COMPARISON BETWEEN CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY IN ADULT PERSONS LIVING WITH T2D AND WITHOUT IN JOHANNESBURG SOUTH AFRICA

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A Research submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the division of Neurology.

Johannesburg 2024

Declaration
I Thendo Nemutudi, do hereby declare that this research is my own unaided work.

It is being submitted for the degree of Master of Medicine in the division of Neurology at the University of the Witwatersrand, Johannesburg.

This Research is submitted in the Publishable format as recognized by the South African Medical Journal (SAMJ). I further declare that this work has not been submitted for any other examination or degree or any other University.

……..

Signature of candidate

The……30……. Day of……June ….2024

Dedication
I dedicate this research to my family for their unwavering support.

Presentations arising from this research project.
The research was presented as an abstract at the Neurological Association of South Africa(NASA) congress on the 6th of May 2023.

Acknowledgement
- I am grateful to Professor G Modi for his supervision and guidance as my supervisor and helping in making this research possible.
- To my family for their unwavering support.

Abstract:

Background: Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is an immune-mediated demyelinating polyneuropathy. It is associated with various conditions. One significant condition studied is type 2 diabetes mellitus (T2D). Some CIDP patients have no identified cause. The global prevalence of CIDP reported ranges from 0.7 to 10.3 cases per 100,000 people. There were approximately 529 million people living with T2D worldwide in 2021. Distinguishing CIDP in patients with and without diabetes poses a clinical challenge. It is crucial to determine if the treatment of diabetes-associated CIDP and its clinical symptoms resemble those of non-diabetic CIDP, as there is limited data available.

Objectives: To evaluate and compare clinical and electrophysiological characteristics of CIDP patients with T2D, compared to those without, to provide insight for diagnosis and treatment.

Methods: This retrospective cohort study was conducted at the adult neurology clinics of Charlotte Maxeke Johannesburg Academic Hospital and Chris Hani Baragwanath Academic Hospital in Johannesburg, South Africa for patients with CIDP. Patient records were extracted from discharge summaries over a 6-year period (January 2016 to December 2022). Patients were grouped and analysed based on their T2D or non-T2D status. Demographics and Clinical features, electrophysiological features, and treatment regimen were evaluated and compared.

Results: A total of 115 patient records with CIDP were retrieved, and a final number of 84 patient records with both clinical and electrophysiological findings were available and used in the study. There were 24 patients diagnosed with T2D and 60 patients without T2D. The T2D patients were poorly controlled with a median HbA1c of 8.22% (interquartile range (IQR) 5.6% to 15.4%). There were no clinical and electrophysiological differences for CIDP patients with T2D in comparison to patients without T2D; however, the diabetic group showed a prolonged mean duration of symptoms onset to diagnosis of 26 weeks (IQR 8-126 weeks) in comparison to a mean of 18 weeks (IQR 8-28 weeks) for the non-diabetic group (p=0.007).

Conclusion: There are no distinct clinical and electrophysiological differences in CIDP among patients with and without T2D, other than individuals with CIDP and T2D have a prolonged period of symptoms before being diagnosed. This results in increased morbidity and poorer prognosis. Additional prospective research is urgently needed to better understand the reasons behind delayed diagnosis in order to improve clinical outcomes.

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ABBREVIATIONS

CHBAH - Chris Hani Baragwanath Academic Hospital

CIDP - Chronic Inflammatory Demyelinating Polyradiculoneuropathy

CMAP - compound motor action potential

CMJAH - Charlotte Maxeke Johannesburg Academic Hospital

CSF - cerebrospinal Fluid

DADS - distal acquired demyelinating symmetric neuropathy

DPN-diabetic polyneuropathy

EFNS/PNS - European Federation of Neurological Societies/peripheral nerve society

HIV - Human Immunodeficiency Virus

IQR-Interquartile range

MADSAM - multifocal acquired demyelinating sensory and motor neuropathy.

MRI - Magnetic Resonance Imaging

T2D - T2D

WHO - World Health Organisations

Introduction

The association between Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and type 2 diabetes mellitus (T2D)is still a topic of debate[1]. More studies have proven associations between the two conditions. Previously published data has shown a nine-fold[2] and 11-fold[3] increased risk of CIDP in patients diagnosed with diabetes; however, clinicians still lack confidence in diagnosing CIDP in patients with diabetes. CIDP is an acquired diverse immune-mediated demyelinating polyneuropathy with the common typical form causing symmetrical limb weakness and sensory deficit over a period of several months; however, other atypical forms, also known as variants, have been well described[3].

Several reasons contribute to clinicians' lack of confidence in the diagnosis of CIDP in patients with T2D. One reason is the various clinical forms of CIDP that may appear similar to diabetic polyneuropathies (DPN) in some cases[3,5]. Additionally, certain DPN may appear similar to demyelinating disorders, according to research conducted by Mercedes Garces-Sanchez[4]. Lastly, the strong focus on electrophysiological criteria when diagnosing CIDP has led to a lack of thorough clinical assessment, causing a high number of misdiagnoses[6,7].

Diagnosing CIDP in patients with T2D can be challenging and time-consuming, leading to delayed treatment and increased morbidity from disease progression. The known therapies for CIDP, such as corticosteroids, intravenous immunoglobulin (IVIG), and plasma exchange, have been shown to improve clinical outcomes, leading to symptom resolution in some cases[6]. It is essential to acquire clinical data from real-world settings to tackle the diagnostic challenges clinicians confront when diagnosing CIDP in individuals with T2D. The aims of this study were to evaluate and compare clinical and electrophysiological features of CIDP in both T2D and non-T2D patients , which can impact diagnostic accuracy and treatment decisions.

Methods

Study design

We conducted a retrospective evaluation of CIDP patient records from the Neurology Departments at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) in Johannesburg, South Africa. We retrieved 115 records of which 84 were eligible for use in the study. This included adult individuals aged 18 and over with CIDP seen in the two hospitals between January 2016 to December 2022. Most of our patients were examined by a training registrar and then a diagnosis is confirmed by a supervising qualified neurologist. Results were interpreted based on the 2010 criteria for CIDP diagnosis by European Federation of Neurological Society/peripheral nerve society (EFNS/PNS)[6]. The identification of T2D relied on World health organization (WHO) criteria, with HbA1c percentage chosen for its extended assessment of blood sugar levels for a 3-month timeframe in this research[8].

setting

Chris Hani Baragwanath Hospital is the third-largest hospital in the world with a total bed capacity of 3400. This tertiary hospital, located in Soweto, Johannesburg, has a general neurology subsection and a dedicated neurophysiology department. Discharge summaries for all patients seen in the ward are written by registrars under the supervision of a qualified neurologist.

Charlotte Maxeke Johannesburg Academic Hospital is a tertiary hospital situated in Parktown, Johannesburg. It has a total bed capacity of 1088. The hospital's neurology department includes

a dedicated ward and a neurophysiology department. Electronic discharge summaries are saved for all admitted patients.

Participants

Following protocol and ethics approval from the University of the Witwatersrand (HREC M200915), we reviewed records from the neurology department and specifically focused on cases with a verified CIDP diagnosis. The study included all individuals over 18 years old who met the diagnostic criteria for CIDP as outlined by EFNS/PNS guidelines[6]. Every person received a study number. The following information was documented: demographics (age, gender and race), clinical features (period of onset of symptoms to diagnosis, clinical characteristics), Electrophysiology (nerve conduction studies were done on both the median and ulnar sensory and motor nerves in the upper limbs, and bilateral tibial and peroneal motor nerves in the lower limbs, as well as bilateral sural nerves in the lower limbs),laboratory findings (HbA1c percentage, cerebrospinal fluid (CSF) results, other tests such as human immunodeficiency virus (HIV) test and CD4),treatment (CIDP regimen offered at diagnosis).

