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Review Article

Chronic inflammatory demyelinating polyradiculoneuropathy – a narrative review

Polineuropatia desmielinizante inflamatória crônica – uma revisão narrativa

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ABSTRACT: *Introduction:* Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disease generated by cellular and humoral immune responses, that act in a synergistic way, will act against antigens of the peripheral nerves, generating a progressive clinical feature of sensorimotor weakness that will change the quality of life of this patient. *Aim*: Summarize the basic and actual concepts of CIDP, such as etiology, disease subtypes, clinical features, pathogenesis, pharmacological and non-pharmacological treatment. *Material and Methods*: This is a narrative systematic review. Medline (Pubmed), Embase and PEDro databases were used to summarize the review' topics. The studies used in this review were selected by convenience. *Results*: CIDP can affect children and adults, and male gender is the most affected. The clinical picture of CIDP is composed of numbness, paresthesia, sensory changes, muscle weakness, hyporeflexia or areflexia, fatigue and balance changes, this picture has a progressive or relapsing character, symmetrical and with slow evolution. The disease has an autoimmune character generated by cellular and humoral immune responses, which will act against peripheral nerve antigens, generating demyelination and axonal degeneration. The treatment of CIDP aims to reduce or attenuate the evolution of symptoms. The main types of treatments are the intravenous of immunoglobulins, corticosteroid, and plasma transfer administration. *Conclusion*: Studies exploring more deeply the pathophysiological mechanisms of CIDP and optimization of diagnosis, are important points that should be investigated to improve care and assertiveness in the treatment of these patients.

Keywords: Acute inflammatory demyelinating polyneuropathy; Physiotherapy; Guillain-Barre syndrome.

RESUMO: Introdução: A Polineuropatia Desmielinizante Inflamatória Crônica (PDIC) é uma doença de caráter autoimune gerada por respostas imunes celulares e humorais que, atuando de forma sinérgica, irão agir contra antígenos dos nervos periféricos, gerando um quadro progressivo de debilidade sensório-motora que irá alterar a qualidade de vida de seus portadores. *Objetivo***:** Sumarizar os conceitos básicos e atuais da PDIC, como etiologia, subtipos da doença, quadro clínico, patogênese e o tratamento farmacológico e não farmacológico. *Material e Métodos:* Trata-se de uma revisão sistemática narrativa. As bases de dados Medline (Pubmed), Embase e PEDro foram utilizadas para sumarizar os tópicos dessa revisão. Os estudos que compuseram os tópicos dessa revisão foram selecionados por conveniência. *Resultados*: A PDIC pode acometer crianças e adultos, e o sexo masculino é o mais afetado. O quadro clínico da PDIC é composto de dormência, parestesia, alterações sensoriais, fraqueza muscular, hiporeflexia ou arreflexia, fadiga e alterações de equilíbrio, esse quadro tem caráter progressivo ou recidivante, simétrico e com evolução lenta. A doença tem caráter autoimune gerada por respostas imunes celulares e humorais, que irão agir contra antígenos dos nervos periféricos, gerando uma desmielinização e degeneração axonal. O tratamento da PDIC visa reduzir ou atenuar a evolução da sintomatologia. Os principais tipos de tratamentos são a administração intravenosa de imunoglobulinas, corticosteroides e transferência plasmática. *Considerações Finais:* Estudos explorando mais profundamente os mecanismos fisiopatológicos da PDIC e otimização do diagnóstico, são pontos importantes que deverão ser investigados para a melhora da assistência e assertividade do tratamento desses pacientes.

Palavras-chave: Polineuropatia desmielinizante inflamatória aguda, fisioterapia, Síndrome de Guillain-Barré.

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INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common form of chronic autoimmune neuropathy[1]. CIDP can present in its relapsing or progressive form, with proximal and distal muscle weakness that develops for at least two months[2,3].

CIDP is most commonly seen in men and usually occurs between the fourth and sixth decade of life; however, CIDP can also be seen in children[4]. The progressive evolution of this disease generates symptoms that may cause physical and functional limitations and negatively impacts the patient's quality of life[5].

In view of the scarcity of national and international articles on this pathology, the aim of this article is to briefly summarize the basic and current concepts of CIDP, such as the subtypes of the disease, epidemiological data, clinical presentation, pathogenesis, and pharmacological and non-pharmacological treatment.

MATERIAL AND METHODS

This is a narrative systematic review. The MEDLINE (PubMed), Embase and PEDro (Physiotherapy Evidence Database) databases were used, and only English articles were selected. The research in these databases included clinical trial and systematic review studies, which addressed the general aspects of the disease covered in this review (definition, epidemiology, etiopathogenesis, clinical presentation, pathogenesis, and treatment).

