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ORIGINAL COMMUNICATION

Relapse rates and long-term outcome in primary angiitis of the central nervous system

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Abstract

Objective To analyze the treatment response in patients with primary angiitis of the central nervous system (PACNS).

Methods In a single-center retrospective observational study, we assessed relapses, remission, and long-term outcome by use of the modified Rankin Scale (mRS) under different immunotherapies. Eligible patients had CNS biopsy in favor of PACNS or neuroimaging compatible with PACNS after exclusion of an alternative diagnosis. Regression models, recurrent event, and linear mixed-effects models were used to estimate the annual relapse rate, relapse and outcome predictors. Favorable outcome was defined as mRS < 3.

Results Of 44 patients, 26 (59%) were female, median age at diagnosis was 43.5 (range 14–83) years, and 25 (57%) had biopsy-proven diagnosis. Median follow-up was 5.1 years. Glucocorticoids were administered in 30 patients at diagnosis (68%), 33 patients (75%) received cyclophosphamide, and 86% of patients had maintenance therapy > 24 months. Overall, 201 treatment episodes with 104 relapses and 4 (9%) deaths occurred. 26 patients had relapses (59.1%). The annual relapse rate was 1.4 (CI 1.1–1.8). Male sex was the only significant predictor of relapse (HR = 3.27, 95% CI 1.57–6.82). Remission occurred in 30 patients (68%). Favorable outcome was evident in 80% of patients after 2 years and 66% of patients at last follow-up.

Conclusions PACNS is a relapsing-remitting disease with a heterogeneous disease course and mostly favorable outcome under immunotherapy. Male patients have a higher relapse risk; no other relapse or outcome predictor could be identified. PACNS subtype stratification is needed to further evaluate predictors of response.

Keywords Primary angiitis of the central nervous system · Cerebral vasculitis · Young stroke · Immunotherapy · Outcome

Introduction

Primary angiitis of the central nervous system (PACNS) is a rare autoimmune disease with inflammation of vessels exclusively in the central nervous system, mainly manifesting with encephalitis or stroke [1–4]. Prior cohort studies characterized different subtypes of the disease with distinct clinical, radiological, and histopathological findings such as angiography-negative small-vessel PACNS or angiographically defined medium-sized vessel PACNS with negative CNS biopsy [5–13]. The defined subtypes were shown to differ in terms of prognosis and optimal therapy regimen [14]. Higher relapse rates were identified in patients with biopsy-proven, angiography-negative PACNS, or initial seizures [9, 10, 13]. Contradictory results were seen for patients with contrast-enhanced lesions on MRI with either a higher [9] or lower [7] relapse risk. High disability scores were associated

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with increased age, strokes on MRI, and angiographically large-vessel involvement [7].

With regard to therapy, no randomized-controlled trials have been performed for PACNS. Current suggestions for treatment derive from therapeutic strategies from systemic vasculitis and retrospectively assessed experience with PACNS [7, 15–19]. Glucocorticoids (GCs), often combined with cyclophosphamide (CYC), are recommended for induction therapy. Alternatively, rituximab (RTX) is considered as the first-line immunotherapy supported by its effective use in anti-neutrophil cytoplasmatic antibody-associated vasculitis [20, 21]. Once remission is achieved, maintenance therapy with azathioprine (AZA), mycophenolate mofetil (MMF), or methotrexate (MTX) for up to 24 months is usually suggested to sustain disease control. A recently published long-term follow-up study showed a better functional outcome and lower relapses in PACNS patients who received maintenance therapy [19, 22].

We describe the relapse rate and long-term functional outcome of PACNS patients under different immunotherapies and aimed to identify predictors of relapse and outcome.

