Long-term outcomes of patients with primary angiitis of the central nervous system

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ABSTRACT

Objective. *Primary angiitis of the central nervous system (PACNS) is a vasculitis confined to the brain and spinal cord, which often presents with severe cognitive and functional deficits. Despite progress in diagnosis, little is still known about long-term outcomes. Our aim was to evaluate long-term functional capabilities, quality of life, and depression, and to determine the effect of treatment duration on patient outcomes.*

Methods. *We identified patients by ICD-9 codes for cerebral angiitis, and included them if they met two of the three following criteria: inflammatory cerebrospinal fluid (CSF), cerebral angiogram typical of vasculitis, or findings of vasculitis on pathologic examination of brain tissue. Disability was assessed by the Barthel Index, quality of life was assessed by EuroQol, and depression was assessed with Patient Health Questionnaire.*

Results. *Seventy-eight patients met the inclusion criteria, of which 27 responded to the questionnaire (34.6%). Mean follow-up of those who responded was 5.5 years (±4.7). Nineteen of 27 patients (70.4%) had mild disability; meanwhile, 5 (18.5%) had severe disability. Fourteen of 27 patients (51.9%) had no mobility problem, 18 (66.7%) had no problems with self-care, 15 (55.6%) had no problems with usual activities, 14 (51.9%) had no pain, and 8 (29.6%) had no anxiety. Approximately 70% of patients had minimal or no depression.*

Conclusion. *This is the longest reported follow-up of patients with PACNS described in the literature to date. Most patients had mild long-term disability and minimal to no depression, which may be reflective of treatment advances.*

Introduction

Primary angiitis of the central nervous system (PACNS) is a rare form of vasculitis limited to the brain and spinal cord. Patients often present with severe cognitive and functional deficits (1). Diagnostic criteria were proposed by Calabrese and Mallek in 1988, which include: 1. the presence of an acquired otherwise unexplained neurological or psychiatric deficit; 2. the presence of either classic angiographic or histopathological features of angiitis within the CNS; and 3. no evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease (2). These criteria were revised by Birnbaum and Hellmann in 2009 by stratifying according to diagnostic certainty to prevent patients with reversible cerebral vasoconstriction syndrome (RCVS) to be diagnosed with PACNS. Diagnosis is considered as definite if biopsy results are consistent with PACNS and probable if both CNS imaging and cerebrospinal fluid findings are consistent with PACNS in the absence of a biopsy.

The last several decades have provided great insight into the diagnosis and treatment of PACNS. Initial reports of this disease suggested a fatal outcome in most patients (3). Cupps *et al*. described the first sustained clinical remission in four patients in 1983 demonstrating the efficacy of cyclophosphamide in combination with glucocorticoids (4). This continues to be the mainstay of treatment over three decades later. Although much has been elucidated about the clinical manifestations and the diagnostic approach of this disease, little is known about the overall patient outcomes. Recent cohort studies have described a generally favorable disease course (5-7). Although we have gained much knowledge on this very rare disease from these

large cohorts, there remains no consistency in the diagnostic approach, where less than half of patients had brain biopsies (5-7). Therefore, the outcomes depicted in these studies may not be generalised. In addition, more recent advances have discerned the importance of ruling out reversible cerebral vasoconstriction syndrome (RCVS), a major angiographic mimic of PACNS. The 2007 definition of RCVS as an entity is considered a major breakthrough in understanding and eliminating the mimics of PACNS. Prior to 2007, RCVS was not well characterised which could have added to the contamination of some of the cohort with this syndrome. Herein, we have used Birnbaum and Hillman criteria to identify a cohort of patients with diagnosis of PACNS (8). We have included in this cohort only patients in whom the diagnosis of PACNS was established by brain biopsy (74.1%) or by the presence of both abnormal cerebral angiography and cerebrospinal fluid findings (25.9%).

Through this patient cohort, we aimed to elucidate patient functional capabilities, quality of life, and frequency of depression after diagnosis and treatment for PACNS. In addition, we attempt to determine the effect of clinical findings, type of treatment, treatment duration, cerebrospinal fluid (CSF) analysis, and brain magnetic resonance imaging (MRI) findings on patient outcomes. To our knowledge, this study has the longest follow-up duration and represents the first evaluation of the quality of life and incidence of depression of patients with PACNS in the literature to date.

