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A practical approach to the diagnosis and management of primary angiitis of the central nervous system

Praktični pristop k obravnavi bolnika s primarnim vaskulitisom osrednjega živčevja

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Abstract

Vasculitides present a rare and heterogeneous group of diseases that affect small, middle-sized and/or large arteries. Most of them are systemic diseases, however, they can also present as an isolated (primary) angiitis of the central nervous system. Among the most common presenting symptoms are: headache, cognitive deficits, and encephalopathy, but they frequently present with ischaemic and/or haemorrhagic stroke, and transitory ischaemic attack too. In the cerebrospinal fluid, lymphocytic pleocytosis and/or elevated proteins can be seen, with acute phase proteins and other laboratory findings (rheumatology and microbiological tests, cytology) being commonly negative. The findings on magnetic resonance imaging of the brain are non-specific in 90%. With negative magnetic resonance imaging and cerebrospinal fluid findings, the diagnosis of primary angiitis of the central nervous system is highly implausible. On angiography, in approximately 40% of patients the vascular beading, a non-specific finding of dilated areas alternating with narrowing of the blood vessels can be seen. Biopsy rpesents the golden standard, although it is false negative in 25% of cases due to its segmental distribution. Most studies suggest corticosteroids and cyclophosphamide as an induction therapy, folowed by a maintenance therapy (azathioprine or mycophenolate mofetil) in 6–12 months. Primary angiitis of the central nervous system still presents a diagnostic challenge with early therapeutic intervention being crucial for a better outcome.

Izvleček

Vaskulitisi so redka in raznolika skupina bolezni, ki prizadenejo male, srednje velike in/ali velike žile. Večinoma gre za sistemske bolezni, vendar lahko v redkih primerih prizadenejo samo žilje v osrednjem živčevju; tedaj jih imenujemo primarni vaskulitisi osrednjega živčevja. Najpogosteje se kažejo z glavobolom, s kognitivnim upadom in z encefalopatijo, neredko pa tudi s sindromom ishemične ali hemoragične možganske kapi ali s prehodno pretočno motnjo. Pri diagnosticiranju se poslužujemo odvzema likvorja, v katerem ugotavljamo limfocitno pleocitozo s povišanimi vrednostmi beljakovin. Vnetni parametri in ostali laboratorijski izvidi krvi (revmatološki, mikrobiološki, citološki izvidi) so praviloma normalni.

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Key words: vasculitis; angiitis; central nervous system; headache; ischemic stroke; angiography; biopsy; cyclophosphamide

Ključne besede: vaskulitis; angiitis; osrednje živčevje; glavobol; ishemična možganska kap; angiografija; biopsija; ciklofosfamid

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Magnetnoresonančno slikanje (MRI) glave nam v 90 % pokaže nespecifične spremembe. V primeru negativnega slikovnega izvida in normalnega likvorskega izvida je diagnoza primarnega vaskulitisa osrednjega živčevja praktično izključena. Na angiografiji pri približno 40 % bolnikov ugotavljamo izmenjujoče se stenoze in ektazije, ki so nespecifične najdbe, saj jih lahko opažamo tudi pri drugih boleznih. Zlati standard za postavitev diagnoze je biopsija, ki je zaradi segmentne prizadetosti žilja lažno negativna v 25 %. Zdravljenje pričnemo z indukcijskimi imunosupresivi, izmed katerih največkrat uporabljamo metilprednizolon in ciklofosfamid, v nadaljevanju (po 6–12 mesecih) pa preidemo na vzdrževalno imunouspresivno zdravljenje, največkrat z azatioprinom ali mikofenolat mofetilom. Bolniki s primarnim vaskulitisom osrednjega živčevja so zaradi omejitev pri diagnostičnih preiskavah še vedno velik diagnostični izziv. Ob vsem tem je zgodnja diagnoza ključna za ugoden izid bolezni.

1 Introduction

Vasculitides are a rare and heterogenous group of diseases whose main characteristics are inflammation and necrosis of small, medium-sized and large artery walls (1,2). Any organ can be affected, including the central and peripheral nervous systems, which are normally secondarily affected (1). They then present with a variety of neurological symptoms that depend on the size and location of the affected vessels, making the diagnosis of central nervous system (CNS) vasculitis all the more difficult (3,4).

