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A clinical approach to hypertrophic pachymeningitis

Abordagem diagnóstica para paquimeningite hipertrófica

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ABSTRACT

Importance: Hypertrophic pachymeningitis (HP) is a non-usual manifestation of rheumatologic, infectious, and neoplastic diseases. Etiological diagnosis is a challenge, but when made promptly it creates a window of opportunity for treatment, with the possibility of a total reversal of symptoms. **Observations:** HP is an inflammatory process of the dura mater that can occur as a manifestation of sarcoidosis, granulomatosis with polyangiitis, and IgG4-related disease. The HP case evaluation is extensive and includes central nervous system imaging, cerebrospinal fluid analysis, serology, rheumatologic tests, and systemic survey for other manifestations sites. After systemic investigation, meningeal biopsy might be necessary. Etiology guides HP treatment, and autoimmune disorders are treated with corticosteroids alone or associated with an immunosuppressor. **Conclusion:** HP is a manifestation of several diseases, and a precise etiological diagnosis is crucial because of the difference among treatments. An extensive investigation of patients with HP helps early diagnosis and correct treatment.

Keywords: Pachymeningitis; Granulomatosis with Polyangiitis; Immunoglobulin G4-Related Disease; Sarcoidosis.

RESUMO

Importância: Paquimeningite hipertrófica (PH) é uma manifestação não usual de doenças reumatológicas, infecciosas e neoplásicas. O diagnóstico etiológico por vezes é um desafio, entretanto quando realizado em tempo cria uma janela de tratamento com a possibilidade de reversão total dos sintomas. **Observações:** A PH é um processo inflamatório da dura-máter que pode ocorrer como manifestação da sarcoidose, granulomatose com poliangeíte e doença relacionada à IgG4. A avaliação dos casos de PH é extensa e inclui imagem do sistema nervoso central, análise de líquor, sorologias, provas reumatológicas e rastreio sistêmico para doença em outros sítios. Por vezes, após toda a investigação sistêmica, a biópsia de meninge é necessária. A etiologia orienta o tratamento da HP, sendo que em doenças autoimunes adota-se o uso de corticosteroides isolados ou associados a um imunossupressor. **Conclusão e Relevância:** A PH é uma manifestação de várias doenças, e seu diagnóstico etiológico preciso é fundamental, visto a diferença entre os possíveis tratamentos. Uma investigação ampla nos casos de PH ajuda no diagnóstico precoce e tratamento adequado.

Palavras-chave: Paquimeningite; Granulomatose com Poliangiite; Doença Relacionada a Imunoglobulina G4; Sarcoidose.

Hypertrophic pachymeningitis (HP) is an inflammatory process which causes thickening of the cranial or spinal dura mater and is associated with variable neurological syndromes such as cranial nerve palsy, stroke, venous thrombosis and intracranial hypertension. The diagnosis of HP is suggested by magnetic resonance imaging (MRI), which discloses dural thickening and contrast enhancement[1]. Several disorders such as infectious and autoimmune diseases may cause HP[1,2,3,4]. The gold standard for HP etiological diagnosis is dural biopsy, but cerebrospinal fluid (CSF) and blood tests, as well as other tissues analyses, lead to a correct diagnosis. Quick diagnosis and treatment are crucial to avoid permanent symptoms. However, the diagnostic workup is usually a complex process, which may delay the specific treatment. This review aims to discuss the causes of HP and propose a practical approach to the diagnosis and treatment of its inflammatory and autoimmune origins.

CONCEPT AND ANATOMY

The meninges comprise three layers of protective tissue enveloping the brain and spinal cord. Dura mater is the outermost and thickest of the meninges and is formed by dense connective tissue closely related to the inner table of the skull. The other layers, pia mater and arachnoid, are much

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thinner and thus referred to as the leptomeninges. The pia mater is a transparent layer directly adherent to the surface of the brain and spinal cord. A complex network of reticular fibers located between the dura and the pia mater constitutes the arachnoid[5].

Numerous pathological processes target the meninges, including neoplasms, infections, and autoimmunity[3]. The term leptomeningitis indicates that the pia mater and/or the arachnoid are affected, while pachymeningitis describes a disease of the dura[6]. Because the dura encases the proximal portion of cranial nerves, the cavernous sinus, and the optic nerve sheath, pachymeningitis may damage these structures[7].

