POEMS syndrome is an unusual multisystem disease. A chronic progressive polineuropathy is a predominant feature and it has been described as a rather stereotyped mixed demyelinating and axonal neuropathy that differs from CIDP for reduced motor nerve conduction velocities more marked in intermediate than distal nerve segments and rarity of conduction block. We describe four patients emphasizing the clinical and the electrophysiological heterogeneity of POEMS-associated neuropathy. Two patients with extraneurologic features (organomegaly, ascites, endocrinopathy) were diagnosed when the clinical and electrophysiological examination disclosed the “characteristic” pattern of POEMS-associated neuropathy. Instead a 52-year-old woman presented with a multifocal sensory and motor demyelinating neuropathy with multiple predominantly proximal partial conduction blocks associated with a IgG lambda paraprotein. IVIG were ineffective. POEMS syndrome was diagnosed several months later by the appearance of scleroderma-like changes, angiofollicular lymph node hyperplasia and a biopsied osteosclerotic bone lesion. A fourth patient was admitted because of an ascending symmetrical demyelinating motor and sensory neuropathy associated with albuminocytologic dissociation and a IgG lambda paraprotein. IVIG, plasma-exchange and corticosteroids were ineffective and the patient became wheelchair dependent over 5 months. An extensive and repeated search for an extraneurologic involvement was negative. Diagnosis was made by means of elevated VEGF serum concentrations (courtesy of Prof Nobile-Orazio). Despite immunosuppressive therapy he died 9 months after the onset of the polyneuropathy. The diagnosis of POEMS syndrome may require a high degree of suspicion because its clinical and electrophysiological picture may be more heterogeneous than generally appreciated.
TREATMENT OF POEMS SYNDROME WITH AUTOLOGOUS STEM CELL TRASPLANTATION. LONG-TERM FOLLOW-UP IN THREE PATIENTS


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POEMS is a rare multisystemic syndrome, characterized by Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin Changes and other features such as ascites, thrombocytosis, edema, papilledema, Castelman disease, Sclerotic bone lesions. Peripheral neuropathy, which represents the main clinical symptom, resembles Chronic Inflammatory Demyelinating Neuropathy but is refractory to standard immunological treatments and runs a severe course. Over the last few years there has been a growing evidence that POEMS responds to autologous stem cell transplantation. Here we describe the long-term follow-up of three patients treated with high dose chemotherapy and autologous peripheral stem cell transplantation. At diagnosis all patients had a rapidly progressive sensory-motor peripheral neuropathy, with severe tetraparesis and inability to walk. All patients had monoclonal component (MC) IgA and 1 had also MC IgG. Bone marrow biopsy documented in all patients mild plasmacytosis (8-10%) Endocrinopathy and melanosis were present in all patients. One patient had splenomegaly, one hepatomegaly and one patient had sclerotic bone lesion.

2 patients had been previously treated with high dose Ig and steroids without any efficacy.

Patients received Cyclophosphamide 1500 mg/m2 on day 1,3 and Methylprednisolone 250 mg from day 1-4 for 2 cycles and G-CSF 5 mcg/kg/die was added after 2 cycle for mobilization. Conditioning regimen was HDMel (Melphalan 100 mg/m2 for 2 consecutive days). The median number of CD34+ cells infused was 4.22 (range 3.08-5.63) x 106/kg. Engraftment was rapid and sustained.

All patients showed a progressive improvement of neurological symptoms. After a follow-up period of 30-42 months all three patients had normal muscle power in the upper limbs and only distal weakness in the lower limbs. Our data confirm that autologous stem cell transplantation is an effective treatment in POEMS syndrome and that improvement is sustained in the long-term follow-up.
RELAPSE OF POEMS SYNDROME AFTER SUCCESSFUL AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION


POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein, Skin changes) is usually associated with osteosclerotic myeloma and related to VEGF (vascular endothelial growth factor) excess. Radiotherapy (for isolated lesions) or high-dose chemotherapy with Auto-Peripheral Blood Stem Cell Transplantation (Auto-PBSCT) often give dramatic improvement. However, long-term outcome after auto-PBSCT is unknown. A 33-year-old woman presented with foot paraesthesias, rapidly progressive limb weakness, sensory loss, disequilibrium. Examination showed moderate distal muscle weakness and wasting, sensory ataxia, distal hypoesthesia, decreased-absent deep tendon reflexes, papilloedema, skin hyperpigmentation. Laboratory tests disclosed hypothyroidism, IgA-lambda monoclonal gammopathy, thrombocytosis, high CSF proteins (192 mg/dL). Electrophysiology was consistent with a severe sensorimotor polyneuropathy. POEMS syndrome was diagnosed. No definite abnormality was found at X-ray survey, spine MRI, bone biopsy. The disease ran a progressive course in spite of high-dose steroids. She was then treated with 3 Vincristine-Adriamicine-Dexamethasone cycles, followed by a cyclophosphamide cycle. PBSCT mobilization was carried out. After high-dose melphalan chemotherapy, auto-PBSCT was performed. She had complete clinical remission. All laboratory abnormalities disappeared, but a subtle and inconstantly present IgA-lambda band at immunofixation (hematological “very good partial response”). Seven years later, she again showed mild peripheral neuropathy, papilloedema, increased platelet count and CSF proteins, and decreased thyroid function. Spine MRI revealed C2 vertebral body osteosclerotic myeloma. VEGF levels, very high at onset, dramatically decreased after auto-PBSCT, but returned high in the relapse phase. She has been treated with local radiotherapy and follow up is ongoing. To date this is the first case of relapse of POEMS syndrome after successful autologous auto-PBSCT.
Clinical association of CIDP and MS has been rarely reported. We describe two patients with a chronic acquired demyelinating motor and sensory polyneuropathy associated with multifocal demyelinating CNS involvement satisfying the McDonald criteria for the diagnosis of MS.

A 34-year-old woman presented with a multifocal demyelinating sensory and motor neuropathy with multiple conduction blocks both in arms and legs. Antiganglioside antibodies were negative. CSF examination revealed a slight protein increase, one cell and an oligoclonal IgG pattern. The patient was treated with IVIg and had a rapid marked improvement. Six months later she had a left facial palsy and, after three months, a left optic neuritis. Eight months later she experienced sensory disturbances affecting both hands and legs and lower limb weakness. Brain and spinal cord MRI showed multiple focal areas of increased signal. Nerve conduction studies revealed a multifocal demyelinating motor and sensory neuropathy without conduction blocks. A 30-year-old woman presented with numbness and weakness in her left arm and leg. MRI disclosed a focal area of increased signal showing enhancement after gadolinium administration at C3 level. Oligoclonal bands were present in CSF. In the next years she experienced three episodes of transient loss of sensation and/or weakness in her left limbs or in both legs. In 2004 MRI showed multiple discrete white matter lesions in brain and spinal cord. Because of generalized tendon areflexia she underwent to EMG-ENG examination that showed a chronic predominantly demyelinating symmetric motor and sensory polyneuropathy with multiple conduction blocks. She started oral prednisone and weekly methotrexate and did not experienced further relapses.

Evidence of clinically manifest concomitant PNS and CNS demyelination has been described in a few patients over the last few years. The pathogenesis of this less frequent than expected association is unknown.
Coincident involvement of peripheral and central myelin has rarely been demonstrated by histopathological and neuroimaging studies in single cases. We observed a 20-year-old woman with clinical and laboratory association between multiple sclerosis (MS) and chronic inflammatory demyelinating polyneuropathy (CIDP). She presented a subacute occurrence of paresthesias at hands, dorsal trunk and lower limbs. Neurological examination showed spastic-ataxic gait, Romberg test positive, finger-to-nose and heel-to-knee testing abnormal especially on the right side. Moderate weakness and diminished superficial sensations and dysesthesias were found at upper and lower limbs, distally. Abdominal reflexes were absent. Tendon reflexes were reduced. Babinski response was positive on both sides. She also presented bilaterally pes cavus. Neurophysiologic exams showed a mixed axonal-demyelinating polyneuropathy, CSF analysis 13 oligoclonal bands, brain and cervical MRI multiple T2-hyperintense lesions with two Gd-enhancing areas and blood examination positive anti-ganglioside GD1a IgM and GM1 IgM titre. Thyroid examination also evidenced the presence of Hashimoto thyroiditis biological markers. The patient was treated with four standard cycles of Immunoglobulin, i.v., with a transient partial recovery of peripheral signs. Afterwards she experienced fatigue and ataxic gait and was treated with steroid, initially i.v. and then orally. After few weeks she experienced a relapse of peripheral and central nervous system disturbances and was treated with periodic plasmapheresis sessions, with an actual stabilization, but not remission, of clinical signs. The rare occurrence of simultaneous MS and CIDP in the same patient can lie on similarities between peripheral myelin P1 protein and central myelin basic protein, this hypothetically leading to a spreading of a cross-reaction between the two epitopes and in turns favoured by an autoimmune susceptibility background of unknown origin, as in the present case.
Multifocal Motor Neuropathy with an Unusual Clinical Feature

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Multifocal motor neuropathy (MMN) is a dysimmune multiple mononeuropathy in which cranial nerve involvement is rarely associated. Previously, partial ophthalmoplegia, VII, IX-X and XII cranial neuropathy were described in MMN patients. We report a 32-years-old man, previously healthy, with left palpebral ptosis followed, after 3 years, by severe inability to the extension of the right wrist against gravity associated with cramps and fasciculations. The neurological examination revealed fluctuating left drooping eyelid, without ophthalmoplegia, areflexia, right wrist drop and weakness of the muscles innervated by ulnar nerve bilaterally. Routine blood examination including cell count, sedimentation rate, glucose, liver, kidney and thyroid function were normal. Serum creatine kinase was slightly elevated; systemic vasculitis was excluded as well as Lyme disease, HCV and cryoglobulinemia, HIV and Herpes virus infections. Anti-AchR and anti-ganglioside antibodies were absent; cerebrospinal fluid proteins and isoelectrofocusing examination were normal. Brain MRI with gadolinium as well as intracranial angio-MRI were normal. Single-fiber electromyography derived by left frontalis muscles was normal. Motor nerve conduction studies showed conduction block (CB) in the right ulnar nerve, slowing of conduction velocity in right radial, median and both ulnar nerves. Sensory nerve conduction studies were normal. Needle EMG showed mild chronic denervation in the upper limbs and normality in the lower limb muscles. The patient started treatment with high dose intravenous immunoglobulins (IVIg) (0.5g/Kg/day for 4 days) with improvement of strength of the right upper limb muscles arms and complete disappearance of the left palpebral ptosis. Neurophysiological examination at follow-ups confirmed an improvement of motor CV of both ulnar nerves. During the following 6 years, the end-of-dose effect of IVIg was revealed by the reappearance of unilateral palpebral ptosis and asymmetrical weakness of the upper limbs that was constantly resolved by periodic infusion of IVIg (40 gr/day each month). In conclusion: weakness of the elevator muscle of the upper lid is probably due to a CB in a branch of III cranial nerve suggesting a widespread involvement than usually thought. The constant clinical response to chronic IVIg in our patient let us to conclude that this unusual presentation could be included in a variant of dysimmune MMN.
CHRONIC INFLAMMATORY MULTINEUROPATHY IN RHEUMATOID ARTHRITIS: VASCULITIC PROCESS OR LEWIS-SUMNER SYNDROME?


