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Primary CNS Vasculitis - A Focussed Review on Treatment

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Abstract: Primary central nervous system vasculitis (PCNSV) is a rare and complex disease that poses formidable diagnostic and therapeutic challenges. Since its initial recognition as a distinct clinical entity in the 1950s, there has been considerable advancement in our understanding of PCNSV histopathology, specific clinical subsets, and their response to treatment. However, PCNSV is one of the rarest vasculitides, and still remains a challenging diagnosis with many unanswered questions regarding optimal management. In this review, we intend to provide a detailed outline of approaches that are currently being employed for the treatment of PCNSV. We exhaustively review available cohort series of PCNSV and critically appraise the data for study definitions, treatment approaches, and predictors of treatment outcomes. Finally, we also propose a treatment approach for PCNSV.

Keywords: primary CNS vasculitis, primary angiitis of CNS, PCNSV, PACNS, treatment, induction, maintenance, remission, relapse, outcomes

Introduction

Primary central nervous system vasculitis (PCNSV) is a rare and complex disease that poses formidable diagnostic and therapeutic challenges. PCNSV is a vasculitic disorder isolated to the brain and/or spinal cord without systemic involvement, causing inflammation of small and medium sized cortical and leptomeningeal blood vessels. Since its initial recognition as a distinct clinical entity in the 1950s, first by Newman and Wolf,[1] then by Cravioto and Feigin,[2] there has been considerable advancement in our understanding of PCNSV histopathology, specific clinical subsets, and their response to treatment. However, PCNSV is one of the rarest vasculitides, with an estimated annual incidence of 2.4 cases per million person-years,[3] and still remains a challenging diagnosis with many unanswered questions regarding optimal management.

There are numerous reviews available regarding PCNSV detailing its epidemiology, clinical manifestations, diagnostic approach, investigations and differential diagnosis.[4–6] Briefly, a disease of middle age with median age of onset approximately 50 years, clinical presentation in PCNSV can be extremely variable with no classic presentation. In addition, there is no single diagnostic test and the sensitivity/specificity of all currently available tests is suboptimal. As such, an exhaustive approach with thorough historical data, physical examination, and corroborating investigations should be performed to exclude or confirm a diagnosis of PCNSV. Differential diagnoses of infectious, neoplastic, and autoimmune origin should be carefully evaluated. Knowledge and uncovering of PCNSV mimics are crucial given the therapeutic and prognostic implications. Many reviews cover the above considerations comprehensively but offer a limited description of treatment options.

In this review, we intend to provide a detailed review of approaches that are currently being employed for the treatment of PCNSV. We specifically focus on the evidence available for treatment, and will not address other aspects of the disease briefly alluded to earlier. PCNSV is also synonymously called primary angiitis of the central nervous system (PACNS), and both have been used in literature. For the purpose of this review, we will uniformly use PCNSV.

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Treatment

There are no uniform guidelines, globally for the treatment of PCNSV. The treatment followed for this debilitating disease is largely derived from retrospective/ambispective studies from the Mayo Clinic,[3,7,8] French,[9–11] Cleveland Clinic,[12,13] German[14] and Indian cohorts.[15,16] On account of the rarity of PCNSV and heterogeneity in treatment approaches, no randomized controlled trials are available to date regarding treatment options. Yet another deterrent in devising a uniform treatment strategy for PCNSV from above referenced cohort studies is the lack of uniformity regarding definition of variables including description of large, medium (LMVV)/small vessel vasculitis (SVV) or prolonged remission. There is also disparity in the prevalence of histological subtypes on biopsy and of LMVV/SVV in the study population[3,7–11] thereby limiting generalizability of the study results. In addition, some of these cohorts were described before 2007 when reversible cerebral vasoconstriction syndrome (RCVS) was not defined in the literature and hence some of the subjects in the older cohorts diagnosed as PCNSV could have been RCVS in reality. Smaller cohort studies from the Indian subcontinent have added valuable information regarding PCNSV management from a different geographic and ethnic background but have the same shortcomings as mentioned above.[15,16] Another important limitation is the discrepancy in PCNSV diagnosis used in different cohorts. While definitive cases were diagnosed by pathologic findings of vascular brain inflammation, probable cases were diagnosed indirectly by abnormal cerebrovascular abnormalities on angiogram, with or without an inflammatory cerebrospinal fluid (CSF). Hence a subset of cases of probable PCNSV, with negative biopsy (or unavailable brain biopsy) and corroborative angiogram abnormalities, but with normal CSF could still potentially represent mimics like RCVS. These shortcomings were mitigated on subsequent studies by encompassing PCNSV subjects diagnosed by brain biopsy[12,13,17] or corroborative cerebral angiogram findings with inflammatory CSF,[12,13] thereby significantly reducing the chances for inclusion of PCNSV mimics. On account of the above-mentioned nuances in devising a uniform treatment strategy in PCNSV, the European Stroke Organization (ESO), published a consensus statement in 2023 outlining the guidelines on management of PCNSV.[18]

Historically, PCNSV has been managed by a broad group of physicians (neurologists, rheumatologists and internal medicine), which contribute to the diversity in treatment regimens and protocols followed worldwide.[8,11,12,14–16] The treatment protocol commonly followed is extrapolated from recommendations laid down by cohort studies of PCNSV[8,11,12,14] as well as guidelines established for management of primary systemic vasculitis from rheumatologists.[19] The basic goal of management in PCNSV as in any other inflammatory disorder is to arrest ongoing inflammatory disease activity thereby inducing remission, long term suppression of disease activity to provide prolonged remission, avoid disease flares or relapses, with the ultimate goal of achieving overall favorable outcomes and reduced mortality. Immunomodulatory or immunosuppressive medications remain the mainstay in the management of PCNSV. Given the disease severity, PCNSV is believed to require potent immunosuppressive medications for a longer duration of time thereby significantly increasing the risks of developing medication related side effects, which in turn adversely affects the overall functional outcomes. Information regarding safety and efficacy of newer immunomodulators in management of PCNSV are also forthcoming in the last few years,[20–23] thereby increasing chances of long term favorable functional outcomes with better tolerability profile while keeping in mind the anecdotal observations of such therapeutic regimen. Being a debilitating disease with long time delay from symptom onset to diagnosis, it is prudent to institute appropriate treatment at the earliest in order to increase the chances of achieving long term favorable outcomes and minimizing tissue damage. In the study from the All India Institute of Medical Sciences (AIIMS), India, delay in diagnosis was the strongest predictor for worse functional outcomes at follow up[15] and in the Chinese study, a prolonged biopsy time window was an independent predictor for recurrent events.[17] In the following sections, we will elaborate on the treatment approaches in PCNSV for achieving remission and prolonged suppression of disease activity.

