Școala doctorală în domeniul Științelor medicale

Cu titlu de manuscris
C.Z.U: ……

GAVRILIUC Pavel

CLINICAL AND IMAGING STUDY OF CEREBELLAR HEMORRHAGES IN CEREBRAL AMYLOID ANGIOPATHY

CLINICAL NEUROLOGY – 321.05

Summary of the Doctoral Thesis in Medical Sciences

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The thesis was developed within the Department of Neurology No. 2 of the "Nicolae Testemițanu" State University of Medicine and Pharmacy.

Composition of the Public Doctoral Thesis Defense Committee
President,
dr. hab. șt. med., prof. univ., academician al AȘM,
Universitatea de Stat de Medicină și Farmacie „Nicolae Testemițanu"
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Tuță Sorin,
dr. șt. med., conf. univ., Disciplina de neurologie,
Universitatea de Medicină și Farmacie „Carol Davila",
București, România

The defense will take place on 18.03.2026 at the "Nicolae Testemițanu" State University of Medicine and Pharmacy, 165 Ștefan cel Mare și Sfânt Blvd., room 205**,** during the meeting of the Public Doctoral Thesis Defense Committee, approved by the decision of the Scientific Council of the Consortium dated _____ **.**

Autor
Gavriliuc Pavel

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INTRODUCTION

Intracerebral hemorrhage is the second most common form of stroke, after ischemic stroke. Frequent causes of spontaneous intracerebral hemorrhage include arterial hypertension, cerebral amyloid angiopathy, aneurysmal hemorrhages, and hemorrhages resulting from vascular malformations [1].

Non-traumatic intracerebral hemorrhages account for 9–27% of all strokes worldwide [2], [3]. Overall, the incidence of intracerebral hemorrhage ranges from 12 to 31 cases per 100,000 individuals [4], [5], [6]. The incidence increases with advancing age, doubling every 10 years after the age of 35 [7].

The major risk factors for intracerebral hemorrhage remain arterial hypertension, cerebral amyloid angiopathy (CAA), advanced age, and the use of anticoagulant medications.

Cerebral amyloid angiopathy (CAA), a pathology characterized by the deposition of beta-amyloid peptide in small and medium-sized vessels of the brain and leptomeninges, is typically the cause of primary lobar intracerebral hemorrhages. It may occur sporadically, sometimes in association with Alzheimer's disease (AD), or as part of a familial syndrome [8], [9], [10]. Although CAA overlaps clinically with Alzheimer's disease, CAA represents a form of vascular dementia, whereas AD is a non-vascular dementia [11]. These two clinically distinct conditions share several pathophysiological and pathological features, including beta-amyloid (Aβ) deposition. Considering that neurodegenerative diseases exhibit characteristics of cerebrovascular pathology involving disruption of the blood–brain barrier, and cerebrovascular diseases display features of neurodegeneration, such as neuronal loss and demyelination [12], there appears to be a common link between neurodegenerative and cerebrovascular diseases that requires further elucidation and documentation [13], [14].

CAA is an increasingly important health concern as the population ages, with its prevalence rising with age and being observed in more than half of elderly individuals [15]. The disease is characterized by the progressive deposition of Aβ in the walls of cortical and leptomeningeal vessels. Other features of CAA include intracerebral hemorrhage and progressive dementia, particularly in older adults [16], [17]. Unfortunately, despite its high prevalence in the elderly, there are no therapies capable of modifying the course of the disease. Understanding the mechanisms underlying its pathology and progression remains crucial, especially as the prevalence of age-related diseases continues to increase, contributing significantly to global disability.

The most important risk factor associated with CAA is advanced age, which encompasses both genetic and non-genetic risk determinants.

Primary lobar intracerebral hemorrhage (ICH) is the hallmark clinical manifestation of cerebral amyloid angiopathy [18]. However, the clinical presentation may vary, and some patients may present with only subacute cognitive decline, focal neurological deficits, headache, or seizures [16].

Neuroimaging is the main component in the diagnosis and monitoring of CAA. Topographical localization of hemorrhagic lesions is based on magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) with amyloid tracers [19], [20], [21], [22], [23].

The widespread use of T2*-weighted MRI sequences over the past 15 years has led to an increased detection of cerebral microbleeds (CMBs)—small, well-defined hypointense lesions not visible on conventional MRI [24]. Histopathological studies show that CMBs correspond to focal hemosiderin deposits adjacent to small vessels affected by hypertensive angiopathy or CAA [25], [26].

The Boston criteria for the diagnosis of CAA were introduced in 1995 and incorporate imaging and histopathological markers [27]. Although these criteria represent the most widely used diagnostic tool, definitive diagnosis can only be made post-mortem, which remains a major limitation.

Cerebellar involvement in CAA is a controversial and insufficiently clarified topic. Spontaneous cerebellar hemorrhages are usually associated with changes secondary to arterial hypertension [28]. However, it is hypothesized that a subgroup of cerebellar hemorrhages—whether isolated or combined with supratentorial hemorrhages—may be associated with amyloid deposition.