Participants younger than 18 years, other co-morbidities other than HIV and T2D were excluded.

Data analysis:

The features of CIDP in individuals with T2D were compared to those without type 2 diabetes. Statistical analysis was done using STATA 14.1.

Results

Demographics

A grand total of 115 files and discharge summaries of patients diagnosed with CIDP were examined to determine if they met the criteria for the study. Thirty-one records were not considered because they had incomplete information and missing data, resulting in 84 CIDP patients for the analysis. There were 45 females 39 males, with. Patients' ages varied between 18 and 80 years old, with a median age of 42.3 years and a mean standard deviation of 16.2 years. Persons with T2Dranged in age from 23 to 68 median age of 52.4 years and a mean standard deviation of 13 years), while those without T2Dranged in age from 18 to 80 (median age of 38.4 years and a mean standard deviation of 16.3 years).

The age gap between individuals with T2D and those without T2D was shown to be significant, indicating that the non-diabetic group with CIDP was notably younger than those with T2D ($p = 0.002$). Of the participants studied, there were 64 African patients (76%), eight Asians (ten percent), six Caucasians (seven percent), and six patients of mixed ancestry (seven percent). Table 1 provides a visual representation of the ethnic breakdown within each hospital.

Table 1.1: Ethnic distribution of patients diagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP) at Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg academic hospital in Johannesburg South Africa (CMJAH) between January 2016 to December 2022.

Ethnicity	CHBAH (n=56)	CMJAH (n=28)
African	51	13
Asians	3	5
Caucasians	2	4
Mixed origin	0	6

Clinical characteristics

Mean duration of CIDP symptoms from onset to diagnosis for all patients included in the study was 16 weeks (IQR 18 to 126 weeks). The duration of symptoms to diagnosis of persons living with T2D had a mean duration of 26 weeks (IQR 8 to 126 weeks). The symptom duration in patients living without T2D was 18 weeks (IQR 8 to 28 weeks).The diabetic group had a markedly longer period from symptom appearance to diagnosis (p=0.007).

Approximately five percent of patients (n=4) had an unclassified pattern of weakness, due to discharge summaries only specifying global weakness. Seventy two percent of the patients (n=61) presented with symmetrical weakness of both upper limbs and lower limbs. Asymmetrical weakness was present in 10.% (n=4), distal weakness was present in eight percent of the population study (n=6), and five percent presented with only sensory involvement (n=4).

Electrophysiological findings.

All patients met definite electrophysiological criteria for CIDP according to EFNS/PNS criteria 2010[6]. There was no significant difference in Nerve Conductions findings between the persons axonal changes. Both groups had demyelinating changes on nerve conduction studies with p- values of 0, 24 and 0,13 in the motor nerve conduction and sensory nerve conduction respectively (see table 2.). Patients were also categorised according to CIDP variants see table 2 and figure 1.

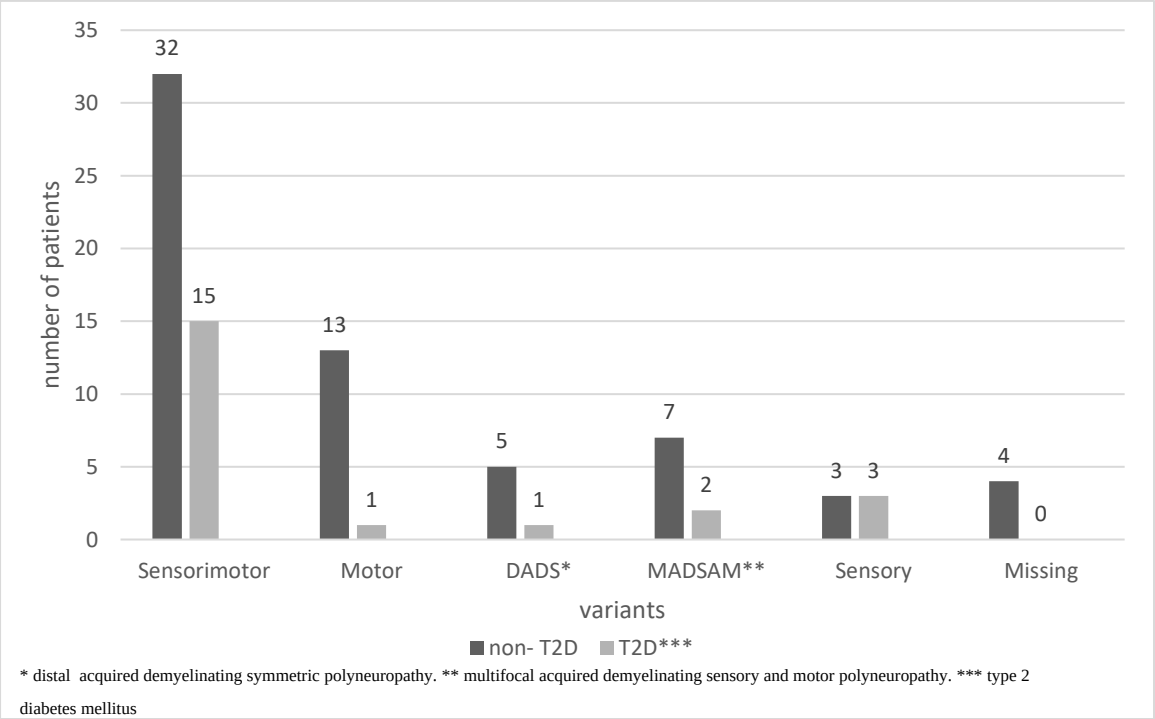
Table 1.2: Nerve conduction study (NCS) results of patients enrolled in our study of CIDP comparison of patients with T2D (T2D) mellitus and those without T2D (non T2D), in public hospitals in Johannesburg, South Africa between January 2016 to December 2022.

NCS results	**Total number**		**T2D****		**Non T2D**	
MOTOR#	**n=84**	**%total number**	**n=24**	**% T2D**	**n=60**	**%Non T2D**
Demyelinating	60	71,4	16	66,7	44	73,3
Axonal	20	23,8	7	29,1	13	21,7
Normal	4	4,8	1	4,2	3	5
SENSORY##						
Demyelinating	66	78,6	19	79,1	47	78,3
Normal	18	21,4	5	20,9	13	21,7

*Number of patients. ** T2D: type 2 diabetes mellitus.

Motor nerve conduction studies result performed on bilateral median, ulnar, peroneal and tibial nerves

##Sensory nerve conduction studies results performed on bilateral median , ulnar and sural nerves



* distal acquired demyelinating symmetric polyneuropathy. ** multifocal acquired demyelinating sensory and motor polyneuropathy. *** type 2 diabetes mellitus

Figure 1. CIDP variants compared between patients enrolled in our study between patients with type 2 diabetes(T2D) and without T2D (non T2D). in public hospitals in Johannesburg , South Africa.

Laboratory findings

Twenty-four of the 84 patients were diagnosed with T2D according to WHO criteria[8]. Out of the people living with T2D, 14 (58%) were poorly controlled with HbA1c above 6.5%, 25% of patients (n=6) had HbA1c below 6.5% and 17% of patients (n=4) were documented as known T2D, but HbA1c was not indicated.

