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Original Article

Dissimilar mechanistic background of peripheral and orofacial hyperkinesia in patients with Parkinson's disease and levodopa-induced dyskinesia

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Abstract

Introduction: Long-term levodopa treatment of Parkinson's disease (PD) is frequently complicated by spontaneously occurring involuntary muscle movements called dyskinesia. The exact pathological mechanism of this complication has not yet been elucidated. We have previously demonstrated that in PD patients the vulnerability to develop peripheral but not orofacial dyskinesia is associated with the presence of two variants of the *GRIN2A* gene. Moreover, we have shown that in tardive dyskinesia (TD) orofacial dyskinesia is associated with other polymorphisms as compared with peripheral dyskinesia. In the present study we investigate whether the peripheral versus orofacial nature of levodopa-induced dyskinesia (LID) in PD can be explained by considering polymorphisms for dopaminergic and serotonergic receptors.

Materials and Methods: 101 Russian patients with PD (38M/63F) were examined. Genotyping was carried out on 19 SNPs for 3 neurotransmitter genes: 10 SNPs for *DRD3* gene (rs11721264, rs167770, rs3773678, rs963468, rs7633291, rs2134655, rs9817063, rs324035, rs1800828, rs167771), 1 SNP for *DRD4* gene (rs3758653), and 8 SNPs for *HTR2C* gene (rs6318, rs5946189, rs569959, rs17326429, rs4911871, rs3813929, rs1801412, rs12858300).

Results: Genotyping patients with PD and LID revealed that only rs3773678 (*DRD3*, dominant, $p = 0.042$) was associated with orofacial dyskinesia.

Conclusion: The findings of the current study are not related to LID in PD itself, but to other forms of orofacial dyskinesia in this patient group.

Abbreviations: PD – Parkinson's disease; TD – Tardive dyskinesia; LID – Levodopa-induced dyskinesia; MSN – Medium Spiny Neuron; NMDA – N-methyl-D-aspartate; HD – Huntington's disease; SNP – Single nucleotide polymorphism

Keywords:

Levodopa-induced dyskinesia;
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Introduction

More than 45 years after its introduction levodopa still remains one of the most effective treatments for Parkinson's disease (PD). However, long-term levodopa treatment of PD is frequently complicated by motor fluctuations and dyskinesia (Thanvi and Lo, 2004; Thanvi et al., 2007; Del Sorbo and Albanese, 2008). Several theories have been developed to explain the pathophysiology of this important treatment complication with the ultimate goal to develop treatments to prevent this side effect (Huot et al., 2013; Bargiotas and Konitsiotis, 2013; Cerasa et al., 2014). However, the exact pathological mechanism has not yet been elucidated.

Recently, we reported our serendipitous finding in a small group of patients we used as a control group in our study on tardive dyskinesia (TD) in patients with schizophrenia, that two variants of *GRIN2A* gene were strongly associated with levodopa-induced dyskinesia (LID) and not with TD (Ivanova et al., 2012; Loonen and Ivanova, 2013). It is important to note that these variants were already known to be associated with the age of onset of symptoms in patients suffering from Huntington's disease (Arning et al., 2007). The *GRIN2A* gene encodes for a protein which is part of the ionotropic glutamatergic N-methyl-D-aspartate (NMDA) receptor. As in Huntington's disease (HD), motor symptoms are linked to NMDA receptor-induced excitotoxicity in striatal medium spiny neurons (MSNs) of the indirect pathway, we propose that the same mechanism causing dyskinesia in LID.

Like hyperkinesia in HD (Sturrock and Leavitt, 2010), LID is also predominantly peripherally localized (Thanvi and Lo, 2004; Del Sorbo and Albanese, 2008). TD is characterized by both peripheral and orofacial dyskinesia, the latter being more prevalent in most patients. We have previously demonstrated that in PD patients the vulnerability to develop peripheral but not orofacial dyskinesia is associated with the presence of two variants of the *GRIN2A* gene (Ivanova et al., 2012). Moreover, we found that these genes were not associated with the likelihood of developing TD. We have demonstrated in the past that in TD orofacial dyskinesia is associated with other single nucleotide polymorphisms (SNPs) than peripheral dyskinesia (Al Hadithy et al., 2009; Al Hadithy et al., 2010). During the present study, we

investigate whether this peripheral versus orofacial nature of LID in PD can be explained by considering SNPs for dopaminergic and serotonergic receptor genes, as a potential mechanism.

