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Case Report

Visual Hallucinations Due to Rivastigmine Transdermal Patch Application in Alzheimer's Disease; The First Case Report^{☆, ☆, ☆}Yıldız Değirmenci^{*}, Hulusi Keçeci

Duzce University School of Medicine, Neurology Department, Duzce, Turkey

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SUMMARY

Rivastigmine is a well-known dual acting acetylcholinesterase and butyrylcholinesterase inhibitor, which is effective on behavioral and psychiatric symptoms including hallucinations, as well as cognitive symptoms of dementia. The most common adverse effects of rivastigmine related to cholinergic stimulation in brain and peripheral tissues are gastrointestinal, cardiorespiratory, extrapyramidal, genitourinary, musculoskeletal symptoms, sleep disturbances, and skin irritations with the transdermal patch form in particular. Despite to the previous reports revealing the improving effects of the drug on hallucinations, we presented a 80 year old woman with Alzheimer's disease suffering from visual hallucinations whose complaints began with rivastigmine treatment. Since the patient had recent memory disturbance without any behavioral and/or psychiatric symptoms before rivastigmine administration, and visual hallucinations disappeared with the discontinuation of the drug, visual hallucinations were attributed to rivastigmine.

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1. Introduction

Rivastigmine is a “pseudo-irreversible” acetyl- and butyrylcholinesterase inhibitor with a phenylcarbamate structure which is an effective treatment option in mild-to-moderate Alzheimer's disease (AD)¹. Since rivastigmine is beneficial in improving patients' cognitive, behavioral, and daily functioning, it is found to be effective in mild to moderate dementia associated with Parkinson's disease, as well as AD². In addition to its oral forms, it is the first cholinesterase inhibitor to be approved as a transdermal patch (TDP) which is applied once daily. It has three sizes; 5, 10, 15 cm² releasing 4.6, 9.5, and 13.3 mg rivastigmine/24 hours, respectively, and available in several countries worldwide³. The most common adverse effects of rivastigmine, related to cholinergic stimulation in brain and peripheral tissues are gastrointestinal (nausea, vomiting, diarrhea, etc), cardiorespiratory, extrapyramidal (dystonic

reactions, etc.), genitourinary (urinary incontinence), and musculoskeletal symptoms (muscle cramps, weakness), as well as sleep disturbances^{4–6}. In addition, skin irritations in the localization area of the patch have been reported for the transdermal formulation^{7,8}.

Regarding to its' useful effect on behavioral symptoms of dementia, previous studies demonstrated a wider use of rivastigmine in the treatment of multiple behavioral and psychological symptoms of dementia including apathy, anxiety, depression, delusions and hallucinations, due to its' dual inhibition effect of acetyl- and butyrylcholinesterase and brain region selectivity through preferential inhibition of the G1 isoform of acetylcholinesterase^{9–11}.

Unlike these previous reports of rivastigmine demonstrating the curative effects on behavioral symptoms, we here presented a woman suffering from visual hallucinations and anxiety due to the transdermal administration of rivastigmine. According to our knowledge and literature review, this is the first reported case in which transdermal administration of rivastigmine lead to visual hallucinations.

2. Case-report

An 80-year old woman presented to our outpatient neurology clinic with visual hallucinations, aggression and loss of appetite.

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^{*} Correspondence to: Dr. Yıldız Değirmenci, Duzce University School of Medicine, Neurology Department, Konuralp, Duzce, Turkey.

E-mail addresses: ydegir@gmail.com (Y. Değirmenci), hulusikececi@hotmail.com (H. Keçeci).

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Her medical records revealed no toxin exposure, drug usage or systemic and/or neurological diseases except AD and its' medications. She had the diagnosis of AD since 5 years, and she was under our dementia outpatient clinic control since 1 year. While she was using donepezil 10 mg daily without any behavioral and/or psychiatric symptoms, donepezil was tapered gradually and discontinued due to the gastrointestinal side-effects as nausea, and diarrhea which the patient couldn't tolerate. So since 1 month, she was under 4. 6 mg/24 hours rivastigmine patch (© Exelon patches) treatment. The medical history taken from her daughter revealed that she was suffering from visual hallucinations since 2 weeks; he was seeing bugs on the wall, and trying to get rid of them, but the loss of appetite and aggression was gradually increased within 1 month. However, her main complaint was recent memory disturbance without any behavioral and/or psychiatric symptoms other than mild depression before rivastigmine administration. Physical examination of the patient was normal. Her vital parameters, and routine blood tests including complete blood count, thyroid function tests, full biochemical screening with electrolytes, liver and kidney function tests were normal. Neurological examination of the patient revealed a recent memory loss with mini-mental state exam score of 20/30 points. Her psychological assessment revealed aggressiveness, anxiety, and visual hallucinations.

Regarding to the psychiatric symptoms of the patient, rivastigmine patch was stopped, and switched to donepezil 5 mg/daily. One week after the discontinuation of rivastigmine, the daughter of the patient stated that the visual hallucinations were diminished, and her aggression was reduced without any antipsychotic treatment.

3. Discussion

Hallucinations in AD, are the symptoms of moderate to severe AD, which are the indicator of cortical cholinergic deficits. Underlying cause of the hallucinations in AD is the cholinergic neuronal loss and a subsequent decline in the acetylcholine levels of brain regions which are responsible for the behavioral and emotional responses, in particular¹². As a moderate to severe complaint of AD, hallucinations may present in 20-40 % of AD patients, and visual hallucinations are the most common form¹³.

We here presented an AD patient with visual hallucinations which began with rivastigmine treatment and disappeared within the discontinuation of the drug. However, the introduction of rivastigmine led to improvements in cognitive and functional abilities, as well as the resolution of behavioural problems and visual hallucinations².

As we know from the previous studies and reports, rivastigmine is a well-known dual inhibitor of acetylcholinesterase and butyrylcholinesterase that shows brain region selectivity. The behavior domains that most consistently showed improvement with rivastigmine therapy are apathy/indifference, anxiety, delusions (psychosis), and hallucinations^{2,9,14}. Suggesting the positive role of cholinesterase inhibitors on psychiatric symptoms, previous reports demonstrated the improvement of visual hallucinations in wide range of dementias including Parkinson's disease dementia, Alzheimer's disease, vascular dementia, and frontotemporal dementia^{2,12,15}.

In conclusion, despite the well-known positive effects of rivastigmine over visual hallucinations, and anxiety as well as other behavioral symptoms of dementia, we would like to share this unique patient as a case report who experienced visual hallucinations under rivastigmine treatment. The existence of hallucinations despite the low dose of rivastigmine in our patient may be

explained by the variable pharmacokinetics of rivastigmine from person to person, which may be responsible for the hallucinatory side-effect similar to an overdose of rivastigmine.

Since the patient had no behavioral symptoms before rivastigmine treatment, and the visual hallucinations disappeared after the discontinuation of the drug, we attributed these hallucinations to rivastigmine itself as a side effect, and shared as a unique case-report.

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Author contributions

Yildiz Degirmenci and Hulusi Kececi worked in the design, analysis of data, draft and writing of the paper. All authors agree with the results and conclusions, made critical revisions, reviewed and approved the final version.

Disclosures and ethics

There are no conflicts of interest reported by the authors. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material.

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