Most patients had elevated CSF protein with a median protein of 0.83 (IQR 0.28g/dl to 1.5g/dl). Six diabetic patients (25%) had normal CSF protein and 18 (75%) had elevated CSF protein. Of the 18 patients with elevated CSF protein, 33% (n=6) had CSF protein of greater than 1g/dl. The non-diabetic group had all the patients' CSF protein elevated.20% (n=12) of patients who were not diabetic had CSF protein of greater than 1g/dl.

Treatment

Every patient was given Methylprednisolone (Solu-Medrol) as the usual therapy for CIDP. The dosage administered was as outlined: administer 1 gram of IVI Methylprednisolone once daily for five days, followed by 1 gram weekly for eight weeks, then switch to 1 gram every two weeks for eight doses, later decreasing to 1 gram monthly for eight doses, and ultimately 1 gram every two months for 8 doses.

HIV

Twenty patients were HIV positive with a median CD4 count of 501 cells/mm3, and 1 patient had both T2D and HIV.

Discussion

CIDP is associated with T2D and can present in patients without T2D. International data found differences in clinical and electrophysiological findings for CIDP in patients with T2D compared to those without T2D. This study compared CIDP in diabetic and non-diabetic population in two public hospitals in South Africa. Data showed a higher proportion of females with CIDP compared to other studies which showed a predominance of the disease in males[3]. Additionally, our study population was unique as the majority individuals were of African descent, compared to Asian and Caucasian populations studied globally.

Amongst the 84 patients reviewed, the median age for our cohort with CIDP was younger at 38.4 years compared to international studies with a higher median age of 61.1 years[10].This is maybe attributed to the HIV status of our cohort, since HIV infection is known to be associated with CIDP. Highly immune-mediated CIDP is common in African patients. Further research on antibody testing in African patients with CIDP will be of added value. Our median age for persons with T2D was 52.4, while international studies showed a median age in T2Dto be 58.2 years in the T2D group[10].

The length of time since onset of T2D was not recorded in our setting, which could have assisted in distinguishing our cohort from global studies on CIDP in patients with T2D[10]. Global information indicates that CIDP occurs mainly in diabetic individuals with a history of diabetes exceeding five years.[10]

There was a 6-month delay in CIDP symptom onset to diagnosis in the persons living with T2D group, which was shorter than the 3,9-years delay in international studies. Although diagnosis in our setting was more efficient, the delay highlights the dilemma clinicians face in diagnosing CIDP in persons living with T2D patients and difficulty differentiating from those with DPN[3,10].

The distribution of weakness was predominantly ascending and symmetrical with equal proximal and distal distribution, which is commonly seen in CIDP. Our study demonstrated 76% of the cohort. which aligns with international data indicating that the most common clinical syndrome is the "typical CIDP" with a symmetrical onset of ascending proximal and distal weakness. The most common variant in both groups in our study was sensorimotor. This differs from the literature as persons living with T2D had more axonal CIDP compared to more demyelinating nerve conduction studies in persons living without T2D[11].These findings will assist to improve confidence in the clinician approach to CIDP in patients with T2D.

There were no variations in nerve conduction tests between individuals with T2D and individuals without T2D. Both groups showed a demyelinating nerve conduction finding as the most common finding. Studies from around the world found that individuals with T2D CIDP showed greater axonal alterations than those without T2D[1]. Research showed evidence of a unique form of small-vessel vasculitis in DPN[3]. This condition involves inflammation caused by immune-mediated processes, leading to damage of nerve fibres. This may provide an explanation for the demyelination discoveries in our nerve conduction tests. This confirms that there is no difference in clinical and electrophysiological features of CIDP in South African patients with T2D compared to those without diabetes mellitus.

CSF protein levels were elevated in both groups, but there was no difference between the persons living with T2D and persons living without T2D groups (p=0.323), which differs from the worldwide study that found a difference in protein levels between the two groups (p=0.040)[12]. Our study shows that both diabetes and CIDP raises CSF protein and should not be used independently for diagnosis of CIDP as mentioned in the literature[6].

The first line treatment for CIDP in the South African public health sector is Methylprednisolone (Solu-Medrol) IVI.A study conducted in 2003 showed a positive response to prolonged tapering regimens of methylprednisolone in CIDP patients over a period of eight weeks to six months[13] . Another study demonstrated the effectiveness of Methylprednisolone IVI when given initially (0.5g/kg/day) for four doses over four days followed by a monthly dose over 6 months[13]. Although the drug regimens vary amongst different countries the idea of tapering the dose over a long period remains the same.

The limitations of the study are that it is retrospective, with missing data including detailed clinical presentation, reasons for delay in presentation in the diabetes group, and length of hospital stays that could not be retrieved. The duration of T2D diagnosis was not provided, which could have helped to correlate with data indicating that a longer duration of T2D is associated with the development of CIDP, especially when poorly controlled. There is no indication of co-management between Physicians/Endocrinologists for individuals living with T2D and patients in terms of initiating steroids. This is crucial in order to prevent side effects such as poorly controlled diabetes and the further development of diabetic polyneuropathy, which may be challenging to treat. Convenient sampling was utilized as our population study consisted of patients seen at neurology clinics and wards.

Future work can focus on a prospective study to better understand patients over a period of time, and or to conduct a study at a metabolic clinic on patients known to have T2D with

polyneuropathy and classify how many have CIDP as well as the reasons for delayed presentation. Lastly, a clinical trial evaluating different treatment regimens and monitoring the side effects profile for CIDP patients with T2D to achieve better glucose control is recommended

Conclusion

We have retrospectively described CIDP comparing clinical and electrophysiological features in patients with T2D to those without in two public sector hospitals in South Africa. overall findings showed that there are no differences found between the 2 groups, other than prolonged duration from symptoms onset to diagnosis. The commonest CIDP variant was sensorimotor for both persons living with T2D and persons living without T2D. Findings highlights the gaps in the diagnosis and treatment of CIDP in patients with T2D and those without T2D, which needs to be addressed.

References

1. Laughlin RS, Dyck PJ, Melton L3, Leibson C, Ransom J, Dyck PJ. Incidence and prevalence of CIDP and the association of Diabetes mellitus. Neurology. 2009 Jul 7;73(1):39-45.
2. Rajabally YA, Peric S, Cobeljic M, Afzal S, Bozovic I, Palibrk A, Basta I. Chronic inflammatory demyelinating polyneuropathy associated with diabetes: a European multicentre comparative reappraisal. J Neurol Neurosurg Psychiatry. 2020 Oct;91(10):1100-1104. doi: 10.1136/jnnp-2020-322971. Epub 2020 Aug 31. PMID: 32868389.
3. Bril V, Blanchette CM, Noone JM, Runken MC, Gelinas D, Russell JW. The dilemma of diabetes in chronic inflammatory demyelinating polyneuropathy. J Diabetes Complications. 2016 Sep-Oct;30(7):1401-7. doi: 10.1016/j.jdiacomp.2016.05.007. Epub 2016 May 10. PMID: 27389526; PMCID: PMC5528142.
4. Garces-Sanchez M, Laughlin RS, Dyck PJ, Engelstad JK, Norell JE, Dyck PJ. Painless diabetic motor neuropathy: a variant of diabetic lumbosacral radiculoplexus Neuropathy? Ann Neurol. 2011 Jun;69(6):1043-54. doi: 10.1002/ana.22334. Epub 2011 Mar 18. PMID: 21425185; PMCID: PMC3117939.
5. Dyck P.J., Norell J.E., Dyck P.J.: Microvasculitis and ischemia in diabetic lumbosacral radiculoplexus neuropathy. Neurology 1999; 53: pp. 2113.
6. Inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force of the European Academy of Neurology/Peripheral Nerve Society guideline first revision J peripher nerve syst.2010;15:1-9.Erratum in J peripher Nerve syst 2010;15:23
7. Rajabally YA, Nicolas G, Pieret F, Bouche P, Van den Bergh PY. Validity of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy: a multicentre European study. Journal of Neurology, Neurosurgery & Psychiatry. 2009 Dec 1;80(12):1364-8.
8. Roglic G. WHO Global report on Diabetes: A summary. International Journal of Noncommunicable Diseases. 2016 Apr 1;1(1):3.
9. Mochan A, Anderson D, Modi G. CIDP in a HIV endemic population: A prospective case series from Johannesburg, South Africa. Journal of the neurological sciences. 2016 Apr 15; 363:39-42.

