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Primary Angiitis of the CNS

A Systematic Review and Meta-analysis

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Abstract

Background and Objectives

To facilitate and improve the diagnostic and therapeutic process by systematically reviewing studies on patients with primary angiitis of the CNS (PACNS).

Methods

We searched PubMed, looking at the period between 1988 and February 2020. Studies with adult patients with PACNS were included. We extracted and pooled proportions using fixed-effects models. Main outcomes were proportions of patients with certain clinical, imaging, and laboratory characteristics and neurologic outcomes.

Results

We identified 46 cohort studies including a total of 911 patients (41% biopsy confirmed, 43% angiogram confirmed, and 16% without clear assignment to the diagnostic procedure). The most frequent onset symptoms were focal neurologic signs (63%), headache (51%), and cognitive impairment (41%). Biopsy- compared with angiogram-confirmed cases had higher occurrences of cognitive impairment (55% vs 39%) and seizures (36% vs 16%), whereas focal neurologic signs occurred less often (56% vs 95%). CSF abnormalities were present in 75% vs 65% and MRI abnormalities in 97% vs 98% of patients. Digital subtraction angiography was positive in 33% of biopsy confirmed, and biopsy was positive in 8% of angiogram-confirmed cases. In 2 large cohorts, mortality was 23% and 8%, and the relapse rate was 30% and 34%, during a median follow-up of 19 and 57 months, respectively. There are no randomized trials on the treatment of PACNS. The initial treatment usually includes glucocorticoids and cyclophosphamide.

Discussion

PACNS is associated with disabling symptoms, frequent relapses, and significant mortality. Differences in symptoms and neuroimaging results and low overlap between biopsy and angiogram suggest that biopsy- and angiogram-confirmed cases represent different histopathologic types of PACNS. The optimal treatment is unknown.

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Glossary

DSA = digital subtraction angiography; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **PACNS** = primary angiitis of the CNS; **RCVS** = reversible cerebral vasoconstriction syndrome.

Primary angiitis of the CNS (PACNS) is a rare and severe form of vasculitis limited to the brain, spinal cord, and leptomeninges, resulting in inflammation of CNS vessels with subsequent cerebral ischemia and less frequently hemorrhage.[1] The exact etiology and pathogenesis of PACNS are unknown. The main histopathologic patterns include granulomatous inflammation, lymphocytic cellular infiltrates, and acute necrotizing vasculitis.[2,3] Clinical features at diagnosis are headache, altered cognition, and focal neurologic deficits (e.g., hemiparesis, ataxia, aphasia, dysarthria, and visual disturbances).[1] The diagnostic criteria proposed by Calabrese and Mallek in 1988 require the presence of an acquired, otherwise unexplained neurologic or psychiatric deficit, the presence of either classic angiographic or histopathologic features of angiitis within the CNS, and excluded evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathologic features of the disease.[4,5] The diagnosis of PACNS can be either biopsy or angiogram confirmed. Newer diagnostic criteria emphasize the inclusion of CSF for establishing the diagnosis of PACNS.[6] However, virtually, all recent cohort studies on PACNS refer to the well-established criteria by Calabrese and Mallek.

PACNS is a rare disease with an estimated prevalence of 2.4/1,000,000 person-years in North America.[7] The diverse disease manifestations and multiple differential diagnoses including reversible cerebral vasoconstriction syndrome (RCVS), secondary cerebral vasculitis, and infections complicate its diagnosis.[7] No prospective randomized studies on PACNS exist; therefore, therapeutic strategies have been derived from the treatment of systemic vasculitides and from cohort studies.

This systematic review and meta-analysis summarizes clinical, imaging, and laboratory characteristics of patients with PACNS separated in biopsy- and angiogram-confirmed cases. In addition, relapse rates, mortality, neurologic outcome, and the association of treatment with outcome are reported.

Methods

The data in our systematic review and meta-analysis were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.[8]

Search Strategy and Study Selection

We systematically searched articles in PubMed, looking at the period between 1988 when current diagnostic criteria for PACNS were established, and February 2020, using the following search terms: "Primary angiitis of the central nervous system" OR "Primary central nervous system vasculitis" OR "Cerebral Vasculitis." A detailed description of the search strategy and study selection is provided in the eMethods, links.lww.com/NXI/A628.

Data Extraction

Data were collected independently by 2 reviewers (D.S. and C.B). Discrepancies were resolved by consensus after further review of the relevant publications (D.S. and C.B.) or, if necessary, by a third reviewer (J.M.). Extracted study and patient characteristics included year of publication, sample size, study period, study location, study design, follow-up period, initial clinical presentation, qualitative changes in CSF parameters and inflammatory markers, radiographic and histologic findings, treatments, and outcomes. Different n-numbers in different parts of our analysis are due to the structure and extent of data given by the respective studies.

Statistical Analysis

We used R version 3.5.0 to perform the statistical analyses. The following packages were used: Metafor and Forestplot. We extracted and pooled proportions using fixed-effects models. To quantify the heterogeneity of the collected data, I^2 was calculated for each item under investigation.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

A total of 46 eligible articles (eFigure 1, links.lww.com/NXI/A629), comprising 911 unique patients diagnosed with PACNS, were included in the meta-analysis: 372 biopsy-confirmed, 394 angiogram-confirmed, and 145 patients who could not be assigned to a diagnostic procedure (eTable 1, links.lww.com/NXI/A628).[3,9-13,14-53] A majority of the included studies (n = 29, 63%) reported cases from Western Europe and the United States between 1988 and 2018. The median follow-up duration ranged from 0.75 to 61.2 months. To assess bias, we created funnel plots of all the studies included in the respective forest plots in our meta-analysis, which conformed to the expected shape of the curve and demonstrated overall left-right symmetry.

Patient Baseline Characteristics

The description and analysis of patients' demographic and clinical characteristics at baseline comprised 311 biopsy confirmed and 327 angiogram confirmed (Table 1; eTable 1, links.lww.com/NXI/A628). For certain patients, neither

brain biopsy nor angiogram could be attributed, although the diagnostic criteria introduced by Calabrese and Mallek were fulfilled.[24,26,30] Further 61 patients, could not be assigned to a specific diagnostic procedure group leading to final diagnosis.[15,31,39,49,53] However, these patients were only indicated in the summary of study characteristics, therapies, and outcome (eTables 1 and 2, links.lww.com/NXI/A628). Patients with both positive brain biopsy and positive angiogram were classified as biopsy confirmed.[6] Given the low number of patients with positive results in both examinations and the far-reaching lack of correspondent (para-) clinical information, we renounced forming a third group of patients for further analysis. Overlapping cases presented in separate studies by de Boysson et al.[9,10] and Salvarani et al.,[11-13] respectively, were not taken into account; only the more informative study was analyzed regarding, e.g., PACNS symptoms and therapeutic strategies.

