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Research Article

CYP2D6*17 polymorphism and tardive dyskinesia in black psychotic patients on typical antipsychotics

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Background: Tardive dyskinesia is a debilitating, intractable, hyperkinetic movement disorder which contributes to an increase in psychiatric morbidity. Reduced function *CYP2D6* alleles have been associated with tardive dyskinesia pathogenesis amongst Caucasians and Asians, with *CYP2D*4* and **6* and *CYP2D6*10* being implicated in these races respectively. No similar study has been successfully conducted in black Africans.

Objective: To determine the relationship between tardive dyskinesia and *CYP2D6*17* (the major reduced function *CYP2D6* allele in Africans).

Methodology: Abnormal Involuntary Movements Scale (AIMS) scoring and *CYP2D6* genotyping were carried out on psychiatric patients exposed to typical antipsychotic medications in an unmatched case control study. A case of tardive dyskinesia was defined as a patient with an AIMS score ≥ 2 in two body areas OR ≥ 3 in one body area

Results: A total of 18 cases and 32 controls made up the study sample.The sample's mean age was 36.9±12.0 years with median treatment duration of 7.0 years (range: 0.25 to 38 years). Multiple logistic regression revealed no significant association between tardive dyskinesia and *CYP2D6*17* (OR=0.252; 95% CI: 0.038 to 1.647; p=0.150). However, use of chlorpromazine (OR=5.754; 95% CI: 1.024 to 32.328; p=0.047) and age at treatment initiation (OR=1.146; 95% CI: 1.021 to 1.287; p=0.021) were independent predictors of tardive dyskinesia.

Discussion: These findings suggest that there is no association between *CYP2D6*17*and tardive dyskinesia in African psychotic patients on typical antipsychotics. However, more studies with larger sample sizes are required to provide more definitive conclusions regarding the nature of the relationship between CYP2D6*17 and tardive dyskinesia.

Key words: Tardive dyskinesia, CYP2D*17, typical antipsychotics

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1. Introduction

Tardive dyskinesia (TD) is a debilitating, intractable hyperkinetic movement disorder characterised by involuntary, repetitive, purposeless choreoathetotic movements. It is a serious iatrogenic adverse effect of dopamine receptor blocking drugs, chiefly antipsychotic medications (Waln & Jankovic, 2013). It can also occur spontaneously in some disorders such as schizophrenia (Ayehu et al, 2014). The condition classically presents as oro-facial movements, but other presentations have been noted including tardive akathisia, dystonia, tics or chorea (Waln & Jankovic, 2013). The annual incidence of TD in a cohort of mostly Afro-Caribbean patients with

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a mean antipsychotic exposure of 18 years was 10.2% (van Harten et al, 2006). In black African or African-American races, the risk of developing TD is up to twice that in Caucasians (Glazer et al, 1994). This disease has also been positively correlated with increasing age, duration of high potency neuroleptic use, neuroleptic dose, being non-white and type of antipsychotic drug (Jeste et al, 1995; Morgenstern & Glazer, 1993). Atypical antipsychotics have a better risk profile for causing TD compared to typical antipsychotics (Correll et al, 2004).

The risk for TD is also increased by carrying the following genes: *Dopamine Receptor D2 (DRD2 Taq1A)*, *Dopamine Receptor D3 (DRD3Ser9Gly)*, *Manganese Superoxide Dismutase Ala9Val (MnSOD Ala9Val)* and certain *Cytochrome P4502D6 (CYP2D6)* variants (Lee & Kang, 2011). Growing evidence suggests that different *CYP2D6* alleles with reduced or null functioning phenotypes are associated with TD across different ethnic groups (Patsopoulos et al, 2005). These *CYP2D6* alleles also vary in their distribution across different ethnicities (Bradford, 2002; Sistonen et al, 2007). In Asian populations exposed to antipsychotic medications, *CYP2D6*10* has been positively correlated to the occurrence of TD while *CYP2D6*4* and *CYP2D6*5* variants in Caucasians has been reported to be associated with TD (Kapitany et al, 1998; Liou et al, 2004; Nikoloff et al, 2002). These studies have shown a relationship between the most prevalent reduced function *CYP2D6* variants and TD in Caucasians and Asians. However, no similar relationship between TD and *CYP2D6*17* has been shown in black psychiatric patients receiving typical antipsychotics.*CYP2D6*17* is the most prevalent reduced function*CYP2D6*variant in blacks with a frequency of 12.2% in the Sub-Saharan black population (Oluka et al, 2014; Sistonen et al, 2007). Determination of the nature of the relationship between specific genotypes of *CYP2D6* may aid in the development of more personalised prescribing strategies which can minimize the risk of extrapyramidal adverse effects in susceptible patients. In addition, typical antipsychotics are cheaper and readily available in resource poor settings and personalised therapy will be more cost-effective (Rosenheck, 2007). Moreover, treatment with typical antipsychotics also avoids the serious adverse effects such as the metabolic syndrome, weight gain and raised triglycerides resultant from use of atypical antipsychotics (Gautam & Meena, 2011; Osser et al, 1999).

