Ataxic Guillain-Barré syndrome and acute sensory ataxic neuropathy form a continuous spectrum.
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Abstract
BACKGROUND: Ataxic Guillain-Barré syndrome is characterised by profound ataxia with negative Romberg sign and no ophthalmoplegia. Its nosological relationship to acute sensory ataxic neuropathy has yet to be discussed.

METHODS: Medical records were reviewed of patients suffering acute ataxia and reduced muscle stretch reflexes but without external ophthalmoplegia. Clinical features and laboratory findings were analysed. Rat muscle spindles were immunostained by anti-GQ1b and -GD1b antibodies.

RESULTS: The Romberg sign was negative in 37 (69%) of 54 patients with acute ataxic neuropathy without ophthalmoplegia, but positive in the other 17 (31%). The negative and positive subgroups had similar features; preceding infectious symptoms (86% vs 83%), distal paraesthesias (70% vs 88%), superficial sense impairment (27% vs 24%), IgG antibodies to GQ1b (65% vs 18%) and GD1b (46% vs 47%) and cerebrospinal fluid albuminocytological dissociation (30% vs 39%). Findings did not differ between the subgroups of 466 patients with Fisher syndrome with and without sensory ataxia. Acute ataxic neuropathy patients more often had anti-GD1b (46% vs 26%) and less often anti-GQ1b (50% vs 83%) antibodies than Fisher syndrome. Anti-GQ1b and -GD1b antibodies strongly stained parvalbumin-positive nerves in rat muscle spindles, indicative that proprioceptive nerves highly express GQ1b and GD1b.

CONCLUSION: Clinical and laboratory features suggest that ataxic Guillain-Barré syndrome and acute sensory ataxic neuropathy form a continuous spectrum. The two conditions could be comprehensively referred to as 'acute ataxic neuropathy (without ophthalmoplegia)' to avoid nosological confusion because Fisher syndrome is not classified by the absence or presence of sensory ataxia. That is, acute ataxic neuropathy can be positioned as an incomplete form of Fisher syndrome.

Comment in
Acute inflammatory neuropathies: new evidence for disease classification from Japan. [J Neurol Neurosurg Psychiatry. 2011]
New insights into the pathophysiology of pes cavus in Charcot-Marie-Tooth disease type 1A duplication.

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Abstract
Forefoot pes cavus is a cardinal sign of Charcot-Marie-Tooth disease (CMT). This review is focused on the pathophysiology of pes cavus in CMT1A duplication, which is the most common subtype of the disease. Assessment of foot deformities in CMT1A, their prevalence and proposed mechanisms, and recent contributions of magnetic resonance imaging studies of lower-leg and foot musculature are revised. Special attention is given to papers on foot deformities at initial stages of the disease. We conclude that pes cavus is an early and age-dependent manifestation of CMT1A duplication. Selective denervation of intrinsic foot musculature, particularly of the lumbricals, and not imbalance of lower-leg muscles, seems to be the initial mechanism causing reduced ankle flexibility and forefoot cavus deformity.

Phenotypic variants of autoimmune peripheral nerve hyperexcitability.