10. Lotan I, Hellman MA, Steiner I. Diagnostic criteria of chronic inflammatory demyelinating polyneuropathy in Diabetes mellitus. Acta Neurologica Scandinavica. 2015 Oct;132(4):278-83.
11. Gorson KC, Ropper AH, Adelman LS, Weinberg DH. Influence of Diabetes mellitus on chronic inflammatory demyelinating polyneuropathy. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2000 Jan;23(1):37-43
12. Stewart JD, McKelvey R, Durcan L, Carpenter S, Karpati G. Chronic inflammatory demyelinating polyneuropathy (CIDP) in Diabetes. Journal of the neurological sciences. 1996 Oct 1;142(1-2):59-64.
13. Ropper AH. Current treatments for CIDP. Neurology. 2003 Apr 1;60(8 Suppl 3):S16-22. doi: 10.1212/wnl.60.8_suppl_3.s16. PMID: 12707418.

Appendices

APPENDIX 1: Protocol and extended review of literature

INTRODUCTION

CIDP

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) is an acquired immune-mediated neuropathy affecting peripheral nerves and roots causing limb weakness and sensory deficit (1-2). Its course can be relapsing-remitting or progressive. (1-2) The main clinical features are symmetrical, mainly motor, with proximal and distal involvement (2-7).

The reported global prevalence of CIDP ranges from 0.7 to 10.3 cases per 100,000 people with a male predominance ranging from 1.5:1 to 4:1(1-2). It primarily affects adults with a median age of 58 years (range 4-83years) (1-2). Two studies done in South Africa showed the median age to be almost 20 years lower than the global median age (2-3).

The diagnosis of CIDP is based on clinical, electrodiagnostic (mandatory), and supportive features included in the European Federation of Neurological societies and the Peripheral Nerve Society (EFNS/PNS) criteria (see Annexure 2) (4). The EFNS/PNS criteria had a sensitivity of 81% and specificity of 91% in comparison with other criteria such as the American Academy of Neurology (AAN) and Koski et al criteria (4).

DIABETES MELLITUS

Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia which result from defects in insulin secretion, insulin action or both.

In 2014 the World Health Organisation (WHO) estimated that 422 million adults worldwide above 18 years have Diabetes (5-6). The Journal of Endocrinology, Metabolism and Diabetes South Africa stated that in 2015 34.9 million people in Sub Saharan Africa were diagnosed with Diabetes and majority of patients being in South Africa (2.3 million), Democratic Republic of Congo (1.8 million), Nigeria (1.6 million) and Ethiopia (1.6 million) (5). In 2015 the estimated population of South Africa was about 51 million of which 2.3 million (20-79 years) had Diabetes (5-6).

Diabetes may present with characteristic symptoms such as polyuria, polydipsia, blurred vision, and weight loss. Diagnosis of Diabetes is confirmed when any one of the following tests confirms that Fasting glucose is >/=7mmol and /or Random glucose is >/= 11.1 mmol, or HbA1c >/= 6.5 mmol (5).

CIDP AND DIABETES MELLITUS

Complications of Diabetes include retinopathy, nephropathy, atherosclerosis, and neuropathy. Diabetes neuropathies are amongst the most common complications targeting about 50% of the patients (6). In common practice Chronic inflammatory demyelinating polyradiculoneuropathy is one of the neuropathies classified under Diabetes polyneuropathies,

however, most of the studies failed to prove whether there is an association between Diabetes and CIDP and if there is any difference between Idiopathic CIDP and Diabetes CIDP (11).

A study done by Rabin medical centre in Israel assessed the diagnostic criteria of CIDP in Diabetes which included clinical, electrophysiological features and Histopathology (7). The study highlighted that CIDP in Diabetes has a slowly progressive course of more than one year, with more sensory symptoms and some cranial involvement, reduced compound motor action potential (CMAP) disproportionate to motor conduction velocities and axonal nerve changes without demyelination on nerve biopsy. The limitation of this study is that most of the features can be explained in atypical CIDP on the EFNS/PNS criteria and they were not excluded (7). The limitation is that only 12 patients out of 57 patients in the study had CIDP and Diabetes, thus a larger study is required to confirm the findings (7).

Another study done in Italy looked at epidemiological relations between CIDP and Diabetes with the total number of 155 patients with CIDP of which 14 (9%) had Diabetes (8). The findings showed that Diabetes patients had higher cerebrospinal fluid (CSF) protein with a Median of 120mg/dl in Persons living with T2DPersons living with T2D CIDP compared to a Median of 103mg/dl in the control group (8). Persons living with T2DPersons living with T2D CIDP had delayed diagnosis with a Median delay onset- diagnosis time of 3.9 years, however the frequency of Diabetes in CIDP was like what is expected in the general population. CIDP in Diabetes did not differ in age, gender and course compared to non-Persons living with T2DPersons living with T2D group (8). The limitation of the study was the fact that there was no clinical comparison in Persons living with T2DPersons living with T2D and Non-Persons living with T2DPersons living with T2D groups.

A Canadian study looked at Persons living with T2DPersons living with T2D CIDP in comparison with other Persons living with T2DPersons living with T2D Sensorimotor Neuropathies, a total of 123 patients of which 67 had Diabetes and CIDP and 56 Diabetes with sensorimotor neuropathies (9). The findings showed that the Persons living with T2DPersons living with T2D CIDP had more demyelinating features on Nerve Conduction Studies compared to the other group. Persons living with T2DPersons living with T2D CIDP group had Median HBA1C of 7.7% compared to 8.9% of the other group (9). The duration of Diabetes in Persons living with T2DPersons living with T2D CIDP had a Median of 16years with comparison of 24 years to the other group (9). The limitation of the study is lack of comparison to the non-Persons living with T2DPersons living with T2D CIDP group, and the duration of Diabetes can be misleading unless previous screening was done prior the diagnosis which is not the case in the study.

In Toronto, a study done on 7 Diabetes patients diagnosed with CIDP where the duration of Diabetes, clinical presentation, Nerve Conduction Studies, and Nerve biopsies were reviewed (10). The Nerve conduction studies were variable and 6 out of 7 showed prolonged distal latencies and 4 out of 7 showed conduction blocks. All the nerve biopsies showed loss of myelin fibres and all patients improved with steroids, Intravenous Immunoglobulin (IVIG) and Azathioprine (10). This study didn't differentiate CIDP in Persons living with T2DPersons living with T2D from non-Persons living with T2DPersons living with T2D CIDP and couldn't explain whether Diabetes is the cause of CIDP. The limitation of the study was the small number of patients enrolled and the lack of comparison with non-Diabetes patients.

