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PHENOTYPICAL AND GENOTYPICAL HETEROGENEITY OF CHARCOT-MARIE-TOOTH DISEASE TYPE 2A ASSOCIATED WITH THE MITOFUSIN 2 GENE (MFN2)

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The mitofusin 2 gene (MFN2) encodes a GTPase protein localized in the mitochondrial outer membrane that regulates the fusion, architecture, and metabolism of mitochondria. A recent report indicated that the MFN2-related Charcot-Marie-Tooth disease (CMT) type 2A accounts for approximately 20% of all cases with CMT2 (Lawson *et al.*, 2005), often manifesting features of multisystem involvement such as pyramidal signs (Zhu *et al.*, 2005) or optic atrophy (Zuchner *et al.*, 2006). We investigated the role of MFN2 in 80 index cases with clinical and electrophysiological criteria of CMT2 without mutations of the myelin protein zero (P0), connexin 32 (C $\times$ 32) and neurofilament light-chain subunit (NEFL); 22 cases had dominant inheritance while the remaining were sporadic without laboratory evidences of acquired neuropathy. Exons 3–19 encoding the full-length protein were scanned by denaturing high performance liquid chromatography (DHPLC) with related exon-intron boundaries; positive amplicons were dissected by nucleotide sequencing. We identified 3 heterozygous mutations in the GTP-ase domain in three cases out 80 (3.75%). A novel Arg259Cys substitution (c.775C $>$ T) in a three-generation pedigree was associated with a mild-to-moderate syndrome and onset in the second decade of life. A novel Val273Leu (c.817G $>$ T) substitution caused a severe disease in a sporadic patient with early infantile onset and a clinical and neurophysiological selective involvement of the lower limbs. An Arg280His (c.838G $>$ A) substitution led to a severe syndrome of both the lower and upper limbs in a sporadic patient with late-infantile onset. Retrospective examinations ruled out pyramidal signs and optic neuropathy. In the index cases sural nerve biopsies disclosed loss of large myelinated fibers, clusters of regenerating fibers with simple onion bulbs and uniformly shortened internodes on teased fibers. The report emphasizes the genetic heterogeneity of CMT2 and the phenotypical variability of CMT2A.

ELECTROPHYSIOLOGICAL PARAMETERS ASSOCIATED WITH RESPONSE TO IVIG IN MULTIFOCAL MOTOR NEUROPATHY

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Multifocal motor neuropathy (MMN) is a relatively rare disorder characterized by focal conduction blocks along motor fibres leading to weakness in the territory of individual nerves. Although its pathogenesis is not clear, MMN is thought to arise from dysimmune mechanisms and responds to treatment with intravenous immunoglobulin (IVIg). The objective of this study was to evaluate the effect of the first administration of high dose IVIg on electrophysiological parameters in MMN. We tested 18 clinically affected nerves from 9 subjects with newly diagnosed MMN before and 7–20 days after the first administration of IVIg (2 g/kg). Only nerves with clinical improvement (at least 1 point in the Medical Council Research scale) were included in the analysis. Distal and proximal CMAP amplitude, conduction velocity (CV), distal latency (DL), and conduction block (CB) were evaluated. CB was considered only in distal tract (i.e., elbow-wrist). At baseline, 10 nerves had abnormal distal and 13 proximal CMAP amplitudes. No significant change in their amplitude was detected after IVIg administration. Seven nerves had CV below lower normal limits at baseline examination including five with definite and two with possible CB. CV increased in six nerves after IVIg (mean 129.4% $\pm$ 13.5; range 84–190%) and slightly decreased in one nerve with a greater than 90% CB at baseline. CB remained unchanged despite clinical improvement in five nerves, improved by at least 20% in two nerves and slightly worsened (8%) in one. No correlation between CV and CB changes was detected. Only 3 of 17 nerves had abnormal DL at baseline and none improved after therapy. Improvement after IVIg therapy has been inconsistently associated with reduction of CB also because the correlation between clinical and electrophysiological improvement in individual nerves has been seldom analysed. In this study only CV, which is a marker of fast conducting fibres, but not CB, consistently improved in parallel with clinical improvement after IVIg. These findings suggests that the improvement of CV or, as recently reported, temporal dispersion may indicate an improved nerve conduction which may explain response to IVIg treatment despite the persistence of CB.

PROGRESSIVE MOTOR NEURON DISEASE IN TWO PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV-1) INFECTION: A CAUSAL RELATIONSHIP?

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Segmental forms of motor neuron diseases such as brachial amyotrophic diplegia (BAD) result in weakness and atrophy of upper extremities usually in absence of bulbar, lower limb involvement, pyramidal signs, sphincter dysfunctions, and sensory loss. We describe two HIV-1-seropositive patients affected by a motor neuron disorder which could be defined as BAD (case 1) whereas in case 2 bulbar muscles were also involved. A 50-year-old man noticed progressive symmetric weakness and wasting of shoulders and arms. On examination, the patient exhibited peculiar posture of both hands hanging loosely at his sides with visible fasciculations. Reflexes were absent in the upper extremities and normal in the lower. Case 2 presented with diplopia, dysarthria, dysphagia, similar symmetric weakness and atrophy. Neurological examination showed an additional paresis of the 6th, right 7th, 9th, and right 12th cranial nerves with tongue atrophy. In both cases routine blood tests and search for anti-GM1 antibodies were negative. In Case 1 creatine kinase was elevated (361 mU/ml, n.v. below 195); test for HIV-1 was positive with RNA level of 144.920 copies/ml and CD4 count 403/mm^3. In Case 2 the test for HIV-1 was positive with RNA level of 25.357 copies/ml and CD4 count 90/mm^3. HIV viral load was 58.093 copies/ml. CSF showed increased protein content (181 mg/dl) and 15 polymorphonuclear cells/mm^3. Electrophysiology showed in case 1 low amplitude of action potentials and reduced motor velocity without conduction block. Motor velocity of case 2 was normal. On EMG there were acute and chronic neurogenic changes in the upper and lower limbs of both. Patient disability remained stable over two years under retroviral therapy. Although there is no proof of a definite relationship between HIV infection and motor neuron disorders, it is necessary to outline such an occurrence. The disorder may represent one end of the spectrum of motor neuron diseases occurring in association with HIV-1 infection.

CLINICAL AND MOLECULAR CHARACTERIZATION OF PATIENTS WITH CHARCOT-MARIE-TOOTH NEUROPATHIES

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Charcot-Marie-Tooth disease (CMT) is the most common inherited disorder of the peripheral nervous system characterized by progressive muscular atrophy and weakness affecting distal extremities. At least 22 genes have been isolated thus far responsible for autosomal dominant, recessive, and X-linked CMTs. The expression pattern of these genes does not correlate in most cases with the associated demyelinating or axonal phenotype. To further investigate the association between CMT mutations and their clinical and pathological manifestations and to identify new mutations, we designed a flow-chart for genetic analysis based on clinical, neurophysiological, neuropathological and family history data. Forty-two unrelated patients affected by demyelinating (40%), axonal (43%) or intermediate (17%) forms of CMT have been enrolled for molecular screening of ten genes (PMP22, MPZ, GJB1, EGR2, LMNA, MFN2, GDAP1, NFL, MTMR2 and MTMR13). Both sporadic (60%) and familial (40%) cases have been included. Overall, we identified mutations in 36% of the enrolled patients, which rises to 71% for cases with positive family history. If we consider the different CMT phenotypes, we could detect a genetic alteration in 80% of familial demyelinating forms, 40% of axonal and 14% of intermediate. Among them, we identified three previously unreported mutations: one in the MFN2 gene (Ala738Val), one in the MPZ gene (Asp224Tyr) and a third in homozygosity in the GDAP1 gene (Leu239Phe). The evaluation of new methods (i.e., multiple ligation probe assay and real time PCR) is currently underway to improve the detection of PMP22 rearrangements in demyelinating cases. Our data suggest that the integration between clinical, histopathological, and genetic data might allow the identification of a consistent number of mutations, even in sporadic patients, and the correlation with patient phenotype. Moreover, the availability of a well-characterized cohort of patients will allow the development of research projects aimed at the identification of new genes associated with CMTs and the evaluation of innovative therapies.

AN UNUSUAL ASSOCIATION OF MULTIPLE SCLEROSIS WITH ANTI-MAG POLYNEUROPATHY: RESPONSE TO RITUXIMAB TREATMENT

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A 59-year-old male patient with an 18-year history of relapsing-remitting multiple sclerosis (MS) came to our observation for an unusually quick progression of his paraparesis. The neurological examination confirmed the presence of a spastic paraparesis, along with distal decreased vibratory sensation and absence of tendon reflexes at four limbs, previously not reported. Nerve conduction studies showed a demyelinating motor and sensory polyneuropathy with extremely prolonged distal latencies. A monoclonal Ig M/K protein was detected by serum and antibodies to myelin-associated-glycoprotein (MAG) were found in the serum and cerebrospinal fluid (CSF). After treatment with Rituximab, a chimeric monoclonal antibody anti-CD20, circulating B-cells in peripheral blood were undetectable and the dosage of anti-MAG antibodies showed a reduction in the serum and CSF. At days 3 and 20 after the last infusion of

Rituximab, the patient presented two relapses of multiple sclerosis, which improved with intravenous steroid therapy. The clinical course then stabilized for 6 months, after which the patient reported a symmetrical clinical improvement in his leg strength. Neurophysiological studies also showed an improvement of nerve conduction velocities and amplitude of sensory and motor action potentials at upper limbs. In conclusion, Rituximab treatment, in this patient, may have caused short-term relapse in MS and, later on, improvement in anti-MAG polyneuropathy, as previously reported.

THE NEUROPROTECTIVE EFFECT OF ERYTHROPOIETIN (EPO) AND OF ITS NON-ERYTHROPOIETIC CARBAMYLATED DERIVATIVE (CEPO) IN CISPLATIN-INDUCED PERIPHERAL NEUROTOXICITY

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Cisplatin (CDDP) is severely neurotoxic, causing the onset of a disabling peripheral neuropathy. Co-treatment with neuroprotective agents and CDDP has been proposed for preventing or reversing CDDP-induced neuropathy. In addition to its hemopoietic effects, erythropoietin (EPO) has neuroprotective and neurotrophic properties and its systemic administration has a wide range of neuroprotective actions in animal models of central and peripheral nervous system damage. However, EPO erythropoietic action represents a potential cause of several side effects in the use of EPO as a neuroprotective drug. In the present study we investigated the effect of EPO or that of the non-erythropoietic EPO-derivative, CEPO, on CDDP-induced neurotoxicity *in vivo*. Systemic injection (i.p.) of CDDP (2 mg/kg/day) given two times per week for four weeks in Wistar rats induced significantly lower growth rate ($p < 0.05$), slower sensory nerve conduction velocity (SNCV, $p < 0.001$) and reduced intraepidermal nerve fibre (IENF) density ($p < 0.001$ vs. controls). Co-administration of CDDP and EPO or CEPO (40 μg/kg/day three times per week) partially but significantly prevented CDDP-induced NCV reduction. Accordingly, both molecules helped in preserving IENF density, thus confirming at the pathological level their neuroprotective effect. In conclusion, our data, obtained in a model of CDDP-induced peripheral neurotoxicity which reproduces the clinical features of CDDP administration in humans, widen the spectrum of possible application of EPO and CEPO as neuroprotectant drugs and strongly support their effectiveness. However, they also indicate the need for further pre-clinical studies in order to optimise their effectiveness, to determine the exact mechanism and site of action and to clarify the issues of long-term tolerability and safety using *in vivo* models, with the final aim to identify a better strategy to be proposed for clinical application.

NEURAL DIFFERENTIATION POTENTIAL OF HUMAN MESENCHYMAL STEM CELLS

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Bone-marrow mesenchymal stem cells (MSC) are multipotent elements with the capacity to differentiate *in vitro* into several cell lineages. Conflicting results have been reported regarding their neural differentiation potential. The objective of this study was to evaluate the neural differentiation potential of human MSC *in vitro* and in co-cultures with Schwann cells. MSC were derived from bone-marrow, spleen, thymus and adipose tissues from healthy human donors. Schwann cells were cultured from human benign schwannomas according to standard protocols. MSC displayed a neural morphology and phenotype after 30 h with a chemical differentiation protocol (Woodbury *et al.*, J Neurosci Res, 2000; 61:364–70). Differentiated cells expressed neuronal and glial markers, like NeuN, MAP2, PSA-NCAM, PMP22, S100, GFAP, GalC and A2B5. This differentiation was transient and MSC returned to basal morphology and phenotype within 3 days. Longer incubation with differentiation medium resulted in massive cytotoxicity. Co-culture with Schwann cells prolonged the survival and neural differentiation of MSC up to 12 days. Neural differentiation was observed in about 15–30% of MSC, needed cell-cell interactions and was characterized by selective expression of Schwann cell markers (PMP22 and S100), but not of neuronal proteins. MSC can be induced to assume neural phenotype; co-culture with glial cells can extend the neuro-ectodermal differentiation of MSC. These results underline the neural differentiation potential of MSC and are promising for the therapeutic use of MSC in degenerative and autoimmune neuropathies.

ANTIBODIES TO THE GANGLIONIC NICOTINIC ACETYLCHOLINE RECEPTOR IN CELIAC DISEASE

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About 2.5% of patients with idiopathic peripheral neuropathy or idiopathic dysautonomia have underlying celiac disease (CD). Antibodies (Abs) to ganglioside have been reported in CD patients with neuropathy. No data are so far available on the presence in CD of ganglionic acetylcholine receptor (AChR) Abs which, at high levels, are found in patients with autoimmune autonomic neuropathy. The objective of this study was to determine the frequency of ganglionic AChR Abs in CD patients and the possible correlations with autonomic manifestations. Seventy CD patients

(16 males, 54 females, mean age 36.6 years) underwent neurological and electrophysiological evaluation. Ganglionic AChR Abs were detected with radioimmunoprecipitation assay. Sera from 25 age-matched patients with other autoimmune diseases (15 systemic lupus erythematosus, 10 Sjogren's Syndrome) were studied as controls. None of our CD patients complained of autonomic symptoms. Borderline titres (30–50 pmol/L) of Abs to the ganglionic AChR were present in 4 patients, one affected by type I diabetes and one with subclinical neuropathy. Three of the 4 patients underwent cardiovascular autonomic function tests, which showed no abnormalities. Low levels of ganglionic AChR Abs (50–100 pmol/L) were found in 2 control lupus patients, one of whom had a severe sicca complex. One patient with Sjogren's had borderline ganglionic AChR Abs. Autonomic symptoms were not present in our CD patients, and none had significant levels of ganglionic AChR Abs. The presence of borderline Abs in 4 CD and in other autoimmune patients may suggest subclinical autoimmune autonomic involvement. A more extensive battery of autonomic function tests may help identify subclinical abnormalities. Further studies will help clarify if ganglionic AChR Abs are found in CD patients with significant autonomic symptoms/signs or if they might predict future autonomic manifestations.

RESTLESS LEGS SYNDROME IN DIABETIC NEUROPATHY

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Restless legs syndrome (RLS) is usually thought to be common in diabetes, but this has not been definitely established. The aim of this study was to evaluate the prevalence of RLS in a cohort of diabetic patients and to analyze the features of the associated neuropathy. We examined the records of patients with polyneuropathy and mononeuropathy multiplex associated with diabetes or impaired glucose tolerance, in a retrospective study, to assess the prevalence of RLS diagnosed in accordance with the criteria of the International Restless Legs Syndrome Study Group. A diagnosis of peripheral neuropathy associated with diabetes or glucose intolerance could be confirmed in 91 patients, 50 male and 41 female, with a mean age of 64.9 years. Comorbidity with other possible causes of peripheral neuropathy was present in 19 cases. RLS was identified in 32 patients (35.2%). RLS patients were more often women (18/32 vs. 23/59), with pure or mainly sensory neuropathy (30/32 vs. 41/59; $p = 0.016$). In many RLS patients polyneuropathy was of small fiber type (15/32 vs. 29/59; $p = 0.016$). Changes of sensory action potentials were significantly less severe in RLS patients. We think that RLS is an important manifestation of diabetic neuropathy, as it is quite common and can be successfully treated. As previously observed in other forms of polyneuropathy, RLS occurs more frequently in polyneuropathy of sensory type and mild entity, mainly in women.

ULTRASTRUCTURAL PROTEIN ZERO (P0) EXPRESSION IN P0-RELATED DEMYELINATING AND AXONAL CHARCOT-MARIE-TOOTH DISEASES

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Protein zero (P0) is the major adhesive structural protein of peripheral compact myelin; it is a single-pass transmembrane molecule that has a large Ig-like extracellular domain (P0ex) with a pivotal role in myelin compaction, and an intracellular domain (P0ic) putatively involved in adhesion and myelination. Mutations of P0ex and P0ic give rise to autosomal dominant demyelinating Charcot-Marie-Tooth (CMT) disease (CMT1B) or hypo-amyelinating Dejerine Sottas disease (DSS); the mutant alleles could act either through a loss of function or a toxic gain of function. A unique immunoelectronmicroscopy study of nerve biopsies in two cases with CMT1B and mutations of P0ex demonstrated a twofold decrease in P0 expression in compact myelin (Sindou *et al.*, 1999). Rarely, mutations of P0 cause autosomal dominant axonal CMT (CMT2); in one case studied by immunohistochemistry, axonal degeneration was thought to be secondary to hypomyelination but P0 was normally expressed (Hanemann *et al.*, 2001). Using a monoclonal P0–7 antibody (a kind gift of Archelos JJ), we performed a semi-quantitative ultracryo-immunogold assay of the protein expression in sural nerve biopsies from three cases with CMT2 and heterozygous mutations of P0ex (Arg7Gly, Ser15Phe, Thr95Met) and two cases with CMT1B and mutations of P0ic: a homozygous Asp195Tyr manifesting myelin outfoldings, and a heterozygous Lys219stop associated with myelin uncompaction. Compared with two age-matched controls, all CMT2 cases showed a correct localization of P0 in the compact myelin; of the two cases with CMT1B, the one with the homozygous Asp195Tyr had also a normal expression, whereas the other with the Lys219stop mutation disclosed a significantly decreased expression ($p < 0.01$). No abnormal accumulation of P0 was detected in the Schwann cell cytoplasm either in the CMT2 or CMT1B biopsies. The study ruled out ultrastructural changes of the myelin sheath and of P0 expression in CMT2 cases. CMT1B cases had a divergent pattern of expression probably reflecting different mechanisms of disease.

