Diagnostic and management difficulties of chronic inflammatory demyelinating polyradiculoneuropathy

Abdulrahman M. Al-Tahan, *MD, FRCP,* ***Kazi N. Asfina,*** *MBBS,* ***Mansour H. Al-Moallem,*** *MD, MRCP.*

ABSTRACT

الأهداف: وصف الأشكال السريرية لاعتلال الجذور والأعصاب المزيل للنخاعين الالتهابي المزمن (CIDP)، إضافة لتقييم طرق تشخيصها وعلاجها محليا. وتحديد العوامل المتسببة في إغفال التشخيص أو تأخيره. وأخيراً السعي لتحسين طرق العلاج بإعداد بروتوكول علاجي.

الطريقة: تمت دراسة كافة المرضى الذين يعانون من اعتلال الجذور والأعصاب المزيل للنخاعين الالتهابي المزمن (CIDP) في مستشفى الملك خالد الجامعي – الرياض – المملكة العربية السعودية، في الفترة من 1986م وحتى 2006م، بصورة إسترجاعية وذلك من خلال تقييم المعلومات السريرية، والاستقصاءات، وطرق العلاج و نتائجه. تمت إعادة تقييم التشخيص بناء على المعايير المعتمدة من قبل الأكاديمية الأمريكية لطب الأعصاب. كما تمت متابعة جميع المرضى الموجودين بصورة متقدمة حتى نهاية الدراسة.

النتائج: شملت الدراسة 22 مريضاً (18 ذكراً و 4 إناث بنسبة 4.5:1). تراوحت الأعمار من 3–70 سنة (وسطي 33 سنة). تأخر التشخيص لدى 80% من المرضى مابين 6 أشهر وحتى 10 سنوات (وسطي 2.5 سنة). لم يشخص أي مريض قبل إحالته. كان المسار المرضي متطوراً لدى 53%، ومعاوداً لدى 47%. ظهر تحسن لدى معظم المرضى لكن أقل من المتوقع، بينما لم يظهر أي تحسن يذكر في مريضين بسبب التأخر في تشخيصهم لمدة طويلة (7.5 وحتى 10 سنوات).

الخاتمة: بينت الدراسة أن تشخيص مرض اعتلال الأعصاب مزيل النخاعين المزمن (CIDP) غالبا ما يتأخر مسبباً آثارا سلبية على استجابة المرضى للعلاج وتحسنهم النهائي. يعود ذلك في الغالب لعدم دراية الأطباء العامين بهذا المرض مما يوجب العمل على تصحيح ذلك. كذلك يتأثرعلاج المرضى بسبب عدم التزام المرضى بالمتابعة طويلة الأمد المطلوبة، الأمر الذي يمكن إصلاحه بالتثقيف الأفضل للمرضى حول طبيعة مرضهم المزمن. كما تبين أن معالجة هذا المرض غير نموذجية على العموم، ويستدعي ذلك إعداد بروتوكول علاجي محدّث.

Objectives: To describe the pattern of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and evaluate its local diagnostic and management practices. To define factors responsible for the delay in reaching a diagnosis and initiating treatment.

Methods: Patients with the diagnosis of CIDP attending King Khalid University Hospital, Riyadh, Saudi Arabia between 1986 and 2006 were retrospectively studied, in relation to diagnosis and management. Diagnosis was reassessed, and patients included in view of American Academy of Neurology as well as Latov's criteria. Available patients were reevaluated and prospectively followed up until the end of the study.

Results: Twenty-two patients were included (18 males and 4 females, 4.5:1). Age at onset range was 3-70 years (mean of 33 years). Diagnosis in 80% of patients was delayed from 6 months to 10 years (mean of 2.5 years). No case was diagnosed before referral. The course was progressive in 53% and relapsing in 47%. Most patients made significant initial improvement, though less than expected. Two patients with long delay in diagnosis (7.5 and 10 years) showed no improvement.

Conclusion: Diagnosis of CIDP is frequently delayed, with a deleterious effect on response to treatment. This is related to some degree to the lack of awareness among general physicians, which needs to be corrected. Treatment was also hindered by patients' suboptimal compliance, which could be improved by better education. Management is not standardized, and this could be improved by establishing up-to-date treatment guidelines.