Mean age was 42 years, ranging from 24 to 63 years. Information on sex was available in 40 studies, with 48% female patients. This proportion amounted to 19% in biopsy- and 25% in angiogram-confirmed cases, but not all authors report on sex distribution. The most frequent onset symptoms were focal neurologic signs (63%), headache (51%), and cognitive impairment (41%) (data not shown). Biopsy- compared with angiogram-confirmed cases had higher occurrences of cognitive impairment (55% vs 39%) and seizures (36% vs 16%), whereas focal neurologic signs occurred less often (56% vs 95%) (Table 1). These data did not differ significantly in subgroup analysis of histopathologic subtypes and autopsy cases.

Neuroimaging

Forty studies reported neuroimaging results (Figure 1). MRI abnormalities such as cerebral infarction, hemorrhage, leptomeningeal and/or parenchymal gadolinium enhancement or other abnormalities as defined by the respective authors were found in 169 (97%) biopsy- and 122 (98%) angiogram-confirmed patients (Figure 1, A and B). Cerebral infarcts were found in 54 (34%) biopsy- and 141 (68%) angiogram-confirmed patients (Figure 1, C and D). Bilateral infarcts were found in 16 (19%) biopsy- and 76 (46%) angiogram-confirmed cases. Intracranial hemorrhage was less frequent and was diagnosed in 34 (25%) biopsy- and in 29 (18%) angiogram-confirmed cases. Ninety-seven (69%) biopsy- and 39 (22%) angiogram-confirmed patients presented with parenchymal and/or leptomeningeal enhancement. Overall, parenchymal gadolinium enhancement was more frequent than meningeal enhancement (37% vs 16%).

Table 1 Patient Baseline Characteristics

	All patients			Biopsy confirmed			Angiogram confirmed		
Clinical manifestation	**n/Total**	**Proportion (95% CI)**	**I^2**	**n/Total**	**Proportion (95% CI)**	**I^2**	**n/Total**	**Proportion (95% CI)**	**I^2**
Focal neurologic signs	192/304	0.63 (0.54, 0.71)	86.4	43/77	0.56 (0.51, 0.76)	0	36/38	0.95 (0.72, 0.98)	0
Paresis	76/369	0.21 (0.16, 0.29)	67.2	30/114	0.26 (0.09, 0.54)	48	12/156	0.08 (0.02, 0.33)	42
Hemiparesis	137/310	0.44 (0.35, 0.51)	3,4	37/114	0.32 (0.18, 0.58)	37	86/159	0.54 (0.44, 0.60)	0
Ataxia	69/365	0.19 (0.16, 0.25)	0	19/115	0.17 (0.09, 0.27)	9,5	35/176	0.20 (0.15, 0.27)	0
Unilateral numbness of the skin	47/160	0.29 (0.23, 0.43)	0	11/31	0.35 (0.10, 0.58)	0	14/54	0.26 (0.18, 0.53)	0
Dysarthria	23/116	0.20 (0.11, 0.25)	0	10/47	0.21 (0.08, 0.30)	0	08/47	0.17 (0.04, 0.43)	0
Aphasia	104/390	0.26 (0.22, 0.31)	0	31/118	0.26 (0.20, 0.36)	0	49/192	0.26 (0.19, 0.32)	0
Headache	387/754	0.51 (0.46, 0.61)	49,6	107/202	0.53 (0.43, 0.60)	0	113/197	0.57 (0.54, 0.69)	14
Dizziness and vertigo	28/170	0.16 (0.10, 0.25)	1,6	07/49	0.14 (0.05, 0.23)	0	15/76	0.20 (0.15, 0.40)	38
Cognitive impairment	266/651	0.41 (0.31, 0.49)	60,2	93/169	0.55 (0.49, 0.66)	17	70/178	0.39 (0.33, 0.48)	46
Seizures	161/685	0.24 (0.19, 0.27)	28,1	64/180	0.36 (0.19, 0.44)	16	28/172	0.16 (0.12, 0.23)	12
Psychiatric symptoms	51/346	0.15 (0.08, 0.27)	63,4	21/114	0.18 (0.08, 0.28)	36	15/163	0.09 (0.05, 0.16)	59
Impaired vilgilance	39/173	0.23 (0.17, 0.33)	7,4	17/46	0.37 (0.13, 0.41)	0	12/69	0.17 (0.11, 0.43)	24
Constitutional symptoms	51/319	0.16 (0.08, 0.20)	50,9	22/107	0.21 (0.09, 0.32)	42	19/167	0.11 (0.04, 0.22)	0
Fever	30/260	0.12 (0.08, 0.16)	0	16/97	0.16 (0.09, 0.24)	0	12/139	0.09 (0.05, 0.14)	0
Visual disturbances	128/472	0.27 (0.18, 0.33)	22,7	36/142	0.25 (0.18, 0.33)	0	54/193	0.28 (0.21, 0.35)	31

Abbreviation: CI = confidence interval.
Not all authors have reported initial clinical symptoms. Therefore, n-numbers are lower than the total number of included cases in other parts of our analysis.
I^2, measure of degree of heterogeneity; n, number of patients with certain characteristic. Angiogram-confirmed, by means of conventional/magnetic resonance or CT angiography; paresis indicates mono- and tetraparesis.

