Clinical Improvement in a Patient with Parkinson's Disease and Vascular Dementia Receiving PCSK9 Inhibitor for Ischemic Heart Disease: A Case Report

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ABSTRACT

Dementia is a disorder that is characterized by a decline in one or more of the cognitive functions (learning and memory, language, executive functions, attention, motor and social abilities). [5]The dysfunctions are usually severe enough to interfere with the patient's daily activities and independence. The main under-lying cause of vascular dementia is cerebrovascular disease or insufficient cerebral microvascular circulation. [7] The vascular dementia should be treated for vascular risk factors, especially hypertension, diabetes, hypercholesterolemia, smoking and inactivity.[8], [9]. The standard pharmacological interventions are Acetylcholinesterase inhibitors (donepezil, galantamine) and N-Methyl- D-aspartate receptor antagonists (Memantine). However, recovery of lost cognitive function beyond the initial recovery from vascular dementia is not likely. Moreover, Parkinson disease is another common neurological disease, caused by loss of dopaminergic neurons of substantia nigra pars compacta. The primary treatments are anticholinergics (benztropine, trihexyphenidyl), dopamine precursors (levodopa, carvidopa), COMT inhibitors (Entacapone), MAO B inhibitor (Selegiline), and Amantadine. Above treatments can slow down the disease progression but they cannot reverse the disease course. Here we are reporting a patient with dementia and parkinson's disease who was significantly improved by adminis- tration of PCSK9 inhibitor.

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Classification: NLMC Code: WG 200, WL 359

Language: English

London Journal of Medical and Health Research

Volume 20 | Issue 1 | Compilation 1.0

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ABSTRACT

Dementia is a disorder that is characterized by a decline in one or more of the cognitive functions (learning and memory, language, executive functions, attention, motor and social abilities). [5]The dysfunctions are usually severe enough to interfere with the patient's daily activities and independence. The main under-lying cause of vascular dementia is cerebrovascular disease or insufficient cerebral microvascular circulation. [7] The vascular dementia should be treated for vascular risk factors, especially hypertension, diabetes, hypercholesterolemia, smoking and inactivity.[8], [9]. The standard pharmacological interventions are Acetylcholinesterase inhibitors (donepezil, galantamine) and N-Methyl-D-aspartate receptor antagonists (Memantine). However, recovery of lost cognitive function beyond the initial recovery from vascular dementia is not likely. Moreover, Parkinson disease is another common neurological disease, caused by loss of dopaminergic neurons of substantia nigra pars compacta. The primary treatments are anticholinergics (benztropine, trihexyphenidyl), dopamine precursors (levodopa, carvidopa), COMT inhibitors (Entacapone), MAO B inhibitor (Selegiline), and Amantadine. Above treatments can slow down the disease progression but they cannot reverse the disease course. Here we are reporting a patient with dementia and parkinson's disease who was significantly improved by administration of PCSK9 inhibitor.

Keywords: vascular dementia, parkinson, pcsk9 inhibitor, microvascular circulation.

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I. INTRODUCTION

Total number of people with dementia worldwide in 2015 is estimated at 47 million. Total number of new cases of dementia each year worldwide is nearly 9.9 millions, implying 1 new case every 3 seconds.[2] Vascular dementia is the second most common form of dementia after Alzheimer's Disease(AD)[6].In 1969, Mayer-Gross et al described this syndrome and reported that hypertension is the cause in approximately 50% of patients.[6] Patients with stroke are at increased risk for vascular dementia.[6] The prevalence rate of dementia is 9 times higher in patients with stroke than in controls[10]. One year after a stroke, 25% of patients develop newonset dementia. [10] Within 4 years following a stroke,

the relative risk of dementia incident is 5.5%. The prevalence of vascular dementia is higher in men than in women.[10].Approximately 60,000 Americans are diagnosed with Parkinson's disease each year, and this number does not reflect the thousands of cases that go undetected.[3] An estimated 7 to 10 million people worldwide are living with Parkinson's disease.[3] Parkinson's disease affects nerve cells in the brain that produce dopamine. Parkinson's disease symptoms include muscle rigidity, tremors and changes in speech and gait. Loss of pigmented dopaminergic neurons of the substantia nigra pars compacta and presence of lewy bodies. By means of improving cerebral vascular supply with PCSK9 inhibitor, the loss of dopaminergic neurons and memory function can be restored .

II. CASE REPORT

88 years old Female presented with 3 months onset of dementia and 6 months duration of parkinsonism features. Her Past medical history was significant for long standing uncontrolled Hypertension diabetes Mellitus with compli-cations, hypercholesterolemia, hypertrigly ceridemia, anxiety disorder, ischemic heart disease, transient ischemic attack, osteoporosis and peripheral vascular disease. She also complained of having essential tremors for years . Medication listincluded Valsartan, oxalate, Digoxin, Hydrochlorothiazide, Aspirin, Omeprazole, Benazepril, Rosuvastatin calcium, Denosumab, Amlodipine besylate, Ticagrelor, Olopatadine, Bupropion, Evolocumab, Hydroxyc hloroquine, Strovite , Carvedilol, Colesevelam hydrochloride, Isosorbide, Doxercalciferol and Sucralfate.