VARIABLES INFLUENCING QUALITY OF LIFE AND DISABILITY IN CMT PATIENTS: ITALIAN MULTICENTER STUDY

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No studies have assessed which variables determine deterioration of Quality of Life (QoL) and disability in Charcot-Marie-Tooth disease (CMT). The aim of our study was to assess which are the variables that influence QoL and disability in patients with CMT. We performed a large prospective multicenter (six centers – see affiliations) multidimensional study by using validated clinical, disability, and quality of life measurements. Multivariate analysis was performed using QoL as dependent variables and duration of symptoms, age, gender and CMT type, depression and disability measurements as independent variables. Two hundred eleven patients were enrolled (60% women, mean age 42.5 years). QoL was highly significantly deteriorated with respect to the Italian normative sample. The physical aspect of QoL was mainly related to disability (but it does not increase with age probably for an adaptation between expectation and reality). The mental QoL is influenced by depression (hence we have to consider this aspect approaching CMT patients). Moreover we observed that women refer more severe symptoms than men and that some CMT subtypes are related to higher and others to lower bodily pain. Multiperspective assessment of CMT showed new aspects of CMT we have to deal with: differences between men and women, presence of pain and depression. *Further researchers involved: Grandis M, Benedetti L, Pazzaglia C, Mignogna T, Foschini M, Fabrizi GM, Laurà M, Mazzeo A, Majorana G, Valentino P, Nisticò R.*

EFFECTS OF DIFFERENT ERYTHROPOIETIN SCHEDULES IN CISPLATIN-INDUCED PERIPHERAL NEUROTOXICITY

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Erythropoietin (EPO) is a multifunctional trophic factor and has a potent neurotrophic activity on neural cells in the central and peripheral nervous system. We investigated a possible dose-response effect of EPO (Epoetin alfa) as a neuroprotectant drug against cisplatin (CDDP)-induced neurotoxicity and if EPO could "cure" CDDP-induced peripheral neurotoxicity once ensued. Wistar rats were divided as follows: untreated controls, high dose EPO-treated (HD-EPO, 50 μg/kg ip 3 times/week), CDDP (2 mg/kg twice weekly × 4 w), CDDP + HD-EPO, CDDP + intermediate dose EPO (ID-EPO, 10 μg/kg ip 3 times/week), CDDP + low dose EPO (LD-EPO, 0.5 μg/kg ip 3 times/week). At the end of the treatment, part of the rats belonging to the CDDP group were left untreated, while the remaining received HD-EPO. At baseline and at the end of the treatment, each animal underwent the determination of sensory nerve conduction velocity (SNCV) in the tail. At sacrifice, hematocrit determination was also performed. Immediately after treatment CDDP significantly impaired SNCV; the co-administration of HD-EPO (+49.7% vs. CDDP, $p < 0.001$) and, to a lesser extent, of ID-EPO ($p < 0.05$) significantly reduced this effect, while LD-EPO was not effective. In the follow-up it was demonstrated that 2 weeks after treatment withdrawal, CDDP + HD-EPO-treated rats were significantly less affected than CDDP-treated rats ($p < 0.001$); this difference was no longer evident after 4 weeks of follow-up, when CDDP rats had a spontaneous recovery. EPO administration only during the follow-up period with the "curative" schedule induced a trend toward a better recovery after CDDP treatment. EPO induced a significant increase in hematocrit level in all groups when administered during CDDP treatment and in the follow-up. The present data, which evidence a clear dose-effect response of EPO administration, give support to its possible use as a neuroprotectant and confirm that neuroprotectant and erythropoietic activities are differently stimulated by EPO. *Supported in part by a grant from "Fondazione Banca del Monte di Lombardia".*

ACUTE ATAXIC NEUROPATHY WITH ANTI-GD1B AND GQ1B ANTIBODIES POST CAMPYLOBACTER JEJUNI INFECTION

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Guillain-Barré syndrome (GBS) is classified in different subtypes on the basis of clinical, electrophysiological, and immunopathological features. In 1962, Richter described an ataxic form of GBS. Since then few additional patients have been reported; some had a preceding upper respiratory tract infection and anti-GD1b or anti-GQ1b antibodies. We report two patients with an acute onset of distal paresthesias followed by impossibility of walking. Both patients had diarrhoea about ten days before the onset of symptoms. Examination showed gait and limb ataxia, loss of proprioception, absent tendon reflexes but no weakness. Stool cultures for Campylobacter jejuni (Cj) were negative but serology demonstrated an IgA to IgG shift of anti-Cj antibodies from the first to the second serum sample compatible with recent Cj infection. Patient 1 had high titer (6400) IgG anti-GD1b antibodies, patient 2 had IgG anti-GQ1b (>3200) and anti-GD1b (800). CSF examination performed within the first week after onset was normal. Motor nerve conduction studies were normal; sensory conductions showed reduced amplitude sensory nerve potentials with normal or slightly slowed conduction velocities. Both patients completely recovered in 2 months and sensory conductions normalized in 6 months. The pathology of acute ataxic neuropathy has yet to be clarified. In the patients, we report that the electrophysiological findings suggest a sensory neuronopathy. GD1b and GQ1b have been localized by immunohistochemical studies in the dorsal root neurons and immunisation with GD1b in rabbits induced an acute sensory neuronopathy. However, clinical and electrophysiological recovery in acute ataxic neuropathy is generally prompter and more efficacious than expected in a degeneration of primary sensory neurons. To our knowledge these are the first acute ataxic neuropathy patients associated with Cj infection. These cases extend the range of clinical presentations of GBS following Cj infection.

RECENT CAMPYLOBACTER JEJUNI INFECTION AND AXONAL GUILLAIN-BARRÉ SYNDROME IN THE CHIETI DISTRICT

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Seventy-seven consecutive patients with Guillain-Barré syndrome (GBS) were diagnosed in a four year period in the Chieti district. Patients were classified according to clinical criteria and nerve conduction studies into six groups: acute inflammatory demyelinating polyradiculoneuropathy (AIDP), axonal (motor and motor-sensory) GBS, Miller Fisher syndrome (MFS), acute ataxic neuropathy, facial diplegia (FD), and unclassified. In all patients serum samples were collected on admission and 2–3 weeks later to assess anti-Campylobacter jejuni (Cj) (IgA, IgG) antibodies and antiganglioside (GM1, GD1b, GD1a, GM2, GQ1b) (IgM, IgG) antibodies. Forty-eight patients were males and 29 females; mean age at onset was 48 ± 21.3 years. Thirty-nine patients (50.6%) had AIDP, 18 (23.4%) had axonal GBS, six (7.8%) MFS, two (2.6%) acute ataxic neuropathy, two (2.6%) FD, and 10 patients (13%) were unclassified. Serological evidence of recent Cj infection was found in a total of 30 (39.0%) patients and specifically in 72.2% of axonal GBS, in 28.2% of AIDP, in 16.7% of MFS, in 100% of acute ataxic neuropathy and in 30% of unclassified patients. Forty-eight patients (62.3%) were positive for at least one anti-ganglioside antibody and specifically in 83.3% of axonal GBS, in 59% of AIDP, in 83.3% of MFS, in 100% of acute ataxic neuropathy, and in 30% of unclassified patients. Compared to published studies in Italy and Europe the GBS population we report has a higher frequency of recent Cj infection and greater representation of axonal subtypes.

METASTATIC BREAST CANCER MIMICKING AXONAL PHARYNGEAL-CERVICAL-BRACHIAL VARIANT OF GUILLAIN-BARRÈ SYNDROME

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We report an unusual case of a 73-year-old female patient with a history of subacute progressive weakness of her arms and neck associated with dysphagia and ataxia. The neurological examination upon admission to our department revealed sensory ataxia, marked motor deficit with tendon reflexes absent in her upper limbs. Electrophysiological findings demonstrated severe acute axonal motor failure with marked reduction of sensory action potentials and normal values of sensory-motor nerve conduction velocity. Cerebrospinal fluid analyses revealed a mild increase in proteins. Cervical MRI and chest TC scan showed a mediastinic infiltrative tissue of dorso-cervical bone and bilateral roots with compression of esophagus. Biopsy revealed breast cancer. The patient improved after chemotherapy.

ASSOCIATION BETWEEN SYSTEMIC ATAXIC NEUROMYOSITIS AND SYNCYTIAL GIANT CELL HEPATITIS: A CASE REPORT

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We present an unusual case of a 41-year-old female who came to our attention for a 2-month history of diplopia in all gaze directions, diffuse myalgias, and severe hyposthenia mainly at the lower limbs. Creatine kinase was slightly elevated. Standard needle electromyography (EMG) showed polyphasic motor unit percentage increase and acute denervation in all examined muscles. Nerve conduction studies were normal. Muscle biopsy showed the presence of both myopathic and neuropathic damage with inflammatory signs. The patient was treated with intravenous immunoglobulin (30 g/day for 5 days) courses, with improvement of muscle strength. Eight months later, preceded by a fever, the patient had an acute relapse manifesting with a severe sensitive ataxic syndrome and worsening of diplopia. The laboratory exams evidenced increase of hepatic enzymes (GOT, GPT, γ-GT, alkaline phosphatase), VES and gamma immunoglobulin, with reduced level of haematic albumin. Acetylcholine receptor autoantibodies were negative as were rheumatologic markers. Abdominal ultrasound did not evidence liver alterations, whereas hepatic biopsy showed the presence of syncytial giant cell hepatitis, similar to what is observed in autoimmune or viral hepatitis. The search for viral, bacterial, or yeast actual infection markers, including CMV, Parvovirus B19, Epstein-Barr, Adenovirus, Paramixovirus, Coxsackie viruses, Borrelia burgdorferi, Clamidias, and Ricketsias was negative. Cerebrospinal fluid exams showed medium damage of haemato-encephalic barrage. A second muscle biopsy showed diffuse fiber atrophy and occurrence of rare eosinophilic inclusions. Electronic microscopy evidenced focal areas of myofibrils rarefactions. The patient was then treated with additional intravenous immunoglobulin courses with a slow improvement of axial and limb ataxia. Although the aetiology of our patient remains obscure, the association of inflammatory involvement of peripheral nerve and skeletal muscle has to be considered as a complication of autoimmune hepatitis.

BORTEZOMIB-INDUCED PERIPHERAL NEUROTOXICITY: A NEUROPHYSIOLOGICAL STUDY IN A RAT MODEL

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The proteasome is a key target for cancer therapy and bortezomib (VELCADE®) is the first proteasome inhibitor entered into clinical evaluation. One of the dose-limiting side effects of bortezomib is severe peripheral neuropathy. Despite its clinical relevance the present knowledge on

bortezomib-induced peripheral neurotoxicity is very limited. In the present study we report the first model of bortezomib-induced peripheral neuropathy investigated with neurophysiological methods. Wistar rats received bortezomib twice (2q7d) or three times (3q7d) weekly for a total of 4 weeks at different IV doses used in two experiments (0.08, 0.15, 0.20, 0.30 mg/kg/day, i.e., 0.48, 0.90, 1.2 and 1.8 mg/m^2/day of treatment). At baseline, on days 14, 21 and 28 (treatment period) and on days 42 and 56 during the follow-up period each animal underwent the determination of sensory nerve conduction velocity (SNCV). The highest, maximally tolerated dose bortezomib schedules induced a significant reduction in SNCV. In the rats treated with the 2q7d schedules, the effect of bortezomib administration on SNCV was evident only in the 0.20 mg/kg group. The SNCV in this group was significantly reduced vs. controls from the determination performed on day 14, and this difference was present until day 42. On the contrary, in the groups treated with the 3q7d schedule, a significant SNCV reduction was observed after 0.15 mg/kg and 0.20 mg/kg dosing. Also in these groups the difference in SNCV was significant vs. the determination performed on day 14 and until day 42. Using the 3q7d schedule a significant difference was observed also between the 0.15 mg/kg and the 0.20 mg/kg groups. Recovery was complete after the follow-up period in all groups. Our study reports for the first time that changes induced by the chronic administration of bortezomib on the peripheral nervous system in a rat model increased with dose and frequency of administration and we believe that this model is relevant to the neuropathy induced by bortezomib in the treatment of human malignancies. *Supported in part by a grant from "Fondazione Banca del Monte di Lombardia".*

TRAUMATIC PERIPHERAL NERVE INJURIES: NEUROPHYSIOLOGICAL EVALUTION BEFORE AND AFTER SURGERY IN A LEVEL I TRAUMA CENTER

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Injuries to peripheral nerves are common and while advances in surgical techniques have improved outcomes, prognosis remains poor. Electrophysiological studies are essential in the management of nerve injuries, providing information regarding the location, severity, and nature of a nerve injury as well as prognosis. The purpose of the study was to discover the number and types of traumatic nerve injuries that were submitted to neurophysiological evaluation during a 4-year period at a level I trauma center. The specific nerves involved, their sites of injury, neurophysiological follow up, and surgical outcomes were also documented. We retrospectively evaluated all patients submitted for electrodiagnostic studies (sensory and motor nerve conduction and needle electromyography) between January 2001 and December 2005 with suspicious traumatic peripheral nerve injury admitted to a level I trauma center in Turin. In most of these injuries, neurological, electrophysiological, and surgical, outcome assessments were performed. Median and ulnar nerves injuries were excluded (because of the high frequency of entrapment syndromes). Two hundred forty peripheral nerve injuries (197 neuropathies, 43 plexopathies) were selected, and particularly in the upper limbs: 42 brachial plexus, 59 radial, 24 axillar, 14 thoracicus longus, 7 musculocutaneous, 5 suprascapular nerves; in the lower limbs: 1 lombar plexus, 55 common peroneal, 29 sciatic, 4 femoral nerves. Follow-up data were available in 185/240 injuries (55 drop out) and 140/185 traumatic nerve injuries were surgically treated (primary repair in the acute setting, neurolysis, nerve grafting, end-to-end anastomosis, neurotization, neuroma resection). Electrophysiological methods are particularly useful for localizing peripheral nerve injuries, detecting and quantifying the degree of axon loss, and contributing toward treatment decisions; with motivated patients and a dedicated and specialized neurophysiological/surgical team, the prognosis for functional recovery can be good and the patients can still lead productive and satisfying lives.

FURTHER OBSERVATIONS ABOUT THE PREDICTIVE VALUE OF CLINICAL AND ELECTROPHYSIOLOGICAL FEATURES FOR RESPONSE TO IVIG IN CIDP PATIENTS

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The literature reports numerous studies as to the efficacy of high dose I.V. immunoglobulin therapy in the treatment of CIDP, showing a 60% positive response rate. It is still not clear why the remaining 40% did not respond. A total of 39 CIDP patients enrolled in a prospective study were administered high dose I.V. immunoglobulin for three consecutive months (1 g/Kg for two days per month). The aim of the study was to determine if there was any clinical electrophysiological phenotype that could predict the efficacy of the treatment, any clinical-electrophysiological factors that could predict the efficacy of the treatment, and if the response differed according to treatment variations. There was a 74% response rate for the intravenous therapy, i.e., an improvement of at least 1 point in the Rankin Scale Score. The positive predictive factors included: a shortening of the disease duration, less muscular atrophy of both the upper and lower limbs, and a higher percentage of elicitable CMAP (indicating less axonal damage). Moreover, as the non-responders were re-evaluated, an alternative diagnosis was made for as many as 30% of the cases that had a preliminary diagnosis of CIDP. Noteworthy was the fact that 33% of the non-responders had a diagnosis of neoplasia: that should be suspected in non-responder patients or in those who became non-responders. Moreover, this study demonstrated that it could be useful to treat the patients for a longer period; in fact, 17% of the subjects became responders after three cycles of immunoglobulins.

NONSYSTEMIC VASCULITIC NEUROPATHY: A CLINICAL, NEUROPHYSIOLOGICAL, AND MORPHOLOGICAL STUDY

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Peripheral neuropathy is a common complication of vasculitis, disorders caused by inflammatory infiltrates of the vessel wall. The vasculitic neuropathy may be a primary disorder of the peripheral nervous system named non-systemic vasculitic neuropathy (NSVN). These patients usually present with a subacute or chronic painful multineuropathy and few or no systemic abnormalities or laboratory investigation. The prognosis and treatment of patients with NSVN remains unclear. Thirty two patients with clinical and neurophysiological evidence of mononeuropathy, multineuropathy, or polyneuropathy considered typical of ischemic involvement of peripheral nerve were selected for this retrospective study. Nerve biopsy was performed in all patients. Of the 32 patients, using diagnostic criteria for NSVN, nine had NSVN. We confirmed that patients with NSVN present with an asymmetrical painful sensory/sensorimotor multineuropathy. We observed that nerve biopsies from these patients present usually indirect sign of vasculitis. These patients responded well to immunosuppressive therapy and in most cases long-term prognosis was good.

MUSCLE HISTOPATOLOGY IN PATIENTS WITH X-LINKED BULBAR AND SPINAL MUSCULAR ATROPHY (KENNEDY'S DISEASE) AND FEMALE CARRIERS

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X-linked recessive bulbar and spinal muscular atrophy (SBMA) is an adult lower motor neuron disease resulting from an expansion of a CAG repeat in the androgen receptor gene. SBMA shares common features with amytrophic lateral sclerosis (ALS). The objective of this study was to investigate skeletal muscle histopathology in patients with SBMA and female carriers. We studied six SBMA patients (age range between 52 and 81 years, mean age 64 years) from five families (one couple of cousins). We also included three female carriers (age range 31 and 53 years, mean age 40 years) from two families (one set of sisters). Diagnosis of SBMA was confirmed by molecular genetic tests in all cases. All patients and carriers underwent clinical assessment, neurophysiological examination (routine middle electromyography and nerve conduction study, transcranial magnetic stimulation, somato-sensory evoked potentials) and routine histochemical analysis of their muscle biopsy. Onset of neurological symptoms ranged between 50 and 70 years of age. All patients showed proximal weakness of both upper and lower limbs and mild bulbar impairment as early signs of disease. The three female carriers were asymptomatic and their neurological examination was normal except for a bilateral mild calf hypertrophy in one of them. Neurophysiological studies demonstrated subclinical involvement of the sensory nerves in addition to denervation changes in all patients, whereas they were normal in carriers. Muscle biopsy of all patients showed several atrophic angulated fibers clustered in small groups and isolated markedly hypertrophic fibers with central nuclei. Mild neurogenic changes were also observed in the muscle biopsies of the obligate carriers. Skeletal muscle histopathology shows peculiar features in SBMA compared to ALS. This can be useful for the differential diagnosis of the two motor neuron diseases. Moreover, our data demonstrate that neurogenic changes are present in the female carriers muscle even in the absence of clinical and neurophysiological abnormalities.

