

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

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Abstract: Chronic inflammatory demyelinating polyneuropathy (CIDP) is a rare neurological disorder characterized by inflammation and demyelination of peripheral nerves and nerve roots. Clinically, it is characterized by predominantly proximal symmetrical motor deficit of upper and lower limbs, accompanied by sensory disturbances with ectromelia. Evolution can be progressive or in flare-ups and remissions. Paraclinical diagnosis is made by electromyography, cerebrospinal fluid examination, nerve biopsy and magnetic resonance imaging of the spinal cord. Basic treatment consists of corticosteroids, immunoglobulins or plasmapheresis. Clinical picture of CIDP is similar to that of Guillain-Barre syndrome, but is different due to the acute onset, more rapid occurrence of the motor deficit (which usually reaches its maximum in 14 days) and favourable prognosis. In CIDP, diagnosis comes after about 8 weeks of persistence of a clinical picture characterized by polyradiculoneuropathy, whose evolution can be progressive or in flare-ups and remissions.

CIDP is a rare condition. Estimated prevalence of the disease is of 0.8 to 7.7 per 100.000 inhabitants. There is no racial predilection. Both genders are affected, but CIDP seems to predominate in males with a ratio of 2: 1. The disease can occur at any age, but the incidence appears to be higher in the 5th or 6th decades of life. The form of flare-ups and remissions occur more frequently in younger patients (3rd, 4th decades of age).

Etiology

CIDP is most often an idiopathic condition. In some cases, it is associated with several autoimmune diseases well defined clinically and paraclinically (lupus, HIV, hepatitis B or C).

- CIDP associated with HIV infection characterized by mild pleocytosis and increased levels of gamma globulins in the spinal fluid. It has been found CIDP occurs both in the early and late forms of the HIV infection,
- CIDP associated with Hodgkin lymphoma, case in which the polyneuropathy is not due to the direct infiltration, but it is a consequence of this autoimmune cascade of this disease,
- CIDP associated with paraproteinemias, such as monoclonal gammopathies, in particular those with IgM. In these patients, distal sensory symptoms prevail against the motor ones. The decrease of the nerve conduction velocity is more pronounced in the distal segments of the nerve. The response to immunosuppressive and/or immunomodulator therapy is weak (although, some studies report a good response to rituximab, a monoclonal antibody directed against B cells),
- CIDP associated with multiple myeloma and Waldenstrom's macroglobulinemia. In neuropathy associated with myeloma, abnormal paraprotein consists of a lambda light chain. The combination of osteoclastic myeloma, organomegaly, endocrinopathy, M protein, sensorimotor neuropathy and skin pigmentation changes constitute the POEMS syndrome. In POEMS syndrome, M protein consists of an immunoglobulin G,
- CIDP associated with active hepatitis (B or C).

Morphopathology

Sural nerve biopsy revealed interstitial and perivascular infiltration in endoneurium. In addition, there are inflammatory T cells and macrophages with a local edema. Segmental demyelination and remyelination arise with the occurrence of “onion bulb” formations, coming from the anarchic accumulation of Schwann cells.

Clinical picture

CIDP begins insidiously and progresses slowly, usually after an acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome). To diagnose CIDP, the duration of symptoms should be greater than 8 weeks. Evolution is slowly progressive (60%) or in flare-ups and remissions (33%) with partial or complete recovery after relapses. Before the occurrence of the specific clinical symptoms, respiratory and digestive infections may sometimes be found, without identifying a causative pathological agent.

The initial symptoms refer to the appearance of a bilateral motor deficit, both proximal and distal and no tendon reflexes. Sensitive symptoms then appear (usually, paraesthesia under the form of numbness and/or tingling resembling to ectromelia (“in gloves” in the upper limbs and “in socks” in the legs). Neuropathic pain rarely occurs in the affected limb. In about 16% of patients (particularly in children), the onset can be subacute or acute. Sometimes, there occur signs of autonomic nervous system damage (balance disorders in standing, cardiac or sphincter disorders).

Cranial nerve examination sometimes reveals peripheral facial palsy, diplopia or papilledema (in patients with cerebrospinal fluid proteins more than 1.000 mg/ml). Gait is difficult due to motor and proprioceptive deficit (bilateral steppage gait, high-heeled gait). Sensory ataxia occurs with positive Romberg's sign. Usually, there is no occurrence of pathological pyramidal reflexes (Babinski, Oppenheim).