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Abstract
Clinicians use many terms including undulating myokymia, neuromyotonia, Isaacs' syndrome and Cramp-Fasciculation Syndrome to describe the motor manifestations of generalized peripheral nerve hyperexcitability (PNH). Our previous findings in a selected group of patients with undulating myokymia or neuromyotonia, and EMG doublet or multiplet ('myokymic') motor unit discharges, indicated that an autoantibody-mediated potassium channelopathy was likely to be the cause of their disorder. This prompted us to search for a common pathogenesis in a wider spectrum of PNH syndromes. We studied the clinical, autoimmune and electrophysiological features of 60 patients presenting with acquired PNH. Patients were grouped according to an EMG criterion: the presence (group A, n = 42) or absence (group B, n = 18) of doublet or multiplet myokymic motor unit discharges. The average ages of onset in the two groups were 45 and 48 years respectively. The relative frequency and topography of the clinical features were similar in both groups. Serum voltage-gated potassium channel (VGKC) antibodies were detected using a (125)I-alpha-
dendrotoxin immunoprecipitation assay in 38% of group A and in 28% of group B. Autoimmune disease and other autoantibodies were present in both groups more frequently than would be expected by chance (59 and 28%, respectively)-particularly myasthenia gravis and acetylcholine receptor (AChR) antibodies. The neurological disorder in both groups could occur as a paraneoplastic condition. Thymoma was detected in 19 and 11%, respectively, and lung cancer in 10 and 6%, respectively. An axonal neuropathy was present in six (14%) of group A and in one (6%) of group B patients. Thus, despite the discrete EMG distinction, both groups share clinical features often associated with autoimmune-related diseases, which can occur as paraneoplastic disorders and, importantly, have an increased frequency of VGKC antibodies. We conclude that autoimmunity, and specifically VGKC antibodies in many cases, are strongly implicated in the pathogenesis of both groups, and that the EMG features reflect quantitative rather than qualitative differences between the diverse clinical syndromes. These findings also have relevance for disease management. A classification is proposed that distinguishes immune-mediated PNH (irrespective of whether VGKC antibodies are detectable by standard assays) from non-immune forms of PNH that include toxins, anterior horn cell degeneration in motor neurone disease and genetic disorders.
BACKGROUND: Consensus guidelines on the definition, investigation, and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been previously published in European Journal of Neurology and Journal of the Peripheral Nervous System.

OBJECTIVES: To revise these guidelines.

METHODS: Disease experts, including a representative of patients, considered references retrieved from MEDLINE and Cochrane Systematic Reviews published between August 2004 and July 2009 and prepared statements that were agreed in an iterative fashion.

RECOMMENDATIONS: The Task Force agreed on Good Practice Points to define clinical and electrophysiological diagnostic criteria for CIDP with or without concomitant diseases and investigations to be considered. The principal treatment recommendations were: (i) intravenous immunoglobulin (IVIg) (Recommendation Level A) or corticosteroids (Recommendation Level C) should be considered in sensory and motor CIDP; (ii) IVIg should be considered as the initial treatment in pure motor CIDP (Good Practice Point); (iii) if IVIg and corticosteroids are ineffective, plasma exchange (PE) should be considered (Recommendation Level A); (iv) if the response is inadequate or the maintenance doses of the initial treatment are high, combination treatments or adding an immunosuppressant or immunomodulatory drug should be considered (Good Practice Point); (v) symptomatic treatment and multidisciplinary management should be considered (Good Practice Point).

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Charcot-Marie-Tooth disease type 1A duplication: spectrum of clinical and magnetic resonance imaging features in leg and foot muscles.

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Abstract
MRI is an ideal method for identifying areas of muscle atrophy and fatty infiltration. Studies comparing clinical and MRI features of foot and leg muscle atrophy in Charcot-Marie-Tooth disease type 1A (CMT-1A) duplication are lacking. The aim of this study is to describe clinical and MRI patterns of lower limb amyotrophy in CMT-1A. A total of 10 secondary CMT-1A patients and 1 proband patient with de novo mutation were prospectively evaluated. Ages of patients ranged from 8 to 61 years (median, 24). Disease severity in terms of ability to walk and run was established using a nine-point functional disability scale (FDS). We administered the CMT neuropathy score (CMTNS), based on patient's symptoms, neurological examination and neurophysiological testing. Muscle strength of flexo-extensor ankle and toe muscles was assessed manually with the standard Medical Research Council scale. In all 11 patients, leg MRI study included T1- and T2-weighted spin-echo sequences in coronal and axial planes, and a T1-weighted spin-echo sequence with chemical sift fat suppression before and after paramagnetic contrast agent injection. In seven patients both feet were simultaneously studied in coronal and axial planes. Six patients had pes cavus, an FDS score of 0 (normal), mild CMTNS and normal muscle power of foot flexo-extensors. In these six patients, MRI showed muscle fatty infiltration of intrinsic foot muscles mainly involving the lumbricals, all four leg muscle compartments being preserved. The remaining five patients had FDS scores from 1 (cramps or fatigability) to 3 (walking difficulty), mild to moderate CMTNS and variable weakness of peroneal musculature. In these five patients MRI showed, besides intrinsic foot muscle involvement, variable and distally accentuated fatty infiltration of the lateral, anterior and superficial posterior leg muscle compartments and, to a lesser degree, of the deep posterior compartment. In four patients muscle oedema and post-contrast enhancement was noted. MRI demonstrated fatty infiltration of clinically normal muscles. We conclude that clinical-MRI patterns of lower limb muscle atrophy vary with evolution of semiology. Selective involvement of intrinsic foot muscles is the characteristic pattern of CMT-1A cases with minimal disease signs. Afterwards this pattern usually combines variable involvement of leg muscles. Our findings help to clarify the pathogenesis of pes cavus in the disease.