In 1893, Gowers provided the first detailed description of pachymeningitis and identified two subtypes of the disorder. External pachymeningitis was related to a local phenomenon provoked by trauma or infection. The internal subtype reflected a more diffuse process, either hemorrhagic (likely corresponding to subdural hematoma) or purulent (likely resulting from the spread of leptomeningeal tuberculosis or syphilis)[8]. Charcot's 1873 description of a case of cervical pachymeningitis, in which "the neighboring leptomeninx (...) was firmly united to the dura" is closer to the definition currently used in medical literature[9].

HP is defined macroscopically by the local or diffuse thickening of the cranial or spinal dura mater, which often becomes adherent to the underlying leptomeninges. Two types of cranial pachymeningitis may occur, depending on the location of the dural thickening: one affects the parasellar and cavernous regions, involving the cavernous and supraclinoidal segments of the internal carotid artery and optic nerves; the other compromises the posterior third of the falx, tentorial, and clival dura mater[10]. Histological findings vary significantly according to the underlying disease[11].

CLINICAL FEATURES

HP has a variable clinical presentation depending on the etiology. Early symptoms often include headache (in up to 92% of patients) and cranial nerve involvement[7]. Cranial nerves II and VII are predominantly affected due to nerve compression or orbital pseudotumor (the optic nerve is often affected, sometimes bilaterally). The involvement of cranial nerves III, IV, and VI can also lead to diplopia and ophthalmoplegia. Other common neurological symptoms include intracranial hypertension, seizures, cerebral venous thrombosis, hearing loss and gait ataxia. The clinical manifestation of HP may vary depending on lesion location and dura mater thickness in brain imaging. The parenchymal manifestations of HP include seizures, hemiparesis, tremors, cognitive impairment, and localized brain edema with "pseudotumor" presentation[7,12,13]. HP is a rare cause of spinal cord compression[14].

The pathophysiological mechanism underlying parenchymal involvement includes venous congestion, ischemia resulting from compression of cortical vessels and inflammatory infiltration into the brain parenchyma.

Extra-neurological or systemic manifestations of HP may help to define the etiology. For example, the involvement of salivary glands, lymph nodes, the pancreas, and the retroperitoneum suggest IgG4-related disease (IgG4-RD); pulmonary, renal and paranasal sinus involvement may suggest granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis; hypothalamic involvement suggests IgG4-RD, sarcoidosis or histiocytosis; and coexistence with neoplasia may suggest meningeal carcinomatosis[7,12].

NEUROIMAGING

MRI in patients with HP demonstrates thickening of the dura mater, which may be diffuse or focal. The sinus cavernous and orbital apex are commonly affected[3,15]. Most of the patients present diffuse and asymmetric thickening of the dura mater. The inflammatory process and increased vessel permeability cause a marked contrast enhancement in HP. Contrast enhancement usually decreases with immunotherapy, and MRI is relevant for the follow-up. Sinus occlusion may occur due to the thickening of the dura, and thrombosis may occur because of hemodynamic changes[3,15]. Figure 1 shows typical thickening of the dura mater in HP and similar findings in autoimmune causes and infections. In addition, a hyperintense signal of the dura mater may occur as a result of intracranial hypotension, as a compensatory edema of the meninges caused by a decreased volume of cerebrospinal fluid[3]. Additionally, other non-inflammatory conditions such as *en plaque* meningioma, post-surgical change, and chronic subdural hematoma may lead to a similar appearance of thickened dura mimicking HP.

MRI features are relevant in differentiating idiopathic hypertrophic pachymeningitis (IHP) from secondary HP. The characterization of MRI features in HP should include: 1) location — supratentorial, infratentorial, diffuse, and spinal canal; 2) configuration — linear and nodular; 3) signal intensity — hyperintense, iso-intense or hypointense[15].

The essential MRI sequencing to evaluate and identify HP is the post-contrast T1-weighted sequence, which demonstrates a marked hyperintense signal caused by contrast enhancement[15,16]. The secondary HP group significantly has dural mater thickening at the anterior and middle cranial fossae when compared with IHP patients. Most of the latter have homogeneous contrast enhancement. Finally, imaging features presenting as hypointense in T2 sequences, and central T2 hyperintense signal with hypointense rim (T2-rim pattern) suggest HP[16].

