A STUDY OF AN ASSOCIATION BETWEEN PERIPHERAL NEUROPATHY AND COGNITIVE IMPAIRMENT IN TYPE 2 DIABETES MELLITUS PATIENTS

DR.V.RUBINI NAIR

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE MASTER OF MEDICINE (INTERNAL MEDICINE)

UNIVERSITI SAINS MALAYSIA

2020

ACKNOWLEDGEMENT

This is dedicated to the almighty lord, my parents, family and the many friends who supported me on the task of completing this study. Thank you.

I would like to express my deepest gratitude to my supervisors Dr.Sanihah and Associate Prof Wan Mohd Izani for their unwavering support, collegiality, and mentorship throughout this project.

I also would like to extend my thanks to those who offered collegial guidance and support over the course of completing this task

Thank you.

V.RUBINI NAIR

TABLE OF CONTENTS

LIST OF TABLES/GRAPHS

LIST OF SYMBOLS

%	percentage
=	equals to

LIST OF ABBREVIATIONS

DM	Diabetes Mellitus
MNSI	Michigan Neuropathy Screening Instrument
MOCA	Montreal Cognitive Assessment
DPSN	Distal Peripheral Sensorineuropathy
MCI	Mild cognitive Impairment
MMSE	Mini Mental State Examination

ABSTRAK

Latar Belakang

Diabetes Mellitus adalah penyakit kronik yang menyebabkan banyak komplikasi kepada organ-organ badan. Komplikasi yang paling kerap berlaku adalah nefropati, retinopati dan neuropati. Komplikasi yang jarang disaring adalah ketakmampuan kognitif. Setakat ini beberapa penyelidikan telah membuktikan bahawa kecacatan kognitif dan neuropati mempunyai patofisiologi yang sama.

Kaedah

279 pesakit yang menghidap Diabetes Mellitus (DM) yang menjalani rawatan di Hospital Universiti Sains Malaysia dari 1hb Julai 2018 sehingga 30hb September 2019 telah dipilih. Demografik, data klinikal dan data makmal direkodkan. Soalan kaji selidik untuk neuropati menggunakan "Michigan Neuropathy Screening Instrument" (MNSI) dan ketakmampuan kognitif menggunakan "Montreal Cognitive Assessment" (MOCA) dijalankan untuk setiap pesakit. Kami meramalkan factor factor yang dikaitkan di antara neuropathi periferi dengan ketakmampuan kognitif menggunakan simple dan multiple logistic regression.

Keputusan

Seramai 279 pesakit terlibat dalam kajian ini. Purata umur pesakit DM dalam penyelidikan ini adalah 62.38 tahun dengan sisihan piawai 8.53. Purata jangka masa DM adalah 9.59 tahun dengan sisihan piawai 5.53. Kebanyakan pesakit adalah wanita iaitu seramai 206(73.8%). Kesemua pesakit dalam penyelidikan ini telah berkahwin dan 97.5% adalah berbangsa Melayu. 183 pesakit (65.6%) didapati mengidap neuropati periferi dan seramai 196(70 %) pesakit didapati menhidap kecacatan kognitif.

Setengah daripada pesakit yang menghidap neuropati periferi juga mengalami kecacatan kognitif (n=141,50.5%) (p <0.001).Selain itu,wanita yang menghidap DM ada 74% kemungkinan yang lebih rendah dari lelaki untuk mendapat kecacatan kognitif.(p<0.001).Pesakit DM dengan dislipidemia ada kemungkinan 2.07 kali lebih tinggi untuk mendapat kecacatan kognitif berbanding dengan pesakit DM yang tiada dislipidemia.(p=0.046).Pesakit DM yang mengalami retinopathi juga ada risiko 2.14 kali lebih tinggi daripada pesakit DM tanpa retinopathi untuk mendapat kecacatan kognitif. (p=0.008)

Kesimpulan

Pesakit DM yang mengidap neuropati periferi akan berkemungkinan besar menghidap kecacatan kognitif . Sehubungan dengan itu wanita yang mengidap Diabetes Mellitus mempunyai risiko yang lebih rendah daripada lelaki untuk mendapat kecacatan kognitif. Pesakit DM yang telah mendapat retinopathi dan mengidap dislipidemia berkemungkinan besar akan mendapat kecacatan kognitif.

