This is the peer reviewd version of the followng article:

Adult primary central nervous system vasculitis treatment and course: analysis of one hundred sixty-three patients / Salvarani, C., Brown, R.D., Christianson, T.J.H., Huston, J., Giannini, C., Miller, D.V., Hunder, G.G.. - In: ARTHRITIS & RHEUMATOLOGY. - ISSN 2326-5205. - 67:6(2015), pp. 1637-1645. [10.1002/art.39068]

Terms of use:

The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

29/11/2026 15:08

(Article begins on next page)

Arthritis & Rheumatology
DOI 10.1002/art.39068

Adult primary central nervous system vasculitis treatment and course: Analysis of 163 patients.

Carlo Salvarani, MD†; Robert D. Brown, Jr, MD MPH; Teresa J. H. Christianson; John Huston III, MD; Caterina Giannini, MD; Dylan V. Miller, MD; Gene G. Hunder, MD

From the Department of Neurology (R.D.B.), the Division of Biomedical Statistics and Informatics (T.J.H.C.), the Department of Radiology (J.H.), the Division of Anatomic Pathology (C.G., D.V.M.), and Division of Rheumatology (GGH, Emeritus Member), Mayo Clinic, Rochester, Minnesota.

†Visiting clinician at the Department of Neurology, Mayo Clinic, Rochester, Minnesota, from Unità Operativa di Reumatologia, Azienda Ospedaliera-IRCCS di Reggio Emilia, Reggio Emilia, Italy.

Address reprint requests to the corresponding author: Dr. Carlo Salvarani, Unità Operativa di Reumatologia, Azienda Ospedaliera-IRCCS di Reggio Emilia, V.le Risorgimento N80, 42100 Reggio Emilia, Italy. Phone: 39/0522/296616 ; FAX: 39/0522/295836; e-mail: salvarani.carlo@asmn.re.it

Text word count: 4,080

Running head: Therapy and outcomes in PCNSV

Key words: therapy, relapses, disability, survival, PCNSV, vasculitis

There were no financial support for this work or other financial interests which could create a potential conflict of interest

Accepted Article

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/art.39068
© 2015 American College of Rheumatology
Received: Aug 14, 2014; Revised: Jan 10, 2015; Accepted: Feb 05, 2015

This article is protected by copyright. All rights reserved.

Abstract

Objective. To describe the treatment and outcomes in primary central nervous system vasculitis (PCNSV).

Methods. We retrospectively studied a cohort of 163 consecutive patients with PCNSV seen at the Mayo Clinic over a 29-year period. We analyzed treatments and responses, and factors predictive of outcomes.

Results. 85% of patients treated with prednisone alone responded favorably as did 80% of those given prednisone and cyclophosphamide. Relapses were observed in 27% of patients. 25% had discontinued therapy by last follow-up. Treatment with prednisone alone was associated with more frequent relapses (OR, 2.90), while large vessel involvement (OR, 6.14) and cerebral infarcts at diagnosis (OR, 3.32) were associated with poor response to treatment. Prominent gadolinium-enhanced lesions or meninges (OR, 2.28) were linked with continued treatment at last follow-up. Higher disability scores at last follow-up were associated with increasing age at diagnosis (OR, 1.44), and cerebral infarctions (OR, 3.74), while lower disability scores were associated with gadolinium enhanced cerebral lesions or meninges (OR, 0.35) and cerebral amyloid angiopathy (OR, 0.24). Increased mortality was associated with increasing age at diagnosis (HR 1.39), diagnosis by angiography (HR 3.28), cerebral infarction (HR, 4.44), and large cerebral vessel involvement (HR, 4.98), while reduced mortality with gadolinium enhanced cerebral lesions or meninges (HR, 0.20).

Conclusion. The majority of patients with PCNSV responded to treatment. Recognition of findings at diagnosis which predict course or outcome may aid decisions regarding therapy.

Accepted Article

This article is protected by copyright. All rights reserved.

Accepted Article

Primary CNS vasculitis (PCNSV) is an uncommon disorder of unknown cause that is restricted to the brain and spinal cord (1-3). Early case reports described PCNSV as a fatal condition (1,4,5). However, in 1983, Cupps et al reported a favorable response to cyclophosphamide and glucocorticoids in 4 patients with PCNSV (6). Subsequently, others also reported a more favorable course with similar treatment (7-9). But, because of the lack of uniform diagnostic criteria (2,10) and the relatively small numbers in most series, optimal management and outcome remain uncertain. In addition, few studies have evaluated findings which may predict response to treatment (7,13).

In this study, we reviewed all cases of PCNSV seen at Mayo Clinic (Rochester, MN) from 1983 to 2011. We analyzed the treatments and outcomes and evaluated findings which may serve as guides for therapy.

