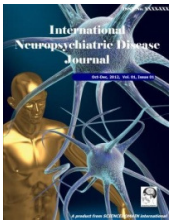

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Cholinesterase Inhibitors in Non-age Related Neurodegenerative Dementias

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Aims: Dementia is common among the elderly but it can also affect the younger age group. Cholinesterase inhibitors (ChEI) in Alzheimer Dementia (AD) are extensively studied and widely used. This case report aims to illustrate the usefulness of ChEIs in other non–age related neurodegenerative dementias apart from AD.
Presentation of Cases: Four cases in which ChEIs was found to be useful in improving the cognition following Traumatic Brain Injury, Nipah Encephalitis, Cerebral Malaria and Meningo-encephalitis. All the four cases were prescribed ChEIs and were followed up in a Memory Clinic. All of them showed substantial and sustained cognitive improvement.
Discussion: Traumatic brain injury causes axonal swelling with accumulation of beta-amyloid and alters progranulin metabolism. Nipah Virus infection of brain parenchyma causes vasculitis, endothelial damage and micro-infarction. While in cerebral malaria, infected and non-infected erythrocytes within the cerebral vessels reduces microvascular flow and initiates inflammatory cascade. Infective encephalitis causes neurotoxin production and inflammatory process. These pathological processes reduce cerebral neurotransmitters concentration including acetylcholine. Cholinesterase inhibitors enhance cognitive function by increasing the amount of acetylcholine at the neuronal synaptic cleft. This clinical significance may be extended to patients with cognitive impairments other than AD.

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Conclusion: This report highlights the usefulness of ChEI in non–age related neurodegenerative dementias. Off label use of ChEI in non-AD dementias warrant proper clinical trials to recommend for clinical practice.

Keywords: Cholinesterase inhibitors; neurodegenerative dementias; non–age related.

1. INTRODUCTION

Dementia is a neurodegenerative condition characterized by cognitive decline, impaired performance of activities of daily living, behavioral disturbances with psychiatric signs and symptoms. Dementia is a rapidly growing problem among the elderly but it can also occur among the younger age group. The role of Cholinesterase Inhibitors (ChEIs) are well established in the symptomatic treatment of dementia [1,2] ranging from mild to moderate as well as in severe [3] Alzheimer's Disease (AD).

Cholinesterase Inhibitors are found to be effective in other age related dementias like Vascular Dementia [4], Parkinson's Disease Dementia [5], and Lewy Body Dementia [6]. Cholinergic dysfunction linked to AD had often detected in other neurological conditions associated with cognitive impairments [7] and cholinergic neurotransmission facilitate cognitive processes [8]. The use of ChEIs in neurological disorders besides AD had been highlighted by Larner [9].

Cholinesterase Inhibitors are prescribed in various neuro-degenerative conditions mostly of off label use. The main aim of this article is to exemplify the usefulness of ChEIs in some Non-age Related Neurodegenerative Dementias as case reports.

2. PRESENTATION OF CASES

2.1 Case 1

A 31 year old housewife sustained head injury in 1997 and was on ventilator for one week. She was seen in the psychiatric clinic on October 2009 for not interested in taking care of her kids or cooking, being lazy, sleeping more and easily irritable for about ten years. Prior to the incident she used to be an active and responsible housewife. Initially she was prescribed Fluoxetine 20mg daily for possible depression for adequate duration. However, no improvement was reported.

On November 2009, she gave away her gold chains and mobiles phones to someone; whom she could not remember. Her husband thought she consciously concealed it and ended up with marital conflict.

On further history; her husband reported that she developed forgetfulness and change in personality two years after her motor vehicle accident in 1997. She became sensitive, easily irritable, talked to strangers and trusted them; she neglected her children and did not attend to their needs.

On January 2010, she scored 19/30 on Mini Mental State Examination (MMSE) and was initiated on Rivastigmine patch 5 daily for a month then followed by patch 10 daily.

She was reviewed three months later; her husband reported that she showed some improvements in cognition as well as personality. She could remember better, she started on sewing and managed to cook simple food.

During next six months, she showed marked improvement that she drove to the hospital and could tell exactly where she had parked her car. She was able to manage most chores at home. She scored 24/30 on the MMSE. She continued to remain well during the subsequent follow ups.