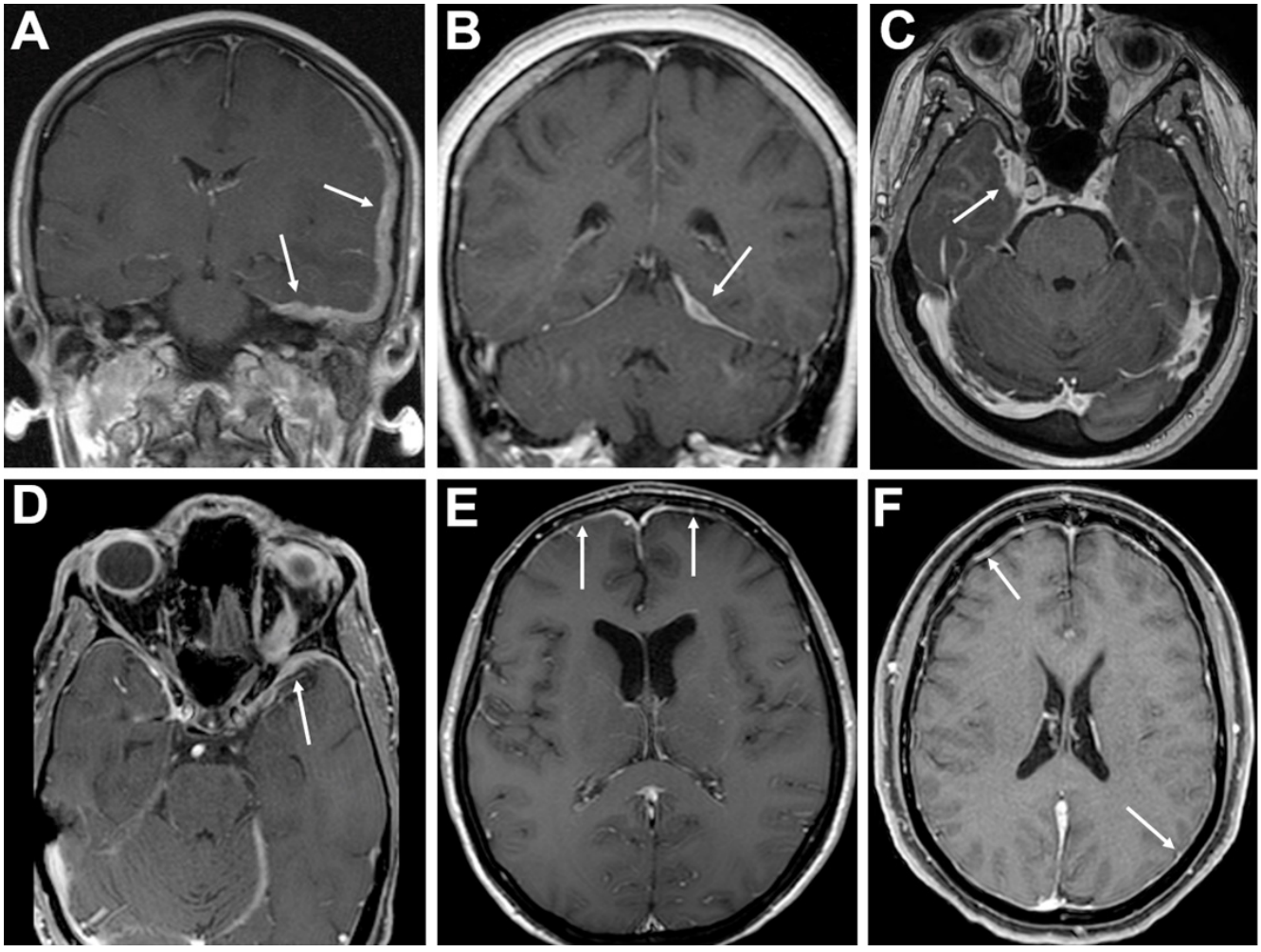


Figure 1. (A) patient with granulomatosis and polyangiitis presenting focal hypertrophic pachymeningitis (arrow); (B) patient with sarcoidosis presenting asymmetric thickening of the dura mater in the cerebellar tentorium (arrow); (C) patient with IgG4-related hypertrophic pachymeningitis presenting a focal thickening of the dura mater in the right cavernous sinus (arrow); (D) patient with neurosyphilis presenting asymmetric thickening of the dura mater mimicking hypertrophic pachymeningitis (arrow); (E) patient with neurotuberculosis presenting anterior thickening of the dura mater mimicking hypertrophic pachymeningitis (arrows); (F) patient with intracranial hypotension after lumbar puncture mimicking hypertrophic pachymeningitis, with hyperintense signal of the dura mater (arrows).