Rarely, vasculitis is predominantly confined to the CNS, in which case it is termed primary angiitis of the central nervous system (PACNS). It was first described by Harbitz in 1922 as an unknown form of angiitis, and then later in 1959 by Cravioto and Feigin as an independent clinical entity which they named non-infectious granulomatous angiitis (5). Our article is a review of the key characteristics of PACNS and, as part of a differential diagnosis, of secondary CNS vasculitides, to significantly facilitate the diagnosis of such diseases. At the end of the article, we also briefly present the treatment of patients with PACNS at the Department of Neurology at the University Medical Centre Ljubljana.

2 Epidemiology

PACNS is an extremely rare disease affecting mostly small and medium-sized leptomeningeal and/or parenchymal arteries (3). The yearly incidence is 2.4/1,000,000 (6). It generally affects middle-aged men with a median age of 50 years, but it can also affect children (2,7). Approximately 3–5% of cerebrovascular events in those under 50 years of age are due to PACNS (8). Its course is slow and progressive (9).

3 Etiopathogenesis

The aetiology and pathogenesis of PACNS are still unexplored. Several factors are thought to be responsible for PACNS and among them, infections with the varicella-zoster virus, West Nile virus, *Mycoplasma gallisepticum* and human immunodeficiency virus (HIV) have most often been mentioned, although a clear pathogenetic link is not known (10-13). Previous infection is thought to be responsible for the loss of integrity of the blood-brain barrier due to the breakdown of tight junctions, leading to increased permeability for leukocytes (1). Leukocyte entry into the CNS causes astrocyte dysfunction with vasogenic oedema, the accumulation of toxic substances in the interstitium and oxidative stress, all contributing to impaired angiogenesis (5,14). These changes lead to the breakdown of vascular walls, which manifests as alternating areas of thickening and stenosis, impairing perfusion in areas of the CNS (15). The weakening of vascular walls can cause them to tear, leading to intracranial haemorrhage (8).

4 Clinical presentation

The clinical presentation is extremely diverse. The course is normally subacute or chronic, but it can also be acute with periods of exacerbations and remissions. Progressive headache is the most common symptom (50–60%) along with qualitative disorders of consciousness (50–70%), followed by focal neurologic deficits (e.g. hemiparesis, ataxia, aphasia, dysarthria, visual disturbances), epileptic seizures and/or psychiatric symptoms (8,9,16,17). Focal neurologic deficits are absent in 25–30% (16,18). Recurrent ischaemic stroke and transitory ischaemic attack (TIA) are present in 30–50% of patients (7).

5 Diagnosis

Diagnostic criteria for PACNS have been established by Calabrese and Mallek in 1988 (2). For confirmation of the diagnosis, patients must have all three of the following criteria (1,19,20):

- acquired and unexplained neurological or psychiatric symptoms or signs,
- classic angiographic or pathohistological characteristics of vasculitis, and
- the absence of signs of systemic vasculitis or other conditions mimicking the angiographic or pathohistological characteristics of vasculitis.

In 2009, Birnbaum and Hellmann divided the criteria according to the degree of certainty into definite and probable PANCS (5). Certain criteria include biopsy-proven vasculitis, while probable criteria include those without histological confirmation but with a pathological angiogram, brain MRI and/or cerebrospinal fluid (CSF) (19).

5.1 Laboratory findings

CSF examination with a lumbar puncture is the most important laboratory test for diagnosing PACNS (21). A pathologic CSF result is present in 74.4% of PACNS patients, similar to that which we find in aseptic meningitis with increased protein, mild lymphocytic pleocytosis and normal glucose (16,22,23). Oligoclonal bands and an increased IgG index are rarer findings (up to 23.5%) (22,24). These findings are non-specific, but the diagnosis of PACNS is less likely with a normal CSF (16).

Ruling out secondary causes of CNS vasculitis is crucial (7). When diagnosing systemic vasculitides, the following investigations are normally performed: inflammatory parameters (estimated sedimentation rate, C-reactive protein), antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies, rheumatoid factor, cryoglobulin, C3, C4 and hepatitis B and C serologies (4,16). Estimated sedimentation rate (ESR) is usually increased in secondary vasculitides and normal in 90% of PACNS cases (16).

