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LETTER TO THE EDITOR

Acute Extrapyramidal Side Effects Following Domperidone Intake in a 48-Year-Old Female Patient: The First Genetic Alteration and Drug Interaction Characterized

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Dear Editor,

Domperidone, a peripheral and central dopamine receptor antagonist with gastroprokinetic and antiemetic effects, is a widely prescribed medication in clinical practice. This agent presents very low rates of extrapyramidal side effects due to its negligible penetration through the blood–brain barrier (BBB).[1] Extrapyramidal symptoms after domperidone usage have only been reported in children, adolescents and individuals with comorbidities thought to alter BBB permeability. In this report, we describe a case of a 48-year-old female with a normal medical history who displayed tongue tremor following administration of the recommended dose of domperidone. We also discuss the factors that might facilitate extrapyramidal manifestation from genetics and drug interaction perspectives.

A 48-year-old female patient without a significant medical history was admitted to our outpatient clinic with spontaneous involuntary movements of the jaw, lips and tongue muscles, which led to difficulties in chewing, speaking and swallowing. She reported that the symptoms (dominantly tongue tremor) appeared soon after she took esomeprazole (40 mg per day) and domperidone (20 mg per day) for the treatment of gastritis (Supplementary Video 1 in the online-only Data Supplement). Mild abdominal gaseous distension was found, but there was no localized abdominal pain. Apart from the abovementioned symptoms, no localized neurological symptoms, meningeal irritation or other signs were observed. Common blood biochemistry tests, urine analysis and complete blood count were unremarkable. Furthermore, cerebral magnetic resonance imaging with contrast was negative for central nervous system (CNS) damage. Subsequently, the diagnosis of domperidone-induced tongue tremor was established. Domperidone was discontinued immediately, and trihexyphenidyl was prescribed. Within 48 hours, her lingual tremor improved, and abnormal movements disappeared, which strengthened the established diagnosis of drug-induced extrapyramidal side effects. After discharge, no recurrence was observed during the three-month follow-up visits. Genetic analysis was later performed by whole exome sequencing (WES) and Sanger sequencing (Supplementary Material 1 in the online-only Data Supplement). Two variants were detected in intron 3 and exon 8 of *CYP3A5* (c.219-237A>G) and *ANKK1* (c. 2137G>A),

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respectively.

The Naranjo algorithm was applied to assess the causal relationship between drugs and adverse events, and our case had a score of six, which indicated a "probable" relationship between domperidone and tremor (Supplementary Table 1 in the online-only Data Supplement). In addition, based on WHO Uppsala Monitoring Centre criteria, this movement disorder had a "certain" relationship with domperidone. In a literature search, domperidone-induced CNS side effects were only observed in infants or young children because of their poorly developed BBB and in older individuals with increased BBB permeability thought to be due to dementia. To the best of our knowledge, the woman in current study, who had no underlying disease and an intact BBB, is the first case in this age group to be reported to have acute adverse reactions. Although several cases exhibiting domperidone-induced extrapyramidal symptoms have been described, the causal factors remain elusive. In 1991, it was suggested that the dystonic reaction was induced by domperidone in young women (16 and 28 years old) with polycystic ovary syndrome due to chronic estrogenic stimulation.[2] However, the woman in current study had a normal medical history; thus, the possibility that estrogen levels affected lingual tremor could be ruled out.

In the present work, from a pharmacogenetics perspective, we investigated the accelerating factors provoking involuntary tongue tremor after domperidone intake. As a result, WES did not reveal any clinically significant variants of *CYP3A4*, *ABCB1*, or *DR2D* genes encoding proteins responsible for domperidone metabolism in the liver, domperidone transporters at the BBB or domperidone targets at the striatum, respectively (Supplementary Table 2 in the online-only Data Supplement). Noticeably, a *CYP3A5* homozygous variant in intron 3 (NM_000777.5:c.219-237A>G, designated *CYP3A5**3) was detected by Sanger sequencing (Figure 1A). In the liver, domperidone is mainly metabolized by CYP3A4/5, producing hydroxylated metabolites. The patient carrying the homozygous genotype *CYP3A5**3/*3 could not produce active enzyme. Even though no defective allele of *CYP3A4* was detected, the contribution of CYP3A5 enzyme deficiency to plasma accumulation of domperidone could not be excluded.