CAUSES

Table 1 shows the many causes of HP. The most common are discussed separately below:

Granulomatosis with polyangiitis

GPA is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, a group of diseases associated with antibodies against neutrophil cytoplasmic structures[17]. It is characterized by the involvement of the respiratory tract and kidney[18,19]. Its serologic marker is the PR3-ANCA (c-ANCA), but some cases could exhibit MPO-ANCA (p-ANCA)[20]. The nervous system impairment is composed of peripheral nerve symptoms (especially mononeuritis multiplex), HP, central nervous system vasculitis, cranial neuropathy, myelopathy, and pituitary involvement[21,22]. HP is mostly associated with the localized phenotype of GPA and MPO-ANCA positivity. When PR3-ANCA

Table 1. Main causes of hypertrophic pachymeningitis.

Inflammatory	Infectious
IgG4-related disease	Tuberculosis
Granulomatosis with polyangiitis	Syphilis
Sarcoidosis	Fungal infections
Idiopathic	Sinusitis complication
Rheumatoid arthritis	**Neoplastic**
Sjögren syndrome	Lymphoma
Systemic lupus erythematosus	En plaque meningioma
Giant-cell arteritis	Carcinomatous meningitis
Behçet's syndrome	Histiocytosis
Relapsing polychondritis	**Other**
	Previous surgical procedure
	Cerebrospinal fluid hypotension

antibodies are present, HP is associated with systemic features and parenchymal brain lesions[20,23].

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease characterized by the presence of noncaseating granulomas[24]. It can appear in practically any organ, in acute or chronic form. The most frequent site of disease activity is the lung, affected in 80–90%[24,25] of cases, with symptoms like cough, wheezing, and stridor[25].

The nervous system is affected in 3–10% of the cases, with variable manifestations[26,27]. The most remarkable features are facial nerve neuropathy, optic neuritis, meningitis (including HP), parenchymal lesions, hypophysitis, peripheral neuropathy, and myelopathy[26]. Other disease-associated symptoms are fatigue, depression, and cognitive impairment[24]. Sarcoidosis can also affect the skin (lupus pernio, papules, infiltrated scars, and nodular skin thickening at tattoos), muscles, eyes (uveitis and conjunctival granulomas), and the exocrine glands (salivary and lacrimal glands)[24].

IgG4-related disease

IgG4-RD is a systemic fibroinflammatory disease that can affect any organ, the most frequent of which are the lacrimal and salivary glands, the pancreas and biliary tree, the retroperitoneal space[12,28,29]. Neurological impairment is rare and frequently occurs without systemic disease[12]. The meningeal involvement is restricted to the dura and causes headaches as a result of its traction, as well as irritation of trigeminal nerves and higher cervical roots[12]. The extension of the inflammation to the cavernous sinus, superior orbital fissure or orbit produces ophthalmoparesis, proptosis, and ocular pain[12]. IgG4-RD can extend to the pituitary gland and stalk, causing hypophysitis; the endocrinological abnormalities cause diabetes insipidus, hypogonadism, and hypothyroidism[30].

Idiopathic hypertrophic pachymeningitis

IHP is diagnosed after the exclusion of other possible causes of pachymeningitis and a negative biopsy[7]. This disorder is restricted to the pachymeninges, and its most typical symptoms are headaches, visual symptoms (due to the optic and oculomotor nerve impairment), and ataxia.

Other inflammatory causes

Other inflammatory diseases can trigger HP. Rheumatoid arthritis is an autoimmune arthropathy that presents with pachymeningitis, generally combined with leptomeningitis. The clinical presentation is acute, with stroke-like events and seizures[31,32,33]. There are reported cases of systemic lupus erythematosus, giant-cell arteritis, relapsing polychondritis, Behçet syndrome, and Sjögren syndrome presenting with HP[34,35,36,37,38].

