

Chronic inflammatory demyelinating polyneuropathy associated with diabetes mellitus

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Various forms of neuropathy are seen diabetic patients; chronic inflammatory demyelinating polyneuropathy (CIDP) seems not to be infrequent neuropathy in patients suffering from diabetes and it seems to be more common than in the general population; on the contrary, some authorities do not support pathogenetic association between diabetes mellitus (DM) and CIDP. Also, there are some controversies on the subject of CIDP treatment in diabetic patients. Some studies showed that patients with CIDP-DM considerably had recovered following treatment with immunotherapeutic modalities like (Intravenous immunoglobulin) IVIG and conversely, some else have argued against the prescription of IVIG in this group and recommend treatment with corticosteroids and provided that resistant, rituximab may be beneficial. The main limitation in most studies is the inadequate number of cases and as a result, problematic decision making in treatment. This article represents an inclusive review of diabetic CIDP presentation and treatment.

Key words: diabetes mellitus; chronic inflammatory demyelination polyneuropathy; intravenous immunoglobulin; treatment

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP), as the name implies, is an autoimmune disorder of unknown etiology in two thirds of the patients; however, in remaining one third, an etiological cause might be found. Some currently described etiologies include: Gammopathies including monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, Castleman's disease and Waldenstrom gammopathy; also, other concurrent disorders like inflammatory bowel disorders, cutaneous melanoma, and Hodgkin's lymphoma have been implied.

Simultaneous occurrence of CIDP and diabetes mellitus (DM) (diabetic CIDP or CIDP-DM) is frequently seen in clinical practice; however, it is ambiguous whether the two disorders are pathogenetically correlated.^[1-3] It is of utmost importance to be familiar with CIDP occurring in diabetics for the reason that contrasting to diabetic polyneuropathy, it may be treatable.^[4]

The main goal of this review is to gather nearly all related viewpoints on the subject of CIDP-DM and to answer below issues: Whether the entity is a real one; how we should diagnose it clinically and electrodiagnostically; and finally, what the optimal treatment is; regarding the fact that the articles on this subject are scarce.

MATERIALS AND METHODS

We searched the MEDLINE and EMBASE databases for all articles, published in peer-reviewed journals between January 1975 and October 2012, for evidence relevant to the presence of CIDP or demyelinating polyneuropathy in diabetic patients. We included case controls, cohorts, case series studies, and case reports. Moreover, we looked for the reference lists from the articles identified by the search to identify additional articles. The focus was on the articles describing concurrent diabetes mellitus and CIDP (CIDP-DM) as a whole or a portion of article described the subject. Our search included the MESH headings chronic inflammatory demyelinating polyradiculoneuropathy or CIDP, and diabetes mellitus. Finally, a total of 24 articles out of 82 found articles were obtained; in which 9 were case report and others were case control or case series studies. In 12 articles, a treatment had been proposed.

Is the diabetic CIDP or CIDP-DM a real entity or an imaginary?

Most publications support the notion of the more occurrence of demyelinating polyneuropathy in diabetic patients.

To determine the similarity between demyelinating polyneuropathy and CIDP, Haq *et al.*,^[5] evaluated 10 patients fulfilling the clinical criteria for idiopathic CIDP with 9 patients with diabetes and demyelinating polyneuropathy. Enthusiastically,

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Received: 19-11-2011; **Revised:** 20-11-2012; **Accepted:** 14-01-2013

clinical, electrophysiologic, along with histologic features in diabetic patients with demyelinating polyneuropathy were akin to those in pure CIDP patients; on the other hand, a positive response to the treatment with immunomodulatory interventions was found in all the patients with diabetes and demyelinating polyneuropathy.

In one study,^[3] the clinical and pathological data of a series of 100 successive diabetic patients with symptomatic neuropathy were reviewed. CIDP was diagnosed in 9% of the patients as the most frequent non-diabetic cause of neuropathy in the studied group.

Besides, some reports have described co-occurrence of DM type I and CIDP,^[6] as well as multifocal motor neuropathy with conduction block (MMNCB) and DM.^[7]

On the contrary, one study demonstrated that the frequency of diabetes mellitus in CIDP patients is equal to general population.^[8] Chio *et al.*,^[1,8] studied all cases with CIDP, in two regions of Northern Italy. They found 155 CIDP patients in whom 14 patients were suffering from DM (9%). Also, according to the prevalence of DM, the number of expected CIDP patients with associated DM was 13.03 indicating that the frequency of diabetes was considerably equal to that anticipated in the general population, and as a result, they concluded coincidental association between CIDP and DM. Noticeably, in comparison with the patients with idiopathic CIDP, those with CIDP-DM had a higher level of CSF protein in addition to a delayed identification of CIDP.