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Introduction:
Rheumatoid arthritis (RA) is an autoimmune disorder leading to a chronic inflammation of the joints. It is a systemic disease, often affecting extra-articular tissues including skin, blood vessels, heart, lungs, nerve and muscles. Sometimes RA is complicated by clinical peripheral neuropathy occurring with several mechanisms, mainly vasculitic process.

Case report: we report a 49-year-old man affected by RA, with a history of subacute asymmetric weakness of both peroneal muscles, beginning with his right leg and leading to progressive difficulty in walking. In the first admission to our hospital he presented with steppage gait, diffuse hyporeflexia and hypoesthesia at the dorsal surface of the feet. Blood exam was positive for elevated sedimentation rate and high titer of rheumatoid factor. EMG findings showed an axonal damage of both peroneal nerves; CFS examination revealed a mild raised level of proteins; sural nerve biopsy, detection of serum anti-ganglioside antibodies and spinal MRI tested normal. He improved rapidly after one cycle of intravenous IgG (2g/kg over 5 days). Steroid therapy (prednisone: 1 mg/kg/die) was started and then he was discharged with diagnosis of possible vasculitic multineuropathy. One month later the patient worsened once again presenting bilateral drop foot. The EMG confirmed report of axonal multineuropathy. Patient underwent another cycle of intravenous IgG followed by partial improvement within several days. At this time steroid therapy was increased (prednisone 1.5 mg/kg/die). Two months later he complained of weakness and paresthesia in the right hand, followed by the usual bilateral drop foot. Blood analysis were unremarkable with normalization of sedimentation rate; CFS examination confirmed mild hyperproteinorrhachia. A new EMG finding showed the presence of conduction blocks in both the right Median and Ulnar nerves; F wave responses from peroneal nerves were absent or markedly delayed. The titer of serum anti-GM1 antibody was negative. Another therapeutic attempt with intravenous IgG was made without rapid clear beneficial effects. Steroid therapy was stopped. Two weeks later he improved regaining muscle strength in his right hand.

Conclusion:
Our opinion is that this patient is affected by Lewis-Sumner syndrome (LSS), a dysimmune multifocal demyelinating sensorimotor neuropathy, what is a clinical asymmetrical variant of chronic immune demyelinating polyneuropathy (CIDP). In our case the differential diagnosis with vasculitic neuropathy is very difficult because many clinical and laboratory findings overlap. The presence of conduction blocks, the hyperproteinorrhachia, no efficacy of prednisone and overall, the prompt efficacy of intravenous IgG, generally supported the diagnosis of LSS.
CHURG STRAUSS SYNDROME: CLINICAL PRESENTATION AND FOLLOW UP OF 5 PATIENTS

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We describe 5 patients presenting with a subacute multineuropathy associated with fever and elevation of inflammation blood index. Anamnesis discovered an history of asthma and allergic reactions while blood laboratory data showed a hypereosinophilia. A sural nerve biopsy was made in 4 of them and it showed direct or indirect signs of vasculitis in most cases. This data together made a final diagnosis of Churg Strauss vasculitis possible.

The Churg Strauss syndrome is a rare, small sized necrotizing vasculitis that develops in patients who have usually asthma, fever and hypereosinophilia. PNS involvement occurs in about 80% of patients and it often represents the clinical onset of the disease.

Three of our patients responded to steroid therapy but with relapses and severe side effects. In these cases association with an immunosuppressive therapy was necessary with often a good outcome. Only one patient had a very severe presentation with pericarditis and intestinal infarct with very poor response to immunomodulating therapies.

In conclusions, we observed that a patient presenting with a sever subacute asymmetric neuropathy could have a vasculitic peripheral neuropathy. Among systemic vasculitis, Churg Strauss syndrome is the more frequently associated with peripheral neuropathy. It often requires immunosuppressive therapy but with good long term outcomes in most cases.
POST INFECTIOUS ACUTE ATAXIA AND AUTONOMIC FAILURE WITH ANTIBODIES TO GD1B GANGLIOSIDE

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We report a patient who presented with acute ataxia and autonomic failure. Four weeks after fever and orchitis, a 56 year old man experienced painful paresthesias in both hands and feet and unsteady gait. On admission (day 6) neurological examination showed areflexia, minimal sensory loss in both feet, cerebellar ataxia at finger-nose and heel-shin tests, positive Romberg sign. Eye movements and cranial nerves were intact. Limb strength was unaffected. Normal laboratory results included thyroid function, tumour markers, autoimmunity tests. Screenings for Campylobacter jejuni, Borrelia burgdorferi, Toxoplasma gondii, Cytomegalo and Epstein-Barr viruses were negative. On day 8, serum IgG and IgM antibody activities against gangliosides GM2, GM1, GM1b, GD1a, GalNAc-GD1a, GD1b, GT1a, and GQ1b were investigated by an enzyme-linked immunosorbent assay. The anti-GD1b IgG antibody titer was within 2,000 and 2,500 and antibodies against other gangliosides were negative. CT scan was unremarkable. Spinal fluid (day 8) showed protein level of 106 mg/dl (normal < 45) and 4 lymphocytes/mm3. Nerve conduction study on day 6 and 8 was normal. On day 11, patient developed vomiting, abdominal distension, intestinal pseudobstruction from which he recovered with hydration within day 16. There were no sphincter problems, orthostatic hypotension either other signs of autonomic dysfunction. On day 22 intravenous immunoglobulin therapy (0.4 g/kg/body weight) commenced and continued for five days with benefit. By day 26, patient was able to stand and walk with minimal assistance. On clinical follow up (day 388) patient had mild tremor and areflexia; the anti GD1b antibody titer was 500. Our patient exhibited an acute neurologic disease with monophasic course and benign prognosis which could be considered a Guillain Barre' syndrome variant. Major signs included intestinal pseudobstruction, limb and truncal ataxia without ophthalmoplegia. The ataxia was mainly cerebellar and not due to mild proprioceptive sensory loss. GD1b ganglioside is localized in paranodal myelin of motor and sensory nerves and in primary sensory neurons. Anti-Gd1b antibody may bind such regions Association of post infectious ataxia and autonomic failure need to be clarified to assess role of implicated antibodies.
PRE AND POST-SYNAPTIC NEUROMUSCULAR ENDPLATE INVOLVEMENT IN SENSORY POLYNEUROPATHY WITH ANTI-GQ1b ANTIBODIES

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A 72 year-old man from Cuba had a six-months history of gait ataxia, paresthesias and progressive paraparesis. In Cuba he was treated with low-dose corticosteroid therapy with a slight improvement. He was admitted for sudden worsening of symptomatology with lower limbs and facial weakness, and dyspnea. Electromyography showed inelicitable SAP in the four limbs and diffuse reduced CMAP, mainly in the lower limbs. Repetitive nerve stimulation at 3 Hz showed 20% decrement in CMAP amplitude, but also 80% increment upon 30 Hz stimulation.

The patient was treated with high dose intravenous corticosteroid and prostygmine. On the basis of the electrophysiological and clinical features, serum was assayed for anti-ganglioside antibodies and was positive for IgG antibodies anti-GQ1b. In three weeks improvement in muscular weakness was observed. Electrophysiological tests showed increasing of CMAP values and the repetitive stimulation test was normal, while SAP remained inelicitable in the four limbs.

Our case report suggests electrophysiological features of pre and post-synaptic neuromuscular endplate involvement, referable to the presence of antibodies anti-GQ1b. The EMG features of our patient evidenced a sensory-motor axonal polyneuropathy. The reduction in CMAP amplitude could be expression of presynaptic block of neuromuscular transmission, since such a dramatic improvement is incompatible with recovery from profound axonal neuropathy.
INFLAMMATORY AXONAL SENSORY-MOTOR POLYNEUROPATHY IN PATIENT WITH MULTIPLE MYELOMA TREATED WITH BORTEZOMIB

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Bortezomib is an inhibitor of proteasome and induces apoptosis in proliferating cells. It is recently considered as treatment in Multiple myeloma.

We describe a 70 year old man affected by multiple myeloma who had autologus bone marrow transplantation on February 2000 and in June 2006 he had a relapse so Bortezomib was started. After 2 cycles of Bortezomib therapy he complained of pain sensation in his legs and his hands controlled by gabapentin. Few days later pain appearance, he became unable to walk alone because of decreased muscle strength in both his lower limbs with bilateral foot drop and peripheral ataxia. EMG revealed an acute sensory motor neuropathy. Sural nerve biopsy revealed an active severe axonal neuropathy. CSF showed increased protein concentration (170mg/dl) and no cells. So IgIV (0.4 g/kg/ die per 5 days) were started. He had a very slightly improvement of his neurological signs for 20 days. From the 21th day pt had a rapid deterioration of muscle strength in his legs and in his hands showing a 60/100 points at MRC scale. Two more cycles of high dose of IVIg were done in two months with good response. (MRC 83/100)

We suggest that Bortezomib besides the known toxic sensory neuropathy could induce an inflammatory acute axonal neuropathy responding to immunomodulatory treatment interfering with immune balance between suppressor and autoreactive lymphocytes.
Paraneoplastic neurological syndromes (PNS) are heterogeneous disorders, including peripheral neuropathies, associated with cancer as small-cell lung carcinoma.