Definition of Variables

Mode of Diagnosis of PCNSV

A definite diagnosis of PCNSV was made in all cohorts by demonstration of transmural vascular inflammation involving the leptomeningeal or parenchymal vessels on corticomeningeal biopsy[3,7–17] once they satisfy the Calabrese and Mallek criteria.[24] On the other hand, in those with negative biopsy, a diagnosis of probable PCNSV was made in Mayo

Clinic,[3,7,8] French,[9–11] German[14] and Indian cohorts[15,16] on the basis of angiographic changes of smooth wall segmental narrowing or dilatation ("beaded appearance") and/or abrupt occlusion affecting multiple cerebral vessels without any proximal changes suggestive of atherosclerosis or alternative causes, with or without concomitant inflammatory CSF (more than five mononuclear cells ± protein level of more than 45 mg/dl) after reliable exclusion of alternative etiologies.[24] On the contrary the Cleveland Clinic study[12,13] mandated the presence of inflammatory CSF in those diagnosed by angiographic findings, thereby significantly reducing the chances of contamination of cohort with alternative etiologies like RCVS.

Remission

In the French cohort, remission was defined as absence of disease activity attributable to PCNSV (no new clinical symptoms or worsening of existing symptoms) after at least three months of induction therapy,[9–11] whereas in the German cohort the lack of relapse from six months of initiation of first line therapy constituted remission.[14]

Relapse

In the Mayo Clinic cohort, relapse was defined as worsening of symptoms, recurrence/progression of existing or new lesions on serial magnetic resonance imaging (MRI) while being on no medications or a stable dose.[3,7,8] In the French cohort, a new neurological event in conjunction with a new significant radiological abnormality constituted a relapse.[9–11] In the German cohort, in addition to the above-mentioned clinical worsening, a clinically silent new neuroimaging finding (either infarct, contrast enhanced lesions, progression of intracranial stenoses) also constituted a relapse.[14] Relapse warranted intensification of therapy in all the cohorts.

Long Term Remission/Prolonged Remission

In the Mayo Clinic cohort, long term remission/prolonged remission was defined as a lack of active disease manifestations of PCNSV after at least one year of treatment discontinuation.[3,7,8] The same was defined as a lack of disease relapse for a year or more from diagnosis in the French cohort.[9–11]

Good Outcome

A modified Rankin Scale (mRS) score of 2 or less at last follow up was defined a good functional outcome in the French,[9–11] German[14] and AIIMS, India cohort.[15] An mRS score of 4–6 was defined as severe disability in the Mayo Clinic cohort.[3,7,8] In Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), India cohort an mRS of 3 or more was defined as a poor outcome.[16] In the Cleveland Clinic study disability, quality of life and depression was assessed by the Barthel Index (BI), European Quality of Life Questionnaire (EuroQol) and Brief Patient Health Questionnaire (BPHQ-9) respectively.[12,13]

Baseline Characteristics of the Major Cohorts

Due to heterogeneity of the study population, mode of diagnosis, histopathological subtypes of PCNSV and study definitions used, baseline demographics of patients from these cohorts are detailed in Table 1. An in-depth review of these cohort studies suggests that PCNSV comprises of two distinct subtypes - SVV where the pathologic finding of vasculitis is the most sensitive diagnostic modality compared to LMVV where the diagnosis is mainly based on cerebrovascular imaging and lesser likelihood of pathologic finding of vasculitis. Hence, discrepancies in the observations derived out of these cohort studies might potentially be from differential distribution of the subtypes of PCNSV as well as from histopathological subtypes [granulomatous with or without amyloid beta related angiitis (AβRA) ; necrotizing and lymphocytic]. In the Mayo Clinic cohort,[3,6,7] diagnosis of PCNSV with biopsy was made in 37% of the total study population, with granulomatous pattern being the predominant subtype (62%). Abnormal CSF was noted in about 63% whereas in the French cohort[11] only 29% were diagnosed by biopsy, with abnormal CSF noted in 65% of the study cohorts. The highest proportion of biopsy proven definitive PCNSV was seen in the Cleveland Clinic study[12] (72%) followed by AIIMS[15] (61%), German[14] (57%) and SCTIMST[16] (42%) cohorts. Cleveland Clinic cohort[12] had inflammatory CSF in all those PCNSV subjects diagnosed by angiogram. In the Mayo Clinic cohort with angiogram

Table 1 Comparison Between Demographic Variables of the Six Largest PCNSV Cohorts