The difference between Persons living with T2DPersons living with T2D CIDP and non-Persons living with T2DPersons living with T2D CIDP has not been well described and few studies done couldn’t describe clinical or electrophysiological difference between the two groups.

HYPOTHESIS

This study aims to look at CIDP, and the hypothesis is that CIDP in Diabetes is not different to non-Persons living with T2DPersons living with T2D CIDP.

AIM

To describe CIDP in Persons living with T2DPersons living with T2D and non-Persons living with T2DPersons living with T2D and asses if there is any difference.

STUDY OBJECTIVES

- To describe patients with chronic inflammatory polyradiculoneuropathy (CIDP) seen at two large academic hospitals in Johannesburg South Africa and describe if Idiopathic CIDP is different from Diabetes CIDP.

STUDY DESIGN

This is a retrospective study on patients with CIDP who meet diagnostic EFNS/PNS criteria.

STUDY POPULATION

All adult patients with CIDP seen at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) and Chris Hani Baragwanath Academic Hospital (CHBAH) from 2010 to 2020.

STUDY METHOD

There is a weekly CIDP clinic at both hospitals with a separate filing system. I will retrieve all the files. Most of the required data will be available in these files.

Missing data will be recovered from discharge summaries, electronically stored Nerve Conduction Studies at the Neurophysiology Laboratory. I will review all the nerve conduction studies. Blood and CSF results will be retrieved from the file.

A data sheet will be completed for each patient which includes Age, Sex, Race, Clinical presentation, and duration, HBA1C, CSF and Nerve conduction Studies.

Clinical findings will be classified as Typical OR Atypical CIDP according to EFNS/PNS classification.

Table A: CLINICAL FINDINGS CRITERIA

INCLUSION CRITERIA	EXCLUSION CRITERIA
All patients with CIDP according to EFNS/PNS classification **Age ≥ 18yrs**	**Age<18yrs**

STATISTICAL METHODS AND ANALYSIS

Convenience sampling method will be used for sampling, I will trace all the files of patients coming to CIDP clinic and get all the information such as Nerve conduction studies, CSF results.

Chi-square test will be used to difference between Idiopathic CIDP and Diabetes-CIDP, so the formula will be ^{x2}= [total CIDP-Diabetes CIDP]^2 ÷ [Diabetes CIDP] and I will ask assistance from biostatician.

DATA COLLECTION AND ANALYSIS

The data will include patients seen in the neurology clinics of both Charlotte Maxeke Academic Hospital and Chris Hani Baragwanath Academic Hospital from 2010 to 2020 which is a 10years period.

Important variables will be a percentage of Diabetes Patients from all CIDP patients enrolled in the study, then compare with the Idiopathic CIDP group and conclude on the differences found and the significance of the differences. Estimated number of patients Diagnosed with CIDP are about 10 patients per year.

The confidence interval of 95% is expected from the study, with an expected margin error of 5%. The estimated prevalence of Diabetes in CIDP is 9% (1-13).The sample size minimum is 126 patients.

ETHICS

- The protocol will be submitted for ethics approval to the Human Research Ethical Committee of the University of Witwatersrand
- Data confidentiality will be maintained by assigning participants study numbers.

LIMITATIONS

- This is a retrospective if there are any missing important data, I will not be able to correct or get from the patient.

FUNDING

- This is a Retrospective study, and most investigations are already done whatever **needs funding will be paid for by me.**

Table B: TIMELINE

	JULY 2020	AUGUST 2020	SEPTEMBER-OCTOBER 2020	NOVEMBER-JANUARY 2021	FEBRUARY-MARCH 2021
PROTOCOL ASSESSMENT					
ETHICS APROVAL					
DATA COLLECTION					
DATA ANALYSIS					
WRITE UP AND SUBMISSION					

REFERENCES

1. Laughlin RS, Dyck PJ, Melton L3, Leibson C, Ransom J, Dyck PJ. Incidence and prevalence of CIDP and the association of Diabetes mellitus. Neurology. 2009 Jul 7;73(1):39-45.

2. Mochan A, Anderson D, Modi G. CIDP in a HIV endemic population: A prospective case series from Johannesburg, South Africa. Journal of the neurological sciences. 2016 Apr 15; 363:39-42.

3. Moodley K, Bill PL, Patel VB. A comparative study of CIDP in a cohort of HIV-infected and HIV-uninfected patients. Neurology-Neuroimmunology Neuroinflammation. 2017 Mar 1;4(2): e315.

4. Rajabally YA, Nicolas G, Pieret F, Bouche P, Van den Bergh PY. Validity of diagnostic criteria for chronic inflammatory demyelinating polyneuropathy: a multicentre European study. Journal of Neurology, Neurosurgery & Psychiatry. 2009 Dec 1;80(12):1364-8.

5. SEMDSA T2DGuidelines Expert Committee. SEMDSA 2017 guidelines for the management of T2D. J Endocr, Metab, Diabetes S Afr. 2017;22(1 Suppl 1): S1-196.

6. Roglic G. WHO Global report on Diabetes: A summary. International Journal of Noncommunicable Diseases. 2016 Apr 1;1(1):3.

7. Lotan I, Hellman MA, Steiner I. Diagnostic criteria of chronic inflammatory demyelinating polyneuropathy in Diabetes mellitus. Acta Neurologica Scandinavica. 2015 Oct;132(4):278-83.

8. Chiò A, Plano F, Calvo A, Leone M, Mutani R, Cocito D, Piemonte and Valle D'Aosta Registry for CIDP (PARCIDP). Comorbidity between CIDP and Diabetes mellitus: only a matter of chance? European journal of neurology. 2009 Jun;16(6):752-4.

9. Dunnigan SK, Ebadi H, Breiner A, Katzberg HD, Lovblom LE, Perkins BA, Bril V. Comparison of Diabetes patients with "demyelinating" Diabetes sensorimotor polyneuropathy to those diagnosed with CIDP. Brain and behavior. 2013 Nov;3(6):656-63.

10. Stewart JD, McKelvey R, Durcan L, Carpenter S, Karpati G. Chronic inflammatory demyelinating polyneuropathy (CIDP) in Diabetes. Journal of the neurological sciences. 1996 Oct 1;142(1-2):59-64.

11. Rajabally YA, Stettner M, Kieseier BC, Hartung HP, Malik RA. CIDP and other inflammatory neuropathies in Diabetes—diagnosis and management. Nature reviews neurology. 2017 Oct;13(10):599.