A 46-year-old man had rapid severe weight loss and a one-month history of coordination disturbance. The neurological symptoms were characterized by asymmetric motor impairment and ataxic gait. Neurological examination showed marked sensory ataxia with sensory deficit without a stocking-glove distribution and diffuse areflexia. EMG revealed absent SAP at all his four limbs, mildly prolonged distal latencies of MAP (see Table 1).

CSF revealed protein increase (300 mg/dL). Serum and CSF analysis showed the presence of antibody anti-Hu., detected by immunocytochemistry on cerebellar tissue and by dot blot on recombinant paraneoplastic proteins. Lung CT scan showed the presence of a neoplastic lesion; broncoalveolar wash was negative, but mediastinic biopsy revealed SCLC.

The patient was treated with only 3 cycles of chemotherapy standard treatment with cisplatin and etoposide for severe intolerance.

Sensory asymmetrical ataxia at four limbs completely prevented patient’s gait so high dose of IVIg therapy (2 g/kg/cycle) was administered. After 6 cycles of IVIg his ataxia mildly improved. Hu-antibodies are still present after six month follow up, but at one year follow-up the tumour was completely disappeared in absence of any more anti-tumour treatment; neurological disorder was stable and anti-Hu antibody became negative. After six-year follow up the patient was still alive, SCLC was still absent, peripheral neuropathy let him walk outdoor with two supports. We can suppose that PNS in our pt was induced by an immune response able to inhibit tumour growth even if can destroy his nervous system. We think that we should use with caution aggressive immunosuppressive therapies in PNS to avoid restarting of tumour proliferation. In our pt IVIg have controlled PNS without giving a severe immunosuppression so immune system of pt could be able to kill cancer cells.
HUMAN LEUKOCYTE ANTIGEN (HLA) DISTRIBUTION IN NEUROPATHY WITH IGM ANTIBODIES TO MYELIN ASSOCIATED GLYCOPROTEIN (MAG)


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Polyneuropathies associated with IgM antibodies to myelin associated glycoprotein (MAG) are chronic immune mediated disorders. Presence of anti-MAG activity is considered crucial for pathogenesis. Human Leukocyte Antigen (HLA) class I and II genes of major histocompatibility complex (MHC) are involved in predisposition and host susceptibility to several autoimmune diseases. Purpose of study was to assess HLA antigen and allele distribution in polyneuropathy associated with IgM antibodies to myelin associated glycoprotein. We recruited 3,528 healthy Caucasian bone marrow donors (1824 females and 1704 males) with age ranging from 30 to 65 and 17 unrelated Caucasian patients with polyneuropathy with IgM antibodies to MAG. Mean age of patients at entry was 67.6 years (range 53-79): 12 were males (mean age 67, range 53-72), 5 females (mean age 67.6, range 56-73). Mean duration of illness prior to entry was 40 months (range 6-96); total mean duration ranged from 9 to 154 (mean 85.1) All patients had homogeneous progressive pattern and electrophysiologic evidence of demyelinating neuropathy. Patient sera were tested for presence of anti-MAG antibodies; initial titre was considered significant when above 1/6,000. Typing of the HLA class I (A and B loci) antigens was performed by complement-dependent microcytotoxicity assay. HLA DRB1* allele typing was performed by protein chain reaction (PCR) amplification with sequence-specific primers or the PCR products were hybridised with sequence-specific oligonucleotides probes. Distribution of HLA A, B antigens and DRB1* allele was compared between patient and control groups by means of independence tests in bi-dimensional contingency tables. To this end, Pearson's chi-square test, Likelihood ratio test, Fisher's exact test were used. Statistical results showed that HLA A, B antigens and DRB1* allele distribution did not differ significantly between controls and anti-MAG neuropathy patients (HLA-A = chi square 18.8; df 18, p ns; HLA B = chi square 35.52, df 34; p ns; HLA-DRB1* chi square 15.33, df 14, p ns; respectively). Our results suggest that HLA A and B antigen and DRB1* allele distribution is not implicated in susceptibility to polyneuropathy with anti-MAG IgM-M protein. Different immunological mechanisms other than HLA I and II class association might be involved.
ASSESSMENT OF DISABILITY AND QUALITY OF LIFE IN CHILDREN WITH CHARCOT-MARIE-TOOTH DISEASE


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Charcot-Marie-Tooth disease (CMT) is a genetically and clinically heterogeneous disorder causing variable degrees of disability both in adult and children. Methodologies for measurement of impairment, activity limitation and quality of life (QoL) are under investigation in adult CMT patients, while specific measures for assessment of the CMT in paediatric population are completely lacking. The aim of this study is the definition and validity assessment of a protocol for the evaluation of clinical impairment, activity limitation, and QoL in a wide sample of children with different forms of CMT. Our series of patients include a total number of 66 cases, with genetically defined and undefined forms: CMT1A (n = 23), with CMT1B (n = 4), or carrying mutations of GJB1/Cx32 (n = 3), GDAP1 (n = 8), NDRG1 (n = 4), MFN2 (n = 1), and EGR2 (n = 1) genes; twenty-two children have unidentified genetic defect. Patients are examined at the time of diagnosis by a team of specialists, including Child Neurologists, a Child Therapist and, when necessary, a Paediatric Orthopedician. All patients are evaluated with a complete neurological examination including the following scales: MRC, hand-held myometer, CMT Neuropathy Score (CMTNS), overall neuropathy limitations scale (ONLS), Walk -12, 9-Hole-Peg test, SF-36 QoL questionnaire, and videotape. The same evaluation is performed every 6-9 months. Some scales, like the SF-36 questionnaire, appear poorly suitable to test children and therefore could be modified and adapted in some specific items. The results of this study could contribute to the definition of specific evaluation scales for children with CMT. The availability of well-defined, valid, reliable and homogeneous outcome measures is critical for any future pharmacological therapeutic trial, like the Ascorbic Acid trial that is ongoing for adult CMT1A cases.
Charcot-Marie-Tooth disease (CMT) is a genetic neuropathy that causes several degrees of gait and handgrip impairment. Patients' life is a continuous challenge to lead as normal a life as possible. This study is aimed at understanding better their difficulties and at ascertaining if they are psychologically stressed.

Materials: 35 patients (Sex: 14 males 21 females; Age: mean 39.9 years range 16-60; Disease duration: mean 26.3 years range 8-50) able to walk independently (stages 1-5 of Vinci's classification) referred to the Italian CMT Association rehabilitation facility and 35 sex and age-matched controls.

74.3% patients had a job vs 88.6% controls.

Methods: Kellner's Symptom Questionnaire (SQ) Italian validated version with modifications to exclude items that are symptoms of CMT; an interview conducted by a psychologist with the aid of an interview guide prepared by persons with CMT including a physiatrist and a psychologist.

Results: Patients did not differ significantly from controls in any of the four SQ scales (anxiety, depression, somatic symptoms, ostility) both as a whole and divided in groups according to sex, age (16-39 and 40-60) and severity (levels 1-2 and 3-5). Patients' majority complained about the need of paying much attention in several semi-automatic daily living activities such as walking and doing the stairs, had troublesome problems with the hands (fall of objects, impossibility to close a zipper or to bring coins), faced qualitative and quantitative limitations (in walking and manual activities), obligations (parking as close as possible) or moral duties ("must" avoid procreation), pain and negative emotions (at watching their skinny or deformed extremities, wearing orthotics and in some social interactions).

Discussion: the SQ results indicate that patients with CMT are able to cope with the numerous problems caused by the disease without psychological distress: this may be due to the early age of onset and slow progression of the disorder which provided them with time to adapt to their limitations; however it is possible that some of them denied and painted too normal pictures of themselves.
MULTIDICIPLINAR APPROACH TO HEREDITARY NEUROPATHIES OF THE CHARCOT-MARIE-TOOTH (CMT) TYPE: A TWO YEAR EXPERIENCE


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CMT is a genetically heterogeneous group of inherited peripheral neuropathies, sharing common clinical, electrophysiological and neuropathological features. Since November 2004, a dedicated team, including a clinical neurologist, a neurologist with expertise in neurophysiology, a genetic consultant and a specialist in rehabilitation, cooperate to visit patients, plan genetic tests and rehabilitation programs. We compared two consecutive time periods: November 2004-October 2005 (first group: 103 patients) and November 2005-October 2006 (second group: 83 patients). The two groups are comparable for age (mean age: 42 yrs) and gender (1:1). Most patients came from our region, with a slight increase in extra-region origin in the second group (46.3% vs 43.8%). 32.7% of the first group of patients had a previously defined genetic diagnosis, compared to 15.6% in the second group. A new molecular diagnosis (CMT neuropathy or spastic paraparesis) was performed in 15.8% of the first group and in 20.4% of the second group of patients. An undefined neuromuscular disease was diagnosed in 2.8% (first group) and in 7.2% (second group). An acquired neuropathy was diagnosed in 1.8% (first group) and 9.6% (second group). A clinical diagnosis of inherited neuropathy was established in 30.8% (first group) and in 26.5% (second group). 12.1% subjects were defined non-neuropathics, including I grade relatives of CMT patients or persons in which a previously suspected inherited neuropathy was excluded, in first group and 15.6% in the second group.

In conclusion, an integrated approach to inherited neuropathies offers a high diagnostic yield, which is unchanged between the different time periods suggesting that a further improvement may be obtained only by the introduction of new genetic tests. However, the higher percentage of acquired neuropathies may mean that a plateau in the diagnosis of inherited neuropathies will be reached in the future.
DOMINANT INTERMEDIATE CHARCOT-MARIE-TOOTH TYPE C: A NEW HETEROZYGOUS MISSENSE MUTATION


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Charcot-Marie-Tooth (CMT) disease is a clinically heterogeneous hereditary peripheral neuropathy, usually transmitted as a dominant trait, characterized by progressive weakness and atrophy of the distal limb muscles, sensory abnormalities and absent deep-tendon reflexes. CMT disease is divided by electrophysiologists into 2 main groups. CMT1, the demyelinating form of the disease, characterized by motor nerve conduction velocity (MNCV) lower than 38 m/s, and CMT2, the axonal form of the disease, characterized by reduced amplitudes of muscle-evoked potentials (CMAP) and subnormal values of MNCV. In some families with CMT, patients have median motor NCVs with a range of 25-45 m/s and these types of CMT are designed as “intermediate CMT”. Here we identify a novel (absence in 50 controls) heterozygous missense mutation with V133M codon substitution in thyrosyl-t-RNA synthetase gene (YARS). Our patient, a 57-year-old man carrying on a cardiac pacemaker, first came to our attention for increase value of CK (500-600 U/L, normal value: 25-195) and for paresthesias in the feet. Neurological examination showed mild ataxic gait with some difficulties in maintaining walk direction, Romberg test positive with closed eyes and moderate weakness in legs. Tendon reflexes were normal, except for ankle reflexes which were reduced. Babinski response was weakly positive on right. He also presented bilaterally pes cavus. Muscle biopsy of femoral quadriceps evidenced moderate aspects of neurogenic damage, while electrophysiological exams evidenced neurogenic damage with rare fasciculations on right first interosseus and gastrocnemius. Sensory-motor conduction velocity and sensory evoked potential were normal. In our patient it was not possible to analyze other family members as his parents have died and he had not other living relatives.