DIAGNOSIS

The etiological diagnosis of HP through clinical, laboratory and imaging workup remains a challenge, and final diagnosis is usually performed with tissue biopsy. It is essential to rule out infectious diseases (tuberculosis, syphilis, fungal infections), autoimmune, or inflammatory diseases (GPA, sarcoidosis and IgG4-RD) and malignancies, especially lymphoma[39]. Table 2 shows a diagnostic workup for patients with HP.

The first step of the diagnostic approach is clinical characterization. An investigation of respiratory and systemic symptoms is essential. The respiratory system is affected frequently by granulomatosis with polyangiitis, neurosarcoidosis, and tuberculosis; complaints like shortness of breath, nasal discharge, and cough can occur under these circumstances[24,40,41]. The next step of the investigation is MRI (see Neuroimaging) and CSF analysis. The latter is a valuable tool to exclude infections; the execution of molecular assays (e.g., polymerase chain reaction), serologies, and cultures are essential to rule out tuberculosis, syphilis, and fungal infections[41,42]. Another possible technique to exclude infections is CSF metagenomics[43]. Cytological and biochemical analyses in HP cases are unspecific, varying from normal parameters to mild pleocytosis and elevated protein levels[21,26]. Angiotensin-converting enzyme (ACE) levels in CSF have limited value for the diagnosis of NS, as they are raised in other inflammatory diseases[44].

The blood workup should include markers for autoimmune disorders (especially antinuclear antibody — ANA, rheumatoid factor, ANCA, and IgG4 levels), HIV serology, venereal disease research laboratory — VDRL, galactomannan (in patients at risk of fungal infections), and pituitary hormones. To confirm the diagnosis of certain diseases, e.g. GPA, the typical clinical picture

Table 2. Diagnostic workup of patients with hypertrophic pachymeningitis.

Initial evaluation	Etiology investigation	Search for biopsy site
MRI with contrast CSF analysis — cytology, flow cytometry, biochemistry, opening pressure, cultures for bacteria, mycobacteria and fungus, PCR for mycobacterium tuberculosis, VDRL	Serum IgG4 ANCA Sinus CT Thorax CT Abdominal MRI Cervical US ANA Serum VDRL Rheumatoid factor HIV serology Galactomannan (patients with risk for Aspergillus infection) Long bones radiography Hypophysis survey (hormones)	Check systemic survey tests, if there are no sites for biopsy other than CNS, consider F18-FDG-PET-CT before final decision.

MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; PCR: polymerase chain reaction; VDRL: venereal disease research laboratory; CT: computerized tomography; US: ultrasound; ANA: antinuclear antibody; 18FDG-PET: positron emission tomography with 18-fluorodeoxyglucose.

in the presence of the serological marker might be sufficient, but IHP, NS, and IgG4-RD diagnoses depend on biopsy findings[7,12,22,27].

The systemic survey for other organs affected by the disease is crucial, since it helps to characterize it and might disclose other possible biopsy sites. This survey should include neck, sinus, thorax, abdomen, and pelvis images. Imaging modality varies, and a possible approach includes cervical ultrasound (US), sinus computerized tomography (CT), thoracic CT, abdominal MRI, and pelvic MRI[24,26,45,46]. A possible alternative after a negative systemic survey is to perform a whole-body Positron Emission Tomography (PET) with 18-fluorodeoxyglucose (FDG) CT; this might reveal a hypermetabolic lesion that was not observed with the conventional imaging techniques[47,48].

The biopsy of these lesions is safer than a central nervous system (CNS) procedure and might disclose the disease's primary process. If it is restricted to the CNS, meningeal biopsy is necessary for a final diagnosis[17,49,50]. It is imperative to perform the conventional pathological analysis and immunohistochemistry with markers for lymphocytes, macrophages, and IgG4.

DIFFERENTIAL DIAGNOSIS

Infectious diseases

Syphilis may present with HP as a meningovascular form. Serologic evaluation is essential to rule out this type of syphilis[6]. Tuberculosis is also associated with leptomeningitis and HP, generally with cognitive behavioral disorders, and systemic symptoms[41]. Typical CSF may guide the diagnosis, although advanced techniques (molecular analysis — polymerase chain reaction — PCR, and biopsy) are paramount[41]. Moreover, complicated bacterial sinusitis or otitis may present with meningeal involvement and cause HP of the dura adjacent to the infectious process[51]. Fungal meningitis causes dural thickening with similar features of other etiologies of HP; the main related specimen is *Aspergillus flavus*[52].