PATIENTS AND METHODS

Identification of the Patients

We extended our earlier cohort of 101 consecutive patients seen at Mayo Clinic (Rochester,MN) over a 21-year period to 29 years, 1983-2011. The same predefined diagnostic criteria were used (7) to include those examined at the Mayo Clinic from January 1, 2004 through December 31, 2011. During the recent period, 62 additional patients were enrolled. Therefore 163 patients with PCNSV, seen at the Mayo Clinic from 1983 to 2011, were included in this retrospective analysis. The study was approved by the Mayo Clinic Institutional Review Board.

Patients were included if a brain or spinal cord biopsy sample showed vasculitis (transmural destructive inflammatory infiltrate) or if angiograms showed changes highly suggestive of vasculitis (smooth-wall segmental narrowing,

This article is protected by copyright. All rights reserved.

dilatation or occlusion affecting multiple cerebral arteries in the absence of proximal vessel changes consistent with atherosclerosis) (7). Angiograms were also divided into two groups: large/proximal artery (intracranial internal carotid and vertebral arteries, basilar artery, and proximal anterior, middle, and posterior cerebral arteries) and small/distal artery (intracranial artery and second division branches or smaller). We excluded patients with vasculitis in other organs and those with other diseases. None had a history of exposure to vasoactive substances, were in the postpartum state, had migraine headaches, thunderclap headaches, or manifestations typical of reversible cerebral vasoconstriction syndrome (RCVS).

Review of biopsy specimens and angiograms

Biopsy specimens were reviewed by two pathologists (D.V.M. and C.G.), and angiograms by a neuroradiologist. Conventional digital subtraction angiograms were the standard and performed and interpreted by a clinical protocol used by the Division of Neuroradiology.

Clinical Data Collection

In cases with an uncertain initial diagnosis, the entire record was reviewed again by 2 rheumatologists (CS and GGH) and 1 neurologist (RDB) to reach a consensus. Comprehensive information was recorded about all medical conditions (previous, on admission, follow-up), all tests and procedures, treatments and outcomes. All patients had a complete neurologic examination by a neurologist at the time of diagnosis and on subsequent visits.

Definition

Accepted Article

This article is protected by copyright. All rights reserved.

Relapse was defined as a recurrence or worsening of symptoms or progression of existing or new lesions on subsequent MRI examinations while the patient received no medication or a stable dose. A relapse required an increase in therapy.

To assess treatment, we used the treating physician's global opinion about response obtained by a detailed record review.

Degree of disability on admission and last visit was defined by a record review and was categorized using the modified Rankin scale. The Rankin scale consists of seven grades (0-6). 0 indicates no neurologic signs or symptoms, 1 no disability in spite of symptoms, 2 through 5 increasing disability and 6 death (7,11).

Subjects were followed until the death or last follow-up visit.

Statistical analysis

Numeric parameters were compared by using a two-sided two-sample t test or a Wilcoxon rank-sum test when the distributions were skewed. Comparisons of categorical variables were performed using the chi square or Fischer's exact test when cell counts were small.

Logistic regression models were used to identify characteristics at diagnosis that increased the odds of a poor outcome, relapses, treatment response, and inability to discontinue treatment at last follow-up. Univariate and age-adjusted odds ratios (ORs) and 95% confidence intervals were reported. The Cox proportional hazards model was used to assess the relation between demographic, clinical, laboratory, radiological, pathological and therapeutic parameters at diagnosis and survival. We reported univariate and age-adjusted hazard ratios (HRs) and 95% confidence intervals. Results were reported as age-adjusted when age was significantly associated with the outcome. Multivariable modeling, adjusted for age, was performed manually in a forward selection method due to the risk factors under

This article is protected by copyright. All rights reserved.

Accepted Article

consideration having differing missing data patterns for the subjects. Due to the limited number of events, the multivariable model could support no more than two additional risk factors. All p values were two-sided; significance was defined at $p < 0.05$. The statistical analysis was performed using SAS version 9.

In some instances Rankin scores were grouped variously to summarize the results.

RESULTS

Table 1 shows the characteristics of the 163 patients at diagnosis. The median follow-up duration was 12 months (range: 0-13.7 years). Brain or spinal cord tissue was obtained in 81 patients and showed vasculitis in 58 (72%) but was negative in the remaining 23. A granulomatous inflammatory histologic pattern was found in 34 (59%) (accompanied by vascular deposits of β-amyloid peptide in 20, 34%), a granulomatous and necrotizing pattern in 1 (2%), an acute necrotizing pattern in 10 (17%), and a lymphocytic pattern in 13 (22%). Angiograms were performed in 129 patients and were consistent with vasculitis in 113 (88%). Angiograms alone were used to confirm the diagnosis in 105 patients including the 23 biopsy negative cases above, and also showed vasculitis in 8 patients in whom brain biopsy were positive. No differences in clinical manifestations at diagnosis, laboratory investigations, including spinal fluid analysis, and histopathological patterns were observed in the new cohort (2004-2011) and earlier cohort (1983-2003) (Table 1). The new cohort had a higher median age at diagnosis ($p = 0.016$), a higher frequency of GAD enhancing meninges on MRI ($p = 0.006$), a reduced frequency of patients with large vessel changes at angiography ($p = 0.036$), and a higher percent of patients with MRA examinations (61.3% versus 31.7%, $p = 0.0001$), performed within 3 months of diagnosis. Also, the new cohort had a higher level of disability (Rankin score 4,5) at presentation (43.5% versus 21.8%, $p = 0.013$) and at

This article is protected by copyright. All rights reserved.