12. Gorson KC, Ropper AH, Adelman LS, Weinberg DH. Influence of Diabetes mellitus on chronic inflammatory demyelinating polyneuropathy. Muscle & Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2000 Jan;23(1):37-43

Table 1.3.1 EFNS/PNS CRITERIA FOR DIAGNOSIS OF CIDP

CLINICAL INCLUSION CRITERIA	
TYPICAL CIDP	➢ Chronically progressive, Stepwise, or recurrent proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 Months; cranial nerves may be affected. ➢ Absent or reduced tendon reflexes in all extremities
ATYPICAL CIDP	➢ Predominantly distal (distal acquired demyelinating symmetric neuropathy [DADS]) ➢ Asymmetric (multifocal acquired demyelinating sensory and motor neuropathy [MADSAM], Lewis-Sumner syndrome); or ➢ Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper limb or lower limb); or ➢ Pure motor; or ➢ Pure sensory (including chronic immune sensory polyradiculopathy [CISP] affecting the central process of the primary sensory neuron
ELECTRODIAGNOSTIC CRITERIA	DEFINITE CIDP ➢ ≥ 50% prolongation of motor distal latencies above the upper limit of normal (ULN) in 2 nerves ➢ ≥ 30% reduction of motor conduction velocity below Lower Limit of Normal (LLN) ➢ Absence of F waves in 2 nerves, if these nerves have amplitude of distal negative peak Compound Muscle Action Potential (CMAP) in at least 2 nerves, or in one nerve plus at least one other demyelinating parameter (meeting any of the definite criteria) in at least one other nerve. ➢ Partial motor conduction block defined by a ≥ 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if the distal negative peak is ≥ 20% of LLN in 2 nerves, or in 1 nerve plus at least one other demyelinating parameter (meeting any of the definite criteria) in at least one other nerve. ➢ Abnormal temporal dispersion defined by a > 30% duration increase between proximal and distal negative peak CMAP in at least 2 nerves. ➢ Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in at least one nerve (median ≥6.6ms, ulnar ≥6,7ms, peroneal ≥7.6ms, tibial ≥8.8ms) plus at least one other demyelinating parameter (meeting any of the definite criteria in at least one nerve

	PROBABLE CIDP - ≥ 30% amplitude reduction of the proximal negative peak CMAP relative to the distal, excluding the posterior tibial nerve, if the distal negative peak CMAP is ≥ 20% of LLN, in 2 nerves, or in one plus at least one other demyelinating parameter (meeting any of the definite criteria) in at least one other nerve.

SUPPORTIVE CRITERIA	- Elevated CSF protein with leukocyte count <10/mm^3
	- MRI showing gadolinium enhancement and/or hypertrophy of cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses.
	- Abnormal sensory electrophysiology in at least one nerve
	  - normal sural with abnormal median (excluding Carpal tunnel syndrome) or radial sensory nerve action potential amplitudes (SNAP)
	  - Conduction Velocity of < 80% LLN
	  - Delayed somatosensory evoked potentials (SSEP) without central nervous system disease.
	- Objective clinical improvement following immunomodulatory treatment.
	- Nerve biopsy showing unequivocal evidence of demyelination and/ or remyelination by electron microscopy or teased fiber analysis

EXCLUSION CRITERIA	- Neuropathy probably caused by B. burgdorferi infection (Lyme disease), diphtheria, drug, or toxin exposure. - Hereditary demyelinating neuropathy - Prominent sphincter disturbance - Diagnosis of multifocal motor neuropathy - IgM monoclonal gammopathy with titre antibodies to myelin associated glycoprotein (MAG) - Other causes for a demyelinating including POEMS.

Ta

APPENDIX 2: ETHICS

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr T Nemutudi
School of Clinical Medicine
Department of Neurosciences
Division of Neurology
Medical School
University

E-mail: nemutudit@yahoo.com

CC: Supervisor: Professor G Modi <Girish.Modi@wits.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/11/04

REF: *R14/49*

PROTOCOL NO: **M200915** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Comparison between chronic inflammatory demyelinating polyradiculoneuropathy in diabetic mellitus and non-diabetic adult patients seen in Johannesburg, South Africa*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Dr T Nemutudi

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200915

NAME: (Principal Investigator) Dr T Nemutudi

DEPARTMENT: School of Clinical Medicine
Department of Neurosciences
Division of Neurology
Medical School
University

PROJECT TITLE: Comparison between chronic inflammatory demyelinating polyradiculoneuropathy in diabetic mellitus and non-diabetic adult patients seen in Johannesburg, South Africa

DATE CONSIDERED: 2020/10/02

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Professor G Modi

APPROVED BY: Dr CB Penny, Chairperson, HREC (Medical)

DATE OF APPROVAL: 2020/11/04

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

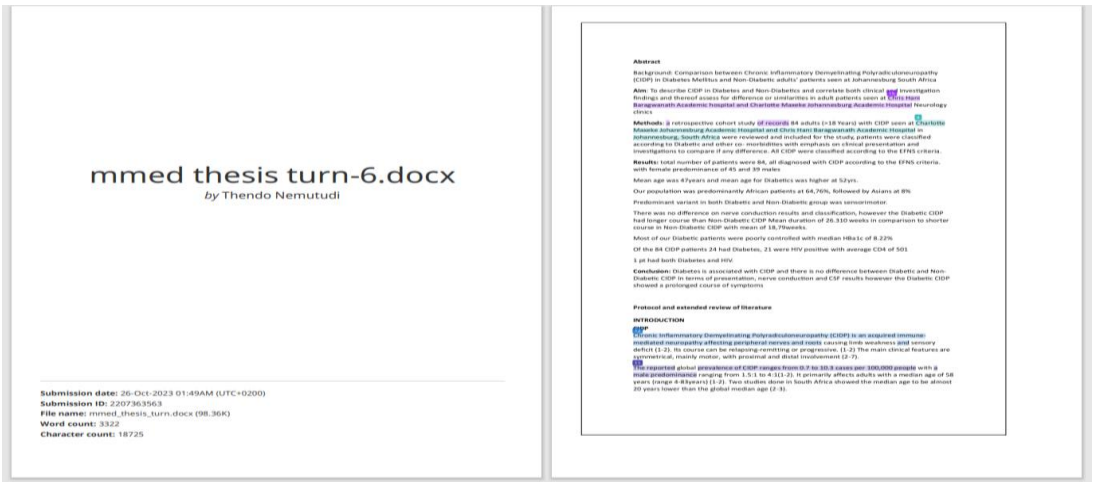
DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report.** When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **September** and will therefore reports and re-certification will be due early in the month of **September** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date