2.2 Case 2

A 57 year old man was referred by Physician on May 2010 for having poor memory and misplacing his belongings for about a year. He was one of the victims of Nipah encephalitis outbreak in Malaysia during 1998-9.

His wife reported that his memory problem started about two years ago and got worst over the last one year affecting his instrumental Activities of Daily Living (ADL). He was able to manage his basic activities of daily living without much help and he scored 24/30 on MMSE.

He was known to have hypertension and hyperlipidaemia on Perindropril 8mg daily,

Aspirin 150mg daily Simvastatin 40mg nocte. His blood-pressure was 118/76 mmHg, Bass-Mass-Index was 23 and his lipids were well controlled. He his brain scan did not reveal any abnormality. On May 2010, he was started on Rivastigmine patch 5 daily for the first month followed by patch 10 daily. He showed some improvement in memory that he repeated himself less frequently. During his subsequent follow up visits he continued to show substantial improvements with his daily activities. He attended to house chores, applied Rivastigmine patch by himself, watched TV more often especially the news but could not retain the details and shopping was still a problem.

The following years he was much alert, talked more clearly and expressed his dissatisfaction for the long waiting time at the clinic. He scored 26/30 on MMSE and continued to remain at the same score.

2.3 Case 3

A 45 year old man was referred on February 2009 by Physiotherapist for poor cognition impeding his rehabilitation process. In June 2006 he had contracted cerebral malaria required to be on respirator for two weeks and remained hospitalized for another two months for rehabilitation. The ordeal caused marked memory loss that he could not recognize his own wife and children and fully dependent on his wife for all his basic activities of daily living.

On February 2009 he scored 12/30 on the MMSE and was prescribed donepezil 5mg daily for the first month and then increased to 10mg daily. Subsequently, he did not attend rehabilitation as his wife could not afford to drive him to hospital twice a week. In May 2009 he scored 14/30 on MMSE with some clinical improvement that he notified if he needs to pass urine or open his bowels. He was not on any ChEI since November 2009 because the hospital had no supply of Donepezil and he developed severe itchiness with Rivastigmine Patches. In May 2010 his MMSE dropped to 10/30 and became more irritable with night-time restlessness. Then, he was initiated on capsule Rivastigmine 1.5mg bid and slowly titrated to 6 mg bid.

He showed marked improvement in December 2010 that he looked alert, clearer in his speech, helped his wife to wash the dishes after any meals and would keep them in right places. In December 2013 his MMSE score increased to 16/30, he became independent on his basic activities of daily living, hence his wife picked up a full-time job.

2.4 Case 4

A 54 year old lady was referred to the Memory Clinic on July 2009 for poor short-term memory and cognitive impairment following her hospitalization for meningo-encephalitis.

She developed high grade fever for a week and was given outpatient treatment. However she got worse and presented to the emergency department with fits and loss of consciousness on the 22nd March 2009. She was ventilated for three days and clinically diagnosed with meningo-encephalitis, though her Cerebrospinal Fluid (CSF) for culture did not identify any pathogen. She was treated with double antibiotics and an antiviral agent for ten days. She recovered from acute illness but subsequently she developed series of cognitive impairments. She needed supervision over her basic ADL. She became depressed mainly because she could not function as before due to her poor cognition.

On July 2009, she scored 20/30 on MMSE and was prescribed Fluoxetine 20mg daily for depression and Donepezil 5mg daily and later it was increased to10mg daily to improve her cognition.

She was reviewed one month later; she was less depressed and stopped crying. She helped her husband in cutting the vegetable but she could not cook as she mixed up with the sequence of cooking and could not remember friends visiting her.

Six months later in January 2010, she scored 24/30 on MMSE. Her husband also reported that her memory was better, she engaged herself in meaningful activities such as house cleaning and simple cooking. The use of Donepezil had improved her cognition by increasing the synaptic acetylcholine concentration that was affected by neuronal damage due to direct invasion of bacteria. Antidepressant alone will not be sufficient to improve the cognition.

She was medically boarded out from her job on October 2010 as she was not fit to go back to her work as a clerk. Four years down the road, she scored 23/30 on the MMSE, and remained the

same with her cognition and her household chores.

3. DISCUSSION

Cholinesterase inhibitors are likely to enhance cognitive function of patients with AD by increasing the amount of acetylcholine at the neuronal synaptic cleft [10]. It is quite possible that this clinical significance may be extended to patients with cognitive impairments other than AD.