ABSTRACT

Background

Type 2 Diabetes Mellitus (DM) is a chronic disease with many complications. Among the well-known complications are nephropathy, neuropathy, and retinopathy. A complication which is rarely looked upon is cognitive impairment which is recently being highly associated with diabetes mellitus. There are a few recent publications which revealed that cognitive impairment and peripheral neuropathy could be brought about by a similar pathophysiology.

Methodology

A total of 279 diabetes mellitus patients were recruited from a diabetes clinic in Hospital Universiti Sains Malaysia from the 1st of July, 2018 until the 30th of September, 2019. Demographic, clinical and laboratory data were recorded from the patients' file. Cognitive impairment was assessed by the Montreal Cognitive Assessment (MOCA) and peripheral neuropathy was assessed by Michigan Neuropathy Screening Instrument (MNSI). The association between peripheral neuropathy and cognitive impairment was analysed using simple and multiple logistic regression method.

Results

A total of 279 patients were included in this study. The mean age of the patients was 62.38 (SD 8.53) years old. The mean duration of diabetes mellitus was 9.59 (SD 5.53) years. Majority of them were females, n=206 (73.8%). All of them were married and 97.5% were Malays. 183 patients (65.6%) had peripheral neuropathy while 196 patients (70.3%) experienced cognitive impairment. There was a significant association between peripheral neuropathy and cognitive impairment ($p<0.001$). Half of the patients with peripheral neuropathy had concomitant

cognitive impairment (n=141, 50.5%). There was also a significant association of gender in which females conferred 74% lower odds to experience cognitive impairment compared to males ($p<0.001$). For patients with hyperlipidaemia, there were 2.07 times odds to experience cognitive impairment as compared to patients without hyperlipidaemia ($p=0.046$). For patients with retinopathy, there were 2.14 times odds to experience cognitive impairment as compared to patients without retinopathy ($p=0.008$).

Conclusion

There was a significant association between the development of cognitive impairment among diabetes mellitus patients with a peripheral neuropathy. Female gender was associated with lower risk of cognitive impairment as compared to male. DM patients with dyslipidaemia and diabetic retinopathy have a higher risk of developing cognitive impairment.

CHAPTER 1: INTRODUCTION

Type 2 Diabetes Mellitus (DM) is a metabolic disorder, which is predominantly insulin resistant and relatively insulin deficient. This is in contrast to type 1 DM, which is purely insulin deficient. DM commonly occurs with other metabolic risk factors, namely hyperlipidaemia, hypertension, and obesity. DM is a state of chronic hyperglycaemia which directly and indirectly causes macro and microvascular complications to the vascular network. Most common microvascular complications of DM would be diabetic retinopathy rendering many blind. This is followed by neuropathy that can manifest into other secondary complications (1).

The prevalence of DM is 20.8% in the age group of 30 and above affecting 2.8 million individuals and a major public health concern (2). Diabetic neuropathies are heterogenous disorders with diverse clinical manifestations, such as peripheral or autonomic neuropathy. Peripheral neuropathy is a very common microvascular complication of type 2 DM. It is reported that 7.5% are frequently diagnosed with peripheral neuropathy at the time of type 2 DM diagnosis. This figure increases gradually within the next five years. This means that the presence of peripheral nerve dysfunction is considered secondary to diabetes after exclusion of other causes (2, 3).

Cognitive impairment is a set of symptoms which include memory loss, difficulties of thinking, problem solving, or language and mood changes perception and behaviour. Cognitive impairment ranges from mild cognitive impairment to dementia. This is a chronic complication which risk increases by two-fold in diabetic patients. Several studies have suggested that peripheral

neuropathy and cognitive impairment may arise from common mechanisms such as oxidative stress, microvasculopathy, hyperlipidemia and inflammation which may cause damage to the nerves in both central and peripheral nervous systems (4). Insulin resistance is associated with a decrease in glucose uptake by neurons, an increase in Amyloid β production and secretion, in the formation of senile plaques, and also in *tau* protein phosphorylation. Other mechanisms also include a decrease in Insulin Degrading Enzyme (IDE) activity and an increase in oxidative stress secondary to hyperglycemia.(18)

Montreal Cognitive Assessment (MOCA) is a brief cognitive screening tool with high sensitivity (90%) and specificity (87%) for detecting Mild Cognitive Impairment (MCI) as currently conceptualised in patients performing in the normal range on the Mini Mental Status Examination (MMSE) (5).