Methods

Study cohort and diagnostic criteria for PACNS

Our single-center cohort consists of patients diagnosed at our hospital between 1 January 2008 and 1 August 2017. Only patients with at least 6 month follow-up were eligible (unless death occurred before). Part of the cohort was already included in a publication about diagnostic findings in PACNS [6]. We used the same predefined diagnostic and exclusion criteria as recently described: A biopsy was demanded for definite diagnosis (biopsy-proven group) and was considered positive if vascular inflammation of intracranial arterioles was present and neuropathologist's overall evaluation resulted in the diagnosis of CNS vasculitis. The different histopathological patterns of inflammation were recorded as previously described and included granulomatous vasculitis with/without amyloid deposition, as well as lymphocytic and necrotizing vasculitic changes [23]. A probable diagnosis was established in patients with abnormal findings on neuroimaging consistent with the diagnosis of PACNS and after thorough exclusion of other vasculopathies (imaging-based group). Findings in favor of the diagnosis of PACNS included alternating areas of narrowing or multilocular occlusions of intracranial vessels in the absence of stenosis or atherosclerotic plaques of the extracranial vessels and the lack of major vascular risk factors. In the presence of an inflammatory CSF analysis, infectious causes or an angiocentric CNS lymphoma were ruled out thoroughly. We also took care not to include patients with features related to reversible cerebral vasoconstriction syndrome (RCVS) such as thunderclap headache, a history of exposure to vasoactive substances, or an occurrence in the postpartum period. Finally, the clinical course was taken into account, and only patients with disease progression or relapsing episodes over a period of > 12 weeks were diagnosed with PACNS to exclude the diagnosis of RCVS.

The retrospective observational study was not submitted to an institutional review board. Our diagnostic and therapeutic protocol that we evaluated was according to national guidelines and standards of current practice.

Data collection and processing

Data collection included demographic data, information about the clinical manifestation, initial cerebrospinal fluid findings, neuroimaging studies, histopathology of brain biopsy specimen, detailed treatment regimen data (compounds, start/ stop dates and dosages), onset and frequency of relapses with clinical and radiological information, and regular functional outcome measures. Treatment data were validated through manual quality checks (SS), as well as by automated logical checks (AKO).

Study variables and definitions

Definition of treatment episodes

A treatment episode is defined as the period of time between the first administration of GC-sparing immunotherapy and the expected end of effectiveness of GC-sparing immunotherapy. Most immunotherapies continue to have an effect after administration of the last dose. Therefore, based on pharmacodynamics and treatment experience, we defined the effectiveness of GC-sparing immunotherapy after the last dose as follows: 180 days for RTX; 90 days for mitoxantrone (Mitox); 60 days for infliximab (IFX); 30 days for CYC, AZA, MMF, ciclosporin A, leflunomide and intravenous immunoglobulins; 14 days for tocilizumab (TCZ); and 7 days for interferon-β (IFN) and methotrexate (MTX). Potential delayed effectiveness after the first dose of GC-sparing immunotherapy was not considered. In recurrent treatment episodes with the same compound, we merged the two cycles if the first dose of the second episode was within the assumed effectiveness period. No therapy was also considered as a treatment episode and was defined as the period of time between the first day without therapy, if there was no GC-sparing immunotherapy before, or the expected end of effectiveness of the previous GC-sparing immunotherapy, and ended with the administration of a GC-sparing immunotherapy. Concomitant use of intravenous and oral GCs during the treatment episodes was not considered as a combination therapy. GC treatment alone was not considered as

a treatment episode due to the lack of dosage data and exact start and stop dates of GC medication. Oral GC comedication is specified if present.

Definition of first-line therapy

First-line therapy was defined as the initial GC-sparing immunotherapy initiated within 3 months after the first diagnosis of PACNS. First-line maintenance therapy was defined as the initial GC-sparing immunotherapy chosen within 3 months after stop of induction therapy. Induction therapies were either CYC or RTX. No therapy was also considered as first-line therapy regimen.

Definition of relapse

Relapse was defined as the reoccurrence or worsening of neurological symptoms attributable to active PACNS, or worsening of existing and/or evidence of new abnormal neuroimaging findings on MRI consistent with PACNS activity, and requirement of treatment change or escalation. Clinically silent neuroimaging changes, e.g., new diffusion-weighted imaging findings, contrast-enhanced lesions or progressive intracranial stenosis, were also considered as relapses and triggered escalation of immunotherapy. MRI monitoring was obtained approximately every 6 months in the first 2 years, afterwards annually, and in between depending on the clinical course of the disease. Due to the retrospective nature of the study, there was no uniform neuroimaging monitoring protocol. CSF analysis was not widely used as a disease monitoring marker and was not included in the definition of relapse.

Definition of remission

Remission was defined as no relapse within 6 months under the first-line therapy.