Parameter	Mayo Clinic Cohort[3,7,8]	French Cohort[9–11]	AIIMS Cohort[15]	Cleveland Clinic Cohort[12,13]	SCTIMST Cohort[16]	German Cohort[14]
Cohort size	191	112	82	78	45	44
Males (%)	89 (46.6)	60 (54)	68 (83)	40 (51)	31 (69)	18 (40.9)
Median age in years(range)	49 (17–85)	47 (18–81)	28.6 (22.9–38.2)	52.5 (36.2–68.8)	36 (19–70)	43.5 (14–83)
Commonest symptom (%)	Headache (58.1)	Motor deficit (74)	Seizures (70.7)	Headache (68.4)	Ischemic stroke (33)	Neurological deficits (81.8)
Abnormal CSF (%)	120 (62.8)	73 (65)	42 (51)	58 (74.4)	25 (55.5)	36 (81.8)
Abnormal catheter/MR angiogram (%)	129 (67.5)	74 (66)	45 (54.8)	33 (42.3)	30 (66.6)	21 (47.7)
Abnormal biopsy (%)	71 (37.1)	33 (29.4)	50 (60.9)	56 (71.8)	19 (42.2)	25 (56.8)
Biopsy subtypes (%)						
Granulomatous	44 (62)	NR	22 (44)	2 (8)	3 (16)	8 (32)
Lymphocytic	17 (24)	NR	27 (54)	15 (60)	11 (58)	8 (32)
Necrotizing	10 (14)	NR	1 (2)	5 (20)	5 (26)	2 (8)
Median follow up in months (range)	19 (0–337.2)	53 (0–198)	NR	60 (0–204)	33.1 (0.7–356)	61.2 (NR)

Notes: The percentages depicted are in reference to the total cohort population and not specifically pertaining to the subsets within the cohort. Data from references.[3,7–16]

based diagnosis, 74% had abnormal CSF (defined as protein > 45 mg /dl and white blood count of > 5 cells/mm3), which reduced to 53% when considering CSF protein >70 mg/dl or white blood cell (WBC) count >10 cells/mm^3.[8] Lymphocytic vasculitis was the most common subtype in Cleveland Clinic,[12] AIIMS[15] and SCTIMST[16] cohorts whereas it was co-dominant with granulomatous subtype in the German cohort,[14] and granulomatous predominance in the Mayo Clinic cohort.

Remission Induction (Initial Phase Treatment)

The primary aim of initial phase treatment is to induce remission with the institution of immunosuppressive medications. The two most commonly used agents across all PCNSV cohort studies were glucocorticoids (GC) and cyclophosphamide (CYC).[8,11–17] This usage was extrapolated from the European League against Rheumatism (EULAR) recommendations for management of primary medium and small vessel vasculitis.[19] In the Mayo Clinic cohort, 184 of 191 (96%) received GC, with 86 (45%) receiving intravenous pulses of methylprednisolone (MP) (average of 1000 mg/pulse; median of 5 with range from 3–42) prior to oral prednisolone (PDN) therapy (median dose of 60 mg/day with range from 16–240 mg/day).[8] In the French cohort, 110 of 112 (98%) received GC, with 68 (61%) receiving intravenous MP pulses prior to oral PDN (median dose of 0.95 mg/kg/day with range from 0.42–1.17 mg/kg/day).[11] The median duration of treatment with oral PDN therapy was 10 months (range – 0.4–259 months) in the Mayo Clinic cohort[8] as against 24 months (range – 3–198 months) in the French cohort.[11] All the subjects in the Cleveland Clinic study[12] and AIIMS cohort,[15] as well as 68% of the German cohort received GC, even though information about dose, route and duration are lacking. In the SCTIMST India cohort, all 45 subjects received GC (PDN 1 mg/kg/day) for a median duration of 6 months (range: 2–36 months).[16]

In the Mayo Clinic cohort, 112 subjects (59%) received an additional immunosuppressive medication along with PDN in the initial phase – cyclophosphamide (CYC) in 90 (47%), mycophenolate mofetil (MMF) in 13 (7%), azathioprine (AZA) in six (3%), with infliximab, rituximab (RTX), and intravenous immunoglobulin administered for a single patient each.[8] In the French cohort, 92 (82%) patients also received an immunosuppressive medication other than PDN, which

included CYC in 89 (79%) and RTX in three (3%).[11] In the German cohort, first line immunotherapy within three months of PCNSV diagnosis comprised of CYC in 33 (75%), RTX in three (6.8%), methotrexate (MTX) in two (4.5%) and azathioprine (AZA) in one (2.2%),[14] whereas in the Cleveland Clinic study, 11 (44%) received GC with CYC (six receiving intravenous and five orally) with one patient treated with GC and mycophenolate mofetil (MMF).[12]

In the French cohort, CYC was given as intravenous pulses in 86 (77%) patients with median dose of 700 mg/m^2/pulse (range: 450–750 mg/m^2), with median of six pulses (range: 2–12) for a median duration of 6 (range: 2–10) months and the remaining three receiving the medication orally.[8] On the other hand, in the Mayo Clinic cohort, 62 patients (32%) received oral CYC (median dose of 150 mg/day with range of 75–200 mg/day) with median duration of 7 months (range of 1–91 months), as against 32 patients (17%) who received a monthly CYC pulse (median dose of 1000 mg/pulse with range: 500–1700 mg) for a median duration of 4 months (range of 1–42 months).[8] The median duration of treatment in PDN with CYC subgroup in the Mayo Clinic cohort was 16.3 months (range: 0.8–211 months).[8] CYC was the most commonly used second immunosuppressive agent in the AIIMS, India cohort (40/82 – 49%)[15] as well as the SCTIMST, India cohort (11/45 – 24%) during the induction phase (Table 2).[16]

Table 2 Comparison Between Treatment Regimens Used, Response to Initial Phase Treatment, Relapse Rates, Prolonged Remission and Parameters at Last Follow Up in the Six PCNSV Cohorts