Accepted Article

last follow-up (14.5% versus 3%, p = 0.022), but mortality was not different at last follow-up (12.9% versus 16.8%), nor was frequency of bad outcome (Rankin score 4-6) at last follow-up (27.4% versus 19.8%, p = 0.259).

Initial Treatment

The details of initial treatment are shown in Table 2. 159 of the 163 patients received treatment and 4 were not treated. Glucocorticoid therapy was used in 157 patients. In 66 , IV pulse methylprednisolone therapy (from 3 to 17 pulses, median: 5 pulses, mostly 1 gm/pulse), preceded the beginning of oral prednisone therapy. The median starting oral prednisone dose in the 157 treated patients was 60 mg/day. The median duration of oral prednisone therapy was 9 months (range: 0.4-107 months). Three fourth of the patients were treated for 17 months or less. In 75 patients, glucocorticoids were the only initial therapeutic agents used.

82 patients were given a second drug in addition to prednisone. 72 of these patients received cyclophosphamide , while 2 others received cyclophosphamide alone. 51 patients had daily oral doses. The median initial dose of oral cyclophosphamide was 150 mg/day (range: 75-200 mg/day) with a median therapy duration of 7 months (range: 1-33 months). Three fourths of the patients were treated for 12 months or less. 23 patients received intermittent IV monthly pulse cyclophosphamide. The median dose was 1,000 mg/month and the median length of the treatment was 2 months (range: 1-17 months). Three fourths of the patients received 6 monthly pulses or less.

Among the 75 patients treated with only prednisone, the median duration of all therapy was 11.1 months (range: 0.2-109 months). Among the 72 patients treated with prednisone and cyclophosphamide, the median duration of all therapy was 11.6 months (range: 0.6-114 months).

Accepted Article

This article is protected by copyright. All rights reserved.

6 of the 82 patients were initially given prednisone and azathioprine at a median initial dose of 100 mg/day (range: 100-150 mg/day). The median duration of treatment was 11 months (range: 0.4-76 months).3 patients received mycophenolate mofetil with prednisone at an initial median dose of 2,000 mg/day, and one patient was given 2 IV rituximab injections.

Aspirin was started at diagnosis in 24/163 patients (15%). Its role in treatment could not be evaluated other than it was not significantly associated with a poor outcome, survival, or intracranial hemorrhage.

Response to Initial Therapy

Adequate information to judge the response to initial therapy was available from the records in 152 patients. Overall, a favorable response was observed in 126 (83%) of the 152.

62 (85%) of the 73 followed on prednisone alone as initial therapy responded favorably. 55 (89%) of the 62 patients had improved within the first 2 months. 55 (80%) of 69 followed on prednisone plus cyclophosphamide responded favorably and 46 (84%) of the 55 had improved within two months The differences between the patients treated with prednisone alone and those treated with prednisone and cyclophosphamide were not significant.

Of the six patients started on prednisone and azathioprine as initial treatment, follow-up information was available on five. Four of the five improved on therapy and all did so within one month.

A favorable response to therapy was observed in 80% of patients with lymphocytic vasculitis, 100% with necrotizing vasculitis and 100% with granulomatous vasculitis ($p = 0.137$).

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

Follow-up treatment

5 patients initially on prednisone alone were also started on mycophenolate mofetil within 3 months of beginning therapy. For analysis, these 5 were added to the 3 started initially on prednisone and mycophenolate. Follow-up information was available for 7 of the 8. All 7 responded favorably within 4 months and 6 within 2 months.

Overall, 91 patients were given cyclophosphamide at some time during the therapy, 74 initially and 17 for relapses.

Of the 55 patients begun on prednisone plus cyclophosphamide and noted to improve at follow-up, 11 patients were changed from cyclophosphamide to azathioprine, 3 to mycophenolate mofetil, and 3 to methotrexate (15-20 mg/weekly) in an attempt to reduce the risk of toxic effects of cyclophosphamide. All of these 17 patients who discontinued cyclophosphamide had last follow-up Rankin scores in the 0-3 range, whereas 31 of 38 (82%) of those still on cyclophosphamide had last follow-up Rankin scores in the 0-3 range ($p = 0.086$). Two patients were given plasma-exchange and 1 infliximab for disease refractory to glucocorticoids plus cyclophosphamide.

There were 53 patients who received only glucocorticoids throughout the course of therapy. The median duration of treatment in these was 6.0 months (range: 0.2-109 months). There were 22 other patients who were given only prednisone initially but an immunosuppressant was added later. The median duration of therapy in these was 22 months, (range: 4.5-100 months). There were 82 further patients who received prednisone plus an immunosuppressant drug at diagnosis. The median duration of treatment in these was 11.8 months (range: 0.4-160 months).