Materials and methods

Ethics Statement

The protocol was approved by the standing Institutional Review Board (Local Ethics Committee at the Siberian State Medical University, Tomsk, Russian Federation). Written informed consent was obtained from each patient. None of the participants had a compromised capacity/ability to consent; hence, obtaining consent from the next-of-kin was not necessary and not recommended by the Local Ethics Committee. 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 Fortaleza, Brazil, October 2013) for experiments involving humans.

Patients

The patients included in this study were retrieved from the Department of Neurology and Neurosurgery of the Siberian State Medical University (SSMU), Tomsk, Siberia, Russian Federation. Included were neurological patients who were suffering from dyskinesia and corresponding patients without dyskinesia having the same diagnosis (usually PD). In order to categorize patients accurately a clinical diagnosis protocol of PD was applied according to ICD-10 (G20) and the international clinical diagnostic criteria of the Parkinson's UK Brain Bank of the PD Society of the United Kingdom (Hughes et al., 1992). The severity of Parkinson's disease was determined by utilizing the Unified Parkinson's Disease Rating Scale - UPDRS (Fahn et al., 1987) in the optimal "on" state. The stage of the disease was assessed using the "Hoehn and Yahr" scale (Hoehn and Yahr, 1967). The degree of movement disorders (hypokinesia, rigidity and resting tremor) was defined according to the section III of UPDRS scale, dedicated to movement disorders. The severity of dyskinesia was assessed according to the Abnormal Involuntary Movement Scale (AIMS) (Loonen and Van Praag, 2007). This scale consists of 12 items, of which 7 are basic indicators and are used for assessment of

severity. Each item is evaluated according to the following points: 0 - no violation; 1 - minimum disruption; 2 - mild disorders; 3 - moderately expressed disturbances; 4 - strongly expressed violations. The AIMS scores were transformed into a binary variable (presence or absence of dyskinesia) with internationally accepted Schooler and Kane's criteria (Schooler and Kane, 1982) according to which, for making a definite diagnosis of the TD, 3 points for one of the items or 2 points for at least 2 items are required. This scale was applied during the 'on' phase in levodopa-induced dyskinesia. Exclusion criteria were: non-Caucasian physical appearance (e.g., Mongoloid, Buryats, or Khakassians), inability to walk unsupported, delirium, amnesia; schizophrenia or schizoaffective disorder, acute myocardial infarction, hypertension IIb-III, severe forms of diabetes; acute infections; exacerbation of chronic diseases.

Of the 143 Siberian patients examined 101 were diagnosed with PD, 21 patients with essential tremor and 21 with different forms of dystonia. Fifty of them (35%) were males and 93 (65%) females and their mean age was 63.6 ± 11.9 (from 22 to 86 years). The age of patients with PD (38M/63F) varied from 44 to 82 years. The age of onset of the PD was 59.7 ± 8.5 years. The mean age of patients with PD was 66.0 ± 7.9 years and the average duration of illness was 6.4 ± 4.5 years.

45.7% of patients had complaints of unintended movements. In 74.4% of patients, abnormal movements were registered in the neck, shoulders and hips (e.g., twisting, swinging, pivoting motion, rotation hips in a circle); 62.8% of the patients had movements in the upper limbs, 60.5% of the patients had movements in the lower limbs. Disability was observed in 65.1% of patients with levodopa-induced dyskinesia. Only 58.1% of patients with unintentional movements realized the presence of abnormal movements.

Apart from physical examination and assessment, a blood sample was taken for DNA isolation and genotyping. All genotyping was performed blind to the patients' clinical status.

DNA analysis

DNA extraction and the Veracode Assay were conducted according to standard protocols (Ivanova et al., 2012). We selected a subset of 19 informative

SNPs, or tag SNPs, that would accurately represent the majority of SNPs for 3 neurotransmitter genes: 10 SNPs for *DRD3 gene* (rs11721264, rs167770, rs3773678, rs963468, rs7633291, rs2134655, rs9817063, rs324035, rs1800828, rs167771), 1 SNP for *DRD4 gene* (rs3758653), and 8 SNPs for *HTR2C gene* (rs6318, rs5946189, rs569959, rs17326429, rs4911871, rs3813929, rs1801412, rs12858300). The selection method was previously described by Xu and Taylor (freely available at <http://www.niehs.nih.gov/snpinfo>). We selected only tag SNPs that captured at least 10 SNPs.

Statistical analysis

After having developed different strategies to account for missing data and interactions between different SNPs, classical logistic regression and a log-linear regression approach were used to analyze the data.

