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Neurology

A Study of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in Diabetics: Clinical Features, Laboratory Findings and Response to Treatment

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ABSTRACT

Introduction: The association of chronic inflammatory demyelinating neuropathy (CIDP) in diabetics is a recently recognized form of neuropathy. It is important to recognize CIDP occurring in diabetics because, unlike diabetic polyneuropathy, it is treatable. These patients can respond to immune therapies similar to patients with CIDP without diabetes.

Objectives: To study the clinical, electrophysiological, and laboratory features and response to immune modulating treatments in diabetic patients with CIDP.

Materials and Methods: This was a retrospective cross sectional study from January 2009 till December 2012 carried out at Mayo Hospital and National Hospital, Lahore. The inclusion criteria included proven cases of diabetes mellitus with subacute motor weakness fulfilling the research criteria for diagnosis of CIDP. All patients underwent electrophysiological (EP) studies and cerebrospinal fluid analysis (CSF) especially for proteins. Diagnosed CIDP patients were treated with oral prednisolone 1mg/kg body weight along with azathioprine 50-150mg/day. The steroids were gradually tapered after achieving normal muscle strength or a static phase of one month without further improvement in muscle strength. The maintenance dose of prednisolone was continued to complete two years therapy. A course of IVIg (400mg/kg body weight daily for five days) or plasmapharesis (five sessions on alternate days) were used in patients with severe motor weakness to expedite the initial recovery phase. Follow was done at monthly interval for one year and bimonthly for subsequent years. The Hughes functional grading scale was used to assess the outcome. Treatment was considered effective when the patient's condition improved by 1 or more grade on the Hughes scale.

Results: There were 10 patients with 6(60%) males and 4(40%) females and M: F ratio of 1.5:1. The mean age of patients was 63.7$\pm$ 7.83 years. Mean duration of diabetes mellitus was 11.3$\pm$3.77 years. All patients had Type 2 diabetes mellitus with six patients on Insulin and 4 on oral hypoglycemic agents. Mean duration of motor weakness before treatment was 5.30$\pm$1.16 months. Mean power as assessed by medical research council(MRC) grading in upper limbs was 3/5 (range 1-5) and lower limbs 1/5(range 0-2). Seven (70%) patients had mixed demyelinating and axonal picture on EMG, and 3(30%) patients showed predominantly demyelinating type of neuropathy. CSF protein was high in all patients with mean CSF protein of 208.4$\pm$93.07 mg/dl. Mean duration of follow up after treatment was 25.10$\pm$15.82 months. Attempt was done to stop immunotherapy after 2 years but relapse occurred in 3 (30%) patients which again responded to steroids. Outcome was assessed by Hughes functional grading scale. Mean Hugh's functional severity grade before treatment was 4.10$\pm$ 0.316 and after treatment was 1.30$\pm$ 1.16.

Conclusions: We conclude that CIDP in diabetics is potentially reversible type of neuropathy and needs careful evaluation for its recognition. The classical demyelinating pattern on EMG may be lacking because of coexistent axonal neuropathy but clinical history of subacute onset predominantly proximal motor weakness (LMN type) and high CSF protein are most sensitive markers to predict response to corticosteroids in these patients. This is more common in males and elderly long standing diabetics. The response to corticosteroids and other immunosuppressive therapies is excellent. The recognition of this entity is important as appropriate management can reverse the disability in these patients.

Key Words: Chronic inflammatory demyelinating polyneuropathy (CIDP), diabetes mellitus (DM), cerebrospinal fluid (CSF), protein, electrophysiology (EP)

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune mediated inflammatory disorder of the peripheral nervous system. It may be idiopathic (I-CIDP) or associated with systemic diseases including diabetes mellitus (DM-CIDP).[1] Its relationship with diabetes is not completely understood but the odds ratio of the occurrence of CIDP has been reported to be 11 times higher in diabetic than in non-diabetic subjects.[2] Both these groups of CIDP present similar clinical and electrophysiological features and have same response rate to various treatments as well.[2,3] The recognized treatments of CIDP include plasma exchange, steroid

and intravenous Immunoglobulin (IVIg). [4] The efficacy of all treatments in I-CIDP seems to be equivalent.[5] We under took this prospective cohort study to find the clinical, electrophysiological and laboratory features, and response to immune modulating treatments in diabetic patients with CIDP.

