Adult Primary Central Nervous System Vasculitis

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Primary central nervous system vasculitis (PCNSV) is an uncommon and poorly understood form of vasculitis that it is limited to the brain and spinal cord [1-3]. PCNSV represents the most frequent vasculitis involving the central nervous system (CNS) [Table 1] [4]. The neurological manifestations are diverse and non-specific. Serological markers of inflammation are usually normal. Cerebrospinal fluid is abnormal in approximately 80–90% of the cases. The diagnosis is unlikely in the presence of a normal brain magnetic resonance imaging (MRI) scan. Biopsy of CNS tissue showing vasculitis is the only definitive test; however, angiography is often used to confirm the diagnosis. Early recognition is important because treatment with glucocorticoids with or without cytotoxic drugs may prevent serious or even lethal outcomes. The differential diagnosis is broad and includes reversible vasoconstriction syndromes, secondary cerebral vasculitis, malignancy, and infections.

Cerebral and meningeal biopsy is the gold standard for the diagnosis of primary central nervous system vasculitis (PCNSV), angiographic results should always be interpreted in conjunction with clinical, laboratory and MRI findings

Modern recognition of PCNSV as a separate entity is generally dated to the mid-1950s when Cravioto and Feigin [5] described several cases of a "non-infectious granulomatous angiitis" with a predilection for the nervous system. The term "granulomatous angiitis of the nervous system" was applied because of the histopathologic findings observed in arteries from initial cases.

Recently, major advances have been made in the field of PCNSV. Studies of additional cases have revealed a more varied histopathologic inflammatory picture and an association with amyloid angiopathy [6-8]. They have also recognized that PCNSV is more heterogeneous than previously thought, encompassing clinical subsets that differ in terms of prognosis and therapy [8-13]. Finally, childhood PCNSV (cPCNSV) has been recognized as possible cause of vascular strokes in children [14,15]. This review aimed to provide an update on the major advances made in adult PCNSV.

Table 1. Vasculitides and connective tissue diseases associated with a diagnosis of CNS vasculitis or angiitis at the Mayo Clinic over a 17 year period*

Condition	No. patients
Isolated CNS vasculitis	73
ANCA-associated vasculitis	13
Behçet's disease	8
Giant cell arteritis	3
Undefined vasculitis	3
Systemic lupus erythematosus	9
Sjögren's syndrome	2
Rheumatoid arthritis	2
Undefined connective tissue disease	1

CNS = central nervous system, ANCA = antineutrophil cytoplasmic antibody
*Table from Salvarani and colleagues [4]

DIAGNOSIS AND DIAGNOSTIC CRITERIA

Diagnostic criteria for PCNSV were proposed by Calabrese and Mallek [16] in 1988 on the basis of their clinical experience and of published evidence [Table 2]. These criteria included angiographic changes indicating a high probability of vasculitis, that is, areas of smooth vessel wall narrowing or occlusions alternating with dilated cerebral arteries affecting multiple cerebral arteries in the absence of proximal vessel atherosclerosis or other recognized abnormalities. A single abnormality in multiple arteries or multiple abnormalities in a single vessel were considered to be less consistent with PCNSV [1].

Because of the more invasive nature of CNS biopsy, angiography has become the most common method for confirming the diagnosis in patients with suggestive clinical findings. However, angiographic changes typical of vasculitis may be seen in non-vasculitic conditions such as vasospasm, CNS infections, lymphomas, cerebral arterial emboli, and atherosclerosis [1].

Table 2. Diagnostic criteria for primary central nervous system vasculitis. A diagnosis of primary central nervous system vasculitis is made if all the below criteria are satisfied

Diagnostic criteria proposed by Calabrese and Mallek in 1988 [16]
• A history or clinical findings of an acquired neurologic deficit, which remained unexplained after a thorough initial basic evaluation
• Either classic angiographic or histopathologic features of vasculitis within the central nervous system
• No evidence of systemic vasculitis or of any other condition to which the angiographic or pathologic features could be secondary
Diagnostic criteria proposed by Birnbaum and Hellmann in 2009 [17]
• Definite diagnosis Confirmation of vasculitis on analysis of a tissue biopsy specimen
• Probable diagnosis In the absence of tissue confirmation, high probability of finding of vasculitis on an angiogram, with abnormal findings on MRI, and CSF profile consistent with PCNSV

PCNSV = primary central nervous system vasculitis, MRI = magnetic resonance imaging, CSF = cerebrospinal fluid

Furthermore, among pathologically documented cases, cerebral angiography may be normal, reflecting vascular involvement in small vessels below the resolution of angiography [10]. Overall, the sensitivity of angiography varies between 40–90%, while the specificity has shown to be as low as 30% [1].

