CLUES TO THE DIAGNOSIS OF CHRONIC IMMUNE-MEDIATED POLYNEUROPATHIES

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INTRODUCTION

Autoimmune mechanisms are implicated in several chronic neuropathic syndromes that are amenable to immune therapy (Table I). Collectively, these neuropathies are relatively common; Barohn et al (1998) reported that approximately 13% of consecutive patients with neuropathy seen at their institution had an immune mediated neuropathy, and Verghese et al (2001) found that 6% of their elderly neuropathy patients had a demyelinating inflammatory etiology. In practice, however, many of the autoimmune neuropathies are difficult to diagnose, due to a lack of generally accepted clinical diagnostic criteria, or availability of reliable serological tests. Consequently, many patients with autoimmune neuropathies are diagnosed as having "idiopathic neuropathy" instead, and left untreated despite progression of their disease.

Clinical or laboratory features suggestive of an autoimmune neuropathy include: 1) acquired demyelination, 2) multifocal distribution, 3) associated systemic immune disease or malignancy, 4) anti-nerve antibodies or monoclonal gammopathies, and 4) nerve biopsies exhibiting vasculitis or other inflammatory changes. An unknown proportion of idiopathic neuropathies, with otherwise no distinguishing features, may also be immune mediated and respond to immune therapy.

ACQUIRED DEMYELINATION AS A HALLMARK OF AUTOIMMUNITY

Acquired, or non-hereditary, chronic demyelinating neuropathies, with the exception of certain drug toxicities as may be seen with Amiodarone, are considered to be autoimmune, and classified under the general heading of chronic inflammatory demyelinating polyneuropathy (CIDP). The typical presentation is that of proximal and distal weakness with distal large fiber sensory loss, but approximately 50% of patients have atypical presentations, probably reflecting the distribution of lesions. These include Multifocal Motor Neuropathy (MMN), Multifocal Acquired Demyelinating Sensory and Motor (MADSAM) neuropathy, Distal Acquired Demyelinating Predominantly Sensory (DADS) Neuropathy, and Sensory CIDP (Saperstein et al, 2001; Rotta et al, 2000; Chin et al, 2003a). Demyelination is typically detected by electrodiagnostic testing, but in sensory CIDP, nerve biopsy studies using semi-thin sections or teased fiber analysis may be needed, as sensory conductions are of limited use (Chin et al, 2003a; Vallat et al, 2003). Research electrodiagnostic criteria for CIDP, which require the demonstration of demyelinating abnormalities in multiple nerves, are highly specific but relatively insensitive, and may miss a substantial proportion of patients. In the appropriate clinical

setting, however, demonstration of demyelinating changes in only one or more nerves would be supportive of the diagnosis (Magda et al, 2003). CIDP is usually unassociated with systemic disease or serological abnormalities, but on occasion, patients have IgG monoclonal gammopathy, hepatitis C, or anti-SSA-Ro/SSB-La antibodies.

CIDP as well as microvasculitis also occur in patients with diabetes mellitus, particularly in multifocal diabetic neuropathy or lubosacral radiculoplexopathy (Sharma et al, 2002a,b; Dyck and Windebank 2002; Said et al, 2003). Inflammatory neuropathies, including CIDP also occur in patients with hereditary neuropathies, possibly due to mutations in peripheral nerve proteins (Miyamoto et al, 2003; Thomas and Ormerod, 1993).

MULTIFOCALITY IN IMMUNE-MEDIATED NEUROPATHIES

Autoimmune neuropathies often present with a multifocal distribution, probably due to multiple focal inflammatory infiltrates. If the lesions are demyelinating, as in MMN or MADSAM, then the neuropathies are presumed to be autoimmune. In the case of axonal neuropathies, however, the presence of multifocality may be the only distinguishing feature. Such neuropathies include nonsystemic vasculitic neuropathy (Davies et al, 1996; Collins et al, 2003) , multifocal axonal sensory and motor neuropathy (MASAM) (Alaedini et al, 2003), and multifocal sensory neuropathy or sensory ganglioneuritis (Zifko and Hahn, 1997; Sobue et al, 2003). If other causes for multifocal neuropathy, such as Lyme disease or diabetes are excluded, then immune mechanisms should be considered.

Brachial or Lumbosacral plexopathies may also be inflammatory in etiology, given their relatively rapid onset, self limiting course, and inflammatory changes on pathological studies (Suarez et al, 1996; Dyck and Windebank, 2002).