Our work confirms that intermediate CMT represents a genetically and phenotypically heterogeneous entity. Clinical and genetic analysis of additional families with this form of CMT could better delineate the prevalent phenotype and will help to identify genotype-phenotype correlations in this disease.
Objective: To evaluate the evolution of clinical picture, disability and quality of life in patients with Charcot-Marie-Tooth 1A (CMT1A).

Methods: The Italian CMT study group performed a multicentre multidimensional longitudinal study (2 years) by using validated measurements of clinical picture (British Medical Research [BMRC] scale), disability (Barthel Index - BI, Deambulation Index - DI, and patient-oriented questionnaires) and quality of life (Short Form 36 [SF-36]). Comparison of results at initial and follow-up evaluations was assessed by matched paired test.

Results: Clinical examination findings showed that during 2 years CMT1A patients have a significant reduction of distal muscle strength and increasing of distal sense deficit. Nevertheless no deterioration of quality of life, no increasing of disability and no depression was observed.

Conclusions: In CMT1A the increasing weakness and sense deficits within 2 years may be compensated for an adaptation between expectations and reality or for development of strategies in performing daily activity balancing the higher motor involvement. The resultant of worsening, adaptation and compensation is that quality of life is not deteriorated in within 2 years.
Neuralgic amyotrophy (NA), also known as Parsonage-Turner syndrome, is a rare disease (incidence 2-3/100.00) typically characterized by attacks of severe neuropathic pain and subsequent patchy paresis in the upper extremities. NA can occur as a sporadic disorder but also as autosomal dominant trait with a high penetrance (>90%) known hereditary neuralgic amyotrophy (HNA). Recently a mutation in the SEPT9 gene (chromosome 17q25) was found in several HNA family. HNA clinically differs from the NA for some aspects: early onset second-third decade; more recurrent attacks, more severe paresis with poorer functional outcome. HNA must be distinguished from another hereditary focal neuropathy with liability to pressure palsy (HNPP).

We described a family with HNA, mother daughter and son, with recurrent episodes (mean episodes=2) of neuralgic amiotrophy. Age of onset was 30,6 yrs (min 22, max 35). All patients showed a severe, intense neuropathic pain radiated from shoulder to arm; motor deficits involved the upper and/or middle plexus including long thoracic nerve. Electromyography studies in acute stage showed denervation with reduction of the M-wave amplitude in involved muscles. Nerve conduction velocity was normal without signs of generalized neuropathy. We also excluded HNPP deletion on chromosome 17q11.2 and mutation in PMP22 gene.

HNA is a very rare form of hereditary brachial plexus neuritis. Actually represents a distinct disease respect to HNPP. In our family, as reported by other authors, we observed typical clinical features represented by onset of first attack in the second-third decade, with frequent relapse and mild-poor recover. Linkage study for SEPT9 gene mutations is ongoing.
ULTRASONOGRAPHIC AND ELECTROPHYSIOLOGICAL FINDINGS OF NF1-ASSOCIATED DIFFUSE POLYNEUROPATHY. CASE REPORT


Neurofibromatous neuropathy, an unusual complication of NF1, is a distal polyneuropathy (PN) with diffuse neurofibromatous changes in thickened peripheral nerves (Thomas, 1990). We describe a 19-year-old man affected with genetically confirmed sporadic NF1. Café-au-lait spots, skin fibromas and plexiform neurofibromas, and cerebral hamartomas were reported from childhood. At age ten he was operated for hydrocephalus and, three years later, he underwent surgical excision of bilateral C2 and C3 neurinomas, causing compression of perimedullary spaces and mild asymmetrical tetraparesis. Further multiple cervical and lumbo-sacral intrathecal neurofibromas are stable on MRI follow up. The patient was referred to us for recent worsening of gait. Neurological examination shows prominent right side spastic tetraparesis, stocking bilateral position sense, vibratory and tactile hypoesthesia, neither radicular signs nor sphincter disturbances. EP study shows mild slowing of central motor conduction from right limbs and normal central sensory conduction. Nerve conduction and EMG examination in lower limbs reveals demyelinating sensory-motor PN and signs of axonopathy on the left side. Minor MCV reduction in median and ulnar nerves was also detected. Ultrasonography (US) of median, ulnar, peroneal and sural nerves revealed ubiquitous thickening of nervous trunks with mean cross section area of 80 mm² (maximum 250 mm²). Fascicular structure was replaced by bulky cysts of homogeneous hypoechoic content and defined borders that resulted in a “sausage” aspect. Intriguingly, changes were much milder within anatomical compression sites. Two recent studies on large series of NF1 patients stated the prevalence of PN in 1.3% and 2.6%, respectively (Ferner, 2004; Drouet, 2004). Notably, Drouet found symptomatic PN, electrophysiological features of demyelination, concurrent axonopathy and diffuse multinodular nerve enlargement at MRI in the majority of cases, and high percentage of these developed malignant peripheral nerve sheath tumour, leading authors to conclude that neurofibromatous PN is a risk factor for malignancy in NF1 population. Thus, the NCV study is mandatory to detect a- or pauci-symptomatic PN and the US could be an alternative imaging tool in the recommended strict follow up of these patients.
CHRONIC ATAXIC NEUROPATHY: A CASE REPORT


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Chronic ataxic neuropathy is a rare kind of neuropathy characterized by sensory ataxia and relative preservation of motor power.
CIAN, Sjogren's syndrome, pyridoxine intoxication, cancer, CIDP, Charcot-Marie-Tooth disease are the major circumstances associated with chronic ataxic neuropathy.
We report a case of chronic ataxic neuropathy the chief pathological feature of which is characterized by the presence of onion bulbs.
The patient, a 69 years old woman, has showed unsteady gait very slowly progressive for twenty years with difficulty in walking and climbing stairs.
The family history was negative for neuromuscular disorders.
Neurological examination has revealed slight symmetrical atrophy and weakness of the distal lower limb and intrinsic hand muscles; bilateral pes cavus; deep tendon reflexes absent in both the upper and lower limbs; vibratory sensation markedly decreased in all four limbs; action tremor of the upper limbs; ataxic gait.
On electroneurography the motor conduction velocities were slowed to 10 m/s.
Magnetic resonance imaging of the brain and spinal cord were normal.
A sural nerve biopsy was performed and specimens have showed severe loss of myelinated fibres, hypertrophic changes with onion bulbs, no active demyelination or inflammatory infiltrates.
The analysis of PMP22 and MP0 genes did not show any mutation.
Phytanic acid, VLCFA, arysulfatase A, galactocerebrosidase were normal.
More than one booster infusion of IVIG induced a slight and transient improvement of balance.
The chronic ataxic neuropathy described may be consistent with the diagnosis both of CIDP and CMT phenotype on the basis of the clinical and morphological characteristics.
In such a type of neuropathy this case points out the importance of further and extensive genetic analyses beside PMP22 and MP0 to rule out a genetic cause of CMT disease.
A 51-years-old male was admitted to out ward because of progressive dysphagia, dysarthria, and dysphonia for 1 year. He had already been suffering from slowly progressive bilateral facial tactile and pain sense impairment for 10 years. He had a past history of alcohol abuse, however he had discontinued alcohol intake for several years. His past medical history was otherwise unremarkable. Neurological examination showed symmetrical atrophy of facial and sternocleidomastoid muscles, weakness of facial muscles, neck extensors and sternocleidomastoid, fasciculations of shoulder girdle muscles. The speech was dysarthric and hypophonic. Blink reflex was bilaterally absent. Touch and pinprick sense was severely impaired in the trigeminal nerve territory and moderately in hand fingers. Nerve conduction studies demonstrated reduced amplitude of sensory action potential at upper limbs, while they were normal at lower limbs. Needle EMG demonstrated the presence of fibrillations and fasciculations in the sternocleidomastoid and shoulder girdle muscles, high amplitude PUM and severely reduced recruitment pattern in facial, neck and shoulder muscles.

The following laboratory and radiological investigations were normal or negative: complete hematological screening, serum levels of ANA, ENA, ACE, cryoglobulin, vitamin B12 and TSH, serum immunofixation, HIV and Borrelia serology, Shirmer’s test, brain and spinal MRI, total body FDG-PET, chest CT scan, BAEPs, SEPs, autonomic nervous system evaluation, CSF examination, onconeural antibody assay, sural nerve and abdominal fat biopsy, genetic screening for Kennedy’s disease and Finnish amyloidosis. Treatment with iv Immunoglobulins (0.4 gr/Kg/days for 5 days) and high dose methylpredisolone were uneffective. Due to the severe dysphagia a PEG was positioned, and the patient needed nocturnal ventilation.

The patient has a motor deficit and clinical course suggestive of progressive bulbo-spinal atrophy, however the concurrent sensory impairment (which has anticipated the motor deficits) makes this diagnosis unsuitable. In our opinion this patient is affected with a novel variant of bulbo-spinal atrophy with marked sensory, not length-dependent, impairment without genetic feature of the Kennedy’s disease, or optic atrophy.
PLATELET INFUSIONS CAN BE EFFECTIVE FOR MNGIE RELAPSING NEUROPATHY NOT RESPONDING TO INTRAVENOUS HIGH-DOSE GAMMAGLOBULIN (IVIG)


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Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an autosomal recessive disease characterized by reduction of thymidine phosphorylase (TP) activity and systemic increase of thymidine (dThd) and deoxyuridine (dUrd), causing deoxynucleotide pool imbalances and mitochondrial DNA (mtDNA) instability. The disease is characterized by progressive ophthalmoplegia, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and leukoencephalopathy. DThd/dUrd reduction may be therapeutic for MNGIE and, recently, Lara et al. have reported that platelet infusions (PI) can transiently restore circulating TP activity, reducing plasma dThd/dUrd levels.

