UPDATE IN NEUROMUSCULAR DISORDERS

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Peripheral nerve disorders

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a chronic and disabling neuropathy that affects approximately 1 to 2 persons per 100,000.[1] It is important to accurately diagnose CIDP because several studies have showed that the neurological symptoms can be effectively reversed using corticosteroids, plasma exchange, and intravenous gamma globulin (IVIg).[2] The typical clinical findings in CIDP consist of progressive or recurrent symmetric proximal and distal weakness, sensory abnormalities, and absent or hypoactive tendon reflexes in the extremities occurring over 8 weeks, and electrophysiological findings consistent with a demyelinating neuropathy.[3] There are more than 15 different diagnostic criteria proposed for the diagnosis of the CIDP, however, an accurate diagnosis continues to be challenging.[456] A recent retrospective study showed that 47 percent of patients referred for evaluation of CIDP did not meet the EFNS/PNS diagnostic criteria and the most common cause for the misdiagnosis was due to error in interpreting the nerve conduction studies.[7] The three most common conditions to be misdiagnosed as CIDP in this study were diabetic neuropathy, amyotrophic lateral sclerosis, and idiopathic small fiber neuropathy. Patient misdiagnosed with CIDP reported improvement after treatment suggesting that treatment benefit as perceived by patients should not be relied upon as an indicator of a correct diagnosis CIDP.

The role of nodal region proteins in the pathogenesis of immune mediated neuropathies is becoming increasing well recognized.[8] Antibodies that target paranodal proteins contactin-1 (CNTN1) and neurofascin-155 (NF-155) have been found in a small subset of CIDP patients.[910] In CIDP patients who have these autoantibodies, there was more severe weakness, poor response to IVIg, and prominent tremor (anti-NF155 only).[910] The findings from these studies suggest that different autoantibodies may predict different CIDP clinical phenotypes and response to therapy. In a recent study of 4 patients who have anti-CNTN1 or NF-155 antibodies unresponsive to IVIg and corticosteroid, treatment with rituximab resulted in substantial improvement in motor function in 2 patients and a mild improvement in the third patient.[11] Anti-CNTN1 and NF-155 antibody titer decreased in all patients treated with rituximab. The results from this study suggest that rituximab may be useful in patients who have antibodies to these paranodal proteins and have failed other conventional therapies, however, a larger prospective study will be necessary to confirm these results.

Neuromuscular junction disorders

Myasthenia gravis (MG) is an autoimmune disorder caused by binding of autoantibodies directed against components of the acetylcholine receptor or other proteins on the post synaptic membrane in the neuromuscular junction.[12] Most patients with MG will require immunosuppressive therapies such as corticosteroid, IVIg, plasma exchange, and non-steroidal immunosuppressive drugs (azathioprine, mycophenolate mofetil, methotrexate) to treat the

symptoms of MG.[12] Thymectomy is an effective treatment in MG and is recommended in all MG patients who have thymoma.[12] Previous retrospective studies have showed symptom improvement or remission after thymectomy in MG patients without thymoma[13], however, this was an inconsistent finding in different studies. In 2016, Wolfe and colleagues published the results of an international randomized trial of extended transsternal thymectomy in nonthymomatous, acetylcholine receptor positive, generalized MG.[14] For the first time, patients who had thymectomy and receiving prednisone was shown to have improved MG outcome measures compared to patients who were treated with prednisone alone. The patients who had thymectomy required lower prednisone dose, had a decreased need for non-steroidal immunosuppressant, and had fewer exacerbations 3 years after surgery. This study confirms the benefit of thymectomy in nonthymomatous MG.

Non-steroidal immunosuppressive treatments are often used in MG to decrease the need for long term high dose corticosteroid therapy. Azathioprine and cyclosporine have been shown to be effective in MG in randomized placebo-controlled studies.[1516] Methotrexate is another immunosuppressive therapy used in MG. Unfortunately, a recent randomized, double-blind, placebo-controlled trial of methotrexate in 50 acetylcholine receptor positive MG patients failed to show a steroid sparing effect after 12 months of treatment.[17]

There is currently no internationally accepted standard of care treatment for MG because of disease heterogeneity. A consensus-based guideline has been developed by a panel of 15 international experts in MG. This statement provides guidance on symptomatic and immunosuppressive therapies, IVIg and plasmapheresis, myasthenic crisis, thymectomy, juvenile MG, MuSK antibody, and pregnancy.[18]

Muscle disorders

Idiopathic inflammatory myopathies currently include six different entities: dermatomyositis, polymyositis, overlap myositis, inclusion body myositis (IBM), immune-mediated necrotizing myopathy, and other nonspecific myositis.[19] The identification of myositis-specific antibodies (MSA) and myositis associated antibodies (MAA) in different forms of inflammatory myopathy is suggested to be helpful for predicting response to treatment, extra-muscular manifestations, and association with cancer.

The pathological features of immune-mediated necrotizing myopathy (IMNM) were described in the 119th ENMC workshop.[20] These patients have very high serum creatine kinase and severe weakness, and the most prominent features on the muscle biopsy are abundant necrotic fibers and spare inflammatory cells. The most common MSA/MAA in IMNM are anti-SRP and anti-HMGCR (3-hydroxy-3methylglutaryl-coenzyme A reductase) antibodies.[19] It is important to identify patients who have IMNM because these patients have an increased risk for cancer. Allenbach and his colleagues reported an increased risk for cancer in patients with IMNM who have anti-HMGCR antibody or have no detectable autoantibodies when compared to the general population.[21] In IMNM patients who have anti-SRP antibody, there was no increase in cancer.

Sporadic inclusion body myositis is a common acquired myopathy in adults. The ENMC research diagnostic criteria for IBM in 2011 include clinical findings, serum creatine kinase level, age at onset, duration, and pathological features.[22] Three categories (clinicopathologically definite IBM, clinically defined IBM, and probable IBM) were proposed based on the presence or absence of the clinical features and muscle biopsy findings. Other proposed diagnostic algorithms for IBM have included the recently discovered antibody to cytosolic 5'-nucleotidase (anti-cN1A).[23] Unfortunately, anti-cN1A is neither sensitive nor specific, and there appears to be no difference in the phenotype or disease progression in seropositive patients compared to seronegative patients.[19]

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