The scientific novelty of this study lies in its original and in-depth exploration of cerebellar involvement in CAA—an area rarely addressed in the literature, which predominantly focuses on supratentorial cortico-subcortical pathology. The study proposes a comparative clinico-imaging analysis between patients with CAA with and without cerebellar involvement, highlighting the topographical relevance of cerebellar hemorrhages as a potential marker for the etiopathogenic mechanism (amyloid versus hypertensive).

At the same time, the research attempts to integrate the concept of the cerebellar affective-cognitive syndrome into the spectrum of cognitive manifestations associated with CAA, suggesting that cerebellar injury may influence cognitive processing.

Research Aim

To investigate the role of cerebellar involvement in cerebral amyloid angiopathy (CAA), with the objective of characterizing its impact on clinico-imaging manifestations, cognitive function, and diagnostic and clinical management strategies.

Objectives

• To identify imaging and clinical differences between CAA patients with and without cerebellar involvement, in order to improve differential diagnosis.
• To investigate the relationship between cerebellar involvement and cognitive status using standardized scores (e.g., MMSE) to highlight potential functional consequences.
• To analyze the implications of cerebellar involvement for the application of the revised Boston criteria and for establishing clinical management strategies, including imaging monitoring and treatment adjustment.

Methodology

The study included patients diagnosed with spontaneous cerebral hemorrhages on initial CT imaging, evaluated through a retrospective–prospective cohort analysis conducted between 2009 and 2019.
The study was approved by the Ethics Committee of the "Nicolae Testemițanu" State University of Medicine and Pharmacy (protocol no. 60 from 21.05.2018), as well as by the Institutional Review Board (IRB) of the Hadassah–Hebrew University Medical Center (approval HMO 1.0 20-0437-20 from 10.06.2020).

Neurological deficit severity in symptomatic hemorrhages was assessed using the National Institutes of Health Stroke Scale (NIHSS), while functional disability was evaluated using the Modified Rankin Scale (mRS). Cognitive status was assessed using the Mini-Mental State Examination (MMSE).

Expected Results

The expected outcomes include identifying the imaging and clinical characteristics of patients with CAA, correlating these with the severity of neurological manifestations, and defining clinico-radiological profiles that may contribute to optimizing diagnosis and treatment.

2. MATERIALS AND METHODS

Study Type and Sample Structure

The final study cohort included 154 patients diagnosed with cerebral amyloid angiopathy (CAA), selected from patients admitted with spontaneous intracerebral hemorrhage during the period 2009–2019 at two university medical centers in Israel: Hadassah–Hebrew University Medical Center in Jerusalem and Tel Aviv Medical Center in Tel Aviv.

Patient selection was conducted in several successive stages. Initially, 718 consecutive patients admitted with hemorrhagic stroke were evaluated. Of these, 189 patients underwent brain magnetic resonance imaging (MRI) performed between days 5 and 10 post-stroke, including blood-sensitive sequences such as SWI.

From this group, 154 patients met the modified Boston criteria (version 1.5) for the diagnosis of CAA and were enrolled in the study. They were divided into two subgroups based on the presence or absence of cerebellar involvement:

- **Subgroup L1:** patients with CAA and cerebellar involvement
- **Subgroup L0:** patients with CAA without cerebellar involvement

Patient Selection Criteria

Inclusion criteria:

- Imaging-confirmed diagnosis (via CT) of spontaneous intracerebral hemorrhage
- Brain MRI performed between days 5 and 10 after the stroke, including SWI sequences

- Presence of a lobar hematoma or an atypical hemorrhagic pattern
- Confirmation of CAA diagnosis according to the modified Boston criteria, version 1.5

Exclusion criteria:

- Deep hemorrhages located in the basal ganglia, suggestive of hypertensive angiopathy
- Absence of adequate MRI or impossibility to perform MRI
- Absolute contraindications to MRI (metallic implants, pacemaker, claustrophobia)
- Hemorrhages secondary to other causes: trauma, vascular malformations, tumors

Justification of Sample Size

The sample size was calculated using formulas specific to observational-analytical research, particularly cohort studies.

The calculation was based on the following parameters:

- Estimated proportion of patients with cerebellar involvement in CAA ($P_0 = 0.20$)
- Proportion of patients with CAA without cerebellar involvement ($P_1 = 0.40$)
- $P = (P_0 + P_1)/2 = 0.30$
- $Z\alpha = 1.96$ (for $\alpha = 5\%$)
- $Z\beta = 1.65$ (for 95% statistical power)
- $f = 10\%$ estimated dropout rate; $q = 1/(1–f)$

Thus, the minimum required sample size was 67 patients per group (L1 and L0).

Research Methods Used

1. **Documentary Method** – involved retrospective analysis of electronically stored medical data, including clinical records and imaging results, systematically recorded in a shared database of the two participating hospitals.
2. **Demographic Method** – included analysis of age, sex, and associated comorbidities (vascular factors, cognitive disorders) in order to outline the profile of patients with CAA.
3. **Clinical Method** – neurological deficit was quantified using the NIHSS, which includes 11 items assessing consciousness, visual fields, motor function, coordination, speech, and sensory function. Scores range from 0 (no deficit) to 42 (severe deficit), allowing the monitoring of clinical evolution.
4. **Imaging Method** – MRI investigations included SWI or T2* sequences to identify microbleeds (MB) and macrobleeds (MH), classified according to the MARS scale. Additional assessments included: presence of cortical superficial siderosis (cSS), white matter hyperintensities (WMH) using the Fazekas scale, cortical subarachnoid hemorrhage, cortical atrophy, and the reversed occipito-frontal gradient. CT imaging was used to confirm hemorrhage and detect the “spot sign” (active contrast

extravasation). Cerebellar hemorrhages were localized in superficial and deep regions, including the dentate, globose, and emboliform nuclei.

