Donepezil for Compulsive Behavior in Degenerative Dementia: Case Series

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Diagnosing and managing dementia, presenting with compulsions is challenging. Presented are three cases, a possible representative subset of the Donepezil responders. Selective degeneration of dorsolateral prefrontal cortex networking striatum leading to compulsions would be amenable to cholinergic modulation.

KEY WORDS: Repetition compulsions; Psychosis; Dementia; Major neurocognitive disorder; Donepezil.

INTRODUCTION

The onset of repetitive, compulsive behaviors at late age usually stems from an organic basis or can be the presentation of a progressive dementing process. Frontotemporal dementia (FTD) is recognized as the commonest neurological cause for new-onset compulsive behaviors in middle to late life. But it can be a presenting symptom in Alzheimer’s and other dementia. In relation to the treatment of the behavioral symptoms in dementia there are limited studies, and anticholinesterase inhibitors such as donepezil have shown mixed results, with worsening of behaviors reported by few studies. Here we present a series of three cases of degenerative dementia with an onset characterized by compulsive and psychotic behavior, which heralded the onset of a dementing process with a seemingly good response to donepezil including a dramatic reduction of the behavioral symptoms.

CASE

Case 1

A 64 years old hypertensive female presented with an acute onset 6 months’ history of forcing her grandson to repeatedly wash the toilet without citing any reasons, compulsive checking of her belongings, intermittent irritability, muttering to herself and reduced sleep with poor attention and insight. Psychotic symptoms and cognitive performance worsened during clomipramine trial of 150 mg/day. A possibility of late onset psychotic disorder was considered. Addition of tablet risperidone 3 mg/day reduced irritability, hallucinatory behavior but not compulsions, with the appearance of word finding, naming difficulties and forgetfulness impacting daily activities. Computed tomography (CT) scan of brain and detailed neuropsychological assessment revealed a degenerative process (Table 1). Addition of oral donepezil 10 mg/day to ongoing risperidone brought slight improvement in the domains of ideational fluency and vigilance and a significant reduction in repetitive behavior.

Case 2

A 75 years old male presented with 8 months’ history of insidious onset of illness, characterized by “sand” or “crawling of insects” like tactile sensations under the eyelids, resulting in compulsive cleaning and washing of eyelids and body parts, along with fleeting 2nd person audi-
Table 1. Neurocognitive domains and structural involvement in the presented cases

| Neurocognitive domains involved | Case 1 | Case 2 | Case 3 |
|--------------------------------|--------|--------|--------|
| Attention, concentration & vigilance | * | | * |
| Working memory | * | | * |
| New learning ability (verbal & visual) | * | | * |
| Delayed recall | | | |
| Motor execution | * | | |
| Ideational fluency | * | | * |
| Verbal fluency | | | |
| Comprehension | | | *
| CT scan-areas showing atropic changes | Frontal & temporal | Bilateral basi-temporal & frontal | Bilateral basi-temporal & frontal (left > right) |

CT, computed tomography.
*Cognitive domains impaired.

...tory hallucinations, irritability and reduced sleep. A provisional diagnosis of monosymptomatic hypochondriacal psychosis, with differential diagnosis of obsessive compulsive disorder (OCD) with poor insight/organic psychotic disorder was considered. On tablet risperidone 3 mg/day, the behavioral symptoms other than hallucinations worsened. The CT scan of brain and neuropsychological tests were suggestive of major neurocognitive disorder (Table 1), tablet donepezil 10 mg/day was gradually added to risperidone 2 mg/day. On follow up after 4 months, there was a significant reduction in cleaning behavior without further deterioration in cognitive functions.

**Case 3**

A 73 years old hypertensive female came with 3 weeks' history of acute onset of repeatedly checking the doors, irritability, persecutory delusions, intermittent 3rd person auditory hallucination, impaired concentration and judgment. A provisional diagnosis of acute and transient psychotic disorder was kept, with a possibility of dementia in evolution. Patient showed significant reduction in the various dimension of delusions and hallucinations with risperidone 3 mg/day. In view of the emerging neurocognitive disorder, which became apparent on neuropsychological assessment and imaging (Table 1), tablet donepezil 5 mg/day was started. On next visit at 2nd month, interestingly there was significant reduction in the frequency of the repetitive behaviors, with improvement of performance in working memory and vigilance.