Magnetic resonance angiography (MRA) is a reasonable initial approach to investigate patients with suspected PCNSV. However, MRA is less sensitive than conventional angiography in detecting lesions involving the posterior circulation and distal vessels [1]. Therefore, if the clinical suspicion is high but MRA is normal, a standard cerebral angiography is warranted.

Primary central nervous system vasculitis (PCNSV) is a heterogeneous condition encompassing clinical subsets that differ in terms of prognosis and treatment

It is important to emphasize that the diagnosis of PCNSV should not be based on the findings of a positive angiography alone, and angiography results should always be interpreted in conjunction with clinical, laboratory, and MRI findings.

To prevent misdiagnosis, particularly with the reversible cerebral vasoconstriction syndromes (RCVS), Birnbaum and Hellmann [17] proposed new criteria based on the levels of certainty of the diagnosis [Table 2]. These criteria may prevent patients with RCVS from being treated with cytotoxic therapy. However, the criteria were not able to categorize patients with high-probability angiographic findings, only those with normal cerebrospinal fluid (CSF) analysis who may have either RCVS or PCNSV. The presence of precipitating factors, the type of onset and the neurological findings may be useful distinguishing features. Onset in the postpartum period or following exposure to vasoactive substances would point to RCVS [18]. RCVS has an acute onset followed by a monophasic course usually without any new complications after 4 weeks. In PCNSV the onset is more insidious and the course is progressive with frequent appearance of cerebral infarcts. Headaches are of the thunderclap type in RCVS, while they are subacute and progressive in PCNSV. MRI is often normal in RCVS, whereas PCNSV is extremely unlikely in the presence of a normal MRI. Several studies have indeed reported a sensitivity of MRI for PCNSV close to 100% [1]. Abnormal findings on MRI scans are non-specific and include cortical and sub-cortical infarction, parenchymal and leptomeningeal enhancement, intracranial hemorrhage, tumor-like mass lesions, and non-specific areas of increased signal intensity on fluid attenuated inversion recovery (FLAIR) or T2-weighted images [1].

Advances in neuro-imaging techniques visualizing the wall of intracranial blood vessels could, in the future, improve the capacity to distinguish inflammatory from non-inflammatory lesions and thus the performance of the criteria [19,20]. Vessel wall thickening and intramural contrast enhancement are quite specific findings in patients with active cerebral vasculitis affecting large arteries. Occasionally, enhancement may be marked and extend into the adjacent leptomeningeal tissue (perivascular enhancement) [21,22]. High-resolution, high-field contrast-enhanced MRI may be able to differentiate enhancement patterns of intracranial atherosclerotic plaques (eccentric), inflammation (concentric), and other wall pathologies. However, the sensitivity and specificity of MRI in this regard remains to be determined [22].

Cerebral and meningeal biopsy remains the gold standard for the diagnosis of PCNSV [6,23]. The procedure is safe, carrying a risk of a persistent sequelae in only about 1% of cases. A positive biopsy confirms vasculitis and excludes its mimickers. An optimal biopsy should include samples of dura, leptomeninges, cortex, and white matter. Diagnostic histopathological features include transmural vascular inflammation affecting small- and medium-sized leptomeningeal and parenchymal arterial vessels.

Vasculitis is characterized by skip and segmental vascular lesions. Therefore, because of sampling errors, a negative biopsy does not entirely rule out the diagnosis of vasculitis. In fact, there is evidence that biopsy has a sensitivity of 53–63% in diagnosing PCNSV [6,23].

Biopsy of a radiographically abnormal area is preferable to random sampling of the non-dominant frontal lobe or temporal tip. Miller et al. [23] showed that 78% of the targeted biopsies were diagnostic, whereas none of the blind biopsies demonstrated vasculitis. Inclusion of leptomeninges may increase the diagnostic yield when PCNSV is suspected. Stereotactic guidance may be used for deeper lesions but is usually unnecessary for more superficial lesions.