Patients and methods

This study was approved by Cleveland Clinic Institutional Review Board and was conducted in accordance with the declaration of Helsinki.

Patients

Patients were identified by the ICD-9 codes for cerebral vasculitis (446.5), cerebral arteritis (437.4), and central nervous system vasculitis (447.6), all having been evaluated by a staff member at the Vasculitis Care and Research Center at Cleveland Clinic between 2002 (when electronic medical records were initiated in our institution) and 2016. Patients who had signs, symptoms, CSF and imaging findings suggestive of systemic vasculitides, systemic autoimmune diseases, infections and malignancy were excluded. Patients were included if they met the Calabrese and Mallek criteria (2); in addition, for those whose diagnosis was based on typical angiographic findings, the presence of an inflammatory CSF pattern was required. The diagnosis of PACNS was further agreed upon by two rheumatologists in the department. Histopathology was considered to be consistent with PACNS diagnosis when granulomatous, lymphocytic or necrotising vasculitis of small and/or medium-sized vessels was present.

Detailed retrospective review of records was performed, which included capturing the demographic, clinical phenotype, laboratory modalities and therapeutic regimens. Brain MRIs performed near the time of presentation was blindly reviewed by two neuroradiologists. Data regarding involvement of pachy- and leptomeninges, as well as cerebral grey and white matter, were recorded for each patient. For each of these sites, the presence and localisation of the involvement were recorded. Presence of mass effect and parenchymal haemorrhage was also recorded for each patient.

Subjects who met the inclusion criteria listed above were mailed four questionnaires, a consent to participate in the study, and a medical release form. Informed consent was obtained from each participant before enrollment in the study. The Modified Rankin Scale was obtained from the last visit. If the questionnaires were not returned within two weeks, subjects were called using a phone script.

Outcomes measures

Patient-centered outcome measures

1. The Barthel ADL Index is a standardised outcome measures tool used primarily to assess post-stroke outcome. Questions explore activities of daily living such as eating, grooming, and toileting, as well as mobility. Scores range from 0 to 100% with higher scores signifying better outcome. A score of 100% indicates no disability; a score of 81–99% indicates mild disability; 61–80%, moderate disability; and 60% or less, severe disability (9, 10).
2. The Brief Patient Health Questionnaire (BPHQ-9) is a brief version of the PHQ that addresses the depression module of the PHQ, and scores each of the 9 DSM-IV criteria as 0 (not at all) to 3 (nearly every day). BPHQ-9 score ≥10 had a sensitivity of 88% and a specificity of 88% for major depression. BPHQ-9 scores of 5, 10, 15, and 20 represented mild, moderate, moderately severe, and severe depression, respectively (11). Furthermore, the BPHQ-9 was demonstrated to be a reliable and valid measure of depression severity (11).
3. The European Quality of Life Questionnaire (EuroQol; EQ-5D-5L) is a standardised instrument for use as a measure of health outcome. It is applicable to a wide range of health conditions and treatments. It provides a simple descriptive profile and a single index value for health status. It assesses quality of life states in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The responses include five levels of severity (no problem/slight/moderate/severe/extreme) within a particular dimension (12).
4. The treatment history questionnaire asks subjects to provide a detailed history of their treatment regimen that includes specific medications as well as dates.

Physician-centered outcomes measures

The Modified Rankin scale (MRS) is a commonly used scale to assess global function or disability post stroke. The scale runs from 0 (no disability) to 6 (death). Although limited by inter-observer variability, it is the most widely used functional outcome measure in contemporary stroke research (10, 13). These data were collected near the same time (limited by variability of response times) of the patients' self-reported outcomes.

Statistical analysis

Descriptive statistics were used to summarise the demographics. Nomi-

nal data were presented as percentages. Continuous data were presented as mean ± standard deviation. Numerical characteristics were compared using two-sided two-sample *t*-test and categorical variables using Fischer's exact test. The Kaplan-Meier method was used to estimate survival. The Cox proportional hazards model was used to assess relation of clinical characteristics and type of outcome. Logistic regression was used to identify characteristics that increased odds of poor outcome. We did an exploratory analysis of clinical features (signs and symptoms) and outcomes to assess for additional factors. All the statistical analysis was performed using JMP software, version 8.

Results

Patients

Seventy-eight patients met the inclusion criteria, of which 27 responded to the questionnaires (34.6%). Through chart review and mortality data from the Social Security Death Index and the Ohio death database, 9 of 78 (11%) patients were found to be deceased at the time of the study.