The aim of this study was to determine whether there is an association between the *CYP2D6*17* allele and TD in black psychotic patients exposed to typical antipsychotic medications. We hypothesised that there is an increased risk of developing TD in patients exposed to typical antipsychotics and carrying the *CYP2D6*17* allele(s). To test this hypothesis we carried out an unmatched case-control study in psychotic patients being managed at two major referral hospitals.

2. Methods

2.1 Study design

An unmatched 1:2 case-control study was carried out with participants selected from the two major psychiatric referral hospitals in Zimbabwe. All consenting cases presenting to the outpatients clinic during the period from the 14th of August to the 4th of November 2013 were recruited into the study. The Abnormal Involuntary Movements Scale (AIMS) (US Department of Health, Education and Welfare, 1974) and the Schooler-Kane criteria were used in the identification of patients with probable TD. A case of TD was defined as a patient with an AIMS score ≥ 2 in two body areas OR ≥ 3 in one body area (Schooler & Kane, 1982). Systematic random sampling was done with every 10th patient in a consultation queue enrolled as a study control participant. A control was defined as any psychotic patient without clinical features of TD and not meeting the Schooler and Kane case definition criteria.

All participants had received typical antipsychotics for at least three months. Two psychiatry residents collected demographic and other patient characteristics. The AIMS score was then determined through use of the AIMS score questionnaire. Thereafter, 5 ml of blood were drawn from each participant, labeled with their study ID and sent to the laboratory for storage and subsequent genotyping. We included stable, psychiatric outpatients exposed to typical antipsychotic therapy for at least three months. Patients below 18 years of age were excluded from the study.

2.2 Sample processing

Every effort was made to avoid contamination with extraneous DNA by strictly following good polymerase chain reaction (PCR) protocols and procedures. The work setup was thoroughly cleaned, with purification, amplification and analysis areas kept separate. DNA extraction was done using the QIAamp DNA Mini kit (Qiagen, CA), according to the manufacturer's manual from blood collected in EDTA tubes. Taqman® genotyping assays (Life Technologies, USA) were used for allelic discrimination of *CYP2D6*17* (assay identification number C_2222771_40) for the SNP 1023C>T. The total reaction volume was 25 µl comprising 2x Taqman® PCR master-mix, 20x drug metabolizing genotyping assay mix and genomic DNA. The PCR reaction was carried out using the Applied Biosystems 7500 Real Time PCR machine. The reaction consisted of 50°C denaturation for 2 minutes and 50 cycles with 95°C for 10 minutes and a final step of 92°C for 15 seconds. The participants were then labeled as heterozygous, hemizygous or homozygous for *CYP2D6*17*.

2.3 Data analysis

Patient characteristics' data were compared between the cases and the controls using the independent sample t-test and the chi-square test for continuous and categorical variables, respectively. For non-normally distributed variables, the Mann-Whitney test was used in place of the independent sample t-test. Logistic regression was used to determine the association of the alleles with tardive dyskinesia, after controlling for covariates. The Hardy-Weinberg equilibrium was tested using the Chi-square goodness-of-fit test.

All the statistical analyses were done using the Statistical Package for Social Sciences Version 17.0 (Chicago, USA).