Parameter	Mayo Clinic Cohort[3,7,8]	French Cohort[9–11]	AIIMS Cohort[15]	SCTIMST Cohort[16]	German Cohort[14]	Cleveland Clinic[12,13]
Treatment regimen						
Glucocorticoids alone (%)	70 (37.6)	15 (13)	5 (6.2)	31 (69)	0	13 (52)
Median dose/day (range)	60 mg (16–240)	0.95 (0.4–1.1) mg/kg/day	NR	1 mg/kg/day	NR	NR
Median duration in months (range)	10 (0.4–159)	24 (3–198)	NR	6 (2–36)	NR	NR
GC with additional immunosuppressive during induction phase/maintenance phase	112 (60)	Induction phase - 92 (82) Maintenance phase – 52 (46)	77 (94)	31 (69)	Induction phase – 39 (88) Maintenance phase – 36 (81)	12 (44)
Cyclophosphamide	90 (47)	89 (79)	40 (48.8)	11 (24)	33 (75)	11 (40.7)
Azathioprine	6 (3.1)	41 (36.6)	24 (29.3)	3 (7)	6 (13.6)	0
Mycophenolate Mofetil	13 (6.8)	4 (3.5)	3 (3.6)	0	10 (22.7)	1 (3.7)
Median duration in months (range)	29.8 (5.8–211)	24 (6–72)	NR	6 (2–36)	17.9 (6–30)	NR
Baseline median mRS	NR	4	NR	NR	2	NR
Response to initial phase treatment (%)	148 (84)	106 (95)	NR	NR	30 (68)	NR
Relapse (%)	58 (30)	36 (34)	10 (21.7)	25 (56)	26 (59)	NR
Prolonged remission	41 (21.5)	70 (63)	NR	NR	NR	NR
Parameters at last follow up						
Median mRS	NR	2	2	2	NR	1
Cessation of immunosuppressive medication (%)	64 (35)	GC – 85 (76)	19 (24.3)	NR	NR	NR
Good functional outcomes (%)	mRS (0–3) 37 (66)	mRS (0–2) 63 (56)	mRS (0–2) 30 (65.2)	mRS (0–2) 33 (73)	mRS (0–2) 29 (66)	BI (85 or more) – 19 (70)
Mortality (%)	54 (28)	9 (8)	4 (8.7)	7 (16)	4 (9)	3 (11)

Note: Data from references.[3,7–16]
Abbreviations: mRS, modified Rankin Scale score; BI, Barthel Index; NR, not recorded.

A favorable response to initial therapy was achieved in 83% (58/70) in the PDN monotherapy group and 81% (69/85) in the PDN+CYC subgroup respectively in the Mayo Clinic cohort,[8] with no significant effect of route of administration of GC or CYC on the treatment response. However, it should be emphasized that the baseline disease severity of those receiving oral versus IV CYC were not reported in the study and hence it is unclear whether the comparable response in the two subgroups is accounted for by the different disease severity to begin with.[8] In the French cohort, 95% (106/112) achieved remission with 14/15 (93%) responding in the PDN only group and 89% (40/45) in the PDN with second immunosuppressive subgroup (CYC or RTX).[11] Although the above results might suggest that PDN only and PDN+CYC subgroups produce comparable rates of remission or initial responsiveness, the Mayo Clinic cohort clearly demonstrated that the PDN+CYC subgroup were likelier to have a more severe disease (mRS of 4/5) at baseline compared to the PDN subgroup (43% versus 24%; p – 0.009), and received a longer duration of treatment (median of 16.3 months versus 10 months in the PDN group), thereby indicating a more aggressive disease sub-type in the PDN+CYC subgroup.[8] Angiographically diagnosed PCNSV (LMVV) with cerebral infarcts on neuroimaging studies and persistent focal neurological deficits representing the more aggressive subset, were likelier to receive treatment with PDN+CYC in the above cohort,[3,7,8] indicating its efficacy to achieve remission when compared to the PDN only subset encompassing less severe cases. It is important to note that only 74.4% of the angiographically diagnosed PCNSV in this cohort had an abnormal CSF (defined as either protein >45 mg/dl or WBC count >5 cells/mm^3) which raises the question on the exact etiology of these cerebral vasculopathies.[8] It is very well known that the specificity of cerebral angiogram in the diagnosis of PCNSV is poor[4–6] and the lack of inflammatory CSF process greatly compromises a reliable diagnosis of PCNSV in the lack of pathologic findings of vasculitis, thereby warranting careful interpretation of the data. In the French cohort[11] and AIIMS, India cohort,[15] the PDN only subgroup constituted a minority (12.5% and 6.2% respectively) thereby limiting the generalizability of the treatment response effect obtained in this subgroup (Table 2).

In the Mayo Clinic cohort, the authors reported that route of administration [IV versus oral] for GC and CYC did not affect the treatment outcomes, disability scores or mortality, and recommended IV CYC over the oral route on account of shorter median duration of treatment (4 months in IV versus 7 months in oral) accounting for lesser cumulative dosage related toxicity.[8] However, in the oral versus IV CYC use, response to therapy was in 85% vs 73%, relapse rate was 24% vs 34%, therapy suspension in 34% vs 25%, long term remission 27% vs 19%, mRS4-5 35% vs 41% and death 24% vs 19% respectively. Further, in the sub-analysis of the CYC route, there was no information on initial disability scores and pathologic findings among patients treated with IV versus oral CYC. Hence it is not known whether the observed similar outcomes among patients treated with IV versus oral CYC is related to differences in the severity of these two groups that buffered the outcomes.[8] In the SCTIMST India cohort, PDN+CYC subgroup was associated with lesser chances of relapse (27% versus 55.6%) but at higher risks of medication toxicity (54% versus 31%).[16] Hence, even though the commonest practice was to institute GC with a second immunosuppressive medication for induction of remission, more impetus was directed to find a safer option to CYC. Monitoring patients receiving CYC varies from one center to another which can alter the rate of development of adverse events and it is unclear as to how patients treated with CYC were monitored over time in various centers. An interesting alternative prospect studied in the Mayo Clinic cohort was MMF (dose of 2000 mg/day), started as initial treatment in 13 patients (7%) along with PDN.[8] The PDN with MMF subgroup had better remission rates (100% versus 81%; p – 0.0001), higher chances of treatment discontinuation (62% versus 32%; p – 0.06) and better functional outcomes with lesser chances of severe disability (mRS of 4–6) at last follow up (8% versus 37%; p – 0.05) as against the PDN+CYC subgroup. The relapse rates were comparable as well.[8] The proportion of subjects with severe disability at baseline (mRS 4–5) were also equivalent in PDN+MMF and PDN+CYC subgroups (46% versus 43% respectively).[8] However, it is important to note that an earlier report from the Mayo Clinic cohort patients treated with MMF had less severe disease at initial presentation (81% had mRS < 3) compared to patients treated with other agents.[22] Furthermore pathologic patterns of patients treated with MMF were not reported as well. A prospective open label study from India recruited 26 PCNSV patients, treated with GC+MMF (dose of 2000 mg/day) with MMF continued for a median of 24 months (range: 14–34 months).[23] Initial response (remission) was noted in 25/26 (96%), with a proportion of patients with severe disability (mRS 4–5) reducing from 73% at baseline to 7.69% at last follow up (p < 0.001), with excellent functional outcomes at last follow up (24 months) noted in 69.2% (18/26) and prolonged remission in 23/26 (88%) of subjects with steroid sparing effect.[23] However, the absence of any control group