Neoplastic diseases

Different neoplastic disorders may cause meningeal involvement mimicking HP. Secondary dural metastasis may be similar to HP, and the most frequent associated tumors are lung cancer (small-cell carcinoma and adenocarcinoma), breast cancer, prostate and gastrointestinal tract tumors[53]. *En plaque* meningiomas have a similar appearance to HP on MRI and the differential is based on biopsy characteristics[54]. Hematological malignancies can present with dural masses and effusion, mainly lymphomas (Hodgkin and non-Hodgkin). Another group of neoplasm related to HP is histiocytosis. There are two main types, Langerhans and non-Langerhans, and both can present with pachymeningeal infiltration[55]. The clues for the diagnosis are systemic impairment (bones, skin, pituitary, spleen, and lungs); biopsy provides the diagnosis with markers for macrophages (CD1a, S100, and CD68)[55].

Other causes

CSF hypotension is another cause of hyperintense signal of the dura mater masquerading as HP, occurring secondary to idiopathic hypotension, lumbar puncture or excessive CSF drainage by derivation devices. The headache pattern helps raise suspicion of this etiology (worse when the patient is in vertical position), and the opening pressure of the CSF is diagnostic[56].

TREATMENT

Specific treatment depends on the etiology, although some patients have a presumptive diagnosis. A rigorous exclusion of infectious causes is mandatory to introduce immunotherapy for inflammatory causes. Figure 2 summarizes the first-line treatments of the most common causes; each of them is discussed in detail below.

Idiopathic hypertrophic pachymeningitis

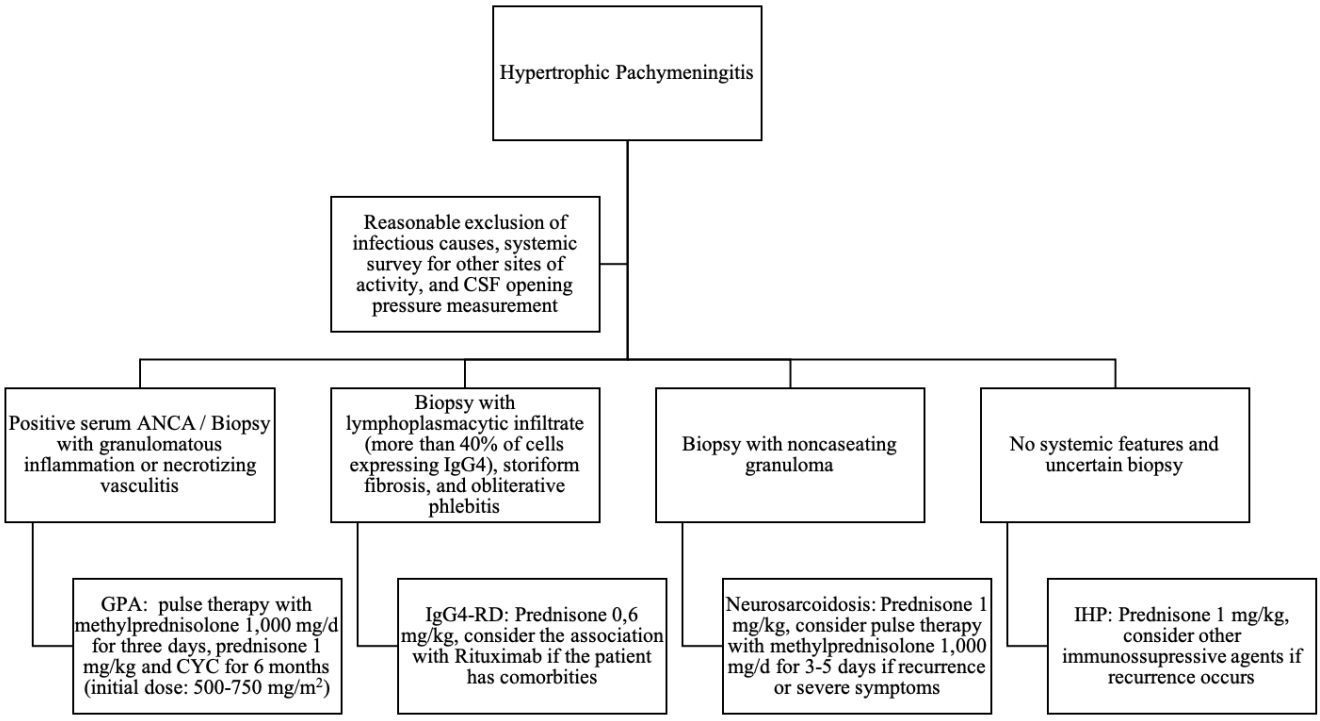
The first line of treatment of idiopathic HP is corticosteroids (prednisone with an initial dose of 1 mg/kg/day). If the patient does not improve or recurs during corticosteroids use, adding immunosuppressive agents such as azathioprine (AZA) (2–3 mg/kg/day), cyclophosphamide (CYC) (initial dose of 500–750 mg/m^2 each four weeks, with dose adjustment according to lymphocytes nadir — 10 to 14 days) methotrexate (MTX) (20–25 mg/week), and rituximab, is a viable option[57,58,59].