ASSOCIATED AUTOIMMUNE DISEASES OR MALIGNANCIES

Immune mediated neuropathies may be associated with systemic autoimmune disease, particularly rheumatological or inflammatory bowel diseases. Vasculitic neuropathies are frequently associated with periarteritis nodosa, Wegeners granulomatosus, Churg-Strauss syndrome, Sjogren's syndrome, or rheumatoid arthritis (Hellmann et al, 1988; Kissel and Mendell, 1992; Puechal et al, 1995; Mellgren et al, 1989; Nemni et al, 1988; Griffin, 2001; deGroot et al, 2001; Nagashima et al, 2002), and Sjogrens syndrome may also be associated with sensory ganglioneuritis or painful sensory neuropathy (Sobue et al, 1993; Griffin et al, 2001; Mori et al, 2003; Font et al, 2003; Gorson and Roper, 2003). Vasculopathy has also been described in nerves of patients with SLE or systemic sclerosis (Mawrin et al, 2003; Nitta et al, 1996). Testing for hepatitis C or cryoglobulins in periartiritis nodosa, ANCA in Wegener's granulomatosus, eosinophilia in Churg-Strauss syndrome, and rheumatoid factor or SSB-La/SSA-Ro antibodies in rheumatoid arthritis or Sjogren's syndrome respectively, can help in the diagnosis of these syndromes.

Immune mediated neuropathies may also be associated with inflammatory bowel diseases. Celiac disease is associated with multifocal sensory neuropathy (Chin et al, 2003b), and CIDP is also more frequent in patients with Crohn's disease or ulcerative colitis (Gondim et al, submitted).

Tumors, particularly small cell cancer of the lung, are occasionally associated with immune mediated neuropathies. Paraneoplastic sensory neuropathy or ganglioneuritis is associated with anti-HU or CV2 antibodies that cross react with antigens in nerve and tumor tissues (Antoine et al, 2001; Darnell et al, 2003).

Neuropathy also occurs in malignant B-cell lymphoproliferative disorders including lymphoma, chronic lymphocytic leukemia, or Waldenstrom's macroglobulinemia. In those cases, the B-cells secrete monoclonal IgM antibodies that react with peripheral nerve antigens (see below). On occasion, the neuropathy is associated with neurolymphomatoses, with the malignant B-cells directly invading the nerves (Dropcho 2002).

MONOCLONAL GAMMOPATHIES AND ANTI-NERVE ANTIBODIES

Monoclonal gammopathies occur more frequently in patients with neuropathy than in the normal population, but are associated with diverse neuropathic syndromes. The monoclonal proteins are generally classified according to their heavy chains, into IgMs or IgG and IgAs, and are typically non-malignant, although they can progress to macroglobulinemia or myeloma (Latov, 2002).

Approximately 75% of IgM monoclonal gammopathies in neuropathy exhibit antibody activity against peripheral nerve antigens (Willison, 2002), most often the Myelin Associated Glycoprotein (MAG), but also against sulfatide, or gangliosides GM1, GD1a, GD1b, GQ1b, or GM2. They are typically associated with a predominately sensory or sensorimotor demyelinating neuropathy, except in the case of anti-GM1 or GD1a antibodies which are associated with multifocal motor neuropathy (MMN). The antibodies are thought to contribute to the neuropathy, as has been shown in experimental models of the disease (O'Leary and Willison, 2000). Polyclonal IgM antibodies with the same specificities are also associated with autoimmune neuropathies in the absence of monoclonal gammopathies.

Non-malignant IgG or IgA monoclonal gammopathies rarely exhibit autoantibody activity, but may be associated with CIDP (Gorson et al, 1997). In osteosclerotic myeloma, neuropathy is present in approximately 50% of the cases, occasionally with the POEMS syndrome (Polyneuropathy, Organomegally, Endocrinopathy, Myeloma, and Skin changes). In primary amyloidosis, the endoneurial amyloid deposits consist of fragments of the monoclonal immunoglobulin light chains (Latov, 2002).

Anti-nerve antibodies are also associated with autoimmune autonomic neuropathies,

where approximately half of the patients exhibit high titer antibodies to the ganglionic nicotinic acetylcholine receptor (Low et al, 2003).