We report a case of a 23-years-old female admitted in our department in January 2007 for relapsing neuropathy. In the 2005 she has been successfully treated by plasma exchange for a Guillain-Barrè syndrome (GBS). In December 2006 she referred a rapidly progressive weakness and numbness in the limbs (within ten days she was not able to walk alone). Weakness involved both upper and lower limbs, prevalently distally (MRC grade 2-3/5). Cranial nerve and sensory examinations were normal. General examination revealed a very low weight, abdominal pain and claw-foot. Routine haematological investigations were normal. Coeliac and porphyria diseases were excluded. Electrodiagnostic studies revealed a sensorimotor peripheral polyneuropathy, conduction velocity decrease (19-32 m/s) and axonal damage at lower limbs. Cerebrospinal fluid examination showed only a mild protein increase (0.52 g/L). Diagnosis of possible GBS relapse was made. A course of IVIg (0.4 g/Kg/day for 5 consecutive days) was administered, without stopping clinical worsening (patient was confined to bed 4 days after the end of IVIg). MNGIE was diagnosed by plasma dThd/dUrd increases, and leukocyte TP activity absence. To try to stop neurological progression, three PI at day 0, 3 and 7 (mean of 510 bilion platelets/single PI) were performed, collecting periodically blood samples. Starting from second PI patient progressively improved and four days after the last PI she returned to walk alone. Plasma dThd and dUrd decreased up to 27-39% of baseline value, returning to baseline value ten days after the last PI. Patient clinical improvement is going on at 1 month follow-up and electrodiagnostic studies reveal progressive increase of conduction velocity.
Neurotoxicity is a potentially limiting side effect of some classes of immunosuppressant and immunomodulatory drugs. Subcellular neuronal structures, from molecular motors to mitochondria (1), are the preferential targets of neurotoxic mechanisms, in most cases yet incompletely elucidated. Cyclosporin A (CsA), a calcineurin inhibitor, is strongly effective against allograft rejection. Thalidomide (Th), primarily an antiangiogenic drug in cancer therapy, is also used as immunomodulant agent in immune-mediated disorders. Neuroprotective as well as neurotoxic effects, involving differential anti-apoptotic or pro-apoptotic regulation, have been documented (2,3). We examined bioptic samples of sural nerve from a case of subacute prominently motor CsA-induced neuropathy and two cases of chronic sensory Th-induced neuropathy. Ultrastructural examination showed differentiated patterns of neurotoxicity. CsA induced recurrent mitochondrial changes in axons characterized by swelling of organelles and marked disarray of cristae. Th caused a severe axonal loss, with active axonal degeneration and no regenerative reactions. Apoptotic phenomena were analyzed in snap-frozen material by TUNEL and immunohistochemistry for anti-apoptotic protein bcl-2 and apoptotic effector caspase-3. Apoptosis was detected in both forms. In Th neuropathy, TUNEL-reactive nuclei were more frequent and vascular endothelial cells showed the highest frequency of apoptosis. Mitochondrial permeability pore is presumably the primary target either of neuroprotective and neurotoxic activity of CsA (1). Thus, mitochondrial impairment and subsequent cytochrome c release might trigger intrinsic pathways of apoptosis in CsA-induced neuropathy. Dramatic axonal loss induced by Th might depend on the inhibition of nuclear factor NF-κB, regulator of sensory neuronal trophic response to NGF (4), whereas endothelial apoptosis is probably related to antiangiogenic activity (5). The observed pathological features further support the hypothesized molecular pathways of CsA and Th neurotoxicity.
LITHIUM-INDUCED GENERALIZED PERIPHERAL NERVE HYPEREXCITABILITY: A CASE REPORT

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It has been estimated that 1 out of every 1000-1500 people in Western countries are receiving lithium treatment mainly, but not always, on account of a diagnosis of bipolar disorder. Side effects on the central nervous system range between 35% and 50% with lithium serum levels within therapeutic levels, and include an acute encephalopathy with cognitive impairment, hallucinations, insomnia, tremor and movement disorders, seizures, a cerebellar syndrome, nystagmus and ocular motor defects. Among peripheral nervous system side effects myopathy, axonal neuropathy and a myasthenic syndrome have been reported.

We describe a 73-year-old man, presenting with an acquired generalized peripheral nerve hyperexcitability (APNH) induced by lithium treatment within the therapeutic range. The drug was withdrawn with complete recovery and normalization of EMG parameters.

PNH is characterized by generalized hyperexcitability of motor nerves resulting in continuous and spontaneous muscle fiber activity (fasciculations or miokimias), representing a response to peripheral nerve dysfunction due to several sources such as autoimmune diseases, anterior horn cell degeneration, genetic disorders, intoxications. Drug-induced PNH has been reported only with gold and oxaliplatin. Basic science studies showed that oxaliplatin modulates voltage-gated sodium channels into an inactivate state, mechanism partly shared also by lithium. Therefore, our case description bring further evidence about the interference of cellular sodium kinetics in the pathogenesis of APNH.
A NEW USEFUL TEST TO INCREASE SENSITIVITY AND SPECIFICITY IN THE NEUROPHYSIOLOGICAL DIAGNOSIS OF ULNAR NERVE AT ELBOW (UNE)


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Objective: In ulnar nerve entrapment at elbow (UNE) the goal of electrodiagnosis is to confirm ulnar nerve dysfunction across elbow and to assess the severity of ulnar nerve dysfunction. However, nerve conduction studies are not sensitive in diagnosing UNE. It is well recognised that nerve fibres innervating the first dorsal interosseous muscle are early involved. The aim of this study is to verify if the ratio between conduction velocity (CV) at the segment across the elbow recording from the first dorsal interosseous muscle (FDI-CV) and the conduction velocity at the same segment recording from abductor digiti minimi (ADM-CV) is a useful new neurophysiological parameter in diagnosing UNE. We called this ratio intra-nerve-ratio (IN-RATIO)

Materials and Method: We prospectively evaluated 96 consecutive patients (52 male, 44 female, mean age 53; SD: 15.52) with symptoms suggestive of UNE, 9 patients had bilateral UNE (105 arms). The gold standard for diagnosis was clinical examination (including also provocative test) and history. We measured FDI-CV and ADM-CV in 40 normal subjects (mean age 51; SD: 18.1; 15 male, 25 female) and in 16 patients with cervicobrachialgia (mean age 55; SD: 12.4; 5 male, 11 female). We used the Roc curve to establish the cut off for IN-RATIO.

Results: By using our normal values, the sensitivity when we measure FDI-CV and ADM-CV is 0.39 and specificity is 1. The identified cut off for the IN-RATIO is £ 0.9, using this cut off the increase of sensitivity in subjects with normal FDI-CV and normal ADM-CV is 0.41 and the specificity is 0.93.

Conclusions: Our results suggest the utility of the IN-RATIO in increasing the sensitivity and the specificity of the neurophysiological diagnosis in clinical case of UNE with normal FDI-CV and normal ADM-CV.
IS ULNAR NERVE NEUROPATHY AT THE ELBOW NECESSARILY CAUSED BY AN ENTRAPMENT? USEFULNESS OF MRI

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It has been recently remarked the utility of Magnetic Resonance Imaging (MRI) for the diagnosis of ulnar neuropathy at the elbow (UNE), especially in those patients where neurophysiologic studies are non-localizing. Here we describe nine patients (mean age 40.6 ± 18) referred to our EMG Laboratory for the symptoms of numbness and paresthesias in the 4th and 5th digits of the hand and/or weakness of one or more ulnar-innervated muscles. Nerve conduction studies disclosed changes consistent with UNE in all patients. To assess possible surgical treatment, we performed MRI through the radio-humeral joint using a 1.5 T magnetic resonance imager looking for nerve compression sites. In all patients MRI revealed high signal intensity along ulnar nerve and nerve enlargement not strictly circumscribed to across-elbow region. Nerve compression at the elbow was not identified in any of our patients. A laboratory screening is ongoing trying to diagnose known causes of demyelinating focal neuropathies. Since increased signal intensity and nerve swelling has been reported in demyelinating disorders, we propose these MRI findings may represent focal demyelination signs which are not necessarily related to an entrapment neuropathy.
ULTRASONOGRAPHY IN ULNAR NEUROPATHY AT THE ELBOW (UNE)

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Introduction: Ultrasonography (US) is commonly considered a useful diagnostic tool in carpal tunnel syndrome and many articles concerning this have been published recently. A PubMed search identified only 4 US papers on UNE. None of these papers measured the cross-sectional area (CSA) of the nerve or US findings of bone and ligamentous elbow structures. The aim of this study was to assess CSA of the ulnar nerve and US of anatomical structures of the elbow in a consecutive sample of subjects with UNE. Patients and methods: 47 UNE patients were consecutively enrolled in the EMG service of Siena Public Health Unit 7. The diagnosis was based on clinical findings and reduction of the motor conduction velocity of the ulnar nerve across the elbow. Before US, education, body mass index (BMI), work, manual hobbies, associated pathologies, duration of symptoms, causes of UNE, clinical and electrophysiological severity, neurographic findings of median, ulnar and radial nerves and a new validated self-assessment of UNE symptoms were assessed. 33 patients agreed to undergo US (mean age 50.1±16.7, range 16-78 ys): 18 were idiopathic cases, and 15 had other possible causes. The ultrasonographer was blinded to clinical and electrophysiological severity of UNE. US was performed with a 10-MHz linear-array transducer. CSA of the ulnar nerve was measured at the level of the medial epicondyle to the elbow (CSA-I) and 2 cm proximal to this level (CSA-P); anatomic elbow findings were also assessed. Results: Mean results of CSA-I and –P were 9.59±8.35 and 9.3±5.5 mm². Eight (24.5%) and 15 (45.5%) cases showed anomalous CSA-I and CSA-P values, respectively (+2SD compared to a control group of the same age). Twelve cases showed nerve dislocation, 2 snapping triceps and one both of these complaints, 9 had medial epicondylitis, 9 osteophytosis, 6 had an anconeus epitrochlearis muscle. Discussion: The US parameters used in literature until now were major and minor diameters of the nerve, the area calculated as a simple product of the diameters (without the ellipsoidal formula), the length of the swollen nerve segments and the ratio of the nerve diameter between the proximal end and the tip of the medial epicondyle to the elbow joint level. Our study takes into account CSA values, which were anomalous in less than half of cases of the electrophysiologically confirmed cases of UNE. Therefore CSA measurement has a low sensibility in UNE. We also report the anomalies that are potentially causes of UNE, which have not previously been systematically evaluated in literature. US may detect possible causes of UNE that may clinically be classified as idiopathic forms such as an accessory muscle, nerve dislocation or snapping triceps.
SEVERITY OF CARPAL TUNNEL SYNDROME: RELATION TO SOCIO-ECONOMIC STATUS (SES)