SMALL FIBRE NEUROPATHY IN PRIMARY SJÖGREN'S SYNDROME: A COMPARATIVE NEUROPATHOLOGIC AND NEUROPHYSIOLOGIC STUDY

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We evaluated the impairment of small fibres in patients with primary Sjögren's syndrome (SS) either asymptomatic or with symptoms of small fibre neuropathy (SFN). Patients underwent clinical, laboratory examination, Neuropathy Pain Questionnaire, and nerve conduction studies (NCS). Small fibre impairment was investigated by skin biopsy at proximal thigh (Pth) and distal leg (Dl), quantitative sensory testing (QST) and laser Doppler flowmetry (LDF) at foot, Dl, and Pth to assess basal cutaneous blood flow (bCBF) and temperature, vasoconstrictor reflexes induced by deep breathing (DB), and postural variation (veno-arteriolar reflex, VAR), and vasodilatation induced by local heating (LH). We examined 10 asymptomatic and 10 symptomatic patients. NCS were unremarkable. QST showed abnormal cooling, warm, and heat-pain thresholds in 80% of asymptomatic and in 90% of symptomatic patients. LDF bCBF and LDF DB were abnormal in 30% of patients; LDF LH in 50%; LDF VAR in 25%. Intraepidermal nerve fibre (IENF) density was reduced in 80% of asymptomatic and in 80% of symptomatic patients. In 16 patients, it was significantly lower at Pth than Dl (8 asymtpomatics and 8 symptomatics), whereas in 2 patients (symptomatics) it was low only at Dl (symptomatics). Our study shows that small fibres are impaired early in SS patients, irrespective of the presence of sensory symptoms. This suggests a subclinical functional impairment of axons that skin biopsy and non-conventional neurophysiologic tests can assess. The non–length-dependent pattern of skin nerve fibre loss and functional test impairment suggest that SS primary affects small size neurons of dorsal root ganglia. *This study is supported by Berco S.p.A. and by a grant of the "Fondazione Cassa di Risparmio di Ferrara".*

ITCHING SYNDROME AS MANIFESTATION OF NEUROPATHIC PAIN – A CASE REPORT

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Itch is a common manifestation in systemic diseases such as malignancy, myeloproliferative disorders, uraemia, and allergy. Recent microneurography studies showed that itch is mediated by a distinct subset of C fibres, the "itch fibres", that are exclusively sensitive to histamine. We described the case of a 68-year-old woman complaining of itch at trunk and legs with acute onset three years before our first observation. Itching was induced by ambient warm and was associated with a persisting burning-like heat sensation. Extensive dermatologic and allergologic investigations were negative unrevealing. Treatment with anti-histaminergic and low-dosage oral steroids for 6 months did not modify the clinical picture. Physical examination was negative. Laboratory investigations revealed only neutrophilic leukocytosis, whereas chemistry profile, thyroid-stimulating hormone, serum and urine immunofixation, and screening for immunologic, infectious, and neoplastic disease was negative. Cerebrospinal fluid examination was normal. Gabapentin (1200 mg/day) reduced itch severity from 10 to 5 of the visual analogue scale (VAS) at 1-month follow-up. Nerve conduction study and needle electromyography was normal. Quantitative sensory testing in foot and distal leg disclosed warm hyperalgesia. Cutaneous blood flow by laser Doppler flowmetry at distal legs showed abnormal vasodilatation function induced by local heating. Skin biopsy demonstrated reduced intraepidermal nerve fibre density at the proximal thigh (8.7/mm) and normal value at the distal leg (7.8/mm) with diffuse axonal swellings. Total body CT-scan showed laterocervical and mediastinic lymphadenopathy. The histological exam of axillary lymph nodes revealed T-lymphocitic T-zone lymphoma (TZL). Itch is a common symptom in lynphoproliferative disease. In our case, the distinctive feature of itch, the histological impairment of small fibres and the success of treatment, suggest the presence of uncommon itching SFN. *This study is supported by Berco S.p.A. and by a grant of the "Fondazione Cassa di Risparmio di Ferrara"*.

IDIOPATHIC UNILATERAL CALF HYPERTROPHY: A CASE REPORT

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Muscle hypertrophy occurs uncommonly in several neurogenic disorders. The underlying pathophysiology is unclear. This unusual phenomenon most frequently occurs in the calf and isolated S1 chronic radiculopathy is the cause in the majority of reported cases. We describe a 43-year-old previously healthy man who presented with a several year history of left calf cramp, fasciculations, "rigidity" and progressive enlargement with neither a past history of low back pain or sciatica nor lumbosacral laminectomy. Diagnostic blood work-up, including search for ANA, ENA, anti-ganglioside antibodies, was normal. Creatine kinase was mildly elevated at 407 U/l (n.v. $<$ 170); MRI (with and without gadolinium) of lumbosacral spine and plexus was normal as was CSF examination. Motor and sensory nerve conduction studies were normal. Right H-reflex was normal. Left H-reflex amplitude was markedly reduced and latency was increased (45 ms vs. 32.4 ms). Needle sampling showed a neurogenic pattern in S1 myotome with frequent single and grouped fasciculations but no complex repetitive discharges. Left gastrocnemius medialis biopsy showed fiber-type grouping, fiber splitting, hypertrophic and more rarely atrophic fibers, internal nucleation, phagocytosis but no inflammatory cells. Treatment with prednisone resulted in marked improvement, abating muscle spasms and ache although some feeling of tension persisted. A diagnosis of unilateral calf hypertrophy due to an idiopathic S1 radiculopathy was made.

PERIPHERAL NEUROPATHY IN A CASE OF VANISHING WHITE MATTER DISEASE WITH A NOVEL EIF2B5 MUTATION

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Peripheral neuropathy is typically associated with demyelinating disorders of the central nervous system such as Metachromatic Leukodystrophy, Krabbe disease and Adrenomyeloneuropathy. We describe an infantile case of Vanishing White Matter Disease (VWMD) with evidence of demyelinating peripheral neuropathy. Sequence analysis of EIF2B5 gene showed that the patient was a double heterozygote, with a novel missense mutation CGA $>$ CAA in codon 269 of exon 6, resulting in the replacement of an arginine residue with glutamine and the recently described 203T $>$ C in exon 2. Sural nerve biopsy showed reduced density of myelinated fibers, thin myelin sheaths and de-remyelination signs. Neurophysiological study showed reduction of the nerve conduction velocities. This association, never reported before, may be coincidental; however, this case suggests that VWMD should be considered even in cases of peripheral neuropathy associated with central demyelination.

HIGH RESOLUTION MRI OF LUMBAR AND BRACHIAL PLEXUS: A USEFUL TOOL IN THE DIAGNOSIS OF PLEXOPATHIES

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Plexopathies, involving either lumbar or brachial region, are peculiar and complex diseases, causing problems in

differential diagnosis for the clinicians. These diseases can be induced by degenerative or inflammatory causes so they can be treated with different therapeutic approaches. Plexus MRI has born as a diagnostic tool in traumatic or generally surgical alterations of the plexus (i.e., tumors), but more recently it is taking place as an important diagnostic tool in "medical plexopathy" also. In fact, it helps in better defining the diagnosis and giving data on the etiology of plexus disease in association with classical laboratory finding (EMG studies and immunological tests). MRI of brachial and lumbar plexus is characterized by a complex high resolution study, made up of T2, T1, T2 fat sat and T1 fat sat TSE sequences oriented on coronal and axial view (sometimes also sagittal view is obtained), with 3 mm thickness. The study is completed with gadolinium injection. We discuss some clinical cases of MRI imaging of plexus to demonstrate the real importance of this diagnostic tool.

THREE-DIMENSIONAL STRUCTURE OF THE TRANSTHYRETIN (TTR) PHE64LEU VARIANT

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TTR is a tetrameric plasma protein synthetized in the liver and choroid plexuses whose function is the transport of thyroxine and of the complex retinol-binding protein (RBP)-retinol. The four identical polypeptide chains in the tetramer, whose secondary structure is almost exclusively beta sheet, are organized as a dimer of dimers with a central channel that accomodates thyroxine. RBP binds on the surface of the tetramer with a stoichiometry of one or at most two molecules per tetramer. Missense mutations of TTR cause familial amyloid polyneuropathy (FAP) or familial amyloid cardiomyopathy (FAC) depending on the tissue in which the amyloid fibrils are deposited. The most frequent FAP mutation in the world is the Val30Met but more than 80 mutations are known. Phe64Leu is frequent in Italy and is associated with a late-onset neuropathy. In order to understand the mechanisms of amyloid formation, the three-dimensional structure of several TTR mutants were determined by X-ray diffraction but the structure of the Phe64Leu mutant is unknown. We generated the TTR Phe64Leu mutant by site-directed mutagenesis of the wild type protein using an expression vector from a strain of Escherichia coli. The mutated protein was crystallized and the structure was solved at 3.1.Å resolution. The crystals are trigonal, space group P32 and contain two tetramers in the asymmetric unit. The two tetramers appear to form an octamer that can be considered as the starting unit in the formation of fibrils. Crystallization experiments in the presence of NaI and other ligands are in progress in order to improve the structure resolution and better define the structural differences between the Phe64Leu mutant and the wild type TTR. Soaking experiments of these crystals with compounds that are known to disrupt fibril formation could give clues as to the relevant parameters to be taken into account in drug design.

QUALITY OF LIFE IN PATIENTS WITH HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES

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Over the last two decades, clinical researchers emphasized the need for a thorough evaluation of concepts such as Health Related Quality of Life (QoL) to study the impact of chronic illnesses and their treatments on the patient's life. Quality of life has never been measured in HNNP. To assess QoL of patients with hereditary neuropathies we performed a prospective multicenter (six centers – see affiliations) multidimensional study by using validated clinical, disability, and quality of life measurements. We enrolled 13 patients affected by HNPP: 5 females, 8 males, mean age 41.2 years (SD 13.6, range 22–66). We used the most common tool for QoL assessment: the SF-36. The large diffusion of SF36 in scientific literature allows the use of the scale as a standard. SF-36 consists of 36 questions that inquire about the general health status of patients. This questionnaire provides eight specific categories of physical and emotional scores (Physical Functioning-PF, Role-Physical-RP, Bodily Pain-BP, General Health-GH, Vitality-VT, Social Functioning-SF, Role Emotional-RE, Mental Health-MH). Low scores indicate deterioration of the health status. The official Italian version was used; administration to the patients was done in agreement with standardized methodologies. We compared the SF36 results of our sample of HNPP patients with those of Italian norms by using the one sample *t*-test. We observed that Quality of Life in HNPP is not impaired except for a mild deterioration of Physical Function domain, but this does not determine inability to perform daily activity due to physical or mental problems (Role Physical and Role Emotional which evaluate this two aspects are not significantly deteriorated with respect to the Italian norms). We think that QoL is not deteriorated in HNPP patients because deficits are usually focal and transitory. Interestingly, the awareness of being affected by an hereditary neurological disease associated with experienced transitory deficits does not determine deterioration of the mental aspects of QoL. We do believe that we should consider these results in approaching HNPP and we should use them to reassure patients with HNPP, especially at the moment we communicate the diagnosis. *Further researchers involved: Grandis M, Benedetti L, Pazzaglia C, Mignogna T, Foschini M, Fabrizi GM, Laurà M, Mazzeo A, Majorana G, Valentino P, Nisticò R.*

POST-INFECTIOUS BICKERSTAFF'S BRAINSTEM ENCEPHALOPATHY WITHOUT DETECTABLE ANTIGANGLIOSIDE ANTIBODIES

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A 48 year-old woman fifteen days after respiratory infection experienced headache, diplopia, and gait unsteadiness which worsened over the next 2 days. Neurological examination (day 3) showed drowsiness, dysarthria, dysphonia, external ophthalmoparesis, nystagmus, left side facial weakness, tongue deviation towards the left, trunk and limb cerebellar ataxia. Muscle strength was normal in upper and lower extremities. Deep jerks were brisk with an extensor plantar response. Sensation was unaffected. Chest x-ray revealed basal pulmonary infiltration. Routine emato-urinary tests were negative, including searches for Campylobacter jejuni and Borrelia burgdorferi. C-reactive protein was 4.88 mg/dl (normal $<$ 0.80). Serum cold hemagglutinin titer was 1 : 512 on day 4. Serum sample for anti-ganglioside antibody assay (day 22) did not reveal anti-GQ1b. Spinal fluid (day 6) was normal. Electrophysiology on day 4 revealed normal findings, whereas on day 11 there were low amplitude of peroneal muscle action potentials. EEG showed diffuse theta changes. MRI scans (day 2 and 6) revealed hyperintense enhancing lesions involving white matter of mid-brain, cerebellar peduncles, forebrain, and cerebellum. Since day 2, the patient was treated with methylprednisolone (1 g e.v. daily for 3 days, 500 mg for 2 days) with dramatic improvement. Steroids were tapered to oral regimen and slowly withdrawn. The patient steadily recovered within a month. In conclusion, this patient had a monophasic remitting illness preceded by pulmonary infection. The disease was characterized by central signs, such as altered consciousness, hyperreflexia, cerebellar ataxia associated with mild electrophysiological changes in nerves. Based on whole features, which included EEG abnormalities, Bickerstaff's brain stem encephalopathy (BBE) was diagnosed. Previous reports outline the occurrence of BBE without detection of antigangliosides antibodies and its relation with Miller Fisher's syndrome.

47 CASES OF FOOT DROP: A CLINICAL AND NEUROPHYSIOLOGICAL STUDY

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Mononeuropathies can occur following direct trauma, compression, stretch injury, ischemia, infection, or inflammatory disease. Nerve entrapments are due to compression of the nerve by either normal structures or an external source. The most common nerve entrapments are those of the median nerve at wrist (i.e., carpal tunnel syndrome) and ulnar nerve at elbow (i.e., cubital tunnel syndrome). Peroneal neuropathy is the most common isolated mononeuropathy in the lower extremity. Compression and entrapment neuropathies are predominantly demyelinating. Myelin loss results in slowing of the nerve conduction through the area involved. When acute compression occurs, this may result in a conduction block. Due to chronic compression, slowing velocity across the involved segment can be seen. When compression is severe, ischemic changes occur causing secondary axonal damage. Pure demyelinating lesions typically have a better capacity to recover. Ischemic injuries and nerve transection result in axonal damage. The aim of the study was to report our neurophysiological data in 47 patients with peroneal palsy from January 2004 to July 2005 to estimate the kind of damage to the peripheral nervous system (axonal or demyelinating) and the pathogenesis (metabolic or traumatic). For that purpose, we studied an analogous number of subjects affected by a selective suffering of the ulnar nerve, comparing two nerves that, for anatomical conditions, can be susceptible to focal injuries. Forty-seven patients with peroneal plasy were subjected to neurophysiological tests: peroneal, tibial, and ulnar motor nerve conduction velocity; sensory nerve conduction velocity of superficial peroneal and sural nerve. The kind of damage was defined as ''axonal'' if the amplitude of SAP and cMAP was reduced at less than 50%; ''demyelinating'' if the conduction velocity was $<$40 m/sec and 38 m/sec in the distal and proximal tract, respectively; or ''mixed'' when tests showed reduction of velocity and amplitude. We found 16 patients with selective lesion of peroneal nerve (34%); 9 with peroneal and tibial posterior nerves involved (19%); 22 cases in which the lesion of peroneal nerve is associated with a diffuse suffering of the peripheral nervous system (47%) due to metabolical diseases

POST-INFECTIOUS HAND WEAKNESS AS MILD FORM OF GUILLAIN-BARRÈ SYNDROME (GBS)

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Usually Guillain-Barrè syndrome (GBS) is characterized by ascending limb weakness, progressing to trunk and cranial regions. However, regional variants are recognized with weakness confined to limited regions. The unpredictability of course of GBS makes it difficult to determine whether the patient's condition will possibly worsen. Three patients presented with post-infectious hand weakness which remained confined to the distal muscles of upper extremities during whole course of the illness. A 68-year-old man (case 1) was admitted because of right anterior interosseus syndrome with onset six days after gastrointestinal infection. Case 2, aged 48 years, experienced bilateral hand paresthesias with inability to extend wrist, fingers and to abduct the right thumb. The third patient, aged 43 years, was admitted because of bilateral small hand muscle weakness developed six days after an influenza-like episode. Extensive emato-urinary tests, B12, folate level, CK, microbiological, viral screenings were negative, including HIV1–2, CMV, HSV1, HSV2, EBV. Search for Campylobacter jejuni and Borrelia burgdorferi were negative as well for Toxoplasma gondii. Tests for antiganglioside antibodies in serum in all patients were unremarkable. Spinal tap in case 2 (day 5) showed

increased protein content (62 mg/dl, normal below 45). Electrophysiology revealed in case 1 (day 5) signs of demyelination, in case 2 (day 13) axonal features, in case 3 (day 3 and 9) normal maximal velocity in upper and lower extremities. Case 1 and 3 recovered spontaneously within day 150 and 540. Case 2 had benefit from high dose of immunoglobulins (0.4 g/kg body weight). In conclusion, these patients were affected by a post-infectious benign neurological illness. Limited regional forms of GBS characterized by unusual focal signs or symptoms mimicking other illnesses such as compression neuropathies suggest that the pathologic and immunologic abnormalities in GBS can be localized and selective.