Mean age, gender distribution, headache frequency, stroke and seizure history, CSF and angiographic findings, and the rate of positive biopsies were similar between responders and non-responders (Table I). However, non-responders had significantly longer average follow-up duration than responders (8.7 years *vs*. 5.5±4.7 years).

The study population (n=27) consisted of 14 males and 13 females, average age of 50.8 years (range: 23–80). The majority of patients presented with headache and stroke (70.4% and 51.9%, respectively), followed by seizure in 29.6% of the patients. Ninety-four percent of the patients underwent lumbar puncture, of which 88% had abnormal cerebrospinal fluid findings as defined by CSF nucleated cells of >5 cells per high power filed or CSF protein >45 mg/dl. Eighty-one percent of patients had angiography, of which 54% had abnormal cerebral angiogram findings. Lastly, 78% of patients had brain biopsy, of which 95% had findings consistent with PACNS. Diagnosis of PACNS was established by brain biopsy in 74.1% of patients; and the remaining 25.9% of patients were diagnosed by the presence of both abnormal cerebral angiography and cerebrospinal fluid findings.

Table I. Comparison of questionnaire responders *vs*. non-responders.

	Total (n=78)	Non-responders (n=51)	Responders (n=27)	*p*-value
Age	52.5 ± 16.3	53.3 ± 17.0	50.8 ± 15.0	0.52
Years since diagnosis	7.6 ± 4.9	8.7 ± 4.7	5.5 ± 4.7	0.006
Male/Female	40/38	26/25	14/13	0.94
Headache				0.67
Present	52 (68.4%)	33 (67.3%)	19 (70.4%)	
Absent	21 (27.6%)	13 (26.5%)	8 (29.6%)	
Unknown	3 (3.9%)	3 (6.1%)	0 (0.0)	
Stroke	39 (51.3%)	25 (51.0%)	14 (51.9%)	0.94
Seizure	26 (34.7%)	18 (37.5%)	8 (29.6%)	0.49
CSF findings				0.67
Abnormal	58 (74.4%)	36 (70.6%)	22 (81.5%)	
Normal	12 (15.4%)	9 (17.6%)	3 (11.1)	
Not obtained	8 (10.3%)	6 (11.8%)	2 (7.4%)	
Angiography findings				0.67
Abnormal	33 (42.3%)	21 (41.2%)	12 (44.4%)	
Normal	26 (33.3%)	16 (31.4%)	10 (37.0%)	
Not obtained	19 (24.4%)	14 (27.5%)	5 (18.5%)	
Biopsy findings				0.85
Positive	56 (71.8%)	36 (70.6%)	20 (74.1%)	
Negative	6 (7.7%)	5 (9.8%)	1 (3.7%)	
Unknown	16 (20.5%)	10 (19.6%)	6 (22.2%)	

Values presented as mean ± standard deviation or n (%).
CSF: cerebrospinal fluid. Abnormal CSF is defined by either wbc >5 hpf or protein >45 mg/dl.

Treatment history

Information regarding the initial/induction treatment history was available for 25 of 27 patients. All the patients were treated with glucocorticoids. Thirteen patients received glucocorticoids only (52%), and 11 patients received glucocorticoids plus cyclophosphamide (CYC) (44%), of which 6 had intravenous (IV) and 5 had oral CYC. One patient received both glucocorticoids and mycophenolate mofetil.

Radiologic findings

Brain MRIs of 21 patients were available for re-examination by an independent neuroradiologist. Findings included pachymeningeal involvement (28.6%) leptomeningeal involvement (23.8%), grey matter enhancement (33%), abnormal signal/enhancement of white matter (86%), cerebral haemorrhage (23%), and mass effect in only 1 patient (0.04%).

Outcome measures

Using the Barthel Index scale, 19 of 27 patients (70.4%) scored 85 or more, indicating mild disability. Meanwhile, three patients (11.1%) scored between 26 and 84, indicating moderate disability and five (18.5%) patients scored 25 or less, indicating severe disability. Severe disability was more common in patients with a history of stroke; however, this difference was not statistically significant given the small sample size ($p>0.99$) (Fig. 1).