5.2 Imaging findings

A head CT can reveal abnormalities, but it is a poorly sensitive method for visualising changes of PACNS (18). For initial assessment, a brain MRI is significantly more sensitive, showing pathologic changes in 93.3%, most commonly those of ischaemic stroke (43.3%), followed by hyperintense lesions in the cortex, subcortical white matter and deep grey matter in T2- and FLAIR sequences (37.5%), tumour-mimicking mass effect lesions or post-contrast meningeal signal enhancement (16,23,25). The latter is present in 10–15% of patients and is a good prognostic indicator (21). In the acute stage of infarction, diffusion weighted imaging (DWI) helps us decide whether the lesion is acute or chronic, while susceptibility weighted imaging (SWI) is used to exclude microhaemorrhages (26). Due to its high negative predictive value, PACNS can be practically ruled out in the case of a normal MRI (7). The spinal cord is affected in less than 5%, while only a few cases of brainstem involvement have been described in the literature (22,27).

In diagnostic criteria, Calabrese and Mallek established alternating stenoses and ectasias (string of beads, beading) visible on angiography as a condition for diagnosis (28). This finding is non-specific, being characteristic of vasculopathy and not vasculitis (16). Other angiographic findings include the narrowing of arteries in individual areas, collateral circulation and regionally extended circulation time (21). Multiple microaneurysms, often found in abdominal or renal angiograms in systemic vasculitides, are rarely found in the CNS (29). On the other hand, a normal angiogram does not exclude vasculitis; only 59.5% of patients have angiographically visible changes. Angiography has a limited sensitivity (20–90%) and specificity (20–60%), particularly due to limited resolution for arteries less than 500 μm, which PACNS affects the most (5,16). A retrospective study of 38 patients was performed at the Department of Neuroradiology in Washington, D.C., of whom 14 had angiographic changes characteristic of vasculitis. All patients also underwent biopsy, none of which confirmed the diagnosis of vasculitis (30). Vasculitic changes are normally found in both hemispheres (26,31).

When the imaging examination reveals the associated findings, they direct us to the secondary causes of vasculitis. Venous sinus thrombosis is most commonly found in patients with Behçet's disease, post-contrast leptomeningeal enhancement in tuberculous meningitis and post-contrast pachymeningeal enhancement in rheumatoid arthritis-associated vasculitis. Paranasal sinus and orbital granulomas are found in granulomatosis with polyangiitis and enlarged lacrimal and salivary glands in Sjögren's disease (26).

5.3 Pathohistological diagnosis

When tests are inconclusive and the diagnosis is unclear, a brain biopsy is performed, which is, despite its low sensitivity (53–74%), the gold standard for diagnosing PACNS (16). A 1999 study of 61 patients with suspected PACNS was published at the University of Michigan. The study included patients with multifocal neurological deficits and brain MRI and/or CT who underwent a brain and meningeal biopsy. After the biopsy, only 28% of patients had a confirmed diagnosis of PACNS, 8% probable PACNS, and the remaining patients either had a confirmed alternative diagnosis (39%) or remained undiagnosed after the biopsy (25%) (32). Alternative diagnoses confirmed by biopsy most often represent hypertensive changes, followed by amyloid angiopathy, infarctions, vascular malformations, infections and others (16). Pathological biopsy results with classical angiographic results are found only in 11.2% (23).

Vascular involvement is usually segmental, leading to a high proportion of false-negative biopsies. The biopsy sensitivity can be increased by sampling the area with a pathological angiographic result, namely both the cortex and leptomeninges (16,22). In case of inaccessibility of the angiographically pathological area, a biopsy of the non-dominant temporal lobe is performed (22). The risk of complications after biopsy is not negligible. In a study by the Neurology Department of New York University, complications occurred in 13 patients (16%). Among the most common, intracerebral haemorrhage, transiently altered mental state, and epileptic seizure were observed. One patient suffered a stroke (33). The procedural mortality is, however, low (0.03–2%) (34). Despite the lack of PACNS treatment guidelines, a biopsy is recommended as it helps with identifying alternative diagnoses, especially those that may initially respond to immunosuppressive therapy (e.g. primary CNS lymphoma) (16,32,34).