In contrast to other dopamine antagonists, including antipsychotics (haloperidol) and antiemetics (metoclopramide), domperidone is normally extruded by the efflux transporter ABCB1 expressed on endothelial cells of the BBB, which explains the minimal central effects of this drug. In our patient, the CNS effect began soon after the first dose, demonstrating that the brain penetrance of domperidone was increased. However, no genetic variant affecting ABCB1 transporter function was detected in the patient. Notably, the patient was also prescribed esomeprazole, a proton pump inhibitor, which was listed in DrugBank as an ABCB1 inhibitor (go.drugbank.com) and approved by the FDA for ABCB1 inhibition activity.[3] Previous animal studies showed increased brain permeability of domperidone when *mdr1* was deleted[4] and following treatment with an ABCB1 inhibitor.[5] At present, although evidence regarding esomeprazole-induced domperidone aggregation in the CNS has not yet been documented, medical doctors still should be aware of extrapyramidal reactions triggered when patients are coadministered these two drugs. WES also resulted in a heterozygous variant of *ANKK1* (NM178510.1:c.2137G>A, p.[Glu713Lys]) (Figure 1B), which was associated with a 40% reduction in D2 receptor expression in the striatum without affinity alteration.[6] Mechanistically, it has been hypothesized that drug-induced movement disorder results from an imbalance in the dopaminergic-cholinergic signaling system in the basal ganglia. In our patient, onset of tremor occurred within 2−3 hours after the first dose and became well defined following the second dose. As previously reviewed, the higher the blocked D2 receptor percentage, the greater the risk of acute dystonia.[7] Due to the reduced density of striatal receptor D2 in the patient, we postulate that she could have been more sensitive to dopamine signaling inhibition via D2

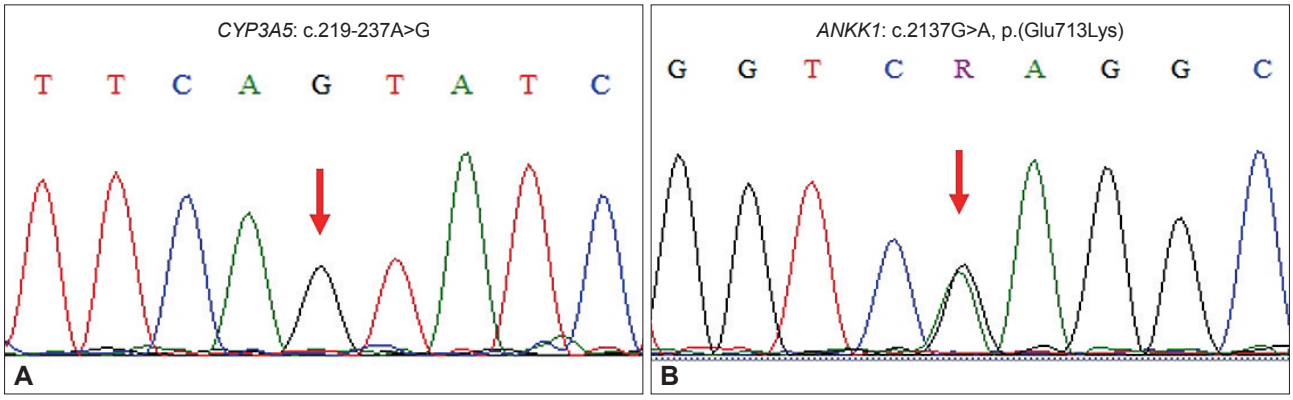

Figure 1. Sequencing analysis showed variants in the *CYP3A5* and *ANKK1* genes. A: Partial sequence of *CYP3A5* with a homozygous substitution in intron 3 (c.219-237A>G). B: Partial sequence of *ANKK1* with a heterozygous variant in exon 8 (c.2137G>A), leading to amino acid replacement p.(Glu713Lys). Mutated nucleotides are denoted by red arrows.

receptor blockade despite using the lowest recommended dose (10 mg, twice per day). Although the pathogenesis of extrapyramidal symptoms cannot be defined solely by this case, both genetics and coadministered drugs still deserve consideration, especially in individuals with an intact BBB. Furthermore, extended clinical observations are critical to investigate whether esomeprazole and genetic susceptibility predispose patients to CNS side effects or these symptoms were coincidental events.

Our study highlights the risk of extrapyramidal side effects when prescribing domperidone with esomeprazole or any ABCB1 inhibitors as concomitant therapy. In addition, genetic screening for pharmacogenes encoding drug metabolism enzymes, drug transporters and drug targets might be beneficial in cautious use of this drug.

Ethics Statement

All procedures in this study were performed in accordance with ethical standards by ethics committees of the Institute of Genome Research, Vietnam Academy of Science and Technology (approval no. 3-2019/NCHG-HĐĐĐ). Written informed consent was received from the patient to publish this report and any accompanying images/videos.