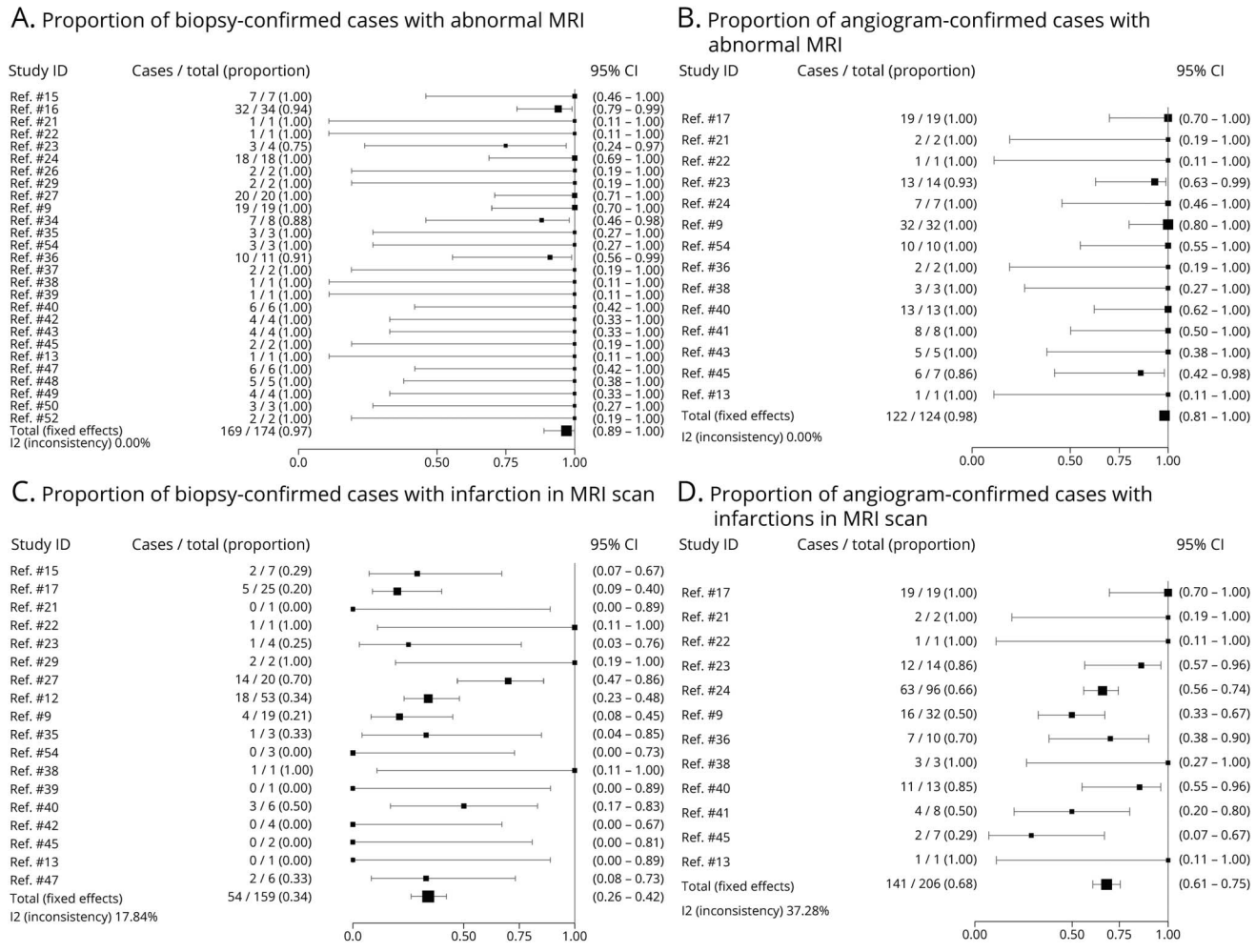
Analyses of histologic subtypes showed that MRI abnormalities were more frequent in lymphocytic (84%) compared with granulomatous (77%) and necrotizing (75%) subtypes (eFigure 2A, links.lww.com/NXI/A630). Infarctions were observed in 39% of lymphocytic, in 23% of granulomatous, and in 25% of necrotizing cases (eFigure 2B, links.lww.com/NXI/A630). Intracranial hemorrhage was found in 50% of necrotizing, in 32% of lymphocytic, and in 31% of granulomatous cases (eFigure 2C, links.lww.com/NXI/A630). Seventy-seven percent of granulomatous cases showed parenchymal and/or leptomeningeal enhancement, whereas only 46% of lymphocytic and 37% of necrotizing cases presented with this abnormality (eFigure 2D, links.lww.com/NXI/A630). In autopsy cases, MRI abnormalities were found in 78% of the patients (eFigure 3A, links.lww.com/NXI/A631). Intracranial hemorrhage (34%) and parenchymal and/or leptomeningeal enhancement (45%) were less frequently found compared with cerebral infarcts (59%) among autopsy cases (eFigure 3, B–D, links.lww.com/NXI/A631).

In patients with spinal cord involvement, parenchymal and/or leptomeningeal enhancement was the most frequent abnormal imaging finding (61%) (eFigure 4, A–D, links.lww.com/NXI/A632).

Of 159 biopsy-confirmed patients who were also examined by means of catheter angiography, 53 (33%) had positive digital subtraction angiographies (DSAs) in terms of segmental stenosis and dilatation (beading), vessel occlusion, collateral circulation, and/or microaneurysms (Figure 2A). In 19 (29%) of 66 biopsy-confirmed patients, magnetic resonance angiography (MRA) showed classical features of vasculitis (Figure 2B). Five of 62 (8%) biopsies conducted in angiogram-confirmed patients showed histologic features of PACNS (Figure 2C). Of 76 DSA-confirmed cases, 56 (74%) had a positive MRA (Figure 2D).

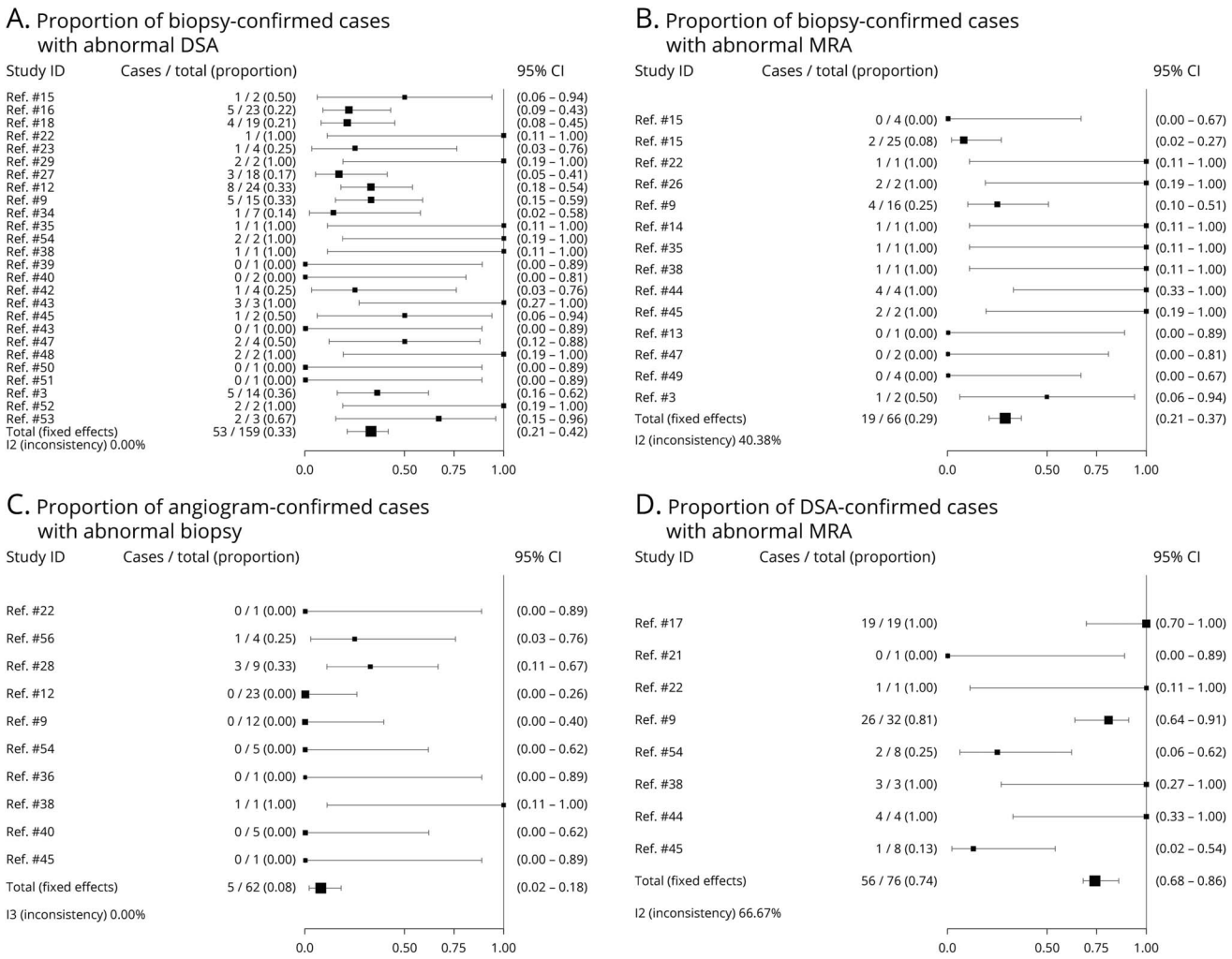
High-resolution contrast-enhanced MRI in terms of vessel wall imaging was performed in 5 studies. Contrast enhancement of