Outcome assessment

Functional outcome status was evaluated using the modified Rankin Scale (mRS), calculated on the basis of medical records: 0 = no neurological signs or symptoms; 1 = no significant disability, despite symptoms; 2 = slight disability (able to look after own affairs without assistance, but unable to carry out all previous activities); 3 = moderate disability (requires some help with activities of daily living, but able to walk unassisted); 4 = moderately severe disability (unable to attend to own bodily needs without assistance, and unable to walk unassisted); 5 = severe disability (requires constant nursing care and attention, bedridden, incontinent); 6 = death; mRS was recorded at the following time points: at first diagnosis, at first-line therapy start, 6, 12, 24, 36, 48, 60, and 72 months after start of first-line therapy. Favorable outcome was defined clinically as mRS ≤ 2.

Statistical analysis

Our statistical analysis was designed (1) to describe prescription reality of immunotherapies at our institution, (2) to analyze relapse rates under different therapy regimen, (3) to investigate long-term functional outcome, and (4) to explore the data set for predictors of response. Descriptive analysis was performed with mean, standard deviation, median, minimum, and maximum for continuous data. Percentages are given for categorical data. The annual relapse rates with 95% confidence intervals were estimated using the negative binomial regression. A multivariable recurrent event analysis was conducted using the model by Andersen and Gill [24] and the following independent variables: age, sex, seizures, contrast enhancement on MRI, diagnostic category (biopsy-proven, imaging-based), and therapy. Relapses and death were considered as events. Hazard ratios are given with 95% confidence intervals. The influence of age, sex, seizures, contrast enhancement on MRI, diagnostic category, and immunosuppressant therapy/no therapy on mRS over time was analyzed with a linear mixed-effects model. Time was included in the model as a continuous variable and autocorrelation [AR1 (0.5)] was used. Judged by the Akaike information criterion, a model with only a random intercept and without a quadratic or cubic time variable fitted the best compared to the models including those terms. As described before, for the negative binomial regression as well as the multivariable recurrent, event analysis and the mixed model only monotherapies with immunosuppressants or "no therapy" were included. A significance level of 0.05 was considered, and due to the explorative design, no adjustment for multiple analysis was conducted. The analysis was performed with the statistic software R version 3.5.1 [25].

Results

Demography and follow-up time

44 patients with PACNS were included in the study. 26 patients were female (59%). The median age at diagnosis was 43.5(14–83) years. Neurological deficits were present in 36 patients (81.8%), headaches in 28 patients (63.6%), cognitive decline in 15 patients (34.1%), and seizures in 12 patients (27.3%). PACNS was biopsy-proven in 25 patients (57%) and imaging-based in 19 patients (43%). In the biopsy-proven PACNS patients, MR angiography showed vessel changes in merely 2 patients, only 5 patients had ischemic strokes, rather gadolinium-enhanced lesions (parenchymal or meningeal) were present in 20 patients, and 5 patients

had mass lesions. In contrast, all patients in the imaging-based group had ischemic strokes and vessel changes on MR angiography, gadolinium-enhanced lesions were only seen in 4 of 19 patients. CSF was abnormal in 81.8% of patients (36/44) initially. The following histopathological patterns were found: 4 patients had a granulomatous PACNS, further 4 patients had a granulomatous vasculitis with beta-amyloid deposition (ABRA), 8 patients had a lymphocytic PACNS, and 2 patients had a necrotizing vasculitis. In 7 patients, the pattern could not be classified in a specific subtype. The median time from first manifestation to first diagnosis was 30.1 days. The median duration of follow-up was 5.1 years.

Treatment regimen

All 44 patients had sufficient baseline and treatment data. Start and stop dates as well as dosages were available for all GC-sparing immunotherapies; detailed dosing data are briefly specified for the most common treatment regimen: Intravenous CYC regimen was 750 mg/m^2, infused once a month, generally for 6 months; dosage was increased in refractory disease to 1000 mg/m^2. RTX was administered as two 1000 mg infusions separated by 14 days, followed by 1000 mg infusions every 6 months. Dosage of MTX was appr. 0.3 mg/kg, dosage of MMF was appr. 2000 mg, and dosage of AZA was appr. 2 mg/kg daily. GC pulse therapy consisted of 1000 mg methylprednisolone intravenously for 3–5 days. Documentation of the GC tapering schemes was insufficient and varied from quick tapering (< 5 mg after 3 months, no GC therapy after max. 6 months) to long-term low-dose GC therapy.