This article is protected by copyright. All rights reserved.

Accepted Article

Relapses

Relapses occurred in 44 (28%) of the 159 treated. 28 of the 44 had 1 relapse, 10 had 2 , and 6 had 3 or more. Patients with relapses had a longer median duration of treatment compared no relapses (18 months versus 9 months, $p<0.001$). There was no evidence from the records that relapses were related to rapid withdrawal of therapies.

Treatment of relapses included cyclophosphamide in 24 patients (oral doses in 15 and intravenous in 9), methylprednisolone pulses in 6, mycophenolate mofetil in 3, chlorambucil in 3, and plasma-exchange in 1. Etanercept was used in 1 patient for a relapsing course despite previous treatment with cyclophosphamide and mycophenolate mophetil. In the remaining patients increased oral glucocorticoids were given. All patients appeared to improve or stabilize in response to the treatments for the relapses. Relapses occurred more frequently in patients treated initially with prednisone alone compared to those treated with cyclophosphamide and prednisone, Table 2, (39% versus 18%, $p = 0.006$). Relapses were observed in 22/71 (31%) patients with large-vessel or large- and small-vessel involvement and in 12/51 (24%) patients with only small-vessel changes or angiography-negative biopsy positive cases. The difference was not statistically significant ($p = 0.417$).

Clinical factors influencing response to treatment

40 of 158 (25%) patients had discontinued therapy by last follow-up. No differences were observed in this regard between patients treated initially with prednisone alone or combined with cyclophosphamide. Twenty one of the 75 (28%) on prednisone alone were off therapy at last follow-up, and 18 of 72 (25%) of those treated with prednisone and cyclophosphamide were off therapy at last follow-up.

This article is protected by copyright. All rights reserved.

Univariate logistic modeling was used to assess an association of findings at diagnosis with response to treatment, relapses, and therapy at last follow-up. Large vessel involvement (OR, 6.14, 95%CI: 1.71-22.0, p = 0.005) and cerebral infarcts at diagnosis on MRI (OR, 3.32, 95%CI: 1.23-8.96, p = 0.018) were associated with a poor response to the treatment, while prominent gadolinium-enhanced lesions or meninges assessed by MRI (OR, 2.28, 95%CI: 1.04-5.00, p = 0.040) was associated with longer therapy which was often continued at the time of last follow-up . Prednisone alone initial treatment was the only finding significantly associated with relapses (OR, 2.90, 95%CI: 1.40-6.00, p = 0.006). Additional multivariate analysis was not possible because of small numbers.

No significant differences were observed between the groups diagnosed by CNS biopsy or by angiography. This included duration of therapy (median, 11.7 versus 11.2 months, respectively), number of patients with relapses (18/54, 33% versus 26/99, 26%), response to treatment (46/53, 87% versus 80/99, 81%), and patients not requiring therapy at last follow-up (11/55, 20% versus 29/103, 28%). The patients diagnosed by angiography were significantly more frequently treated with cyclophosphamide than prednisone alone (55/105, 52% versus 19/58, 33%, respectively, p = 0.016).

Cerebral amyloid beta-related angiopathy (ABRA).

We compared the 20 patients whose CNS biopsies showed vasculitis with amyloid deposits (Aβ-related angiitis or ABRA) to the 38 whose biopsies were positive without amyloid. No significant differences were observed between the two groups regarding numbers treated with IV pulse glucocorticoids (11/20, 55% versus 14/38, 37%), oral prednisone (19/20, 95% versus 36/38, 95%), daily oral cyclophosphamide (5/20, 25% versus 7/38, 18%), and IV pulse cyclophosphamide (3/20, 15% versus 4/38, 11%). The therapy duration was shorter in patients with

This article is protected by copyright. All rights reserved.

Accepted Article

ABRA (median, 6 versus 15 months, p=0.30). No significant differences were observed regarding the frequencies of ABRA patients and those without amyloid deposits regarding relapses (5/19, 26% versus 13/35, 37%), response to treatment (16/19, 84% versus 30/34, 88%), and number of patients who had discontinued therapy at last follow-up (3/19, 16% versus 8/36, 22%).

Status at last follow-up

Table 3 compares the Rankin disability scores at presentation with those at last follow-up. In the Table, scores at diagnosis were divided into three groups of increasing disability (0-2,3, 4-5). Last follow-up scores were divided into three groups also, (0-3, 4-5, 6 or death). Duration of follow-up was separated into three intervals. Of the 114 patients with low or intermediate disability scores at diagnosis (score 0-3) 101 continued to have low or intermediate scores at last follow-up. Half of the 49 patients with severe disability at diagnosis (score 4-5) had less disability at follow-up (score 0-3). 25 of 163 (15.3%) died during follow-up. Most deaths occurred within the first year, especially those presenting with severe disease (score 4-5). However some deaths occurred during all follow-up intervals.