INFLAMMATORY IDIOPATHIC NEUROPATHIES

Neuropathies of unknown etiology are generally classified as idiopathic, and left untreated. A number of patients with idiopathic sensory or sensorimotor neuropathies, however, have been reported to respond to immune therapy (Cavaletti et al, 1999; Chroni et al, 1995; Gorson and Roper 1995), and patients with peripheral nerve vasculitis or perivasculitis may present similarly to those with idiopathic neuropathy (Kelkar et al, 2002; Mendell and Sahenk, 2003). A nerve and muscle biopsy or a trial of immune therapy may therefore be considered in a patient with an unexplained progressive neuropathy, as otherwise the neuropathy may progress to debilitations.

THERAPY

Therapeutic intervention is directed at suppressing the immune reactivity or blocking the effector mechanisms. The choice of therapy in any given patient or syndrome depends on the efficacy and safety of the treatment being considered (Donofrio, 2003).

In controlled clinical trials, CIDP has been shown to be responsive to corticosteroids, plasmapheresis, or IVIg (Kissel, 2003), MMN has been demonstrated to be responsive to IVIg (Taylor et al, 2000; Nobile-Orazio et al, 2002), and demyelinating neuropathy with IgM monoclonal gammopathy has been reported to be effective in approximately half the patients (Comi et al, 2002). In case reports or small uncontrolled series, individual patients with CIDP have also been reported to respond to chemotherapeutic agents such as cyclophosphamide or azathioprine, interferons, or Etanercept (Hughes et al, 2003; Brannagan et al, 2002; Chin et al, 2003c). Corticosteroids are useful for short term therapy, but prolonged use is associated with potentially severe side effects including osteoporosis, fractures, avascular necrosis, coronary artery disease, and stroke, as well as hypertension, obesity, and diabetes (Stein and Hanauer 2000; Zonana-Nacach et al, 2000).

In case reports or small series, patients with neuropathy and IgM monoclonal gammopathy have been reported to respond to IVIg or agents that reduce the IgM concentration, including chlorambucil, fludarabine, or Rituximab (Comi et al, 2002; Wilson et al, 1999; Renaud et al, 2003). Vasculitis is responsive to cyclophosphamide and corticosteroids, or azathioprine (Griffin, 2001; Jayne et al, 2003), Sjogren's neuropathy has been reported to respond to prednisone, IVIg or infliximab (Takahashi et al, 2003; Caroyer et al, 2002), and patients with neuropathy and rheumatological or inflammatory bowl disease, tumor, or hepatitis C, are also treated for the underlying systemic disease.

FUTURE DIRECTIONS

There is a pressing need for: 1) reliable serological tests that would aid in the diagnosis and classification of the various immune mediated neuropathies, 2) Controlled trials to help guide therapy, and 3) laboratory research into the underlying pathogenic mechanisms

Table I: Chronic Immune-Mediated Neuropathies

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Symmetric, with proximal and distal weakness, and large fiber sensory loss
- Multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy
- Sensory CIDP
- Distal Acquired Demyelinating Predominately Sensory (DADS) Neuropathy
  - With or without IgM monoclonal gammopathy or antibodies to MAG, Sulfatide, or GD1b/GQ1b ganglioside

Mutifocal Motor Neuropathy (MMN)
- With or without IgM anti-GM1 or GD1a antibodies

Multifocal axonal sensory and motor neuropathy (MASAM)

Sensory ganglioneuritis or multifocal sensory neuropathy
- With or without Sjogren's syndrome, Ca of the lung, or celiac disease

Vasculitic Neuropathy
- Systemic or non-systemic

Autoimmune Autonomic Neuropathy
- Associated with antibodies to ganglionic nicotinic acetylcholine receptor

REFERENCES

Alaedini , A, Sander HW, Hays AP, Latov N. Anti-ganglioside antibodies in multifocal inflammatory sensory and motor neuropathy. **Arch Neurol 2003**;

Antoine JC, Honnorat J, Camdessanche JP, Magistris M, Absi L, Mosnier JF, Petiot P, Kopp N, Michel D. Paraneoplastic anti-CV2 antibodies react with peripheral nerve and

are associated with a mixed axonal and demyelinating peripheral neuropathy. Ann Neurol 2001; 49: 214-21.

Azulay JP, Blin O, Pouget J, Boucraut J, Billie-Turc F, Carles G, et al. Intravenous gammaglobulin treatment in patients with motor neuron syndromes associated with anti-GM1 antibodies: a double blind, placebo-controlled study. Neurology 1994; 44: 429-32.

Barone RJ, Approach to peripheral neuropathy and neuronopathy. Sem Neurol 1998; 18: 7-18.