First-line GC-sparing immunotherapy (within 3 months after establishing the diagnosis) were cyclophosphamide ($n = 33$), rituximab ($n = 3$), methotrexate ($n = 2$), and azathioprine ($n = 1$). 5 patients had no GC-sparing immunotherapy as first-line therapy regimen, of whom 2 had oral GC therapy initially, while 3 patients did not receive any therapy. Those patients either had low disease activity or refused treatment. Rituximab was given privilege to cyclophosphamide in younger patients. GC pulse therapy and/ or oral GC tapering were administered in 30 patients (68.2%) as part of the first-line therapy regimen. 19 of 33 patients with CYC induction had concomitant GC therapy (58%).

First-line maintenance GC-sparing immunotherapy (after induction with CYC or RTX, $n = 36$, within 3 months after end of induction treatment) were MTX ($n = 11$), MMF ($n = 10$), AZA ($n = 5$), and RTX ($n = 5$); 2 patients had no further therapy, 1 patient died during CYC induction, 1 patient had no further follow-up, and 1 patient had overlapping treatment afterwards and was, therefore, excluded from the analysis. Overall, 94% of patients received maintenance GC-sparing immunotherapy after induction therapy. After 24 months, 86.4% of patients, and after 48 months, 63.3% of patients still received maintenance treatment.

In total, 12 different immunotherapeutic drugs were used and 201 treatment episodes could be identified during the follow-up. The median number of different treatment episodes (including no therapy) per patient was 3 (range 1–12). The sequence of compounds used after the first-line therapy was very heterogeneous.

The most commonly used immunotherapies summing up to 104 treatment episodes were CYC ($n = 41$) with 20 patient years in 35 patients, MTX ($n = 24$) with 40 patient years in 18 patients, RTX ($n = 14$) with 16 patient years in 14 patients, AZA ($n = 13$) with 32 patient years in 10 patients, and MMF ($n = 12$) with 28 patient years in 12 patients. GC comedication was present in 39 of the 104 treatment episodes (38%). 52 treatment episodes without GC-sparing immunotherapy were registered in 35 patients with 87 patient years, of which 15 had GC medication (29%). In 39 treatments, an overlap of treatment durations or a combination of two or more compounds occurred including immunotherapy with intravenous immunoglobulins, ciclosporin A, and tocilizumab. Those data were too heterogeneous to reliably analyze combination therapies. Therefore, our investigations were restricted to monotherapies and were excluded from the analysis. Seldom monotherapies ($n = 6$ treatment episodes) in our cohort were IFN and IFX ($n = 2$); Mitox and LEF ($n = 1$).

Besides immunotherapy, 31 of 44 patients (70.5%) received antiplatelet drugs, including all patients with strokes and vessel changes on MR angiography.

Relapses

26 patients had relapses (59.1%): 5 had one relapse, 9 had two relapses, and 12 had more than 2 relapses. The median time span from diagnosis to relapse was 579 (range 0–2529) days.

In total, 104 relapses occurred in 201 treatment episodes, 3 resulting in death. One death additionally occurred, which was not related to PACNS summing up to an overall mortality rate of 9%. Relapses and death during non-overlapping treatment episodes ($n = 162$) are visualized in Fig. 1 for all patients and in Fig. e-1 for biopsy-proven and imaging-based PACNS patients separately (supplementary material).

61 relapses were seen under the most common treatment regimen of our cohort including CYC, MTX, RTX, AZA, MMF, and no GC-sparing immunotherapy, with an annual relapse rate of 1.4 (CI 1.1–1.8). Descriptive statistics per treatment are shown in Table 1.

In a multivariable recurrent event analysis, we investigated, if sex, age at disease onset, seizures, initial contrast enhancement on MRI, the diagnostic category used (biopsy-proven vs. imaging-based), or therapy may influence relapse