Figure 1 Imaging Characteristics of Biopsy- and Angiogram-Confirmed Cases



All estimators represent the proportions of abnormal results in relation to the number of performed examinations. The size of the estimator is proportional to the size of the cohort in the respective study. The indicator I-squared indicates the heterogeneity of the data. Error bars indicate 95% CIs. Abnormalities may, e.g., consist of infarction, hemorrhage, or gadolinium enhancement or other characteristics as defined by the respective author. CI = confidence intervals; gd = gadolinium.

Figure 2 Imaging and Histologic Characteristics: Overlap Between Biopsy- and Angiogram-Confirmed Cases



All estimators represent the proportions of abnormal results in relation to the number of performed examinations. The size of the estimator is proportional to the size of the cohort in the respective study. The indicator I-squared indicates the heterogeneity of the data. Error bars indicate 95% CIs. The term abnormal refers to findings typical of primary angiitis of the CNS (PACNS). CI = confidence interval; DSA, digital subtraction angiography; MRA, magnetic resonance angiography.

the vessel wall was more often found among patients with angiogram- compared with biopsy-confirmed PACNS. This difference was statistically significant ($p < 0.0001$).

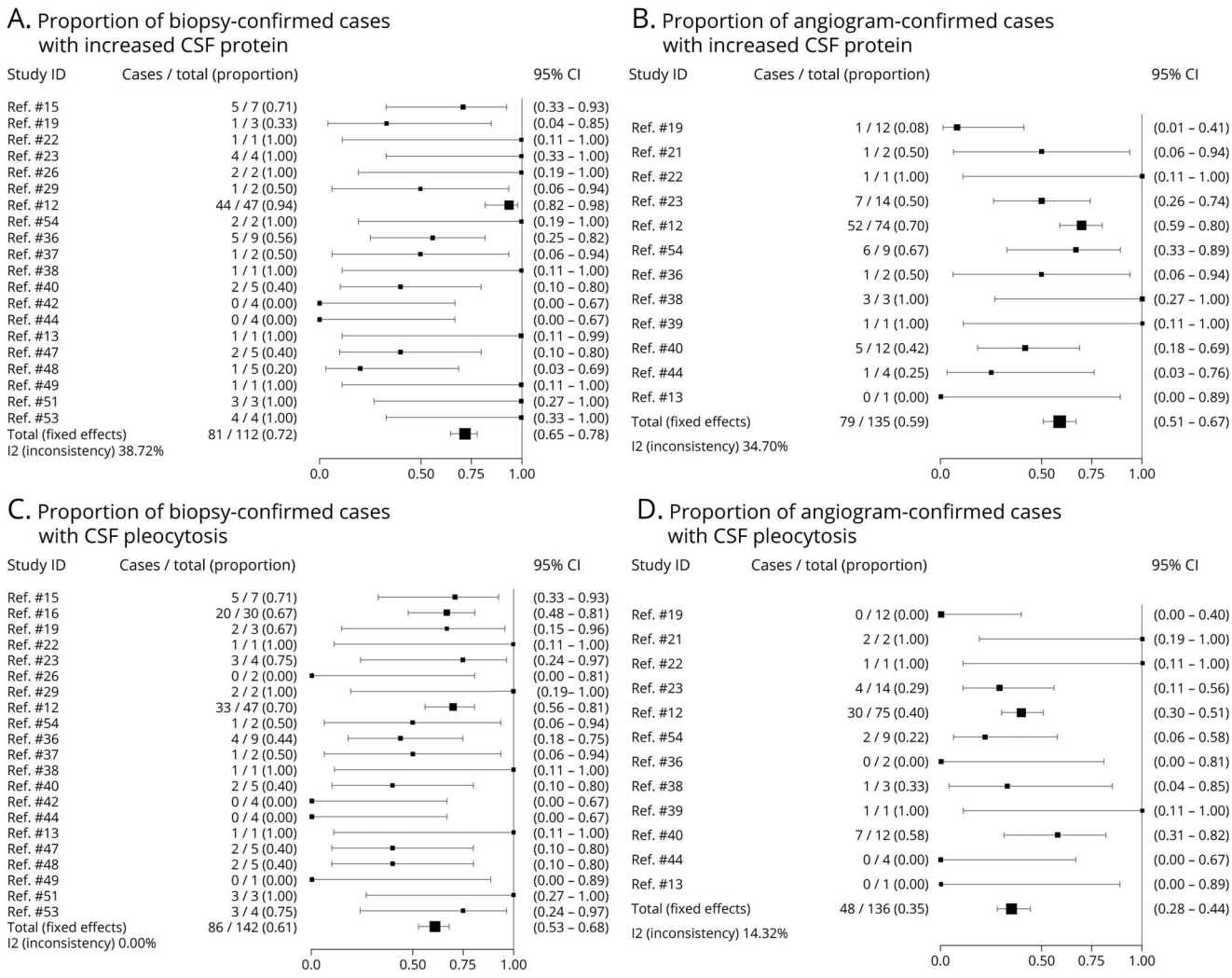
Blood and CSF Analyses

Thirty-one studies reported results of blood and CSF analyses (Figure 3). A lumbar puncture was performed in 581 patients with PACNS. Pathologic results in terms of elevated leukocyte count (>4 cells/μL) and/or increased protein concentration (>450 mg/L) were apparent in 134 (75%) biopsy- and 115 (65%) angiogram-confirmed cases. A pleocytosis was present in 86 (61%) biopsy- and 48 (35%) angiogram-confirmed cases (Figure 3, C and D). An elevated protein concentration was found in 81 (72%) biopsy- and 79 (59%) angiogram-confirmed cases (Figure 3, A and B). Abnormal CSF findings were apparent in all histologic subtypes in more than 50% of the cases (eFigure 5, A–C, links.lww.com/NXI/A633). In both, autopsy cases and patients with spinal cord involvement, lumbar puncture more often revealed pathologic findings (77%, 80%) in comparison to angiogram-confirmed cases (eFigures 6 and 7, links.lww.com/NXI/A634 and links.lww.com/NXI/A635).

