Polymorphisms of Catechol-O-Methyl Transferase (COMT) Gene in Vulnerability to Levodopa-Induced Dyskinesia

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ABSTRACT - Purpose. Parkinson's disease (PD), a common neurodegenerative disorder, is usually treated with Levodopa (L-DOPA). The use of this drug, however, is severely limited by the development of side effects of the motor system: Levodopa-induced dyskinesia (LID). The aim of this study is to investigate the association between seven *COMT* gene single-nucleotide polymorphisms (SNPs) and the development of LID in patients with PD. **Methods.** 232 Caucasian patients with PD were investigated. 212 patients with PD received Levodopa therapy. Dyskinesia was assessed with the use of the Abnormal Involuntary Movement Scale (AIMS). Genotyping was carried out on seven SNPs of the *COMT* gene (rs4680, rs6269, rs4633, rs4818, rs769224, rs165774, rs174696) using a real-time PCR method, and blind to the clinical status of the subjects. **Results.** We found association between four SNPs, rs165774, rs4818, rs4633, rs4680, and LID. When the duration of disease was added as a covariate in regression analysis, however, the results did not reach statistical significance. Only the additive model for rs165774 was found to be close to be statistical significance (OR = 1.627 [0.976–2.741], permutation p = 0.057). **Conclusions.** The results failed to clearly support a contribution of the studied polymorphisms; this may be related to a dominant relationship with the disease duration confounding the effect on the prevalence of LID.

INTRODUCTION

Over 55 years after the discovery of its beneficial effects,[1,2] Levodopa remains the mainstay of treatment for Parkinson's disease (PD). The use of Levodopa for the treatment of motor symptoms at all stages of PD is supported by strong evidence.[3] Long-term treatment with Levodopa for PD, however, is frequently complicated by motor fluctuations and dyskinesias.[3-6] Monotherapy with dopamine agonists in the early phases of the disease does reduce the risk for dyskinesias compared with the use of Levodopa, but dopamine agonists are unable to prevent dyskinesias once Levodopa is added, and which is always required once disease severity progresses.[7] Chronic Levodopa treatment has been reported to result in LID in up to 45% of Levodopa users within five years.[8] Clinical heterogeneity of LID suggests a significant role of endogenous factors in determining their prevalence, although no effective drug treatment of levodopa-induced dyskinesia (LID) has yet been developed.[9] Several theories have attempted to explain the pathophysiology of this treatment complication with an ultimate goal to develop such treatments[9-11], but the exact pathological mechanism has also not yet been elucidated. Recently, Ivanova and Loonen developed the hypothesis that LID is related to an increased vulnerability to excitotoxicity of indirect pathway striatal medium spiny neurons potentiated due to the contribution of increased intracellular oxidative stress.[12] This last phenomenon is expected to be caused by the same genetic composition which causes the degeneration of dopaminergic nigrostriatal neurons in patients with PD.

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Abbreviations: COMT, catechol-O-methyltransferase; LID, levodopa-induced dyskinesia; MB-COMT membrane-bound form of COMT; PD Parkinson's disease; PFC, prefrontal cortex; SNP single-nucleotide polymorphism; S-COMT, soluble form of COMT.

Dopamine can be considered to be a particularly neurotoxic endogenous substance: dopamine metabolism results in the release of hydrogen peroxide, which, in turn results in the production of free radicals, which then cause cell damage.[13] This damage is limited by the influence of certain enzymes such as manganese superoxidedismutase (MnSOD), which scavenge these free radicals.[14] This neurotoxicity is expected to be potentiated by biological factors which increase the intracellular levels of dopamine.

Catechol-O-methyltransferase (COMT; EC 2.1.1.6) is one of the most important enzymes in levodopa metabolism. It was identified by Julius Axelrod at the National Institute of Mental Health (USA) in the second half of the 1950s.[15,16] COMT catalyzes methyl group transfer from S-adenosyl-L-methionine to one of the hydroxyl groups of catechol in the presence of Mg2+ ions. COMT substrates include a wide variety of catechols (catecholamines, their hydroxylated metabolites, catecholestrogens, ascorbic acid, dietary phytochemicals, and medicinal compounds).[15,16] The major physiological role of COMT is the elimination of biologically active or toxic catechols. Of special importance is the methylation of Levodopa to 3-O-methyldopa in Levodopa/aromatic amino acid decarboxylase inhibitor-treated Parkinson's disease (PD) patients, because this metabolism markedly limits the availability of Levodopa to the brain.[15] It has also been suggested that COMT plays a relevant role in modulating prefrontal dopamine neurotransmission.[17] Polymorphic variants of the *COMT* gene determine the activity level of this enzyme.[17-19] COMT exists in two forms: the soluble form (S-COMT) which is located in cytosol, and the membrane-bound form (MB-COMT) which is anchored to the rough endoplasmic reticulum. The two forms differ only by a 50 residue long extension in the MB-form, which is the signal sequence for membrane anchoring.[20,21] In humans, the *COMT* gene is located on chromosome 22 band q11.21, and is composed of six exons.[15] The first two exons are noncoding, while the translation initiation codons for the membrane bound and soluble isoforms are located on the third exon. Two separate promoters direct the synthesis of two partially overlapped transcripts: one of 1.5 kb that is constitutively expressed, and another of 1.3 kb which is subject to tissue-specific transcription regulation. The short transcript translates S-COMT and the longer transcript translates MB-COMT, and also the soluble form by the leaky scanning mechanism of translational initiation.[15] The long transcript has been found in all tissues analyzed. The short transcript, on the other hand, is only found in very small amounts within the human brain. There is, however, no direct correlation between transcript and protein levels. In the human brain S-COMT represents about 30% of the total COMT.[15]