5. **Differential Diagnostic Method** – involved excluding other etiologies of intracerebral hemorrhage, such as severe arterial hypertension (BP > 150 mmHg), trauma, arteriovenous malformations, or tumors, based on CT/MRI findings and clinical context.
6. **Questionnaire Method** – cognitive status was evaluated using the MMSE (Mini-Mental State Examination), a 30-item test assessing orientation, memory, attention, language, and constructional abilities. A score ≥ 24 was considered normal, while scores below 24 indicated varying degrees of cognitive impairment (mild, moderate, severe), adjusted for age and educational level.
7. **Ethical Method** – The Institutional Review Board (IRB) of Hadassah approved the study and waived the need for informed consent, given its retrospective nature and the absence of direct patient risk.

Statistical Data Processing

Statistical analysis was performed using R software (version 3.6.3). Categorical variables were expressed as absolute frequencies and percentages, while continuous variables were reported as means and standard deviations. For comparison of categorical variables, the chi-square test or Fisher's exact test was used; for continuous variables, the independent-samples t-test (Welch) was applied.

To evaluate associations between cerebellar involvement and relevant factors, logistic regression analysis was performed—initially univariate, followed by multivariate analysis—including variables such as age, total number of MBs, history of hemorrhage, degree of leukoaraiosis (Fazekas), use of antiplatelet or anticoagulant agents. The threshold for statistical significance was set at $p < 0.05$.

The study presents several methodological limitations that must be considered when interpreting the results. First, the observational design—mixed retrospective–prospective—and recruitment from two university centers introduce potential selection and center bias, reflecting possible differences in clinical practice and inclusion criteria. Additionally, MRI was performed at the discretion of the attending physician and only in a subset of 189 patients, between days 5–10 after the hemorrhagic event, which introduces possible indication bias, survival bias, and temporal heterogeneity of the data.

Another limitation is the definition of etiology based solely on the modified Boston criteria v1.5, without histopathological confirmation, which may result in misclassification—especially in cases with mixed etiology. The inclusion criteria requiring age ≥55 years, availability of MRI, and presence of cortical microbleeds restrict applicability of the findings to typical CAA patients, limiting generalizability to atypical cases or younger populations.

Furthermore, cognitive assessment relied exclusively on the Mini-Mental State Examination (MMSE), a global screening tool with low sensitivity for detecting executive, attentional, and visuospatial deficits. Consequently, the true extent of cognitive impairment may be underestimated, particularly in patients with cerebellar involvement, where executive dysfunction may be more prominent.

Overall, these methodological limitations do not invalidate the results but warrant caution in extrapolating conclusions and support the need for prospective, multicenter studies with standardized imaging and cognitive evaluation.

3. COMPARATIVE ANALYSIS OF THE STUDY GROUPS

Out of a total of 718 patients, 189 (26.3%) underwent brain MRI. One hundred fifty-six patients from the MRI group met the Boston criteria for the diagnosis of cerebral amyloid angiopathy (CAA) [29]. Thus, two study groups were created: one group with 75 patients with CAA without cerebellar involvement, and another group with 79 patients with CAA and cerebellar involvement.

The graph below shows the distribution of CAA patients according to cerebellar involvement and age group.

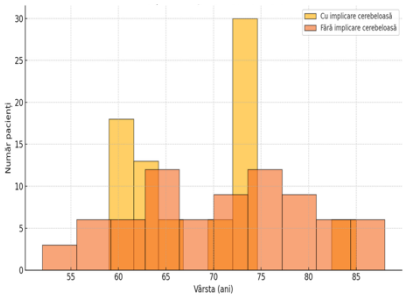

Figure 3.1. Distribution of patients by age

Overall, patients diagnosed with CAA with cerebellar involvement were younger than those without cerebellar involvement, a difference with statistical significance. The mean age of patients with CAA without cerebellar involvement was 72 ± 10 years, whereas the mean age of patients with CAA and cerebellar hemorrhages was 67 ± 5 years, with $p < 0.001$. These data are shown in Figure 3.2.

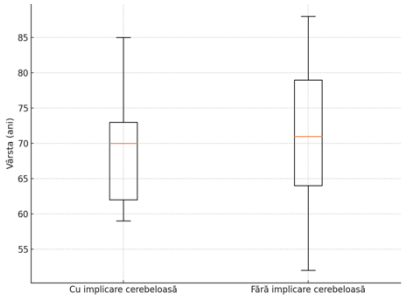

Figure 3.2. Mean age of patients with and without cerebellar hemorrhages

It was also observed that patients with CAA and cerebellar involvement had more microbleeds compared to patients without cerebellar involvement. Patients with CAA without cerebellar involvement had on average 3 ± 9 microbleeds on brain MRI. In the group of patients with CAA and cerebellar involvement, the mean number of microbleeds was 33 ± 23. A statistically significant difference was found between the study groups for this parameter ($p < 0.001$). The comparative analysis of these parameters is represented graphically in Figure 3.3.