Pathogenetic Mechanisms

The pathogenesis of PACNS is largely unknown. Infectious agents such as varicella zoster virus have been associated with PACNS.[1] However, the detailed mechanisms of infection mediating PACNS have not been clarified. To date, PACNS is defined as a noninfectious disease distinct from infectious (secondary) CNS vasculitis. It is known from histopathologic studies that different types of immune cells infiltrate cerebral vessels resulting in distinct histopathologic subtypes.[1] For instance, the necrotizing vasculitis subtype is frequently found to be associated with vessel wall destruction and intracerebral bleeding.[1] Among the reviewed studies, only a few data on etiology, pathogenesis, and immunologic mechanisms involved in PACNS were provided. Mandel-Brehm et al.[14] found evidence of a deregulated alternative

Figure 3 CSF Abnormalities in Biopsy- and Angiogram-Confirmed Cases



All estimators represent the proportions of abnormal results in relation to the number of performed examinations. The size of the estimator is proportional to the size of the cohort in the respective study. The indicator I-squared indicates the heterogeneity of the data. Error bars indicate 95% CIs. CSF is considered abnormal when the cell count exceeds 4/μL (pleocytosis) or the protein concentration exceeds 450 mg/L. CI = confidence interval.

pathway of complement activation in CSF from biopsy-proven PACNS compared with a group of mimicking conditions. In a histopathologic study from Mihm et al.,[32] PACNS was shown to be characterized by MRP8-positive intermediate/late-activated macrophages. Regarding PACNS subtypes, ABRA is suspected to be a spontaneous form of autoimmune disease directed at amyloid β peptide (Aβ) characterized by an immune response directed against Aβ and causing leptomeningeal and parenchymal inflammation, clearance of parenchymal Aβ, and increased deposition of Aβ in cortical and leptomeningeal blood vessels. Hence, further research is needed to unravel the pathophysiologic mechanisms of distinct PACNS subtypes and to be able to develop subtype-specific treatment options.

Neurologic Outcomes

Reporting of outcomes was heterogeneous and thus could not be summarized by means of meta-analysis (eTable 2). Follow-up duration ranged from discharge up to 356 months. Only a few studies reported relapse frequencies. In 2 of the largest cohorts, relapses occurred in 34% and 30% of patients during a median follow-up of 57 and 19 months, respectively.[9,11] Reported mortality was also very heterogeneous across the included studies: 8% (9 of 112 patients) during a median follow-up of 57 months in a study by de Boysson, 16% (7 of 45 patients) during a median follow-up of 33 months in a study by Sundaram, and 23% (44 of 191 patients) during a median follow-up of 19 months in a study by Salvarani.[9,11,17]

In the largest included cohort, 131 (69%) of 191 patients had a modified Rankin Scale (mRS) score of 0–3, indicating a low or intermediate disability, and 16 (8%) of 191 patients had an mRS score of 4 or 5, indicating a severe disability at last follow-up (median 19 months, range: 0–337 months).[11,54] De Boysson et al.[9] report an mRS score of 0–2, indicating a good neurologic outcome in 63 (56%) of 112 patients at last follow-up (median 53 months, range 0–198 months).

Treatment of PACNS

PACNS treatments can be divided into induction and maintenance therapies. However, not all included studies adhere to this classification (eTable 2).[9] Induction treatment comprised glucocorticoids and/or cyclophosphamide in the majority of studies. The 2 largest included studies giving information on neurologic outcome report oral or IV glucocorticoid treatment in the induction phase for 110 (98%) of 112 patients and for 184 (96%) of 191 patients.[9,11] Explicitly mentioned oral glucocorticoids, administered with the usual dosage of 1 mg/kg/day or more in 16 of 30 studies reporting therapeutic strategies, were administered over a treatment period of 0.4–159 months, followed by or including tapering of the dose.[9,11] IV glucocorticoids, chosen in 17 of 30 studies, were mostly administered in a daily dosage of 1 g for 3–5 days.[9,11] Some authors draw the conclusion that the path of administration chosen for glucocorticoids should depend on the initial severity of the disease course.[40] A minority of patients received glucocorticoids as induction treatment only. In the majority of studies, a combination of glucocorticoids and at least 1 further immunosuppressive drug was given. Among these complementary drugs, cyclophosphamide plays the most prominent role. IV pulses were the preferred form of administration, given 2–12 times (median of 6 according to de Boysson et al.) over 2–10 months (median of 6 according to de Boysson et al. 2020).[9,35,40] IV cyclophosphamide was administered in 13 of 30 studies. Salvarani et al. report a median dose of 1 g and Oon et al. a median dose of 800–1000 mg/mo[11,35] Oral cyclophosphamide was administered in 9 of 30 studies and was given daily with a median starting dose of 150 mg/day and a median treatment duration of 7 months, with a median starting dose of 100 mg/day and a median treatment duration of 10 months, or with 2 mg/kg/day and a treatment duration of 6 months.[11,25,34,43,49,52] Five studies did not report whether glucocorticoids or cyclophosphamide were given orally or IV.[3,37,38,47,48] Other induction treatments include cyclophosphamide alone or combinations of glucocorticoids with azathioprine, mycophenolate mofetil, rituximab, or methotrexate.[9,11,39,46] IV immunoglobulins, infliximab, and plasma exchange were applied as well in single cases.[11]

With regard to maintenance therapy, a combination of immunosuppressants with oral glucocorticoids being gradually tapered is frequently reported.[13,40,43,46,47,49] Common immunosuppressive agents are azathioprine (1.5 or 2 mg/kg/day or 100–200 mg/day), mycophenolate mofetil (2–3g/day), and methotrexate (0.3–0.5 mg/kg/wk or 7.5–20 mg/wk).[9,11,12,16,20] Rituximab was used for induction (2 1000 mg infusions separated by 2 weeks or weekly rituximab admission (375 mg/m^2) for 4 weeks) and/or maintenance therapy (1,000 mg every 6 months) in 5 of 30 studies.[9,11,16,19,20] Patients with disease resistant to conventional immunosuppressive agents including azathioprine, mycophenolate mofetil, and methotrexate treated with rituximab were found to have improvement of neurologic findings and imaging and reduction in the number of relapses.[11,20] In the cohort of de Boysson (n = 112), all 106 (95%) patients who achieved remission after induction therapy were treated with glucocorticoids, most frequently combined with cyclophosphamide (n = 89) as an additional immunosuppressive treatment.[9] The most frequently administered immunosuppressive agent in this (n = 41) and also in other cohorts was azathioprine.[9] Best functional outcome was achieved by patients being treated with a combination of glucocorticoids and another immunosuppressive drug, followed by maintenance therapy. According to the data of de Boysson, maintenance drugs were started at a median time of 4 (3–18) months after initiation of induction therapy for median duration of 24 (6–72) months.[9] In relapsing patients, a reinduction was performed with the same drugs as applied as induction treatment.[9] Salvarani et al.[13] described 2 cases refractory to first-line treatment with glucocorticoids and cyclophosphamide, for which infliximab and etanercept provided successful treatment options.