Using the EQ-5D-5L questionnaire, 14 of 27 patients (51.9%) had no problems with mobility, 18 (66.7%) had no problems with self-care, 15 (55.6%) had no problems with usual activities, and 14 (51.9%) had no problems with pain, but only 8 (29.6%) had no problems with anxiety (Fig. 1). Approximately 70% of patients had minimal or no depression using both the PHQ-9 scale (67%) and EuroQol (70%) (Fig. 1).

Correlations between clinical findings and outcome measures

Age and gender did not predict any of the outcome measures or mortality (Table II). Further, no statistically significant difference was observed

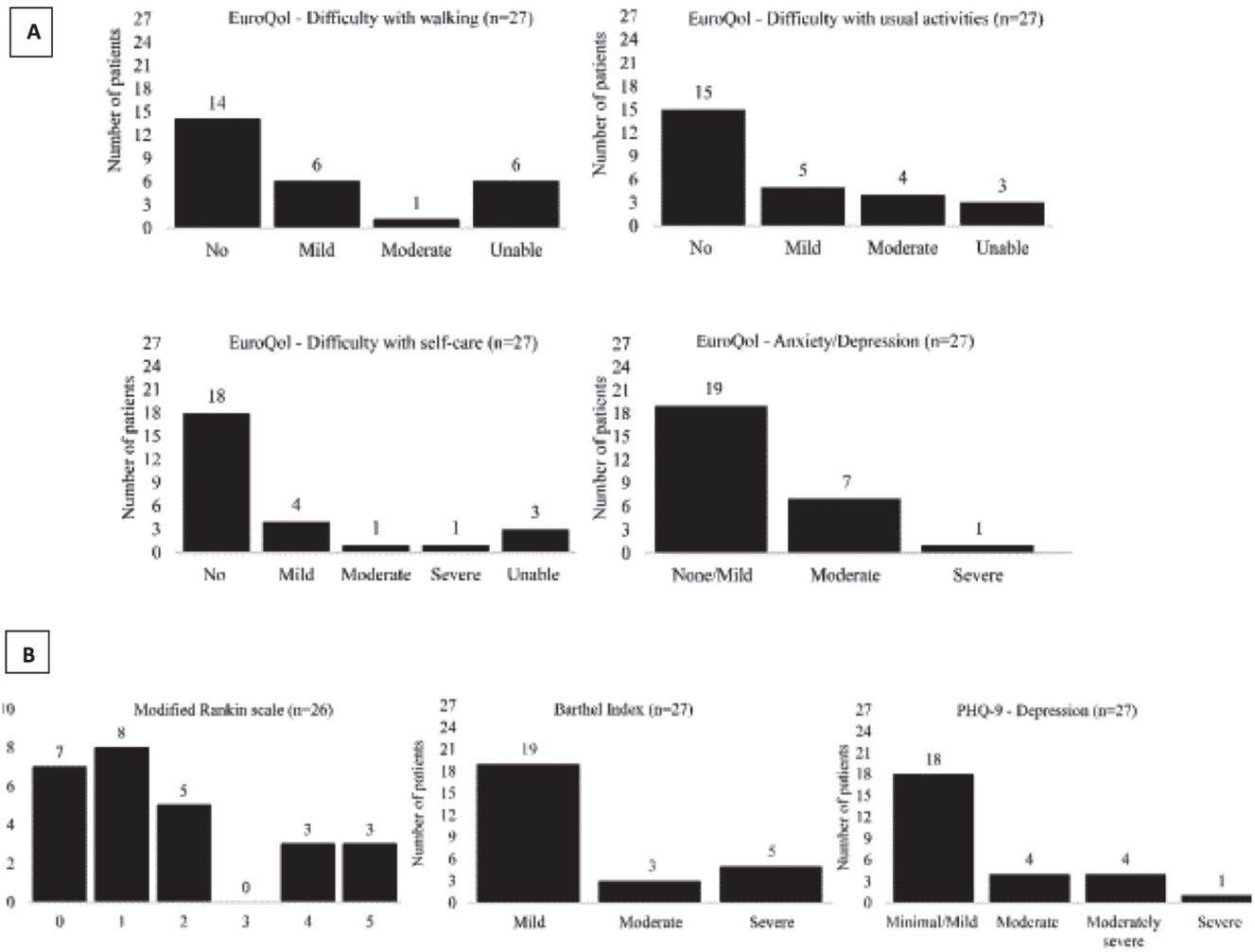

Fig. 1. A-Functional capabilities, quality of life of patients with PACNS. B- Modified Rankin Scale, Barthel Index and PHQ9 in patients with PACNS.