High disability scores (Rankin scores, 4-6) were equally frequent at last follow up in patients with relapsing disease (10/44, 23%) and in those without relapses (27/119, 23%). No significant differences in the patients who died during follow-up were observed in patients with and without relapses (8/44, 18% versus 17/119, 14%).

High disability scores at last follow-up were more frequent in angiography-diagnosed patients than biopsy-diagnosed (27/105, 26% versus 10/58, 17%), but the difference was not significant.

Univariate logistic analysis adjusted for age was also used to assess association of specific findings at diagnosis with Rankin score outcomes (data not

This article is protected by copyright. All rights reserved.

Accepted Article

shown). High disability scores (Rankin scores, 4-6) at last follow-up were significantly associated with increasing age (calculated per 10-year increments) (OR, 1.44; 95% CI, 1.11-1.86; p = 0.005), and cerebral infarction present at diagnosis assessed by MRI (OR, 3.74; 95% CI, 1.55-9.06; p = 0.003). Patients with prominent gadolinium enhanced meninges or lesions (OR, 0.35; 95% CI, 0.15-0.86; p = 0.020) and patients with ABRA (OR, 0.24; 95% CI, 0.06-0.94; p = 0.040) had lower disability at follow-up. Other factors were not associated with a high Rankin score, including treatment by prednisone alone or cyclophosphamide and prednisone.

In a multivariable model, increasing age (per 10 years) (OR, 1.47; 95%CI: 1.10-1.96; p = 0.009) and MRI findings of infarcts (OR, 3.41; 95%CI: 1.39-8.34; p = 0.007) were associated with high disability scores (Rankin scores, 4-6) at last follow-up, while MRI findings of Gadolinium-enhanced lesions or meninges (OR, 0.40; 95%CI: 0.16-1.00; p = 0.05) were associated with less disability.

The univariate Cox proportional hazards model was used to assess the association between increased mortality and findings at diagnosis (Table 4). Increasing age (calculated per 10-year increments) (HR, 1.39), method of diagnosis (angiography versus biopsy) (HR, 3.28), cerebral infarction versus no infarction (HR, 4.44), and large vessel involvement versus small-vessel involvement (HR, 4.98) were associated with an increased mortality rate. Patients with prominent gadolinium-enhanced lesions or meninges (MRI) had a lower risk for death (HR, 0.20) than patients with no such lesions at presentation. Patients with ABRA also had a lower risk of death (HR, 0.17), however the difference was not statistically significant. No differences in mortality were observed when patients were stratified by treatment (prednisone alone versus prednisone and cyclophosphamide).

In a multivariable model (Table 4), increasing age (per 10 years) (p = 0.011) and MRI findings of infarcts (p = 0.013) were associated with increased mortality, and MRI

This article is protected by copyright. All rights reserved.

Accepted Article

findings of Gadolinium-enhanced lesions or meninges (p = 0.024) were associated with less mortality.

Outcome varied according to histologic pattern in those with biopsy proven disease but the differences were not significant. Of the 13 with a lymphocytic pattern all had a good outcome at last follow-up (Rankin score 0-3). 80% of the 35 with a granulomatous pattern and 70% of the 10 with a necrotizing pattern also had a good outcome. We registered a trend toward a higher frequency of patients with a good outcome at last follow-up in the lymphocytic vasculitis group compared to granulomatous and necrotizing groups (100% versus 77.8%, p = 0.096). Less patients with lymphocytic vasculitis died at last follow-up compared to the other 2 groups (0 versus 11.1%, p = 0.577).

DISCUSSION

The majority of patients in the study responded to either prednisone alone or combined with cyclophosphamide in doses used in other vasculitides (12). The response rate was similar in both regimens and the majority of patients showed improvement within two months. In both treatment groups the clinical findings at diagnosis were comparable as were Rankin disability scores at diagnosis and at last follow-up. The response was also not different in patients diagnosed by biopsy and by angiography. The only difference between the therapy results was a higher relapse rate in the group of patients treated with prednisone alone. In that sense the two regimens were not completely equivalent. However, more than half of the patients (72%) achieved a sustained therapeutic response (no relapses) during the follow-up. Patients with relapses needed longer therapy compared to those without relapses but there was no association of relapses with increased mortality or higher disability (Rankin score) at last follow-up.

This article is protected by copyright. All rights reserved.

Accepted Article

The mortality rate over the follow-period was 15% (25/163) indicating the seriousness of this disease in spite favorable response in many. The mortality rate in our cohort was higher than that found in a recent French series of 52 patients (6%) (8). In the French series >80% of patients received glucocorticoid combined with cyclophosphamide, while in our series this combination was prescribed as initial therapy in 44%. However, as noted above therapy with prednisone alone in our series was not associated with an increased mortality rate, nor higher Rankin disability score at last follow-up than those on combination therapy. Therefore, the higher mortality observed in our study was not likely related to less aggressive treatment. Differences in the population of PCNSV patients enrolled in the two studies may explain the disparity. In our patients the majority of biopsy-proved patients had a granulomatous or necrotizing histopathology while in the French cohort lymphocytic vasculitis was the prevalent pattern. In our cohort we noted an association between increased mortality and large cerebral vessel lesions and CNS infarctions on MRI regardless of type of therapy. CNS biopsy in such cases had a predominant granulomatous and/or necrotizing pattern (13,14). Furthermore, we showed that patients with lymphocytic vasculitis had a better outcome and less mortality compared to the other 2 patterns. Therefore, differences in disease severity, linked to differences in the histopathologic patterns, may explain the higher mortality in our series.