Neurosciences 2008; Vol. 13 (3): 291-295

From the Department of Medicine, King Khalid University Hospital, College of Medicine, King Saud University, Riyadh, Kingdom of Saudi Arabia.

Received 12th November 2007. Accepted 20th April 2008.

Address correspondence and reprint request to: Prof. Abdulrahman M. Al-Tahan, Professor in Neurology, Department of Medicine, King Khalid University Hospital, King Saud University, Riyadh, Kingdom of Saudi Arabia. Tel. +966 (1) 4671532. Fax. +966 (1) 4672424. E-mail: Atahan45@hotmail.com

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a well defined acquired immune-mediated neuropathy.[1,2] In 1982, Dyck et al[1] described the disease as a progressive or relapsing limbs weakness, extending for 8 weeks or more, associated with hyporeflexia, and is due to an inflammatory demyelinating process. The prevalence of CIDP is greatly underestimated due to many factors, including the uncertainty in making the diagnosis.[3] It accounts for approximately 20% of acquired chronic polyneuropathies, and is the most commonly recognized type of the chronic immune-mediated neuropathies.[4] If untreated, CIDP causes a progressive quadriparesis in more than 60% of patients associated with significant disability, as they become gradually weaker, and unable to work and perform their main duties, and later on become dependable in daily activities, and finally wheelchair-bound and bedridden.[5] Treatment is associated with significant improvement in more than 80% of cases and full recovery in 40%, especially if it is started early and continued for 6 months or more.[6] Medications used in the treatment of CIDP include steroids, plasma exchange (PE), intravenous immunoglobulin (IVIG) and cytotoxics.[7] This study aims to evaluate the local diagnostic and management practices among CIDP patients seen at KKUH, and define the factors responsible for missing or delaying its diagnosis. Results are expected to aid in formulating practical diagnostic and management protocols.

Methods. All patients admitted to King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia from early 1986 to June 2006 with the diagnosis of CIDP and related neuropathies were studied. Demographic information, clinical features, and investigations as well as different treatments and its effects over the follow-up period were reviewed. Diagnosis on referral and information on possible reasons for a delayed referral to the neurology clinic was specifically looked for. All available patients attending the outpatient clinic, as well as those newly diagnosed, were reevaluated and followed-up prospectively until the end of the study. The diagnosis of CIDP was reassessed as per the American Academy of Neurology (AAN) Ad-Hoc Sub-Committee criteria.[8] Depending on several clinical, physiological, pathological, and CSF features, these criteria define the CIDP diagnosis as definite, probable, or possible. Patients were included if at least they satisfy the criteria required for possible diagnosis. These include first the clinical mandatory inclusion criteria of progressive or relapsing motor and sensory, rarely only motor or sensory dysfunction of more than one limb of a peripheral nerve nature, developing over at least 2 months, with hypo or areflexia. The second requirement is a mandatory clinical exclusion criterion requiring absence of mutilation of hands or feet, retinitis pigmentosa, ichthyosis, sensory level, or unequivocal sphincter disturbance, or history of drug or toxic exposure known to a similar peripheral neuropathy, or a family history of a genetically based neuropathy. The last requirement is the mandatory neurophysiologic criteria that require clear evidence of a predominantly demyelinating process in the proximal nerve segments. These include 3 of the following 4 features in 2 or more nerves: slow conduction velocity, partial conduction block, or temporal dispersion, prolonged distal latencies, and absent F waves or prolonged minimum F wave latencies. Response to treatment was assessed according to a disability scale that includes 5 grades. It starts with "1" if the patient were still working, "2" if weakness affects work but not activity of daily living, "3" if the patient become dependent to a variable degree but still ambulatory, "4" describes wheelchair bound state, and "5" bedridden state. The Research Ethical Committee of King Saud University approved this study and informed consent was obtained accordingly.