The studies selected to contemplate the definitions and topics of this review were chosen from these databases for convenience. Thus, the articles included in this narrative review were read in an analytical and interpretative way to give broader meaning to the findings and definitions found.

RESULTS AND DISCUSSION

Epidemiology

The prevalence of CIDP has ranged from 1 to 7.7 per 100,000. Although it is considered a rare disease, CIDP is the most common form of chronic autoimmune neuropathy. Due to its diversity of clinical presentations and the absence of a specific marker for its diagnosis, epidemiological studies present values that differ from its incidence[6,7].

CIDP can also affect children, usually between 5 and 18 years old. However, peak incidence occurs in adults between 40 and 60 years of age. Males are more commonly affected by this disease[7].

Distinguishing CIDP from Guillain-Barré Syndrome

CIDP and acute inflammatory demyelinating polyradiculoneuropathy, also known as Guillain-Barré syndrome (GBS), share several clinical features, similarities, and electrophysiological and histopathological findings; however, the beginning of the diseases' appearances, the peak and course of their symptoms and their clinical presentation are distinct[1].

GBS is a monophasic disease that is generally associated with a previous event, such as a vaccine, infection or diarrheal disease. It has an acute beginning, and the nadir is generally reached in less than four weeks. In contrast, the symptoms of CIDP typically have a longer progression of around eight weeks. Unlike GBS, patients with CIDP may experience a recurrent course of symptoms, and CIDP is rarely associated with a previous event, like a vaccination or illness. In addition, the involvement of the respiratory musculature, autonomic nervous system and peripheral nerves are rare, and they are associated with advanced disease states[1,3,8].

Pathogenesis and Pathophysiology

CIDP is an autoimmune disease generated by cellular and humoral immune responses, which, acting synergistically, will act against peripheral nerve antigens, generating demyelination and often secondary, axonal degeneration[2]. There are reports of patients who report infections prior to the onset of neurological symptoms; however, there is still not enough evidence to relate infectious events to the onset of the disease[6,9]. In fact, the autoimmune etiology is well accepted for the efficacy of treatments to the immune system, such as IVIg, plasma exchange and use of corticosteroids, and through the evidence of the inflammatory response of blood and the peripheral nerves[2,10].

The main inflammatory components found in the peripheral nerves after death are T cells and macrophages in the epineurium and endoneurium; macrophages are considered final effector cells after the demyelination process. Studies suggest that these T cells activate in the peripheral nervous system and generate the production of pro-inflammatory cytokines that produce a cytotoxic activity against myelin[4,10]. This process occurs through the alteration of the blood hematoneural barrier, which, under normal conditions, will maintain endoneurium homeostasis, preventing the free movement of soluble factors, such as serum blood proteins, to the nerve microenvironment[1,2,11]. When activated, T cells will adhere to endothelial cells, interacting with adhesion molecules and then migrating through the hematoneural barrier[1]. As they migrate through blood vessels, T cells continue to secrete inflammatory mediators, such as metalloproteinase and pro-inflammatory cytokines, contributing to increased permeability of the hematoneural barrier and generating a positive regulation of the immune response to the nerve[2].

T cells do, in fact, appear to play a crucial role in the evolution of this disease. Studies show that the imbalance between Th1 and Th2 cells plays an important

role in the development of inflammatory and autoimmune diseases, including CIDP[12]. In addition, studies have shown that another subset of T cells, called Th17 cells, may be responsible for pathogenic effects previously attributed to Th1 cells[13]. Th17 cells were identified in animal and human models, which were associated with the orphan factor related to the retinoic acid receptor (ROR) and STAT3 (signal transducers and activators of transcription), in addition to an extensive network of pro-inflammatory cytokines, which include some interleukins[11,12].

Additionally, evidence supports that the arachidonic acid pathway is highly activated in the nervous system of patients with multiple sclerosis, and this also seems to be true in patients with CIDP[14]. It has been demonstrated that COX-2 is expressed both in active demyelinating lesions and in oligodendrocytes, Schwann cells, macrographs and microglia in the process of cell death, which is a possible target for investigation in future research on the pathophysiology of this disease[14,15].

Although CDIP is known to be caused by the loss of immune response regulation in response to unknown antigens, some myelin-related antibodies have been considered as potential autoantigens, including the myelin zero protein, myelin basic protein, connexin-32 and ganglioside. In general, the mechanisms for the generated immune responses and their repercussions in the peripheral nervous system have not yet been fully elucidated[7,16,17].