MATERIALS AND METHODS

This was a retrospective cross sectional study carried out at Mayo hospital and National Hospital, Lahore. Informed consent was taken from all patients included in the study. The clinical, electrophysiological and laboratory findings were recorded on a special proforma. The inclusion criteria included proven cases of diabetes mellitus with history of subacute motor weakness fulfilling the research criteria for diagnosis of CIDP.[6] The Exclusion criteria were a clinical picture of diabetic amyotrophy or lumbosacral plexopathy; a typical picture of diabetic chronic distal sensory neuropathy, unless there were new symptoms of progressive weakness involving proximal and distal muscles; concomitant disease (paraproteinemia, endocrinopathy other than diabetes, idiopathic CIDP, connective tissue disorder, vitamin B_{12} deficiency, heavy metal intoxication, human immunodeficiency virus infection, hepatitis, Lyme disease, cancer, and kidney failure); or a family history of neuropathy. Detailed neurological examination including muscle strength (according to MRC grading[7]), tendon reflexes, pin prick, touch, and vibratory sensations was done on entry to the study and every follow up visit. A functional assessment was undertaken using the Hughes functional grading scale to see the outcome: grade 0, normal; grade 1, able to run with minimal symptoms and signs; grade 2, able to walk 5 meters independently; grade 3, able to walk 5 meters with aids; grade 4, chair or bed bound; grade 5, requiring assisted ventilation; and grade 6, dead.[8] Regarding mode of onset, the classification "subacute" was used when immune treatment was begun within six months of onset because of difficulty in carrying out daily activities. Patients underwent electrophysiology (EP) testing to evaluate whether the peripheral neuropathy was predominately demyelinating and met the EP criteria for the diagnosis of CIDP[6]. All patients had a lumbar puncture and CSF analysis especially for high proteins along with baseline laboratory investigations including ESR, complete blood count, serum creatinine, and liver function tests. Patients fulfilling the criteria for CIDP were started on oral prednisolone 1mg/kg body weight along with azathioprine 50-150 mg /day as steroid sparing agent to avoid poor diabetic control due to steroids. A course of IVIg (400mg/kg body weight daily for five days) or plasmapharesis (five sessions on alternate days) were used in patients with severe motor weakness to expedite the initial recovery phase. The steroids were gradually tapered after achieving normal muscle strength or a static phase of one month without further improvement in muscle strength. The maintenance dose of prednisolone was continued to complete two years therapy. Follow up was at monthly interval for one year and every two months for subsequent years. Treatment was considered effective when the patient's condition improved by 1 or more grade on the Hughes scale. Statistical analysis was done by SPSS version 16.

RESULTS

There were 10 patients with 6(60%) males and 4(40%) females and M: F ratio of 1.5:1. The mean age of patients was 63.7$\pm$ 7.83 years. Mean duration of diabetes mellitus was 11.3$\pm$3.77 years. All patients had Type 2 diabetes mellitus with six patients on Insulin and four were taking oral hypoglycemic agents.

Table No.1: Clinical and laboratory findings in diabetic patients with CIDP

	Features	Number of patients (N)	Minimum	Maximum	Mean	Std. Deviation
1	Sex Males Females	10 6 (60%) 4 (40%)				
2	Age (yrs)	10	52	76	63.70	7.832
3	Duration of diabetes Mellitus (Yrs)	10	7	20	11.30	3.773
4	Duration of CIDP (months)	10	3	6	5.30	1.160
5	CSF proteins mg/dl	10	75	350	208.40	93.077
6	Follow up in months	10	14	48	25.10	15.822
7	Hughes functional severity grade before treatment	10	4	5	4.10	.316
8	Hughes functional severity grade after treatment	10	0	3	1.30	1.160
9	EMG pattern Demyelinating Mixed (Demyelinating +Axonal)	 3 (30%) 7 (70%)				

Mean duration of motor weakness before treatment was 5.30±1.16 months. Mean MRC power grading in upper limbs was 3/5 (range 1-5) and lower limbs 1/5 (range 0-2). Mean Hugh's functional severity grade before treatment was 4.10± 0.316. Seven patients (70%) had mixed demyelinating and axonal picture on EMG, and 3(30%) patients showed predominantly demyelinating type of neuropathy. CSF protein was high in all patients with mean CSF protein of 208.4±93.07 mg/dl. The clinical features are shown in Table1.