Results. From a total of 27 patients, 5 were excluded due to insufficient clinical data and or investigations, precluding minimum requirement for "possible" CIDP diagnosis. **Table 1** summarizes the most relevant demographic, clinical, and follow-up data in these patients. One patient had type 1 Charcot Marie Tooth (CMT). On final analysis, only 22 patients with CIDP were included, 18 men and 4 women (4.5:1). Age of onset was 3-70 years, with a mean of 33 years. Diagnosis was significantly delayed in 80% of our patients, ranging from 6 months to 10 years (average approximately 2.5 years). Eleven patients were labeled non-specifically as chronic neuropathy or neuro-muscular disorder. Three patients were misdiagnosed as CMT, 2 as severe diabetic neuropathy, and one as Guillain-Barré Syndrome. No patient was referred with a diagnosis of CIDP. After referral to the neurology service all patients were correctly diagnosed, apart from a 37-year-old patient who was misdiagnosed as CMT for 4 years until a repeat nerve conduction study detected partial block and significant asymmetry between both sides. Another patient was misdiagnosed as CIDP, but a positive family history and non-responsiveness to prednisolone indicated the proper diagnosis of CMT. Weakness was the predominant symptom in all patients, except one with predominantly sensory symptoms (disability grade 1). Weakness affected both proximal and distal muscles, varying from very severe requiring artificial ventilation in one patient, to moderate weakness (disability grade 2) in 2 patients. Deep tendon reflexes were absent or diminished in most patients, except in 2 patients in

Table 1 - Summary of 22 patients with CIDP, seen at King Khalid University Hospital, Riyadh, Saudi Arabia from 1986 to 2006.

Patient	Age of onset /gender	DID	Disability grade "pre"	Follow-up period	Diagnostic category	Treatment	Disability grade "post"	Follow-up
1	47/M	3 y	3	4 m	Definite	Pred 60 mg	2	Short follow-up
2	23/F	2.5 y	3	12 y	Definite	PE, Pred 60 mg	2	No R, no maint
3	28/F	1.5 y	5 (ventilator)	1.5 y	Definite (-CSF)	PE X 5 Pred 80 mg→20	5	No R, maint
4	28/F	2 y	5	3.2 y	Definite	Pred 60 mg AZT	2	R X 2, maint
5	52/M	6 m	4	9 y	Definite (myeloma)	IVIG, 6 m course Pred 80 mg→15	2	R X 3, maint Myeloma 3 y
6	39/M	2 y	4	4.3 y	Definite	IVIG X 5 course Pred 80mg→20	1	R X 2, maint
7	37/M	1 y	3	1 y	Definite	Pred 80 mg→20	2	No R, maint
8	27/M	6 m	4	3 m	Definite	IVIG X 5, Pred 80 mg	3	Short follow-up
9	23/M	2 y	3	3 y	Definite	Pred 80→20	2	No R, maint
10	45/M	1 y	4	2.5 y	Possible	Pred 60→7.5	1	No R, maint
11	3.3/M	3 m	4	1.5 y	Definite	PE X 5 Repeated on relapse	1	R X 1
12	46/M	3 m	2	2.3 y	Probable (DM)	IVIG X 2, +3 monthly maint	1	R X 2, maint NIL for 13 m
13	13/M	7 y	4 (wast)	4 y	Definite	IVIG X 1, Pred	3	R X 2, maint
14	60/M	4 m	2	2.3 y	Definite (DM)	IVIG X 2 Pred	1	R X 1, maint
15	70/M	6 m	4	2.5 y	Definite	Pred 60 mg→10	3	R X 1, maint
16	37/ M	4 y	3 (wast)	1 y	Probable	Pred 80 mg→20	2	No R, maint
17	54/ M	1.5 y	3	1 y	Possible	IVIG course	2	No R
18	45/ F	10 y	4 (wast)	6 m	Definite	IVIG, Pred 80 mg	4	Short follow-up
19	39/M	3 y	3	2 y	Possible (HIV+)	AZT	1	Improved, no treatment
20	64/M	6 m	4	3 m	Probable	PE, Pred 80 mg	3	Short follow-up
21	7/M	7.5 y	4 (wast)	4.5 y	Definite	Pred 80→DC	4	No maint
22	38/M	1 y	1 (sensory)	6 m	Probable	Pred 80 mg	1	++clinical response