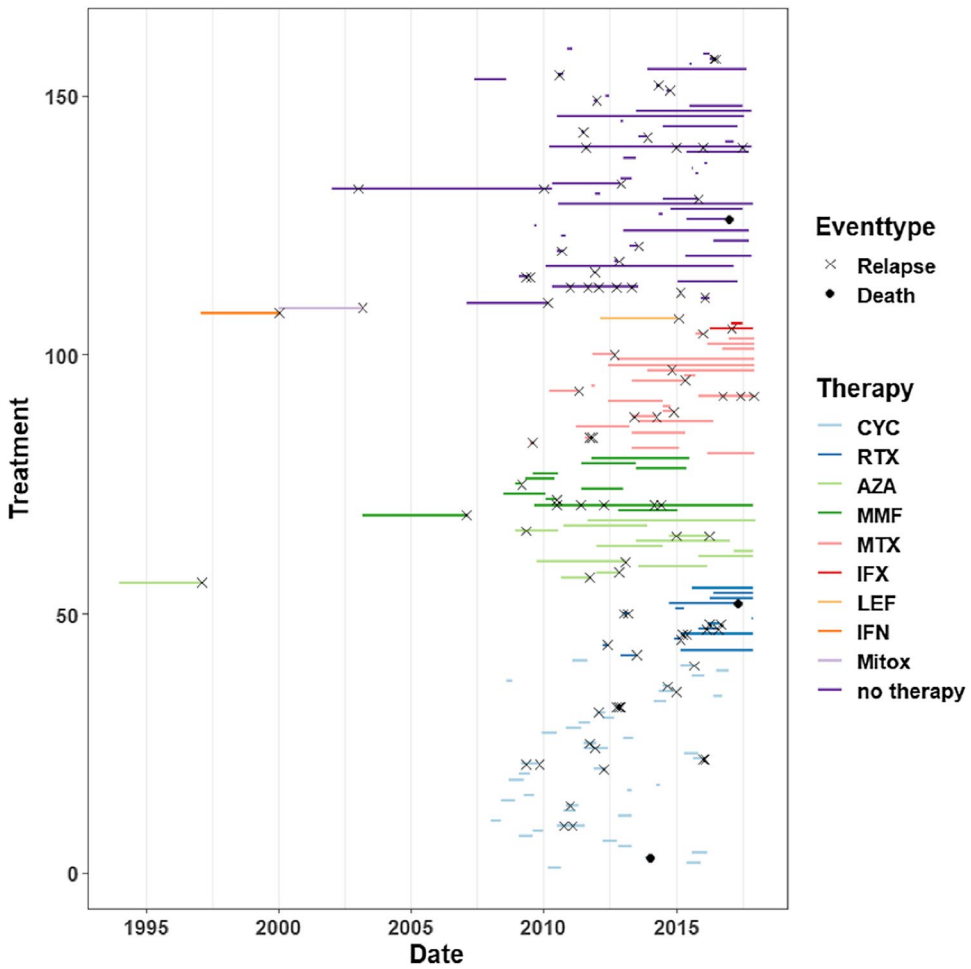

Fig. 1 Non-overlapping treatment episodes in our single-center cohort. Lines represent all treatment episodes over time. Relapses are marked as crosses and death as dots. Data are sorted by treatment regimen. *CYC* cyclophosphamide, *RTX* rituximab, *AZA* azathioprine, *MMF* mycophenolate mofetil, *MTX* methotrexate, *IFX* infliximab, *LEF* leflunomide, *IFN* interferon-β, *Mitox* mitoxantrone

occurrence. Only male sex increased the relapse risk compared to female sex (HR = 3.27, 95% CI 1.57–6.82). Age at onset, seizures, initial contrast enhancement on MRI, diagnostic category, or the therapy regimen did not significantly influence the occurrence of relapses.

29 patients had a follow-up of at least 60 months. 19 of them had relapses within 30 months after start of first-line therapy (65.5%) and 12 patients had further relapses beyond 30 months (41.4%). All 12 patients who relapsed > 30 months had relapses before, while patients without relapses < 30 months stayed relapse-free > 30 months.

Rate of remission and long-term functional outcome

The median baseline mRS at the first diagnosis was 2. Remission occurred in 30 patients (68.2%), and the remaining 14 patients had relapses within 6 months after diagnosis under first-line therapy regimen. 20 of 30 patients in remission (66.7%) and 13 of 14 patients (92.9%) without remission had CYC induction treatment.