in this study along with the paucity of histopathological confirmation of this cohort (only five patients had positive brain biopsy) poses a difficulty in assessment of the precise effect of MMF. These findings reinforce the potential utility of MMF as an effective immunosuppressive agent in both the induction and maintenance phase of PCNSV treatment,[8,22,23] but needs to be tested in larger cohorts globally and better stratified on the basis of histopathologic subtypes and disease severity.

Yet another novel immunomodulator which has been reported in a limited number of PCNSV patients either refractory or intolerant to other regimen, is the anti-CD20 monoclonal antibody rituximab (RTX).[20,21] The dosage regimens utilized for remission induction are either two doses of 1000 mg weekly two weeks apart or weekly intravenous injections of 375 mg/m^2/week for four weeks. Subsequent doses are planned on the basis of monitoring of CD19/CD20 cells, usually every 6 months, which constitutes the maintenance phase. Given the anecdotal and limited data of RTX in PCNSV, RTX is not considered the first choice in the treatment of PCNSV. Other less commonly used options include anti-Tumor Necrosis Factor (TNF) α agents like infliximab, etanercept, intravenous immunoglobulin as well as plasmapheresis, but evidence bases for these treatments are limited.

Maintenance Therapy

Once remission is induced with initial phase treatment, the next goal is to maintain prolonged remission and avoid disease flares or relapses which are reported in about 34% of patients with a range from 21% to 59% in various PCNSV cohorts.[8,11,14–16] The German cohort had the highest relapse rate of 59%, which is probably attributed to the more stringent definition of relapse utilized, encompassing clinical as well as clinically silent neuroimaging worsening[14] unlike other cohorts which gave primary importance to clinical worsening with or without imaging abnormalities.[8,11,15,16] This phase of treatment is referred to as maintenance therapy which uses immunosuppressive medications with better tolerability profiles, lesser cumulative toxicity and steroid sparing potential. Robust evidence for utility of maintenance phase treatment in PCNSV was garnered from findings observed in the French cohort study.[11] After achieving remission, 52/106 (46%) PCNSV subjects received maintenance immunosuppressive therapy while still being on GC treatment in 45 of them (42%). This included AZA in dose of 2 mg/kg/day (41/52 – 78%), MTX in dose of 0.3–0.5 mg/kg/week (7/52 – 13%) and MMF in dose of 2000 mg/day (4/52 – 7%). Maintenance therapy was started after a median of 4 (range: 3–18) months from initiation of GC and continued for a median of 24 (range: 6–72) months. Relapses were noted in 34% (36/106) with least rates in those on maintenance therapy 20% (9/45; p – 0.01). On multivariate analysis, use of maintenance therapy was predictive of prolonged remission (OR – 4.32; 95% CI 1.67–12.19; p – 0.002) and higher chances of good functional status (mRS of 2 or less) at last follow up (OR – 8.09; 95% CI 3.24–22.38; p < 0.002).[11] The relevance of this finding is strengthened by the fact that median baseline mRS scores of those with and without maintenance therapy in the French cohort was 4, indicating similar disease severity in both the groups to begin with.

In the Mayo Clinic cohort of 191 PCNSV patients, 35/185 (19%) received maintenance therapy after a response to the initial phase treatment, started at a median of 6 (range: 3–91) months from initiation of induction regimen.[8] Similar to the French cohort, AZA (19/35 – 54%; dose of 100–200 mg/day), MMF (8/35 – 23%; dose of 2–3 gm/day) and MTX (5/35 – 14%; dose of 7.5–20 mg/week) were the regimens used for maintenance, continued for a median duration of 17 (range: 4–141) months.[8] Those with maintenance therapy were less likely to have high disability scores (mRS of 4–6) (11% versus 37%; p – 0.003) and death (6% versus 27%; p value – 0.006) at last follow up. However, no significant differences were noted with respect to chances of prolonged remission or response to therapy between those with and without maintenance therapy. On the contrary, relapses were more common in those receiving maintenance therapy in the Mayo Clinic cohort (46% versus 19%; p – 0.003), with overall relapse rates of 30% (58/191), which is contradictory to the observation in the French study.[8]

After induction therapy almost 94% of the German cohort received maintenance therapy, with MTX in 11 (33%), MMF in 10 (30%), and AZA and RTX in five (15%) each.[14] The relapse rate was 59% with male sex associated with increased relapse rate on multivariate logistic regression analysis (HR – 3.27; 95% CI 1.57–6.82).[14] Yet another interesting phenomenon noted in the German cohort was the presence of late relapses even beyond 30 months of initial diagnosis. However, all those who had relapses at later stages invariably had relapses beforehand, or in other words those who had no relapses within the first 30 months of disease diagnosis stayed relapse free even after that.[14] Despite

heterogeneity of maintenance therapy results in the Mayo Clinic, German and French cohorts, these studies have substantiated the utility of maintenance therapy in PCNSV beyond doubt (Table 2).[3,7–11,14]

Predictors of Relapses, Prolonged Remission, Functional Outcomes and Mortality

Table 3 details predictors of treatment non-responsiveness, relapse, long term remission, functional outcomes at last follow up and mortality from individual PCNSV cohort studies, a few of which reveal contradictory results, thereby