Although several polymorphisms have been reported for the *COMT* gene, most of them appear not to have any physiological significance. However, the genetic variant Val158Met (rs4680) with low thermal stability and low COMT activity is a well-established polymorphism that could contribute to various neuropsychiatric manifestations.[18,19] Low COMT activity appears to have predominantly clinical effects within the prefrontal cortex (PFC) as in the PFC DA-transporters are expressed in low abundance within synapses, contrary to, for example, the striatum.[19,22] Furthermore, the nonsynonymous Ala72Ser (rs6267) polymorphism has been associated with reduced COMT enzyme activity and with a risk for schizophrenia[23] Apart from the above mentioned Val158Met (rs4680), three single-nucleotide polymorphisms (SNPs) were found: one in the S-*COMT* promoter region (rs6296) and two in the S- and MB-*COMT* coding region (c.186C>T, p.62His (rs4633), c.408C>T, p.136Lys (rs4818), next to rs4680). These were associated with differences in pain sensitivity and the likelihood of developing a chronic musculoskeletal pain condition.[24] It was shown that these haplotypes modulate protein expression by altering mRNA secondary structure, thus stressing the functional significance of synonymous variations and importance of haplotypes.[18] Another relevant synonymous variation includes c.597G>A, p.199Pro (rs769224).[18] Xu et al demonstrated an association of the G–G–G vs. A–G–G haplotype of rs4633, rs4818 and rs769224 concerning response to non-SSRIs in major depressive disorder.[25] Recently published results revealed that homozygosity for rs4633 (TT), rs4680 (AA) and of the two linked rs4633-rs4680 (TT/AA) was significantly associated to Levodopa effects in PD patients, while no significant differences were observed in patients who carried individual rs6269 and rs4818, the two linked rs6269-rs4818 and the four combined *COMT* SNPs.[26] These last observations contrast to the findings in patients with Attention-Deficit/Hyperactivity Disorder (ADHD) (64% using medication for it) in who the c.-98A>G (rs6269) was associated with the largest influence on the hyperactivity/impulsivity scores. In

PD patients, any existing significant differences were found for individual SNPs (rs6269; rs4633; rs4818; and rs4680) in the allele and genotype frequencies between PD cases and controls, but their division into haplotypes with low, medium and high COMT activity revealed that the high activity haplotypes needed a significantly higher levodopa dosage.[27] In their study, the *COMT* haplotype seemed to have little influence on the development of Levodopa-induced dyskinesias. Meloto et al identified a functional marker situated in the 39 untranslated region of a newfound splice variant (c.615+739G>A; rs165774) which displays unique substrate specificity, exhibiting enzymatic activity with dopamine, but not with epinephrine.[28] They established that the pain-protective A allele of rs165774 coincides with lower COMT activity due to increased dopaminergic tone. Associations of rs165774 were also found by Higashiyama et al in patients with schizophrenia vs. healthy controls and by Seib et al in older women with depression.[29,30] Ittiwut et al found an association between rs4680 and c.615+1354C>T (rs174696) in European American patients with cocaine-induced paranoia.[31]

In our current study we have investigated a possible existence of an association between rs4680, rs6269, rs4633, rs4818, rs769224, rs165774, as well as rs174696 and levodopa-induced dyskinesia in 232 Caucasian PD patients from the neurological department of the Siberian State University Hospital of Tomsk, Russian Federation. The rationale for our study was that these polymorphisms have been demonstrated to induce certain functional changes. It was hypothesized that at least some of the biochemical alterations causing these functional changes might also affect the intracellular dopamine concentration, which could result in changed vulnerability for developing levodopa-induced dyskinesia.