At the time of diagnosis, 27 patients had mRS scores ≤ 2 (61.4%). 33 patients with a median mRS score of 3 received first-line induction treatment with CYC and 11 patients were treated otherwise (median mRS = 2). The median mRS score was stable in the non-CYC group, while the median mRS improved 1 point in patients receiving CYC (in a 6 month time period). 6 months after start of first-line therapy, 33 of 42 patients (78.6%) had favorable outcomes; 25 of the 33 patients with favorable outcome had CYC induction, the remaining 8 had another initial therapy. After 2 years, favorable outcome was seen in 31 of 39 patients (79.5%), of whom 23 had CYC induction and 8 were treated otherwise initially. Most of the patients still received immunotherapies at month 24 after diagnosis (33/38, 86.4%). After 4 years, 19 of 30 patients (63.3%) had mRS scores ≤ 2. 17 of 28 patients (60.7%) still received immunotherapy 48 months after diagnosis. After 6 years, 13 of 20 patients had a favorable outcome (65%). 8 of 18 patients were still under treatment (44.4%). Figure 2 shows mRS scores of all patients during a follow-up of 6 years. Figure e-2 (supplementary material) illustrates functional outcome separately for the biopsy-proven or imaging-based cohort. Worsening occurred

Table 1 Descriptive statistics per treatment

	CYC	RTX	MTX	AZA	MMF	No GC-sparing immunotherapy
Patients receiving treatment	35	14	18	10	12	35
Females, *n* (%)	17 (48.6)	7 (50)	7 (38.9)	6 (60)	8 (66.7)	22 (62.9)
Age, median (SD)	47 (14.34)	40.5 (12.94)	49.5 (14.74)	46.5 (16.29)	39 (15.07)	43 (14.49)
Biopsy-proven, *n* (%)	19 (54)	8 (57)	10 (55.6)	6 (60)	10 (83.3)	21 (60)
Treatment episodes	41	14	24	13	12	52
Episodes without relapse, *n* (%)	28 (68.3)	6 (42.9)	14 (58.3)	7 (53.8)	8 (66.7)	32 (61.5)
First-line treatment	33	3	2	1	0	5
Maintenance therapy (after induction with CYC or RTX)	NA	5	11	5	10	2
Rate of 1st line therapy per drug, %	80.5	21.4	8.3	7.8	0	9.6
Rate of drug as first-line treatment in the cohort, %	75.0	6.8	4.5	2.3	0	11.4
Rate of first-line maintenance therapy per drug, %	NA	35.7	45.8	38.5	83.3	3.8
Rate of drug as first-line maintenance therapy after RTX or CYC induction in the cohort, %	NA	11.4	25.0	11.4	22.7	4.5
GC comedication, *n* (%)	23 (56)	5 (35.7)	6 (25)	4 (30.8)	1 (8.3)	15 (28.8)
Treatment duration, median (days)	181	243	539	913	640	122
Cumulative treatment years	19.55	16.48	39.93	32.45	28.01	87.49
Annualized relapse rate, median (95% CI)	1.944 (1.209–3.318)	1.167 (0.6956–2.179)	1.286 (0.6588–2.587)	1.429 (0.5576–3.902)	1.5 (0.4345–4.586)	1.167 (0.7115–1.921)
Duration in days from date of first diagnosis to treatment start	0 (0–2130)	411.5 (0–2381)	228.5 (0–2221)	212 (−5903 to 1218)	197 (−2558 to 272)	167.5 (−4017 to 2556)

only in patients still treated and was not due to cessation of immunotherapy.

With a linear mixed-effects model, the influence of age, sex, seizures at diagnosis, initial contrast enhancement on MRI, diagnostic category, and therapy regimen on the functional outcome measure mRS was investigated. None of the variables could be identified as a predictor of functional outcome.

Discussion

Immunotherapy is, in general, recommended in PACNS patients, as ongoing disease activity may cause serious and often irreversible disability. We retrospectively investigated "real-life" management of PACNS in our single-center cohort of 44 patients with an observation period of 240 treatment years.

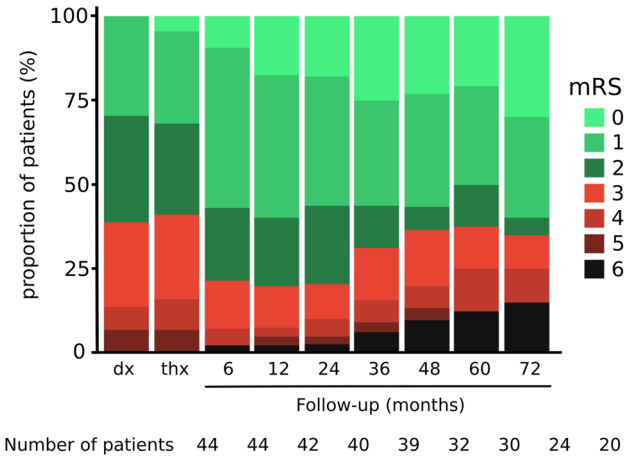

Fig. 2 Clinical outcome in all patients during 72 months of follow-up. dx, first diagnosis; thx, start of therapy