Table 3 Predictors of Treatment Non-Responsiveness, Relapse, Long Term Remission, Functional Outcomes at Last Follow Up and Mortality from Individual PCNSV Cohort Studies

Parameters	Odd's Ratio (OR)	95% Confidence Interval	P value
Non-responsiveness to treatment			
Cerebral infarcts in MRI[8]	3.92	1.49–10.31	0.005
Large vessel involvement on cerebral angiogram[8]	2.80	1.04–7.52	0.041
Relapse			
Male sex[14]	3.27	1.57–6.82	<0.05
Symptomatic epilepsy[17]	4.69	1.51–14.54	0.007
Prolonged biopsy time[17]	1.11	1.00–1.22	0.043
CD20 expression in brain biopsy[17]	5.33	1.07–26.61	0.041
Prolonged remission (Long term remission)			
Aspirin use[8]	2.59	1.21–5.52	0.013
Gadolinium enhanced MRI lesions[8](intracranial or meningeal)	0.20	0.05–0.81	0.023
Maintenance therapy[11]	4.32	1.67–12.19	0.002
Gadolinium enhanced MRI lesions[11](intracranial or meningeal)	0.20	0.07–0.51	0.0007
Good functional status at last follow up (mRS of 2 or less)			
Headaches at baseline[11]	3.46	1.41–9.12	0.006
Maintenance therapy[11]	8.09	3.24–22.38	<0.0001
Vigilance impairment[11]	0.32	0.12–0.85	0.02
Worse functional outcomes at last follow up			
Age (per 10-year difference)[8]	1.48	1.19–1.84	0.0004
Cerebral infarcts in MRI[8]	2.09	1.06–4.10	0.032
Spinal cord involvement[15]	0.04	0.004–0.392	0.006
Delay in diagnosis[15]	0.31	1.15–10.92	0.031
Mortality			
Cognitive dysfunction[8]	3.56	1.34–9.46	0.010
Cerebral infarcts in MRI[8]	1.99	1.03–3.82	0.039
Age (per 10-year difference)[8]	1.46	1.17–1.83	0.001

Notes: Data from references.[8,11,14,15,17]

limiting its generalizability. Historically, cases of PCNSV diagnosed by imaging (LMVV) were considered to represent a more aggressive spectrum of the disease with higher chances of harboring cerebral infarcts on neuroimaging studies and persistent focal neurological deficits on baseline assessment. Observations from the Mayo Clinic cohort also consolidated the fact that those with large vessel involvement on angiogram (OR 3.92; 95% CI 1.49–10.31; p – 0.005) and cerebral infarcts on MRI (OR 2.80; 95% CI 1.04–7.52; p – 0.04) were likelier to have non-responsiveness to therapy.[8] However, this was disproved in the Cleveland Clinic cohort of 34 patients (LMVV of 11 and SVV of 23) with stringent inclusion criteria of LMVV diagnosed on the basis of imaging abnormalities on vessel wall magnetic resonance (MR) imaging and/or digital subtraction angiography (DSA) with inflammatory CSF and SVV by positive brain biopsy.[13] The latter study categorically found that there were no statistically significant differences in the relapse rates, median scores of mRS, BI, PHQ-9 as well as Euro-QOL subscales between LMVV and SVV subsets.[13]

Relapse

Relapse rates ranged from 21.7% in the AIIMS study[15] to 59% in the German cohort.[14] As mentioned previously the broad range noted in different cohorts is probably accounted for by the heterogeneity of the study population, especially with respect to the mode of diagnosis, histopathological subtypes as well as disparity in the definition of relapse utilized.[8,11,12,14–16] The main reason for highest relapse rates seen in the German cohort is accounted for by the fact that they included both clinical and clinically asymptomatic neuroimaging worsening as a relapse, unlike other cohorts.[14] The latter study also showed that about 41% of relapses occurred beyond 30 months of initiation of first line therapy.[14] On account of the heterogeneity of the PCNSV cohorts, predictors of relapse could not be generalized, accounting for conflicting results obtained in some cohorts.[8,11,12,14–16] The presence of gadolinium enhanced lesions (either meningeal or intraparenchymal) on MRI predicted relapses with lesser chances of prolonged remission on multivariate analysis in the French cohort,[11] whereas male gender was the sole predictor in the German cohort.[14] Previous studies have demonstrated that gadolinium enhanced lesions on MRI in the meninges or parenchyma were more common in the SVV sub-group.[3,7,9,10] Hence on extrapolation of results obtained from the Mayo Clinic, French and SCTIMST cohorts, it might seem that the presence of gadolinium enhanced lesions in MRI and normal angiogram at baseline, both being more common in the SVV subtype could correlate with increased relapses and lesser chances of prolonged remission (Table 3).[8,11,16] However, this notion was disproved by the Cleveland Clinic and German cohorts.[12–14] In the Cleveland Clinic study, which had a robust diagnostic criterion for LMVV and SVV, out of the 12 relapses in the study population (32%), seven occurred in the LMVV (58%) and five (21.7%) in the SVV subtypes, with no statistical significance (p – 0.059).[12,13] Yet another observation from a Chinese study carried out on 76 biopsy proven case reports of PCNSV in literature from 2000 to 2023 is that among relapses seen in 41 (53.9%) subjects, symptomatic epilepsy (p – 0.007), prolonged biopsy time window (p – 0.043) and presence of CD-20 expression in the pathological tissue (p – 0.041) were considered to be risk factors for recurrence.[17] The predictors of relapse noted in individual cohorts need re-assessment with future studies incorporating more uniform treatment regimen and standardized relapse definition.

