Genetic association study reveals impact of interleukin 10 polymorphisms on cognitive functions in schizophrenia

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ABSTRACT

Aim: Cognitive deficits are the core factors impacting quality of life among patients diagnosed with schizophrenia. Effective method of treatment for this domain of symptoms remains lacking. Recent evidence suggests the link between impaired cognition and aberrant inflammatory response. Severity of symptoms might be linked to individual genetic predispositions and single-nucleotide polymorphisms (SNPs) in genes encoding interleukins and their receptors. Current genetic association studies include anti-inflammatory interleukins, such as IL10. Functional polymorphisms of IL10 (rs1800871, rs18008729) have been indicated to affect information processing in schizophrenia.

Materials and methods: In this study, we analyzed the potential impact of 27 functional SNPs in 8 cytokine genes on cognitive parameters measured by Wisconsin card-sorting test (WCST) in schizophrenia group (n = 150) and healthy controls (n = 152).

Results: We found significant associations of two functional polymorphisms of IL10 (rs1800871, rs1800872) and WCST results. Allele A carriers in rs1800871 performed significantly better in Percent of Conceptual Level Responses (CLR%). Allele A carriers in rs1800871 and allele T carriers in rs1800872 obtained better results in Completed Categories (CC). The impact of illness duration was observed, with better performance of recent-onset patients.

Conclusions: Results of this study indicate that genetic variants of inflammatory response are associated with cognitive deficits in schizophrenia. The role of cytokines in schizophrenia need to be investigated in the aspect of pro-/anti-inflammatory imbalance. Altered inflammatory response promote chronic mild inflammation in the brain and aberrant synaptic plasticity.

1. Introduction

Cognitive deterioration concerns 80% of patients suffering from schizophrenia [1] and was recently linked with inflammation [2]. Aberrant immune response may lead to chronic mild inflammation within the central nervous system and subsequent impairment in neural plasticity [2]. Dysregulation in cytokine balance, both systemic and central was observed in schizophrenia [3] and may impact cognitive functions [4].

Genetic studies on immune system genes revealed associations of...
single-nucleotide polymorphisms (SNPs) in major histocompatibility complex (MHC) [5], IL1b, IL6, IL10 and their receptors [6] with schizophrenia. Results of association studies on IL1 gene complex were inconsistent, due to ethnic heterogeneity and gender differences in investigated groups. For IL1b association of rs16944 with schizophrenia was confirmed in Spanish [7] and Italian [8], but not for Polish population [9]. Divergent results were obtained for the role of: IL1b (rs1143634, rs1143633), ILRN gene (rs4251961) [10–12], IL6 (rs1800795, rs1800797) [13–16], or IL6R (rs2228145, rs485617) polymorphisms [16–18]. Meta-analysis confirmed significant association between schizophrenia and IL1b, IL6 and IL10 gene polymorphisms (rs1143627, rs1800795, rs1800871) [6]. Studies in Caucasian [15], Spanish [19] and Saudi [20] population on IL10 promoter region functional SNPs (rs1800896:1082 A/G, rs1800871:–819 T/C, rs1800872:–592A/C) revealed association with the diagnosis. It was confirmed by a meta-analysis [21].

Genetic studies indicated that interleukins’ polymorphisms may play a role in treatment effect on cognitive functioning: a link between rs11677416 (IL1A) and olanzapine-mediated working memory improvement was shown [22].

For IL10, studies on elderly populations indicated a higher serum level as increasing the odds of mild cognitive impairment [23]. Two SNPs, rs1800896 and rs1800871, were associated with the risk of AD [24–26].

Wang et al. [27] described an interaction between IL10 rs1800872 and catechol-o-methyltransferase (COMT) rs4680 on neuropsychological outcomes in chronic schizophrenia. They used Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) in the study. Data using the Wisconsin Card Sorting Test (WCST), a valuable method in assessment of real-life cognitive functioning, are scarce.

The use of WCST in schizophrenia allows for measurement of real-life abilities to make decisions, abstractive thinking, and elastic react assessment of real-life cognitive functioning, are scarce. Using the Wisconsin Card Sorting Test (WCST), a valuable method in functional SNPs (rs1800896:1082 A/G, rs1800871:–819 T/C, rs1800872:–592A/C) revealed association with the diagnosis. It was confirmed by a meta-analysis [21].

2.1. Participants

We investigated the potential impact of 27 functional polymorphisms in the inflammatory genes: IL1A, IL1B, IL1RN, IL6, IL6R, IL10, IL10RA, and TGFBI on cognitive domains measured by WCST in patients diagnosed with schizophrenia and healthy controls. We combined genotypes of rare homozygotes and heterozygotes into one group (rare allele carriers). The effect of common homozygotes vs. rare allele carriers on WCST performance was investigated. Results were corrected regarding sex and age. The impact of illness duration (recent onset < 5 years vs chronic schizophrenia ≥ 5 years) on WCST measures was considered, as well.