Brannagan TH, Pradhan A, Heiman-Patterson T, Winkelman AC, Styler MJ, Topolsky DL, Crilley PA, Schwartzman RJ, Brodsky I, Gladstone DE. High dose cyclophosphamide without stem-cell rescue for refractory CIDP. Neurology 2002; 58: 1856-8.

Caroyer J-M, Manto MU, Steinfeld SD. Severe sensory neuronopathy responsive to infliximab in primary Sjogren's syndrome. Neurology 2002; 59: 1113-1114.

Cavaletti G, Santoro P, Agostoni E, Zincone A, Gori C, Frattola L, Tredici G. Chronic axonal sensory and autonomic polyneuropathy without motor involvement: a new chronic inflammatory neuropathy ? Eur J Neurol 1999; 6: 249-53.

Chin RL, Latov N, Sander WH, Hays AP, Croul S, Magda P, Brannagan TH. Sensory CIDP presenting as cryptogenic sensory polyneuropathy. Neurology 2003a; 60: A314

Chin RL, Sander HW, Brannagan TH, Green PH, Hays AP, Alaedini A, Latov N. Celiac Neuropathy. Neurology 2003b; 60: 1581-5.

Chin RL, Sherman WH, Sander HW, Hays AP, Latov N. Etanercept (Enbrel) therapy for chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2003c; 210: 19-23.

Chroni E, Hall SM, Hughes RA. Chronic relapsing axonal neuropathy: a first case report. Ann Neurol 1995; 37: 112-5.

Collins MP, Periquet MI, Mendell JR, Sahenk Z, Nagaraja HN, Kissel JT. Nonsystemic vasculitic neuropathy: insights from a clinical cohort. Neurology 2003; 61: 623-30.

Comi G, Roveri L, Swan A, Willison H, Bojar M, Illa I, Karageorgiou C, Nobile-Orazio E, van den Bergh P, Swan T, Hughes R, Aubry J, Baumann N, Hadden R, Lunn M, Knapp M, Leger JM, Bouche P, Mazanec R, Meucci N, van der Meche F, Toyka K; Inflammatory Neuropathy Cause and Treatment Group. J Neurol 2002; 249: 1370-7,

Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med 2003; 349: 1443-1545.

Davies L, Spies JM, Pollard JD, McLeod JG. Vasculitis confined to peripheral nerves.

Brain 1996; 119: 1441-8.

De Groot K, Schmidt DK, Arit AC, Gross WL, Reingold-Keller E. Standardized neurologic evaluation of 128 patients with Wegener granulomatosis. Arch Neurol 2001; 58: 1215-21.

Donofrio PD. Immunotherapy of idiopathic inflammatory neuropathies. Muscle Nerve 2003; 28: 273-92.

Dropcho EJ. Remote neurologic manifestations of cancer. Neurol Clin 2002; 20: 85-122.

Dyck PJ, Litchy WJ, Kratz K, Suarez GA, Low PA, Pineda AA, Windebank AJ, Karnes JL, O'brien PC. A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 1994; 36: 838-845.

Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. Ann Neurol 1981; 10: 222-226.

Dyck PJ, Windebank AJ. Diabetic and nondiabetic lumbosacral radiculoplexopathies: new insights into pathophysiology and treatment. Muscle Nerve 2002; 25: 477-91.

Federico P, Zochodne DW, Hahn A, Brown WF, Feasby TE. Multifocal motor neuropathy improved by IVIg; randomized double-blind, placebo controlled study. Neurology 2000; 55: 1256-62.

Font J, Ramos-Casals M, de la Red G, Pou A, Casanova A, Garcia-Carrasco M, Cervera R, Molina JA, Vails J, Bove A, Ingelmo M, Graus F. Pure sensory neuropathy in primary Sjogren's syndrome. Longterm prospective followup and review of the literature. J Rheumatol 2003; 30: 1552-7.

Gondim FdAA, Brannagan TH, Sander HW, Chin RL, Latov N. Peripheral neuropathy in patients with inflammatory bowel disease. Submitted

Gorson KC, Ropper AH. Idiopathic distal small fiber neuropathy. Acta Neurol Scand 1995; 92: 376-80.

Gorson KC, Allam G, Ropper AH. Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy. Neurology 1997; 48: 321-8.

Gorson KC, Ropper AH. Positive salivary gland biopsy, Sjogren syndrome and neuropathy: clinical implications. Muscle Nerve 2003; 28: 553-60.

Griffin JW. Vasculitic neuropathies. Rheum Dis Clin North Am 2001; 27: 751-60.