HISTOPATHOLOGICAL PATTERNS

Three main histopathological patterns are seen in PCNSV [6,23]. Granulomatous vasculitis is the most common (58%

of cases). It is characterized by vasculocentric mononuclear inflammation associated with well-formed granulomas and multinucleated cells. Beta-4 amyloid deposition is present in almost 50% of these patients. Amyloid angiopathy is associated with granulomatous vasculitis.

Lymphocytic vasculitis is the second most common pattern (28% of cases). It is characterized predominantly by lymphocytic inflammation with occasional plasma cells extending through the vessel wall with features of vascular distortion and destruction.

Necrotizing vasculitis is the least seen pattern (14% of cases). It is characterized by acute necrotizing vasculitis similar to polyarteritis nodosa with transmural fibrinoid necrosis. This process involves predominantly the small muscular arteries with disruption of the internal elastic lamina. Necrotizing vasculitis is strongly associated with intracranial hemorrhage [13]. The destructive vasculitic process with fibrinoid necrosis may cause severe vessel wall weakening, thus predisposing blood vessel rupture and aneurysm formation. This mechanism may account for the association between necrotizing vasculitis and intracranial hemorrhage.

The majority of the patients with primary central nervous system vasculitis (PCNSV) have a favorable response to prednisone alone or prednisone combined with cyclophosphamide

The three histologic patterns have similar clinical manifestations, treatment responses and outcomes. Furthermore, histological patterns, as observed in patients who underwent repeat biopsies, remain stable over time, suggesting that they are truly distinct patterns rather than different stages of the disease.

SPECIAL SUBSETS

Several subsets of PCNSV, which differ in terms of prognosis and optimal management, have been identified.

Spinal cord involvement has been documented in 5% of patients, but it is rarely the only manifestation [3]. Most patients have concurrent or subsequent brain involvement during the disease course. The thoracic cord is predominantly affected.

A careful medical evaluation must be performed to confirm the diagnosis of PCNSV and to exclude other conditions associated with acute or subacute transverse myelitis.

Angiography-negative PCNSV is characterized by normal angiograms, but brain biopsies are positive for vasculitis [10]. These findings suggest that the vasculitis is limited to small vessels below the resolution of conventional angiography. Patients with angiography-negative PCNSV often present with cognitive dysfunction and have markedly elevated CSF protein, meningeal or parenchymal enhancing lesions on MRI. They respond well to therapy and have favorable outcomes.

A subset of patients with PCNSV demonstrate prominent leptomeningeal enhancement on MRI [11]. These patients typically have an acute clinical onset, frequent cognitive dysfunction at presentation, and negative cerebral angiography and/or MRA. CNS biopsies show a granulomatous vascular inflammation, often associated with vascular amyloid angiopathy. Almost all patients have a good clinical response to corticosteroid therapy (alone or combined with immunosuppressive agents) with resolution of MRI enhancement and an overall favorable course.

Approximately one-quarter of PCNSV biopsy-positive patients and half of those showing granulomatous vasculitis present evidence of CAA [8]. Brain biopsies show granulomatous vasculitis and vascular deposits of amyloid β peptide. Patients with PCNSV and CAA are older at presentation than those with PCNSV only, but younger than patients with CAA and no inflammation. They often present with cognitive dysfunction, while MRI results show enhanced meningeal lesions. These patients usually have a monophasic disease course and generally respond well to immunosuppressive treatment. The inflammatory reaction related to the presence of amyloid β-peptide varies from little or no inflammation to perivascular infiltrates and to frank granulomatous vasculitis. Patients with CAA-related perivascular inflammation have characteristics similar to those of patients associating CAA and granulomatous vasculitis [24].

Rapidly progressive PCNSV represents the worst end of the clinical spectrum of this vasculitis [12]. These patients have a rapidly advancing course often with fatal outcome. The disease is characterized by bilateral, multiple, large cerebral vessel lesions on angiograms and multiple bilateral cerebral infarctions on MRI. The predominant histopathological pattern is of granulomatous and/or necrotizing vasculitis. These patients respond poorly to traditional immunosuppressive treatment.

Solitary tumor-like mass lesions are an under-recognized subset of PCNSV, which are found in approximately 4% of the patients [25]. An association with CAA was observed in 29% of these patients. Excision of the lesion may be curative; however, in some patients aggressive immunosuppressive therapy has led to a favorable outcome, thus obviating the need of surgery.