The association between treatment and outcome was analyzed in some studies (eTable 2). However, no randomized clinical trials on treatment of PACNS exist. A (partially) prospective study included in this systematic review reports a significant association in a multivariate analysis of maintenance therapy with prolonged remission (odds ratio 4.32, $p = 0.002$) and better functional outcome (odds ratio 8.09, $p < 0.0001$) compared with no maintenance therapy.

Discussion

In this systematic review and meta-analysis, we summarize data from 46 cohort studies with 912 patients with PACNS. Our analysis yields the following main findings: (1) MRI shows abnormal findings in virtually all patients with PACNS regardless of biopsy- or angiogram-confirmed diagnosis (97% vs 98%); (2) CSF is abnormal in about two-thirds (66%) of patients, whereas less than half (47%) of the patients have a CSF pleocytosis, questioning the applicability and reliability of newer diagnostic criteria; (3) about one- third of patients have relapses during the first years after diagnosis, and mortality after diagnosis is up to one-fourth—although outcomes differ considerably between cohorts; (4) initial treatment usually includes glucocorticoids and cyclophosphamide, administered IV or orally; and (5) PACNS represents a spectrum of disorders with different sized vessels involved, requiring different diagnostic approaches, i.e., biopsy vs angiogram (Figure 4).

Considering the severity of the disease, an accurate and timely diagnosis of PACNS is required but remains challenging due to the absence of specific clinical, imaging, and laboratory characteristics. Serologic tests for PACNS are not available, and established markers for inflammation including C-reactive protein and erythrocyte sedimentation rate have normal levels in the majority of patients. MRI and CSF examinations are usually performed in patients with suspected PACNS but are not part of the established diagnostic

criteria.[55] MRI is highly sensitive but less specific. A normal MRI almost rules out PACNS. However, the most frequently observed changes, including cerebral infarcts, intracranial hemorrhages, and parenchymal or leptomeningeal contrast enhancement, often have other causes. CSF analysis is considered a central part for evaluating patients with PACNS.[6,7] However, sensitivity is moderate and specificity is low. In this context, our systematic analysis contradicts more recent diagnostic criteria that attribute a high relevance to CSF tests for diagnosing PACNS.[6] Nevertheless, the major role for CSF analysis is to exclude malignant or infectious diseases.[6] Altogether, the definite diagnosis can only be proven by brain biopsy in case of PACNS suspicion. However, due to the focal and segmental distribution of the disease, the sensitivity of brain biopsy is often reduced as a result of sampling errors.

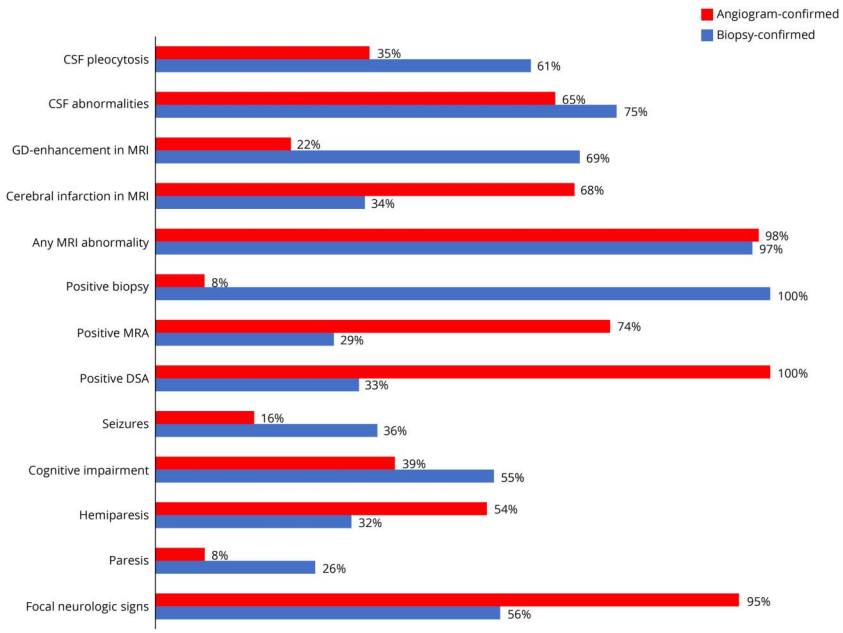
Glucocorticoids combined with cyclophosphamide are the standard for treating PACNS. However, there are no randomized clinical trials investigating optimal initial glucocorticoid and cyclophosphamide dose, administration route, or tapering regimes. Current treatment recommendations are based on observational studies or are derived from the management of systemic vasculitides. Glucocorticoid treatment should be initiated as soon as PACNS is diagnosed. Pizzanelli et al.[40] suggest that glucocorticoid dosage and administration route should be chosen according to the degree of disease severity at onset. In most observational studies, daily oral or intermittent (usually monthly) IV cyclophosphamide is given in addition to glucocorticoids. These recommendations are in line with recent nonsystematic reviews.[6,7]

Drawing conclusions on the long-term disease development of PACNS is limited due to the heterogeneity of the reviewed studies regarding follow-up duration and selection of outcome assessments. The only (partly) prospective study included in the review reported a relapse frequency of 34% and a mortality of 8% during a median follow-up of 57 months[9]

We found a low agreement between histology and angiography. One explanation could be sample artifacts (i.e., including biopsies of nonaffected tissue due to the patchy pattern of the disease).[56] Another reason could be that biopsy- and angiogram-confirmed cases represent different parts of the PACNS spectrum (Figure 4). The most striking difference between biopsy- and angiogram-confirmed cases is the affected vessel size. Based on the size of predominantly affected vessels, a small- and a medium-vessel vasculitis have been described.[57] Growing evidence supports the fact that biopsy-confirmed PACNS represents small-vessel vasculitis, whereas angiogram-confirmed PACNS represents medium to large-vessel vasculitis.[58] Further clinical and laboratory differences summarized in Figure 4 support this concept.