The most severe end of the clinical spectrum of PCNSV is represented by patients diagnosed by angiography with bilateral multiple large/proximal cerebral vessel lesions in the presence of multiple CNS infarctions. These patients had a rapidly progressive clinical course and responded poorly to therapy (13,14). In such patients it is reasonable to start more aggressive treatment with prednisone and cyclophosphamide.

Patients with small vessel involvement appear to have less severe disease. They responded to therapy, had a better survival and less disability at follow-up.

Accepted Article

This article is protected by copyright. All rights reserved.

Among these are angiography negative, biopsy positive PCNSV cases with vessel lesions beyond the resolution of angiography. They require a biopsy for diagnosis (15-18). Such patients often presented with cognitive dysfunction, had greatly raised concentrations of CSF proteins, and the presence of gadolinium enhanced lesions or meninges on MRI. ABRA cases could be included in this subset (15,16). Such patients might be treated from the start with glucocorticoids, reserving cyclophosphamide or a different immunosuppressant in case of relapses. The relatively large number of patients who received glucocorticoids alone throughout the course of their illness supports this idea.

We also found that patients with gadolinium-enhanced lesions or meninges required longer therapy and continued treatment at last follow-up. These MRI lesions were also found in patients with a higher risk for relapses (OR,1.49), although the association was not significant. Our data partially confirm the recent observation of de Boysson et al that meningeal gadolinium enhancements on MRI were associated with higher relapse rates (8) but we did not find an association between clinical manifestations at diagnosis and relapses.

Almost a fifth of the patients given both immunodepressive treatment and glucocorticoids were treated with a second drug different from cyclophosphamide (mainly azathioprine or micophenolate mophetil). Most of these patients showed a favorable response, suggesting that these drugs can replace the more toxic cyclophosphamide for induction of remission.

Seventeen (24%) of the 72 patients treated initially with cyclophosphamide were switched to a different immunodepressive agent for maintenance therapy. The most used drug was azathioprine, followed by mycophenolate mofetil, and methotrexate. These drugs appeared to be effective as the improvement in the patients' status was maintained. In other words cyclophosphamide did not appear essential to the improved outcome of the disease. It could also be noted that

This article is protected by copyright. All rights reserved.

Accepted Article

although aspirin therapy had no noted beneficial effect it was not associated with a harmful effect such as an increased in subsequent intracranial hemorrhage. However, because of the low number of patients treated, further studies are needed to define the real benefit of these drugs.

Three patients were treated with biological agents, and a favorable response was observed in all. One patient was given rituximab because she declined the use of cyclophosphamide. Two other patients were treated with TNF-alfa blockers, one for refractory disease, the second for relapsing vasculitis. Therefore, although the experience is limited to few case reports (19-21), biological agents may represent a useful therapeutic option for patients intolerant to conventional immunodepressive agents or as second-line therapy for refractory or relapsing cases.

The investigation had a number of limitations. As in all retrospective studies, incomplete datasets may have influenced findings. Other limitations include possible referral bias of cases, relatively short follow-up, and lack of tissue at diagnosis in the majority of patients even though follow up of this group tended to confirm the diagnosis of PCNSV. Lack of uniformity of treatment regimens was also a limitation. Strengths of the study were the large number of unselected consecutive cases defined by uniform pathological criteria, the extensive clinical data available, and follow up information.

Accepted Article

This article is protected by copyright. All rights reserved.

References

1. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. Lancet 2012; 380(9843):767-77.

2. Calabrese LH, Mallek JA. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore) 1988; 67:20-39.

3. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis: an update. Curr Opin Rheumatol 2012; 24:46-52.

4. Cravioto H, Feigin I. Noninfectious granulomatous angiitis with a predilection for the nervous system. Neurology 1959; 9:599-609.

5. Lie JT. Primary (granulomatous) angiitis of the central nervous system: a clinicopathologic analysis of 15 new cases and a review of the literature. Hum Pathol 1992; 23:164-171.

6. Cupps TR, Moore PM, Fauci AS. Isolated angiitis of the central nervous system. Prospective diagnostic and therapeutic experience. Am J Med 1983;74:97-105.

7. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Weigand SD, Miller DV, Giannini C, Meschia JF, Huston J 3rd, Hunder GG. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol 2007; 62:442-51.

8. de Boysson H, Zuber M, Naggara O, Neau JP, Gray F, Bousser MG, et al; French Vasculitis Study Group and the French NeuroVascular Society. 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; 66:1315-26.

9. 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; 43:685-92.