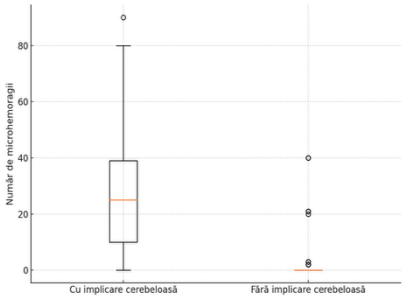

Figure 3.3. Number of microbleeds

White matter changes, reflected by the Fazekas score, represent an important imaging marker of chronic microvascular damage. In the context of CAA, these lesions are frequently encountered and may indicate the severity of the pathological process and the degree of diffuse involvement of the brain parenchyma. The comparative analysis of Fazekas scores revealed a statistically significant difference ($p = 0.0006$) between patients with and without cerebellar involvement. Patients with cerebellar involvement had higher Fazekas scores, suggesting more extensive and severe white matter damage.

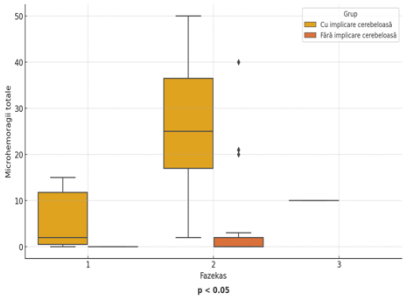

Figure 3.4. White matter lesions according to the Fazekas scale

These data support the hypothesis that cerebellar involvement in CAA may represent an imaging marker of disease progression, reflecting not only topographical extension but also a generalized neurovascular dysfunction. Integrating the Fazekas score into the evaluation of these patients may contribute to risk stratification and guide clinical management and prognostic strategies.

The analysis of cognitive impairment in the patients included in the study, according to the severity of clinical manifestations, is presented in Figure 3.5.

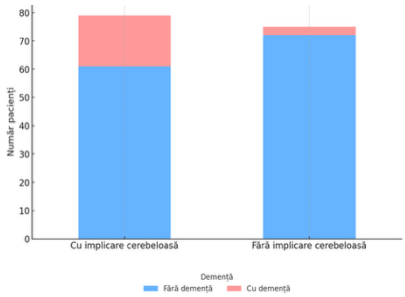

Figure 3.5. Number of patients with and without dementia in the study

Severe dementia, with an MMSE score < 9, was documented in 2 patients (1.3%); an MMSE score between 10–18 points, characteristic of moderate dementia, was recorded in 19 patients, representing 12% of all examined patients. The majority of patients did not exhibit severe cognitive impairment, with 86% of patients having an MMSE score greater than 24 points.

Table 3.1. MMSE scores of patients in the study

MMSE	n (%)
≤ 9	2 (1.3%)
10–18	19 (12%)
19–23	0 (0%)
≥ 24	133 (86%)

The correlation between the number of microbleeds and dementia was assessed using the median (IQR). The distribution of microbleeds and a significantly higher number of microbleeds were statistically significant in patients with dementia ($p < 0.001$, Wilcoxon Rank Sum test), both in patients without cerebellar involvement and those with cerebellar involvement (Figure 3.12).

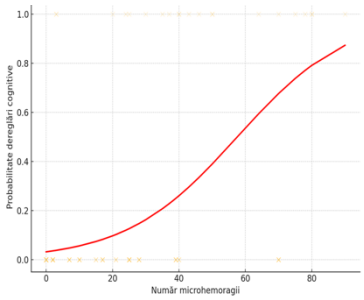

Figure 3.6. Probability of cognitive impairment and number of microbleeds

The graph illustrates the relationship between the number of microbleeds and the probability of cognitive impairment (MMSE < 24) in patients with CAA. As the number of microbleeds increases, the estimated probability of cognitive decline also increases. The red line represents the logistic prediction curve, demonstrating this clear upward trend. This model supports the hypothesis that cerebral hemorrhagic burden is significantly associated with cognitive impairment in CAA.

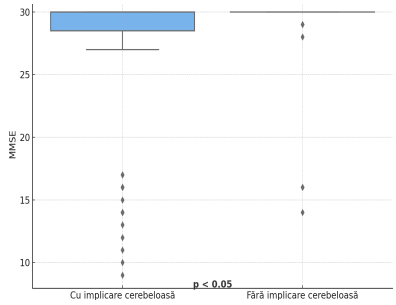

Figure 3.7. Distribution of MMSE score according to cerebellar involvement

The distribution of MMSE scores suggests a clustering of values in the normal range in patients without cerebellar involvement, whereas patients with cerebellar involvement show a wider dispersion and more frequent scores in the range of mild cognitive impairment. These results support the hypothesis that cerebellar involvement in CAA is a marker of a more severe clinical phenotype, associated not only with a higher number of microbleeds but also with detectable cognitive dysfunction on standardized evaluation.