Michigan Neuropathy Screening Instrument (MNSI) scoring is used to assess peripheral neuropathy as it is a useful screening test with high specificity and moderate to good post-test probability. It gives a high diagnostic impact that makes it relevant for referral for further neurophysiological studies (6).

Literature Review

Partanen et al. (1995) concluded that the prevalence of polyneuropathy among patients with DM increases with time and the risk may be greater in patients with hypoinsulinemia (7). In Eurodiab Iddm Complications Study (1996), significant correlations were observed between the presence of diabetic peripheral neuropathy with age, duration of DM, quality of metabolic control, height, the presence of background or proliferative diabetic retinopathy, cigarette smoking, high-density lipoprotein cholesterol, and the presence of cardiovascular disease (8). The case-control studies by Strachan et al. (1997) concluded that moderate cognitive impairment was observed in diabetic subjects in the domain of verbal memory (9). In a large study by Bruce DG et al. (2008), it was reported that diabetics had significantly lower MMSE scores with higher odds ratio for low or borderline MMSE score after adjusting for potential cofounders (10).

The 1997 Rotterdam population study revealed significant association of dementia with DM in women and insulin-treated diabetes in both sexes (11). The 2010 Hisayama study revealed high association of dementia with DM patients (12). Meanwhile, José A. Luchsinger et al. (2007) revealed that DM was associated with a higher risk of incidents of all-cause mild cognitive impairments in a population with a high prevalence of this disorder (13).

G. Cheng et al. (2012) noted risks of dementia or MCI is higher among people with DM than in the general population (14). Rosebud O. Roberts (2008) suggests an association of MCI with earlier onset, longer duration, and greater severity of DM (15).

Several studies have suggested that peripheral neuropathy and cognitive impairment may arise from common mechanisms, which may cause damage to the nerves in both central and peripheral nervous systems. Mirena Valkova et al. (2011) revealed that polyneuropathy is associated with cognitive impairment in all domains; where else, SM Manchott et al. (2008), in their research, concluded that peripheral neuropathy does not occur together with cognitive impairment in DM patients, indicating a possibility of a different pathophysiology (16,17). Moreira et al. (2015) revealed that although DM patients do have a worse cognitive function, but it is not associated with the presence or severity of peripheral neuropathy (18).

Many studies have reported conflicting results for the association between dyslipidaemia and cognitive impairment. An observational study of 1,037 postmenopausal females with coronary heart disease reported that those in the highest total and LDL-C quartile showed an increased likelihood of cognitive impairment compared to subjects in the lower quartiles. However, no association was observed between HDL-C and TG quartiles and cognitive impairment (19). One U.S. prospective community-based cohort study of 854 participants ≥65 years with a follow up of 4,189 participants, reported that higher levels of total cholesterol and LDL are associated with a decreased risk of total MCI in models adjusted for age and sex. However, these associations were attenuated after adjusting for other vascular risk factors. In that study, observed between HDL-C and TG levels and cognitive impairment (20). In a Japanese longitudinal study that enrolled 261 patients with diabetes (aged ≥65 years), higher serum TG, and lower HDL-C at baseline were significantly associated with a cognitive decline after 6 years (21). In

the present study, HDL-C and LDL-C did not show associations with MCI. Serum TG level was found to be associated with MCI in an age- and sex-adjusted comparison.

The Edinburgh type 2 diabetes study in 2010 demonstrated that retinopathy is independently associated with a cognitive decline in older males with type 2 diabetes, suggesting that cerebral microvascular disease may contribute to the observed cognitive decline (22).

A considerable number of studies examining the relationships between hypertension with dementia and cognitive decline have reported inconsistent results. A diabetes study of Japanese elderly reported that higher SBP at baseline is significantly associated with cognitive decline after six years (21). In contrast, a U.S. longitudinal cohort study of 824 older Catholic clergy reported that neither SBP nor DBP was related to AD incidence during a 6-year follow-up (23).

Diabetic cognitive impairment is closely correlated with the nephropathy in patients with type 2 diabetes. With the decline in glomerular filtration function, the cognitive disorder tends to be aggravated. The hippocampal brain metabolism may have some changes in the left side in patients with diabetic nephropathy (24).

For the methods of assessing cognitive impairement MOCA scoring was used as its sensitivity and specificity was superior to MMSE.MOCA had a sensitivity of 90% in detecting mild cognitive impairment and 100% in detecting Alzheimers disease compared to 1.8% and 78% for

MMSE(45).Another study revealed that MOCA has higher sensitivity and specificity in detecting MCI which is 80 % compared to 66 % sensitivity and 81 % compared to 72 % specificity (46).

