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CHRONIC IMMUNE-MEDIATED NEUROPATHY: AN UPDATE ON THE MANAGEMENT

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ХРОНИЧЕСКИЕ ИММУННЫЕ НЕЙРОПАТИИ: СОВРЕМЕННОЕ ЛЕЧЕНИЕ
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Хронические иммунные нейропатии являются редкими заболеваниями и в основном включают в себя хронические воспалительные демиелинизирующие полирадикулонейропатии (ХВДП), мультифокальные двигательные нейропатии с постоянными блоками проводимости и парапротеинемичные нейропатии. Первый шаг имеет решающее значение для характеристики этих нейропатий посредством клинических, электрофизиологических, а иногда и иммунохимических и патологических критериев, так как ответ на лечение отличается в зависимости от типа нейропатии. Второй шаг — выбор наилучшего типа и режима иммуномодулирующего лечения, которым может быть только краткосрочная терапия препаратами первой линии, например, при рецидивирующих или быстро прогрессирующих ХВДП, но часто используется длительная терапия, если неврологическое состояние этого требует. Наконец, выбор результатов для использования в исследованиях лечения хронической иммунной нейропатии является новым, но важным для будущих исследований.
Ключевые слова: хронические иммунные нейропатии, полирадикулонейропатии, парапротеинемические нейропатии, иммуномодулирующее лечение.

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Chronic immune-mediated neuropathies are orphan diseases and mainly include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy with persistent conduction blocks (MMN), and paraproteinemic neuropathies. The first step is crucial in characterizing these neuropathies on clinical, electrophysiological and sometimes immunochemical and pathological criteria, as the response to treatment is different according to the type of the neuropathy. The second step is to choose the best type and the regimen of the immunomodulatory treatment, which may be only a first-line short-term therapy, for example in relapsing or rapidly worsening CIDP, but frequently has to be a long-term therapy if the neurological condition needs it. Lastly, the selection of outcome measures for use in trials of treatment of chronic immune-mediated neuropathy is an emerging but essential concern for future trials.
Key words: chronic immune-mediated neuropathy, polyradiculoneuropathy, paraproteinemic neuropathies, immunomodulatory treatment.

Introduction

Chronic immune-mediated neuropathies are orphan diseases and mainly include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy with persistent conduction blocks (MMN), and paraproteinemic neuropathies. The first step is crucial in characterizing these neuropathies on clinical, electrophysiological and sometimes immunochemical and pathological criteria, as the response to treatment is different according to the type of the neuropathy. For example, polyneuropathy associated with anti myelin-associated-glycoprotein (MAG) IgM monoclonal

gammopathy (MG) do not respond to corticosteroids, and MMN may worsen under plasma exchanges (PE), while CIDP may respond to either corticosteroids, PE or intravenous immunoglobulin (IVIg). The second step is to choose the best type and the regimen of the immunomodulatory treatment, which may be only a first-line short-term therapy, for example in relapsing or rapidly worsening CIDP, but frequently has to be a long-term therapy if the neurological condition needs it. Lastly, the selection of outcome measures for use in trials of treatment of chronic immune-mediated neuropathy is an emerging but essential concern for future trials [1].

1. Chronic Inflammatory Demyelinating Polyradiculoneuropathy

1.1. Diagnosis

CIDP has been firstly reported in 1958, and following descriptions allowed to distinguish progressive from chronic relapsing forms. The prevalence is estimated around 2–3 per 100.000 in the rarely published epidemiologic studies. The usual clinical picture is made of symmetrical motor weakness in both proximal and distal muscles of the upper and lower extremities for > 2 months, sensory involvement predominant in large myelinated fibers and hypo/areflexia. CSF examination discloses raised protein levels with a cell count < 10/mm^3. Electrophysiological investigations show demyelinating features including slowed motor nerve conduction velocities (MNCV), prolongation of motor distal latencies (DL), absence or prolongation of F-waves, and conduction blocks (CB) on motor nerves. However, there is a wide range of atypical presentations including purely sensory forms, and the asymmetrical form, also called Lewis-Sumner syndrome (LSS) or multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy. Nerve biopsy may be useful for the diagnosis, but remains optional for most experts. When performed, it may show unequivocal evidence of demyelination. Some authors have proposed that nerve biopsy should be systematically performed in doubtful cases, mainly purely sensory forms.

Several sets of criteria have been proposed since that published by an Ad Hoc Subcommittee of the American Academy of Neurology (AAN) in 1991. Recently a group of experts, working for a joint task force of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS), edited a guideline on management of CIDP, including revised clinical and electrophysiological criteria [2]. These criteria are reasonably easy to apply, and are as specific and more sensitive than the AAN criteria. They would therefore increase the number of CIDP patients identified to participate in clinical trials.