NEUROMYOTONIC DISCHARGES FOLLOWING OXALIPLATIN TREATMENT FOR COLORECTAL CANCER: CASE REPORT

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Neuromyotonic discharges are repetitive discharges of motor unit potentials, of high frequency (150–300 Hz) and short duration (0.5–5 sec.). They are the expression of a state of hyperexcitability either of motoneurons cell bodies (as in Stiff-man syndrome and in Tetanus) either of motor nerves fibers (as in channelopathies like Isaac's syndrome). Neuromyotonia has been described in some tumors and as a side effect of antineoplastic medications, typically oxaliplatin. This is a cytotoxic platinum compound first approved in Europe for the treatment of advanced colon and rectal cancer in association with fluorouracil and leucovorin. Neurological toxicity, which is different from cisplatin toxicity, can manifest in two forms: acute and chronic. Acute toxicity manifests as an acute, sensory, self-limited axonal neuropathy that often presents during infusion of medication, is increased by cold exposure, dissapears after infusion but can reappear during the following cycle even if is not associated with functional impairment. Chronic toxicity manifests as a sensory axonal neuropathy or neuronopathy, dose related and cumulative, does not regress between cycles and can cause chronic functional impairment in 10% of patients. Acute toxicity has a very high incidence (range from 81.5 to 98%) while chronic toxicity is more variable and is related to the numbers of cycles performed and to the amount of the individual dose for each cycle. We report a 58-year-old woman who developed the typical symptoms and EMG signs of acute oxaliplatin toxicity after 2 days of administration of this medication.

PATHOGENIC MECHANISMS IN MPZ MUTATIONS

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Myelin protein zero (MPZ), the main structural protein of peripheral myelin, is supposed to play an important role in myelin compaction, acting as an adhesion molecule. Missense mutations in MPZ (MPZmts) cause inherited neuropathies characterized by different grades of severity. Based on age of onset and disease severity, MPZmts were divided into early onset and late onset mutations. The aim of the project was to study the different pathogenic mechanisms underlying the two groups of mutant proteins. The human cDNA coding for the human MPZwt (MPZwt) and four MPZmts associated with early onset (H52R, Deletion 22–28) and late onset phenotype (T95M, H10P) were cloned in mammalian expression vectors. HeLa cells were transiently transfected with the plasmids coding for the MPZmts to investigate the protein trafficking, glycosylation and insertion into the cell membrane. The effects of MPZmts on cell viability, induction of apoptosis and intercellular adhesion were also studied. By co-transfecting each mutation with the wild type MPZ we evaluated a possible dominant negative effect. The two early onset mutations showed two different pathogenic mechanisms. H52R was correctly processed, glycosylated and inserted into the plasma membrane without exerting any effect on cell viability but strongly affecting the adhesive properties of the molecule. On the contrary, the deletion 22–28 was only partially expressed into the cellular surface, showing an intracellular retention and significantly affected the cell viability. Both the mutations associated with a late onset phenotype reached the cell membrane and promoted the intercellular aggregation in a comparable way with the MPZwt. Interestingly T95M was not glycosylated, while H10P was normally processed. When MPZmts were co-transfected with MPZwt, the wild type protein was never prevented from reaching the cellular membrane. These data suggest a more disruptive effect on the protein structure of MPZ early onset mutations, compared with MPZ late onset ones. The impaired glycosylation in T95M, a late onset axonal neuropathy, might play a role, interfering in axon-glia interactions.

HNPP-LIKE PHENOTYPE IN A CASE OF DUNNIGAN LYPODYSTROPHY

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Dunnigan Lypodystrophy (DL) is characterized by progressive loss of subcutaneous tissue in limbs and glutei beginning in puberty, excess of fat deposition in other regions and insulin resistance. Mutations in the LMNA gene, encoding the nuclear envelope protein lamin A/C, have been found in about half of the cases. A mutation in the PPARG gene has been later reported. The large spectrum of identified laminopathies also includes Emery-Dreyfuss

muscular dystrophy, LGMD1B, dilated cardiomyopathy, CMT2B1, mandibuloacral dysplasia, Hutchinson-Gilford progeria syndrome and some combinations of these different diseases. A 25-year-old woman, suffering from typical DL and bilateral recurrent tingling in IV and V fingers, weakness of ulnar nerve supplied muscles and plantar burning paresthesiae, complained of sub-acute drop shoot and leg hypoesthesia on left side. Physical and electrophysiological examinations showed sensory-motor left peroneal mononeuropathy at fibular head with partial conduction block, sensory-motor ulnar neuropathy at elbow, absence of achilleous tendon reflexes and sural neuropathy. Nerve biopsy showed loss of myelinated fibres and large Renaut bodies in more than 1/3 of fascicles. A previously unreported silent nucleotide substitution in the LMNA gene has been identified in the proband and her healthy mother (c.1551G > A). The mRNA analysis has been unable to demonstrate a role of this change in the splicing process. No mutation was found in the PPARG gene. Molecular analysis ruled out the presence of a PMP22 deletion or point mutations. Various types of neuropathy have been described in muscular laminopathies. Moreover, a co-segregation of LMNA and PMP22 mutations leading to a combined phenotype of muscular dystrophy plus HNPP has been recently reported (Pegoraro, 2005). The coexistence of DL and neuropathy has not been described until now. Our findings could be purely explained by a nerve mechanical liability to pressure due to loss of subcutaneous fat in anatomical sites of entrapment. The amount of Renaut bodies seems to confirm this hypothesis. However, the symmetry of ulnar and sural electrophysiological abnormalities, and the severity of sural involvement do not exclude completely the possibility of an underlying congenital neuropathy.

MONONEUROPATHY OF THE COMMON PERONEAL NERVE AS UNUSUAL COMPLICATION OF MULTIPLE MYELOMA IGA LAMBDA: A CASE REPORT

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Peripheral neuropathy is a rare complication of multiple myeloma (MM). Amyloidosis (AL) complicates MM in 30–40% of patients. A symmetrical, distal sensory-motor or sensory with or without autonomic involvement is the most common type of neuropathy; atypical presentation of AL neuropathy has also recently been reported. We describe a patient with a mononeuropathy of the common peroneal nerve as atypical presentation of the disease.

INAPPROPRIATE SECRETION OF ANTIDIURETIC HORMONE (SIADH) IN A PATIENT WITH SUBACUTE DEMYELINATING POLYNEUROPATHY: A PARANEOPLASTIC DISORDER?

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We report a patient with SIADH associated with subacute demyelinating polyneuropathy preceding the diagnosis of a remote tumour. This 73-year-old woman was admitted because of delirium, lower limb weakness, and frequent falls. Routine laboratory tests were normal, except for decreased serum Na concentration (119 mEq/l, normal 136–145). Sodium urinary excretion was normal. The patient was diagnosed as having SIADH and treated with hypertonic saline combined with furosemide. By day 15, the patient developed areflectic paraplegia, distal weakness, sensory loss for touch and pin-prick. Serum concentration of immunoglobulins was within normal. Anti-ganglioside antibodies could not be detected; tumor marker titer was normal. Viral screening for HIV, hepatitis, and vasculopathies were negative. Cerebrospinal fluid examined on day 60 revealed increased protein (561 mg/dl, normal below 45 mg/dl). On electrophysiology, a severe sensorimotor neuropathy was diagnosed in upper and lower extremities. Total body CT-scan and exhaustive searches for remote tumour did not reveal malignancies. Brain CT and MRI scans were negative. Treatment with high dose of immunoglobulins (0.4 g/kg/day for 5 days) was administered. Three months after admission, the patient could only sit in a wheelchair. Her sensory-motor neuropathy had no improvement. Neck CT scan one year after onset of symptoms revealed a mass lesion in the right pharynx diagnosed as an epithelial tumour. SIADH may result from various disorders, such as stroke, brain tumors, sinus thrombosis, or meningitis. It can occur in association with acute post-infectious polyradiculopathy, acute autonomic sensory neuropathy, or paraneoplastic sensorimotor neuropathy. The pathogenic mechanism of SIADH in neuropathies is yet undetermined.

RELAPSING GUILLAIN-BARRÉ SYNDROME FOLLOWED BY CHRONIC INFLAMMATORY POLYRADICULONEUROPATHY IN CHILDHOOD

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We report the case of a girl who was affected by 2 episodes of acute inflammatory polyradiculoneuropathy with almost complete regression followed by a chronic progressive form many years after the first event. When she was 4 years old, the patient presented a first episode of acute polyradiculoneuropathy characterized by diffuse weekness affecting particularly the deambulation. At cerebrospinal fluid exam, a pattern of hyperproteinorrachia without pleiocytosis was found. She was than treated with steroids and immunoglobulins e.v. with complete regression in three months. When she was 12, she had a second similar episode. After treatment with immunoglobulins e.v. the condition improved in two months with residual slight leg weakness. Two years later, she complained of subacute alteration of sensibility and strength. A neurologic evaluation evidenced symmetrical hypoesthesia and paresthesias at fingers and at legs distally from knees, associated with distal

weekness and ataxic gait. The cerebrospinal fluid exam showed augmentation of protein and immunoglobulin G concentration (respectively, 1.04 g/l and 230 mg/l), without pleiocytosis. In spite of 2 cycles of immunoglobulins e.v., she presented a gradual worsening of sensory and motor deficits. She is currently being treated with steroids and immunosuppressant (azathioprine) with stabilization of the clinical picture. The transformation from a relapsing Guillain-Barré syndrome into a chronic progressing form of inflammatory polyradiculoneuropathy is an unusual evolution in childhood.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN DIABETIC PATIENTS AND CLASSICAL SENSORY MOTOR DIABETIC POLYNEUROPATHY: COMPARISON AND LONG TERM FOLLOW-UP BETWEEN 2 CONSECUTIVE SERIES OF PATIENTS

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CIDP is a common, underdiagnosed, potentially treatable disease and recently more and more diabetic patients with a peripheral neuropathy indistinguishable from chronic inflammatory demyelinating polyneuropathy have been described (CIDP-DM). The recognition of this disorder as distinct from common chronic sensorimotor polyneuropathy that accompanies diabetes (DPN) is important because it is a treatable condition where immunosuppressive treatment is indicated. There is controversy over whether the clinical, CSF, electrodiagnostic, and histologic features distinguish between CIDP and diabetic polyneuropathy. In order to focus on the differences between these two conditions we have prospectively followed up 2 consecutive series of diabetic patients, with DPN or CIDP. All diabetic patients with a clinical polyneuropathy referred to our neuromuscular disease unit during the 18 months of the study were exaustively examined and prospectively followed-up (24 months). All patients were treated for diabetes and followed by trained diabetologists. One hundred ninety eight consecutive patients were referred to our neuromuscular unit during the 18 months of the study. Forty eight patients (24.2%) had an axonal, sensory-motor, sometimes painful, diabetic polyneuropathy (DPN) and 16 other diabetic patients (8%) had a demyelinating polyneuropathy fulfilling the most restrictive diagnostic criteria for CIDP (CIDP-DM). Fourteen other diabetic patients (7%) had a demyelinating polyneuropathy not fulfilling the requested diagnostic criteria for CIDP. All patients underwent tight glycemic control. CIDP-DM patients were treated with IVIg and treatment responders were retreated in case of relapse. At the end of the follow-up (24 months) the median number of treatments was 3. NDS score changed from 38 at presentation to 18 at the end of the follow-up ($p = 0.0004$). NDS score in the DPN patients changed from 23 to 22. As previously underlined, beside attempts to achieve tight regulation of blood glucose, there is no specific effective treatment for classical diabetic neuropathy. Once set up, the distal polyneuropathy is irreversible. Our study enhances the importance to recognize diabetic patients with an autoimmune neuropathy because of the therapeutic implications.

LATE-ONSET AXONAL CHARCOT-MARIE-TOOTH DISEASE ASSOCIATED WITH A NOVEL MPZ MUTATION

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Myelin protein zero (MPZ) is a major component of compact myelin in peripheral nerves where it plays an essential role in myelin formation and adhesion. MPZ gene mutations are usually responsible for demyelinating neuropathies, namely Charcot-Marie-Tooth (CMT) type 1B, Dejerine-Sottas neuropathy and congenital hypomyelinating neuropathy. Less frequently, axonal CMT (CMT2) associated to MPZ mutations have been described. We report five patients (a sporadic case and four subjects from 2 apparently unrelated families) with a late-onset, progressive, axonal peripheral neuropathy. All patients developed gait difficulties between age 47 and 55. Disease course was quite severe with progressive wasting and weakness of lower limbs (LL). All patients needed ankle foot orthoses or aid for walking after some years from onset, some developed proximal LL weakness. Sensory involvement was milder. None of them had pes cavus. Electrophysiological studies showed severe sensori-motor axonal neuropathy, with absent or markedly reduced CMAPs in LL motor nerves, but normal CMAPs in upper limbs. Nerve conduction velocities were normal or only slightly reduced, in the CMT2 range. Sensory nerves were affected in all limbs, but to a lesser extent. Nerve biopsy was performed in two patients and findings were consistent with a classic CMT2 pathology, disclosing a severe axonal neuropathy with clusters of regeneration, but no evidence of myelin outfoldings, tomacula, or other abnormalities. In all patients, molecular analysis demonstrated a novel heterozygous missense mutation in MPZ exon 2 (208C > T), causing the Pro70Ser substitution in the extracellular domain. The diagnosis of CMT2 associated to MPZ mutations should be considered in patients with either familial or sporadic progressive, late-onset polyneuropathy. The mechanism by which a compact myelin protein mutation results in axonal neuropathy remains to be elucidated. *Partially supported by Telethon-UILDM grant GUP02169.*

THE "ANTERIOR TARSAL TUNNEL SYNDROME": A MISLEADING MONONEUROPATHY

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The "anterior tarsal tunnel syndrome" is a misleading neuropathy: firstly, no true anatomic "anterior tarsal tunnel" exists; secondly, this often asymptomatic distal deep peroneal mononeuropathy at the ankle involves a nerve (the

peroneal nerve) and a muscle (the extensor digitorum brevis muscle) frequently examined in routine EMG-ENG studies. Its incidence is unknown. In our clinical EMG-ENG laboratory between January 2000 and December 2005 we performed 9385 examinations using Nicolet Viking IV equipment. Diagnosis of deep peroneal mononeuropathy at the ankle (DPNA) was made when, in the absence of polyneuropathy, peroneal motor distal latency was more than 3 SD above the mean and (if unilateral) more than 130% of the contralateral value and when chronic neurogenic MUAP changes were found in EDB muscle. According to these electrophysiological criteria 47 patients had a DPNA; its incidence (about 5%) was higher than that of ulnar neuropathy at the wrist. On specific enquiry the patients were always asymptomatic although a remote cause could often be identified. DPNA was often (70%) an incidental finding in patients referred for aspecific leg pain and suspected lumbosacral radiculopathy. In these patients a high degree of suspicion is necessary in order to avoid a wrong electrophysiological diagnosis.

MULTIPLE ANTIBODIES MAY COEXIST IN A PATIENT WITH SQUAMOUS CELL LUNG CARCINOMA

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Patients affected by cancer may develop signs due to damage of the nervous system with a variety of clinical syndromes. Combination of indolent tumours and progressive neurologic disability, in absence of metastases, may suggest antitumour immunity. A 78-year-old female smoker was admitted after ten months of progressive paresthesias in hands and feet and severe gait instability. Examination showed normal mental state, spontaneous nystagmus towards to left, scanned speech, severe limb, trunk ataxia. There was distal extremity weakness graded as 4 (MRC scale) areflexia, impaired sensation for touch, pin-prick, temperature position. Electrophysiologically an axonal sensory-motor polyradiculopathy was diagnosed. Normal results included routine blood tests, neoplastic markers, viral, microbiological, autoimmune, rheumatological screenings. Serum antineuronal nuclear autoantibodies type 1 (anti Hu ANNA-1) and anti Ri (ANNA-2) determined by Western blot were positive. Total body TC and F-deoxyglucose positron emission tomography revealed a 13-mm lesion in the right lung, diagnosed as squamous cell carcinoma. The patient was treated with immunoglobulins intravenously (0.4 g/kg body weight for 5 days). IVIg were repeated monthly for 5 months with transient improvement. The patient received combined chemotherapy with gemcitabine 8 (1 g/mq^2 for 3 days every 4 weeks). Paraneoplastic syndromes may rarely occur. Neurological symptoms are related to production of antibodies against tumoral antigens showing cross-reaction with nervous system structures. In our case, coexistence of multiple antibodies may reflect targeting of multiple autoantigens. The occurrence of multifocal symptoms may reflect immune responses to multiple onconeural antigens related to intermolecular epitope spreading.

MOTOR NEUROPATHY RESPONSIVE TO A GLUTEN-FREE DIET IN ASYMPTOMATIC CELIAC DISEASE: A CASE REPORT

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Celiac disease (CD) is an inflammatory autoimmune enteropathy resulting from sensitivity to ingested gluten. Since 1966 CD has been associated with neuropathy, both as a complication of a diagnosed CD and as an initial manifestation of CD. Whether serological tests for CD should be part of the diagnostic screening in patients with neuropathy of unknown cause is controversial. A 62-year-old woman presented in June 2005 complaining of progressive limb weakness lasting for two months. Neurological examination showed weakness of finger extensors (MRC 2/5) and foot dorsiflexors (she was not able to walk on her heels, MRC 4/5). Needle electromyography showed fibrillation potentials in the following muscles: right and left extensor digitorum communis, right and left tibialis anterior, left deltoid, left biceps brachii and right I dorsal hand interosseous. The recruitment was markedly reduced in extensor digitorum communis and tibialis anterior, and minimally reduced in right I dorsal hand interosseous. Motor and sensory neurography were normal, except mild slowing of motor conduction of radial nerves. Spinal MRI failed to show any nervous system lesion. Serological screening of autoimmunity revealed increased titers of anti-gliadin IgA, EMA IgA, tTG IgA and anti-thyroid antibodies. Anti GM1 IgM assay was negative. Duodenal biopsy showed villous atrophy, crypt hyperplasia and lymphocytic infiltration. There was no biochemical evidence of malabsorption. In January 2006 she can walk normally on her heels; extensor digitorum communis strength is 4/5 (left) and 3/5 (right). Fibrillation potentials are detectable only in right digitorum communis. Motor nerve conduction velocity is slightly reduced in right radial nerve and borderline in left radial nerve. In our patient clinical and electrophysiological data were consistent with multifocal motor neuropathy or lower motor neuron disease. The neurological picture was associated with asymptomatic CD and anti-thyroid autoimmunity, and markedly improved during a gluten-free diet. Although a chance association is possible, we suppose in our patient a causal relationship between CD and motor neuropathy, and suggest to perform EMA and tTG IgA tests in similar cases.