Granulomatosis with polyangiitis

In GPA, CNS involvement is considered an organ-threatening manifestation, so the corticosteroid (pulse therapy with methylprednisolone 1,000 mg/day for three to five days followed by prednisone 1 mg/kg) is combined with CYC (initial dose of 500–750 mg/m^2 each four weeks, with dose adjustment according to lymphocytes nadir — 10 to 14 days) as first-line induction therapy. The switching to maintenance remission phase can be done with oral MTX (20–25 mg/week), AZA (2-3 mg/kg), or mycophenolate mofetil (MMF) (500–2,000 mg/day)[23]. Some literature evidence shows that in refractory GPA with severe systemic manifestations rituximab is an effective alternative[59].

Neurosarcoidosis

NS treatment is initiated with 1 mg/kg/day prednisone-equivalent[60]. If the patient does not respond or has a rapidly progressive disease, pulse therapy of methylprednisolone at 1,000 mg/d for three to five days should be considered. After disease control, a gradual tapering can be done within four to eight weeks[61]. Neurosarcoidosis usually requires at least six to 12 months of corticoid therapy[60]. For patients who do not tolerate the adverse effects of corticosteroids and have relapses during the tapering, immunosuppressive agents are required as second-line therapy[62]. MTX has the most extensive efficacy data for NS, with doses ranging from 10 to 25 mg per week, and less adverse effects by the concomitant use of



ANCA: anti-neutrophil cytoplasmic antibody; CYC: cyclophosphamide; GPA: granulomatosis with polyangiitis; IgG4-RD: IgG4-related disease; IHP: idiopathic hypertrophic pachymeningitis.

Figure 2. A guide showing clinical and pathological features of main disease presenting with HP and its first-line therapy.

folic acid[62]. Other options are CYC, MMF, AZA, and thalidomide[26,63]. Infliximab is effective in glucocorticoid and immunosuppressive refractory NS.

IgG4-Related Disease

Corticosteroids are the cornerstone of treatment for IgG4-RD[64]. The corticosteroid (prednisone 0.6 mg/kg) is almost always used alone or in combination with conventional disease-modifying antirheumatic drugs (DMARDs) (AZA, MMF, MTX, leflunomide, and CYC)[46]. The treatment is divided into two phases: induction, in which glucocorticoids are discontinued within three to six months, and maintenance therapy, since the disease is prone to recurrence. The maintenance strategy is individualized according to the patient's disease features, such as the extent of disease-related damage, comorbidities, and previous treatment responses[65]. Biological agents that promote B-cell depletion, such as rituximab (two intravenous doses of 1 g, separated by two weeks, repeated at six-month intervals) in combination with prednisone (40-60 mg/d for a month and tapering to discontinuation over two to three months), are used in the initial treatment in patients with severe neurological disease and multiorgan IgG4-RD. CNS imaging should be repeated three months later to check response[12].

CONCLUSION

HP is a highly complex disorder with variable etiologies and heterogeneous clinical presentation. Etiology of HP is a challenge, despite a thorough clinical, laboratory and imaging investigation. Tissue biopsy remains the gold standard for final diagnosis. Early clinical and etiological diagnosis is relevant in order to decide about therapy. This review may serve as a guide to general neurologists by helping the diagnostic workup and management of the several different forms of HP.

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