Clinical features

In their classic form, the clinical manifestations of CIDP are monophasic, progressive or relapsing, symmetrical and evolve slowly over at least two months. Numbness, paresthesia, sensory changes, muscle weakness, hyporeflexia or areflexia, fatigue and imbalance are the main clinical findings that usually begin in the lower limbs. In rare cases, the cranial nerves can be affected, especially the seventh pair[4,7].

The typical form of the disease corresponds to 50% of the cases, with the remainder being variations of the classic form with motor or sensory predominance, presentation in the upper limbs or asymmetric presentation, such as Lewis-Sumner syndrome (Table 1)[2,6].

CIDP can also affect children, usually between 5 and 18 years old, and can cause serious disabilities if not treated properly. In general, children respond well to treatment and tend to have a better outcome compared to adults. Some children may show complete remission of CIDP or residual stability of the condition without the need for additional interventions[1,17,18].

When the disease progresses, the patient may report difficulty in performing functional activities, such as going up and down stairs, difficulty in walking and getting up from a chair, falls and decreased manual dexterity in activities such as buttoning blouses and zipping. Approximately 50% of patients with CIDP will experience severe temporary disabilities, including not walking without a walking aid or wheelchair restriction, and 10% will have a persistent and progressive disability or will die from complications related to the disease. Some patients, however, may experience the disease with only subtle clinical manifestations, and some may even be asymptomatic[1,6,19].

Table 1. Differences clinical presentation of CIDP

Clinical Presentation	Onset	Clinical Symptoms	Distribution
Typical CIDP	Chronic	Sensory and motor	Symmetrical, proximal, and distal
Sensory CIDP	Chronic	Sensory predominant; motor involvement may develop	As per typical CIDP
Lewis-Sumner syndrome	Chronic	Sensory and motor	Asymmetrical; often upper limb onset
Focal CIDP	Chronic	Sensory and motor	Focal; may progress to diffuse CIDP over time
Motor CIDP	Chronic	Motor predominant	As per typical CIDP
Acute onset CIDP	Acute onset	Sensory and motor	As per typical CIDP

Legends: CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy. Adapted table from Mathey et al.[2]

Pharmacological treatment

One of the primary goals of the treatment of CIDP is to reduce or attenuate the evolution of symptoms (muscle weakness, fatigue, sensory loss, alteration of balance control). The three main types of pharmacological treatments for CIDP are the intravenous administration of immunoglobulins, corticosteroids and plasma transfer. The response rate is 53%–80% for plasmapheresis, 40%–60% for corticosteroids and 54%–63% for the administration of immunoglobulins, according to prospective studies[10,20-23].

In general, the use of prednisone or dexamethasone, immunoglobulins or plasma transfer have very similar effects in the short term, and in the long term, the choice should be made based on the individual characteristics and preference of the patient due to the adverse effects of the treatments. Treatment with prednisone is usually

started if the patient does not have contraindications, such as hypertension, osteoporosis, diabetes or obesity. If the administration of corticosteroids is not effective, immunoglobulins can be used, followed by plasma transfer[1,6,24].

The treatment of patients with PDIC should be well thought out in relation to the cost-benefit of treatment options due to the adverse effects that may negatively impact the patients' quality of life. The participation of a multidisciplinary team is also important in order to offer the patient a more targeted and integrated treatment.

Non-pharmacological treatment

Several studies highlight the importance of physical activity for CIDP patients' quality of life. Indeed, the symptoms presented by these patients, including fatigue, could be attenuated with physical activities and physical exercise[25].

Physical therapy can benefit patients with CIDP by employing activities that help to maintain range of motion, strengthen specific muscles, prevent shortening and contractures, sensorimotor stimulation, improve balance and gait training in order to avoid possible falls[19]. In turn, physical educators can play an important role in prescribing physical activities and exercises in order to reduce fatigue, which is often experienced by CIDP patients, and improve cardiorespiratory fitness. In addition, physical exercise can mitigate negative psychological aspects of the disease, such as anxiety, depression, anger and frustration[26,27].

Physical education and physical therapy could use important therapeutic resources to prevent complications caused by the disease, as well as to improve physical well-being and quality of life. A multidisciplinary and integrated approach can generate greater benefits for CIDP patients.

FINAL CONSIDERATIONS

Understanding CIDP is crucial for selecting the best pharmacological treatment options and consequently improving the patient's physical well-being.

Future studies are necessary to understand the pathophysiology of this disease, as well as to improve the criteria for diagnosis. There is also a need for studies that observe the real benefits of non-pharmacological interventions to patient health.

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