Korski criteria of the American Academy of Neurology for classifying patients with CIDP are the following:

- patients with chronic polyneuropathy, progressive for at least 8 weeks if there is no serum paraprotein or proven genetic abnormality,

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CLINICAL ASPECTS

- and one of the following conditions:
 - o abnormal distal latency in over 50% of motor nerves;
 - o abnormal nerve conduction velocity in more than 50% of the motor nerves;
 - o abnormal F-wave latency in over 50% of the tested nerves.
- or one of the following:
 - o symmetrical onset;
 - o motor deficit in all 4 limbs;
 - o at least one limb with proximal motor deficit.(1,2,3)

Paraclinical diagnosis

Serum examination - blood count, erythrocyte sedimentation rate, antinuclear antibodies (ANA), biochemistry test, serum and urinary immunoelectrophoresis (to exclude associated systemic diseases). Cerebrospinal fluid examination reveals typically an albumino-cytological dissociation with high cerebrospinal fluid proteins and normal cellularity. About 10% of patients show lymphocytic pleocytosis and increased gamma globulins. It is useful to make tests that highlight antiganglioside antibodies: anti-GM1, anti GD1 and anti-Ga1b. Human leukocyte antigens DW3, DRw3, A1 and B8 occur more frequently in patients with CIDP than in the healthy population.

Genetic testing (Charcot-Marie disease, hereditary neuropathy with pressure sensitivity) especially in CIDP cases in children.

Electromyography (EMG) distinguishes between axonal and demyelinating neuropathy. Demyelinating neuropathy signs are the following: multifocal conduction block or temporal dispersion of compound muscle action potentials; prolonged distal latencies in at least two nerves; decreased nerve conduction velocities of no more than 70% of the normal values; absence or extension of F wave latencies at least two motor nerves.

Nuclear magnetic resonance, especially after the administration of gadolinium reveals a thickening of the spinal nerve roots. Sural nerve biopsy reveals changes described in the chapter of pathology. This was recommended in the past, before the establishment of the immunosuppressive therapy. Currently, biopsy indications are increasingly rare.

Differential diagnosis

It will be made with one of the following conditions: Acute inflammatory demyelinating polyradiculoneuropitis, Polyneuropathy in disseminated lupus erythematosus, Neuromuscular complications of HIV, Polyneuropathy associated with Hodgkin's disease, Polyneuropathy in paraproteinemias and vasculitis, Polyneuropathy in Waldenstrom's macroglobulinemia, Polyneuropathy in multiple myeloma, Polyneuropathy in Wegener's granulomatosis, Polyneuropathy in polyarteritis, Diabetic polyneuropathy, neurosarcooidosis.

Prognostic

Like multiple sclerosis, another demyelinating disease, it is difficult to set an accurate prognosis. Relapses and remissions vary from patient to patient. If the diagnosis is made early, earlier treatment initiation prevents demyelination and axonal loss. Many patients remain with residual symptoms such as numbness, muscular weakness, fatigue which are often debilitating and cause a decrease in their quality of life.

Treatment

The main targets of CIDP treatment aim at improving the functional status of the disease and preservation of long-term remissions. Currently, the standard treatment consists of corticosteroids, immunoglobulins and plasmapheresis. Clinical improvement occurs in approximately 60-80% of patients.(4,5,6) Corticosteroid therapy consists of oral prednisone at a dose of 1-1.5 mg/kg (40-100 mg) per day.

Improvement may occur at 2 weeks after dosing and is maximal after 6 months of treatment. Numerous adverse effects limit the use of this medication.(7) Intravenous immunoglobulins are considered, by some authors, the treatment of choice. The starting dose is 2 g/kg for 2-5 days. In most of the patients, clinical improvement occurs after 1-2 weeks. Maximal effect lasts several weeks or months. Plasmapheresis involves performing five sessions every two days for 10 days. The method is particularly made in acute exacerbations. Contraindications are represented by hemodynamic instability, heart disease, coagulopathy, sepsis. Alternative treatments are used in patients who do not respond to conventional therapies or to minimize the use of high doses of corticosteroids. These consist in:

- Azathioprine, 2-3 mg/kg daily in one or two administrations per day. It is an analogue that decreases purines metabolism and in addition, inhibits the synthesis of DNA and RNA,
- Mycophenolate mofetil, 1.2 g/day 2 times per day. It inhibits the synthesis of lymphocytic purines,
- Intravenous Cyclophosphamide, 0.75 to 1.0 g/m² per month up to 6 months. It is an immunosuppressant that acts as alkylating agent,
- Interferon beta-1a in the dose of 3 million units subcutaneously, 2-3 times a week,
- Rituximab, 375 mg/ m² intravenously once weekly for four weeks,
- Etanercept, 25 mg subcutaneously 2 times per week,
- Cyclosporine inhibits T cell activation in the first phase and does not affect humoral immunity.(8)

The symptomatic treatment, in cases where neuropathic pain prevails, consists of antiepileptic drugs (AEDs) (carbamazepin, neurontin, pregabalin) or tricyclic antidepressants (amitriptyline). Lately, there has been tried the experimental use of monoclonal antibodies (rituximab, alemtuzumab) or medicines that modulate the lymphocytes (fingolimod), medication that is administered successfully in multiple sclerosis.

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