10. Birnbaum J, Hellmann DB. Primary angiitis of the central nervous system. Arch Neurol 2009;66:704-709

11. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trials. Stroke 1999; 30:1538–41.

This article is protected by copyright. All rights reserved.

Accepted Article

12. Molloy ES, Langford CA. Advances in the treatment of small vessel vasculitis. Rheum Dis Clin North Am. 2006; 32:157-72.

13. Salvarani C, Brown RD Jr, Calamia KT, Christianson T, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG. Rapidly progressive primary central nervous system vasculitis. Rheumatology (Oxford) 2008; 50:349-58.

14. Salvarani C, Brown RD Jr, Morris JM, Huston J 3rd, Hunder GG. Catastrophic primary central nervous system vasculitis. Clin Exp Rheumatol 2014; 32(3 Suppl 82):3-4.

15. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG. Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. Rheumatology (Oxford) 2008; 47:1671-7.

16. Salvarani C, Hunder GG, Morris JM, Brown RD Jr, Christianson T, Giannini C. Aβ-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. Neurology 2013; 81:1596-603.

17. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG. Angiography-negative primary central nervous system vasculitis: a syndrome involving small cerebral vessels. Medicine (Baltimore). 2008; 87:264-71.

18. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG. Primary central nervous system vasculitis with prominent leptomeningeal enhancement: a subset with a benign outcome. Arthritis Rheum 2008; 58:595-603.

19. Salvarani C, Brown RD Jr, Calamia KT, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG. Efficacy of tumor necrosis factor alpha blockade in primary central nervous system vasculitis resistant to immunosuppressive treatment. Arthritis Rheum 2008; 59:291-6.

20. Salvarani C, Brown RD Jr, Huston J 3rd, Morris JM, Hunder GG. Treatment of primary CNS vasculitis with rituximab: case report. Neurology 2014; 82:1287-8.

Accepted Article

This article is protected by copyright. All rights reserved.

21. De Boysson H, Arquizan C, Guillevin L, Pagnoux C. Rituximab for primary angiitis of the central nervous system: report of 2 patients from the French COVAC cohort and review of the literature. J Rheumatol 2013; 40:2102-3.

Accepted Article

This article is protected by copyright. All rights reserved.

Table 1. Findings at diagnosis in the 163 patients with PCNSV* according to the study period

	All patients (n=163)	1983-2003 cohort (n=101)	2004-2011 cohort (n=62)	P#
Male	72 (44.2)	43 (42.6)	29 (46.8)	0.600
Age at diagnosis, median (range) years	48 (17-85)	47 (17-84)	51.5 (20-85)	0.016
Interval from symptom onset to diagnosis, median (range) years	0.1 (0.0-5.2)	0.1 (0.0-5.2)	0.1 (0.0-5,2)	0.708
Clinical manifestations at presentation				
Headache	97 (59.5)	64 (63.4)	33 (53.2)	0.200
Cognitive dysfunction	88 (54)	50 (49.5)	38 (61.3)	0.143
Persistent neurologic deficit or stroke	66 (40.5)	40 (39.6)	26 (41.9)	0.768
Seizures	33 (20.2)	16 (15.8)	17 (27.4)	0.074
Intracranial hemorrhage	16 (9.8)	8 (7.9)	8 (12.9)	0.299
Systemic manifestations§	15 (9.2)	9 (8.9)	6 (9.7)	0.869
Fever	16 (9.8)	9 (8.9)	7 (11.3)	0.620
CSF abnormality**				
Protein > 70 mg/dl ^	63 (52.1)	38 (52.1)	25 (52.1)	0.998
Protein > 45 mg/dl or WBC count > 5 cells/mm³	100 (81.3)	56 (75.7)	44 (89.8)	0.051
Protein > 70 mg/dl or WBC count > 10 cells/mm³	77 (63.6)	46 (63)	31 (64.6)	0.861
ESR, median (range) mm/hour	8 (0-124)	9 (0-110)	7.5 (0-124)	0.501
Initial MRI findings£				
Infarcts	81 (54.4)	48 (53.3)	33 (55.9)	0.755
Gadolinium-enhanced lesions (intracerebral or meningeal)	60 (40.3)	33 (36.7)	27 (45.8)	0.268
Meningeal gadolinium enhanced lesions	29 (19.5)	11 (12.2)	18 (30.5)	0.006
Angiographic findings***				
Large/proximal vessel vasculitis	75 (65.8)	55 (72.4)	20 (52.6)	0.036
Small /distal vessel vasculitis	103 (90.4)	70 (92.1)	33 (86.8)	0.370

*Excepted where indicated otherwise, values are the number (%) of patients. #1983-2003 cohort of patients versus 2004-2011 cohort of patients. PCNSV = primary central nervous system vasculitis. CSF = cerebrospinal fluid. WBC = white blood cell. ESR = erythrocyte sedimentation rate. §Defined as the presence of at least 1 of the following: fatigue, anorexia, weight loss, arthralgia. **Cerebrospinal fluid (CSF) data were available for 121 patients for protein > 70 mg/dl , 123 patients for protein > 45 mg/dl or white blood cell (WBC) count > 5 cells/mm3, and 121 patients for protein > 70 mg/dl or WBC count > 10 cells/mm3. ^ the normal range of protein is 14-45 mg/dl. £Magnetic resonance imaging (MRI) was performed in 149 patients. ***Cerebral angiography was performed in 129 patients. Information on vasculitis type (large vessel and small vessel) was available for 113 patients.