More than half of the patients had a biopsy-proven diagnosis (57%), while the previous cohort studies had approximately 30% biopsy-proven cases [7, 19]. With a median follow-up time of 61 months, we come up with the longest observation period of all published cohorts. Twelve different immunotherapies were used reflecting the challenges in management of the disease. CYC was commonly used as first-line induction therapy in three quarters of patients (75%), comparable to the French COVAC cohort (79%) and more often than in the Mayo clinic cohort (45%). Concomitant oral GC therapy was only used in approximately two-thirds of patients (68.2%), while initial GC medication was used in almost all patients in the Mayo clinic and French cohort (96% and 98%). The main reason for the restricted use of concomitant GC therapy was the prevention of long-term adverse effects of steroids. 94% of our patients received long-term maintenance therapy after induction therapy, which is a very high coverage compared to previous cohorts with 24% in the Mayo clinic cohort and 46% in the French COVAC cohort.

Relapses were seen in more than half of the patients (59%) in contrast to the previous studies, where 27.7% [7] and 34% [19] of patients had relapses, which might be due to different cohort structures (e.g., more biopsy-proven patients in our cohort) and longer follow-up time. Less frequent GC therapy might be another reason; in this regard, we can only speculate, as the influence of GC treatment on the relapse rate could not be assessed due to lack of dosage data and exact start and stop dates of GC comedication in our cohort. Relapses occurred up to 6 years after diagnosis and were not limited to the first 18–30 months after diagnosis which are usually covered by immunotherapy according to guidelines (6 months induction therapy, followed by 12–24 months of maintenance therapy). Interestingly, our data show that only patients who relapsed within 30 months after start of the first-line therapy relapsed beyond 30 months, while patients without relapses in the first 30 months remained relapse-free in the follow-up period of at least 60 months. However, cessation of immunotherapy after 30 months in patients without relapses is not justified based on retrospective findings, and further studies are needed to clarify this point. In any case, careful long-term monitoring of PACNS patients is advisable, as relapses can occur any time and beyond the recommended treatment period.

Male patient had a higher relapse risk compared to female patients in our cohort. Discordant with the previous studies of the French COVAC study group and the study by MacLaren et al., we could not show that patients with seizures, contrast-enhanced lesions on MRI, or biopsy-proven, angiography-negative PACNS (small-vessel PACNS subtype) had more frequent relapses [10, 13, 19, 22]. In our cohort, biopsy-proven PACNS patients were considered as patients with small-vessel PACNS as MR angiography was negative in most of the biopsy-proven patients (92%). The Mayo clinic study group found contradictory results with contrast-enhanced lesions being associated with less frequent relapses. Thus, predictors of relapses need reassessment in future studies with more uniform treatment regimen for distinct PACNS subtypes.

The unadjusted annual relapse rate (ARR) under the most common treatment regimen in our cohort was 1.4. Under CYC treatment, ARR was the highest (1.9), followed by MMF (1.5), AZA (1.4), MTX (1.3), RTX (1.2), and no therapy (1.2). However, it is not admissible to compare the ARR under different therapy regimen, mainly because therapy regimen were chosen at specific time points after diagnosis and strongly dependent on the individual disease activity. Different GC comedication schemes and demographic factors (RTX for younger patients) are other biases that need to be considered. The unadjusted ARR of the immunotherapies should, therefore, be interpreted with caution. Our data confirm that PACNS is a relapsing disease and relapses can occur any time with a high variability amongst patients.