Intracranial hemorrhage is not infrequent at presentation of PCNSV, having been reported in 11–12.2% of patients [13]. Intracerebral hemorrhage is the most common presentation, followed by subarachnoid hemorrhage. These patients have less frequent altered cognition as a presenting manifestation of PCNSV, persistent neurologic deficit or stroke at presentation, as well as MRI evidence of cerebral infarctions. Necrotizing vasculitis is the predominant histopathologic pattern.

TREATMENT

No randomized clinical trials of medical management in PCNSV exist. Treatments for PCNSV have been similar to those first used in other vasculitides. In 1983, Cupps and colleagues [26] first found cyclophosphamide in combination with corticosteroids to also be effective in PCNSV. However, optimal management and treatment outcomes remained uncertain because

the lack of uniform diagnostic criteria and the small study sizes. The earliest reports suggested a poor prognosis with fatal outcomes in the majority of the cases, and transient or doubtful efficacy of glucocorticoids [27]. The most recent PCNSV cohort studies have described a more favorable course of PCNSV [1].

A recent report describing the treatments and outcomes evaluated the findings at diagnosis predicting the response to treatment and outcome in a series of 163 consecutive patients with PCNSV who were seen at the Mayo Clinic over a 29 year period [28]. In the study, 157 patients received glucocorticoids (median starting dose of oral prednisone: 60 mg/day). In 66 patients, intravenous pulse methylprednisone therapy preceded oral prednisone. Seventy-five patients were initially treated with prednisone alone, while in 82 patients prednisone was combined with a second drug, mainly cyclophosphamide (72 patients were treated with oral or intermittent intravenous pulses). A favorable response was observed in most of the patients treated with prednisone alone or in combination with cyclophosphamide. Response rates were similar (about 83%) in both treatment groups with improvement of disability (Rankin scale scores) over time. Of the total number of patients, 72% achieved a sustained therapeutic response (no relapses) during follow-up. The median duration of all therapies was approximately 11 months in both treatment groups. No differences in outcomes (disability and mortality) were observed in the two treatment groups. The only difference was the frequency of relapses. Treatment with glucocorticoids alone was associated with more frequent relapses (39% vs. 18%, $P = 0.006$). Patients with relapses needed longer therapy compared with those without relapses (median duration: 18 vs. 9 months, $P < 0.001$), but relapses were not associated with increased mortality or worse disability (Rankin score) at the last follow-up visit.

This study also evaluated clinical characteristics by diagnosis associated with treatment response, relapses and inability to discontinue treatment at the last follow-up. Large-vessel involvement (odds ratio [OR] 6.14) and cerebral infarcts on MRI at diagnosis (OR 3.32) were significantly associated with a poor response to treatment, while prominent gadolinium-enhanced cerebral lesions or meninges assessed by MRI (OR 2.28) were significantly associated with longer therapy, which was often continuing at the time of last follow-up. No other findings, except the treatment with prednisone alone (OR 2.90), were associated with relapse.

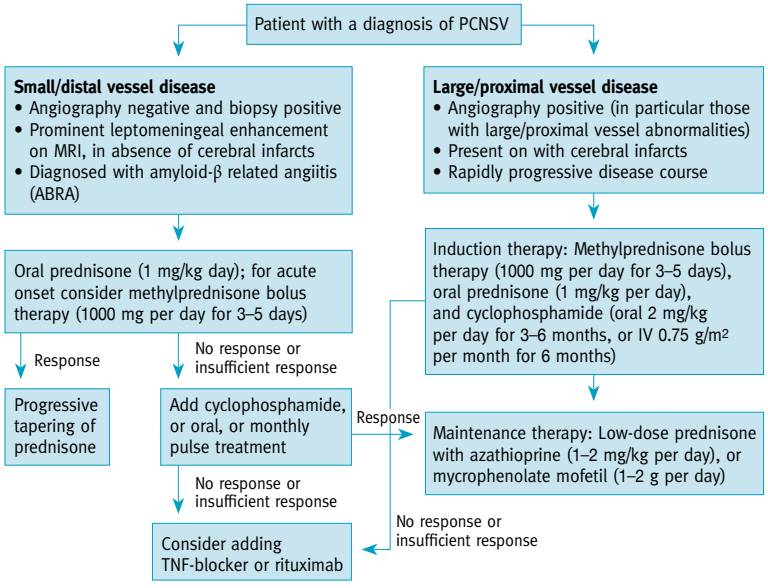
Most of the 15 patients initially treated with an immunosuppressive agent other than cyclophosphamide (mainly azathioprine or mycophenolate mofetil) had a favorable response, suggesting in some patients the possible use of a less toxic alternative to cyclophosphamide for the induction of remission.