M - male, F - female, y - year, m - month, DID - delay in diagnosis, pre and post - before and after starting treatment, DM - diabetes mellitus, wast - wasting, pred - prednisolone, PE - plasma exchange, IVIG - intravenous immunoglobulin, R - relapses, RX - relapses number, maint - maintenance, AZT - Azathioprine, DC - discontinue

whom it was normal. Muscle wasting, both proximal and distal was noted in 4 patients, all of who had delayed diagnosis of 4-10 years. Sensory symptoms were generally mild, of distal distribution, and predominantly of large fiber modality. No patient had a sensory level, squint, or urinary sphincter dysfunction. According to diagnostic categories, 15 patients (68%) were classified as definite (CSF was normal in one patient), 4 patients as probable (biopsy was normal in one patient), and 3 patients as possible. The certainty of diagnosis was enhanced in all probable and possible cases after obtaining a good response to steroids, according to Latov's criteria.[3] Concomitant diseases, include diabetes mellitus in 3 patients, multiple myeloma in one, and positive HIV in another.

Treatment modalities. Prednisolone was given to all patients as 60-80 mg daily dose initially alone or in combination with other medications. Later on it was titrated according to clinical response to 7.5-20 mg daily or on alternate days as maintenance therapy. Ninety percent showed significant improvement of motor function by one grade or more. One patient became independent of ventilator. Fifteen patients (68%) became ambulatory and independent. Seven patients (31%) returned to work. Two patients (9%) did not improve after 3 months of initiating treatment.

Plasma exchange (PE) was used in 4 patients, usually as 4-5 consecutive sessions (total volume approximates 250 ml/kg), with significant response in 3 patients only. Intravenous immunoglobulin (IVIG) was given to 8 patients (daily dose of 20-40 mg/kg). One patient only did not respond to either IVIG or steroids. She had severe wasting and her diagnosis was delayed for more than 10 years. Otherwise, IVIG resulted in significant improvement in 7 patients, and was repeated successfully on each relapse. Two patients received maintenance infusions every 3-4 months with remission for 1.5-4 years.

Response to treatment. The response to treatment is illustrated by comparing the disability scores in all patients before and after treatment, which show that more than 85% of patients were dependent or non-ambulatory, while more than 68% became independent and ambulatory.

Follow-up assessment. The follow-up period varied widely from 3 months to 12 years. The reasons for that are variable and can only be guessed in most patients, because of frequent absence of contact addresses or phone-numbers. For this reason, long-term follow-up was restricted to those with a follow-up assessment period of one year or more. Seventeen patients were followed up for 1-12 years, with an average of 4.7 years. Eight (47%) of them sustained 1-3 relapses and 7 of them were on maintenance therapy. In 9 patients (53%), the course was rather steady or progressive. Maintenance therapy was given to 12 of the 17 follow-up patients (70.5%), and included low dose (5-20 mg) prednisolone in 8 patients, azathioprine in 2 patients, and regular IVIG 3-4 monthly infusion in 2 patients. One patient was stable for 12 years after initial treatment while on no maintenance therapy, representing a spontaneous recovery. Two patients with very much delayed diagnosis of 7.5 and 10 years did not show any response to steroids or even a course of IVIG, which was used in the second patient. There were no records of mortality among patients, whether CIDP related or non-related.