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Socioeconomic status is considered a major social basis for inequalities. Differences in SES are shown to have direct and indirect impacts on health outcome indicators including mortality, morbidity, psychosomatic and somatic illness, as well as self-reported health. The main aim of this study was to investigate the electrophysiological and clinical gravity of carpal tunnel syndrome (CTS) in relation to level of education, used as an indicator of SES. The secondary objective was to analyse the importance of involvement in one's own care as a factor linking SES and severity of CTS. METHODS A medical history form was filled in by the neurophysiologist before undertaking EMG of 371 consecutive patients with idiopathic CTS (273 females, mean age 54.4 SD=15 and 98 males, mean age 57.3 SD=15.6 years) recruited from December 2004 to December 2005 at the EMG service of Local Health District of Siena. The form contained questions about: level of education, profession, duration of symptoms, first doctor consulted, time elapsing between first symptoms and seeing doctor, number of visits to doctor, time elapsing between first visit to doctor and referral for EMG, which doctor referred patient for EMG, waiting time to have EMG, whether patient was informed about the aims of EMG and what it involved, and by whom, any other diagnostic tests prescribed. The patient also answered the Levine self-administered questionnaire on symptom severity. Our hypothesis was that persons with low SES experienced severer STC than persons with high SES due to delayed diagnosis. After all variables had been dichotomised, the probability of reaching a diagnosis of CTS at higher electrophysiological or clinical severity (stages 3-4-5 vs 1-2) or with severer self-reported symptoms was determined in relation to level of education by multivariate logistic regression models, adjusting for age, sex, manual or non-manual occupation and time elapsing between onset of symptoms and first visit to doctor. RESULTS Patients with a low level of education were more likely to have greater electrophysiological severity at diagnosis (OR=2.2, 95%CI 1.1-4.4), whereas level of education was not associated with clinical severity (OR=1.3, 95%CI 0.7-2.3) or severer self-reported symptoms (BQ-syp OR=1.5, 95%CI 0.9-2.7; BQ-Mot OR=1.4 95%CI 0.8-2.4). Irrespective of SES, patients who consulted a specialist took significantly fewer medical visits to solve their problem (OR=0.2, 95%CI 0.1-0.7) than patients who consulted their family doctor. Moreover, there were statistically significant differences in the probability of being given information about what EMG involved (p=0.01) and its aims (p=0.04), as well as in waiting times for EMG (p<0.001), between groups with low and high levels of education. CONCLUSIONS Level of education was determinant in the pattern of CTS diagnosis. The results suggest that a better understanding is needed of how SES factors affect diagnosis and treatment of CTS.
Objective. Patients with carpal tunnel syndrome (CTS) usually complain of pain and paresthesia in the hand or wrist, but pain proximally to the wrist has been frequently reported in this condition. The study is aimed to understand which clinical features are associated with the presence of proximal pain in the upper-limb of CTS patients.

Methods. We recruited 250 patients with clinical and neurophysiological evidence of CTS. After thorough selection to rule out concomitant upper-limb painful conditions, 112 patients (175 hands) were included. Proximal pain was defined as the presence of pain or paresthesia in the upper-limb proximally to the wrist (neck excluded) in concomitance with sensory complaints in the hand. Patients were asked on the presence and severity of proximal sensory complaints and underwent an objective evaluation and a neurographic study. They were also asked on the distribution of sensory complaints in the hand.

Results. Thenar muscle hypasthenia and the neurophysiological measures were significantly less severe and hand paresthesia was significantly greater in patients with proximal pain. The neurographic score and the measures of median nerve damage were inversely correlated with the severity of proximal pain. Proximal pain was related to extra-median spread of symptoms in the hand. None of the objective/neurographic variables was related to severity of sensory complaints restricted to the hand.

Conclusions. Proximal pain may be found in a consistent number of CTS patients. Proximal pain may represent a clinical marker of mild median nerve damage. The presence of proximal complaints might be related to peripheral or central nervous system mechanisms.
ANALYSIS OF THE RECRUITMENT PROPERTY OF THE MOTOR AXONS AS METHOD TO REVEAL SUBCLINICAL CONDUCTION ABNORMALITY IN ENTRAPMENT NEUROPATHIES

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The evidences that motor axons recruitment reveals focal axon conduction slowing are recent and not widely confirmed, however, as a method to estimate axonal recruitment properties, the stimulus–response relationship was recently included among tests to assess patients with CTS. In a recent paper, wrist-to-APB motor axon conduction was studied by analysing parameters (threshold, slope and plateau) of the relationship between intensity of electrical stimulation and size of motor response (input-output relationship: I/O) in CTS patients with selective involvement of sensory conduction to conventional electrodiagnostic techniques. The slope of the I/O curve was significantly lower in CTS than in controls. Then, the axons recruitment study has been able to reveal minimal motor damage, demonstrating an inability of standard median motor electrodiagnostic techniques to detect such abnormality. The I/O relationship analysis, has been also extended to the study of a possible ulnar nerve motor involvement in CTS cases with ulnar motor nerve electrodiagnostic-negative tests. Indeed, a close contiguity exists between carpal tunnel and Guyon canal at the wrist level; therefore, pathological processes causing CTS might also be expected to affect ulnar nerve. Our results revealed that ulnar nerve I/O curve was strikingly abnormal: the slope of the curve was significantly less than in controls and decreased with increasing abnormalities of the median nerve. This suggested that pathological process involving the ulnar nerve was contingent on the severity of median nerve involvement. We propose that the ulnar nerve may be subject to compression in Guyon’s canal as a consequence of high pressure in the carpal tunnel in CTS patients. So far, the I/O curve has been mainly utilized to study the recruitment property of both corticospinal and monosynaptic reflex pathways; our data demonstrate that I/O curves could be also applied for the analysis of the properties of peripheral axons.
**ULNAR NEUROPATHY AT THE ELBOW (UNE) IN DIABETICS**

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Introduction Polyneuropathies, multineuropathies and entrapment syndromes are common peripheral nervous system complications in diabetics. The aims of the this study were: 1) to report the prevalence of diabetes in a consecutive sample of cases with UNE; 2) to compare this prevalence with that of diabetes in a consecutive sample of cases with carpal tunnel syndrome (CTS); 3) to assess differences in clinical and electrophysiological severity between diabetic, idiopathic and post-traumatic UNE. Patients and Methods 21,217 subjects were consecutively admitted to the EMG service of Siena ASL 7 from 1995 to 2006; 434 (mean age 54.7±16.7 years) had UNE (diagnosis based on clinical findings and reduction of ulnar nerve MCV across elbow), of whom 26 had diabetes (6 type I and 20 type II); 6,871 had CTS (diagnosis based on clinical findings and distal delay of median nerve), of whom 452 had diabetes. The differences in age, sex, work, association with CTS, symptom duration, clinical severity (ordinal scale and elbow pain) and electrophysiological severity (ordinal scales and neurographic findings) between idiopathic (224 cases, mean age 54.3±16.8, 137 M, 87 F), post-traumatic (85 cases, mean age 50.4, 59 M, 29 F) and diabetic UNE (26 cases, mean age 66.7±11.6, 16 M, 10 F) were assessed using non parametric tests. Kruskal-Wallis test was used to check for any differences in variables between groups. If a difference was found, further statistical analysis was performed between diabetic and other groups (Mann-Whitney test for continuous variables, and chi square test for ordinal and dichotomous variables). Bonferroni correction of P values was used. Results The overall prevalence of diabetes in UNE was 6% and was not statistically different from that in CTS (6.6%). There were more male diabetics with UNE (61.5%) than with CTS (35.8%). There were differences in age, work, duration of symptoms, association with CTS and many neurographic findings of the ulnar, median and radial nerves between diabetic, idiopathic and post-traumatic UNE. Many of these differences disappeared when UNE diabetics were matched by sex and age with idiopathic (1:2) and post-traumatic (1:1) cases. The only remaining differences were in nerve SAP amplitudes with respect to both groups and in elbow pain with respect to the post-traumatic group. Conclusion The prevalence of diabetes is the same in UNE and CTS (about 6%), but the sex prevalence is opposite, males prevailing in diabetic UNE and females in diabetic CTS, as in the corresponding idiopathic entrapment syndromes. There were no differences in clinical and electrophysiological severity of UNE between diabetic, idiopathic and post-traumatic cases matched by sex and age. Only SAP amplitudes of median, ulnar and radial nerves were reduced in diabetics with respect to the other groups of UNE likely due to asymptomatic polyneuropathy of upper limbs.
PERIPHERAL NERVE INJURIES. A RETROSPECTIVE SURVEY OF 235 CASES


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Objective: we retrospectively evaluated consecutive patients affected by nerve injuries in order to classify them in accidental or iatrogenic traumatic lesions.

Materials and methods: in each patient an extensive clinical and neurophysiological (also ecographic one) evaluation was performed to detect the kind, level, severity of lesion and the outcome.

Results: we evaluated, in a period of 6 years, 235 patients with nerve injuries. Most of nerve lesions were traumatic (169 cases) while the iatrogenic ones were about three times less frequent (66 cases). The former were more common in males (Male/ Female ratio: 2,8) while the latter were equally distributed (Male/ Female ratio: 0,9). Brachial plexus lesions was observed in 25.1% of cases, peroneal mononeuropathy in 24.3%, sciatic mononeuropathy in 16.6%, median mononeuropathy in 6.4%, crural mononeuropathy 4.7%, others nerves (axillary nerve, suprascapular nerve, facial nerve, radial nerve, ulnar nerve, tibial nerve) in 22.9%.