We also evaluated the association of clinical findings at diagnosis with Rankin score outcomes at the last follow-up and survival. High disability scores at the last follow-up as well as increased rates of mortality were both significantly associated with aging (OR 1.44, hazard ratio [HR] 1.39) and presence of cerebral infarction observed on MRI at presentation (OR 3.74, HR 4.44), while patients with gadolinium-enhanced meninges or lesions on MRI (OR 0.35, HR 0.20,) had lower disability and less risk of death. Patients with amyloid angiopathy (0R 0.24) had lower disability at follow-up, while diagnosis by angiography alone (HR 3.28), compared with biopsy and the presence of large vessel involvement on angiograms (HR 4.98), were significantly associated with an increased mortality. These differences were related to the different sizes of cerebral vessels involved by the inflammatory process. Patients with rapidly progressive PCNSV and often fatal outcome were characterized by the angiographic presence of bilateral, multiple, large vessel lesions and MRI evidence of multiple cerebral infarctions. They represented the worst end of the clinical spectrum of PCNSV [1,29]. A more benign course was associated with angiography-negative patients, but biopsy evident involvement of small cortical and leptomeningeal vessels often presenting with a cognitive disorder and MRI evidence of prominent leptomeningeal enhancement [1,29]. Patients with amyloid-β related angiitis (ABRA) defined by deposition of amyloid-β in the media and adventitia of small cortical and leptomeningeal vessels belong to this clinically less aggressive subset [8,24,29].

Early recognition and treatment of primary central nervous system vasculitis (PCNSV) will help avoid serious outcomes

In view of these findings we proposed a treatment algorithm

Figure 1. Suggested treatment algorithm for primary central nervous system vasculitis (PCNSV)



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mainly based on the size of the vessels involved by the inflammation [Figure 1] [29]. In patients with inflammation restricted to small cortical and leptomeningeal vessels who have a more benign disease, prednisone alone was recommended as initial therapy (initial dose of 1 mg/Kg/day). Whereas, in patients with more severe large/proximal vessel disease and in those with a rapidly progressive course, high-dose intravenous methylprednisolone (1000 mg daily for 3-5 days) and cyclophosphamide can be used to attempt to induce remission immediately after diagnosis. There is insufficient reported experience to suggest replacing cyclophosphamide with the less toxic azathioprine or mycophenolate mofteil (MMF) for the induction of remission. However, these two immunosuppressors appear to be effective for the maintenance of remission. Methotrexate was rarely evaluated in published studies, and therefore was not included in the algorithm. A small number of case reports have shown the efficacy of tumor necrosis factor-alpha blockers and rituximab in adult PCNSV [30-32] indicating these agents may be helpful in patients who are intolerant or respond poorly to cyclophosphamide.

A recent study [33] evaluated the efficacy and safety of MMF in PCNSV and compared long-term neurological outcomes in patients treated with this drug to those receiving other therapies. Most of the 11 patients who were initially treated with MMF, or who received this drug for a recurrence of vasculitis, went into disease remission and did not have flare-ups while on treatment. Four of the five patients who received MMF as maintenance treatment continued in remission without flare-ups at the last visit and all four were able to suspend/reduce glucocorticoids. Furthermore, the patients treated with MMF had less severe disability at the last follow-up compared to those receiving cyclophosphamide and prednisone. Only one patients had important toxicity (leukopenia) necessitating stopping the drug. The overall results indicated that MMF is an effective and safe therapy for adult PCNSV. However, more research is needed to determine if MMF combined with glucocorticoids reliably works as first line induction or maintenance therapy in PCNSV.

A recent French study evaluated the effect of maintenance therapy after induction on the outcomes of adult patients with PCNSV [34]. Maintenance therapy was prescribed in 48/97 patients (49%), following cyclophosphamide in 42. Maintenance therapy was started 4 (3–18 months) months after glucocorticoid initiation. At the last follow-up, good outcomes were significantly more frequently observed in patients who had received maintenance therapy compared to those who had not (67 vs. 20%). Relapses were significantly less frequent in patients receiving maintenance therapy (22 vs. 45%). In the multivariate analysis, maintenance therapy was the only independent predictor of good outcome (OR 7.8). Therefore, maintenance therapy in patients with PCNSV seems to be associated with better functional outcomes and lower relapse rates. Further studies are needed to confirm these findings.