On the subject of age, the relationship seems to be unclear, probably because of occurrence of CIDP in wide range of ages and the small percentage of the reports of CIDP-DM; however, in one study, patients with CIDP-DM were older than patients with idiopathic CIDP (55.3 vs. 41.3 years).^[5]

How is it diagnosed by paraclinics?

In the earliest study,^[9] the frequency of conduction block (greater than 20% drop in peak-to-peak amplitude with temporal dispersion less than 15%) in diabetic patients was analyzed by in 24 diabetics with a total of 76 nerve segments. The criteria for conduction block were met in only 6 segments in 6 patients suggesting that conduction block over long nerve segments is uncommon in diabetic neuropathy.

In other larger study,^[10] 543 patients with diabetic neuropathy without clinical evidence of CIDP were evaluated. Twenty out of 169 (11.8%) diabetic patients fulfilled the electrophysiologic criteria of CIDP. Most of the CIDP-DM patients fulfilled the motor conduction velocity criteria (90); furthermore, F-wave latency criteria is seen in 90% of 20 patients, distal motor latency in 70%,

and conduction block in 65%. Other common interesting findings were incomplete conduction block in the peroneal nerve and disproportionately prolonged distal latency in the median nerve of CIDP-DM patients.

To find evidences assisting in discerning CIDP in diabetics from diabetic polyneuropathy, in other smaller study,^[4] the electrophysiological and pathological findings of seven diabetic subjects with a principally motor polyneuropathy with CIDP features were compared with a group of diabetics visited for symptomatic diabetic polyneuropathy. Of the seven diabetics with CIDP, six met at least three and one patient two of the four electrophysiological criteria of demyelination (conduction block/temporal dispersion, prolonged minimal F wave latency, reduced nerve conduction velocity (NCV), prolonged distal latency). Of the 100 patients referred for diabetic polyneuropathy, only four fulfilled two criteria and none of them fulfilled three ones. What is more, findings of nerve biopsy were not supportive in making differential diagnosis between two groups, because demyelination changes, were additionally seen in diabetic polyneuropathy.^[4]

In an fascinating study by Valls-Canals *et al.*,^[11] they compared the sural and peroneal nerves and the electromyographies of leg muscles in 50 completely healthy subjects versus 50 diabetic patients showing clinical manifestations of polyneuropathy. Similar amplitude of sural and peroneal nerves in healthy and diabetic subjects were detected; on the other hand, conduction velocity of sural and peroneal nerves was slower in diabetics in comparison with healthy persons; additionally, signs of acute and chronic denervation/reinnervation were discovered in the leg muscles indicating a mixed pattern of axonal/demyelinating pattern in diabetic patients; however, that is responsible for most of the symptoms.

Noticeably, in diabetic neuropathy conduction velocity reduces that cannot be interpreted by axon loss alone, and that separation of diabetic neuropathy and CIDP seems to be difficult.^[12]

In sum, the electrodiagnostic criteria for determining CIDP in diabetic patients is similar to the non-diabetic subjects; however, it seems that attention to the alterations of NCV and F-wave minimal latency may be more helpful than other parameters. On the other hand, electrodiagnostic suspicion is essential to find the cases particularly in the patients in whom concurrent axonal and demyelination changes have occurred; furthermore, the nerve biopsy may not be necessary to differentiate between demyelination and axonal changes in diabetic patients.

Regarding CSF study, the CSF sample of 35 patients affected by immune mediated CIDP and 17 patients with CIDP-DM

were compared.^[13] Significantly, Oligoclonal bands were found in one third of immune mediated CIDP and 70% of CIDP-DM patients; in addition, CSF protein was marginally higher in CIDP patients with DM.

In another study,^[14] sural nerve was studied by electron microscopy with the goal of differentiating between idiopathic CIDP and CIDP with simultaneous diseases. Edema was detected in around 80% of biopsies of patients with idiopathic CIDP while seen just above half of those with CIDP-DM patients; on the other hand, thick walled blood vessels were seen in 90% of biopsies of CIDP-DM patients and in 100% of those of patients with collagen diseases and hepatitis while present only in 55% of those with idiopathic CIDP patients.

What is the best treatment?

In treating CIDP, corticosteroids, IVIG, or plasma exchange are equally effective;^[15] indeed, in CIDP-DM, there is some matter of debate. Evidence exists to suggest that immunomodulation may be effective in diabetic patients with CIDP regardless of the coexistence of diabetic sensorimotor polyneuropathy [Table 1].^[16]

Most studies agree with the administration of IVIG in CIDP patients:^[17-19] Jann *et al.*,^[17] studied 198 consecutive diabetic patients of whom 16 (8%) had a demyelinating polyneuropathy in electrodiagnostic tests. At least one course of IVIG was given to the patients. Notably, all patients with diabetes CIDP got better subsequent to immunotherapy.