Table II. Univariate analysis of independent variables and outcome measures.

Variable	Rankin score (4-6 *vs*. 0-3) OR (95% CI)	Barthel score (0-84 *vs*. 85-100) OR (95% CI)	PHQ-9 score (5-27 *vs*. 0-4) OR (95% CI)	EuroQOL Mobility (2-5 *vs*. 1) OR (95% CI)	EuroQOL Self-care (2-5 *vs*. 1) OR (95% CI)	EuroQOL Usual activities (2-5 *vs*. 1) OR (95% CI)
Gender (male *vs*. female)	0.82 (0.13 – 5.08)	1.85 (0.34 – 10.05)	1.17 (0.26 – 5.29)	1.67 (0.26 – 5.29)	2.50 (0.47 – 13.27)	1.60 (0.35 – 7.40)
Headache (yes *vs*. no)	0.67 (0.09 – 4.81)	1.38 (0.21 – 8.98)	0.44 (0.08 – 2.38)	4.13 (0.65 – 26.01)	1.75 (0.27 – 11.15)	3.33 (0.53 – 20.91)
Stroke (yes *vs*. no)	2.00 (0.30 – 13.51)	1.85 (0.34 – 10.05)	2.13 (0.46 – 9.94)	2.13 (0.46 – 9.94)	1.25 (0.25 – 6.23)	1.60 (0.35 – 7.40)
Seizure (yes *vs*. no)	1.17 (0.17 – 8.19)	0.72 (0.11 – 4.69)	1.11 (0.21 – 5.80)	1.11 (0.21 – 5.80)	1.30 (0.23 – 7.32)	1.38 (0.26 – 7.22)
CSF (abnormal *vs*. normal)	N/A	N/A	0.50 (0.04 – 6.35)	0.50 (0.04 – 6.35)	1.14 (0.09 – 14.68)	0.42 (0.03 – 5.30)
Age (50+ years *vs*. <50)	0.50 (0.07 – 3.38)	0.67 (0.12 – 3.62)	0.33 (0.07 – 1.62)	1.14 (0.25 – 5.22)	1.96 (0.39 – 9.93)	0.82 (0.18 – 3.78)
Angiographic findings (abnormal *vs*. normal)	0.88 (0.13 – 5.82)	1.17 (0.19 – 7.12)	2.10 (0.38 – 11.59)	1.00 (0.19 – 5.36)	0.75 (0.13 – 4.29)	0.71 (0.13 – 3.87)
Diagnosis mode (angiography *vs*. biopsy)	2.00 (0.27 – 15.08)	2.25 (0.37 – 13.71)	1.63 (0.29 – 9.26)	0.75 (0.13 – 4.25)	1.75 (0.30 – 10.34)	0.92 (0.16 – 5.21)
Cyclophosphamide (yes *vs*. no)	3.33 (0.33 – 34.12)	1.75 (0.27 – 11.15)	1.25 (0.25 – 6.23)	0.64 (0.13 – 3.20)	1.00 (0.18 – 5.46)	0.51 (0.10 – 2.57)

in the following outcome measures (Rankin scores, Barthel index, PHQ -9, and mobility, self-care, usual activity domains of the European quality of life) and the presence of headache, seizure, stroke at presentation, or the presence of CSF abnormality. When the analysis was done comparing the entire distribution with the slightly more powerful Kruskal-Wallis test, patients with stroke had significantly higher incidence of depression/anxiety, as assessed by the European quality of life measures of depression, than those who did not (p=0.04).

Lastly, presenting with headache, stroke or seizure did not predict mortality (p=0.1, >0.99, 0.2, respectively).

Correlations between mode of diagnosis and outcome measures

Comparison of angiographically-diagnosed patients with biopsy-proven patients showed no significant differences in outcome measures. (Table III).

Correlations between treatment history and outcome measures

Longer duration of immunosuppressive treatment was associated with improvement in Barthel index (p=0.8), self-care (p=0.7), usual activities (p=0.8), pain/discomfort (p=0.1) and PH-9 scores (p=0.9); however, none of these results reached statistical significance. Further, the use of cyclophosphamide did not affect the outcome.

Correlations between radiological findings and outcome measures

Presence of grey matter enhancement was significantly correlated with worse mobility (R=0.4, p=0.04), anxiety/depression (R=0.4, p=0.04), visual analogue scale (R=-0.6, p=0.009), and PHQ-9 scores (R=0.5, p=0.03). However, no significant correlation was found between radiologic white matter changes and outcome measures.