Remission

The different study definitions used for prolonged/long term remission in the Mayo Clinic[8] and French cohort[11] was primarily thought to be responsible for the variability of prolonged/long term remission rates in the two studies (21.5% versus 66% respectively). Aspirin use (OR 2.59; 95% CI 1.21–5.52; p – 0.013) and use of maintenance therapy (OR – 4.32; 95% CI 1.67–12.19; p – 0.002) significantly increased the chances of prolonged remission in the Mayo Clinic[8] and French cohorts[11] respectively, whereas presence of gadolinium enhanced lesions (either meningeal or intraparenchymal) on MRI reduced chances of prolonged remission as explained before (Table 3).[8,11] Another interesting observation from the Mayo Clinic cohort was that those in long term remission had longer median duration of CYC treatment as against those who are not (11 months versus 5 months; p – 0.002).[8] However, no such conclusions could be derived from the Cleveland Clinic[12,13] and German cohort study.[14] Hence, these observations from individual cohort studies could not be generalized on account of the limitations highlighted in the previous sections.

Functional Outcome

In the majority of PCNSV cohort studies, a good functional outcome at last follow up was defined as an mRS score of 2 or less and worse functional outcomes as 4–6.[3,7–16] In the Mayo Clinic cohort, high disability scores (mRS 4–6) at last follow up were significantly associated on univariate logistic regression analysis with advancing age (per 10-year difference) (p – 0.0004) and presence of cerebral infarcts on MRI (p – 0.032).[8] In the French cohort good functional outcomes at last follow up were noted in 56% (63/112) of cases, with presence of headaches at baseline (p – 0.006), maintenance therapy (p <0.0001) and vigilance impairment predictive of poor functional status (p – 0.02) on multivariate analysis.[11] In the AIIMS, India cohort, 65.2% (30/46) had achieved good functional outcomes at last follow up, with delay in diagnosis (p – 0.031) and spinal cord involvement by disease (p – 0.006) strongly predicting worse functional outcomes (Table 3).[15] Good functional outcomes were noted in 33/45 (73%) of the SCTIMST, India cohort at 6 months after treatment initiation, with baseline cognitive dysfunction (p – 0.014), National Institute of Health stroke scale (NIHSS) of 5 or more at admission (p - <0.0005) and abnormal electroencephalogram (EEG) (p – 0.046) associated with poor functional outcomes.[16] Interestingly the only study which focussed specifically on long-term functional capabilities, quality of life and depression in the PCNSV cohort was the one from Cleveland Clinic.[12] 27 of the 78 patients in the cohort (34.6%) were included in the study and followed up for a mean duration of 5.5 years. Almost 71% of patients had BI scale of 85 or more indicating mild disability, 52% had no mobility issues on the European Quality of Life Questionnaire (EQ-5D-5L) with approximately 70% having minimal or no depression on EuroQol and the Brief Patient Health Questionnaire (BPHQ-9) at last follow up.[12] Most noteworthy was that this study on PCNSV patients was diagnosed by stringent criteria, requiring that all patients were diagnosed with angiography to have an abnormal CSF, thereby reducing the chances of mimics, indicated that none of the clinical, neuroimaging or treatment variables were associated with any of the functional outcomes in a statistically significant manner.[12,13] Nevertheless, it was noted from this study that those with strokes were likelier to have depression/anxiety on EuroQol assessment.[12] A similar observation was made in the German cohort, with 65% of patients having good functional outcomes (mRS of 2 or less) at 6 years of follow up and no specific variables predicting functional outcomes.[14] Hence, as mentioned before in the discussion, conflicting results from individual PCNSV cohorts could not be generalized and need to studied in a more uniform patient population with standardized diagnostic and management protocol.

Mortality

The mortality rates ranged from 8% to 28% in the various PCNSV cohorts.[8,11,12,14–16] The predictors of mortality in the Mayo Clinic cohort included increasing age (per 10-year difference), baseline cognitive dysfunction and cerebral infarcts in MRI (Table 3).[8] However, the Mayo Clinic cohort provided robust information regarding the correlation of histopathological subtype and outcomes in PCNSV. Among those with progressive disease culminating in poor functional outcomes (mRS 4.5 or death), a granulomatous and/or necrotizing pattern with or without amyloid beta-related angiitis (ABRA) were the exclusive pathological subtypes, with none having lymphocytic vasculitis.[8] The wide variation in mortality rates among PCNSV cohorts was primarily attributed to heterogeneity of the study population with respect to histopathological subtypes noted on biopsy. The predominant histopathological subtype in the Mayo Clinic cohort was granulomatous (62%), followed by lymphocytic (24%) and necrotizing subtypes (14%).[8] On the contrary, the commonest subtype in the Cleveland Clinic,[12] AIIMS[15] and SCTIMST[16] cohorts was lymphocytic vasculitis (60%, 54% and 58% respectively). In the German cohort, granulomatous and lymphocytic vasculitis were co-dominant (32%).[14] Data on differential distribution of histopathological subtypes in the French cohort study is inadequate, with information available for the initial 52 subjects published in 2014, documenting lymphocytic infiltrates in 79% (15/19) of brain biopsy specimens.[9] The Mayo Clinic cohort provided valuable information regarding the lower frequency of worse functional outcomes (mRS 4–6) and mortality at last follow up in those with lymphocytic vasculitis as against granulomatous/necrotizing subtypes (0 versus 39%; p – 0.002 and 0 versus 30%; p – 0.008 respectively).[8] At the same time, long term remission was likelier in those with granulomatous or necrotizing subtypes as against lymphocytic vasculitis (20% versus 0; p – 0.050).[8] In other words, even though the lymphocytic

vasculitis subtype was postulated to have lesser chances of prolonged remission, they have significantly lower chances of poor functional outcomes and mortality at last follow up when compared to granulomatous/necrotizing subtypes, thereby accounting for a better prognostic variant of PCNSV.

An important observation despite the similar mode of diagnosis in the French and Mayo Clinic cohorts is that mortality rate was worse in the latter group (8% versus 28% respectively).[8,11] This could be potentially explained by the higher percentage of granulomatous pattern on brain biopsy in the Mayo Clinic cohort compared to lymphocytic pattern in the French cohort. On the same note, higher disability scores (Rankin score of 4–6) and deaths at last follow-up were twice as frequent in patients with ABRA as against those without (42% versus 23% and 33% versus 17.0% respectively) even though the differences were not statistically significant.[8] These critical observations shed light on the plausible role played by the histopathological subtype on functional outcomes and mortality in PCNSV which needs to be studied on larger cohorts in the future.