Serial MRI and MRA (4–6 weeks after the onset of treatment, then every 3–4 months during the first year of treatment, or in case of a new neurological deficit), as well repeat careful neurological examinations, are useful to monitor the disease course. In patients with stable imaging but worsening clinical symptoms, a repeat CSF exam and a repeat angiography may be indicated.

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References

1. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. *Lancet* 2012; 380 (9843): 767-77.
2. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis: an update. *Curr Opin Rheumatol* 2012; 24: 46-52.
3. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary CNS vasculitis with spinal cord involvement. *Neurology* 2008; 70: 2394-400.
4. Salvarani C, Giannini C, Miller DV, Hunder G. Giant cell arteritis: Involvement of intracranial arteries. *Arthritis Rheum* 2006; 55: 985-9.
5. Cravioto H, Feigin I. Noninfectious granulomatous angiitis with a predilection for the nervous system. *Neurology* 1959; 9: 599-609.
6. Giannini C, Salvarani C, Hunder G, Brown RD. Primary central nervous system vasculitis: pathology and mechanisms. *Acta Neuropathol* 2012; 123: 759-72.
7. Scolding NJ, Joseph F, Kirby PA, et al. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* 2005; 128: 500-15.
8. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. *Rheumatology (Oxford)* 2008; 47: 1671-7.
9. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. *Ann Neurol* 2007; 62: 442-51.
10. Salvarani C, Brown RD Jr, Calamia KT, et al. Angiography-negative primary central nervous system vasculitis: a syndrome involving small cerebral vessels. *Medicine (Baltimore)* 2008; 87: 264-71.
11. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis with prominent leptomeningeal enhancement: a subset with a benign outcome. *Arthritis Rheum* 2008; 58: 595-603.
12. Salvarani C, Brown RD Jr, Calamia KT, et al. Rapidly progressive primary central nervous system vasculitis. *Rheumatology (Oxford)* 2011; 50: 349-58.
13. Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis presenting with intracranial hemorrhage. *Arthritis Rheum* 2011; 63: 3598-606.
14. Cellucci T, Benseler SM. Central nervous system vasculitis in children. *Curr Opin Rheumatol* 2010; 22: 590-7.
15. Hunder GG, Salvarani C, Brown RD Jr. Primary central nervous system vasculitis: Is it a single disease? *Ann Neurol* 2010; 68: 573-4.
16. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. *Medicine (Baltimore)* 1988; 67: 20-39.
17. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. *Arch Neurol* 2009; 66: 704-9.
18. Ducros A, Bousser MG. Reversible cerebral vasoconstriction syndrome. *Pract Neurol* 2009; 9: 256-67.
19. Zuccoli G, Pipitone N, Haldipur A, Brown RD Jr, Hunder G, Salvarani C. Imaging findings in primary central nervous system vasculitis. *Clin Exp Rheumatol* 2011; 29 (Suppl. 64): S104-9.
20. Küker W, Gaertner S, Nagele T, et al. Vessel wall contrast enhancement: a diagnostic sign of cerebral vasculitis. *Cerebrovasc Dis* 2008; 26: 23-9.