METHODS

Patients

The work described in this article was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013) for experiments involving humans. Patients were recruited from the neurology department of the Siberian State Medical University Hospital in Tomsk, Russian Federation. Written informed consent was obtained from each patient after obtaining approval for the study (protocol N 3604 10.02.2014) from the Local Bioethics Committee of the Siberian State Medical University. None of the participants had a compromised capacity/ability to consent; therefore consent from the next-of-kin was not necessary, and was not recommended by the local ethics committee. The inclusion criteria were a clinical diagnosis of Parkinson's disease according to ICD-10 (G-20) and also prior long-term use of Levodopa. Exclusion criteria were non-Caucasian physical appearance (e.g., Mongoloid, Buryats or Khakassians), relevant psychiatric symptoms or any organic brain disorders other than Parkinson's disease. These patients had not been treated with dopamine antagonists (antipsychotic or antiemetic drugs, including clozapine) for at least three years. Patients were assessed for the presence or absence of dyskinesia during 'on'-phase according to the abnormal involuntary movement scale (AIMS).[32-34] The AIMS scores were transformed into a binary form of LID (presence or absence of dyskinesia) with Schooler and Kane's criteria.[35]

DNA analysis

DNA was isolated from the leukocytes in whole peripheral blood using the standard phenol-chloroform micro method.[36] Genotyping was carried out on the MassARRAY Analyzer 4 (Agena Bioscience) using the set SEQUENOM Consumables iPLEX Gold 384. DNA sample preparation for SEQUENOM MassARRAY Analyzer 4 includes several steps: a standard PCR reaction to obtain the amplification products, a shrimp alkaline phosphatase reaction to neutralize the unincorporated dNTPs in the amplification products, the PCR iPLEX Gold extension reaction, and then placing the samples on a special chip (SpectroCHIP array) using Nanodispenser RS1000 prior to loading them into the analyser. Genotyping was carried out on 7 SNPs of *COMT* genes (rs4680, rs6269, rs4633, rs4818, rs769224, rs165774, rs174696), which were selected after reviewing the literature for possible relevance.

Statistical analysis

Statistical analyses were performed using SPSS software for Windows, release 17. The Mann–Whitney test (MWT) was used to compare qualitative traits and $\chi 2$ test for categorical traits. The Hardy–Weinberg equilibrium (HWE) of genotypic frequencies was tested using the $\chi 2$ test. The $\chi 2$ test and the Fisher's exact test, if necessary, were used for between-group comparisons of genotype or allele frequencies.

The analysis of association between the SNPs and the phenotype was carried out using logistic regression with adjustment for covariates. Additive, dominant and recessive models were tested, and the optimum model has been chosen

using Akaike Information Criterion (AIC). Experiment-wise permutations were used to address the multiple testing issue, hence Bonferroni correction was not applicable. Models with permutation p-value < 0.05 were considered statistically significant. Odds ratio (OR) and 95% confidence intervals were estimated to assess the strength of genetic effect. The following filters were applied to the SNPs: minor allele frequency, 5%; deviation from Hardy-Weinberg equilibrium, p=0.007 (assuming α=0.05 for 7 SNPs).

RESULTS

A total of 232 Caucasian patients with PD were included, consisting of 149 females and 83 males (age range from 40 to 86 years, average age 68.7±7.6 years). These patients demonstrated typical PD demographics, with a mean age of onset of 59.0 ± 9.5 years, and a mean disease duration of 9.8 ± 5.6 years. The distribution of genotypes of studied genes corresponds to the Hardy-Weinberg equilibrium (data not shown). According to the predefined criteria, 58 patients suffered from dyskinesia. We found that four out of seven tested SNPs passed the significance thresholds for association with LID. Since associations can in part be explained by the effects of additional factors, such as sex and age, we carried out a regression analysis using LID as the dependent variable, the genotypes as the fixed factor and sex and age as covariates. Using linear regression models, we found association between four SNPs, rs165774, rs4818, rs4633, and rs4680, and LID; the best model (according to AIC values) was additive for rs165774 and rs4818 and dominant for rs4633 and rs4680 (Table 1). In case of rs165774, the rare allele was associated with an increased risk of LID (OR = 1.75 [95% CI 1.14-2.72]), while in case of rs4818, rs4633 and rs4680, the rare allele or homozygote genotype for the rare allele were protective against LID (OR = 0.57 [0.34-0.92], 0.45 [0.23-0.89] and 0.46 [0.23-0.91], respectively). However, when the duration of disease was added as a covariate in regression analysis, the results did not reach statistical significance. Only the additive model for rs165774 was found to be close to statistical significance (OR = 1.627 [0.976–2.741], permutation p = 0.057).