MNSI has been confirmed useful in detecting peripheral neuropathy where it had increased detection of peripheral neuropathy from 16 % to 43% (47). It has been validated measure of peripheral neuropathy and to judge patients to be sent for electrophysiological studies (7).This scoring has part A and part B which part A goes by symptoms reported by patient and part B goes by clinical examination of vibration, reflexes and monofilament testing.

Study rationale and significance

Mechanism of nerve damage resulting in neuropathy might share a common mechanism between peripheral neuropathy and cognitive impairment. Based on this we postulate that there is an association between both of this microvascular complication. Thus the purpose of this study to identify the proportion type 2 DM patients with peripheral neuropathy and cognitive impairment and the association of the above.

CHAPTER 2: OBJECTIVES

2.1 General

To determine the proportion and factors associated with cognitive impairment in type 2 DM patients with peripheral neuropathy.

2.2 Specific

1. To determine the proportion of type 2 DM patients with peripheral neuropathy using MNSI.

2. To determine the proportion of type 2 DM patients with cognitive impairment using MOCA.

3. To determine the association between peripheral neuropathy and cognitive impairment in type 2 DM patients.

4. To determine the factors associated with cognitive impairment among type 2 DM patients.

CHAPTER 3: MANUSCRIPT

TITLE PAGE

A STUDY OF AN ASSOCIATION BETWEEN COGNITIVE IMPAIRMENT AND PERIPHERAL NEUROPATHY IN TYPE 2 DIABETES MELLITUS (DM) PATIENTS

AUTHOR: V. Rubini Nair

Department of Internal Medicine

School of Medical Sciences Universiti Sains Malaysia

16150 Kubang Kerian Kota Bharu Kelantan Malaysia

Corresponding Author: Dr. Sanihah Abdul Halim

Department of Internal Medicine

School of Medical Sciences Universiti Sains Malaysia

16150 Kubang Kerian Kota Bharu Kelantan Malaysia

Email: vrubininair@gmail.com Tel: 097676590

Disclosure of finding:

None of the authors received financial support for the study

Journal: Malaysian Journal of Medical Sciences

ABSTRACT

Background

Type 2 Diabetes Mellitus (DM) is a chronic disease with many complications. Among the well-known complications are nephropathy, neuropathy, and retinopathy. A complication which is rarely looked upon is cognitive impairment which is recently being highly associated with diabetes mellitus. There are a few recent publications which revealed that cognitive impairment and peripheral neuropathy could be brought about by a similar pathophysiology.

Methodology

A total of 279 diabetes mellitus patients were recruited from a diabetes clinic in Hospital Universiti Sains Malaysia from the 1st of July, 2018 until the 30th of September, 2019. Demographic, clinical and laboratory data were recorded from the patients' file. Cognitive impairment was assessed by the Montreal Cognitive Assessment (MOCA) and peripheral neuropathy was assessed by Michigan Neuropathy Screening Instrument (MNSI). The association between peripheral neuropathy and cognitive impairment was analysed using simple and multiple logistic regression method.

Results

A total of 279 patients were included in this study. The mean age of the patients was 62.38 (SD 8.53) years old. The mean duration of diabetes mellitus was 9.59 (SD 5.53) years. Majority of

them were females, n=206 (73.8%). All of them were married and 97.5% were Malays. 183 patients (65.6%) had peripheral neuropathy while 196 patients (70.3%) experienced cognitive impairment. There was a significant association between peripheral neuropathy and cognitive impairment ($p<0.001$). Half of the patients with peripheral neuropathy had concomitant cognitive impairment (n=141, 50.5%). There was also a significant association of gender in which females conferred 74% lower odds to experience cognitive impairment compared to males ($p<0.001$). For patients with hyperlipidaemia, there were 2.07 times odds to experience cognitive impairment as compared to patients without hyperlipidaemia ($p=0.046$). For patients with retinopathy, there were 2.14 times odds to experience cognitive impairment as compared to patients without retinopathy ($p=0.008$).

Conclusion

There was a significant association between the development of cognitive impairment among diabetes mellitus patients with a peripheral neuropathy. Female gender was associated with lower risk of cognitive impairment as compared to male. DM patients with dyslipidaemia and diabetic retinopathy have a higher risk of developing cognitive impairment.