GABA-A AND GABA-B RECEPTORS PARTICIPATE IN THE AXON-SCHWANN CELL INTERACTIONS

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The gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter responsible for neuron-to-neuron communication and also neuron-to-glia interactions in the nervous system. In fact, different mechanisms involving the GABA receptors (i.e., GABA-AA and GABA-B receptors)

seem to play pivotal roles during the development and differentiation of glial precursor cells. In the rat peripheral nervous system (PNS), both the rat sciatic nerve and the Schwann cells express the GABA-A and the GABA-B receptor isoforms, which are proved to be functionally active. A physiological role for GABA and its receptors in the PNS might be hypothesised. In particular, we have demonstrated that the selective ligands of the GABA-A and GABA-B receptors, respectively muscimol and baclofen, control Schwann cell proliferation and the expression of some specific myelin proteins (e.g., glycoprotein P0; peripheral myelin protein 22, PMP22; connexin 32; myelin associated glycoprotein, MAG). Moreover, we have also reported that some neuroactive steroids, such as the allopregnanolone (THP) and androstenediol (3alpha-diol), known to be allosteric modulators of the GABA-A receptor, are able to control PMP22 synthesis in the Schwann cell. In addition, we have recently observed that THP is the main modulator of the different GABA-B subunit (i.e., 1a, 1b, 2) expressions in Schwann cells; some of these effects are mimicked by muscimol and GABA, indicating GABA-A-mediated effects in such a control. Collectively, our observations suggest that, in the PNS, the cross-talk between the GABAergic system (via the GABA-A and GABA-B receptors) and the neuroactive steroids may play an important role in the neuron-Schwann cell interactions, which are modified in case of peripheral degenerative neuropathies. *Supported by E.C. QLK6-CT-2000–00179.*

GUILLAIN-BARRÈ SYNDROME ASSOCIATED WITH MENTAL STATUS ABNORMALITIES: FOUR CONSECUTIVE PATIENTS

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Guillan-Barrè syndrome (GBS) is often associated with mental status abnormalities such as vivid dreams, illusions, and hallucinations. Risk factors for the mental status abnormalities are autonomic dysfunction, CSF (cerebrospinal fluid) high protein level, and assisted ventilation requiring intensive care unit (ICU) admission. The biological determinant of this status is unknown but it appears to be a strong association with lower level of CSF hypocretin-1. We describe four consecutive patients affected by GBS who came to our observation within one month. They all experienced hallucinosis and sleep disorders characterized by insomnia, vivid dreams and hypnagogic hallucinations. These symptoms were present at the beginning of the disease, excluding a possible effect of hospitalization. Moreover none of our patients needed ICU admission or assisted ventilation, excluding the diagnosis of ICU delirium. None of our patients developed autonomic dysfunction, hyponatriemia, or other central nervous system (CNS) dysfunctions. CSF hypocretin-1 dosage is currently ongoing in three of these patients. Finally we describe a cluster of GBS patients who experienced mental status abnormalities, in absence of the above risk factors. All patients were treated with IV immunoglobulin and they had a good and quick strength recovery and in the meantime hallucinations disappeared. In absence of the described risk factors for hallucination in GBS patients it could be that the same infectious pathogen triggers both the motor deficit and the mental status and that the same autoimmune pathogenetic mechanism causing demyelination in the nerve induces CNS dysfunction.

MOLECULAR PROFILE OF PARANEOPLASTIC PERIPHERAL NEUROPATHY: A MICROARRAY ANALYSIS

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Paraneoplastic peripheral neuropathy (PPN) is a clinical and immunological heterogeneous disorder. In the majority of paraneoplastic neurological disorders, circulating autoantibodies directed against neurons have been found in the serum and/or the CSF suggesting disimmunity in the pathophysiology of these diseases. The aim of the present study was to investigate the molecular profile of PPN. We performed a microarray analysis in 4 patients with definite PPN according to PNS Euronetwork criteria (2 patients with sensory neuronopathy with anti-Hu and anti-amphiphysin antibodies, respectively; 1 patient affected by lung cancer with sensory neuronopathy and anti-Hu antibodies; 1 patient with sensory-motor neuropathy and osteosclerotic myeloma) and in 2 normal subjects; 3 patients with axonal type CMT were studied as disease controls. Microarray experiments were performed using amplified RNA isolated from cryostat sections of sural nerve biopsy. A GeneChip microarray panel of cDNA human gene array containing approximately 40000 genes from human genome was used. We found different clusters of greatly activated genes including heat shock protein, chaperone binding protein, MHC I and II protein, nuclear factor of activated T cell (NTAT) protein binding, tau protein and cell development protein (neuron differentiation, regulation of cell differentiation, vasculogenesis). Other gene clusters appered downregulated such as blood vessel development and neurite regeneration proteins. Our preliminary data of microarray gene profile suggest the involvement in PPN of molecules implicated in inflammatory, oxidative stress, and DNA damage responses. Microarray analysis could be an effective tool for identifying genes differently involved in PPN and for better understanding of the pathogenetic mechanisms of PPN.

ACQUIRED IDIOPATHIC GENERALIZED ANHIDROSIS: A CASE REPORT

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We report the case of a 31-year-old man who, after a viral infection 4 years earlier, had developed heat intolerance

with episodes of hyperthermia and burning pain all over his body, tachycardia, symptoms of exhaustion and fainting during the summer and after physical exertion. The patient referred a partial improvement of the symptoms in the last year. Family history and neurological examination were negative. The whole body skin was xerotic. Routine haematological, thyroid function tests, onconeural antibodies and collagen profile, including rheumatoid factor, antinuclear factor and complement were normal. Nerve conduction study and a battery of cardiovascular automonic tests were also normal. Sympathetic skin response was absent. A slight impairment of sensory perception was observed by quantitative sensory testing (QST) including pinprick, tactile and thermal thresholds. Thermoregulatory sweat test showed complete anhidrosis, except for small areas of sweating in the axilla. Silastic imprint test revealed a severe reduction of functional sweat glands after stimulation with pilocarpine by iontophoresis. Histopathological analysis showed a normal morphology of sweat glands and absence of inflammatory infiltrates. The immunohistochemical study of cutaneous innervation allowed detection of a normal density of epidermal nerve fibers (ENF) although they showed mild qualitative abnormalities, and a normal VIP immunoreactive sudomotor innervation. Generalised anhidrosis is a rare congenital or acquired disease. In our patient the normal number of nerve terminals associated with histologically normal eccrine glands suggests that a functional alteration of sympathetic cholinergic nerves is responsible for the anhidrosis. The subacute onset with a monophasic course and partial remission may suggest an autoimmune origin.

HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES: CLINICAL MANIFESTATIONS DO NOT FIT THE NAME

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Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominantly inherited disease of the peripheral nerves associated with a 1.5-megabase deletion on chromosome 17p11.2–12 containing the PMP22 gene. Recurrent mononeuropathies manifesting as transient episodes of weakness or sensory loss, often preceded by minor trauma, are usually considered the clinical hallmark of this condition. However, a minority of patients have been described disclosing atypical phenotypical pictures, including symmetric chronic polyneuropathy, brachial plexopathies, Guillain-Barrè syndrome, chronic mononeuropathies. To characterize the phenotype of the deletion of chromosome 17p11.2–12 we evaluated the clinical picture and neurophysiological finding of 34 patients from 24 families admitted to our Neurological and Medical Genetic Institutes. Eleven patients (32%) presented with classic episodes of transient mononeuropathy related to trivial nerve trauma. In the remaining 23 patients (68%) the clinical picture was atypical and included 9 patients with chronic mononeuropathy (4 carpal tunnel syndrome and 5 ulnar compression at the elbow), 7 patients with a Charcot-Marie-Tooth phenotype, 1 patient with a Guillain-Barrè-like pattern, 2 patients with a chronic sensory polyneuropathy, 1 patient with fatigue, and 1 patient with acute recurrent brachial plexopathy. Two patients were asymptomatic. In all patients electrophysiological studies showed generalized neuropathy with moderately slowed conduction velocities, more obvious over entrapment sites. Our data show that phenotypic manifestations of 17p11.2 deletion are very heterogeneous and that classic recurrent focal neuropathy is not the most frequent one. Genetic tests should be performed based on the peculiar electrophysiological findings more than on clinical examination.

THALIDOMIDE NEUROPATHY: IS LOW-INTERMITTENT DOSES OF THALIDOMIDE IN THE MAINTEINANCE TREATMENT OF MULTIPLE MYELOMA LESS NEUROTOXIC?

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In recent years thalidomide has been reintroduced into clinical use for some refractory dermatologic and oncologic diseases, primarily multiple myeloma. With avoidance of thalidomide use during pregnancy, peripheral neuropathy has become the most important complication that is dose limiting in more than 25% of patients. For this reason we have investigated if low doses of thalidomide are not toxic but effective in maintenance treatment of patients with multiple myeloma. Among 20 patients with a good response after thalidomide treatment, we selected 8 patients with peripheral neuropathy and reduced the dosage of thalidomide at 100 mg/day only for 10 days a month as maintenance treatment. We prospectively performed longitudinal clinical neurologic and nerve conduction studies, before and during thalidomide treatment, every 3 months. In the subsequent 6–31 months follow-up evaluation no progression of clinical and electrophysiological findings was demonstrated. Our study shows the low toxicity of this schedule but the number of patients who employed this schedule is too small. Larger randomised studies must be performed to demonstrate the real efficacy of this new maintenance treatment.

THREE NOVEL MUTATIONS IN THE MFN2 GENE CAUSING FAMILIAL AND SPORADIC AXONAL CHARCOT-MARIE-TOOTH DISEASE TYPE 2 (CMT2)

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Axonal CMT (CMT2) is genetically highly heterogenous, with at least 14 loci and 10 genes identified thus far. Mutations in the gene encoding the mitochondrial protein mitofusin-2 (MFN2) have been shown to be responsible for autosomal dominant CMT2 type A2 (CMT2A2). The MFN2 gene maps to chromosome 1p36.2 and encodes a 757-amino acid protein which is an essential component of mitochondrial fusion in mammalian cells. The CMT2A2 phenotype is

largely indistinguishable from that of CMT2A1 (KIF1B), CMT2E (NEFL), and CMT2F (HSPB1). However, in a subset of CMT2A2 patients, pyramidal involvement and visual impairment have been reported. The disease exhibits reduced penetrance: studies in large families have shown that individuals with MFN2 mutations may present no signs of disease even at the electrophysiological examination. We studied 54 index patients with axonal CMT who had been previously found to be negative for mutations in the NEFL gene (8p21). Familiarity was reported in one case only. Three novel mutations were detected in 3 unrelated patients. DHPLC analysis of the 17 MFN2 exons and exon-intron boundaries showed an alterated profile in exon 9, 15 and 19 but in none of 47 control patients. Sequence analysis revealed three heterozygous missense mutations (Cys281Ser, Asn525Ser, Ala739Val) in two sporadic cases (Pt. 1 and Pt. 2) and in the familial index case (Pt. 3). Pt. 1 and Pt. 2 manifested an adult- or juvenile-onset CMT2, respectively. By contrast, early-onset, severe progression, and proximal involvement characterized the disease in Pt. 3 and his affected daughter who also carried the mutation. Interestingly, Pt. 3 had brisk reflexes suggesting pyramidal involvement. Our results indicate that: 1) MFN2 mutations are not rare causes of axonal CMT; 2) genetic testing for CMT2 should begin from the MFN2 gene; and 3) MFN2 mutation analysis should be performed in both familial and sporadic cases. *Supported by Telethon-UILDM (GUP04009) and Fondazione Mariani (R-05–44).*

REVERSIBLE SEVERE SUBACUTE RESPIRATORY FAILURE IN A CASE OF CHRONIC LONG-STANDING DYSIMMUNE MOTOR POLYNEUROPATHY

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We report the case of a 60-year-old man with an 11-year history of a chronic, distal, mainly symmetric, upper limb predominant lower motor neuron syndrome. Neurophysiological studies were consistent with a chronic primary demyelinating pure motor polyneuropathy without definite conduction blocks. He never had sensory symptoms or upper motor neuron signs. CSF and sural nerve biopsy were normal. He had high anti-GM1 IgM antibody titres on several assays. Steroids worsened the symptoms. He was successfully treated for 4 years with IGev, which lost efficacy over time. Six years after disease onset he developed a marked axonal loss leading to a very severe distal symmetric upper limb predominant muscle wasting, which no longer progressed after monthly ev cyclophosphamide for 6 months. The clinical picture did not worsen over the following 3 years without therapy until he was admitted to the ICU because of a hypercapnic acidotic respiratory coma. During the past 3 weeks he had complained of marked daytime sleepiness without impairment of motor performances. Neurological examination in the ICU showed no cranio-bulbar signs, slight and unchanged proximal weakness and complete respiratory paralysis. EMG from proximal limb muscles showed scattered denervation with a mild neurogenic sub-interferential recruitment pattern. Diaphragm EMG also showed scattered denervation but with a markedly neurogenic single motor unit firing pattern. Phrenic motor responses were bilaterally absent; two CSF examinations were normal, making a diagnosis of superimposed GBS unlikely. He was treated with IGev plus ev cyclophosphamide. Ten days later he gradually recovered active respiratory movements. Spirometric parameters steadily improved over the following 5 months and phrenic motor responses reappeared. At 1-year follow-up he has normal spirometric values and is normocapnic during the daytime. This case exemplifies that dysimmune motor neuropathies represent a spectrum of disorders encompassing typical MMN, motor CIDP and lower motor neuron type syndromes. While most of the cases are reported to have a chronic benign course, we describe a subacute life-threatening evolution with prominent phrenic nerve involvement, which needs to be considered as it is potentially reversible by aggressive immunomodulatory treatment.

TORTUOUS DOLICHOECTASIC ULNAR ARTERY AS A CAUSE OF GUYON'S SYNDROME: REPORT OF TWO CASES NOT RELATED TO TRAUMA

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Among the several causes of ulnar neuropathy at the wrist (UNW), compression by vascular abnormalities is rare. It has been mainly described in association with post-traumatic aneurysms of the ulnar artery. We describe UNW due to a neurovascular conflict with an evident tortuous dolichoectasic ulnar artery impinging the nerve at the piso-hamate hiatus level in two patients. To our knowledge only three similar cases have been described in the literature. Both patients were males, aged 47 and 50, respectively; they had no history of acute or chronic wrist or hand trauma and the neuropathy occurred in the non-dominant hand. One patient presented with slowly progressive weakness and wasting of all ulnar intrinsic hand muscles (UIHM) without sensory symptoms over four months. EMG study was consistent with a type II° UNW. The second patient presented with continuous slowly progressive hypoesthesia and paresthesias in the distal palmar ulnar region followed by wasting of all UIHM over three months. EMG study disclosed a type I° UNW with markedly predominant axonal loss in the deep motor branch. In both patients pain was not a relevant feature; no pulsatile masses were evident at inspection; signs of ischemia or vasomotor changes were absent and Allen's test was negative. In case 1 the vascular abnormality was seen only during surgery, while in case 2 wrist MRI studies, before surgery, disclosed a serpiginous ulnar artery that could be the cause of ulnar nerve compression. Neurolysis was followed by complete functional recovery in both patients. These two cases suggest the need of a thorough investigation of the nerve-artery relationships in UNW, even when the search for vascular abnormalities is negative on clinical examination. This can be done first by Eco-Color-Doppler techniques and then by angio-MRI or CT.

Smaller ulnar artery abnormalities might represent an underdiagnosed cause of UNW. In fact, they might be overlooked during surgical exploration at wrist because this is generally performed with limb ischemia, not allowing direct appreciation of a pulsatile abnormality as the aetiological factor. From a surgical point of view, we emphasize the need of an extended approach exploring the whole length of Guyon's canal and the relevance of piso-hamate ligament resection during the surgical procedure.