Our study has strengths and limitations. Left-right symmetry in the funnel plots indicates that studies with high and low proportions were equally represented in the literature, and concordance with the expected shape of the curve shows that larger studies had proportions closer to the overall proportion than smaller studies. As stated by Egger et al.,[59] these observations argue against the presence of bias. Recommendations regarding the treatment of PACNS are limited by the scarcity of randomized clinical trials, and conclusions on the long-term outcome are limited by the lack of prospective studies. Interpretation of data on both response to treatment and outcome is further limited by the heterogeneous data

Figure 4 PACNS—A Disease Spectrum



There are overlapping (para-)clinical attributes between biopsy- (blue bars) and angiogram-confirmed (red bars) cases of PACNS, and also distinct characteristics. DSA = digital subtraction angiography; GD = gadolinium; MRA = magnetic resonance angiography; PACNS = primary angiitis of the CNS.

reported. We included several rather small observational studies resulting in a considerable degree of heterogeneity. Furthermore, angiogram-confirmed cases bear the risk of representing a mimic of PACNS such as RCVS, intracranial atherosclerosis, and secondary vasculitis. Therefore, the necessity of additional examinations ruling out such differential diagnoses is unquestionable. Another weakness of our study is the inclusion of patients with highly probable PACNS, that bear the risk of being misdiagnosed, to treatment and outcome analysis. Nevertheless, our systematic review combines the available evidence on PACNS and gives a concise overview of clinical characteristics, diagnostics, treatment, and outcome of PACNS.

In conclusion, PACNS is a severe disorder with disabling symptoms, frequent relapses, and significant mortality. Differences in symptoms and neuroimaging results and the only moderate overlap between biopsy and angiogram indicate that biopsy- and angiogram-confirmed cases represent different parts of the PACNS spectrum (i.e., small vessel vs medium-sized and large vessel affection). Most frequently used for induction therapy are glucocorticoids combined with cyclophosphamide and for maintenance therapy azathioprine, mycophenolate mofetil, rituximab, or methotrexate.

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Name	Location	Contribution
Carolin Beuker, MD	University of Münster, Germany	Acquisition of data, analysis and interpretation of data, and writing of the manuscript
Daniel Strunk, MD	University of Münster, Germany	Acquisition of data, analysis and interpretation of data, and writing of the manuscript
Rajesh Rawal, PhD	University of Münster, Germany	Analysis and interpretation of data
Antje Schmidt-Pogoda, MD	University of Münster, Germany	Interpreted the data and revised the manuscript for intellectual content
Nils Werring, MD	University of Münster, Germany	Interpreted the data and revised the manuscript for intellectual content
Lennart Milles, MD	University of Essen, Germany	Interpreted the data and revised the manuscript for intellectual content
Tobias Ruck, MD	University of Düsseldorf, Germany	Interpreted the data and revised the manuscript for intellectual content
Heinz Wiendl, MD	University of Münster, Germany	Critical revision of the manuscript for intellectual content
Sven G. Meuth, MD	University of Düsseldorf, Germany	Critical revision of the manuscript for intellectual content
Heike Minnerup, MD	University of Münster, Germany	Acquisition of data, interpreted the data; and revised the manuscript for intellectual content
Jens Minnerup, MD	University of Münster, Germany	Study concept and design and critical revision of the manuscript for intellectual content

References

1. Giannini C, Salvarani C, Hunder G, Brown RD. Primary central nervous system vasculitis: pathology and mechanisms. *Acta Neuropathol*. 2012;123(6):759-772.
2. Miller DV, Salvarani C, Hunder GG, et al. Biopsy findings in primary angiitis of the central nervous system. *Am J Surg Pathol*. 2009;33(1):35-43.
3. Alrawi A, Trobe JD, Blaivas M, Musch DC. Brain biopsy in primary angiitis of the central nervous system. *Neurology*. 1999;53(4):858-860.
4. Calabrese LH. Primary angiitis of the central nervous system: reflections on 20 years of investigation. *Clin Exp Rheumatol*. 2009;27(suppl. 52):S3-S4.
5. 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(1):20-39.
6. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. *Arch Neurol*. 2009;66(6):704-709.
7. Salvarani C, Brown RD, Hunder GG. Adult primary central nervous system vasculitis. *Lancet*. 2012;380(9843):767-777.
8. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
9. de Boysson H, Arquizan C, Touzé E, et al. Treatment and long-term outcomes of primary central nervous system vasculitis. *Stroke*. 2018;49(8):1946-1952.
10. de Boysson H, Zuber M, Naggara O, et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. *Arthritis Rheumatol*. 2014;66(5):1315-1326.
11. Salvarani C, Brown RD, Christianson TJH, Huston J, Giannini C, Hunder GG. Long-term remission, relapses and maintenance therapy in adult primary central nervous system vasculitis: a single-center 35-year experience. *Autoimmun Rev*. 2020;19(4):102497.
12. 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.