The genotype prevalence was calculated separately in patients with and without dyskinesia to define the percentage of missing genotypes. The Hardy-Weinberg equilibrium test was applied with Fisher's exact test to groups. For the SNPs in the X-chromosomal *HTR2C gene*, deviation from HWE was not calculated. One SNP for *HTR2C gene*, rs12858300, was monomorphic; therefore, it was included analysis.

To analyze associations between the SNPs and the phenotypes, we used logistic regression for binary response traits and log-linear regression for continuous traits.

The following genetic models were tested:

1. Co-dominant; both alleles of a SNP influenced the phenotype
2. Dominant; rare allele homo- and heterozygotes were tested against common allele homozygotes.
3. Recessive; common allele homo- and heterozygotes were tested against rare allele homozygotes.
4. Over-dominant; heterozygotes were tested against both homozygote alleles.
5. Log-additive; a trend test for the genotypes, similar to the allele model, but comparisons were made among subjects (N) instead of chromosomes (2N). The test and estimates were based on a logistic regression model that coded the genotypes as 0, 1, or 2 to reflect the number of minor alleles.

The statistical significance of a SNP was established with a likelihood-ratio test that compared the effect of

a polymorphism with the null model. Age, sex, and duration of disease were included into the models as covariates. The Akaike information criterion was applied to identify the model that best fits the data. SNP effects were quantified with the odds ratio (OR) and 95% confidence intervals. In the result tables, an OR for a log-additive model corresponds to an association between a rare allele and the presence of dyskinesia. The ORs for other models correspond to associations between the presence of dyskinesia and rare allele homo- and heterozygotes (Dominant), common allele homo- or heterozygotes (Recessive), or heterozygotes (Over-dominant).

For the statistical analysis, we used both qualitative traits (represented by the existence or absence of dyskinesia) and quantitative traits (the severity of dyskinesia represented by the sum of the AIMS scores). Separately, the calculations for the total dyskinesia and its subtypes: orofacial and limb-truncal were done. Therefore, the following phenotypes were analyzed.

1. Levodopa-induced dyskinesia (Schooler-Kane criteria):
 - a. Orofacial LID (AIMS 1-4);
 - b. Limb-truncal LID (AIMS 5-7);
 - c. Orofacial and limb-truncal LID (AIMS 1-7).
2. The severity of dyskinesia; total score for 1-4, 5-7, and 1-7.

Dyskinesia was considered a qualitative trait (present/absent), but the degree of dyskinesia expression was analyzed as a quantitative trait. To avoid 0 values, 1 was added to the dyskinesia expression values, and then they were log₂-transformed to obtain a log-normal distribution.

The statistical power was estimated based on the prevalence of the tested phenotypes in the Siberian sample and assumptions of a complete penetrance and disease allele prevalence of 0.2-0.3. For orofacial dyskinesia, to detect associations under different genetic models with OR of 1.5, 2.0, and 2.5, the power estimates varied between 14%-50%, 44%-94%, and 78%-99%, respectively. For limb-truncal dyskinesia, the power estimates varied between 10%-31%, 27%-75%, and 53%-95%, respectively. For either type of dyskinesia, the power estimates varied between 18%-65%, 58%-99%, and 91%-99%. Overall, it would be fair to say, that our study was reasonably powered to detect associations with OR, as little as 2.0.

Results

First, the Hardy-Weinberg equilibrium test was applied to analyze the frequency distribution of investigated polymorphisms. One SNP of *HTR2C* gene, rs12858300, was monomorphic; therefore, it was removed from further analysis. The Hardy-Weinberg equilibrium in patients was observed for the following polymorphisms: rs3758653 ($p = 0.894691$), rs2134655 ($p = 0.562467$), rs324035 ($p = 1$), rs3773678 ($p = 0.125774$), rs167770 ($p = 0.067768$), rs167771 ($p = 0.397278$), rs7633291 ($p = 1$), rs1800828 ($p = 0.795681$). The Hardy-Weinberg equilibrium was not calculated for polymorphic variants rs6318, rs5946189, rs569959, rs17326429, rs4911871, rs3813929, rs1801412, rs12858300 due to the fact that the serotonin receptor gene *HTR2C* is located on the X-chromosome.

The next step of the statistical analysis was calculation of the best genetic models based on Akaike information criterion (AIC); the log-additive model is presented only in the case of statistical significance. The correction for multiple comparisons was not yet applied.