Comment in
Guidelines for treatment of autoimmune neuromuscular transmission disorders.
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Abstract
BACKGROUND: Important progress has been made in our understanding of the autoimmune neuromuscular transmission (NMT) disorders; myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS) and neuromyotonia (Isaacs' syndrome).

METHODS: To prepare consensus guidelines for the treatment of the autoimmune NMT disorders, references retrieved from MEDLINE, EMBASE and the Cochrane Library were considered and statements prepared and agreed on by disease experts.

CONCLUSIONS: Anticholinesterase drugs should be given first in the management of MG, but with some caution in patients with MuSK antibodies (good practice point). Plasma exchange is recommended in severe cases to induce remission and in preparation for surgery (recommendation level B). IVlg and plasma exchange are effective for the treatment of MG exacerbations (recommendation level A). For patients with non-thymomatous MG, thymectomy is recommended as an option to increase the probability of remission or improvement (recommendation level B). Once thymoma is diagnosed, thymectomy is indicated irrespective of MG severity (recommendation level A). Oral corticosteroids are first choice drugs when immunosuppressive drugs are necessary (good practice point). When long-term immunosuppression is necessary, azathioprine is recommended to allow tapering the steroids to the lowest possible dose whilst maintaining azathioprine (recommendation level A). 3,4-Diaminopyridine is recommended as symptomatic treatment and IVlg has a positive short-term effect in LEMS (good practice point). Neuromyotonia patients should be treated with an antiepileptic drug that reduces peripheral nerve hyperexcitability (good practice point). For paraneoplastic LEMS and neuromyotonia optimal treatment of the underlying tumour is essential (good practice point). Immunosuppressive treatment of LEMS and neuromyotonia should
Bulbar involvement in patients with antiganglioside antibodies against NeuNAc(alpha2-3)Gal.

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Abstract
BACKGROUND: Reactivity against terminal NeuNAc(alpha2-3)Gal, common to several gangliosides such as GD1a, GT1b and GM3, has rarely been reported. The authors recently described a patient with a clinical picture of acute relapsing sensory ataxic neuropathy and bulbar involvement in whom they demonstrated concomitant reactivity against NeuNAc(alpha2-3)Gal and disialosyl epitopes. The authors suggested a correlation between NeuNAc(alpha2-3)Gal reactivity and bulbar involvement.

AIM: To determine the frequency of reactivity against terminal NeuNAc(alpha2-3)Gal in acute and chronic immune-mediated disorders, and its possible correlation with bulbar involvement.

METHODS: The authors retrospectively reviewed reactivity in the serum of more than 3000 consecutive patients with acute and chronic disorders in which antiganglioside antibodies were studied. The authors selected those patients who were simultaneously positive, by ELISA or thin-layer chromatography, for IgG or IgM antibodies anti-GM3, GD1a and GT1b, and reviewed their clinical features.