Griffin JW, Cornblath DR, Alexander E, et al. Ataxic sensory neuropathy and dorsal root

gagnlioneuritis associated with Sjogren's syndrome. Ann Neurol 2000; 27: 304-315.

Hellmann DB, Laing TJ, Petri M, Whiting-O'Keefe Q, Parry GJ. Mononeuritis multiplex: the yield of evaluations for occult rheumatologic diseases. Medicine 1988; 67: 145-153.

Hughes R, Bensa S, Willison HJ, van den Berg P, Comi G, Illa I, Nobile-Orzio E, van Doorn P, Dalakas M, Bojar M, Swan A, and the Inflammatory Neuropathy Cause and Treatment (INCAT) Group. Randomized controlled trial of intravenous immunoglobulin vs oral prednisone in chronic inflammatory demyelinating polyradiculoneuropathy.Ann Neurol 2001;

Hughes RA, Swan AV, van Doorn PA. Cytotoxic drugs and interferons for chronic inflammatory demyelinating polyradiculoneuropathy. Cochrane Database Syst Rev 2003; (1) CD003280.

Jayne D, Rasmussen N, Andrassy K, et al. A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. New Eng J Med 2003; 349: 36-44.

Kelkar P, McDermott WR, Parry GJ. Sensory-predominant, paiful, idiopathic neuropathy; inflammatory changes in sural nerves. Muscle Nerve 2002; 26: 413-6.

Kissel JT, Mendell JR. Vasculitic neuropathy. Neurol Clin 1992; 10: 761-81.

Kissel JT. The treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Semin Neurol 2003; 23: 169-80.

Latov N. Prognosis of neuropathy with monoclonal gammopathy. Muscle Nerve 2000; 23: 150-2.

Low PA, Vernino S, Suarez G. Autonomic dysfunction in peripheral nerve disease. Muscle Nerve 2003; 27: 646-61.

Magda P, Latov N, Brannagan TH, Weimer LH, Chin RL, Sander HW. Comparison of electrodiagnostic abnormalities and criteria in a cohort of patients with CIDP. Arch Neurol 2003, in press.

Mawrin C, Brunn A, Rocken C, Schroder JM. Peripheral neuropathy in systemic lupus erythematosus; pathomorphological features and distribution pattern of matrix metalloproteases. Acta Neuropathol. 2003; 105: 365-72.

Mendell JR, Barohn RJ, Freimer ML, Kissel JT, King RPT, Nagaraja HN, Rice R, Campbell WW, Donofrio PD, Jackson CE, Lewis RA, Shy M, Simpson DM, Parry GJ, Rivner MH, Thornton CA, Bromberg MB, Tandan R, Harati Y, Giuliani MJ, and the working group on peripheral neuropathy. Neurology 2001; 56: 445-449.

Mendel JR, Sahenk Z. Painful sensory neuropathy. N Engl J Med 2003; 348: 143-55.

McLeod JF. Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. Ann Neurol 1999; 46: 910-3.

Mellgren SI, Conn DL, Stevens JC, Dyck PJ. Peripheral neuropathy in primary Sjogren's syndrome. Neurology 1989; 39: 390-4.

Miyamoto K, Miyake S, Schachner M, Yamamura T. Heterozygous null mutation of myelin P0 protein enhances susceptibility to autoimmune neuritis targeting P0 peptide. Eur J Immunol 2003; 33: 656-65.

Mori K, Iijima M, Sugiura M, Koike H, Hattori N, Ito H, Hirayama M, Sobue G. Sjogren's syndrome associated with painful sensory neuropathy without sensory ataxia. JNNP 2003; 74: 1320-1322.

Mygland A, Monstadt P. Chronic polyneuropathies in Vest-Agder, Norway. Eur J Neurol 2001; 8: 157-165.

Nagashima T, Cao B, Takeuchi N, Chuma T, Mano Y, Fujimoto M, Nunomura M, Oshikiri T, Miyazaki K, Dohke M, Kashimura N, Shinohara T, Orba Y, Ishizawa S, Nagashima K. Clinicopathological studies of peripheral neuropathy in Churg-Strauss syndrome. Neuropathology 2002; 22: 299-307.

Nemni R, Corbo M, Fazio R, Quattrini A, Comi G, Canal N. Cryoglobulinemic neuropathy, a clinical, morphological and immunocytochemical study of 8 cases. Brain 1988; 111: 541-52.