Then, she started getting PCSK9 inhibitor injection.

Before treatment, her total cholesterol level was 189 mg/dl, HDL 61 mg/dl, LDL 101 mg/dl. Post treatment cholesterol was 134 mg/dl, HDL 76 mg/dl, LDL 45 mg/dl respectively.

After 3 months of PCSK9 inhibitor therapy, her Minimental state examination (MMSE) scoresubsequently increased and her dementia stage declined from stage 3 to stage 1 according to Global Deterioration Scale for Assessment of Primary Degenerative Dementia (GDS).

III. GLOBAL DETERIORATION SCALE FOR ASSESSMENT OF PRIMARY DEGENERATIVE DEMENTIA (GDS).[1]

The most common scale is often referred to simply as GDS or by its more formal name theReisberg Scale. The GDS divides the disease process into seven stages based on the amount of cognitive decline. This test is most relevant for people who have Alzheimer's disease, since some other types of dementia (i.e, frontotemporal dementia) do not always include memory loss.

Diagnosis	Stage	Signs and Symptoms
No dementia	Stage 1: No Cognitive Decline	In this stage the person functions normally, has no memory loss and is mentally healthy.People with No dementia would be considered to be in stage 1.
No dementia	Stage 2: Very Mild Cognitive Decline	This stage is used to describe normal forgetfulness associated with aging; for example, forgetfulness of names and where familiar objects were left. Symptoms are not evident to loved ones or the physician.
No dementia	Stage 3: Mild Cognitive Decline	This stage includes increased forgetfulness, slight difficulty concentrating, decreased work performance. People may get lost more often or have difficulty finding the right words. At this stage, a person's loved ones will begin to notice a cognitive decline. Average duration: 7 years before onset of dementia.

Early stage	Stage 4: Moderate Cognitive Decline	This stage includes difficulty concentrating, decreased memory of recent events and difficulties managing finances or traveling alone to new locations. People have trouble completing complex tasks efficiently or accurately and may be denial about their symptoms. They may also start withdrawing from family or friends because socialization becomes difficult.At this stage a physician can detect clear cognitive problems during a patient interview and exam.Average duration: 2 years
Mid stage	Stage 5: Moderately Severe Cognitive Decline	People in this stage have major memory deficiencies and need some assistance to complete their daily activities (dressing,bathing,preparing meals).Memory loss is more prominent and may include major relevant aspects of current lives; for example, people may not remember their address or phone number and may not know the time or day or where they are. Average duration : 1.5 years
Mid stage	Stage 6: Severe Cognitive Decline (Middle Dementia)	People in stage 6 require extensive assistance to carry out daily activities. They start to forget names of close family members and have little memory of recent events. Many people can remember only some details of earlier life. They also have difficulty counting down from 10 and finishing tasks. Incontinence (loss of bladder or bowel control) is a problem in this stage.Ability to speak declines. Personality changes such as delusions (believing something to be true that is not), compulsions (repeating a simple behavior such as cleaning) or anxiety and agitation may occur. Average duration: 2.5 years
Late stage	Stage 7: Very	People in this stage have essentially no ability to speak or
	Severe	communicate. They require assistance with most activities
	Cognitive	(e.g using the toilet, eating). They often lose psychomotor
	Decline (Late	skills, for example, the ability to walk. Average duration: 2.5
	Dementia)	years

IV. DISCUSSION AND CONCLUSION

In patients with vascular risk factors, there is an inadequate cerebral circulation in microvascular level from high cholesterol. The impaired circulation can lead to damaging of nerve cells which can result or worsen dementia and parkinsonism.

Currently available treatments can slow down the disease progression but they can not reverse the disease course.Numerous new treatments are being investigated in various stages of clinical trials. However much can be offered to support and improve the lives of people with dementia, their careers and families.

PCSK9 inhibitor is a human monoclonal IgG2 directed against Human Proprotein Convertase Subtilisin Kexin 9 (PCSK9). [4]It binds to PCSK9 and inhibits circulating PCSK9 from binding to low-density lipoprotein (LDL) recept or (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface.[4] Thereby, it increases the number of LDLRs available to clear LDL from the blood, and lowers LDL-C levels to reduce the risk of myocardial infarction, stroke and improve coronary and cerebral revascularization in adults with stablished cardiovascular disease[4]

Evaluation of this patient shows that she had impaired microvascular circulation resulting from hypercholesterolemia, Peripheral vascular disease, DM and hypertension which could damage the neuronal cells.

PCSK 9 inhibitor is a game changer in management of hypercholesterolemia which can effectively lower LDL level. Lowering of LDL level can have a beneficial effect in microvascular circulation resulting in revascularization. The improvement of signs and symptoms of Parkinsonism and dementia was assumed to be from restoration of blood supply to dopaminergic neurons and memory neuronal cells by PCSK 9 inhibitor therapy.

ABBREVIATIONS

NMDA: N- Methyl- D- aspartic acid or N-Methyl-D-aspartate; HCTZ: Hydrochloro thiazide; LDL: low density lipoprotein; HDL: high density lipoprotein; MMSE; mini mental state examination; COMT: catechol- O-methyltransferase.

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