RESULTS: Reactivity against NeuNAc(alpha2-3)Gal, shared by GM3, GD1a and GT1b gangliosides, was detected in 10 patients: isolated in one patient, and concomitant with reactivity against other gangliosides in the remaining patients. Reactivity against NeuNAc(alpha2-3)Gal was frequently associated (8/10) with symptoms suggestive of bulbar involvement, such as dysphagia, dysarthria or dysphonia. Severe respiratory failure requiring mechanical ventilation was observed in four patients.

CONCLUSIONS: Reactivity against the NeuNAc(alpha2-3)Gal epitope is rare and is generally found in association with reactivity against the disialosyl epitope. It can be detected in patients with acute or chronic disorders and could be a serological marker of clinical bulbar involvement and, to a lesser extent, associated with the development of severe respiratory failure.
Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies.
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Abstract
Lambert-Eaton myasthenic syndrome (LEMS) is a neuromuscular autoimmune disease that has served as a model for autoimmunity and tumour immunology. In LEMS, the characteristic muscle weakness is thought to be caused by pathogenic autoantibodies directed against voltage-gated calcium channels (VGCC) present on the presynaptic nerve terminal. Half of patients with LEMS have an associated tumour, small-cell lung carcinoma (SCLC), which also expresses functional VGCC. Knowledge of this association led to the discovery of a wide range of paraneoplastic and non-tumour-related neurological disorders of the peripheral and central nervous systems. Detailed clinical studies have improved our diagnostic skills and knowledge of the pathophysiological mechanisms and association of LEMS with SCLC, and have helped with the development of a protocol for early tumour detection.
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Comparison of IVIg and PLEX in patients with myasthenia gravis.
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Abstract
OBJECTIVE: Both IV immunoglobulin (IVIg) and plasma exchange (PLEX) are immunomodulatory treatments used to treat patients with myasthenia gravis (MG), but the choice of which treatment to administer to patients is limited due to lack of evidence from adequately powered, masked, randomized, standardized trials.

METHODS: We randomized 84 patients with moderate to severe MG defined as a Quantitative Myasthenia Gravis Score for disease severity (QMGS) of >10.5 and worsening weakness to IVIg (Gamunex®, Talecris Biotherapeutics) 1 g/kg/day for 2 consecutive days or PLEX (Caridian Spectra) 1.0 plasma volume exchanges for 5 exchanges. The patients were evaluated at day 14 after treatment for the primary efficacy parameter of change in QMGS and secondary clinical and electrophysiologic parameters and were followed for a total of 60 days.

RESULTS: Both IVIg and PLEX reduced the QMGS, and IVIg was comparable to PLEX in efficacy. The dropout rate was the same for both treatment arms and both treatments were well-tolerated. The presence of acetylcholine receptor antibodies and greater baseline disease severity predicted a better response to therapy. The postintervention status revealed that the same proportion of patients improved with treatment: 69% on IVIg and 65% on PLEX. The duration of improvement was similar with both treatments.

CONCLUSIONS: IVIg has comparable efficacy to PLEX in the treatment of patients with moderate to severe MG. Both treatments are well-tolerated, and the duration of effect is comparable. Either treatment may be offered to patients depending on availability of resources. Classification of evidence: This study provides Class I evidence that IVIg and PLEX have comparable efficacy and are equally tolerated in adult patients with moderate to severe MG within 2 weeks of treatment.
Abstract
Stiff person syndrome (SPS) is a disabling autoimmune central nervous system disorder characterized by progressive muscle rigidity and gait impairment with superimposed painful spasms that involve axial and limb musculature, triggered by heightened sensitivity to external stimuli. Impaired synaptic GABAergic inhibition resulting from intrathecal B-cell-mediated clonal synthesis of autoantibodies against various presynaptic and synaptic proteins in the inhibitory neurons of the brain and spinal cord is believed to be an underlying pathogenic mechanism. SPS is most often idiopathic, but it can occur as a paraneoplastic condition. Despite evidence that anti-GAD and related autoantibodies impair GABA synthesis, the exact pathogenic mechanism of SPS is not fully elucidated. The strong association with several MHC-II alleles and improvement of symptoms with immune-modulating therapies support an autoimmune etiology of SPS. In this review, we discuss the clinical spectrum, neurophysiological mechanisms, and therapeutic options, including a rationale for agents that modulate B-cell function in SPS.