NOVEL GDAP1 MUTATIONS ASSOCIATED WITH SEVERE EARLY-ONSET CHARCOT-MARIE-TOOTH DISEASE

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Mutations in the GDAP1 gene cause autosomal recessive demyelinating (CMT4A) and axonal (AR-CMT2K) Charcot-Marie-Tooth disease. The gene encodes a protein possibly involved in the maintenance of the mitochondrial network. Patients with GDAP1 mutations usually exhibit severe early-onset peripheral neuropathy, inconstantly associated with vocal cord paralysis. We studied 7 patients from 3 families with early-onset and severely progressive sensory-motor peripheral neuropathy. All patients presented at 1.5–2 years with gait difficulties, progressive wasting and weakness of distal lower limbs, followed by upper limbs involvement. At the age of 6–7 years, they developed a complete foot-and-hand plegia. The oldest patient lost autonomous gait at 13 years of age. At that time, a vocal cord paresis was also noticed. In all patients, SAPs and CMAPs could be evoked neither in upper nor in lower limbs. Four cases belong to a highly consanguineous Southern Italian family (Family 1). Sequence analysis of GDAP1 exon 2 revealed a homozygous nonsense mutation (Gln99stop) that would result in the premature truncation of the protein and would predict its complete absence. In Family 2, two affected siblings were found to be compound heterozygous for a nonsense mutation in exon 3 (Arg125stop, of paternal origin) and a missense mutation in exon 6 (Leu239Phe, of maternal origin). In Family 3, a boy carried a paternally inherited missense mutation in exon 5 (Val 219Asp) and a maternally-inherited missense mutation in exon 6 (Asn297Lys). Sural nerve biopsy was performed in patients from Family 1 and Family 2 at the age of 3 and 4 years, respectively. Both cases showed a severe neuropathy characterized by a predominant axonal involvement with loss of myelinated and unmyelinated fibres and regenerative clusters associated with signs of chronic demyelination and simple onion-bulb formation. *Supported by grants from Telethon-UILDM (GUP04009) and Fondazione Mariani (R-05–44).*

USEFULNESS OF MULTIDISCIPLINARY APPROACH TO INHERITED NEUROPATHIES

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Inherited neuropathies are a heterogeneous group of PNS disorders, which may present with common clinical phenotypes, but show extremely variable genetic, neurophysiological and neuropathological features. Charcot-Marie-Tooth (CMT) disease and related neuropathies represent the most frequent type of inherited neuropathies. Mutations in more than 35 genes and 50 genetic loci have been linked to different CMT phenotypes. A multidisciplinary approach to these diseases could give a better diagnostic definition and help in addressing patients to rehabilitation therapy. In the Department of Neuroscience, Ophthalmology and Genetics we organized a team where specialists in neurology, clinical neurophysiology, clinical genetics, and physical medicine cooperate to diagnose and plan genetic tests and rehabilitation programs. From November 2004 through July 2005, 97 subjects (52 males and 47 female, median age 44 years) were evaluated. Neurological examination, CMT neurological score, Ambulation Index (AI) and nerve conduction studies were performed in most patients. A complete genetic and physical examination were also carried out. 29/97 (31%) have already had a defined genetic diagnosis (24 CMT1A, 3 CMT1B and 2 HNPP). In 26 patients (27%) a clinical diagnosis of inherited neuropathy was supposed (4 subject) or confirmed (22); in 14 subjects (14%) a neuropathy was excluded, in 12 (12%) patients a new genetic diagnosis was performed. In 7 (7%) spastic paresis was diagnosed and in 2 of them the genetic defect was defined. Five patients (5%) were affected by acquired neuropathies, two (2%) by an acquired motor neuron disease. In two cases (2%) diagnosis was uncertain. In conclusion a multidisciplinary approach to inherited neuropathies could give a better diagnostic accuracy, revealing other or acquired neuromuscular disorders, providing adequate rehabilitation therapy to the patients.

IMMUNOHISTOCHEMICAL EVIDENCE OF CUTANEOUS AUTONOMIC IMPAIRMENT IN A CASE OF CHAGAS DISEASE

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Chagas disease (American Trypanosomiasis) is caused by the infection with the haemoflagellate parasite Trypanosoma cruzi, which is transmitted from animals to man by the Reduviidae bug. The involvement of visceral autonomic nervous system is the pathological basis of the main clinical features of this diseases: arrhythmias, megaesophagus and megacolon. Electrophysiological study on a large series of Chagas patients demonstrated an involvement of somatic peripheral nervous system in a percentage of 5–10%. We present the case of a 60-year-old female patient, born in Brasil, affected by Chagas disease without visceral involvement. She complained of burning pain at lower extremities for several years. Neurological and standard electrophysiological evaluation

were normal. We performed quantitative sensory testing, silastic imprint test and skin biopsies. We found an increase of tactile and thermal thresholds and an impairment of mechanical and thermal pain perception. Silastic imprint test revealed a reduction of activated sweat glands after stimulation with pilocarpine by iontophoresis. The immunohistochemical study of skin samples showed abnormalities of cutaneous innervation involving mainly autonomic fibers to sweat glands, arrector pilorum muscles and blood vessels. Although epidermal nerve fiber density was normal we observed evident predegenerative aspects such as varicosities, fragmentation and anomalies of distribution. Our findings suggest that skin biopsy could be a suitable tool to detect an impairment of autonomic nervous system in Chagas disease before cardiac or gastroenteric denervation becomes manifest.

MULTIFOCAL DEMYELINATING NEUROPATHY WITH ANTIGANGLIOSIDE ANTIBODIES SUPERIMPOSED TO VASCULITIS

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Conduction block (CB) and excessive temporal dispersion are the electrophysiological correlates of de-remyelination. However CB has been described also in vasculitic neuropathy. In the reported cases distal compound muscle action potentials (CMAP) had small amplitudes and CB could be explained by interphase shift and cancellation in nerves with a small number of surviving motor fibers. Another criticism advanced is the lack of sequential recordings and the possibility of a pseudo-conduction block due to ischemic focal axonal damage with subsequent recordings likely to show a progressive fall in distal CMAP amplitude because of advancing Wallerian degeneration. We report a 30-year-old man who presented with numbness and tingling in both legs, more on the left, and difficulties in walking on heels and toes. Laboratory tests showed type I cryoglobulinemia with IgG kappa monoclonal gammopathy. Serology for HCV was negative and a lymphoproliferative disorder was excluded. Conduction velocities showed an axonal moneuritis multiplex. Sural nerve biopsy documented a severe axonal neuropathy with signs of vasculitis. The patient was treated with steroids, plasma exchange and azathioprine. After four years, in correspondence of a worsening with weakness of intrinsic hand muscles, conduction velocities showed excessive temporal dispersion with possible partial CB in the elbow-wrist segment of right median and ulnar nerves and left median nerve. These findings persisted at sequential recordings for two years. Antibody testing showed high titre (>3200) IgM anti-GM1 and anti-GD1a. We deem that in this patient persisting excessive temporal dispersion of proximal CMAPs is due to a possibly immunomediated de-remyelination superimposed to the primitive vasculitis.

ANTIRETROVIRAL TOXIC NEUROPATHY IN HIV INFECTED PATIENTS: NEUROPROTECTIVE AND SYMPTOMATIC TREATMENT WITH ACETYL-L-CARNITINE (ALCAR GROUP STUDY)

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Nucleoside analogue reverse transcriptase inhibitors disrupt neuronal mitochondrial DNA synthesis, resulting in antiretroviral toxic neuropathy (ATN). Experimental data showed that Acetyl-L-carnitine (ALCAR) has an analgesic, neuroprotective and neurotrophic effect on sensory neurons, potentially causing symptom relief and nerve regeneration. Data from a previous open study, based on clinical assessment and punch skin biopsies, showed that after 6 months of treatment, mean immunostaining area for small sensory fibres increased by more than that for all fibre types or for sympathetic fibres. Innervation improvements continued (epidermis and dermis) or stabilized (sweat glands) after 24 months of treatment. Neuropathic grade improved in 76% of patients and remained unchanged in 19%. The objective of this study was to assess the safety and efficacy compared to placebo of intramuscular ALCAR in HIV-positive patients with symptomatic ATN. Ninety patients were enrolled and randomised to receive ALCAR (500 mg b.d., $n = 43$) or placebo ($n = 47$) i.m. for 14 days followed by 42 days of oral ALCAR 1000 mg b.i.d. Assessment of pain was obtained by a visual analogue scale, the total symptom score, a clinical global impression of change, the McGill Pain Questionnaire, and each patient's need for rescue analgesics. ALCAR treatment produced a statistically significant difference ($p = 0.022$) in changes in VAS (-1.4 ± 1.8) over the first 14 days between groups compared to placebo (-0.5 ± 1.4). The proportion of patients with an improvement in total symptom score over 14 days was greater in the ALCAR group compared to placebo but the differences were not statistically significant. During the open-label phase, patients experienced an improvement in pain, as measured by the VAS score, total symptom score and McGill Pain Questionnaire. ALCAR, administered b.i.d. i.m. to HIV 1 patients with symptomatic ATN, reduced mean pain ratings on the VAS to a significantly greater extent than placebo. Treatment with oral ALCAR improved symptoms for the patient group. Intramuscular and oral ALCAR were generally safe and well tolerated.

REELIN IS TRANSIENTLY EXPRESSED IN THE PERIPHERAL NERVE DURING EARLY DEVELOPMENT AND IS UPREGULATED FOLLOWING NERVE INJURY

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Reelin is an extracellular matrix protein which is critical for the positioning of migrating post-mitotic neurons and the laminar organisation of several brain structures during development. We investigated the expression and localization of Reelin in the rodent sciatic nerve during postnatal development and following crush injury in the adult stage. As shown with Western blotting, immunocytochemistry and RT-PCR, Schwann cells in the developing sciatic nerve and in primary cultures from neonatal nerves produce and secrete Reelin. In the sciatic nerve Reelin co-localizes with the compact myelin marker MBP and with the Schwann cell marker S100. While Reelin levels are down-regulated in adult stages, they are again induced following sciatic nerve crush. A morphometric analysis of sciatic nerve sections of reeler mice suggests that Reelin is not essential for axonal ensheathment by Schwann cells, however, influences the caliber of myelinated axons and the absolute number of fibers per unit area. This indicates that Reelin may play a role in peripheral nervous system development and repair by regulating Schwann cell-axon interactions.

MULTICENTRE PLACEBO-CONTROLLED RCT OF ASCORBIC ACID TREATMENT IN CHARCOT-MARIE-TOOTH DISEASE TYPE 1A: PRESENTATION OF STUDY PROTOCOL

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To date there is no pharmacological treatment for Charcot-Marie-Tooth disease 1A (CMT1A). Treatment with ascorbic acid (AA) has been shown to be effective in transgenic mice overexpressing peripheral myelin protein 22 (PMP22), a model of the human disease. The objective of this study was to assess the efficacy and safety of long-term AA treatment in CMT1A, to develop and validate an evaluation protocol suitable for future trials in CMT, and to better define the natural history of the disease (placebo arm). This study was a Phase III prospective, randomised, double blind, placebo-controlled study involving 8 Italian centres. The participants included 202 genetically-confirmed CMT1A adults, with CMT Neuropathy Score (CMTNS) between 1, excluding electrophysiology, and 35 (Shy et al., Neurology 2005;64:1209–14). Treatment consisted of oral therapy with AA (1500 mg/day) or placebo in two divided doses, for two years. The primary efficacy endpoint was improvement in CMTNS overall score. Secondary efficacy endpoints were changes in electrophysiological parameters, and in the following clinical scales: distal arm and leg strength (measured by maximum voluntary isometric contraction); 10 meter timed walking; 9-hole-peg test; Overall Neuropathy Limitations Scale; Visual analogue scale for pain and fatigue; health-related quality of life (SF-36). Clinical and electrophysiological assessment will be performed at baseline and every 6 months thereafter. In a subset of patients, skin biopsy will be performed to evaluate PMP22 expression at baseline and study-end. Serum AA concentration and anti-oxidant activity will be assessed at 6-month intervals. *Funded by Telethon-UILDM grants GUP04002 and GUP05007.*

SURGICAL MANAGEMENT OF ULNAR NERVE ENTRAPMENT AT THE ELBOW: OUR EXPERIENCE

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Although there is a high incidence of ulnar nerve entrapment at the elbow and despite more than 100 years of clinical experience in the diagnosis and treatment of this nerve compression, there is no commonly accepted strategy. Since the first reported surgical treatment of ulnar nerve entrapment at the cubital tunnel by Henry Earle in 1816 debate continues regarding the most appropriate surgical technique. It is well known that a number of surgical options are available: epicondilectomy, ulnar nerve anteposition (submuscular, intramuscular, subcutaneous), simple decompression. Still now, there remains only personal bias and the choice of the operative procedure is dependent on the surgeon's preference. Here we report our experience on 61 cases (the present series is not small according the literature criteria: see Bartels et al., J Neurosurg 1998;89:722–7). Symptoms and signs were those commonly discovered in this disease. In 31 patients, having severe arthrosic or posttraumatic elbow alterations, subcutaneous anteposition of the nerve was performed; in 30 patients, without significant cubital tunnel changes, simple decompression was carried out. In all cases overall satisfactory results were obtained (full recovery or clear improvement; no worsening). With appropriate patient selection we prefer the simple decompression that can achieve good results avoiding the possible complications of the anteposition (kinking of the nerve, its vascular compromission, sacrifice of nervous branches). However, we believe that the postoperative outcome mostly depends on the timing of the surgery rather than the surgical procedures.

CARPAL TUNNEL SYNDROME: CLINICAL, ELECTROPHYSIOLOGIC AND SURGICAL CORRELATIONS

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We undertook a retrospective study of sixty consecutive patients (49 women and 11 men, ranged in age from 20 to 75

years), who have been diagnosed as having carpal tunnel syndrome, to evaluate whether there was a correspondence of electrodiagnostic, clinical and intraoperative findings. All patients underwent surgical decompression through "miniopen surgery". For the purpose of the study we used a neurophysiological classification (four grades) according the nerve conduction velocity, a clinical grading (four grades) based on the clinical symptoms severity, a surgical scale (four grades) based on intraoperative findings of the transverse carpal ligament and of the median nerve. The results of the review showed that frequently there was not clinical-neurophysiological correlation, between symptoms severity and nerve conduction score, electrodiagnostic abnormalities suggesting more severe disease than expected on the ground of clinical findings (our experience is somewhat discordant with the literature). On the basis of these data, we conclude that often the "electrophysiological damage" of the median nerve compression at the wrist is observed before the clinical changes: it suggests early surgical treatment to prevent irreversible structural median nerve damage due to prolonged entrapment. We believe that clinical pictures rather than preoperative electrophysiological assessment have an important role in predicting the postoperative outcome.

CHARCOT-MARIE-TOOTH TYPE 1A: THE NEUROPHYSIOLOGICAL PATTERN IS POORLY RELATED TO QUALITY OF LIFE

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CMT type 1a is the most frequent inherited neuropathy, neurophysiologically characterised by marked slowing of nerve conduction velocity. The aim of this study was to evaluate whether and how the neurophysiological severity of CMT1a is related to the severity of QoL impairment. We performed a multicentric (six centers – see affiliations), multiperspective and multi-measurement assessment in CMT1a patients by using clinical, neurophysiological (sensory and motor nerve conduction parameters) and patient-oriented QoL measurements. QoL is poorly related to the neurophysiological pattern. The few domains related were the physical ones and, as expected, they concern the physical function focused on the relationship with social aspects of life. The study showed that functional assessment of the nerve did not reflect patient's daily life impairment. Probably, QoL is a more complex aspect influenced by many variables and it is not simply related to the myelin involvement. On the basis of recent observations, the clinical trial on neuropathy will increase in the future. The current results clearly show that nerve conduction findings are not useful to indirectly assess QoL. These observations suggest to directly assess QoL in clinical trials on CMT1a. *Further researchers involved: Grandis M, Benedetti L, Pazzaglia C, Mignogna T, Foschini M, Fabrizi GM, Laurà M, Mazzeo A, Majorana G, Valentino P, Nisticò R.*

ANALGESIC EFFECT OF TRANSDERMAL BUPRENORPHINE IN PATIENTS WITH UNCONTROLLED PAINFUL NEUROPATHY

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Buprenorphine is a low molecular weight, lipophilic, opioid analgesic, recently avaliable as a transdermal matrix patch formulation (Buprenorphine TDS). The efficacy of Buprenorphine TDS in chronic painful neuropathies has not been adequately examined. The aim of this open-label, pilot, non-randomized study was to assess if Buprenorphine TDS administered as an add-on treatment allowing achievement of satisfactory pain control in patients with chronic painful neuropathies. Secondary aims were to assess the optimal dose schedule and the sparing of pre-trial analgesic medication. Information on withdrawal symptoms and pain rebound immediately after treatment cessation has been collected. Patients with peripheral neuropathy and unsatisfactory pain control (VAS score >5) with pre-trial analgesic medication under stable regimen for at least 4 weeks were recruited. Primary endpoint was a reduction $\geq 30\%$ in pain severity at the visual analogue scale (VAS). Secondary efficacy variables were number of responders, patient global impression of change (PGIC), and short sleep quality questionnaire (SQNRS). Buprenorphine TDS was started at the dosage of 35.0 μg/h and increased to 52.5 and 70.0 μg/h in case of unsatisfactory pain control as assessed by fortnightly therapeutic result visits. After achieving a satisfactory pain control, patients could start a progressive scaling down of pre-trial analgesic medication, whereas Buprenorphine TDS was maintained for 20 weeks at the same level applied. Preliminary data on efficacy in 10 patients recruited so far are presented. Three patients discontinued the therapy during the first week because of side effects (nausea, blood hypotension, or daily sleepiness). In 6 patients, Buprenorphine TDS induced a significant improvement of pain severity, which did not change in one patient. In responders, mean VAS score at baseline was 6.4 and decreased 46% at the 15-day visit and 34% at the 60-day visit. Accordingly, PGIC and SQNRS improved 42% and 36%, respectively. Three patients needed to increase the dosage from 35 to 52.5 μg/h to achieve satisfactory pain control. *This study is supported by Grünenthal-Formenti, Italia*

ASSESSMENT OF DIABETIC NEUROPATHY USING A MULTIMODAL APPROACH: RESULTS OF A CORRELATION STUDY – THE DEMAND STUDY

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Several tools to assess the severity of diabetic polyneuropathy in clinical trials are available. However, most of them investigate only few aspects of peripheral nerve function. A comprehensive examination including clinical, neurophysiological, and psychophysical tests could provide more useful information in neuroprotective trials. The aim of this work was to present the first data on a multimodal approach to the assessment of diabetic polyneuropathy as part of a multicenter, randomized, prospective, double-blind study to evaluate the nephroprotective effect of delapril alone or combined with manidipine in patients with type 2 diabetes (DEMAND – delapril and manidipine for nephroprotection in diabetes). Neurological evaluation included the Neuropathy Symptoms Score (NSS), the Neuropathy Impairment Score Lower Limbs (NIS-LL) and the Total Neuropathy Score (TNS). Vibratory sensation was assessed using the Rydel-Seiffer 64 Hz graduated tuning fork. Neurophysiological examination included assessment of sural nerve, dorsal sural nerve, peroneal nerve, and tibial nerve conduction; assessment of cooling, warm, heat-pain, and vibratory threshold by quantitative sensory testing (QST); autonomic evaluation by RR interval and deep-breathing test. We examined 238 patients (mean age 60 years, mean duration of diabetes 7.6 years, mean BMI 29.4, mean glycosylated hemoglobin 5.7%, mean urinary albumin excretion rate 15.6 μg/min). Preliminary data analysis showed a significant ($p < 0.0001$; i.e., $r > 0.5$) correlation between TNS, NIS-LL, and NSS. Sensory nerve action potential (SNAP) amplitude of sural nerve was significantly correlated with TNS but not with NSS and NIS-LL. No correlation was found between QST and any of the neurological scores examined or their items on sensory functions. Vibratory sensation assessed by tuning fork was significantly correlated with TNS and NIS-LL but not with NSS. Our results confirm the usefulness of TNS as a composite clinical and neurophysiological tool to assess diabetic polyneuropathy. QST did not provide reliable data and does not appear a useful diagnostic tool. We emphasize that the Rydel-Seiffer 64 Hz graduated tuning fork is a reliable tool to assess large fiber impairment and could replace psychophysical tests. This cohort of patients will be re-evaluated after 3 years of treatment to investigate the neuroprotective effect of delapril and the reliability of the outcome measures. *This study is sponsored by Chiesi Farmaceutici S.p.A, Parma, Italy*.