In PACNS, transmural inflammation with vascular wall damage is observed. The most common subtype is the granulomatous pattern (58%), followed by the lymphocyte pattern (28%) and acute necrotizing vasculitis (14%) (16,31). The granulomatous form is in some cases associated with β amyloid deposits. In this case, it is called amyloid β-related angiitis (ABRA) (16). The latter is a unique form of CNS vasculitis as it occurs in elderly patients and often appears on a brain MRI with contrast as a mass effect lesion with meningeal enhancement (22). Necrotizing vasculitis is statistically significantly more common in patients with intracranial haemorrhage. Granulomatous and/or necrotizing patterns are found in patients with a rapidly progressing clinical presentation, poorer response to treatment and often fatal outcome, while lymphocytic vasculitis is more benign and more common in children (31).

6 Differential diagnosis

As part of the differential diagnosis of PACNS, causes of secondary vasculitis, occurring as part of various diseases, e.g. systemic vasculitis, autoimmune disease or infection, need to be ruled out first (35). Some microorganisms are angioinvasive, and the rest trigger a defensive inflammatory response that causes secondary tissue damage (29). The most common causes are presented in Table 1.

An important differential diagnostic option is also reversible cerebral vasoconstriction syndrome (RCVS), which is more common in women and usually manifests as an acute, sudden headache ("worst ever headache") (6,7). It can occur spontaneously, but it can be secondary to postpartum angiopathy or in connection with the use of vasoactive substances (cannabis, selective serotonin reuptake inhibitors, nasal decongestants) (22,26). The key to diagnosis is the reversibility of angiographic findings, normally occurring spontaneously within one to three months (36). The main complications of RCVS include cerebral oedema (38%), subarachnoid haemorrhage (22%), posterior reversible encephalopathy syndrome (PRES) (9–14%), and less commonly stroke or intracranial haemorrhage (26,37). The distinction between PACNS and RCVS is crucial and the demarcation is usually relatively clear with a thorough history and appropriate diagnostic tests. The main differences between them are presented in Table 2.

Angiographic mimics also include atherosclerosis, fibromuscular dysplasia, Moyamoya disease, radiation-related vasculopathy, and intravascular lymphoproliferative diseases (19,38-40). Stroke in different areas of circulation also occurs in coagulopathies, e.g. antiphospholipid syndrome, or in left atrial myxoma. Atherosclerotic and thromboembolic infarctions are rarely accompanied by inflammatory CSF changes (41).

In case of reasonable suspicion, genetic diseases, e.g. cerebral autosomal dominant or recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL, CARASIL), retinal vasculopathy with cerebral leukodystrophy (RVCL), and mitochondrial

Table 1: Causes of secondary vasculitis (3,5,47,48).

Types of disease	Examples
Systemic vasculitides	Gigantocellular arteritis, Takayasu's arteritis, polyarteritis nodosa, Kawasaki disease, eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), granulomatosis with polyangiitis (Wegener's granulomatosis), microscopic polyangiitis, cryoglobulinemia, Bürger's disease, Cogano's syndrome, Behcet's disease, Henoch-Schönlein purpura, Goodpasture's syndrome
Other systemic diseases	Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, dermatomyositis, polymyositis, antiphospholipid syndrome, sarcoidosis, systemic scleroderma, chronic inflammatory bowel disease (Crohn's disease, ulcerative colitis), mixed connective tissue
Infections	Syphilis, tuberculosis, meningococcal meningitis, rickettsiosis, Lyme borreliosis, bartonelosis, brucellosis, endocarditis, leptospirosis, Whipple's disease
	HIV, varicella-zoster virus, herpes simplex virus, cytomegalovirus, hepatitis B and C virus, parvovirus B19
	Echinococcosis, cryptococcosis, cysticercosis, schistosomiasis, trichinosis, toxocariasis, candidiasis, mucormycosis, invasive aspergillosis, histoplasmosis, coccidioidomycosis
Haematological diseases and tumours	Hodgkin's and non-Hodgkin's lymphoma, myelodysplastic syndrome, hairy cell leukemia, paraneoplastic vasculitis, malignant angioendotheliomatosis
Toxic vasculitis/ vasculopathy	Amphetamines and derivatives, cocaine, sympathomimetics, marijuana, contraceptives, ecstasy
Other	Histiocytosis, familial hemophagocytic histiocytosis, graft-versus-host disease, Eales disease, C4 complement deficiency