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Management of voltage-gated potassium channel antibody disorders.
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Abstract
Syndromes from antibodies to voltage-gated potassium channels include neuromyotonia (NMT), limbic encephalitis (LE) and Morvan syndrome (MVS). There are distinct clinical features for NMT (cramps, stiffness, fasciculations, myokymia, hyperhidrosis; afterdischarges and continuous motor activity on electromyogram), LE (encephalopathy with seizures, deficient recent memory; hyponatremia, temporal lobe magnetic resonance imaging and electroencephalographic abnormalities) and MVS (NMT plus hyperhidrosis, dysautonomia, encephalopathy, severe insomnia, and sleep disorders). There may be associated myasthenia gravis or thymoma, and rarely lung cancer (small cell or adenocarcinoma), mandating that chest imaging be part of the evaluation. Most cases respond favorably to immunosuppression with plasma exchange, intravenous immunoglobulin or pulse intravenous methylprednisolone, usually followed by oral steroids.
Cramp-fasciculation syndrome: a treatable hyperexcitable peripheral nerve disorder.
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Abstract
We report nine patients with muscle aching, cramps, stiffness, exercise intolerance, and peripheral nerve hyperexcitability. Neurologic examination showed calf fasciculations in seven, quadriceps myokymia in two, and deltoid myokymia in one patient. Two patients had mild increase in serum creatine kinase. Muscle biopsy showed either no abnormality (three patients) or mild neurogenic changes (four patients). Fasciculations were the only abnormality on routine electrodiagnostic studies. Supramaximal stimulation of the median, ulnar, peroneal, and posterior tibial nerves at frequencies of 0.5, 1, 2, and 5 Hz produced showers of electrical potentials following the M response in at least one nerve. In three patients, the fasciculations and evoked electrical potentials were abolished by regional application of curare but not nerve block. Carbamazepine therapy caused moderate-to-marked reduction of symptoms and nerve hyperexcitability. We designate this hyperexcitable peripheral nerve disorder as the "cramp-fasciculation syndrome."

Redefining dysferlinopathy phenotypes based on clinical findings and muscle imaging studies.


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Abstract

BACKGROUND: The most frequent phenotypes of dysferlin myopathy are limb-girdle muscular dystrophy 2B (LGMD2B) and Miyoshi myopathy (MM). Our objective was to find clinical or MRI markers to differentiate phenotypes of dysferlin myopathy regardless of initial symptoms.

METHODS: This retrospective study included 29 patients with confirmed mutations in the DYSF gene (14 MM, 12 LGMD2B, 1 asymptomatic hyperCKemia, and 2 symptomatic carriers). All underwent an annual clinical examination (Medical Research Council scale), functional status assessment, and creatine kinase, pulmonary, and cardiac testing. For research purposes, we performed lower limb MRI studies in all 29 patients to identify the pattern of muscle impairment and to quantify involvement. Statistical correlations between MRI findings and phenotype, disease duration, and functional status were determined.

RESULTS: The mean clinical follow-up was 6.4 +/- 5.7 years. No significant differences were found in the rate of progression, functional prognosis, or mutations between patients with MM and patients with LGMD2B. The MRI pattern of muscle involvement was the same for patients with MM and patients with LGMD2B. The adductor magnus and gastrocnemius medialis were the first to be impaired in both phenotypes. The progression of muscle involvement correlated with clinical status.