DISCUSSION

We have failed in this study of 232 white patients with Parkinson's Disease (PD) to establish a clear relationship between any of the seven polymorphisms of the *COMT* gene and the prevalence of Levodopa-induced dyskinesia (LID). The associations that were found lost their statistical significance after correcting for disease duration. This last observation may correspond with the previously described association between some *COMT* gene polymorphisms and the onset of disease in 143 patients with PD.[26] Watanabe et al found a slightly higher prevalence of PD in 30/118 patients with homozygosity for the low-activity allele of Val158Met (rs4680),[37] but these findings were not reproduced by Contin et al in 104 patients, and by Cheshire et al in 285 patients.[38,39] We had observed previously a significant association with PD for the c.615+739G>A (rs165774), but not Val158Met (rs4680), polymorphism and PD of the same patient population vs. 127 healthy controls.[40] De Lau et al described the existence of a prospectively assessed correlation between the A-allele of the *COMT* Val158Met polymorphism and an increased risk of developing dyskinesias in 219 patients with PD.[41] A comprehensive meta-analysis in which a total of 363 datasets were included, consisting 56,998 cases and 74,668 healthy controls from case control studies, as well as 2,547 trios from family based studies, showed a definite relationship between several psychiatric disorders, including, for example, attention-deficiency hyperactivity disorder (ADHD) and panic disorder for Caucasian samples.[42]

We conclude that the tested polymorphisms, and in theory at least the *COMT* Val158Met polymorphism as described above, may have an influence on the prevalence of LID in PD, but this influence is small, and in our study confounded by a possible increased likelihood for PD to manifest itself, thus causing an increased disease duration in our patient population. In previous studies, we have observed that in both tardive dyskinesia as well as in LID,[14,36,43] limb-truncal dyskinesia may have a genetic background other than orofacial dyskinesia. Unfortunately, the number of patients in this study with LID is relatively small (N = 58), and too many suffered from both orofacial and limb-truncal dyskinesia to make further statistical analysis feasible.

The strengths of our study include the relatively large number of patients (N = 232); the thorough assessment of the severity of dyskinesia by direct clinical assessment with AIMS; the application of Schooler and Kane's criteria to conclude to the presence of LID, and the assessment of seven putatively relevant polymorphisms of the *COMT* gene after carefully reviewing previous findings. The weaker points are the relatively low number of patients suffering from LID (N = 58, 25%), and the co-occurrence of limb-truncal and orofacial dyskinesia in many of them.

Table 1. SNPs associated with levodopa-induced dyskinesia

SNP	Best model	OR [95% CI]	Permutation *p*-value
rs165774	Additive	1.75 [1.14-2.72]	0.011
rs4818	Additive	0.57 [0.34-0.92]	0.025
rs4633	Dominant	0.45 [0.23-0.89]	0.027
rs4680	Dominant	0.46 [0.23-0.91]	0.025

The results of this study illustrate that genetic variations of the activity of the COMT enzyme have only a modest influence on the clinical presentation of PD, and its treatment complications such as LID. The vulnerability in PD apparently differs from that in other neuropsychiatric disorders, such as ADHD.[42] It can been suggested that this may be related to low expression of DA-transporters within the prefrontal cortex and not within synapses, contrary to, for example, the striatum.[19,22] It is possible that the abundance of DA-transporters within the striatum limits the influence of variations in COMT activity, because after re-uptake within dopaminergic terminals dopamine is generally processed differently (e.g., through mitochondrial monoamine oxidase). Moreover, the highly adaptive capacity of the functional nigrostriatal extrapyramidal connectivity may limit the influence of genetic variations in enzyme activity. This influence on the activity of the cortico-striato-thalamo-cortical circuitry may be less than that within the prefrontal cortex or corticoid amygdala, which may play a role in causing other neuropsychiatric disorders.[12] However, other PD manifestations, including cognitive symptoms, may be more dependent on the functioning of the prefrontal cortex. Recently, Zhang et al have demonstrated that *COMT* Val158Met polymorphism is probably not associated with increased risk of PD, but has an effect on the prefrontal executive function interacting with gender and dopaminergic medication.[44] Specifically addressing manifestations related to dysfunction of the PFC (vigilance), corticoid amygdala (delusions) and hippocampal complex (hallucinations) may, in future, be more awarding when studying *COMT* gene polymorphisms.

CONCLUSIONS

The possible association between seven putatively relevant genetic variants of *COMT* gene and prevalence of LID in 232 Caucasian patients with PD was studied. Although the association of four polymorphisms reached statistical significance, the relationship was masked after discounting the time frame of the proportion of patients in the sample suffering from PD.

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