CIDP has an unpredictable course. Unless death remains rare, the majority of patients have a severe disability resulting from sensorimotor deficit after years.

1.2. Treatment

Prednisone has been firstly proposed in the treatment of CIDP since 1969. It has been shown to be more effective than no treatment in a randomized controlled trial (RCT) conducted in 1982 [3]. Other ways in giving steroids, such as sequential dexamethasone and pulsed high-dose methylprednisolone have been recently published. PREDICT study compared pulse oral high-dose dexamethasone to continuous oral prednisolone, and demonstrated a high proportion of remission after these 2 ways of administration [4; 5]. However the side-effects and the risk of dependence under steroids made the authors try other treatments. PE have been proposed in CIDP since 1979. The results of 2 RCTs published in 1986, then in 1996, indicated significant improvement of the clinical condition, when compared with placebo. IVIg have been firstly proposed in 1991 in an open study of 52 patients with CIDP. Four RCTs with IVIg have to date been published in CIDP, which all indicated significant improvement of the clinical deficit, when compared with placebo. The last and largest RCT was published in 2008 [6]. In this multicentric trial, 117 patients were included, receiving either monthly 2 g/kg IVIg during 6 months, then 1 g/kg IVIg every 3 weeks, or placebo: 32 out of 59 patients (54%) in the IVIg group improved by one INCAT score point, versus 12 out of 58 patients (21%) in the placebo group (p=0.0002). In addition, the rate of relapses was lower in the group treated with IVIg, during the following 18 months period.

Three RCTs compared first-line treatments in CIDP [2; 3]. The first one did not show any difference between PE and IVIg on a 6 weeks period of treatment. The second one comparing a course of IVIg and oral prednisone found no statistical difference concerning the primary outcome measure (change in a 11-point disability scale, 2 weeks after randomization), but slightly not significant greater improvement favoring IVIg in the secondary outcome measures. A meta-analysis summarising the results of these single and comparative RCTs confirmed the superiority of IVIg when com-

pared to placebo, but does not find a significant difference between IVIg and corticosteroids. More recently, an Italian multicenter trial demonstrated better efficacy and tolerability of IVIg given at the dose of 2 g/kg over 4 days in comparison to intravenous steroids (given at the dose of 2 g of methylprednisolone over 4 days) in the short-term [7].

However and interestingly, significantly more patients appeared to deteriorate after the 6 month course amongst those who had received IVIg compared to those having received intravenous steroids. The evidence of efficacy of corticosteroids, PE and IVIg in CIDP is therefore supported by several RCTs and assessed by systematic reviews. Although these treatments provide short-term benefit, the value of their immunomodulatory action in the long-term (> 2 years) has not been adequately evaluated. In addition, there are no recognised clinical or electrophysiological criteria for proposing one of these treatments as the first choice in an individual patient. Lastly, some patients who initially respond to one or more first-line treatments show progressive deterioration of their neurological condition, and therefore need long-term therapy. The lack of understanding of the pathogenesis of CIDP hinders the choice of immunosuppressive drug to be tried in long-term therapy. Furthermore, review of the non-randomised trials in the literature does not reveal a favourite drug to be tested [8]. Two RCTs have been recently conducted with interferon-β 1α (IFN-β) and methotrexate. A trial with Avonex® at different regimens, showed no benefit when given during a 6 months period. The other one failed to show a significant efficacy of methotrexate versus placebo on the primary outcome measure (reduction of doses of IVIg or steroids), over a 6 months period [9].

2. Multifocal Motor Neuropathy

2.1. Diagnosis

MMN was fisrtly reported in 1986. Patients with MMN have a fairly stereotyped clinical picture made of a chronic asymmetrical motor syndrome, starting usually in a distal upper limb and remaining prominent in the arms [10–12]. The motor deficit involves individual motor nerves, and is frequently accompanied by cramps and fasciculations. Tendon reflexes are diminished or abolished in the affected territories. The hallmark of the disease is the evidence, on electrophysiological studies, of CB at any level on motor nerves, more frequently in the forearms. The reduction of the amplitude between proximal and distal stimulation may be as much as 80%, and is usually accompanied by slowing of MNCV restricted to corresponding segments of nerves. Serum IgM anti-GM1 antibodies are found in 40 to 60% of cases. The course of the disease is slowly progressive, with possible involvement of other motor nerves in the upper then the lower limbs, leading to a marked motor deterioration.