13. Salvarani C, Brown RD, 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(2):291-296.
14. Mandel-Brehm C, Retallack H, Knudsen GM, et al. Exploratory proteomic analysis implicates the alternative complement cascade in primary CNS vasculitis. *Neurology*. 2019;93(5):e433-e444.
15. Raghavan A, Wright JM, Huang Wright C, et al. Concordance of angiography and cerebral biopsy results for suspected primary central nervous system vasculitis: a multi-center retrospective review. *Clin Neurol Neurosurg*. 2019;185:105482.
16. Schuster S, Ozga AK, Stellmann JP, et al. Relapse rates and long-term outcome in primary angiitis of the central nervous system. *J Neurol*. 2019;266(6):1481-1489.
17. Sundaram S, Menon D, Khatri P, et al. Primary angiitis of the central nervous system: clinical profiles and outcomes of 45 patients. *Neurol India*. 2019;67(1):105-112.
18. Wang LJ, Kong DZ, Guo ZN, Zhang FL, Zhou HW, Yang Y. Study on the clinical, imaging, and pathological characteristics of 18 cases with primary central nervous system vasculitis. *J Stroke Cerebrovasc Dis*. 2019;28(4):920-928.
19. Marrodan M, Acosta JN, Alessandro L, et al. Clinical and imaging features distinguishing Susac syndrome from primary angiitis of the central nervous system. *J Neurol Sci*. 2018;395:29-34.
20. Patel S, Ross L, Oon S, Nikpour M. Rituximab treatment in primary angiitis of the central nervous system. *Intern Med J*. 2018;48(6):724-727.
21. Van Rooij JL, Rutgers DR, Spliet WG, Frijns CJ. Vessel wall enhancement on MRI in the diagnosis of primary central nervous system vasculitis. *Int J Stroke*. 2018;13(9):NP24-NP27.
22. Strunk D, Schulte-Mecklenbeck A, Golombeck KS, et al. Immune cell profiling in the cerebrospinal fluid of patients with primary angiitis of the central nervous system reflects the heterogeneity of the disease. *J Neuroimmunol*. 2018;321:109-116.
23. Becker J, Horn PA, Keyvani K, et al. Primary central nervous system vasculitis and its mimicking diseases–clinical features, outcome, comorbidities and diagnostic results–A case control study. *Clin Neurol Neurosurg*. 2017;156:48-54.
24. Niu L, Wang L, Yin X, Li XF, Wang F. Role of magnetic resonance imaging in the diagnosis of primary central nervous system angiitis. *Exp Ther Med*. 2017;14(1):555-560.
25. Zhu DS, Yang XL, Lv HH, et al. Seizure syndrome as a first manifestation of solitary tumor-like mass lesion of PACNS: two case reports. *Medicine (Baltimore)*. 2017;96(9):e6018.
26. Singhal AB, Topcuoglu MA, Fok JW, et al. Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. *Ann Neurol*. 2016;79(6):882-894.
27. Torres J, Loomis C, Cucchiara B, Smith M, Messé S. Diagnostic yield and safety of brain biopsy for suspected primary central nervous system angiitis. *Stroke*. 2016;47(8):2127-2129.
28. Kempster PA, McLean CA, Phan TG. Ten year clinical experience with stroke and cerebral vasculitis. *J Clin Neurosci*. 2016;27:119-125.
29. Vera-Lastra O, Sepúlveda-Delgado J, Cruz-Domínguez MdelP, et al. Primary and secondary central nervous system vasculitis: clinical manifestations, laboratory findings, neuroimaging, and treatment analysis. *Clin Rheumatol*. 2015;34(4):729-738.
30. Geri G, Saadoun D, Guillevin R, et al. Central nervous system angiitis: a series of 31 patients. *Clin Rheumatol*. 2014;33(1):105-110.
31. Kim SS, Richman DP, Johnson WO, Hald JK, Agius MA. Limited utility of current MRI criteria for distinguishing multiple sclerosis from common mimickers: primary and secondary CNS vasculitis, lupus and Sjogren's syndrome. *Mult Scler*. 2014;20(1):57-63.
32. Mihm B, Bergmann M, Brück W, Probst-Cousin S. The activation pattern of macrophages in giant cell (temporal) arteritis and primary angiitis of the central nervous system. *Neuropathology*. 2014;34(3):236-242.
33. Suri V, Kakkar A, Sharma MC, Padma MV, Garg A, Sarkar C. Primary angiitis of the central nervous system: a study of histopathological patterns and review of the literature. *Folia Neuropathol*. 2014;52(2):187-196.
34. Coronel-Restrepo N, Bonilla-Abadía F, Cortes OA, et al. Primary angiitis of the central nervous system: a report of three cases from a single colombian center. *Case Rep Neurol Med*. 2013;2013:940438.
35. Oon S, Roberts C, Gorelik A, Wicks I, Brand C. Primary angiitis of the central nervous system: experience of a Victorian tertiary-referral hospital. *Intern Med J*. 2013;43(6):685-692.
36. Pagni F, Isimbaldi G, Vergani F, et al. Primary angiitis of the central nervous system: 2 atypical cases. *Folia Neuropathol*. 2012;50(3):293-299.
37. Pfefferkorn T, Linn J, Habs M, et al. Black blood MRI in suspected large artery primary angiitis of the central nervous system. *J Neuroimaging*. 2013;23(3):379-383.
38. Pourmahmoodian H, Ghelichnia Omrani HA, Harrirchian MH, Ghabaee M, Zamani B, Ghaffarpour M. Primary angiitis of the central nervous system. *Acta Med Iran*. 2012;50(3):216-221.
39. Kraemer M, Berlit P. Primary central nervous system vasculitis: clinical experiences with 21 new European cases. *Rheumatol Int*. 2011;31(4):463-472.
40. Pizzanelli C, Catarsi E, Pelliccia V, et al. Primary angiitis of the central nervous system: report of eight cases from a single Italian center. *J Neurol Sci*. 2011;307(1-2):69-73.
41. Myung J, Kim B, Yoon BW, et al. B-cell dominant lymphocytic primary angiitis of the central nervous system: four biopsy-proven cases. *Neuropathology*. 2010;30(2):123-130.
42. White ML, Zhang Y. Primary angiitis of the central nervous system: apparent diffusion coefficient lesion analysis. *Clin Imaging*. 2010;34(1):1-6.
43. Yin Z, Li X, Fang Y, Luo B, Zhang A. Primary angiitis of the central nervous system: report of eight cases from southern China. *Eur J Neurol*. 2009;16(1):63-69.
44. Küker W, Gaertner S, Nägele T, et al. Vessel wall contrast enhancement: a diagnostic sign of cerebral vasculitis. *Cerebrovasc Dis*. 2008;26(1):23-29.
45. Josephson SA, Papanastassiou AM, Berger MS, et al. The diagnostic utility of brain biopsy procedures in patients with rapidly deteriorating neurological conditions or dementia. *J Neurosurg*. 2007;106(1):72-75.
46. Scolding NJ, Joseph F, Kirby PA, et al. Aβ-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain*. 2005;128(Pt 3):500-515.
47. Volcy M, Toro ME, Uribe CS, Toro G. Primary angiitis of the central nervous system: report of five biopsy-confirmed cases from Colombia. *J Neurol Sci*. 2004;227(1):85-89.
48. Singh S, John S, Joseph TP, Soloman T. Primary angiitis of the central nervous system: MRI features and clinical presentation. *Australas Radiol*. 2003;47(2):127-134.
49. Campi A, Benndorf G, Filippi M, Reganati P, Martinelli V, Terreni MR. Primary angiitis of the central nervous system: serial MRI of brain and spinal cord. *Neuroradiology*. 2001;43(8):599-607.
50. Panda KM, Santosh V, Yasha TC, Das S, Shankar SK. Primary angiitis of CNS : neuropathological study of three autopsied cases with brief review of literature. *Neurol India*. 2000;48(2):149-154.
51. Pomper MG, Miller TJ, Stone JH, Tidmore WC, Hellmann DB. CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. *AJNR Am J Neuroradiol*. 1999;20(1):75-85.
52. Koo EH, Massey EW. Granulomatous angiitis of the central nervous system: protean manifestations and response to treatment. *J Neurol Neurosurg Psychiatry*. 1988;51(9):1126-1133.
53. Deb M, Gerdes S, Heeren M, et al. Circulating endothelial cells as potential diagnostic biomarkers in primary central nervous system vasculitis. *J Neurol Neurosurg Psychiatry*. 2013;84(7):732-734.
54. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J*. 1957;2(5):200-215.
55. Beuker C, Schmidt A, Strunk D, et al. Primary angiitis of the central nervous system: diagnosis and treatment. *Ther Adv Neurol Disord*. 2018;11:1756286418785071.
56. Amara AW, Bashir K, Palmer CA, Walker HC. Challenges in diagnosis of isolated central nervous system vasculitis. *Brain Behav*. 2011;1(1):57-61.
57. de Boysson H, Boulouis G, Aouba A, et al. Adult primary angiitis of the central nervous system: isolated small-vessel vasculitis represents distinct disease pattern. *Rheumatology (Oxford)*. 2017;56(3):439-444.
58. Krawczyk M, Barra LJ, Sposato LA, Mandzia JL. Primary CNS vasculitis: a systematic review on clinical characteristics associated with abnormal biopsy and angiography. *Autoimmun Rev*. 2021;20(1):102714.
59. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.