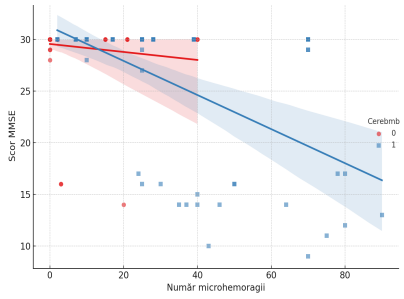

Figure 3.8. Relationship between MMSE score and number of microbleeds

- Total correlation (all patients): Spearman = –0.47, p = 8.39e-10
- With cerebellar involvement: Spearman = –0.56, p = 3.99e-07
- Without cerebellar involvement: Spearman = –0.16, p = 0.149

The number of microbleeds is significantly negatively correlated with MMSE score, especially among patients with cerebellar involvement, suggesting a possible contribution of cerebellar involvement to cognitive decline.

Comparison of MMSE scores between patients with and without cerebellar involvement showed a statistically significant difference: the mean MMSE score was 26.3 in the group with

cerebellar involvement, compared with 29.4 in the group without involvement ($p < 0.05$, Mann–Whitney U test).

To determine whether this difference could be explained by other risk factors, correlations between MMSE and relevant clinical variables were assessed. In the group with cerebellar involvement, age ($\rho = –0.263$; $p = 0.019$) and active smoking ($\rho = –0.269$; $p = 0.017$) were negatively correlated with cognitive score, suggesting an additive impact on cognitive dysfunction. In contrast, in the group without cerebellar involvement, only hyperlipidemia was associated with lower MMSE ($\rho = –0.296$; $p = 0.010$).

These parameters do not fully explain the difference between groups, indicating that cerebellar involvement in CAA reflects a distinct pathological subtype, characterized by more pronounced cognitive impairment and a higher burden of microangiopathic lesions. Integration of these data supports the idea that cerebellar involvement may constitute an imaging biomarker of disease severity in CAA, with prognostic value for cognitive decline.

We also analyzed the influence of recurrent symptomatic hemorrhages on disease course in patients from both groups, CAA without and CAA with cerebellar involvement (Figure 3.9). The proportion of patients with prior intracerebral hemorrhages was higher in the group with cerebellar involvement (22.8%) compared with the group without cerebellar involvement (12%). However, this difference did not reach statistical significance ($p = 0.122$, chi-square test), suggesting a trend but without robust validation in this sample. Nevertheless, patients with CAA are considered to have a higher risk of recurrent hemorrhage, which is one of the main causes of death in patients diagnosed with this disease. In our cohort, 6 patients died, of whom 3 had recurrent hemorrhages and one had a primary cerebellar hematoma.

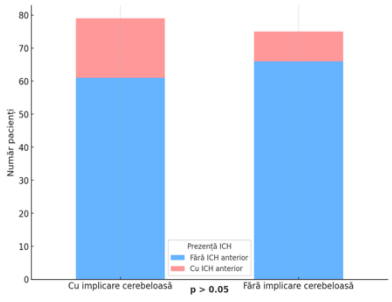

Figure 3.9. Previous intracerebral hemorrhages

To identify other factors that could influence the occurrence of prior hemorrhages, Spearman correlations were analyzed between several clinical and imaging factors. Age was positively and significantly correlated with the presence of prior intracerebral hemorrhages ($\rho = 0.300$; $p = 0.0002$), indicating increased susceptibility in older patients. Interestingly, arterial hypertension showed a weak negative correlation ($\rho = –0.184$; $p = 0.022$), possibly reflecting a higher proportion of lobar hemorrhages in the context of "pure," non-hypertensive CAA.

Other factors such as diabetes mellitus, hyperlipidemia, and active smoking did not show significant correlations. These results suggest that advanced age remains the main risk factor associated with recurrent or previous hemorrhagic events, while cerebellar involvement, although frequently associated with extensive lesions, is not sufficient on its own to independently explain the occurrence of prior hemorrhages.

To explore the potential relationship between a history of stroke and lesion location in CAA, the prevalence of previous strokes was analyzed in patients with and without cerebellar involvement. The graph below illustrates their distribution, highlighting trends in the association between cerebellar involvement and a possible history of cerebrovascular events.

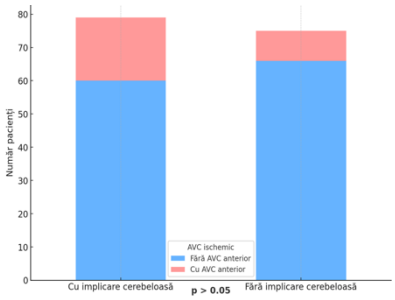

Figure 3.10. Prevalence of prior stroke

The graph shows the distribution of patients with and without prior stroke according to cerebellar involvement in CAA. Although patients with cerebellar involvement had a higher proportion of previous ischemic stroke (24.1%) compared with those without involvement (12%), this difference did not reach statistical significance ($p = 0.084$, chi-square test).

To identify other factors potentially associated with the presence of ischemic stroke, Spearman correlations were calculated between clinical variables and the presence of ischemic stroke. The analysis revealed a significant positive association with diabetes mellitus ($\rho = 0.345$; $p < 0.0001$) and arterial hypertension ($\rho = 0.239$; $p = 0.0028$), suggesting a classic vascular risk profile. Surprisingly, smoking was negatively associated with a history of ischemic stroke ($\rho = –0.187$; $p = 0.0200$), possibly reflecting confounding influences or selection characteristics in the sample.