This article is protected by copyright. All rights reserved.

Accepted Article

Accepted Article

Table 2. Treatment in the 163 patients with PCNSV* according to the study period

	All patients (n=163) n (%)	1983-2003 cohort (n=101)	2004-2011 cohort (n=62)	P#
Initial treatment				
Prednisone alone	75 (46)	48 (47.5)	27 (43.5)	0.066§
Prednisone and cyclophosphamide**	72 (44)	46 (45.5)	26 (41.9)	
Prednisone and azathioprine	6 (3.7)	4 (4.0)	2 (3.2)	
Prednisone and other therapy£	4 (2.5)	0	4 (6.5)	
Cyclophosphamide alone	2 (1.2)	2 (2.0)	0	
No therapy	4 (2.5)	1 (1.0)	3 (4.8)	
Duration of therapy, median (range) months				
Prednisone	9.0 (0.4-107.0)	9.5 (0.4-107.0)	6.0 (1.0-87.0)	0.346
Cyclophosphamide**	7.0 (1.0-33.0)	10.0 (1.0-25.0)	6.0 (1.0-33.0)	0.248
Patients with relapses/total cohort	44/163 (27.0)	26/101 (25.7)	18/62 (29.0)	0.646
Prednisone alone	29/75 (38.7)			
Prednisone + cyclophosphamide**	13/72 (18.1)			
Patients not requiring therapy at last follow-up	40/158 (25.3)	28/99 (28.3)	12/59 (20.3)	0.267
Prednisone alone	21/75 (28.0)			
Prednisone + cyclophosphamide**	18/72 (25.0)			
Patients responding to the treatment&	126/152 (82.9)	80/97 (82.5)	46/55 (83.6)	0.267
Prednisone alone	62/73 (84.9)			
Prednisone + cyclophosphamide**	55/69 (79.7)			

* Except where indicated otherwise, values are number (%) of patients. #1983-2003 cohort of patients versus 2004-2011 cohort of patients. § Patients receiving immunosuppressive therapy versus patients receiving prednisone alone. ** including oral + pulse cyclophosphamide therapy. £including 3 patients treated with mycophenolate mofetil and 1 treated with rituximab. &Response to therapy defined by the clinical judgment of the treating physician was assessable in 152 patients

This article is protected by copyright. All rights reserved.

Table 3. Rankin Disability Score at Diagnosis and at Last Follow-up Visit

Rankin Score at Diagnosis	Patients, n	Rankin Score at Last Follow-up Visit								
		< 1yr			1-4.9 yr			5-15 yr		
		0-3	4-5	Deceased	0-3	4-5	Deceased	0-3	4-5	Deceased
0-2	83	38	0	3	30	0	4	7	0	1
3	31	14	0	2	9	0	1	3	0	2
4-5	49	7	8	10	17	2	2	1	2	0

Accepted Article

This article is protected by copyright. All rights reserved.

Table 4. Characteristics associated with increased mortality

Characteristics	HR	95% CI	Univariate P	Multivariate HR (95% CI)
Age (per 10-year difference)	1.39	1.05-1.85	0.022	1.52 (1.10-2.09)
Male vs female	0.80	0.34-1.88	0.61	
Main symptom at presentation				
Headache or constitutional symptom	1.00			
Focal manifestation vs headache or constitutional symptom	2.42	0.69-8.52	0.17	
Cognitive disorder vs headache or constitutional symptom	3.40	0.82-14.0	0.090	
Diagnosis by angiography only compared with biopsy	3.28	1.09-9.82	0.034	
MRI findings				
Infarct vs no infarct	4.44	1.61-12.2	0.004	3.60 (1.31-9.90)
Gadolinium-enhanced lesions or meninges vs normal or minimal changes	0.20	0.06-0.67	0.009	0.24 (0.07-0.83)
Large-vessel involvement vs small vessel involvement*	4.98	1.47-16.9	0.01	
Increased cerebrospinal fluid protein level (> 70 mg/dl)	1.29	0.49-3.39	0.61	
Cerebral amyloid angiopathy, presence vs absence	0.17	0.02-1.33	0.092	
Prednisone alone vs cyclophosphamide and prednisone	1.03	0.46-2.35	0.94	
Rapid (< 1 mo) vs slow onset (> 1 mo)	1.27	0.55-2.94	0.57	

Univariate and multivariate Cox proportional hazards models were used for age-adjusted analysis. *For this measurement, n = 129. HR = hazard ratio; CI = confidence interval; MRI = magnetic resonance imaging.

Accepted Article

This article is protected by copyright. All rights reserved.