Conclusions: according to the statistical data we observed that the number of traumatic injuries due to road accident of nerve has increased in the last years. Thanks to protective measures nowadays the mortality has reduced but the consequences are relevant in term of disability and social costs. We think that great effort should be done in order to standardize approaches to nerve lesion.
MULTIPLE ARM LIPOMATOSIS AND POSTERIOR INTEROSSEUS NERVE PALSY

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Lipomas are common benign soft tissue tumours which tend to be indolent and risk free. Lipomas of the upper limb rarely spread in the deep soft tissue causing posterior interosseous nerve (PIN) neuropathy. We present two patients with multiple lipomatosis of the arms and PIN paralysis, with a brief review of the cases reported in literature. We emphasize the role of electromyography study as unique methodical capable to reveal an early radial nerve damage, permitting an optimal post-surgical nerve function recovering. This is important especially in the elderly patients, where the occurrence of multiple lipoma lasting from many years, the absence of sensory symptoms and the restrict area of motor deficit, might delay the diagnosis and then the surgical nerve decompression. It is known that the prognosis is significantly influenced by the preoperative nerve damage and duration between symptoms onset and operation. In our cases, a nerve decompression performed three and six months after symptoms onset, allowed a good recovery of nerve function.
BRACHIAL PLEXOPATHY AND RHABDOMYOLYSIS: A COMPRESSIVE, IMMUNOLOGICAL OR TOXIC PATHOGENESIS?

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Introduction: Brachial plexus involvement and rhabdomyolysis was mainly reported as a complication of heroin intoxication. Other causes are much less frequent, one of these being carbon monoxide poisoning.

Patient 1: 31 years old, female, referred to our neurological division for left arm weakness, after having reported a compressive trauma of the left shoulder during unconsciousness state. Neurological examination were consistent with left brachial plexopathy. Laboratory tests showed signs of rhabdomyolysis (CPK 11,598 UI/l) and ruled out any drug consumption. Electrophysiology showed axonal and demyelinating left brachial plexus neuropathy, with only sparing of sovrascapular nerve. CO intoxication was the final diagnosis. Forty days after onset patient showed an initial recover of the deficits.

Patient 2: 46 years old, male, developed acute right arm weakness 12 hours after intravenous heroin self-administration on the left arm. He did not report any trauma. Neurological exam at the admission showed findings consistent with upper trunk plexopathy. Laboratory tests showed signs of rhabdomyolysis (CPK 9280 UI/l). Neurophysiology was inconclusive, being the lesion too acute. No follow-up was possible.

Discussion: During heroin or CO intoxication, rhabdomyolysis is frequently associated with brachial plexus neuropathy. Pathogenesis of this syndrome is discussed. Some authors referred it as a consequence of a compressive trauma, while the finding in some cases of elevated serum acute-phase proteins, immunoglobulin-E and pANCA led to an immunological hypothesis. A direct toxic action of heroin against muscular and nervous structures was supposed for patients without trauma and inflammatory markers increase.

Regarding our patients, for the first one it is possible to suppose a traumatic pathogenesis, while for the second one toxic hypothesis seems more likely. Consequently, it would seem that different mechanisms play a pathogenetic role from case to case.

However, the close association between rhabdomyolysis and plexopathy, being other peripheral nervous lesions much less frequent, makes it possible to suppose a common pathogenesis, characterized from a toxic action direct against muscular and plexus targets.
Peripheral neuropathy (PN) is a rare complication of Chronic lymphocytic leukaemia (CLL), with isolated cases reported. CLL is the most common human leukaemia but infrequently causes neurologic manifestations. Here we report a 70-year-old man with a two years history of intense pain sensation associated with a progressive, first asymmetrical, sensory motor neuropathy involving the lower limbs. In the clinical records a 16 years history of CLL (stage 0), without organ involvement was reported. Neurological examination revealed a bilateral foot drop, absence of ankle jerks and lower limbs sensory loss. Nerve conduction studies showed axonal sensorimotor neuropathy with an asymmetrical reduction of deep peroneal nerve CMAP. Suspecting vasculitic neuropathy, a sural nerve biopsy was performed. Morphological analysis showed signs of acute axonal degeneration and clusters of myelinated fibers. Some fascicles had greater myelinated fiber loss than others, suggesting ischemic damage to the nerve. Diffuse and perivascular pleomorphic mononuclear cell infiltrate involving the endoneurium, perineurium and epineurium was observed. In the endoneurium, many infiltrating cells were scattered in the interstitial and with perivascular inflammation. Interestingly, direct immunocytochemical studies showed almost all of the mononuclear cells to be CD20 positive, thus suggesting an atypical monoclonal large B-cell population. Routine blood examination disclosed an increase of white blood cells count with lymphocytosis and a previously unknown IgG lambda monoclonal gammopathy. This case indicates that lymphoid infiltration of peripheral nerve should be considered as a possible pathogenetic mechanism of PN in patients with CLL; thus in such patients the presentation of an asymmetric polyneuropathy should raise a strong suspicion of tumor infiltration of nerve and lead to nerve biopsy performance for a correct diagnosis and subsequent therapy.
RESTLESS LEGS SYNDROME IN PAINFUL NEUROPATHY IS RELATED TO NOCICEPTIVE DEAFFERENTATION

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Background. Restless legs syndrome (RLS) is a known manifestation of polyneuropathy, often in association with small fiber involvement, and it has been suggested that it may represent a peculiar form of neuropathic pain.

Methods. To investigate the relationship between pain and RLS, we evaluated retrospectively for the occurrence of RLS a series of 102 consecutive patients (43 men, 59 women) with polyneuropathy, and neuropathic pain or dysesthesia as main symptom, using the criteria of the International Restless Legs Syndrome Study Group.

The patients were classified on the basis of presumed pathogenic mechanisms of pain in the “hyperphenomena” subgroup (characterised by allodynia) and in the “hypophenomena” subgroup (identified on the basis of pinprick hypoalgesia).

Results. RLS was present in 41/102 patients (40.2%). It occurred more often in the “hypophenomena” subgroup (23/37), with respect to the “hyperphenomena” subgroup (9/31; p = .008) and the not classifiable cases (9/34; p = .004).

Conclusions. RLS is frequent in painful polyneuropathy, and it is significantly associated with decreased small fiber input. Thus nociceptive deafferentation may be a factor contributing to overactivity of the spinal structures implicated in RLS.
DIABETIC-CRYOGLOBULINEMIC “DOUBLE-WHAMMY” NEUROPATHY. A RETROSPECTIVE STUDY OF 16 CASES.

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It is well known that a single disease affects the peripheral nervous system through multiple pathogenic mechanisms targeting the same structures with a “layering” of different pathologies. It is also obvious that, especially for polyneuropathy in old age, several potential causes of peripheral nervous system may coexist as comorbidity in the same subject, confounding the clinical picture and the diagnostic work-up.

In our experience, diabetes and mixed cryoglobulinemia represent an example of comorbid neuropathy, either as a casual association of relatively frequent diseases, or due to the common possibility for both diseases to be triggered by HCV infection.

Methods. We report the features of neuropathy associated with coexisting diabetes mellitus and mixed cryoglobulinemia (DM-MC), identified in a retrospective survey of neuropathy outpatients at the Department of Neurosciences of Parma.

Results. We identified 16 patients (12 females, 4 males), aged 51-85 years (mean 70.5, SD 7.9) with DM-MC-associated neuropathy. Neuropathy was purely or mainly sensory in most patients (13/16), and sensorimotor or mainly motor in 3. Patients with sensory neuropathy included 5 cases of small fiber sensory neuropathy (SFSN), 4 with small and large fiber neuropathy, 4 with large fiber neuropathy characterized by ataxia (3 cases) or numbness. In 2 patients an additional mononeuropathy was superimposed.

We compared the features of this series with those of a group of 71 patients (59 women, 12 men) with “pure” cryoglobulinemic neuropathy, and with 74 patients (23 women, 51 men) with “pure” diabetic neuropathy. The distribution of neuropathy patterns was similar in the different groups. Pain as main symptom was more frequent in the DM-MC group (8/16) than in cryoglobulinemic neuropathy (21/71; p=.146) and in diabetic neuropathy (17/74; p=.061). Patients with Rankin score >2 were slightly more represented in the DM-MC group (5/16) than in cryoglobulinemic neuropathy (11/71; p=.161) and in diabetic neuropathy (9/74; p=.120).

Conclusions. “Double” neuropathy due to diabetes plus cryoglobulinemia causes a greater impact on pain symptoms and disability than the single diseases occurring separately. Further investigations should evaluate the long-term prognosis of this entity of comorbid neuropathy.
NEUROPATIE METABOLICHE: ASPETTI CLINICI E PATOGENETICI

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Verranno discussi gli aspetti clinici e patogenetici delle neuropatie periferiche secondarie a disordini del metabolismo, con particolare riguardo alle forme legate ad un disturbo delle funzioni lisosomiali (Leucodistrofia metacromatica, malattia di Krabbe, malattia di Wolmann, malattia di Fabry, malattia di Tangier, etc), mitochondriali (deficit degli enzimi della catena respiratoria, etc), perossisomiali (adrenoleucodistrofia ed adrenomielioneuropatia, malattia di Refsum, etc), della riparazione del DNA (atassia teleangiectasia, etc), del metabolismo dei lipidi (S. Bassen Kornzweig, xantomatosi cerebrotendinea, etc), dell'assorbimento di nutrienti (celiacia, deficit di Vitamina E, etc), illustrando i diversi fenotipi clinici, l'approccio diagnostico biochimico-molecolare, i reperti morfologici della biopsia nervosa. Per le malattie in cui è possibile una terapia, verranno illustrate le varie strategie terapeutiche. Verranno infine effettuate considerazioni su modelli sperimentali animali e verranno individuate le prospettive future.
Sensory conduction velocity evoked by tactile stimulation to the tip of a digit and recorded via near nerve electrodes is a reliable and sensitive conduction test of the most distal nerve part. However, near nerve recordings are not tolerated very well by most patients, and therefore, the aim of the study was to find a non-invasive, sensitive technique able to detect early alteration of sensory conduction velocity.