oesophageal encephalopathy and mitochondrial encephalitis, lactic acidosis, and stroke-like episodes (MELAS), should be excluded (42-45).

One of the differential diagnostic options is also Susac syndrome, an autoimmune endotheliopathy affecting the CNS, inner ear and retinal microvasculature and is manifested by the classic triad: encephalopathy, sensorineural hearing loss and visual disturbances. Susac syndrome brain MRI is characterized by changes in the corpus callosum (snowball lesions), which help us to distinguish this diagnosis from PACNS (46).

Table 2: Main characteristics and differences between primary vasculitis of the central nervous system and reversible cerebral vasoconstriction syndrome (7,22).

	PACNS	RCVS
Sex and median age at onset	More frequent in men (50 years)	Women (42 years)
Disease onset	Chronic	Acute
Disease course	Chronic, response to immunosuppresive treatment	Self-limiting
Trigger	Unknown	Identified in 50%
CSF	Elevated leukocytes and protein	Normal
MRI	Hyperintense vascular walls	Minimally higher signal intensity
Haemorrhagic infarction	Rare	Frequent
Biopsy	Vasculitis	No signs of vasculitis
Treatment	Glucocorticoids, cytotoxic treatment	Calcium channel blockers, avoiding triggers

Legend: CSF – cerebrospinal fluid , PACNS – primary angiitis of the central nervous system), RCVS – reversible cerebral vasoconstriction syndrome.

7 Treatment

PACNS treatment focuses on the control of intramural inflammation, the prevention of secondary ischaemic events, and the management of neurological symptoms such as epileptic seizures and psychiatric symptoms (6). Treatment of secondary vasculitis depends on the cause (infection, cancer, systemic inflammatory or autoimmune disease), but sometimes we still decide on short-term glucocorticoid treatment (49).

The proposed algorithm for PACNS treatment distinguishes between small-vessel vasculitis, where glucocorticoid treatment is indicated and, in case of poor response, cyclophosphamide (CYC) combination therapy, and large-vessel vasculitis, in which combination therapy is advised regardless of the success of glucocorticoid treatment (34). Combination therapy is generally used, although examples of induction therapy with glucocorticoids without CYC have been reported in the literature (50). The first-line treatment are glucocorticoids with high initial doses (7.5–15 mg/kg or 1 g of methylprednisolone per day for three days, then 1 mg/kg or 64 mg of methylprednisolone per day). As the second-line treatment, we use pulsed CYC at a dose of 15 mg/kg or 1 g per day once a month. The dose should be adjusted according to the patient's age and renal function (51). After approximately six months, when a satisfactory response is achieved, it is recommended to change CYC for less toxic maintenance treatment with azathioprine (AZA) (1–2 mg/kg/day), methotrexate (20–25 mg/week) or mycophenolate mofetil (MMF) (1–2 g/day) for a further 1–2 years (25,51,52). According to some studies, a relapse is expected in 33% of patients, making maintenance treatment crucial with a recommended duration of 12–18 months (25,53). Mortality is still high (6–15%) despite treatment. Poorer prognostic factors are higher age at diagnosis, involvement of larger vessels, focal neurological deficits in the clinical presentation, and, in general, greater burden of disease at onset. Rituximab and infliximab have also been shown to be effective in relapsed patients, but a higher risk of lymphoma has been observed in the latter, which is why it is not recommended in combination with high doses of glucocorticoids and CYC (17,25).

After 4–6 weeks of treatment, a repeat MRI is recommended, followed by repeat MRIs every 3–4 months. In follow-ups, the absence of new changes, signifying disease activity, is crucial; the old changes persist, as a rule (4). In some patients we can rely only on symptom improvement to judge the treatment response.