21. Salvarani C, Brown RD Jr, Huston J 3rd, Hunder GG. Prominent perivascular enhancement in primary central nervous system vasculitis. *Clin Exp Rheumatol* 2008; 26 (3 Suppl 49): S111.
22. Swartz RH, Bhuta SS, Farb RI, et al. Intracranial arterial wall imaging using high-resolution 3-tesla contrast-enhanced MRI. *Neurology* 2009; 72: 627-34.
23. Miller DV, Salvarani C, Hunder GG, et al. Biopsy findings in primary angiitis of the central nervous system. *Am J Surg Pathol* 2009; 33: 35-43.
24. Salvarani C, Hunder GG, Morris JM, et al. Aβ-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology* 2013; 81: 1596-603.
25. Molloy ES, Singhal AB, Calabrese LH. Tumour-like mass lesion: an under-recognised presentation of primary angiitis of the central nervous system. *Ann Rheum Dis* 2008; 67: 1732-5.
26. Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Prospective diagnostic and therapeutic experience. *Am J Med* 1983; 74: 97-105.
27. Moore PM. Diagnosis and management of isolated angiitis of the central nervous system. *Neurology* 1989; 39: 167-73.
28. Salvarani C, Brown RD Jr, Christianson TJ, et al. Adult primary central nervous system vasculitis treatment and course: analysis of one hundred sixty-three patients. *Arthritis Rheumatol* 2015; 67: 1637-45.
29. Salvarani C, Brown RD Jr, Christianson T, et al. An update of the Mayo Clinic cohort of patients with adult primary central nervous system vasculitis: description of 163 patients. *Medicine (Baltimore)* 2015; 94 (21): e738.
30. Salvarani C, Brown RD Jr, Calamia KT, et al. Efficacy of tumor necrosis factor alpha blockade in primary central nervous system vasculitis resistant to immunosuppressive treatment. *Arthritis Rheum* 2008; 59: 291-6.
31. De Boysson H, Arquizan C, Guillevin L, Pagnoux C. Rituximab for primary angiitis of the central nervous system: report of 2 patients from the French COVAC cohort and review of the literature. *J Rheumatol* 2013; 40:2102-3.
32. Salvarani C, Brown RD Jr, Huston J 3rd, et al. Treatment of primary central nervous system vasculitis with rituximab: case report. *Neurology* 2014; 82: 1287-8.
33. Salvarani C, Brown RD Jr, Christianson TJ, et al. Mycophenolate mofetil in primary central nervous system vasculitis. *Semin Arthritis Rheum* 2015; 45: 55-9.
34. De Boysson H, Parienti JJ, Arquizan C, et al. Maintenance therapy is associated with better long-term outcomes in adult patients with primary angiitis of the central nervous system. *Rheumatology (Oxford)* 2017; 17. {Epub ahead of print].

Capsule

Interferon-independent antiviral defense

Antiviral responses are normally initiated by interferon production, which stimulates the phosphorylation and activation of STAT1 and STAT2. These transcription factors, together with the transcriptional regulator IRF9, mediate antiviral gene expression. Wang et al. reported that interferon-stimulated gene expression can be mediated by unphosphorylated STAT1 and STAT2 with IRF9 in the absence of interferon production or signaling. This complex protected cells from viral infection and, thus, mediates homeostatic, interferon-independent antiviral responses.

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Eitan Israeli

Capsule

Early disease activity or clinical response as predictors of long-term outcomes with certolizumab pegol in axial spondyloarthritis or psoriatic arthritis

Early identification of patients unlikely to achieve good long-term disease control with anti-tumor necrosis factor therapy in axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) is important for physicians following treat-to-target recommendations. Va de Heijde and colleagues assessed associations between disease activity or clinical response during the first 12 weeks of treatment and attainment of treatment targets at week 48 in axial SpA and PsA patients receiving certolizumab pegol. The relationship between disease activity or clinical response during the first 12 weeks of treatment and achievement of week-48 targets was assessed post hoc using RAPID-axSpA and RAPID-PsA trial data. For axial SpA, it was inactive disease based on Ankylosing Spondylitis Disease Activity Score (ASDAS) using the C-reactive protein (CRP) level or Bath Ankylosing Spondylitis Disease Activity Index ‹ 2 with normal CRP level. For PsA it was minimal disease activity. A clear relationship between disease activity from week 2 to 12 and achievement of week-48 treatment targets was observed in both axial SpA and PsA populations. In axial SpA, week-48 ASDAS inactive disease was achieved by no patients (0 of 21) with ASDAS very high disease activity at week 12, compared to 68% of patients (34 of 50) with week-12 ASDAS inactive disease. For PsA, week-48 minimal disease activity was achieved by no patients (0 of 26) with Disease Activity Score in 28 joints (DAS28) using the CRP level >5.1 at week 12, compared to 73% of patients (57 of 78) with DAS28-CRP <2.6. Similar results were observed regardless of the disease activity measure used. Clinical response at week 12 also predicted week-48 outcomes, though to a lesser extent than disease activity.

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Eitan Israeli

"Neither genius, fame, nor love show the greatness of the soul. Only kindness can do that"

Jean Baptiste Henri Lacordaire (1802–1861) preacher, journalist, and activist