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2.4 Ethical consideration

The study was approved by the following institutional review boards: the Joint Research Ethics Committee (University of Zimbabwe and Parirenyatwa Hospital), Harare Central Hospital and the Medical Research Council of Zimbabwe (MRCZ reference number: MRCZ/B/562). The participants' caregivers gave voluntary informed assent for inclusion into the study. The participants' identities were then coded, creating a study ID. No personal identifiers were collected during the study.

3. Results

A total of 52 patients out of 59 approached (88.1% response rate) participated in the study. Of these, genotyping for *CYP2D6*17* was successful in 50 participants. The results reported here are based on these 50 patients (18 cases and 32 controls). **Table 1** shows the demographic and clinical characteristics of the patients in the study. The mean age of the patients was 36.9±12.0 years and the majority were female (56.0%). The median duration of treatment was 7.0 years (range: 0.25 to 38 years).

Table 1: Demographic and clinical characteristics of cases and controls

Patient characteristic	Total (N = 50)	Cases (n = 18)	Controls (n = 32)	Intergroup comparison p value
Gender				
Male	22 (44.0%)	9 (50.0%)	13 (40.6%)	0.522‡
Female	28 (56.0%)	9 (50.0%)	19 (59.4%)	
Current age/years (mean ± sd)	36.88 ± 12.04	44.94 ± 13.47	32.34 ± 8.40	0.001†
Treatment duration/years (mean ± sd)	9,71 ± 9.11	12.78 ± 10.75	7.86 ± 7.69	0.085ϕ
Age at drug initiation/years (mean ± sd)	27.00 ± 8.97	31.61 ± 8.05	24.41 ± 8.51	0.005†
Benzhexol exposure status				
Exposed	39 (78.0%)	18 (100%)	21(65.6%)	0.001‡‡
Not exposed	11 (22.0%)	0	11 (34.4%)	
CPZ exposure status§				
Exposed	24 (48.0%)	15 (83.3%)	9 (71.9%)	<0.0001‡‡
Not exposed	26 (52.0%)	3 (17.7%)	23(28.1%)	
FD exposure status§				
Exposed	35 (70.0%)	14 (77.8%)	21 (65.6%)	0.0361‡‡
Not exposed	15 (30.0%)	4 (22.2%)	11 (34.3%)	
Haloperidol exposure status§				
Exposed	39 (78.0%)	15 (83.3%)	24 (75.0%)	0.488‡‡
Not exposed	11 (22.0%)	3 (16.7%)	8 (25.0%)	
CYP2D6*17 allele				
Yes	17 (34.0%)	4 (22.2%)	13 (40.6%)	0.187‡‡
No	33 (66.0%)	14 (77.8%)	19 (59.4%)	

The majority of the patients were on haloperidol (78.0%), benzhexol (78.0%), and fluphenazine decanoate (70.0%). Less than half of the patients were on chlorpromazine (48.0%). **Table 2** shows results of multivariate logistic regression. There was no significant association between TD and *CYP2D6*17* (OR=0.252; 95% CI: 0.038 to 1.647; p=0.150), after controlling for covariates. A similar observation was seen with duration on antipsychotics (p=0.105), fluphenazine decanoate (p=0.598) and gender (p=0.646). However, use of chlorpromazine (OR=5.754; 95% CI: 1.024 to 32.328; p=0.047) and age at treatment initiation (OR=1.146; 95% CI: 1.021 to 1.287; p=0.021) were independent predictors of tardive dyskinesia.

Table 3 shows the distribution of the CYP2D6*17 genotype profiles according to cases and controls. The frequencies suggest that the genotypes were not in Hardy-Weinberg equilibrium. The frequency of the *CYP2D6*17* allele was 22.0%.