APPENDIX 3: TURNITIN REPORT



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by Thendo Nemutudi

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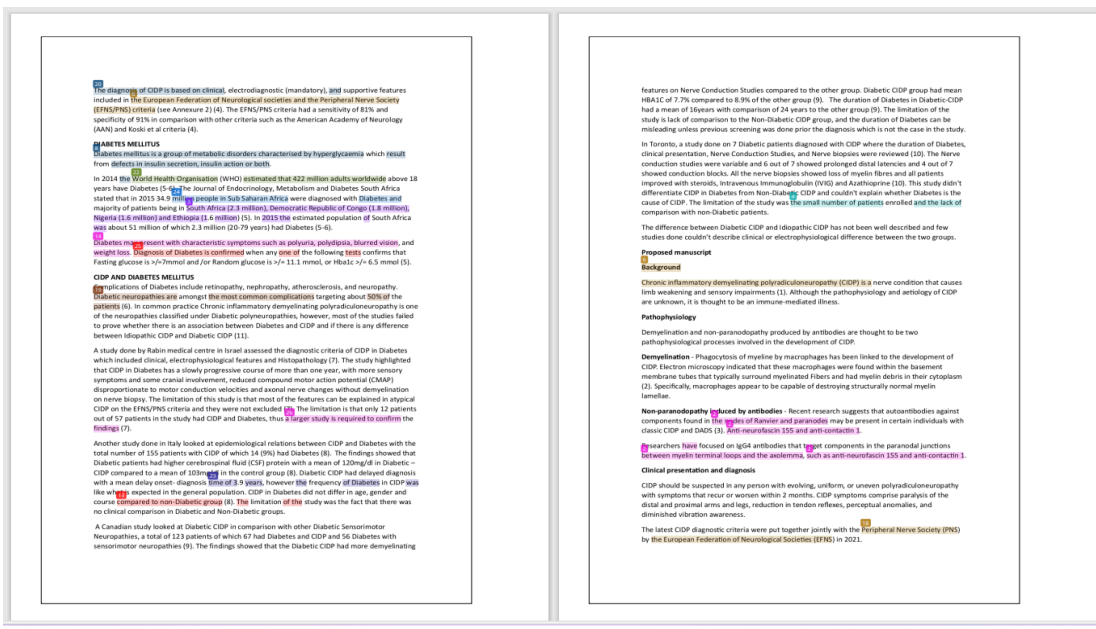
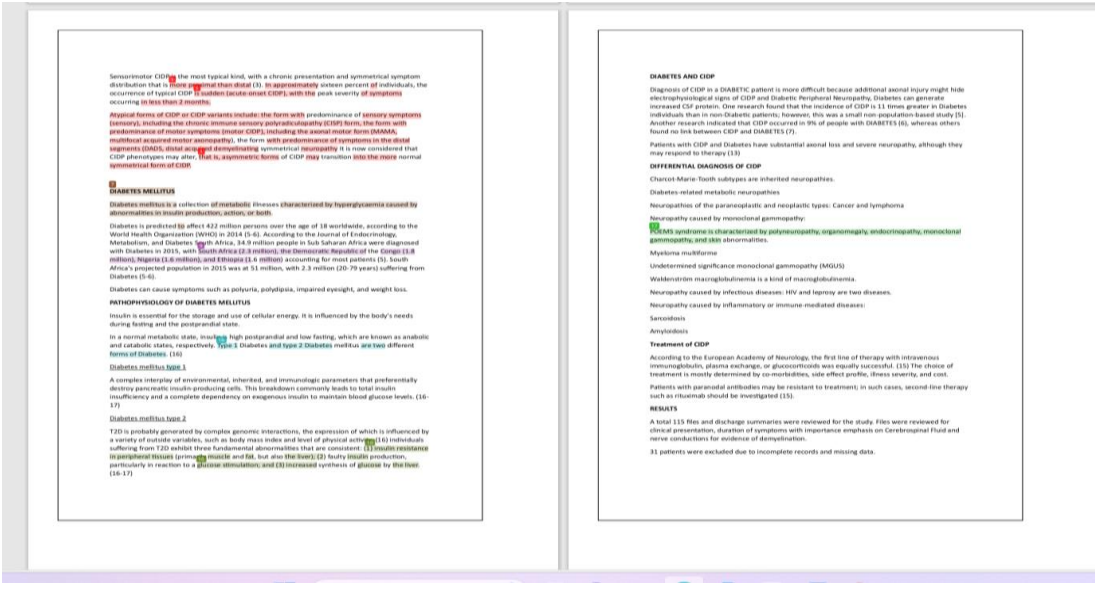
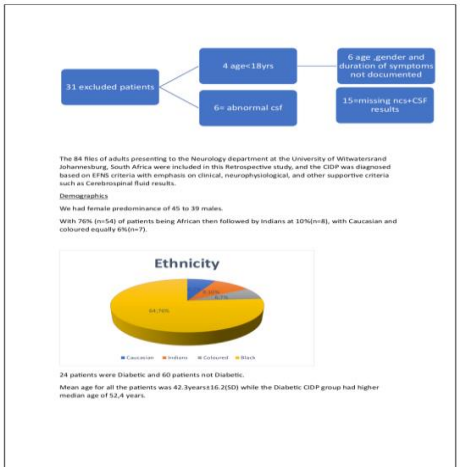






The 84 files of adults presenting to the Neurology department at the University of Witwatersrand Johannesburg, South Africa were included in this Retrospective study, and the CIDP was diagnosed based on EFNS criteria with emphasis on clinical, neurophysiological, and other supportive criteria such as Cerebrospinal fluid results.

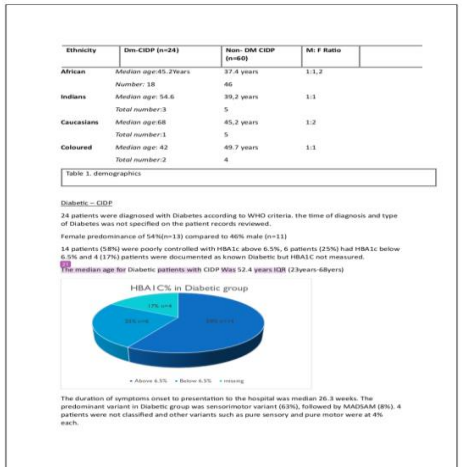
Demographics

We had female predominance of 45 to 39 males.

With 76% (n=54) of patients being African then followed by Indians at 10%(n=8), with Caucasian and coloured equally 6%(n=7).

24 patients were Diabetic and 60 patients not Diabetic.

Mean age for all the patients was 42.3years±16.2(SD) while the Diabetic CIDP group had higher median age of 52,4 years.



Ethnicity	Dm-CIDP (n=24)	Non- DM CIDP (n=60)	M: F Ratio
African	*Median age:*45.2Years	37.4 years	1:1,2
	Number: 18	46	
Indians	*Median age:* 54.6	39,2 years	1:1
	*Total number:*3	5	
Caucasians	*Median age:*68	45,2 years	1:2
	*Total number:*1	5	
Coloured	*Median age:* 42	49.7 years	1:1
	*Total number:*2	4	

Table 1. demographics

Diabetic – CIDP

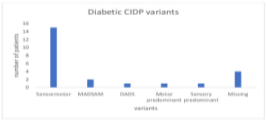
24 patients were diagnosed with Diabetes according to WHO criteria. the time of diagnosis and type of Diabetes was not specified on the patient records reviewed.

Female predominance of 54%(n=13) compared to 46% male (n=11)

14 patients (58%) were poorly controlled with HBA1c above 6.5%, 6 patients (25%) had HBA1c below 6.5% and 4 (17%) patients were documented as known Diabetic but HBA1C not measured.

The median age for Diabetic patients with CIDP Was 52.4 years IQR (23years-68yers)

The duration of symptoms onset to presentation to the hospital was median 26.3 weeks. The predominant variant in Diabetic group was sensorimotor variant (63%), followed by MADSAM (8%). 4 patients were not classified and other variants such as pure sensory and pure motor were at 4% each.



Most patients had elevated CSF protein with mean protein of 0.83 IQR (0.28g/dl to 1.5g. dl.

6 patients (25%) had normal CSF protein and 18 patients (75%) had elevated CSF protein. Of the 18 patients with elevated CSF protein, 6 (33%) had CSF protein of greater than 1g/dl.

Non- Diabetic CIDP

Much of the study population was non- Diabetic (71%), female predominance of 53% and 47% of the study population of the non-Diabetic group were males.

The median age for the non-Diabetic population is 38,4 years IQR (18years to 69years)

Symptom onset to presentation in weeks was mean duration of 18weeks IQR (8-49 weeks)

The commonest variant in this group was sensorimotor type 55% of patients, followed by pure motor 21%, Madsam 11%, dads 8% and pure sensory 5%

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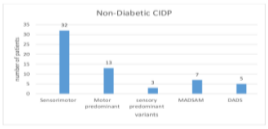


OTHER COMORBIDITIES

2 patients had Hepatitis B of which 1 was a known IVI drug user , however the other patient was unspecified.