Table III. Comparison of angiography- and biopsy-diagnosed PACNS patients.

	Angiography-diagnosed (n=7)	Biopsy-diagnosed (n=20)	p-value
Gender (Male/Female)	5/2	8/12	0.15
Headache	4 (57%)	15 (75%)	0.37
Stroke	5 (71.4%)	9 (45%)	0.22
Seizure	0	8 (40%)	0.04
Abnormal CSF	7 (100%)	12 (84.2%)	0.29
Total Barthel score	69.2 ± 44.9	83 ± 29.9	0.57
Visual analogue scale	70.6 ± 27.6	62.2 ± 28.3	0.54
PHQ-9 score	9.5 ± 9.2	6.4 ± 5.8	0.55
Modified Rankin scale	2 ± 2.3	1.6 ± 1.5	>0.99
Euro-QOL subscales			
Mobility	2.2 ± 1.8	2.1 ± 1.6	0.92
Self-care	2.3 ± 1.8	1.6 ± 1.1	0.40
Usual activities	2.2 ± 1.8	1.8 ± 1.1	0.80
Pain discomfort	1.8 ± 1	1.7 ± 0.8	0.80
Anxiety/depression	2 ± 1	2.1 ± 0.9	0.92

Values presented as mean ± standard deviation or n (%).
PHQ-9: patient health questionnaire-9; EuroQOL: EQ-5D-5L: European quality of life questionnaire; MRS: modified Rankin scale.

Table IV. Comparison of published PACNS cohorts.

Cohort n.	Salvarani 101	De Boysson 52	Present cohort 78
Mode of diagnosis			
Biopsy (%)	30%	36.5%	74.1%
Angio (%)	70%	63.5%	25.9%
Abnormal CSF‘	*58% & 37%**	*61%*	*100%*
Median follow-up (mo)	13 (0- 163)	35 (2-148)	60 (0-204)
Mortality rate (%)	17.0%	6.0%	11%
Modified Rankin scale	MRS 0-3 77 %	Median MRS≤2 (1-5)	Median MRS 1 (0-5)
Number of patients analysed	39	52	27
Follow-up period	1-4.9 years	35 months (2-148)	60 months (0-204)

‘Percentage of patients with abnormal CSF who are diagnosed by angiogram.
*58% had abnormal CSF protein and 37% had abnormal CSF wbc.

Discussion

The present study represents the first evaluation of the quality of life and incidence of depression in patients with PACNS with the longest follow-up duration in the literature to date (median follow-up was 60 months). The findings of this study indicated that the majority of PACNS patients had mild long-term disability with median Rankin disability score of 1 (range: 0–5) along with the majority indicating mild to no depression. Further, this is the first study to evaluate patient centered outcome measures in PACNS, using different surveys.

Compared to other reported cohorts in the literature, two additional studies used a modified Rankin disability scale (MRS) to measure disability in PACNS patients. The first cohort published by Salvarani *et al*. reported on 101 patients, diagnosed between 1983–2003, with a median follow-up of 13 months (0-13.7 years); 57 (56%) patients had MRS scores of 0–2 at diagnosis (5); long-term follow-up using Rankin scores was available on 39 patients (follow-up of 1–4.9 years) with 77% (30/39) having a Rankin score of 0–3; long-term follow-up >5 years was reported in only 14 patients with Rankin score of 0–3 in 71% (10/14) of patients. It was not clear in this study how many patients had no, mild or moderate disability since patients were reported together as one category. De Boysson *et al*. analysed 52 patients with median follow-up of 35 months (2–148); the majority of survivors had MRS ≤2 at follow-up (6).

The disability score differences among the various cohorts can be related to diverse inclusion criteria, differences in treatment regimens and follow-up duration of the reported cohorts. Median follow-up in our cohort was 60 months, compared to 35 and 13 months in the other cohorts (5, 6). The diagnosis was secured based on pathologic findings in 74% of our cohort compared to 36.5% and 30% in de Boysson and Salvarani cohorts, respectively. In this current study, patients with angiographic diagnosis should have demonstrated an inflammatory CSF pattern; in contrast to the Salvarani cohort where only 58% and 37% of patients angiographically diagnosed had abnormal CSF protein and leukocyte count, respectively. Only 61% of angiographically diagnosed PACNS in the de Boysson cohort had abnormal CSF findings. These differences in the inclusion criteria could have affected the outcome measures in the different cohorts. In addition, more recent advances have discerned the importance of ruling out

RCVS, a major angiographic mimic of PACNS. The definition of RCVS as an entity in 2007 is considered a major breakthrough in understanding and eliminating the mimics of PACNS. Prior to 2007, RCVS was not well characterised which could have added to the contamination of some of the cohort with this syndrome.