2.2. Treatment

Patients with MMN do not usually respond to steroids or PE, which may worsen the motor deficit in some cases. On the other hand, several open studies have shown since the first description that IVIg, given at 2 g/kg, are followed by an early and often dramatic response, mainly an improvement of the motor deficit in the affected nerves. Four controlled studies were therefore conducted with IVIg in MMN and all demonstrated efficacy of IVIg when compared with placebo [13].

Several studies have tried to assess natural history and long-term effectiveness of treatments in MMN. A longitudinal study of 46 MMN patients, followed for a median of 2.3 years, demonstrated that spontaneous improvement or resolution may not occur. Four studies focused on long-term efficacy of IVIg, given as the only treatment in periodic infusions, whose results are controversial [13; 14]. The first one performed a long-term follow-up of 11 patients with MMN, who received maintenance treatment with IVIg during 4–8 years. Muscle strength improved significantly within 3 weeks of the start of IVIg treatment and was still significantly better at the last follow-up examination than before treatment, even though it decreased slightly and significantly during the follow-up period. CB disappeared in 6 nerve segments but new CB appeared in 8 nerve segments during the follow-up period. Same data and conclusions were outlined by another study which reported 10 patients with MMN receiving periodic infusions for 5 to 12 years (mean 8.2 years). At last follow-up, only 2 patients had maintained the maximal improvement achieved during therapy, while 8 worsened despite increasing IVIg dosage. This decline started after 3 to 7 years (mean 4.8 years) of therapy and correlated with a reduction of distal compound muscle action potentials amplitude ($p<0.019$). On the other hand, the third study reviewed medical records of 10 MMN patients receiving IVIg (2 g/kg) for 3 consecutive months, then monthly maintenance therapy at same doses, and followed for an average of 7.25 years. All patients kept significant a sustained improvement in muscle

strength and functional disability while on IVIg therapy. In addition, there were significant improvement in CB decrease. The difference from previous findings may be explained by the different regimen in giving IVIg, the patients in this study being treated with significantly higher IVIg maintenance doses. Lastly, our group reported a retrospective study of 40 MMN patients treated with periodic IVIg infusions (Mean follow-up: 2.2 years). At the last follow-up examination, only 8 patients (20%) had prolonged remission (> 6 months) without further treatment, after an initial IVIg periodic treatment of 6–18 months, while 25 patients (62.5%) had stabilization strictly dependent on IVIg periodic infusions.

Only one RCT has been reported in long-term treatment of MMN with mycophenolate mofetil given in addition with IVIg over a 6 month period, and showed no efficacy, when compared with placebo.

3. Paraproteinemic Neuropathies

3.1. Diagnosis

The association between peripheral neuropathy and monoclonal gammopathy (MG) has been increasingly recognized in the past 20 years [15]. The first descriptions concerned peripheral neuropathy associated with myeloma and Waldenström's disease. In 1978, Kyle proposed the term of Monoclonal Gammopathy of Undetermined Significance (MGUS) to regroup cases with "benign" paraproteinemia. Lastly, an activity of the M-protein directed to peripheral nerve antigens (MAG, glycolipids, sulphatides) has been demonstrated in a high proportion of polyneuropathies associated with IgM MGUS, but not found in polyneuropathies associated with IgG and IgA MGUS.

Polyneuropathy associated with anti-MAG IgM MG is a chronic sensory neuropathy occuring in the 6th and the 7th decades. On clinical examination, vibration and joint position sensation are impaired in the distal lower limbs and later in the distal upper limbs. Generalized areflexia is a common feature. Motor deficit occurs later in the course of the disease and affects mainly the distal lower limbs. An ataxia is present in 2/3 of patients, and a tremor of the upper limbs in 30% of cases. The course of the polyneuropathy is usually slowly progressive. Electrophysiological studies allow this polyneuropathy to be classified as a demyelinating neuropathy with a specific profile also called DADS neuropathy for distal acquired demyelinating sensory neuropathy.

3.2. Treatment

Therapeutical aspects of neuropathies associated with MG are different in polyneuropathies associated with a characterized lymphoproliferative disorder and those associated with MGUS [15].

In lymphoproliferative disorders, the treatment is that of malignancy, which may also improve the peripheral neuropathy. The best results are obtained in osteosclerotic myeloma and solitary plamocytoma, even when associated with a POEMS syndrome.