2. Materials and methods

2.1. Participants

The investigated group consists of 302 subjects: patients diagnosed with schizophrenia (SCH, n = 150) versus the healthy control group (HC, n = 152). The demographic structure of the studied population is presented in the table (Table 1). Exclusion criteria were: chronic or acute general medical conditions and increased CRP blood level. Clinical population was recruited in inpatient clinic of Department of Psychiatry, Poznan University of Medical Sciences. Healthy control group was recruited at Kazimierz Wielki University in Bydgoszcz. The diagnosis of schizophrenia was established according DSM-IV and ICD-10 criteria and the differential diagnosis was performed according to the best experience of the attending psychiatrist. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 2007) and Operational Criteria for Psychotic Illness (OPCRT) [31] were used in evaluating symptoms for each patient. Screening of the control group was done with the use of MINI plus scale [32]. The study was designed and conducted following the Declaration of Helsinki, and approved by the local medical ethics committee at Poznan University of Medical Sciences (no. 149/10) and Kazimierz Wielki University in Bydgoszcz (no. KB 149/2012). All study participants gave the written informed consent.

2.2. Cognitive testing

To assess cognitive functions, we used a computerized version of Wisconsin Card Sorting Test (WCST) [33]. We analyzed the following domains of WCST: the percentage of perseverative responses (using the same incorrect pattern of response due to relevant stimuli ignorance PR %), the percentage of non-perseverative errors (failure to avoid attentional distraction, NE %), the percentage of conceptual level response (possessing an elaborated, intentional pattern of response for a stimulus, CLR %), trials to complete first category (conceptual thinking, TCC) and the number of correctly completed categories (based on new information and previously achieved knowledge, CC) [47]. Patients performed WCST when achieving clinical improvement in pharmacological treatment, that enabling cooperation in neuropsychological testing and continuation of treatment in the outpatient clinic.

2.3. Molecular analysis

DNA was extracted from anticoagulated whole-blood samples (10 ml EDTA, salting out method) [34]. The genetic analysis included 27 polymorphisms, selected due to evidenced functionality (details published previously: [9,10,13] IL1A gene: rs1800587, rs17561; IL1B gene: rs1143634, rs1143634, rs16949, rs4848306, rs1143623, rs1143633, rs1143627; ILRN gene: rs419598, rs315952, rs9005, rs4251961; IL6 gene: rs1800795, rs1800797; IL6R gene: rs4537545, rs485617, rs2228145, IL10 gene: rs1800896, rs1800871, rs1800872, rs1800890, rs6676671; IL10RA gene: rs2229113, rs3159392, TGFBI gene: rs1800469, rs1800470. For genotyping, we used TaqMan SNP Assays (Life Technologies), and performed reactions on ABI PRISM® 7900HT Sequence Detection System.

2.4. Statistical analysis

The concordance with HWE was determined for each polymorphism using Hardy-Weinberg equilibrium exact test (https://www.cog-genomics.org/software/stats). The normality of data distribution was checked using Kolmogorov–Smirnov and Lillifors tests. Non-parametric tests were applied in the analyses. Kruskal-Wallis ANOVA with post-hoc tests (corrected for the number of comparisons) for a two-sided test of significance, was used to compare WCST results with genotypes. Subsequently, genotypes of rare homozygotes and heterozygotes were
combined into one group (rare allele carriers). The effect of common homozygotes vs. rare allele carriers on WCST results was investigated using the U-Mann-Whitney test. General Linear Model (GLM) analysis with WCST measures with sex and age as covariates was performed. Levene’s test for equality of variances has revealed that variance including factor “sex” was not homogenous; thus, differences in WCST measures with regard to sex were estimated using the U-Mann-Whitney test. General Linear Model (GLM) analysis with WCST measures as a dependent variable, combined genotypes and age as covariates was conducted.

For the purposes of multiple testing, False Discovery Rate (FDR) correction was performed using an online calculator (https://www.sdnproject.com/utilities/?show=FDR). FDR correction was applied to each SNP of WCST separately. We did not applied stringent Bonferroni correction (27 SNP x 5 WCTS domains) because our study is an exploratory one. Post-hoc power analysis was performed using GPower v 3.1.9.7 program [35]. Analyses were performed using Statistica v13 software.