Supplementary Video Legends

Video 1. This video shows abnormal involuntary movement of the patient's tongue and mouth after administering a dose of 20 mg domperidone. She had no control over her tongue. This is a sign of induced extrapyramidal symptoms.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.21151.

Conflicts of Interest

The authors have no financial conflicts of interest.

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Author Contributions

Conceptualization: Nguyen Dang Ton, Nguyen Duc Thuan. Data curation: Vu Phuong Nhung, Hoang Thi Dung, Nhu Dinh Son, Nguyen Hai Ha. Investigation: Vu Phuong Nhung, Hoang Thi Dung, Nhu Dinh Son, Nguyen Hai Ha. Supervision: Nguyen Dang Ton, Nguyen Duc Thuan. Writing—original draft: Nguyen Duc Thuan, Vu Phuong Nhung. Writing—review & editing: all authors.

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SUPPLEMENTARY MATERIAL 1

For whole exome sequencing: Genomic DNA was extracted from leukocytes of patient's peripheral blood using standard protocol (GeneAll, Korea). Total DNA concentration was determined by Qubit dsDNA BR Assay kit (ThermoFisher Scientific, Waltham, Massachusetts, USA). Paired-end sequencing was carried on the NovaSeq platform (Illumina, San Diego, California, USA) following the manufacturer's instructions. The mean exome coverage was more than 100× and each target base having at least 20× coverage.

For sanger sequencing, ABI Prism BigDye Terminator Cycle Sequencing kit V3.1 was used (Applied BioSystem, Waltham, Massachusetts, USA), on an ABI genetic analyzer 3500 (Applied Biosystems, Waltham, Massachusetts, USA). The primer sequences used for PCR and sequencing were as follows:

*CYP3A5**3-F: CTTGCAGCATTTAGTCCTTGTGA

*CYP3A5**3-R: CTGATCACGTCGGGATCTGTGA

ANKK1-F: GGAGCACCTTCCTGAGTGTC

ANKK1-R: ATCTCGGCTCCTGGCTTAG

All primers were provided by PHUSA Biochem Company (Can Tho, Vietnam).

Supplementary Table 1. Naranjo algorithm for adverse drug reaction (ADR)

Clinical question	Yes	No	Do not know	Score
1.Are there previous conclusive reports on this reaction?	+1			1
2.Did the adverse event appear after the suspected drug was administrated?	+2			2
3.Did the adverse reaction improve when the drug was dis-continued or a specific antagonist was administered?	+1			1
4.Did the adverse reaction reappear when the drug was re-administered?			0	0
5.Are there alternative causes (other than drug) that could on their own have caused the reaction?		+2		2
6.Did the reaction reappear when a placebo was given?			0	0
7.Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?			0	0
8.Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?			0	0
9.Did the patient have a similar reaction to the same or similar drugs in any previous exposure?			0	0
10.Was the adverse event confirmed by any objective evidence?			0	0
Total score	4	2	0	6

Scoring: >9 = definite ADR, 5–8 = probable ADR, 1–4 = possible ADR, 0 or less = doubtful ADR.

Supplementary Table 2. Genetic variants of candidate genes identified by WES and Sanger sequencing

Gene (transcript)	Nucleotide change	AA change	Zygosity	Clinsig† Pharmvar*	Method
CYP3A4	99365943C>A (26)	-	Hom	-	WES
CYP3A5 (NM_0000777.5)	c.219-237A>G (CYP3A5*3)	-	Hom	*Splice defect	Sanger
ABCB1 (NM_001348945)	87168749C>T (78)	-	Hom	-	WES
	c.210A>G (35)	p.70G=	Hom	-	WES
DRD2 (NM016574)	c.852T>C (51)	p.284H=	Het	-	WES
ANKK1 (NM_178510)	c.2137G>A (116)	p.E713K	Het	†Reduce dopamine receptor D2 density in striatum Drug response	WES
	c.1683C>T (126)	p.Y561Y	Hom	-	
	c.1324G>C (194)	p.G442R	Het	-	
	c.453A>C (35)	p.I151I	Het	-	
	c.T255C (96)	p.S85S	Het	-	

The mean coverage of each variant was shown in the parentheses.
AA, amino acid; Het, heterozygous; Hom, homozygous; Clinsig, Clinical significance (ncbi.nlm.nih.gov/clinvar); Pharmvar, Pharmacogene Variation Consortium (pharmvar.org).