THE LEWIS-SUMNER SYNDROME: A VARIANT OF MULTIFOCAL MOTOR NEUROPATHY

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We report on a 55-year-old man with one year history of cramps and fasciculations in the lower limbs, paresthesias at hands and electromyography occurrence of motor conduction blocks and blood-cerebrospinal fluid (CSF) barrier damage, a condition termed as Lewis-Summer syndrome (LSS). The patient had suffered from peripheral type facial paralysis 30 years before. We performed electromyography (EMG) in the upper and lower limbs, para-vertebral and tongue muscles, motor and sensitive nerve conduction studies, as well as motor and sensitive evoked potentials. CSF examination and blood antibody against gangliosides, sulfatides and neurofilaments were also performed. EMG showed neurogenic damage with active denervation and fasciculations in all examined muscles. The study of nerve conductions demonstrated the presence of conduction blocks in upper and lower limbs motor nerves; motor evoked potentials showed upper motor neuron impairment, while sensitive evoked potentials were consistent with central pathway delay. The CSF analysis revealed the presence of abnormal increase of albumin. In this case association of motor neuropathy and nerve conduction blocks, increased protein concentration in CSF and fasciculations reproduces the picture of Lewis-Summer syndrome. Presence of cranial nerve involvement is also reported in this syndrome. Upper motor neuron and central sensitive impairment, as revealed by evoked potentials, further underlines as LSS can represent a border entity between chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy or motor neuronopathies.

CORTICOSTEROID-RESPONSIVE SENSORY ATAXIC NEUROPATHY AND ESOPHAGEAL ACHALASIA IN A PATIENT WITH SJÖGREN'S SYNDROME

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We report a case of a 63-year-old patient who initially developed an ataxic sensory syndrome associated with xeroftalmia and xerostomia. EMG was consistent with a sensory axonal neuropathy and NMR findings showed axial T2-weighted high signal intensity in the posterior columns of the cervical and dorsal spine. Anti-SSA /SSB antibodies, positive ANA and RF were detected in the serum of the patient, and a diagnosis of Sjögren's Syndrome was made. Sympathetic skin response was absent. Sural nerve biopsy showed a marked myelin fiber reduction with epineurial inflammation. Repeated IV immunoglobulins were not effective in ameliorating symptoms and electrophysiological abnormalities. After six months she developed progressive dysphagia and weight loss resulting in esophageal achalasia. Ataxic clinical manifestations were improved after pulsed high-dose prednisolone administration, without resolution of achalasia. We suggest that there may be a common autoimmune mechanism directed to different targets on the basis of this syndromic association, confirmed by the response to corticosteroid therapy. A multisystem neuronal involvement should be investigated in patients presenting sicca complex.

CLINICAL AND ELECTROPHYSIOLOGICAL CORRELATIONS IN A THREE-GENERATION-HNPP PEDIGREE

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Hereditary neuropathy with liability to pressure palsy (HNPP) is an autosomal dominant disorder usually associated with the deletion of the peripheral myelin protein 22 gene (PMP22). Episodes or recurrent attacks may affect the common peroneal, ulnar, radial and median nerves; painless brachial plexus neuropathies are also seen. Episodes are unpredictable and provoked even by trivial traumas. Nerve biopsy reveals segmental demyelination and focal myelin thickening (tomacula). The pathophysiology of nerve damage is still uncertain. We tried to establish clinical and electrophysiological correlations in a three-generation pedigree with the PMP22 deletion. We evaluated clinically 21 patients aged 17–91 years; 16 subjects underwent needle EMG, conventional nerve conduction studies and somatosensory evoked potentials (SEPs). The onset of disease varied between 5 and 65 years (mean 24). A 5-year-old child developed a peroneal palsy after surgical procedure. Nine patients complained of a painless brachial plexus palsy consisting with an involvement of the ascellar nerve (7 cases) or of the long thoracic nerve (2). Four patients had recurrent brachial plexus palsy. Six patients had a carpal tunnel syndrome (3 underwent surgery). Five patients developed a peroneal palsy. Three patients showed short-term recurrent sensory symptoms and chronic sensory-motor neuropathy without signs of focal mononeuropathy. Distal slowing of motor conduction velocity was overall recorded by median and peroneal nerve stimulation; focal slowing or blocks were found by ulnar and peroneal nerve stimulation; sensory distal slowing of conduction velocity was rather diffuse and SEPs showed that the delay of conduction is generally distributed along the entire length of the peripheral nerve. The pedigree exhibited the complete spectrum of HNPP including the rarer phenotype of chronic polyneuropathy and prompts to investigate the epigenetic or acquired modulators of disease.

LOSS OF GFAP IMPAIRS SCHWANN CELL PROLIFERATION AND DELAYS AXONAL REGENERATION AFTER INJURY

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The peripheral nerve should maintain the capacity to regenerate after damage. This process depends on a series of events that include dedifferentiation of the Schwann cells, macrophage invasion, proliferation of Schwann cells, and constitution of the bands of Bungner that allow axonal regrowth. Adhesion receptors, extracellular matrix components and cytoskeleton rearrangement are at the basis of nerve regeneration. We evaluated whether loss of GFAP, a Schwann cell specific constituent of the cytoskeleton up-regulated after damage, may affect nerve regeneration. We observed that axonal regeneration after damage was delayed. Mutant Schwann cells maintained the ability to dedifferentiate but showed defective proliferation. Consistently, ERK phosphorylation, which is initiated by adhesion and TK receptors, was reduced in GFAP null-injured nerves. Loss of GFAP seems to alter specific adhesion pathways involved in Schwann cell proliferation after damage. GFAP might participate to form macro-complexes to initiate mitogenic and differentiating signaling for efficient nerve regeneration.

AXONAL DEGENERATION IN SYSTEMIC SCLEROSIS CAN BE REVERTED BY FACTORS IMPROVING TISSUE OXYGENATION

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Systemic sclerosis (SSc) is a connective tissue disease affecting skin as well as blood vessels and internal organs. We have recently observed a reduction of sensory and autonomic innervation in both sclerotic and apparently uninvolved skin, but pathogenetic mechanisms of axonal degeneration in SSc remain unclear. To study the evolution of cutaneous neuropathy in SSc, we used skin biopsy and immunohistochemical techniques to perform a follow-up study of cutaneous innervation in three sclerodermic patients. Skin samples were taken from thigh, leg and third fingertip using disposable 3 mm punches under local anesthesia. After a period ranging from two to six years we obtained a second skin sample from the same sites 3 to 5 mm from the first biopsy. Between the first and the second time point (x to y months before the second biopsy) the three patients had undergone a cycle of intravenous iloprost, a prostacyclin analogue used in SSc patients to treat Raynaud's phenomenon and pulmonary hypertension. Mean epidermal nerve fiber density per linear mm was greatly reduced with respect to control values at the first time point (2.7 ± 3.1 and 1.2 ± 2.0 at thigh and leg, respectively; normal values 27.2 ± 7.7 and 19.1 ± 8.8 at thigh and leg, respectively). The only glabrous skin sample taken at this time counted 1.9 ENFs per linear millimeter (normal values 7.5 ± 3.6). At the second time point we observed a significant increase of epidermal nerve fiber density in all three subjects and in all the examined sites paralleled by an increase in the vascular bed area. Mean epidermal nerve fiber density per linear millimeter resulted 20.9 ± 5.5, 6.6 ± 2.9 and 7.8 ± 3.2 for thigh, leg and fingertip, respectively. This observation suggests that epidermal denervation in SSc is due to a defect in tissue oxygenation and that this pathological process can be reverted increasing cutaneous blood flow.

AUTOSOMAL DOMINANT HYPOMYELINATING NEUROPATHY WITH A NOVEL MUTATION IN THE INTRACYTOPLASMIC DOMAIN OF P0

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Myelin protein zero (P0), a single-pass transmembrane protein with a large Ig-like extracellular domain, is the major component of peripheral myelin. Mutations of P0 cause a spectrum of hereditary demyelinating or axonal neuropathies including Charcot-Marie-Tooth disease type 1B (CMT1B), Dejerine-Sottas disease (DSD), congenital hypomyelinating neuropathy (CHN) and CMT type 2 (CMT2). Most mutations affect the extracellular domain (P0ex); a minority are localized in the intracellular domain (P0ic) in association with DSD or CHN. We examined clinically and electrophysiologically five patients from a four-generation pedigree affected with a peroneal atrophy syndrome. Mutational analysis of P0 was done by denaturing high performance liquid chromatography (DHPLC) and nucleotide sequencing after excluding molecular lesions of PMP22 and EGR2. The disorder co-segregated in the family with a previously unreported c.742 A > T mutation at codon 248 that introduced a premature stop codon (Lys248stop); the predicted mutated protein lacked the last 10 residues. The mutations was absent in 150 healthy controls and was likely pathogenic. Patients had variable ages at examination: 61, 35, 30, 16 (two dizygotic twins). The disorder disclosed marked variation of severity, from mild to severe CMT, even between twins. Nerve conduction studies were consistent with a demyelinating polyneuropathy with motor nerve conduction velocity (MNCV) at the median nerve ranging from 22.5 to 26 m/s. Sural nerve biopsy in the 37-year-old female proband revealed a hypertrophic hypomyelinating neuropathy. We described a novel mutation of P0ic associated with an unusual phenotype characterized clinically and electrophysiologically by Charcot-Marie-Tooth type 1B but pathologically by a hypomyelinating neuropathy.

CELIAC DISEASE-ASSOCIATED NEUROPATHY PRESENTING WITH PROXIMAL WEAKNESS AND EFFECT OF GLUTEN FREE-DIET

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Ten percent of patients with celiac disease (CD) present neurological manifestations, including peripheral neuropathy. A 26-year-old woman complained of progressive weakness in the lower limbs for 2 years, which limited the activities of daily living. She was referred to our Institute for muscle biopsy and genetic analysis for spinal muscle atrophy. Neurological examination showed weakness of proximal and distal muscles of both upper and lower limbs, impairment of light touch and pain sensation on palms and soles, normal vibratory and joint position sensation, and absent deep tendon reflexes in the lower limbs. Laboratory exams showed sideropenic anemia, increased CK, IgG-k monoclonal gammopathy, IgM anti-GM1 antibodies at low titer, and normal cerebrospinal fluid examination. Neurophysiological evaluation showed an axonal sensorimotor peripheral neuropathy with active denervation in lower limbs. Skin biopsy showed a non-length dependent pattern of reduced epidermal innervation density. Skeletal radiogram, hepatic echography, bone marrow biopsy, and PET total body were negative. IVIG (0.4 g/kg/d for 5 days) and prednisone (50 mg/day for 3 months) did not change the clinical picture. At follow-up, we re-investigated the clinical history. Mild and occasional discomfort after eating carbohydrates since childhood, with no bowel abnormality, was reported. This finding, along with the presence of sideropenic anemia, prompted us to investigate a celiac disease. High titer of anti-transglutaminase and anti-endomysium antibodies and digiunal biopsies confirmed the diagnosis. The patient started a gluten free-diet (GFD). One year later, she showed a partial, but significant improvement of both clinical picture and neurophysiologic examination. GFD is the only treatment available for CD-associated neuropathy but its efficacy remains uncertain since either improvement, such as in our patient, or lack of benefit were reported.

PROGESTERONE AND ITS DERIVATIVES AS NEUROPROTECTIVE AGENTS FOR ACQUIRED PERIPHERAL NEUROPATHIES

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It is now well known that peripheral nerves possess both classical steroid receptors (e.g., progesterone receptor, PR, androgen receptor, AR, etc.) as well as non-classical steroid receptors (e.g., GABA-A and GABA-B receptors, sigma 1 receptor, NMDA receptor 1 subunit, etc.) and consequently may represent a target for the action of neuroactive steroids. Indeed, we have demonstrated that progesterone (P) and its derivatives, dihydroprogesterone (DHP) and tetrahydroprogesterone (THP) stimulate both in vivo and in vitro (Schwann cell cultures) the expression of two important proteins of the myelin of peripheral nerves, the glycoprotein P0 (P0) and the peripheral myelin protein 22 (PMP22) (Melcangi et al., Brain Res. Rev. 2005;48:328–338 for review). Moreover, recent data have indicated that, similar to what occurs in the central nervous system, also in the peripheral nervous system P, DHP and THP are neuroprotective agents. For instance, we demonstrate that P and DHP are able to counteract the decrease in the levels of P0 observed in the sciatic nerve of the rat raised diabetic by treatment with streptozotocin (STZ-rat). These findings are similar to what we have observed in other models of peripheral neurodegeneration. Indeed, P and derivatives are able to increase this myelin protein after peripheral nerve injury and to counteract age-associated decreases in levels of P0 and PMP22; moreover, these neuroactive steroids also reduce the morphological abnormalities of myelin and myelin fiber loss occurring in the sciatic nerve of aged male rats. Protective effect of these neuroactive steroids in STZ-rat has been confirmed by neurophysiological, behavioral and

biochemical analyses. Altogether, the present observations suggest that neuroactive steroids themselves or synthetic ligands of their receptors might represent an interesting therapeutic perspective for acquired peripheral neuropathies. *European Community-RTD program QLK6-CT-2000–00179, FIRB 2001-RBAU01kje4_001.*

SOLITARY SCIATIC NERVE LYMPHOMA

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Lymphoma occasionally affects the peripheral nervous system and the diagnosis can be elusive since many patients present without known lymphoma. Most peripheral nerve complications are plexopathy, generalized neuropathy or mononeuropathy as in our case report. Here we present a case of a 44-year-old woman who came to our attention in February 2005 for a 6 month history of stumbling, paresthesias and pain associated with a progressive weakness in the right lower limb. Neurological examination revealed absence of Achilles' tendon and plantar flexor stretch reflexes on the right side, decreased strength in all distal muscle of the right leg. A reduced soft touch and pin prick sensation was present in thigh and leg posterior surface and in plantar and dorsal foot face. Nerve conduction studies revealed absence of right tibial motor response. Right peroneal CMAP and MCV as right sural SAP and SCV were under lower limits of normality. EMG revealed profuse denervation in the muscles innervated by the sciatic nerve, but also in the gluteus maximus. No voluntary activity was seen. Lumbosacral MRI, abdomen-pelvis TC, pelvis radiography and CSF examination results were negative, as well as all laboratory work-up for connective tissue, infectious and paraneoplastic disease. The pelvis MRI showed a T2, DUAL and STIR hyperintense signal of proximal part of right sciatic nerve that appeared oedematous and showed Gd enhancement. A high dose parenteral steroid therapy was started for 5 days and then prosecuted with methylprednisolone 1 g/week for the following 3 months with a partial resolution of pain and paresthesias and apparent strength amelioration. Five months later nerve conduction studies showed a worsening (right sural SAP and peroneal CMAP absent). Lumbosacral MRI was unchanged. Because of progressive worsening and lack of steroid therapy response, the patient underwent a lumbar-pelvis CT and MRI in November 2005, that revealed a tumoral lesion with Gd enhancement extending from L4, L5 and S1 right roots to the leg along the sciatic nerve. Histologic diagnosis on biopsy specimen of the nerve revealed a diffuse large B-cell lymphoma. PET total body did not evidence other disease localization. Since December 2005 the patient underwent three chemotherapy cycles with a program of a control MRI in March 2006.

TREATMENT WITH CILIARY NEUROTROPHIC FACTOR (CNTF) PREVENTS AXONAL DAMAGE IN AN IN VITRO MODEL OF CHARCOT-MARIE-TOOTH TYPE 1A (CMT1A) DISEASE: PRELIMINARY RESULTS

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Clinical worsening in human and experimental CMT1A is mainly due to a progressive axonal atrophy. Molecular and morphological signs of axonal damage may be reproduced in long-term, dys-demyelinating dorsal root ganglia (DRG) cultures obtained from a CMT1A rat model. In this model a selective dowregulation of the CNTF was also found. CNTF is a surviving factor for sensory and motor neurons, and promotes oligodendrocytes growth and myelin formation. Therefore, CNTF is a promising molecule in the therapy of demyelinating neuropathies like CMT1A, particularly when secondary axonal atrophy occurs. We treated, for 30 days, CMT1A and wild type cultures with various dilutions of CNTF (0.5 ng/ml, 1 ng/ml, 5 ng/ml and 10 ng/ml) or culture media vehicle as a control, aiming to assess possible toxic effects of the molecule in our culture system and to detect a protective effect on the myelination process and on the occurrence of axonal damage. Cultures were evaluated by morphological (light and electron microscopy) and molecular techniques (Western blot) for amount of myelin, axonal atrophy and neurofilament (NF) phosphorylation. CNTF showed a dose-dependent inhibitory effect on the myelination process at 1 ng/ml and above. 0.5 ng/ml were not toxic for normal and CMT1A cultures. The density of myelinated segments was similar in CMT1A cultures treated with CNTF (229/mm^2, n. 11) vs. untreated (233/mm^2, n. 11). As expected, treated (557/mm^2, n. 4) and untreated (490/mm^2, n. 4) wild type cultures showed significantly ($p < 0.05$) higher values than CMT1A. NF phosphorylation was studied only in treated (n. 20) and untreated (n. 20) CMT1A cultures. The relative levels of non-phosphorylated NF were significantly ($p < 0.05$) lower in treated (0.93) vs. untreated (1.15) CMT1A cultures. In conclusion, our preliminary results suggest that CNTF does not improve myelination in CMT1A cultures but is able to prevent molecular signs of axonal damage.