INTRODUCTION

Type 2 Diabetes Mellitus (DM) is a metabolic disorder with predominant insulin resistant and relatively insulin deficient which causes many micro and macrovascular complications. This is in contrast to type 1 DM which is purely insulin deficient. Type 2 DM commonly occurs with other metabolic risk factors, hyperlipidaemia, hypertension, and obesity. The most common microvascular complication of diabetes would be diabetes retinopathy rendering many blind, followed by nephropathy and neuropathy (1).

The prevalence of DM is 20.8% in the age group of 30 years old and above affecting 2.8 million individuals and a major public health concern. Peripheral neuropathy is a very common micro-vascular complication of type 2 DM. It is reported that 7.5% are diagnosed with peripheral neuropathy at them time of type 2 DM diagnosis and increases gradually (2,3).

Cognitive impairment is a set of symptoms which include memory loss, difficulties of thinking, problem solving, or language and mood changes perception and behaviour. This risk increases by two-fold in DM patients and it can vary from mild cognitive impairment to dementia (15, 16). Cognitive impairement can be divided to mild ,moderate and severe.

Montreal Cognitive Assessment (MOCA) is a brief cognitive screening tool with high sensitivity and specificity for detecting Mild Cognitive Impairment (MCI) as currently conceptualised in patients performing in the normal range on the Mini Mental State Examination (MMSE) (5).This scoring allows subdomain evaluation such visuospatial,naming,memory and etc.

Michigan Neuropathy Screening Instrument (MNSI) is used to assess peripheral neuropathy as it is a useful screening test for diabetic neuropathy with high specificity, moderate to good post-test probability. It gives a high diagnostic impact and makes it relevant for referral of further neurophysiological study (6).It has 2 parts including symptoms reported by patients and signs elicited by the examiner.

Chronic hyperglycaemia and microvascular disease contribute to both cognitive impairment and peripheral neuropathy in DM (15). The mechanisms of nerve damage in peripheral and central nervous system of DM patients may share a similar pathology. However, several studies show contradictory results (16). Based on the mechanism of disease, we postulate that, diabetics with microvascular complications, particularly with underlying peripheral neuropathy, are at risk of concomitant cognitive impairment.

Thus, the purpose of this study is to identify the proportion of DM patients with peripheral neuropathy and cognitive impairment, and subsequently to determine the association between these two complications. In addition to that, we also would like to assess other factors that may be associated with cognitive impairment among diabetic patients treated in Hospital Universiti Sains Malaysia.

METHODOLOGY

Study Population

This was a cross sectional study initiated on type 2 DM patients between the 30th of September, 2019 to 30th October 2019 from Hospital Universiti Sains Malaysia.

The study sample was 279 participants. Demographic, clinical, and laboratory data were retrieved from the patients' records.

The inclusion criteria were type 2 DM patients aged between 20 to 80 years old with at least duration of DM of two years. The exclusion criteria include dementia due to other apparent causes, offending drugs, and loss of physical ability which prevented them to participate in the questionnaire.

The participants were screened for peripheral neuropathy using the MNSI (Part A and B) and subsequently assessed for cognitive impairment using MOCA questionnaire.

Definition of Outcome Events

Peripheral neuropathy: Presence of symptoms and signs consistent with distal symmetrical peripheral neuropathy (DSPN) with MNSI combined score (Part A and Part B) ≥ 4.

Cognitive impairment: Impairment of higher mental function assessed by the MOCA scoring where a score of more than 26 is normal and less than 26 considered as cognitive impairment. (with addition of 1 point for less than 12 year education and Bahasa melayu version was used when necessary)

HbA1C: Glycated haemoglobin assessment of blood glucose level in the past three months. HbA1Clevel of ≥8 % is considered as poorly controlled DM.

Statistical Analysis

Data entry was performed and analysed using SPSS software version 24. Data exploration was done to check for missing values and distribution of numerical data. The data obtained was expressed as mean (SD=standard deviation) for numerical variables and n=frequency (%) for categorical variables. Descriptive analysis was used to analyse the proportion of patients with cognitive impairment and peripheral neuropathy and to describe the socio demographic between type 2 DM subjects with or without cognitive impairment.

Pearson chi square test was used to examine the association between the groups of peripheral neuropathy and cognitive impairment. Simple Logistic Regression was used to examine the association between sociodemographic and DM characteristic with the cognitive impairment status. Multiple logistic regression was conducted to examine the association between each socio demographic with the cognitive impairment status when adjusted for other variables.