Final Remarks

In this review we have tried to present and analyze the available literature on treatment and outcomes of patients with PCNSV, derived from retrospective heterogenous patient cohorts. Some cohorts did not mandatorily require CSF abnormalities in all patients diagnosed on the basis of angiographic findings, thereby raising serious questions about the possibility of other undetermined vasculopathies in these cohorts. Thus, generalization on treatment options derived from these cohort studies should be carefully appraised. The most robust information from the Mayo Clinic cohort[8] which encompassed the largest number of pathologically confirmed cases was the prognostic value of histopathologic pattern on brain biopsies. A granulomatous and necrotizing pathologic pattern carries a worse prognosis than the lymphocytic subtype. In the recent ESO guidelines on PACNS, authors appraise the available evidence in literature for diagnosis and management of PCNSV.[18] The ESO acknowledge that lymphocytic vasculitis seems to be a relatively less severe condition than necrotizing or granulomatous vasculitis, being associated with lower disability and mortality, but at the same time caution against the use of the histological subtype alone to guide treatment decisions given the low quality of evidence derived from the relevant studies. High resolution intracranial vessel wall MR imaging (HRVWI) has played a pivotal role in differentiating intracranial vasculopathies, thereby adding to the diagnostic armamentarium in PCNSV.[25,26] Being a noninvasive imaging tool, future studies should also investigate the therapeutic utility of the latter investigative modality, as it could provide valuable information when performed at periodic intervals pertaining to imaging correlation with clinical relapses, response to treatment as well as functional outcomes, especially in the LMVV sub-category of PCNSV.[25]

On the basis of the above extensive discussion, we would like to propose a treatment approach in PCNSV. After establishing a reliable diagnosis of PCNSV, patients should be started as early as possible with pulse IV MP for 3–5 days followed by GC (oral PDN 1 mg/kg/day) with a slow taper of GC over 6 months. The selection of GC sparing agent should be determined based on 1) the burden of disease, 2) the degree of neurologic deficits on an individual basis, 3) certainty of the diagnosis and 4) the pathologic pattern. CYC should be added during the induction phase in those with granulomatous and necrotizing patterns on pathology. Information about the outcomes of patients treated with IV vs oral CYC is not very robust, as the Mayo Clinic cohort[8] did not stratify patients who received oral vs IV CYC according to initial disease severity or by pathologic patterns. Hence if CYC is indicated, based on pathologic pattern, selection of CYC route will be determined based on the feasibility and logistics of either treatment route in an individual patient. For instance, those receiving oral CYC should have the ability to empty their bladder frequently to reduce bladder toxicity. But in a non-ambulatory patient this may not be feasible and thus IV should be the preferred route. We reserve the use of MMF induction therapy for those with a mild disease having a non-necrotizing/non-granulomatous pattern on pathology, low disease burden, with a probable diagnosis having low diagnostic confidence despite thorough work up and low disease burden as well as when CYC is not a plausible option due to alternative reasons like medical co-morbidities. If remission is not achieved within two months of induction phase or the patient develops a relapse while on the initial phase treatment, revisiting the diagnosis is essential, occasionally necessitating a second brain biopsy. Otherwise, the regimen can be switched to an alternative agent (MMF, RTX or rarely anti-TNF α agents) or a different administration route could be tried. Once remission is achieved with initial phase treatment, a steroid sparing immunomodulator (AZA

or MMF) should be started directly after stopping the induction agents. The duration of maintenance phase treatment is not clear and treatment should be continued for at least a median of 18–24 months with periodic clinical, laboratory and neuroimaging monitoring including HRVWI to ensure long term remission and to minimize side effects from immunosuppressive medications. Individual discussion along with shared medical decisions should be ongoing to educate the patient on the risk of discontinuing maintenance therapy as relapses can occur beyond 24 months after initial therapy. Hence, the authors apply a longer maintenance period than 24 months. MTX is not the preferred maintenance agent as it does not penetrate the blood brain barrier significantly. Treatment regimen should be intensified with alternative immunomodulatory medication along with an increase in the dose of GC in case of the development of disease relapse at any time point. Assessment of disease activity should be ideally based on new or progressive neurologic deficits along with documentation of new or worsening neuroimaging findings as modifying treatment directions based on clinical symptoms alone without neuroimaging correlate might not represent an accurate assessment of disease activity in PCNSV. Impetus should also be on concomitant speech, physical and occupational therapies to the patient population in addition to adequate psychological support for coping with the diagnosis of a debilitating disease. Furthermore, bone health protection in addition to bacterial, fungal and viral prophylaxis is indicated when immunosuppressive therapy is ongoing during the intensive and maintenance phase of PCNSV treatment as appropriate. Those in the LMVV subset of PCNSV, concomitant aspirin therapy may have a beneficial effect on account of a combined antithrombotic and anti-inflammatory mechanism having a synergistic benefit with GC therapy.[18]

Conclusion

PCNSV is a heterogenous, polymorphic disease with kaleidoscopic manifestations. Hence a high index of clinical suspicion with exhaustive diagnostic work up is essential to rule out diagnostic mimics and arrive at a plausible diagnosis. Prompt initiation of treatment with immunosuppressive medications significantly determines overall functional outcomes and survival in this rare disease entity. This treatment approach increases the chances of prolonged remission while achieving good functional outcomes eventually. Novel noninvasive neuroimaging tools like HRVWI lend invaluable additional radiological information in differentiating intracranial vasculopathies thereby enabling the physicians to arrive at an appropriate diagnosis by ruling out PCNSV mimics as well as potentially monitoring radiological responsiveness to immunomodulators in PCNSV when performed at periodic intervals on follow up. However, impetus should be on larger multicentric cohort studies or even randomized controlled trials in the future to explore the utility of safer immunosuppressive regimens in PCNSV and derive a uniform treatment protocol for treatment of this rare disease.

Disclosure

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