7.1 Prophylactic treatment

Long-term treatment with glucocorticoids is associated with a number of side effects such as osteoporosis, myopathy, dyslipidaemia, glucose intolerance, gastritis, peptic ulcers and gastrointestinal bleeding, so a prophylactic administration of proton pump inhibitors, bisphosphonates, calcium and vitamin D are required (4,34). With a combination of high-dose glucocorticoids and another immunosuppressive drug, prophylaxis against *Pneumocystis jirovecii* pneumonia is crucial. The European League Against Rheumatism (EULAR) advises prophylaxis with trimethoprim/sulfamethoxazole at a dose of 800/160 mg every other day or 400/80 mg daily during CYC treatment (54). According to some guidelines, patients receiving CYC require controls of blood count every 14 days, but in any case, blood count should be monitored before each CYC application (55).

As part of the secondary prevention of vascular events, antithrombotic protection with acetylsalicylic acid is advised, but it does not affect the outcome of treatment with effective immunosuppression (56). Depending on concomitant symptoms, we also use symptomatic treatment (antiepileptic drugs, antipsychotics, antidepressants) and drugs for the management of cardiovascular risk factors (statins, antihypertensive treatment).

8 Management of patients with PACNS at the Department of Neurology at the Medical Centre Ljubljana

Between 2014 and 2019, nine patients with PACNS were treated at the Department of Neurology at the University Medical Centre Ljubljana: seven women and two men. As we manage about half of neurological patients in Slovenia, we estimate the incidence of PACNS at 1.62/1,000,000. The mean age of patients at the onset of symptoms was 50.6 (36–59) years.

The majority of patients (7; 77.8%) complained of headache with associated symptoms of stroke in the anterior and/or posterior circulation; only two patients (22.2%) had isolated headache at the onset of symptoms. Concomitant epileptic seizures were observed in only one patient.

In five (55.6%) patients, mild lymphocytic pleocytosis with elevated protein was detected in the CSF; oligoclonal bands in the CSF and at the same time not in the serum were present in only two patients. In blood work, slightly elevated inflammatory parameters were observed in four (C-reactive protein) or five (ESR) patients, the

remaining laboratory results to exclude secondary vasculitis were negative. The brain MRI showed significant changes in the areas of the anterior and/or posterior circulation in all patients, whilst only six (66.7%) patients had a positive angiography. Based on the clear clinical presentation and potential procedural complications, we did not decide to perform a biopsy in any patient. All patients received recommended treatment with glucocorticoids and CYC. The latter was introduced on average within 19.9 (7–29) days after hospital admission. CYC treatment lasted an average of 13.2 (11–16) months, after which 66.7% of patients were transitioned to MMF and 33.3% to AZA. Maintenance treatment was discontinued in one patient after 37 months, with treatment of remaining patients still ongoing. Glucocorticoid therapy was gradually reduced to complete discontinuation after 31.8 (11–63) months. No patient suffered relapse or died, the median NIHSS (National Institute of Health Stroke Scale) ratings at discharge and after six months were 3 (0–10) and 1 (0–11). Acetylsalicylic acid treatment was also initiated in all patients as part of secondary prevention, except for one patient who was treated with clopidogrel.

Based on our clinical experience, switching from CYC to MMF/AZA after 12 months is safe with a low risk of relapse, while data are unfortunately insufficient to estimate the duration of MMF/AZA maintenance treatment.

9 Conclusion

The diagnosis of PACNS is difficult due to the diverse clinical presentation and the lack of specific laboratory and imaging tests. Secondary causes of vasculitis should be ruled out. The gold standard for diagnosis is a biopsy of the leptomeninges and brain parenchyma, which also helps us rule out alternative diagnoses. An important mimic of PACNS is RCVS, which can also manifest without a characteristic acute headache. Treatment includes glucocorticoids, CYC, and appropriate symptomatic treatment, with MMF/AZA most commonly used for maintenance treatment. In the future, we expect new diagnostic markers, as well as guidelines that would facilitate the diagnosis and treatment of patients with PACNS.

Conflict of interest

None declared.

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