Further, we have used both patient-reported and physician-reported outcome measures to assess long-term disability in PACNS. Results from these scales correlated with each other (70% of patient self-reported mild disability by the Barthel index compared to 76% of patients deemed to have mild disability by physicians using the Rankin scale).

Although patients with PACNS appear to have improvement in their overall disability scores following the diagnosis of PACNS, to our knowledge, there has not been any research done to measure the quality of life and incidence of depression in these patients. It has been demonstrated that one-third of patients who had a stroke will experience "post-stroke depression" (15). Given that an estimated 30–50% of patients with PACNS present with stroke, depression is likely to be under recognised in this patient population (16). In this study, the majority of patients had minimal to no depression, anxiety, or difficulty with walking, usual activities, and self-care. However, the incidence of clinical depression was 30% in PACNS cases, which demonstrates the importance of depression counseling during follow-up with these patients. Further, depression correlated with stroke in this cohort.

Studies have reported mild long-term disability in the majority of the patients with PACNS; however the mortality rate remains high compared to the general population, although it has improved dramatically since the initial description of PACNS (6). The mortality rate of patients with PACNS varies from 6% to 17% (5, 7). The mortality rate was 6% in the de Boysson *et al*. cohort which had a median follow-up of 35 months (range, 2–148 months) (6). In our cohort, 11% of patients were dead at 60 months follow-up (0-204 months), and Salvarani *et al*. reported 17% mortality at 12 months (0–164.4) (Table IV) (7).

Unpredictable course, lack of prognostic predictors and biomarkers for follow-up of PACNS patients lead to challenges in the management of these cases. A number of studies have been performed recently to identify such predictors (6, 7). Candidate predictors that have shown some prognostic factors such as meningeal gadolinium enhancement on MRI, history of seizure, diagnosis by angiography, increasing age, cerebral infarction on MRI presence of large-vessel involvement on angiogram and amyloid angiopathy. This prognostic stratification should be examined with caution given the low number of patients and the lack of validation of these findings in other cohorts (7). In our cohort we did not find any correlation with any of the outcome measures and the presence of headaches, seizures or strokes at presentation, except that patients with stroke had significantly higher incidence of depression/anxiety. The presence of grey matter enhancement carried a worse prognosis.

Our study has limitations; although the rate of survey response in our study (34.6%) is similar to what has been reported in the literature (39%), sample size is small rendering the extrapolation of prognostic factors, but considering the rarity of PACNS, the data derived from responders are very valuable. Further there was no statistically significant difference in the characteristics of responders and non-responders; however, our results should be further validated in a larger cohort which could be challenging in this rare disease.

Another limitation of the study is the retrospective capture of information on treatment. Nevertheless, longer duration of immunosuppressive treatment was associated with a trend in improvement in different outcome measures; however, none of these results reached statistical significance and should be interpreted carefully given the bias in capturing medication duration. Further, the use of cyclophosphamide did not predict a better outcome in this cohort. These data must be interpreted with caution since PACNS is a heterogeneous disease and the treatment is not standardised. Almost every patient is treated with glucocorticoids, the addition and the selection of other immunosuppressive medications is dictated by the extent of the disease, the degree of patient deficit and the certainty of the diagnosis. The selection of an immunosuppressive in this cohort was not randomised, and conclusion on the use of cyclophosphamide should be carefully interpreted.

Conclusion

This is the longest reported follow-up of patients with PACNS described in the literature to date and the first evaluation of the quality of life and incidence of depression in these patients. Most of the patients had mild long-term disability, no difficulty with walking, usual activities, and self-care, which may be reflective of improved management of this disease and/or earlier diagnosis and recognition. One-third of patients with PACNS had depression, which should be kept in mind during the long-term follow-up of these patients. Lastly, the mortality rate is high in patients with PACNS, and potential prognostic markers should be identified and validated in large cohorts.

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