Nitta Y, Sobue G. Progressive systemic sclerosis associated with multiple mononeuropathy. Dermatology 1996; 193: 22-6.

Nobile-Orazio E, Cappellari A, Meucci N, Carpo M, Terenhi F, Bersano A, Priori A, Barbieri S, Scarlato G. Multifocal motor neuropathy: clinical and immunological features and response to IVIg in relation to the presence and degree of motor conduction block. J Neurol Neurosurg Psychiat 2002; 72: 761-6.

Puechal X, Said G, Hilliquin P, Coste J, Job-Deslandre C, Lacroix C, Menkes CJ. Peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis. A clinicopathologic and prognostic study of thirty two patients. Arthritis Rheum 1995; 38: 1618-29.

Renaud S, Gregor M, Fuhr P, Lorenz D, Deuschl G, Gratwohl A, Steck AJ. Rituximab in the treatment of polyneuropathy associated with anti-MAG antibodies. Muscle Nerve 2003; 27: 611-5.

Rotta FT, Sussman AT, Bradley WG, Ram Ayyar D, Sharma KR, Shebert RT. The spectrum of chronic inflammatory demyelinating polyneuropathy. J Neurol Sci 2000; 173; 129-139.

Said G, Lacroix C, Lozeron P, Ropert A, Plante V, Adams D. Inflammatory vasculopathy in multifocal diabetic neuropathy. Brain 2003; 126: 376-85.

Saperstein DS, Katz JS, Amato AA, Barohn RJ. Clinical spectrum of chronic acquired demyelinating polyneuropathies. Muscle Nerve 2001; 24: 311-324.

Sharma KR, Cross J, Farronay O, Ayyar DR, Shebert RT, Bradley WG. Demyelinating neuropathy in diabetes mellitus. Arch Neurol 2002a; 59: 758-65.

Sharma KR, Cross J, Ayyar DR, Martinez-Arizala A, Bradley WG. Diabetic demyelinating polyneuropathy responds to intravenous immunoglobulin therapy. Arch Neurol 2002b; 59: 751-7.

Sobue G, Yasuda T, Kachi T, Sakakibara T, Mitsuma T. Chronic progressive sensory ataxic neuropathy: clinicopathological features of idiopathic and Sjogren's syndrome associated cases. J Neurol 1993; 240: 1-7.

Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. Drug Saf 2000; 23: 429-48.

Suarez GA, Giannini C, Bosch EP, Barohn RJ, Wodak J, Ebeling P, Anderson R, McKeever PE, Bromberg MB, Dyck PJ. Neurology 1996; 46: 559-61.

Taylor BV, Wright RA, Harper CM, Dyck PJ. Natural history of 46 patietns with multifocal motor neuropathy with conduction block. Muscle Nerve 2000; 23: 900-8.

The Neuropathy Association. The incidence, characteristics and costs of Medicare beneficiaries with Neuropathy. 2001.

Thomas PK, Ormerod IE. Hereditary neuralgic amyotrophy associated with a relapsing multifocal sensory neuropathy. J Neurol Neurosurg Psychiat 1993; 56: 107-9.

Vallat JM, Tabaraud F, Magy L, Torny F, Bernet-Bernady P, Macian F, Couratier P. Diagnostic value of nerve biopsy for atypical chronic inflammatory demyelinating polyneuropathy: evaluation of eight cases. Muscle Nerve 2003; 27: 478-85.

Van den Berg-Vos RM, Van den Berg LH, Franssen H, Vermeulen M, Witkamp TD, Jansen GH, van Es HW, Kerhoff H, Wokke JH. Multifocal Inflammatory demyelinating neuropathy: a distinct clinical entity? Neurology 2000; 54: 26-32.

Verghese J, Bieri PL, Gellido C, Schaumburg HH, Herskovitz S. Peripheral Neuropathy in young-old and old-old patients. Muscle Nerve 2001; 24: 1476-1481.

Willison HJ. Anti-glycolipid antibodies in the diagnosis of autoimmune neuropathies. Rev Neurol 2002; 158: S15-20.

Wilson HC, Lunn MP, Schey S, Hughes RA. Successful treatment of IgM paraproteinemic neuropathy with fludarabine. J Neurol Neurosurg Psychiat 1999; 66: 575-80.

Zifko UA, Hahn AF. Migrant sensory neuropathy; report of 5 cases and a review of the literature. J Peripher Nerv Syst 1997; 2: 244-9.

Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthr Rheum 2000; 43: 1801-1808.