Age, hyperlipidemia, number of microbleeds, and Fazekas score did not show significant associations. These results indicate that traditional vascular risk factors, particularly diabetes and hypertension, remain important determinants of ischemic stroke risk, independent of cerebellar involvement in CAA.

In this context, the influence of prior ischemic strokes and intracerebral hemorrhages (ICH) on cognitive function, quantified by MMSE score, was investigated. The analysis was performed using the non-parametric Mann–Whitney U test in a sample with complete data for MMSE, prior ischemic stroke, and prior intracerebral hemorrhage. The results did not show a statistically significant difference in MMSE scores between patients with and without prior

ischemic stroke (U = 1637.5; p = 0.387), nor between those with and without prior ICH (U = 1503.5; p = 0.142). These findings suggest that, in this sample, previous vascular events do not significantly influence global cognitive performance. It is possible that their effect is masked by other dominant determinants of cognitive dysfunction in CAA, such as white matter lesions (Fazekas), number of microbleeds, or overall disease burden. Further studies with more detailed neuropsychological assessment are needed to validate these observations.

Previous research [30] has shown that the number of incidentally detected cerebral microbleeds on brain MRI is higher in patients using antiplatelet agents such as aspirin or clopidogrel for secondary prevention.

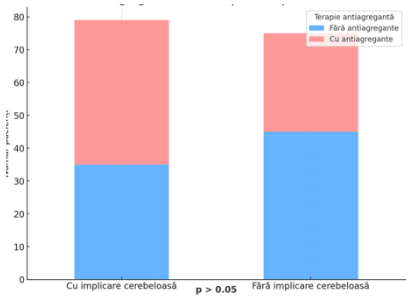

Figure 3.11. Use of aspirin in the study groups

In a cohort of patients with CAA, the use of antiplatelet therapy (aspirin or clopidogrel) was evaluated according to cerebellar involvement. Results showed more frequent use of antiplatelets in the group with cerebellar involvement (55.7%, 44 patients) compared with the group without involvement (40%, 30 patients). The difference was not statistically significant (p = 0.074), but it highlights a clinically relevant trend.

The frequency of anticoagulant therapy use (warfarin, heparin, or DOACs) was also evaluated. Results showed that patients with cerebellar involvement received anticoagulant treatment significantly more often (15.2%) than those without cerebellar involvement (4.0%), with the difference being statistically significant (p = 0.039, chi-square test).

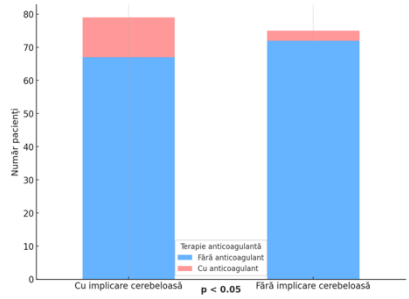

Figure 3.12. Use of anticoagulants in the study groups

This finding may reflect a higher prevalence of cardioembolic comorbidities, particularly atrial fibrillation, among patients with cerebellar involvement. It may also indicate a more severe or

mixed vascular profile (hemorrhagic and ischemic), prompting clinicians to adopt more aggressive prevention strategies. At the same time, this subpopulation may have an increased cumulative risk of recurrent cerebral events, thus justifying the use of anticoagulants.

In the analyzed cohort of patients with CAA, the influence of anticoagulant treatment (warfarin, heparin, DOACs) on the number of cerebral microbleeds was investigated. The analysis included patients with complete data on anticoagulant use and microbleed quantification.

Comparison of the two groups—patients with and without anticoagulant treatment—was carried out using the Mann–Whitney U test, due to the asymmetric distribution of the variable. The results did not show a statistically significant difference ($U = 902.0$; $p = 0.379$), indicating that anticoagulant treatment was not associated with a significant increase in the number of microbleeds in this sample.

A particular point of interest in our research was the first-time analysis of the effects of the new non–vitamin K oral anticoagulants (NOACs), or direct oral anticoagulants (DOACs), on the evolution and number of microbleeds in patients with CAA with and without cerebellar involvement. However, since treatment with NOACs is relatively recent, only 2 patients in the CAA group without cerebellar involvement were receiving this type of treatment. No patients in the group with CAA and cerebellar involvement were on NOACs at the time of enrollment.

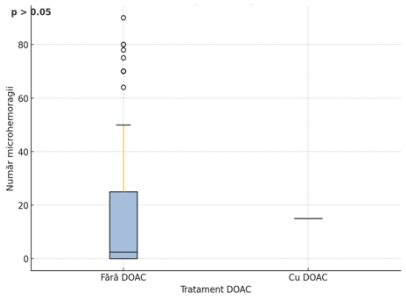

Figure 3.13. Use of direct oral anticoagulants

The analysis of the distribution of microbleeds according to DOAC use in the CAA cohorts did not show a clear and consistent difference. Although the graph suggests a slight tendency towards a higher hemorrhagic burden in patients treated with direct anticoagulants, this result must be interpreted with caution given the very small size of the NOAC user subgroup in this sample. Therefore, although the data do not allow firm conclusions, the analysis suggests the need for an individualized and cautious approach to anticoagulant therapy in CAA patients, with careful imaging assessment of hemorrhagic risk and ongoing monitoring if treatment is deemed necessary.