Traumatic brain injury (TBI) is a growing problem in the fast moving world [11] and this can result in clinically significant cognitive impairments. Brain injury causes swelling of axons which are accompanied by accumulation of proteins, including beta-amyloid which is the hallmark of AD [12]. Traumatic brain injuries also increase the risk of frontotemporal dementia by altering progranulin metabolism [13]. Drugs that block the formation of amyloid plaques or increase its removal may protect TBI from developing dementia. A randomized controlled trial of patients with TBI at 6 weeks of treatment with donepezil showed a statistically significant increase in the cerebral cortical metabolism [14]. Two-year follow up study among patients with TBI prescribed with donepezil demonstrated clinically significant improvement in cognition [15]. Thus ChEI can be a useful option in the management of TBI with cognitive complications.

The pathogenesis of Nipah Virus (NiV) infection is primarily due to endothelial damage, vasculitis-inducing thrombosis, ischemic vascular micro-infarction and infection of neurons and glial cells of brain parenchyma [16] causing permanent disabilities. Dementia is one of the neuropsychiatric sequelae of Nipah encephalitis [17]. However, neuro-protective effects of ChEI have not been investigated in Nipah encephalitis.

Cerebral malaria is the most severe neurological complication of infection with Plasmodium falciparum. Cognitive deficits after malaria in adults are not well documented, but widely studied among sub-African pediatric age group. Survivors of cerebral malaria often develop neurological and cognitive deficits, behavioral difficulties, and epilepsy [18].

The pathogenesis of cerebral malaria consists of infected and non-infected erythrocytes occluding cerebral vessels. Sequestration caused by infected erythrocytes within the cerebral vessels reduces the microvascular flow and also initiates inflammatory cascade [19]. Cognitive deficits in cerebral malaria may be due to ischemic effects coupled with inflammatory processes.

Infection of the brain caused by viral, bacterial or fungal does not spare the brain from developing some cognitive deficit. Herpes virus is the most common cause of encephalitis [20] causing disabling symptoms. Though modern antiviral medication use seems to improve the cognitive outcome, but much less is known about other non-herpes virus encephalitis [21].

The pathophysiology of infective encephalitis and clinical manifestation has been poorly understood, it is thought due to direct invasion of the bacteria in the brain tissue, neurotoxin production or immune mediated mechanism [22]. Early diagnosis of encephalitis is essential to ensure early intervention, but often causative organism is not identified. Australian studies found that only 30% of encephalitis patients were discharged with a pathogen diagnosis and many had no specific aetiological pathogen confirmed [23].

The case of meningo-encephalitis reported here too was treated without a pathogen been identified; possible delay between initial presentation and intervention had resulted in cognitive dysfunction. This had inflicted strong negative impact on her socioeconomic status that she had to take early retirement. Though she had shown improvements in her cognition and ADL with ChEI, but not to the extent of resuming to her job. This highlights the need to use a suitable regional clinical algorithm for early diagnosis of encephalitis to enhance better outcome.

The role of ChEIs in dementia secondary to cerebral infection and TBI has limited literature. It was felt that ChEIs would benefit in all forms of dementia. Hence, ChEIs were prescribed empirically and had shown significant clinical benefits. It would be worth confirming these findings by larger multi-centre studies.

4. CONCLUSION

These case reports clearly demonstrated the usefulness of ChEI in non-age related, non-AD dementias. In clinical practice we often observe clinical benefits with medications though randomized clinical trials do not reflect the same. It could be due to methodological problems such

as underpowered trials, difficult to get large number of homogenous subjects, too short duration of clinical trials, or use of suboptimal dose of medications. Nevertheless, the indication of ChEI in non-age related neurodegenerative dementias warrants proper clinical trials to recommend for clinical practice. Meanwhile, people with dementia presenting with disabling symptoms and desperate care givers deserve doable medical interventions. Cautious and judiciary use of ChEI for off label indications should not be prohibited.

CONSENT

The identities of the cases were concealed and obtaining informed consent is not applicable.

ETHICAL APPROVAL

Ethics approval was obtained from the Medical Ethics and Research Committee (MREC), Ministry of Health, Malaysia. The author would wish to thank the Director General of Health (Malaysia) for permission to publish this article.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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