Discussion. It is clear from analyzing the referral pattern of patients, that most referring physicians were not aware of the significance of CIDP as a treatable entity among the commonly untreatable chronic polyneuropathies. It can only be supposed that lack of awareness is an important factor behind the prolonged delay in reaching the diagnosis, which averaged 2.5 years, and reached 4-10 years in 4 patients. Latov has noted that even neurologists may encounter such difficulty, especially when the diagnosis is scrutinized by the stringent AAN research criteria, or when an atypical presentation such as sensory CIDP, is encountered.[3,8] This, however, needs to be considered within the limitations of this essentially retrospective study. Another cause of diagnostic difficulty in our patients is the relatively high association with diabetes mellitus, which was probably the reason behind misdiagnosing 4 patients as diabetic neuropathy. The significance of this association, however, cannot be assessed in this study in view of the high prevalence of diabetes mellitus in Saudi Arabia reaching 23.7%.[9] The diagnosis of multiple myeloma in one of our patients was rather unusual, as CIDP is typically associated in relevant literature with osteoclastic myeloma.[10] Another patient had AIDS, which is a well-recognized association, however, most of these patients were noted to be asymptomatic at the time of diagnosing CIDP.[11] The course of the disease was progressive in 53% and relapsing in 47%, which is almost identical to the figures in Barohn et al's series.[5] However, the exact nature of the steady course in the first group and whether the course is actually relapsing or of step-wise progression in the second group cannot be determined accurately. The reason for this is mainly the incomplete data and irregular follow-up noted in most of our patients, which is related to the retrospective nature of a large part of this study. Other reasons are the relatively short follow-up period for most patients (less than 2.3 years), and the high number of those who were lost for follow-up.

The mean age of onset was 33 years similar to 35 years in McCombe et al's series,[12] however, the predominance of males was more than doubled in our patients, in comparison with the latter study. There is no clear explanation for this difference. Clinical features were also similar to those described in earlier reports.[1,6,12] Weakness was the predominant feature, while sensory symptoms were noted in approximately 50% of patients similar to the findings of McCombe et al of 94% and 65% respectively.[12] A pure sensory variety that was noted in one of our patients is a well recognized but rather rare variety, affecting only 3 of the 53 patients reported by Dyck et al.[1] Biopsy was normal in one patient, however his diagnosis was confirmed by the presence of all other criteria, as well as a clear response to therapy. This finding is well recognized in the literature, reaching 26% in the study by Prineas and McLeod.[13] Twenty (90%) of our patients had mandatory CSF criteria. In one patient with typical pathological changes, the CSF protein was within normal limits, implying that in individual patients this criterion is highly supportive, but not exclusive. This is similar to the assumption made by Barohn et al[5] who reported that 5% of their patients had normal CSF protein.

Response to long-term prednisolone was noted in the majority of patients, reaching 85% when assessed as improvement by one disability grade or more.

This is comparable to previous reports such as that of Dyck et al[2] who reported significant improvement in 68% of their patients. Two of our patients with very prolonged delay in the diagnosis of 7.5 and 10 years, showed no improvement after 6 months treatment with prednisolone. Such non-responsiveness and even worsening after steroids has been well described before by Dalakas and Engel.[14] Plasma exchange was used in 4 patients, before IVIG became widely available. Three of them responded well, and a 3.5-year-old child responded unexpectedly well within a few days by improving from grade 4 to 1. A similar very rapid response was reported by Gross and Thomas.[15] The IVIG resulted in significant improvement in all patients, except one in whom the diagnosis was delayed for 10 years. This negative response to IVIG is probably related to the marked muscle wasting noted in this patient. A similar experience was previously reported by van Doorn et al.[16]

Describing the long-term outcome in this group of CIDP patients was hindered by the limited available clinical data. Many patients have no updated contact numbers, did not keep regular follow-ups, and were non-compliant to variable degrees. This is more likely to occur if patients are not well informed of the different aspects of their illness, and most importantly its chronic nature and the need for long-term treatment. However, in spite of these limitations it is still possible to formulate general prognostic conclusions in our patients, and especially in some individual cases. One patient had probably a spontaneous recovery as she had no relapses during 12 years of follow up and while off medication. A similar outcome was noted in 4% of Dyck et al's series.[1] Another patient required ventilation, and continued afterwards to be bedridden for 1.5 years. The prognosis is expected to be poor in this patient as he showed evidence of severe denervation on EMG. Respiratory failure requiring ventilation has already been noted as a poor prognostic sign by Haden and Hughes,[17] together with old age and a relapsing-remitting course. In McCombe et al's series,[12] 10% of their patients, either died or became severely disabled, while 30-40% had a mild degree of disability. They noted that 50% had a favorable long-term prognosis, being able to lead an independent life for more than 10 years follow-up. In our patients who were followed for a mean of 2.3 years, 31% returned to work, 54% became ambulatory but unemployed, and 14% were confined to wheelchair or bed, compared with 60%, 8%, and 11% in the series of Dyck et al,[1] pointing to a less favorable outcome in our patients. An important cause of this finding probably includes the prolonged delay in making the diagnosis and staring appropriate treatment, which ranged in 18 patients (80%) from 6 months to 10 years.