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Table 2: Predictors of developing tardive dyskinesia

Predictor variable	Wald Chi square	P value	Odds Ratio	95% C.I. for odds ratio	
				Lower	Upper
CPZ	3.948	0.047	5.754	1.024	32.328
Duration	2.622	0.105	1.091	0.982	1.211
Age at drug initiation	5.339	0.021	1.146	1.021	1.287
Haloperidol	0.115	0.734	1.412	0.193	10.336
FD	0.278	0.598	1.720	0.229	12.920
Gender	0.211	0.646	1.473	0.282	7.698
CYP2D6*17	2.072	0.150	0.252	0.038	1.647

Table 3: Comparison of CYP2D6*17 genotype profiles between cases and controls

		Participants		Frequency	
		Case	Control	Total observed	*H-W freq
Genotypes	**ww**	14(13.35)	19 (17.26)	33 (30.42)	60.84%
	mw	3 (4.31)	9 (12.48)	12 (17.16)	34.32%
	mm	1 (0.35)	4 (2.26)	5 (2.42)	4.84%
Total		18 (13.01)	32 (29.99)	50 (44.95)	
*HWE calculation: χ^2		1.66	2.49	4.52	
*P value		0.198	0.114	0.033	
*Allele freq	**m**			78.00%	
	w			22.00%	

4. Discussion

In the present case control study, we found no association between TD and *CY2D6*17* – the major reduced function *CYP2D6* allele in a black African population. These findings are supported by those of Lohmann et al. where the reduced function *CYP2D6* genotype did not have any influence on the development of TD in Caucasian patients (Lohmann et al, 2002). However, the findings are in contrast to those reported by Kapitany et al. where Caucasian patients heterozygous to *CYP2D6* reduced function mutations were more susceptible to TD than those without these mutations (Kapitany et al, 1998).Similarly, a recent study observed, that the number of functional *CYP2D6* genes was positively associated with an increased risk of TD in an English Caucasian population exposed to typical antipsychotics (Koola et al, 2014).

The inconsistent association results are possibly due to the differences in the sample sizes, study design, the primary psychiatric diagnosis, participant ethnic group investigated and heterogeneous inclusion criteria used (Lee & Kang, 2011). Interactions between certain genetic loci and factors such as inflammatory cytokines and growth hormone, which influence CYP450 enzyme expression, may further explain the inconsistent pharmacogenetic association results (Dhir et al, 2006; Koola et al, 2014).

Furthermore, it would appear that extensive metabolism and not necessarily poor metaboliser status increases TD susceptibility (Koola et al, 2014). Previously and in this study, efforts have been on defining a relationship between the reduced function alleles and TD, but it appears carrying functional alleles is more likely to have a causal association with TD. The reasons as stated by Koola et al. could be due to*CYP2D6* generated neurotoxic metabolites such as haloperidol pyridinium– the (haloperidol) pyridinium hypothesis (Koola et al, 2014; Ulrich & Genz, 2005). However, at higher haloperidol doses (> 20 mg daily), *CYP3A4* may be enzyme responsible for haloperidol pyridinium production (Roh et al, 2001; Usuki et al, 1996). The major question still remains on the pathogenetic mechanism of TD development and its association with other typical antipsychotics.

The major limitation of the present study was the small sample size obtained. In addition we could not determine the exact antipsychotic doses and duration of exposure to each medication beyond the three months.

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These factors were not factored in the design and analysis of the study. However, this study encourages further examination of the relationship between *CYP2D6* and TD in black psychotic patients receiving typical antipsychotic medications. This could be done through a prospective well-designed study exploring the effects of polymorphic interactions, HIV, alcohol, smoking, *CYP2D6* metabolites and P450 enzyme expression levels. Steady state levels of haloperidol pyridinium could be included as this metabolite is a known neurotoxin and its presence is associated with TD – the (haloperidol) pyridinium hypothesis (Ulrich & Genz, 2005).

5. Conclusion

In conclusion, this study failed to find an association between *CYP2D6*17* and tardive dyskinesia in African psychotic patients on typical antipsychotics. However, more studies with larger sample sizes are required to provide more definitive conclusions regarding the nature of the relationship between CYP2D6*17 and tardive dyskinesia Coupled with plasma level antipsychotic level determination, this could help elucidate the pathogenesis of this disease. In turn, this will further the formulation of prescription algorithms for the safe use of typical antipsychotics allowing for personalised therapy. Through this strategy, cost–effective typical antipsychotic medicines such as haloperidol can then be safely used in resource-poor, underfunded psychiatric services.

Conflict of Interest declaration

The authors declare no conflict of interest.

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