**DISCUSSION**

The compulsive behaviors in dementia are usually atypical, with lack of insight into the irrationality and excessive nature of the repetitive acts. In our cases, the thought behind the repetitive behavior could hardly be elicited; however, appeared secondary to hypochondriacal or persecutory doubts. Furthermore, the additional rapid cognitive decline and deterioration in personality, were suggestive of a dementing process with repetitive behaviors being the initial symptom presentation. However, there were quite a few atypicalities in our cases, in relation to the nature and age of onset of the illness.

FTD which is the commonest degenerative etiology of compulsions usually emerges before 65 years of age with an insidious onset. Two of our three patients had an onset after 65 years. The perceptual disturbances at presentation, particularly with well-formed third person auditory hallucinations are another atypicality found in our cases. Though rare, but schizophrenia like psychotic illness have been described in few histologically proven FTD cases, having relatively younger onset, with comorbid motor neuron disorder. The association between late-onset compulsive symptoms and dementia may arise from at least 3 different scenarios. First, dementia may be the final end-point of some form of primary, resistant OCD. Second, late-onset compulsive behaviors, or stereotypies and dementia may result from a common pathophysiologic basis, such as in FTD. Finally, the association may result from the interaction between vulnerability towards obsessive compulsive (OC) symptoms and the nonspecific effects of a neu-
The combination of psychosis, compulsions and dementia found in our cases, can be explained by a common glutaminergic system dysfunction. Unstable prefrontal glutamatergic system with hyper-glutamatergic orbitofrontal (OFC) and hypoglutamatergic dorsolateral prefrontal (DLPFC) regions has been theorized to be the pathophysiology behind the schizo-obssessive disorder. Similar glutamate mediated degenerative process involving the DLPFC along with striatal circuits would be resulting in the symptom presentation in our cases.

Another variation was that, apart from repetitive behavior, all of them lacked the other classical symptoms of behavioral variant (bv) FTD as follow; apathy, disinhibition, asociality, and change in dietary choices. This lack of common ‘frontal’ bv FTD features such as disinhibition or apathy suggests relative sparing of OFC and ventromedial prefrontal cortices (VMPFC). Language, memory and executive functions deficits implicates the temporal and DLPFC involvement. Moreover in stereotypic form of FTD, marked striatal changes and variable cortical involvement are reported, with advanced temporal rather than frontal lobe pathology. Thus, the imaging, neuropsychological tests and symptoms in present series implicate prominent temporal region and DLPFC with relative sparing of OFC and VMPFC. The current cases though has features of selective frontal and temporal lobe involvement, they would not fit into the classical descriptions of any defined categories of dementia. Histopathological and genetic tests could have confirmed the diagnosis, which were not done due to the resource constraints.

The most important finding in our case series was the dramatic reduction in repetitive and compulsive behaviors with donepezil. Striatal circuits have dense array of cholinergic interneurons which have modulatory role in the repetitive behaviors and stereotypies. Cholinergic depletion reportedly produces repetitive behaviors in animal models which responds to donepezil. Donepezil is known to improve behavioral symptoms in Alzheimer’s dementia.

Summary of the possible biological underpinnings is as follows: degeneration of cortical neurons at DLPFC and temporal regions might have resulted in hypoglutamatergic DLPFC and relative hyperglutamatergic OFC regions, the circuitry changes often seen in patients with schizo-obssessive disorder. Cortical glutamatergic neurons modulate the striatal output through GABA modulating cholinergic interneurons. A deficiency in cortical glutamate led to reduced striatal cholinergic activity, which in turn increased the OC symptoms. Donepezil by reducing the hydrolysis increases the concentration of acetylcholine in striatal synapses, thereby effectively modulating the excitatory-inhibitory balancing and ameliorates the OC symptoms.

In conclusion, detailed neurocognitive and neuroimaging investigations are imperative to unmask dementias that present with complex atypical psychiatric manifestations. Role of donepezil in management of repetitive behaviors during degenerative process needs further systematic evaluation.

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