20 patients were HIV positive with median CD4 count of 300, and 1 patient had both Diabetes and HIV

Other patients had no documented co- morbidities.

Discussion

We assessed records of 84 patients seen at 2 large hospitals in Johannesburg with diagnosis of CIDP.

Our patients were predominantly females in comparison to the world data with male predominance (14-8). Our study population was predominantly African race which due to our background population, however most studies were done in Asian and Caucasian population with less data on the African race (8-4). South African studies did confirm predominance of African race in Diagnosis of CIDP (2-3)

The median age for both Diabetic CIDP and Non-Diabetic CIDP was much younger compared to the international studies (38.4 versus 61.1 in the non- Diabetic group, 52,4 versus 58.2 in the Diabetic

group) (8). Caucasians where of higher age group (Diabetic- 68yrs, non-Diabetic 45yrs) which is younger than the international study group.

The type of Diabetes was not classified in our population study, which could have helped to differentiate if our Diabetic -CIDP who are younger compared to international studies with predominantly type 2 Diabetes (8). This, however, is consistent with other international studies that found no distinction between type 1 and type 2 Diabetes (15).

There was a 6 month delay in symptoms onset to diagnosis in the diabetic group, which was shorter than the 3.9-year delay in international studies, highlighting the dilemma clinicians face in diagnosing CIDP in diabetic patients and difficulty differentiating Diabetic-CIDP from other Diabetic polyneuropathies (4-7-8).

CSF protein levels were higher in both groups, but there was no difference between the diabetic and non-Diabetic groups (p=0.323), (p=0.323), which differs with the worldwide study, which found a difference in protein levels between the two groups (p=0.040).

In nerve conduction investigations, there was no difference between the diabetic and non-Diabetic group.

LIMITATIONS.

This is a retrospective study, there were missing data such as: detailed clinical presentation, reason for delay in presentation in the Diabetic group, length of hospital stays, NCS and such data could not be recovered.

Duration of diagnosis for Diabetes not indicated and this could have helped to correlate if duration of Diabetes was related to development of CIDP.

Convenient sampling as our population study was from patients seen at neurology clinics.

Conclusion

CIDP is common in both Diabetic and non- Diabetic group, and in contradiction to the literature, our patients were younger compared to international studies.

Progression of the disease is much shorter in the non-Diabetic group compared to a longer duration of symptoms in the Diabetic group.

Our study population was predominantly Africans, and this resulted to about 80% of our study population being African with male to female ratio of 1:2.

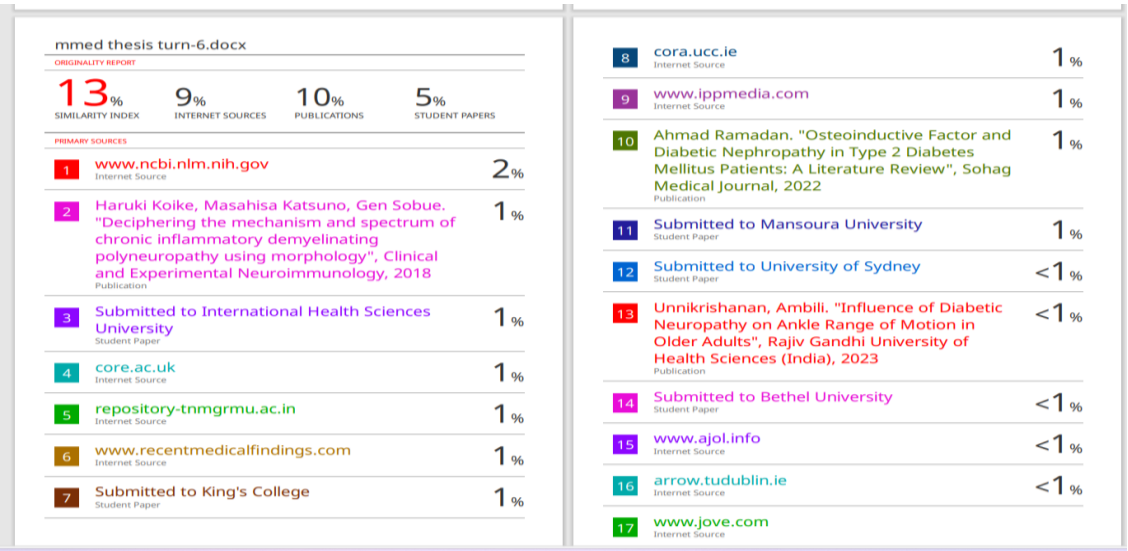
The commonest CIDP variant was sensorimotor for both Diabetic and non- Diabetic group and there was no significant difference on CSF and nerve conduction studies results for both groups.

About 58% of the Diabetic group had poorly controlled HbaIc and this was in keeping with international studies which confirms that CIDP is common in poorly controlled Diabetes.(2)

Therefore, one need to have high index of suspicion for CIDP in Diabetics.

Other comorbidities present where HIV and Hepatitis B

This study proves the hypothesis that there is no marked difference in Diabetic and Non-Diabetic CIDP with regards to Nerve conduction studies, CSF and predominant variant.



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ORIGINALITY REPORT

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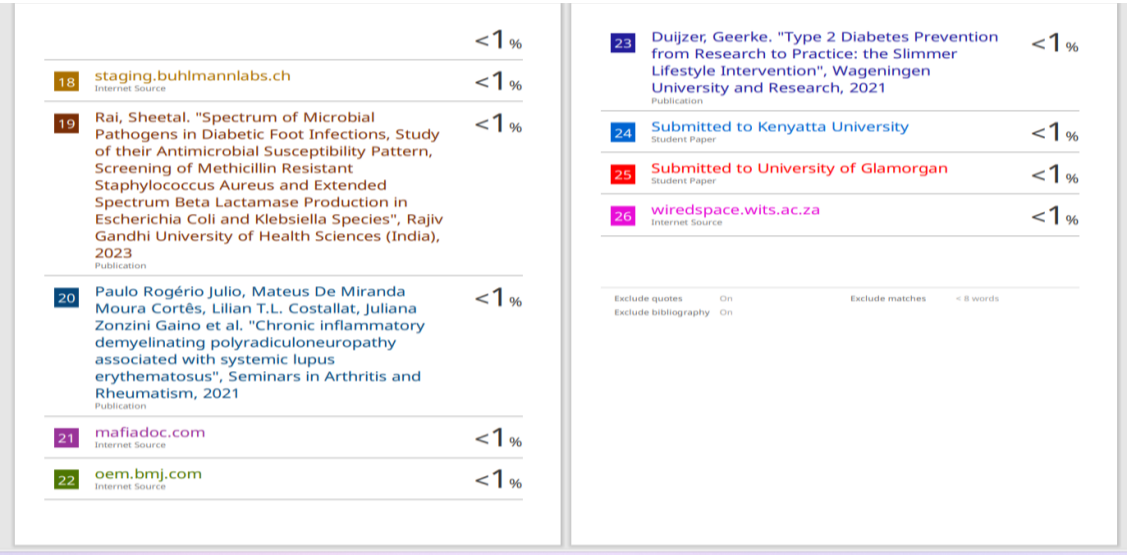

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