Nerve conduction studies of the median and ulnar nerves, recorded at the wrist and evoked by tactile stimulation of digits III and V, were performed in 31 diabetic patients. Furthermore the median, ulnar, peroneal and sural nerves were studied using conventional conduction techniques. All patients (mean age 45.7 years) were diagnosed within one year, clinically asymptomatic, with normal neurological and autonomic evaluations. Results were compared with those of a group of 72 controls (mean age 43.1 years).

Sensory conduction study was pathologic in 57% of the patients using electrical stimulation, and in 75% of the patients using tactile stimulation.

Surface recording from the median and ulnar nerve of responses to tactile stimulation at the tip of Digits III and V is a non-invasive, well tolerated technique that increases the diagnostic yield in diabetic patients with distal neuropathy.
Introduction: neurophysiological techniques contribute both to diagnostic definition and quantitative assessment of the different forms of peripheral neuropathy, but standard motor and sensory conduction studies do not provide information on small nerve fibers pathophysiology. Cutaneous silent period consists of the momentary suppression of voluntary muscle contraction activity after a supramaximal electrical stimulus applied to a cutaneous nerve. It represents a nociceptive reflex mediated via Adelta afferent fibers. This method has been used previously for the assessment of small sensory fiber function and their central connections in several neurological disturbances.

Objective: to evaluate the use of cutaneous silent period as a valid technique to identify small fibers length-dependent sensory neuropathies in asymptomatic patients when usual neurophysiological approaches are not yet abnormal. We correlated cutaneous silent period latency and duration to small intra-epidermal nerve fibers density, which in several studies has been demonstrated to be a valid marker for the diagnosis of small fiber neuropathies, and to correlate to thermal threshold and to disease progression.

Materials and methods: in 8 patients referring to our neurophysiology lab with sensory neuropathic symptoms and normal sensory and motor conduction studies we performed: cutaneous silent period with supramaximal stimulation of sural nerve and registration of the contraction activity from soleus muscle and intra-epidermal nerve fibers density with immunohistochemistry for protein gene product 9.5 in dermo-epidermal junction of specimens obtained from distal lateral leg punch skin biopsy.

Results: we found a correlation between cutaneous silent period parameters and intra-epidermal nerve fibers density and their abnormality represents a predictor for neuropathy development. Cutaneous silent period can be considered an effective neurophysiological tool for the diagnosis of small fibers neuropathies.
Different pain phenomena and clinical pictures characterize painful neuropathies. The relationship between clinical and electrophysiological features of neuropathy, including presence of spontaneous and/or evoked pain, intensity and quality of pain, involvement of small and/or large fibers, and intraepidermal nerve fiber (IENF) density, is unclear. Aim of this study was to compare etiology and clinical features of painful neuropathy with skin innervation pattern in a large group of patients.

A total of 450 consecutive patients who underwent skin biopsy from 2004 to 2006 were reviewed. Patients who met the following criteria were included: 1) presence of pain and/or symptoms suggestive of neuropathy and 2) availability of medical records. Severity of pain (measured with the Visual Analogic Scale) and pain characteristics (spontaneous, stimulus-evoked, and different qualities), neurological examination, nerve conduction studies, IENF density at proximal thigh and distal leg, and response to pain therapy were analyzed. Neuropathy was diagnosed if at least 2 changes among clinical, electrophysiological, and neuropathological were present. We examined 104 subjects (47 males, 57 females, age range 27-84 years, mean 61±13.7). Pain severity was >4 in 84 patients and <4 in 20 patients. Neuropathy was associated with diabetes (16%), impaired glucose tolerance (4%), Sjögren syndrome (4%), MGUS associated neuropathy (4%), HCV (4%), anti-MAG (2%), sensory GBS (2%), and other conditions (4%). In 47% of patients etiology was undetermined. Patients were classified as affected by pure small fiber neuropathy (48%), large fiber neuropathy (16%), small and large fiber neuropathy (16%), sensory neuronopathy (3%), sensory demyelinating neuropathy (2%), mononeuropathy (2%), and multiplex mononeuritis (1%). In 10 patients (9.6%) complaining of pain in the lower limbs with atypical distribution, no abnormality was found and neuropathy was not diagnosed. A trend toward direct correlation between intensity of spontaneous pain and IENF density was found. There was no correlation between stimulus-evoked pain and IENF density.
MORPHOMETRY OF CUTANEOUS MYELINATED FIBERS IN IDIOPATHIC SMALL FIBER SENSORY NEUROPATHY


Immunohistochemical study of skin samples has been widely used to study unmyelinated cutaneous fibers. Skin biopsy has been used to study also dermal myelinated endings and normal morphometry of cutaneous myelinated terminations has been described. Recently an involvement of cutaneous myelinated terminations in patients affected by small fiber neuropathy has been suggested based on the observation of morphological anomalies and a reduction of density of papillary myelinated endings and mechanoreceptors.

We studied cutaneous myelinated endings in 15 patients with a diagnosis of idiopathic small fiber sensory neuropathy, to evaluate possible distal morphometric anomalies of myelinated terminations in a condition supposedly involving only unmyelinated fibers. All patients complained of sensory symptoms as burning pain, tingling or numbness. Neurological and electrophysiological examination were normal in all of them. Patients were compared with a group of 30 healthy age matched subjects. Skin samples were taken from glabrous (third fingertip) and hairy (thigh and leg) skin using 3 mm disposable punches. Myelinated fibers were visualized using primary antibodies to myelin basic protein and to pan neuronal marker PGP 9.5. Fiber diameter, internodal length and nodal gap length were measured using dedicated software on digital confocal images.

In glabrous skin, we observed a significant increase of nodal gap length (4.8 ± 1.5 mm) and fiber diameter (4.1 ± 0.6 mm) in dermal myelinated terminations from neuropathic patients compared to controls (3.3 ± 0.6 and 3.4 ± 0.6 mm respectively). No significant difference in mean internodal length was observed between patients (78.3 ± 18.8 mm) and controls (83.0 ± 22.5 mm). In hairy skin no significant difference in internodal length and nodal gap length were observed, while mean fiber diameter was significantly reduced in neuropathic patients (2.6 ± 0.2 and 2.7 ± 0.2 mm at thigh and leg respectively) compared to controls (2.9 ± 0.4 and 3.1 ± 0.3 mm at thigh and leg respectively).

Morphometric abnormalities are present in distal cutaneous terminations of large myelinated fibers in patients affected by idiopathic small fiber sensory neuropathy. Such anomalies show different patterns in glabrous and hairy skin that immunohistochemical study of cutaneous innervation can reveal.
MOTOR NERVE BIOPSY IN THE DIAGNOSIS OF LOWER MOTOR NEURON SYNDROME

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Morphometric studies on motor nerve biopsy have been reported to help distinguishing motor neuropathy (MN) from motor neuron disease (MND) (Corbo et al. 1997). No systematic study on the application of this procedure has been however performed since the original report. We performed motor nerve biopsy in 12 patients with symptoms and signs of lower motor neuron impairment with no definite sign of upper motor neuron or sensory impairment whose origin (MN versus MND) remained uncertain after extensive neurophysiological, neuroimmunological and neuroradiological studies. Biopsy of the motor branch from the anterior division of the obturator nerve to the gracilis muscle was performed under local anaesthesia after written informed consent of the patient. Nerve specimens were examined by routine pathological studies while light microscopy morphometric analysis was performed in a double-blinded fashion using a computer-assisted Image Analyzer (Image measure, Phoenix Technology Inc., Seattle, WA). Results were correlated with clinical and electrophysiological findings and with the follow-up of the patients. No consistent difference were observed among patients in the density of myelinated fibers, g-ratio and number of large myelinated fibers while there was a marked variability in the density of regenerative clusters of small myelinated fibers. In five patients the density was >100/mm^3, in four was 7-53/mm^3 and in two patients there was no cluster of regeneration. Patients with high number of regenerative clusters either had a slow progression or long duration of symptoms and none developed signs of upper motor neuron impairment. Both patients with no regenerative cluster developed respiratory involvement or other signs of motor neuron disease in the months following nerve biopsy. In patients with an intermediate density of clusters the diagnosis at follow-up was quite variable. In this preliminary study on a small series of patients with a no better classifiable lower motor neuron syndrome at presentation, motor nerve biopsy permitted to predict the final diagnosis in seven of the twelve patients examined (58%) indicating that this method may be useful in the assessment of patients with lower motor neuron impairment of uncertain origin.
SENSORY AND AUTONOMIC CUTANEOUS INVOLVEMENT IN PARKINSON DISEASE


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Autonomic symptoms and sensory disturbances have been described in patients with Parkinson disease (PD). Several observations point to a postganglionic degeneration of sympathetic fibers as the cause of the autonomic impairment while sensory disturbances are attributed to a defect in sensory-central integration. However, an extensive study of cutaneous innervation to assess the peripheral involvement of sensory and autonomic nerve fibers is lacking. We studied sensory (unmyelinated and myelinated) and sympathetic (cholinergic and noradrenergic) nerve fibers in the skin of patients with PD.

Sixteen patients (mean age 62.8±7.9) with idiopathic PD and 30 age and sex matched controls were enrolled. PD was diagnosed according to UKPDSBB criteria and classified according to the Hoehn and Yahr stage. Functional impairment was assessed by means of UPDRS. We excluded patients with coincidental conditions potentially affecting the peripheral nervous system. All subjects underwent sensory and autonomic assessment by means of nerve conduction, quantitative sensory testing, silastic imprint test, sympathetic skin response (SSR), and 3-mm punch skin biopsies (fingertip, thigh and calf). Skin biopsies were processed with indirect immunofluorescence techniques applied to thick sections. Digital images were acquired using a non-laser confocal microscope (CARV). Density of Meissner’s corpuscles, intrapapillary myelinated endings and epidermal nerve fibers (ENFs) was calculated following previously described procedures. A semi-quantitative evaluation of sudomotor, pilomotor and vasomotor innervation was performed.

Nerve conduction was normal in all PD patients while SSR was abnormal in 3. An increase of sensory thresholds and mechanical pain perception, and a marked reduction of sweat drop density was detected in our patients. In the skin we found a significant (p<0.01) loss of ENFs and Meissner's corpuscles, and a reduction of autonomic innervation involving both noradrenergic and cholinergic populations. We also observed morphological abnormalities of nerve fibers suggesting the coexistence of both degenerative and regenerative processes.

Our findings demonstrate a cutaneous denervation in PD. This pathological process could have a role in the development of sensory and autonomic disturbances.