More than two-thirds of our patients (68%) were in remission 6 months after start of the first-line treatment regimen. Compared to the French COVAC cohort with remission rates of 95% (defined as remission after 3 months of initial treatment), our remission rate was lower, but similar to their prolonged remission rate (66%, defined as no relapses at ≥ 12 months after diagnosis). Prolonged remission in the French cohort was mainly seen in patients with CYC induction therapy combined with GCs followed by maintenance therapy (82%), but also in patients with induction therapy alone, either with GC only or in combination with CYC. We could not observe a higher remission rate in CYC-treated patients compared to the other treatment regimen. This finding suggests a possible use of less toxic therapy for the induction of remission in some patients with lower disease

activity. Salvarani et al. made similar observations; however, to date, no valid predictor of remission could be identified; in their cohort study, 72% of patients achieved sustained therapeutic response without relapses during follow-up [7]. With regard to maintenance therapy, de Boysson et al. showed that the subsequent use of maintenance therapy was associated with prolonged remission [19, 22]. We were not able to analyze this effect, as most of our patients had maintenance therapy in the first place.

Regarding the long-term functional outcome, 66% of patients had favorable outcomes at last follow-up (mRS $\leq$ 2), compared to 85% (with GCs only) and 80% (GCs combined with CYC) in the Mayo clinic cohort (median follow-up time 12 months) and 56% of patients in the French COVAC cohort (median follow-up 57 months). Favorable outcome in our cohort was not age- or sex-dependent, and not associated with strokes, a certain MRI pattern, pathological MR angiography, a distinct PACNS subtype (biopsy-proven, imaging-based), or a specific therapy regimen. In contrast, high disability scores at last follow-up (mRS 4–6) were associated with increasing age, strokes on MRI, or angiographically large-vessel involvement in the Mayo clinic cohort, while lower disability scores were seen in patients with contrast-enhanced lesions on MRI. In the French COVAC cohort, good functional outcome was mainly observed in patients who received maintenance therapy. The discrepant findings in the different cohorts may be due to differences in case documentation and selection, cohort sizes, and the varying use of immunotherapies. Valid predictors for disease activity and outcome are difficult to assess and may only be reliably investigated in larger prospective studies with prior power calculation. Collection of a uniform cohort of PACNS patients is particularly challenging, because the term PACNS unifies a clinical, radiological, and pathological spectrum of the disease, and distinct inclusion criteria need to be carefully specified.

Using a retrospective data set, our study has some limitations. As patients with PACNS generally require immunotherapy, we could not directly compare treated versus untreated patients. Therapy was not uniform in the cohort and follow-up times were variable. Detailed dosing including tapering schemes for GC comedication was not available, which could also influence treatment effects. Treatment decisions were influenced by the duration and severity of the disease or by the individual patient will, leading to bias that we cannot control. Therefore, we cannot give general recommendations whether or not CYC induction therapy should be used or which maintenance therapy should be administered. Due to the limited sample size, we were not able to provide differentiated treatment efficacy estimates for different PACNS subtypes. Moreover, the severity of relapses was not analyzed, only the frequency of relapses was assessed. In general, validated outcome measures for PACNS do not exist, why we needed to resort to more general outcome measures such as the mRS. Finally, although we carefully selected patients, 43% of patients had no biopsy-proven diagnosis, diagnostic uncertainty remains in those cases.

In conclusion, the study illustrates heterogeneous disease activity in PACNS patients requiring individualized management in a center with expertise in stroke medicine and neuroimmunological diseases. Relapses were commonly seen and occurred any time under different immunotherapies. Male sex was associated with a higher relapse risk; nevertheless, we recommend close monitoring of disease activity independent of sex. No further predictor of relapse or functional outcome could be identified. Remission and favorable long-term outcome were seen in most of the patients irrespective of the therapy regimen. However, a mortality rate of 9% within a 5 year observation period is a concerning finding compared to other neurovascular or neuroimmunological diseases. The heterogeneity in terms of relapse rate and long-term functional outcome in our PACNS cohort once more underlines that the term PACNS unifies a spectrum of neurovascular inflammatory diseases with variable response to therapy. National and international collaborative initiatives are needed to engage prospective data collection and further evaluate predictors of response for distinct PACNS subtypes.

Author contributions SS: study concept and design, data acquisition, analysis and interpretation of data, drafting the manuscript, and revising the manuscript. A-KO: study design, statistical analysis and interpretation of data, and revising the manuscript. J-PS: study concept and design, analysis of data, and revising the manuscript. MD-C: revising the manuscript. VH: revising the manuscript. JM: data acquisition and revising the manuscript. CG: interpretation of data and revising the manuscript. GT: Data acquisition, analysis and interpretation of data, and revising the manuscript. TM: analysis and interpretation of data, and revising the manuscript.

Compliance with ethical standards

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Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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