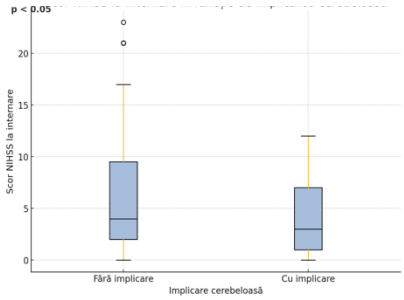

Figure 3.14. NIHSS scores at admission

NIHSS scores at admission were compared between patients with and without cerebellar involvement. The analysis was performed using the Mann–Whitney U test, given the asymmetric distribution of the data. The results showed a statistically significant difference ($U = 2409.5$; $p = 0.044$); however, patients with cerebellar involvement had significantly lower NIHSS scores at admission compared with those without cerebellar involvement. This finding may appear counterintuitive but is consistent with the clinical picture of cerebellar hemorrhages, which may have more subtle motor manifestations and lower initial NIHSS scores, in contrast to cortical or deep supratentorial lesions that induce aphasia, hemiplegia, or other marked deficits. Furthermore, the NIHSS is known to underestimate the severity of cerebellar involvement, which may explain this result (Figure 3.14).

The severity of disability in the patients included in the study was evaluated using the modified Rankin Scale (mRS) [31]. The mean score for patients with CAA without cerebellar involvement was 3.15 ± 1.39 points, whereas for patients with CAA and cerebellar involvement the mRS score at discharge was 2.13 ± 1.01 points. These values showed a statistically significant difference between the two study groups ($p < 0.001$).

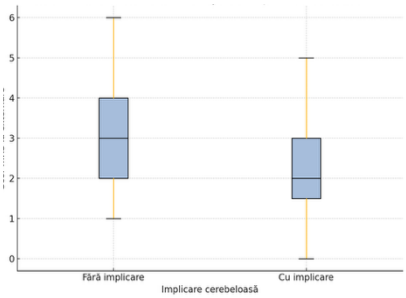

Figure 3.15. Neurological disability at discharge

Analysis of mRS score at discharge was performed using the Mann–Whitney U test, given the potentially non-Gaussian distribution of the variable. The results revealed a statistically significant difference ($U = 2002.5$; $p = 0.0003$), with significantly lower mRS scores in patients with cerebellar involvement. This suggests better functional recovery in this subgroup despite the presence of hemorrhagic lesions. The finding is consistent with clinical observations that cerebellar hemorrhages, although sometimes severe in the acute phase, often allow satisfactory

neurological recovery, with relatively preserved functional reserves compared with supratentorial lesions.

In the multivariate analysis assessing the relationship between age and stroke severity, prior intracerebral hemorrhages, and number of microbleeds, the only variables that showed a significant correlation with cerebellar involvement in CAA were the total number of microbleeds and the use of anticoagulant medications.

We also found that patients with cerebellar involvement in CAA are younger and have more microbleeds, both in the cerebral hemispheres and in the cerebellum. This supports the assumption that cerebellar involvement denotes a more aggressive course of the disease or the presence of a different underlying pathophysiological mechanism. These findings lead to the assumption that CAA patients with and without cerebellar involvement, with pre-existing dementia and microbleeds and who receive anticoagulants, carry an increased risk of developing a macrohemorrhage in the brain or cerebellum and require particular caution when prescribing these medications, carefully weighing the risk–benefit ratio.

4. CONSIDERATIONS ON THE RESULTS AND COMPARISONS WITH PREVIOUS STUDIES

The analysis presented highlights the complex relationship between advanced age, cerebral hemorrhagic burden, and lesion topography in cerebral amyloid angiopathy (CAA), with particular emphasis on cerebellar involvement. Comparison of patients with and without cerebellar involvement revealed a paradoxical finding: those with cerebellar lesions were, on average, younger, yet had a much higher number of microbleeds. This suggests that cerebellar involvement is not a random phenomenon, but rather a marker of a more advanced disease stage, with greater vascular fragility and a higher global burden on brain networks.

The cognitive consequences of this involvement are evident. Cognitive deterioration, one of the most disabling manifestations of CAA, correlates directly with the total number of microbleeds and the presence of cortical microinfarcts. Patients with cerebellar involvement have a higher likelihood of low MMSE scores and even formal dementia diagnoses, supporting the hypothesis that cumulative hemorrhagic burden is a key determinant of cognitive dysfunction. Thus, cognitive decline in CAA is not the consequence of a single type of lesion, but the cumulative result of microbleeds, white matter hyperintensities, and microinfarcts, which progressively disrupt cerebral connectivity.

The literature has proposed the differentiation of CAA into two imaging phenotypes: a macrohemorrhagic phenotype, characterized by lobar hematomas and cortical superficial siderosis, and a microhemorrhagic phenotype, in which multiple lobar microbleeds predominate. Studies have not clearly demonstrated that microbleeds predict the occurrence of a macrohemorrhage, but data suggest that these phenotypes are not mutually exclusive and may coexist. Among the imaging markers analyzed, cortical microinfarcts have proven to be the

most relevant for cognitive decline, confirming observations from other studies on their prevalence in CAA and Alzheimer's disease.