In an older study by the same author,^[20] 31 consecutive patients with untreated CIDP, fulfilling the most restrictive diagnostic criteria, were enrolled over 18 months. Among the patients, 16 were diabetic and all patients were treated with IVIG, and the responders were treated again if they relapsed; significantly, improvement took place after the treatment.

In another pilot study in 10 CIDP-DM patients with IVIG and tight glycemic control, the patients had a better outcome than patients treated with lone tight glycemic control.^[21]

Sharma *et al.*,^[18] administrated IVIG for 26 diabetic patients (type 2) who met the electrophysiological criteria for CIDP (2 gm/kg body weight divided in equal five doses given in five consecutive days) in a prospective open-label pilot study. After four weeks, in 21 patients (80%), the amount of physical impairment (measured by mean Neuropathy Impairment Score) recovered drastically. It is noticeable that in patients with conduction block, improvement in the neuropathy impairment score was more significant.

Also in another study,^[22] anti-inflammatory and/or anti-immune treatment was given to 21 patients with DM who had progressive neuropathy during the past six years. Six patients had demyelinating neuropathy by electrophysiologic criteria. In all patients, worsening of their conditions binged with starting improvement following the commencement of treatment.

Stewart *et al.*,^[23] treated seven diabetic patients with a progressive, moderately severe, motor neuropathy predominantly affecting the lower extremities meeting clinical and electrophysiological criteria for CIDP with combinations of corticosteroids, azathioprine, plasmapheresis and IVIG in whom all improved to a large extent.

In a reported case of CIDP presenting as mononeuritis multiplex with accompanying cranial nerve involvement in an insulin-dependent diabetic,^[19] treatment with IVIG was successful.

Also, significant improvement of CIDP-DM in a 64-year-old man after treatment with IVIG has been described.^[24]

It seems that IVIG is also successful in CIDP-DM accompanying gammopathies: Micco *et al.*,^[25] described a man in his sixties, who had type 1 diabetes mellitus, as well as monoclonal IgM gammopathy of undetermined significance (MGUS) and high anti-MAG antibody titer with a CIDP-like polyneuropathy in whom IVIG was advantageous. Also, according to associated malignancies, Katsuoka *et al.*,^[26] described a 77-year-old diabetic man with CIDP and gastric cancer who was treated with immunological absorption therapy and corticosteroids.

Interestingly, one report,^[27] described considerable benefits after treatment with methylprednisolone and IVIG in a 68-year-old male.

Table 1: Treatments proposed for CIDP-DM

First author	Case numbers (CIDP-DM)	Proposed treatment (s)
Jann ¹⁷	16	IVIG
Jann ²⁰	16	IVIG
Jann ²¹	10	IVIG
Sharma ¹⁸	26	IVIG
Rajabally ¹⁹	1	IVIG
Nakano ²⁴	1	IVIG
Micco ²⁵	1	IVIG
Katsuoka ²⁶	1	IVIG
Stewart ²³	7	combinations of corticosteroids, azathioprine, plasmapheresis and IVIG
Romedenne ²⁷	1	IVIG+Corticosteroids
Pedersen ²⁸	1	Corticosteroids
Munch ²⁹	1	Rituximab

CIDP-DM=Chronic inflammatory demyelinating polyneuropathy-diabetes mellitus; IVIG=Intravenous immunoglobulin

Only one report mentioned the inferiority of IVIG: Pedersen et al.,^[28] described a middle aged diabetic female patient with CIDP who experienced rapid deterioration after two courses of intravenous immunoglobulins (IVIG) administration and remarkable improvement following one month of steroid treatment.

Also, one case report pointed out the successful treatment with rituximab in a 57-year-old patient with CIDP-DM who was treated successfully with rituximab.^[29]

In summation, to sum up, it seems that diabetic patients suffering from demyelinating polyneuropathy acquire benefit from treatment with IVIG [Table 1]. In recalcitrant cases, the addition of corticosteroids might be assisting; on the other hand, it is noteworthy that we did not find any study administering plasma exchange in such patients.

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How to cite this article: Fatehi F, Nafissi S, Basiri K, Amiri M, Soltanzadeh A. Chronic inflammatory demyelinating polyneuropathy associated with diabetes mellitus. *J Res Med Sci* 2013;18:438-41.

Source of Support: We did not receive any found for this research, **Conflict of Interest:** None declared.