EFFECTS OF ANKLE-FOOT ORTHOSES IN A PATIENT WITH CHARCOT-MARIE-TOOTH DISEASE. A STUDY ON GAIT KINEMATICS

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Patients suffering from Charcot-Marie-Tooth (CMT) disease generally present a length-dependent degeneration of the motor and sensory nerve fibres, and consequently a distal muscle atrophy and sensory reduction. The effects of such a disease are shown on muscle weakening and on other biomechanical problems (ankle sprains, stumbling, shuffles, clumsy gait, pain, poor balance, steppage gait,

foot and knee deformities), starting from foot and spreading progressively to leg muscles. The effects on thigh and pelvic girdle muscles have been reported only for a few cases. We examined a patient (woman, 24 years old) suffering from axonal CMT form as defined on pathological ground who had a very poor performance during stance and gait. She developed an early weakness of peroneal and tibialis anterior muscles. Subsequently, she developed a contracture of the plantar fascia and "Pes cavus". At the age of 18 she underwent surgical elongation of Achilles tendon and correction of cavus deformity. When first examined in our rehabilitation ambulatory she was able to walk with an increased knee flexion during all gait phases and with dropfoot during the swing phase (these gait abnormalities were bilaterally represented). We decide to test the effect of an ankle foot orthoses (AFO) on gait of this patient. To this aim, before and after wearing the AFO, we examined gait parameters by means of the "Gaitrite", a 7 meter portable carpet provided with sensors that captures electronic footprints instantly. Gaitrite is able to measure step cadence, length, velocity and other gait parameters. The patient was required to walk on the carpet at her favoured velocity. Three gait passages for each testing condition (barefoot and with AFO and shoes) were recorded. Changes in mean gait velocity, length of step, base support, and time of step were examined. After wearing the AFO, the patient showed an increase in length of step (13.77% at the left foot and of 23.68% at the right), in base support (19.93% on left foot and 20.54% on right foot) and in speed (33.62%), and a recution in time of step (17% at left foot and 13.56% at right foot) and the gait time (31.16%). She was more stable during all daily life activities and said she was satisfied with the use of the AFO. It can be concluded that the AFOs can improve parameters of independent ambulation in selected patients with CMT.

RECURRENT MILLER FISHER SYNDROME (MFS)

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A 34-year-old woman experienced five months after delivery of her first child, twelve days after febrile cystitis, inconstant diplopia, gait unsteadiness, tingling paresthesias, and distal numbness. Her unsteadiness worsened over the next 2 days. Neurological examination (day 3) showed restricted external eye movements, normal force except for mild loss of strength (MRC 4) in hand muscles. There was tremor, both postural and intentional and ataxia on heel to shin test. Deep jerks were absent throughout. Vibration and position were moderately impaired distally in UE, whereas light touch, temperature and pin-prick were normal. CSF (day 4) revealed normal findings. Extensive emato-urinary tests, B12, folate level, CK, microbiological, viral screenings were negative, including HIV1–2, CMV, HSV1, HSV2, EBV. Search for Campylobacter Jejuni and Borrelia Burgdorferi were negative as well for Toxoplasma Gondii. Serum sample for anti-ganglioside antibody assay (day 4) was unremarkable. Brain CT and enhanced MRI scans did not show lesions. Electrophysiology (day 4) revealed normal motor conduction. SAPs had low amplitude (within 2–4 uV). The patient did not receive immunotherapy as she experienced gradual improvement. In November 2000, six months after her second delivery, ten days after viral febrile episode, the patient experienced diplopia in either direction and unsteady gait. Enhanced brain MRI scan as well as anti-ganglioside antibodies remained negative. Her ataxia ultimately disappeared within day 90. In conclusion, this patient exhibited a post-infectious benign neurological illness, which developed in both occasions 10 to 12 days after a febrile episode during late post partum. Ataxia and tremor did not correlate with weakness and loss of proprioception, which was mild. Electrophysiology suggested an axonal neuropathy, mainly involving upper limb. Anti-ganglioside antibodies were absent in sera obtained during acute phases; however, an autoimmune mechanism must be implicated.

FURTHER EVIDENCE THAT MUTATIONS OF DYNAMIN 2 ARE ASSOCIATED WITH CHARCOT-MARIE-TOOTH DISEASE

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Dominant intermediate Charcot-Marie-Tooth disease (DI-CMT), a neglected neuropathy with mixed demyelinating and axonal features, was associated with dynamin 2 (DNM2) (Zuchner *et al.*, 2005) and, more recently, with tyrosyl-tRNA synthetase (YARS) (Jordanova *et al.*, 2006). DNM2, a ubiquitous GTPase-protein involved in endocytosis, membrane trafficking, actin assembly and centrosome cohesion, is also associated with dominant centronuclear myopathy (CNM) (Bitoun *et al.*, 2005). The divergent phenotypes (DI-CMT versus CNM) correlate with different mutated domains; the three reported pedigrees with DI-CMTA had mutations in the plekstrin-homology (PH) domain. DNM2 exons 13–16 encoding the PH domain were analysed by DHPLC and sequencing in 160 index CMT cases not linked to PMP22, P0, Cx32, NEFL, MFN2; motor nerve conduction velocity (MNCV) at the median nerve was >38 m/s in 68 patients and <38 m/s in 92; 50 cases had dominant inheritance whereas 110 were sporadic. A singleton 45-year-old female harbored a novel heterozygous c.1697 T>A mutation resulting into a Leu566His change. The mutation was absent in 100 healthy controls and affected a residue conserved in hortologues and paralogues genes; the father and paternal grandmother, reported as affected, were unavailable for testing. The patient complained of clumsy gait since 35–40 years of age; examination disclosed bilateral pes cavus, hypotrophy of legs and lower thigs, prominent in the left side, severe dorsiflexor weakness of left toes and foot and bilateral weakness of plantar flexion, diminished vibration sense of feets, and abolished ankle jerks. Conduction studies demonstrated a selective involvement of the lower limbs with marked reduction of tibial CMAP and absence of sural SNAP. The sural nerve biopsy showed severe loss of large-diameter fibers, numerous clusters of regeneration sometimes

surrounded by simple onion bulbs. Mutations of DNM2 are a rare cause of axonal CMT.

INTRAVENOUS IMMUNOGLOBULINS FOR THE TREATMENT OF DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

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Diabetic lumbosacral radiculoplexus neuropathy (DLRPN) is a rare painful condition that may occur in diabetic patients. At the moment there is no proven treatment for DLRPN. The objective of this study was to evaluate the effect of intravenous immunoglobulin (IVIg) therapy in the treatment of DLRPN. We recruited two patients affected by type II diabetes mellitus and DLRPN. Both of them complained of thoracic and abdominal pain and developed painful lower-limb proximal weakness. Clinical examination and instrumental findings were suggestive of lumbosacral plexopathy and bilateral distal neuropathy. Sural nerve biopsy showed degeneration and loss of fibers with perivascular inflammation. Treatment with gabapentin, amitriptyline, carabamazepine, clonazepam and tramadole, even at high doses, could not alleviate truncal and lower-limb pain. Both patients were treated with IVIg (0.4 g/kg/day for 5 days). After IVIg treatment both patients improved. In particular, pain was alleviated and both patients could reduce the dosage of analgesic drugs. One of the patients needed a second treatment with IVIg after six months. IVIg treatment may improve pain of patients with DLRPN. Our data could represent a starting point for a double-blind study aimed to evaluate the role of IVIg in the treatment of patients affected by DLRPN. (Dyck and Windebank, Muscle Nerve 2002; 25:477–491).

GUILLAIN-BARRÉ SYNDROME AFTER COMBINED CHEMOTHERAPY AND RITUXIMAB IN NON-HODGKIN'S LYMPHOMA

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Different forms of neuropathy including Guillain-Barré syndrome (GBS) have been reported in patients with lymphoma and have been attributed to several pathogenetic mechanisms. We report on a 51-year-old man with non-Hodgkin's lymphoma (NHL) who developed GBS three weeks after combined therapy with Rituximab and CHOP. In August 2005 the patient was first diagnosed non-Hodgkin's B-cell lymphoma after biopsy of a symptomatic inguinal lymph node. After an initial course of CHOP the patient performed four courses of R-ICHOP (combined CHOP and Rituximab) at two week interval. After the first three courses the patient only complained of mild finger paresthesias without motor impairment while three weeks after the fourth course (two weeks after transient fever without additional symptoms) he developed rapidly progressive flaccid tetra paresis. Neurological examination two days after onset of motor symptoms showed severe symmetrical predominantly distal weakness more pronounced in the legs, absent deep tendon reflexes and normal sensation. Routine laboratory tests were normal as were IgG anti-ganglioside antibodies. CSF proteins were increased (72 mg/dl) with normal cells. Nerve conduction studies were consistent with a demyelinating neuropathy with conduction blocks in the right peroneal and left posterior tibialis nerves, reduced motor conduction velocity and increased distal latency and F wave in the median nerves, while distal CMAP amplitudes were only moderately reduced. By the end of the first week the patient became bedridden despite 3 plasma exchanges. He was therefore treated with IVIg (0.5 g/kg) and intravenous methylprednisolone (500 mg) for four days with a moderate though transient improvement followed by the end of the second week by a rapid deterioration with respiratory insufficiency requiring assisted ventilation. The patient was treated again with IVIg (0.5 g/kg) and intravenous methylprednisolone (500 mg) for two days and gradually improved over the following three weeks when a slight worsening was treated again with the same regimen with further progressive improvement. One month later the patient was able to walk a few meters without support while NHL is in remission. Even if lymphoma itself or a possible antecedent infection suggested by the transient fever might be implicated in GBS in this patient, the close temporal relationship between onset of symptoms and combined CHOP and Rituximab therapy suggests their possible implication in the disease. In addition, since CHOP has been seldom associated with GBS it is possible that its combination with Rituximab had a relevant role in GBS pathogenesis.

NEUROFIBROMATOUS NEUROPATHY: AN ULTRASTRUCTURAL STUDY

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Neurofibromatosis 1 (NF1) is a common genetic disorder characterized by the presence of neurofibromas arising from the proliferation of Schwann cells (SC) and perineurial cells. At variance with NF2, the incidence of an associated polyneuropathy is very low in NF1, and its histopathological features are poorly characterized. We report the sporadic case of a 46-year-old woman presenting with bilateral subclavicular painful masses. MRI showed bilateral plexiform lesions extending from cervical roots to the elbows; a malignant nature of lesions was ruled out by PET-TC. A biopsy of the larger lesion had histological features of plexiform neurofibroma. Although the patient had no peripheral nerve symptoms, nerve conduction studies documented a sensory-motor polyneuropathy, which was confirmed by sural nerve biopsy.

Electron microscopy showed dramatic loss of large and small myelinated, as well as unmyelinated axons together with numerous regeneration clusters. An increased number of fibroblast cell processes and a large amount of collagen fibrils characterized the endoneurium. A combined involvement of myelinating and non-myelinating SC was evidenced by the high frequency of alterations such as: irregularities and degradation figures of myelin, lipofuscin deposition, pseudo-onion bulb structures and collagen pockets substituting unmyelineted axons. These changes suggest that in neurofibromatous neuropathy, a widespread axonal degeneration takes place independently of the presence of tumoral infiltration, possibly due to an impairment in SC-axon cross-talk.

GASTRIC STRONGYLOIDIASIS FOLLOWING CORTICOSTEROIDS THERAPY IN A PATIENT WITH ACUTE BRACHIAL PLEXUS NEURITIS

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Idiopathic brachial neuritis (Parsonage-Turner syndrome) is a well-defined clinical condition. Treatment includes analgesics and physical therapy, with resolution of symptoms usually occurring in three to four months. Although there is no evidence that steroids change the course of the denervation or speed recovery, many physicians prescribe them in cases of refractory pain with uncertain results. We report a case of gastric ulcer caused by Strongyloides stercoralis after steroid therapy in a patient with brachial neuritis. A 58-year-old farmer had left shoulder pain followed three weeks later by marked upper arm weakness. Spinal MRI showed a discal protrusions at C4-C5, and C5-C6. Steroids were given for a month without improvement. Later, he presented because of severe gastrointestinal symptoms and weight loss. Gastroscopy revealed erosive gastritis and histopathology of stomach mucosa showed nematode larvae. Microscopy of gastric secretion confirmed strongyloides stercoralis. Eosinophilia was absent. Electrophysiology: reduced SAP amplitudes of median nerve recorded from thumb, abnormally prolonged latency from Erb's point to spinati, deltoid and biceps, denervation pattern at needle EMG on proximal muscles but cervical paraspinals. CSF was normal. Steroid stop, specific therapy for strongyloidiasis were associated with fast improvement, also of plexus neuritis. Strongyloidiasis is endemic in developing countries, but also in some rural areas of Europe. In a healthy host it is a chronic enteric infection usually not causing any symptoms. In the setting of compromised cellular immunity (such as in steroid use), it can result in hyperinfenction and rarely in gastric involvement. This case highlights the importance of: 1) early diagnosis of brachial neuritis to avoid unnecessary and potentially harmful therapy; 2) critical evaluation of so-called "ex iuvantibus therapies, especially without clear evident indication"; and 3) screening for S. stercoralis in patients starting immunosuppressive therapy, especially if they are from endemic areas.

SMALL HEAT-SHOCK PROTEIN HSPB8 AND HSPB1: SCREENING IN ITALIAN PATIENTS WITH CHARCOT-MARIE-TOOTH DISEASE TYPE II AND WITH DISTAL HEREDITARY MOTOR NEUROPATHIES

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The heat-shock proteins are a large family of molecular chaperones, which can be further subdivided into groups including that of the small heat-shock proteins (sHSP). A number of heat-shock proteins have been demonstrated to be upregulated in a number of neurodegenerative diseases. Recently, disease-causing mutations within HSPB8 and HSPB1 genes were identified in a number of families diagnosed as having either distal hereditary motor neuropathies (dHMN) or Charcot-Marie-Tooth disease type II (CMT2). The underlying pathological mechanism in these disorders is not clear but recent findings suggest that mutations in these genes may lead to preferential motor neuron loss by disrupting selective components essential for axonal structure and transport. A cohort of 62 unrelated Italian patients affected with CMT2 and 33 patients with distal HMN were screened for mutations in the HSPB8 and HSPB1 genes. The three coding exons and flanking intron nucleotide sequence was examined by single strand conformation polymorphism (SSCP), Denaturing High Performance Liquid Chromatography (DHPLC) and direct sequencing. All CMT2 patients were negative for mutations in the GJB1 and MPZ genes. SSCP analysis showed few electrophoretic variants in exon 1 and exon 2 of HSPB8 gene in three cases. Direct sequencing is in progress to evaluate the possible role of these variants in the pathophysiology of the disease. *This work was partially supported by grants Fondazione Mariani 2004 to P.M. e Telethon 2004 to E.B.*

SCREENING FOR MUTATIONS IN GJB1 GENE IN ITALIAN PATIENTS WITH CHARCOT-MARIE-TOOTH DISEASE (CMT)

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The X-linked form of Charcot-Marie-Tooth disease (CMTX) is a hereditary peripheral neuropathy and is the second most common form of CMT after CMT1A associated with the 17p11.2 duplication. Males are often more severely affected than females. The CMTX is associated with mutations in GJB1 gene encoding the connexin 32 (C $\times$ 32). C $\times$ 32 is a gap junction protein mainly found in the paranodal regions and the Schmidt-Lanterman incisures of peripheral nerve myelin which forms reflexive gap junctions, providing a greatly shortened diffusion pathway for transferring ions, second messengers and metabolites from the perinuclear region to periaxonal region of Schwann cells. C $\times$ 32 contains four transmembrane domains, two extracellular loops and

three cytoplasmic segments. Although more than 287 mutations in GJB1 have been reported in patients with CMTX (www.molgen.ua.ac.be/CMTMutations/), most are missense mutations and a few nonsense, frameshifting and noncoding region mutations have been reported. A series of 89 Italian patients with peripheral neuropathy was screened for mutations in the GJB1 gene. All patients were negative for the 17p11.2 duplication and a male to male inheritance was excluded. The entire coding region of the gene, including exon-intron boundaries, was examined by direct sequencing. Fourteen mutations were detected and, among these, six mutations were not previously reported in the literature. One mutation was identified in the promoter P2 region. The clinical and molecular features of the patients will be presented. The overall C × 32 mutation frequency, in our series, is 15.7%, confirming that C × 32 mutations are the second most common cause of CMT1 in the Italian population. *This work was partially supported by grants Fondazione Mariani 2004 to P.M. e Telethon 2004 to E.B*.

THE EXTRA-MEDIAN SPREAD OF SENSORY SYMPTOMS IN CARPAL TUNNEL SYNDROME IS RELATED TO PAIN MECHANISMS

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Carpal tunnel syndrome (CTS) represents the most common cause of median nerve lesion. Patients with CTS may complain of sensory symptoms outside the typical median nerve distribution. The study is aimed to understand which clinical features are associated with the extra-median distribution of symptoms in CTS. We recruited 241 consecutive CTS patients. After selection, 103 patients (165 hands) were included. A group of 11 electrodiagnostic-negative CTS hand served as control. The symptoms distribution was evaluated with a self-administered hand symptoms diagram. Patients underwent an objective evaluation, a neurographic study, and a self-administered questionnaire on subjective complaints. Median distribution of symptoms was found in 60.6% of hands, glove distribution in 35.2% and ulnar distribution in 4.2%. Objective measures of median nerve lesion (tactile hypaesthesia and thenar muscles hypasthenia) and neurographic involvement were significantly more severe in median hands than in the other groups. Subjective complaints (nocturnal pain, numbness and tingling sensations) were significantly correlated to symptoms distribution, being more severe in glove hands. The remaining clinical variables did not influence the symptoms distribution. Neurophysiological and objective measures were not correlated with subjective complaints. The subjective complaints were statistically more severe in the control group. The severity of the objective and neurographic involvement and the intensity of sensory complaints appear to be independent factors that influence the symptoms distribution. Extra-median spread of sensory symptoms was associated with higher levels of pain and paresthesia. Central nervous system mechanisms of plasticity may underlie the pain-related spread of symptoms in CTS.