3. Results

Hardy-Weinberg equilibrium was confirmed for all the studied polymorphisms. The control group was not matched regarding sex and age. Hence, we did not compare directly HC and SCH, but the direct impact of specific polymorphism on WCST parameters was performed.

We detected significant associations between IL10 genotypes and WCST parameters in SCH group:

1. rs1800871 and NE% (p = 0.023) and CLR% (p = 0.037);
2. rs1800872 NE% (p = 0.030) and CLR% (p = 0.047).

For IL10RA rs3135932 the association with trials to complete first category (TCC) (p = 0.026) was found. In HC group association was found between IL-1RA SNP rs4251961 and %PE (p = 0.040). All the associations were insignificant when FDR correction for multiple testing was applied.

Subsequently, we performed analysis of common homozygotes vs. rare allele carriers for each polymorphism. In schizophrenia group we found an association of allele A in IL10 rs1800871 with CLR% (p = 0.020, power 83.96%), and CC (p = 0.007, power 96.22%). Allele T in rs1800872, was associated with CC (p = 0.005, power 95.11%). Multiple testing corrections confirmed the statistical significance of these associations (p = 0.049, p = 0.034, and p = 0.026, respectively). Results are presented in Fig. 1 (Fig. 1).

GLM analysis with WCST scores, combined genotypes and age as covariates was performed. No higher-order interactions were detected between WCST measures, age, and studied polymorphisms in the schizophrenia group, as well as within the control group.

Significantly better performance in WCST variables: CLR% (p = 0.01), CC (p = 0.01), and TCC (p = 0.002) was detected in the recent-onset compared to chronic SCH patients. A statistical trend towards significance in lower scores of PE% (p = 0.06) and NE% (p = 0.09) results in recent-onset patients was noticed (Fig. 2). GLM analysis revealed no effect (PE% p = 0.43, NE% p = 0.98, CLR% p = 0.65, CC p = 0.46, and TCC p = 0.65) of age on these results.

4. Discussion

Our study assessed the potential association of 27 functional polymorphisms of inflammatory genes with cognitive functioning in schizophrenia, using Wisconsin Card Sorting Test. WCST outcomes revealed significant differences due to IL10 polymorphisms (rs1800871, rs1800872). Allele A carriers in rs1800871 achieved a significantly better level of conceptual response (CLR%) and categories completed (CC). Regarding rs1800872, allele T carriers performed better in categories completed (CC). We analyzed each SNP with WCST domains (quantitative variables) separately. Results indicates strong Linkage Disequilibrium (LD) only between rs1800871 and rs1800872. Although, in our previously published analysis, haplotype block consisting of 5 studied polymorphisms in the interleukin-10 gene was detected [10].

Both mentioned polymorphisms have known functionality, deciding about IL10 expression rate. Polymorphisms of IL10 promoter sequences (rs1800871, rs1800872 and rs1800896) are in linkage disequilibrium and form up three major haplotypes (GCC,ACC,ATA) that determine IL10 secretion rate (high, moderate and low, respectively) [36]. Homozygous genotype of rs1800871 correlates with higher IL10 expression compared to T allele carriers [37,38]. Regarding rs1800872, impact of the genotype is not fully understood. Allele A was linked to higher promoter expression in human Raji cell lines [39]. On the other hand, rs1800872C allele was correlated with higher affinity of poly [ADP-ribose] polymerase 1 (PARP-1) protein and thus subsequent higher expression of IL10 [36].

Research assessing IL10 polymorphisms and cognitive functions in schizophrenia for both rs1800871 and rs1800872 are sparse. Allele C of rs1800872 was shown to exert protective effect on infection-mediated neurocognitive difficulties, assessed in psychometric questionnaires [40]. Similar results were found in elderly population, where CC genotype was linked to better verbal intelligence (VIQ) [41].

Rs1800872 was also described regarding cognitive deficits in first-episode drug naïve patients diagnosed with schizophrenia. Xiou et al. [42] found worse attentional performance and reduced serum IL10 levels to be connected with allele A carrier [42]. Another study investigating chronically ill patients did not confirm the association of rs1800872 (rs952A/C) with cognitive decline [27]. Our study suggests a better cognitive performance in T allele carriers for rs1800872. There is a difficulty in interpreting the obtained differences due to different allele frequencies in comparison with Chinese population. Abovementioned

Fig. 1. Impact of rs1800871 and rs1800872 in IL10 gene on WCST parameters. A: Percentage of conceptual level responses (CLR%) among rs1800871 frequent homozygotes. (GG) (p = 0.034) and allele A carriers. B: Comparison of the number of categories completed. (CC) among rs1800871 frequent homozygotes (GG) and allele A carriers (p = 0.049). C: Comparison of the number of categories completed among rs1800872 frequent homozygotes. (GG) and allele T carriers (p = 0.026).