An association was found between presence or absence of orofacial dyskinesia (according to the Schooler-Kane criteria) and two investigated polymorphisms in all 143 neurological patients: rs3758653 (*DRD4*, Log-additive, Odds Ratio (OR)=2.31 [95%CI=1.10-4.87], $p=0.032$) and rs4911871 (*HTR2C*, dominant, OR=2.88 [1.03 – 8.05], $p=0.041$). These polymorphic variants, in addition to a marker rs2134655 (*DRD3*, recessive $p=0.040$), are associated with dyskinesia and are represented as a quantitative indicator according to the sum of features from 1 to 4.

None of the studied polymorphisms was significantly associated with qualitatively assessed limb-truncal dyskinesia with the exception of rs963468 (*DRD3*, dominant, $p=0.034$ based on the quantitative measures (table 1). Discovering this polymorphism cannot help in calculating odds ratio, since all 11 patients with dyskinesia possessed G/G genotype.

When only the 101 patients suffering of Parkinson's disease (PD) are considered, the results are even less convincing. Only rs3773678 (*DRD3*, dominant, $p=0.042$) was associated with orofacial dyskinesia. No significant associations were found with respect to limb-truncal dyskinesia or quantitative measures of

Table 1: Statistically significant associations between studied SNPs and phenotypes of dyskinesia in all neurological patients

SNP	Gene	Orofacial LID	Limb-truncal LID	LID	1-4	5-7	1-7
rs3758653	<i>DRD4</i>	+		+	+		
rs4911871	<i>HTR2C</i>	+			+		
rs2134655	<i>DRD3</i>				+		
rs963468	<i>DRD3</i>						+

1-4 items represent the sum of the first four parameters on the AIMS used for assessment of orofacial dyskinesia (these parameters include facial expressions and mouth area); 5-7 items represent the sum of 5-7 parameters to the expression of limb-truncal dyskinesia (movement of the limbs and trunk); 1-7 items assess a total dyskinesia.

dyskinesia in this more limited, but pathologically more homogenous patient group.

Discussion

The results were inconsistent between the extended (N = 143) and limited (N = 101) patient populations. The following methodological problems may explain these differences: multiple testing of *DRD3* and *HTR2C* polymorphisms, diagnostic heterogeneity, and poor clinical diagnosis of dyskinesia in comparison to other movement disorders using the AIMS. However, we previously established a strong relationship with two polymorphisms of the *GRIN2A* gene and dyskinesia in the same patient population and with the same study design (Ivanova et al., 2012). In that study the association increased when we limited the extended population to the patients with PD. Therefore, it could be concluded that the currently described associations probably do not have a great clinical relevance.

A feature of our study is the separation of dyskinesia into two variants which phenotypically differ from each other and according to our hypothesis may have a different genetic background. The sum of the first four parameters on the scale was used for AIMS assessment of orofacial dyskinesia (these parameters include facial expressions and mouth area), the sum of 5-7 parameters correspond to the expression of limb-truncal dyskinesia (movement of the limbs and trunk). We have previously found that orofacial tardive dyskinesia is associated with other polymorphisms than peripheral ones (Al Hadithy et al., 2009; Al Hadithy et al., 2010). A peculiar finding is that such associations are more prominent with

respect to orofacial dyskinesia. The association we have previously found for LID with *GRIN2A* polymorphisms was limited to limb-truncal movements (Ivanova et al., 2012). These polymorphisms are also known to be associated with the age of onset of Huntington's disease. The motor deficiency manifestations in HD are also localized in the limbs and trunk. This is another reason to believe, that the findings of the current study are not so much related to LID in PD, but to other orofacial dyskinesia in this patient group. Dyskinesia is known to occur spontaneously, particularly in elderly patients and patients with poorly fitted dentures (Woerner et al., 1991). Both essential tremor as well as dystonia may be accompanied with orofacial manifestations. Moreover, since the PD patients used levodopa and/or dopamine agonists, therefore the orofacial dyskinesia could be a normal symptom of dose-related side effects of these dopaminergic compounds. Levodopa-induced dyskinesia has been proposed to be related to oxidative stress caused by toxicity which leads to degeneration of striatal indirect pathway of medium sized spiny neurons (Loonen and Ivanova, 2013). This neurotoxicity could have other underlying genetic causes than dose-dependent dopamine receptor stimulation.

Conclusion

In conclusion, the studied variants of dopamine and 5-hydroxytryptamine receptor genes may not contribute to the development of LID. However, they may be related to orofacial dyskinesia via a different mechanism. The exact role of these neurotransmitter receptors in the pathogenesis of the orofacial

dyskinesia remains to be elucidated.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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