In conclusion, CIDP is not uncommonly seen and readily diagnosed with an acceptable degree of certainty locally. However, its diagnosis is frequently delayed with deleterious effects on patients' response to treatment and outcome. It is referred through internists who are apparently not well aware of this entity, which is easily misdiagnosed as diabetic neuropathy or other chronic untreatable neuropathies. It requires prolonged follow-up and a high degree of patient's compliance. This is expected to improve with more intense patients education. Finally, we recommend an objective evaluation of this issue among internists and general practitioners.

References

1. Dyck PJ, Lais AC, Ohta M, Bastron JA, Okazaki H, Groover RV. Chronic inflammatory polyradiculoneuropathy. ***Mayo Clin Proc*** 1975; 50: 621-637.
2. Dyck PJ, O'Brien PC, Oviatt KF, Dinapoli RP, Daube JR, Bartleson JD, et al. Prednisolone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. ***Ann Neurol*** 1982; 11: 136-141.
3. Latov N. Diagnosis of CIDP. ***Neurology*** 2002; 59 (12 Suppl 6): S2-S6. Review.
4. Saperstein DS, Katz JS, Amato AA, Barohn RJ. Clinical spectrum of chronic acquired demyelinating polyneuropathies. ***Muscle Nerve*** 2001; 24: 311-324.
5. Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyneuropathy. Clinical characteristics, course, and recommendation for diagnostic criteria. ***Arch Neurol*** 1989; 46: 878-884.
6. Koski CL. Therapy of CIDP and related immune-mediated neuropathies. ***Neurology*** 2002; 59 (12 Suppl 6): S22-S27. Review.
7. Ropper AH. Current treatments of CIDP. ***Neurology*** 2003; 60 (8 Suppl 3): S16-S22. Review.
8. Research criteria for diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP). Report from the Ad Hoc Sub-Committee of the American Academy of Neurology AIDS Task Force. ***Neurology*** 1991; 41: 617-618.
9. Al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, Arafah MR, Khalil MZ, Khan NB, et al. Diabetes Mellitus in Saudi Arabia. ***Saudi Med J*** 2004; 25: 1603-1610.
10. Kelly JJ Jr. Polyneuropathies associated with plasma cell dyscrasias. ***Semin Neurol*** 1987; 7: 30-39.
11. Cornblath DR, McArthur JC, Kennedy PG, Witte AS, Griffin JW. Inflammatory demyelinating peripheral neuropathies associated with human T-cell lymphotropic virus type III Infection. ***Ann Neurol*** 1987; 21: 32-40.
12. McCombe PA, Pollard JD, McLeod JG. Chronic inflammatory demyelinating polyradiculoneuropathy. A clinical and electrophysiological study of 92 cases. ***Brain*** 1987; 110: 1617-1630.
13. Prineas JW, McLeod JG. Chronic relapsing polyneuritis. ***J Neurol Sci*** 1976; 27: 427-458.
14. Dalakas MC, Engel WK. Chronic relapsing (dysimmune) polyneuropathy: pathogenesis and treatment. ***Ann Neurol*** 1981; 9 Suppl: 134-145.
15. Gross ML, Thomas PK. The treatment of chronic relapsing and chronic progressive idiopathic inflammatory polyneuropathy by plasma exchange. ***J Neurol Sci*** 1981; 52: 69-78.
16. van Doorn PA, Vermeulen M, Brand A, Mulder PG, Busch HF. Intravenous immunoglobulin in treatment of patients with chronic inflammatory demyelinating polyradiculoneuropathy. Clinical and laboratory characteristics. ***Arch Neurol*** 1991; 48: 217-220.
17. Hadden RD, Hughes RA. Management of inflammatory neuropathies. ***J Neurol Neurosurg Psychiatry*** 2003; 74 Suppl 2: ii9-ii14.