Mean duration of follow up after treatment was 25.10±15.82 months. Attempt was done to stop immunotherapy after 2 years but relapse occurred in 3 (30%) patients which again responded to slightly increased dose of steroids. Outcome was assessed by Hughes functional grading scale. Mean Hugh's functional severity grade after treatment was 1.30± 1.16. Three (30%) were in grade 0; 3 (30%) in grade 1; 2 (20%) in grade 2; 2(20%) in grade 3.

DISCUSSION

Recent studies have reported that patients with diabetes mellitus (DM) have a predisposition to develop chronic inflammatory demyelinating polyneuropathy (CIDP) [9,10,11,12] This is the first study on CIDP in diabetics from Pakistan. Generally diabetic neuropathies are considered irreversible and incurable. This study highlights the fact that subacute progressive motor weakness in diabetic patients needs careful evaluation for the presence of CIDP. In our study CIDP occurred in older diabetics with mean age 63.70±7.83 years. In a previously published study, the median age was 58 years (range 4-83 years).[13] There was a slight male dominance with a ratio of 1.5:1 in our study. This slight male dominance was also observed in another study in which, out of 120 patients with DM-CIDP, 74 were male and 46 female with M:F ratio of 1.6:1. [2] The mean duration of DM in our study was 11.30± 3.77 years and all had type 2 diabetes mellitus. Although CIDP has been reported in both Type 1 and 2 DM with longer disease duration in type 1 than type 2 DM. [2] In our study the electrophysiology (EP) revealed that only 3(30%) had predominantly demyelinating neuropathy and 7(70%) had a mixed demyelinating and coexistent axonal neuropathy. All patients also had high CSF proteins with mean levels of 208±93mg/dl in our study. These levels are much higher than previously observed.[2] This may be because of more severe neuropathy in our study with mean Hugh's severity grade 4.10 ± 0.3. Our study suggests that the EP diagnostic criteria for DM-CIDP need modification with more emphasis on clinical history of subacute development of motor weakness and/or high CSF proteins as important features for making diagnosis. Current CIDP criteria may have high specificity but may lack sensitivity as it may miss diabetic patients with clinical course and CSF findings consistent with CIDP without fulfilling the EP criteria for CIDP because of coexistent severe distal axonal polyneuropathy.

Most CIDP patients are treated with corticosteroids, immunoglobulins, or plasma exchange, but there is no standard first line therapy. Accordingly, CIDP patients have received variable or combination of treatments. The long term outcome of patients with CIDP after receiving these immune modulating treatments is unclear. There are various reports investigating long term course and outcome of CIDP patients, but follow up periods were variable among the studies, including patients with only a few year of follow up. [14,15,16,17]

All our patients were treated with oral prednisolone and simultaneously started on immunosuppressive agents like azathioprine as sparing agent to avoid poor diabetic control and other side effects of steroids in anticipation for long term use (minimum of 2 years). The steroids were gradually tapered after achieving normal muscle strength or a static phase of one month without further improvement in muscle strength. The maintenance dose of prednisolone was continued to complete two years therapy. Two patients with severe motor weakness were also given an initial course of IVIg and one patient had five sessions of plasmapharesis to expedite the initial recovery phase. Our follow up of 48 months (mean 25.10±15.8) showed good neurological recovery as assessed by Hugh's severity scale[12] in most patients. Eighty out the total 10 patients (80%) achieved independent functional status with in three months. Previously IVIg has also been used with significant improvement in clinical deficit and electrophysiological parameters within 4weeks. [2] We also observed that simultaneous use of steroids and immunosuppressive therapy prevented poor diabetic control and minimized other steroids associated side effects. Relapse occurred in 3(30%) patients when drugs were discontinued after two years of therapy. These patients improved quickly with slight increase in their previous maintenance dose of steroids.

CONCLUSION

We conclude that CIDP in diabetics is potentially reversible neuropathy and needs careful evaluation for its recognition. The classical demyelinating pattern on EMG may be lacking because of coexistent axonal neuropathy but clinical history of subacute onset predominantly proximal motor weakness (LMN type) and/or high CSF protein are most sensitive markers to predict response to steroids in these patients. This is more common in males and elderly long standing diabetics. The response to corticosteroids and other immunosuppressive therapies is excellent. The early recognition of this entity is important as appropriate management can reverse the disability in these patients.

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