No correlation between age and WCST results was obtained. Comparison between sex groups revealed better performance in NE% (p = 0.001), CLR% (p = 0.004), and CC (p = 0.002) among healthy men.
Less results were reported on rs1800871 influence on cognitive functions. T allele was found to associate with AD risk \[24,25\]. In a recent meta-analysis this result was not confirmed \[43\].

Our results indicate rather A allele as the protective variant for cognitive functioning in schizophrenia. In the case of rs1800872, A allele may enhance IL10 expression, that may play neuroprotective effect due to reduced microglial activation \[44\].

Deficits in cognitive inhibition (cognitive control deficits) and distractibility were described in schizophrenia, that was reflected by WCST performance \[28,45,46\]. Genetic association studies were performed in the area of monoamine neurotransmission \[47\]. Typical impairments include the number of categories completed and percent of conceptual level responses, which was confirmed in our study.

Another interesting result of this study derives from analysis between illness duration and WCST outcome. The topic of cognitive deterioration due to illness chronicity is broadly discussed in the current literature. Wang et al. \[27\] underlined that the cognitive outcome is linked with the illness duration. It may also depend on function of IL10, or prescribed medication.

Investigations on the link between illness duration and WCST score have shown so far inconsistent results. Some research suggest impairment in WCST as the consequence of normal aging process, independent from the course of disease (age-related changes) \[48\]. Clinical observations suggest decrease in WCST due to conversion from prodromal state into psychosis \[49\], and further progression during the course of illness \[50\]. We found WCST performance related to schizophrenia duration, but not age-dependent.

Obtained results suggest the influence of IL10 functioning on cognitive deficits. It is in line with recent research that confirm associations between serum IL10 level and neurocognitive symptoms in schizophrenic patients \[51\].

Anti-inflammatory properties of IL10 derive possibly from the impact on other cytokines production and circulating level, hence the particular interest in IL10 as the inflammatory linking hub. IL10 is also thought to be engaged in an inflammatory response within the central nervous system \[52\]. As the main source of IL10 in CNS are perceived microglial cells, stimulated directly due to TLR pathway, or further regulated by molecules like glutamate, prostaglandins and cytokines \[52\]. Studies both in vivo and in vitro confirmed microglial production of IL10 in response to Toll-like receptor (TLR) stimulation, glutamate, or activation of purinergic receptors \[52\]. The direct effect of IL10 on cognitive functions may be explained by synaptic plasticity defects by altered regulation of the kynurenine pathway \[53\]. This enzymatic pathway in the central nervous system is responsible for the metabolism of tryptophan. The final product, the kynurenic acid (KA), is the derivate tryptophan due to indolamine 2,3-dioxygenase (IDO) and kynurenic aminotransferase (KAT) activity. Proinflammatory cytokines increase the production of KA by stimulation of IDO. The increased concentration of KA in brain tissue was found in the hippocampus of schizophrenic patients. High KA levels exert a probable inhibitory effect on NMDA receptors. Aberrations in glutamatergic synaptic plasticity due to inflammatory response could result in decreased ability to form connections and further cognitive deterioration as the clinical outcome in patients \[54\]. Excepting the kynurenicine pathway, IL10 revealed a direct impact on glutamatergic transmission and homeostatic plasticity mechanisms in cellular studies on cultured hippocampal neurons \[55\]. Nenov et al. \[55\] described dose-dependent potentiation of miniature excitatory postsynaptic currents (mEPSC) by IL10 and induction of homeostatic plasticity in tetrodotoxin (TDX) model. IL10 appears as the neuroprotective factor, modulating AMPA and NMDA receptor functioning.

5. Conclusions

Results of our study showed significant association of IL10 SNPs: rs1800871 and rs1800872 with cognitive functions in schizophrenia measured by WCST.

Understanding of immunological factors may be crucial in searching for new medication supporting excitatory - inhibitory balance. Especially in subpopulations of treatment-resistant patients, the
immunological response seems to play a compensatory role as the natural homeostatic mechanism (Compensatory immune-regulatory Reflex System, CIRS) [56].

6. Limitations
The main limitations of this study is a relatively small number of the patient investigated. The control group was not matched regarding to sex and age structure. The current research did not include the analyses of potential biases linked to duration of untreated psychosis, the pharmacological treatment, menopause or nicotine intake.

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Institutional review board statement
The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board at Poznan University of Medical Sciences (no. 149/10) and Kazimierz Wielki University in Bydgoszcz (no. KB 149/2012).

Informed consent statement
Informed consent was obtained from all subjects involved in the study.

Conflicts of interest
The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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