CONCLUSIONS: Splitting dysferlin myopathy into separate phenotypes does not reveal significant differences in terms of rate of progression, prognosis, genotype, or MRI pattern. The finding that proximal and distal muscles are already impaired in the MRI at onset in both MM and LGMD2B favors grouping all phenotypes under the term dysferlin myopathy.

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Abstract
Muscular dystrophies primarily affect skeletal muscle. Mutations in a large number of genes, mainly encoding cytoskeletal proteins, cause different forms of dystrophy that compromise patient mobility and quality of life, and in the most severe cases lead to complete paralysis and premature death. Although muscular dystrophies still lack an effective therapy, several novel strategies are entering or are ready to enter clinical trials. Here we review the main experimental strategies, namely drug, gene and cell therapies, outlining their goals and limitations. We also provide an update of ongoing or planned clinical trials based on these strategies.

Diagnosis, natural history, and management of Charcot-Marie-Tooth disease.

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Abstract
Charcot-Marie-Tooth disease is the most common inherited neuromuscular disorder. There have been substantial advances in elucidating the molecular bases of this genetically heterogeneous neuropathy and, in most cases, molecular diagnosis is now possible. The diagnostic approach requires careful assessment of clinical presentation and mode of inheritance, nerve-conduction studies, and DNA testing, and current research is focused on assessing natural history and finding effective treatments. Disease course is variable because of genotypic and phenotypic heterogeneity. At present, there is no drug therapy for Charcot-Marie-Tooth disease, and rehabilitation therapy and surgical procedures for skeletal deformities are the only available treatments, although best practice has not been defined. Animal models are proving useful for the identification of therapeutic targets and approaches. Progesterone antagonists, neurotrophic factors, ascorbic acid, and curcumin have shown promising results in experimental models, and ascorbic acid is being studied in large randomised controlled trials.

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Pericytes of human skeletal muscle are myogenic precursors distinct from satellite cells.


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Abstract

Cells derived from blood vessels of human skeletal muscle can regenerate skeletal muscle, similarly to embryonic mesoangioblasts. However, adult cells do not express endothelial markers, but instead express markers of pericytes, such as NG2 proteoglycan and alkaline phosphatase (ALP), and can be prospectively isolated from freshly dissociated ALP(+) cells. Unlike canonical myogenic precursors (satellite cells), pericyte-derived cells express myogenic markers only in differentiated myotubes, which they form spontaneously with high efficiency. When transplanted into severe combined immune deficient-X-linked, mouse muscular dystrophy (scid-mdx) mice, pericyte-derived cells colonize host muscle and generate numerous fibres expressing human dystrophin. Similar cells isolated from Duchenne patients, and engineered to express human mini-dystrophin, also give rise to many dystrophin-positive fibres in vivo. These data show that myogenic precursors, distinct from satellite cells, are associated with microvascular walls in the human skeletal muscle, may represent a correlate of embryonic 'mesoangioblasts' present after birth and may be a promising candidate for future cell-therapy protocols in patients.
Abstract
Advances in the treatment of myasthenia gravis (MG) have reduced mortality rates due to the disease and improved patients' quality of life. Nowadays, attending neurologists can choose among different treatment strategies for MG patients. An exhaustive revision of published data on the efficacy of the different therapeutic options for MG indicates that there are insufficient evidence-based results. However, recommendations based on expert opinion can be provided. Thymectomy is indicated in all patients with a thymoma or for generalized acetylcholine receptor-seropositive patients aged 18 - 55 years. Steroids are the most widely used immunosuppressive drug for MG. They are recommended as the first-line drug in all patients with generalized MG without response to thymectomy, or in those patients who do not fulfill criteria for the surgery. The selection of second-line drugs may vary between protocols. We recommend to start with azathioprine if insufficient remission is achieved with steroids, followed by ciclosporin, mycophenolate and others. We use rituximab or cyclophosphamide only in severely drug-resistant patients. Finally, we recommend intravenous immunoglobulins or plasma exchange in MG crisis, or for unstable patients before thymectomy or in clinical exacerbations.