Quite different is the treatment of neuropathy associated with MGUS, which has been the matter of a wide number of mostly open trials. The vital prognosis is most of time rather good in these neuropathies but the disability has probably been underestimated, and frequently warrants fited treatments. In polyneuropathy associated with anti-MAG IgM MG, a recent Cochrane review did not disclose evidence for any beneficial immunosuppressive treatment [16]. Rituximab, a monoclonal antibody directed to CD 20 lymphocytes subtype seems to be the more promising therapy. The results of a double-blind RCT comparing rituximab with placebo in patients with worsening anti-MAG neuropathy showed a significant, unless modest, efficacy of rituximab on the INCAT score, selected as primary outcome measure [17]. Another yet unpublished placebo-controlled trial (RIMAG study) failed to show any significant improvement with riruximab on INCAT sensory score as primary outcome [18].

REFERENCES

1. Merkies I.S.J., Lauria G. 131st ENMC International workshop: selection of outcome measures for peripheral neuropathy clinical trials. 10–12 December 2004, Naarden, the Netherlands. *Neuromuscul. Disord.* 2006; 16: 149-156.

2. Van den Bergh P.Y.K., Hadden R.D.M., Bouche P. et al. European Federation of Neurological Societies/ Peripheral Nerve Society Guideline on management of CIDP. Report of a joint task force of the EFNS and the PNS – First Revision. *Eur. J. Neurol.* 2010; 17: 356-363.

3. Léger J.M. A review of the medical management of CIDP. *Expert Opin Pharmacother* 2005; 6: 569-582.

4. Van Schaik I., Eftimov F., van Doorn P.A. et al. Pulsed high-dose dexamethasone versus standard prednisolone for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial. *Lancet Neurol* 2010; 9: 245-253.

5. Eftimov V., Vermeulen M., van Doorn P.A. et al. PREDICT. Long-term remission of CIDP after pulsed dexamethasone or short-term prednisolone treatment. *Neurology* 2012; 78: 1079-1084.

6. Hughes R.A.C., Donofrio P., Bril V. et al. ICE Study Group. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment

of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol.* 2008; 7: 136-144.

7. Nobile-Orazio E., Cocito D., Jann S. et al. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyneuropathy: a randomised controlled trial. *Lancet Neurol.* 2012; 11: 493-502.

8. Mahdi-Rogers M., Swan A.V., van Doorn P.A., Hughes R.A.C. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyneuropathy. *Cochrane Database Sys. Rev.* 2010; 11: CD003280.

9. Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyneuropathy (RMC trial): a pilot, multicentre study. *Lancet Neurol.* 2009; 8: 158-164.

10. Nobile-Orazio E., Capellari A., Priori A. Multifocal motor neuropathy: current concepts and controversies. *Muscle Nerve* 2005; 31: 663-680.

11. Van Schaik I.N., Léger J.M., Nobile-Orazio E. et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of multifocal motor neuropathy: report of a joint task force of the EFNS and the PNS-First revision. *J. Peripher Nerv. Syst.* 2010; 15: 295-301.

12. Cats E.A., van der Pol W.L., Piepers S. et al. Correlates of outcome and response to IVIg in 88 patients with multifocal motor neuropathy. *Neurology* 2010; 75: 818-825.

13. Léger J.M., Vargäs S., Lievens I. Efficacy of intravenous immunoglobulin in multifocal motor neuropathy. *Ann New York Acad. Sci.* 2007; 110: 248-255.

14. Umapathi U., Hughes R.A.C., Nobile-Orazio E., Léger J.M. Immunosuppressant and immunomodulatory treatments for multifocal motor neuropathy. *Cochrane Database Syst. Rev.* 2012; CD003217.

15. Hadden R.D.M., Nobile-Orazio E., Sommer C. et al. European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of paraproteinemic demyelinating neuropathies: report of a joint task force of the EFNS and the PNS-First revision. *J. Peripher. Nerv. Syst.* 2010; 15: 185-195.

16. Dalakas M.C., Rakocevic G., Salagegheh M. et al. Placebo-controlled trial of rituximab in IgM anti-myelin associated glycoprotein antibody demyelinating neuropathy. *Ann. Neurol.* 2009; 65: 286-293.

17. Lunn M.P.T., Nobile-Orazio E. Immunotherapy for IgM anti-myelin associated glycoprotein paraprotein-associated peripheral neuropathies. *Cochrane Database Syst. Rev.* 2012; CD002827.

18. Léger J.M., Viala K., Nicolas G. et al. Placebo-controlled trial of rituximab in IgM anti-myelin associated glycoprotien demyelinating neuropathy (RIMAG study). *Neurology* 2013, in revision.

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