Another important observation is the association between cerebellar involvement and a history of ischemic stroke, which was more frequent in this group of patients. This trend suggests the existence of a particular CAA phenotype, characterized by extensive microvascular vulnerability, predisposing to both hemorrhagic and ischemic lesions. Furthermore, amyloid PET studies have confirmed that beta-amyloid positivity is associated with cognitive decline even in the absence of neuropathological criteria for CAA or Alzheimer's disease, suggesting a synergistic effect between degenerative and vascular processes.

The importance of the cerebellum in the clinical picture of CAA also emerges from its role in higher cognitive networks. Structural and functional cerebellar changes have been reported in several types of dementia, and genetic factors appear to influence the severity and distribution of these lesions. Cerebellar connectivity plays a significant role in maintaining cognitive functions, and its impairment may modulate the intensity and type of cognitive deficits. Thus, the cerebellum should not be viewed solely as a motor structure, but as an integral component of cortico-subcortical networks responsible for cognition.

Our clinical results provide important details regarding prognosis. Patients with cerebellar involvement had lower NIHSS scores at admission and better mRS scores at discharge, suggesting lower initial neurological severity and less functional disability at discharge. However, these patients had a higher risk of conversion to dementia, associated with the increased number of microbleeds and higher Fazekas scores. This discrepancy between a relatively favorable motor functional prognosis and a major cognitive risk demonstrates the limitations of standard scales, which do not adequately capture cognitive impairment.

In conclusion, cerebellar involvement in CAA is not merely a secondary imaging marker, but an important indicator of disease severity and extent. It is associated with greater hemorrhagic burden, an increased risk of cognitive decline, and conversion to dementia. Therefore, patient management must integrate the topographic evaluation of lesions, the total number of microbleeds, white matter hyperintensities, and cortical microinfarcts. Only a comprehensive approach, which takes into account the cumulative burden of small vessel disease and cerebellar involvement, can provide a valid prognosis and guide clinical interventions and long-term monitoring strategies.

GENERAL CONCLUSIONS

1. **Cerebellar involvement in cerebral amyloid angiopathy (CAA)** represents a significant clinical, imaging, and biological marker. In the analyzed cohort, patients with cerebellar involvement were significantly younger than those without involvement (67 ± 5 years vs. 72 ± 10 years, $p < 0.001$), and multivariate analysis confirmed an independent association between younger age and cerebellar involvement (log OR = –0.36; 95% CI –0.59 – –0.20; $p < 0.001$). These data suggest that cerebellar involvement occurs more frequently in earlier and more severe forms of CAA, representing a potentially distinct and aggressive vascular phenotype.
2. **The neuroimaging profile of patients with CAA and cerebellar involvement** was significantly characterized by a higher mean number of cortical microbleeds (33 ± 23 vs. 3 ± 9, $p < 0.001$, Mann–Whitney U test) and an increased prevalence of white matter hyperintensities (Fazekas 2–3 in 68.4% of patients with cerebellar involvement vs. 44.0% in the group without involvement, $p = 0.004$, chi-square test). These differences suggest a diffuse pathological pattern in which cerebellar involvement correlates with overall angiopathy severity and impaired microvascular integrity.
3. **Cognitive screening using the Mini-Mental State Examination (MMSE)** revealed more pronounced impairment in patients with CAA and cerebellar involvement compared to those without cerebellar involvement. The mean MMSE score was significantly lower in patients with cerebellar involvement (26.3 vs. 29.4, $p < 0.05$), and the number of microbleeds correlated negatively with cognitive score ($\rho = –0.56$; $p < 0.001$). These data confirm that cerebellar involvement is associated with more marked cognitive decline, justifying the systematic inclusion of cognitive testing in the evaluation of CAA patients.
4. **Integrating cerebellar involvement into diagnostic and monitoring algorithms for CAA patients** is justified by its prognostic value and its potential to stratify disease severity. Systematic assessment of the cerebellum is recommended in blood-sensitive MRI protocols (T2*, SWI), as it can improve prediction of clinico-cognitive evolution and optimize personalized management strategies, particularly in selecting patients for secondary prevention and in monitoring cognitive decline.

PRACTICAL RECOMMENDATIONS

1. **Advanced imaging evaluation of the cerebellum**
   Patients with cerebral amyloid angiopathy (CAA) should undergo magnetic resonance imaging, including detailed assessment of the cerebellum, regardless of the location of hemorrhages, in order to enable early detection of microbleeds and other relevant changes.
2. **Risk stratification for recurrence and progression**
   A personalized approach is recommended in the management of patients with CAA and cerebellar involvement, based on identified risk factors such as age, number of microbleeds, and white matter hyperintensities, in order to prevent recurrent hemorrhages and progression to dementia.
3. **Integration of cerebellar assessment into diagnostic algorithms**
   Cerebellar involvement should be considered an important marker in the overall evaluation of patients with CAA, including for estimating the risk of cerebral involvement and its impact on functional disability.
4. **Neurocognitive monitoring and dementia prevention**
   Patients with CAA and cerebellar involvement, especially those without large intracerebral hematomas, should be closely monitored for cognitive decline, with early implementation of interventions aimed at reducing the risk of dementia.

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