi.org/10.1016/j.advms.2015.12.008
1896-1126/

are also observed during periods of remission [7]. According to Quinn and Joormann [8] effectiveness of executive function and cognitive control are linked with depressive symptoms appearance.

Thyroid and mainly TH and TH-related signals play an important role in various brain networks and areas, including those affecting cognition. Receptors for TH are widely expressed in the brain and especially T3, affects brain function and cognitive processes by participating in many biological mechanisms such as neurogenesis, neurotransmission and gene expression [9,10]. In addition, higher levels of T4 are also correlated with the number of neocortical neuritic plaques and neurofibrillary tangles in Alzheimer disease and Alzheimer-type neuropathologies [11]. Thyroid dysfunctions and changes in TH levels are known to be involved in cognitive deficits. For example, patients with hypothyroidism are characterized by working memory impairment [12] and disturbances in abilities such as visual perception, memory, attention, reduced executive function or poor learning [13,14]. In addition, treating different kinds of hypothyroidism with a combined therapy based on T4 and T3 resolves cognitive disturbances in most cases [15]. Longer P300 latencies – markers of cognitive activity – in subjects with hypothyroiditis were significantly longer than in control subjects and decreased substantially after thyroxine treatment [16]. There are findings that hyperthyroidism is also related to cognitive impairment including attention, verbal memory and executive function [17]. Cognitive disturbances in depression may be also associated with non-thyroidal illness syndrome, known as low T3 syndrome [18].

TH metabolism and levels are determined by many different mechanisms. Important factors that participate in the conversion of T4 to T3 and reversed (rT3) are type 1, 2, 3 iodothyronine deiodinases (D1, D2, D3) [19]. D1 is mainly expressed in thyroid, kidney and liver, and is responsible for 80% of circulating T3 levels. Moreover, the enzyme plays an important role in the determination of T3 levels in neurons, as produced by D1 circulating T3 may enter neurons directly from blood and cerebrospinal fluids [19,20]. Certain results indicate an association between genetic variants of the molecules involved in TH metabolism and signal transduction and the development of diseases with cognition impairment. For example, Goumidi et al. [21] revealed a tendency toward an association between gene *THRA* encoding for TH receptor, which increased the risk of developing Alzheimer's disease, while Lou et al. [22] found that the *DIO2* gene variant may participate in incidents of mild cognitive impairment.

Genes encoding for the molecules involved in TH metabolism could determine TH levels. There are results which indicate that a polymorphism within deiodinase encoding genes may affect enzyme activity, protein concentration and, consequently, the levels of TH in healthy subjects. The relationship between genetic variants within the *DIO1* and TH serum concentration was demonstrated in several studies and described by Verloop et al. [23]. The functionality of polymorphisms within the *DIO1* gene was presented by de Jong et al. [24], and revealed that *DIO1* variants are associated with iodothyronine levels [24]. Peeters at el. [25] found that single nucleotide polymorphisms (SNPs) *DIO1*a-C/T and *DIO1*b-A/G within *DIO1* are related to levels of TH. For example, allele T of the *DIO1*aC/T variant is associated with higher serum rT3 levels and lower T3/rT3 ratio, while allele G of the second polymorphism is related to higher T3/rT3 ratio.

The relationship between cognitive performance and T3 action is rather confirmed; in addition, low levels of T3 are characteristically found and confirmed in depression. There are also results which underline the importance of the *DIO1* gene in the development of late life major depression Philibert et al. [26] and indicate effectiveness of an antidepressant therapy with T3, which depends on a respective genotype [27]. Moreover, doses of TH improved mood and learning abilities [28]; while D1 was found to be important in the synthesis and determination of T3 concentration not only in the periphery, but also in the brain cells [29].

Considering the above, the aim of this study was to investigate whether functional polymorphisms within the *DIO1* gene are related to cognitive frontal functions (working memory, executive functions and verbal fluency) in patients suffering from recurrent depressive disorder (rDD).

2. Patients and methods

2.1. Subjects

The study was carried out in a group of 128 subjects aged 20–67 (M = 47.74 yrs., $SD \pm 10.99$). All the patients were native inhabitants of central Poland and were unrelated to one another. To avoid a population stratification effect, genotypes were determined only in individuals of Polish origin. Selection of individuals for the tested group was performed randomly without replacement sampling.

Patients were selected for the study based on the inclusion criteria for rDD outlined in ICD-10 (F32.0-7.32.2, F33.0-F33.8) [30]. All the subjects were examined during the course of their hospitalization and no concurrent diagnoses of somatic diseases or axis I and II disorders other than depressive episode were made. Other exclusion criteria included inflammatory or autoimmune disorders, thyroid diseases, unwillingness to give informed consent, and injuries to the central nervous system that could have affected cognitive function. For all the subjects, a case history was obtained prior to participation using the standardized Composite International Diagnostic Interview (CIDI) [31,32]. Before deciding to participate in the study, the subjects were informed of its purpose, assured that participation was voluntary, and guaranteed that personal data and the results of the tests would be kept confidential. Written informed consent for participation was obtained from each subject according to the study protocol that was approved by the Bioethical Committee of the Medical University of Lodz no. RNN/110/10/KE.

2.2. Cognitive functions assessment and severity of depression

Assessment of cognitive function was based on the Trail Making Test (TMT), the Stroop Test, and the Verbal Fluency Test (VFT). Depression severity was assessed on the basis of the 21-item Hamilton Depression Rating Scale (HDRS). Further, the number of depressive episodes and duration of the disease were recorded for each individual. Descriptions of these tests and scales are presented elsewhere [33].

The following cognitive functions were evaluated: information processing speed (Digit Symbol from WAIS-R), executive functions and working memory (TMT, Stroop test), and verbal fluency (VFT).

The HDRS, Stroop Test, TMT, and VFT were administered at the onset of the therapy. All the patients were examined on admission during the symptomatic phase, which would generally be either before or shortly after a modification of the previous antidepressant drug regimen. Examination of the patients was conducted by the same person in each case – the same psychologist examined the patients with neuropsychological tests, including an evaluation of the obtained results, while the HDRS test was performed by the same psychiatrist.

2.3. Genotyping

Peripheral blood was collected and genomic DNA was extracted using a standard procedure and an isolation kit according to the manufacturer's protocol (A&A Biotechnology, Gdansk, Poland). The