# Clinical and Neuroimaging Patterns of Ischemic Stroke in Ph-negative Myeloproliferative Neoplasms

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**Abstract**

***Introduction.*** *Philadelphia-negative myeloproliferative neoplasms (MPNs) are a rare blood disorder characterized by pancytosis and thrombohemorrhagic complications.*

*The* ***aim*** *of this article is to describe clinical and neuroimaging patterns of brain changes in patients with MPN.*

***Materials and methods.*** *The study included 152 patients with an established diagnosis of MPN (according to WHO criteria 2008, 2016). A clinical and neurological examination, laboratory tests, and magnetic resonance imaging of the brain were performed.*

***Results.*** *In patients with polycythemia vera and primary myelofibrosis, neuroimaging patterns are represented by small (up to 1.5 cm) post-infarction lesions in the brainstem, cerebellum, and cortex in adjacent perfusion territories after hemorheological microocclusive stroke. In patients with essential thrombocythemia, the neuroimaging pattern is more often represented by massive post-infarction changes in cortical-subcortical brain tissue with atherosclerotic lesions of the major head arteries, which appear to be atherothrombotic. Stroke preceded hematologic diagnosis in 30% of polycythemia vera cases, 40% of essential thrombocythemia cases, and 25% of primary myelofibrosis cases.*

***Keywords:*** *blood disorders; myeloproliferative neoplasms/diseases; thrombosis; stroke; magnetic resonance imaging of the brain*

**Ethics approval.** The study was conducted with the informed consent of the patients. The research protocol was approved by the Ethics Committee of the Research Center of Neurology (protocol No. 11/14, dated November 19, 2014).

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**Conflict of interest.** The authors declare no apparent or potential conflicts of interest related to the publication of this article.

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# Клинико-нейровизуализационные паттерны нарушений мозгового кровообращения на фоне гематологической патологии (Ph-негативных миелопролиферативных новообразований)

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**Аннотация**

***Введение.*** *Ph-негативные миелопролиферативные новообразования (МПН) – редкая патология крови, характеризующаяся панцитозом и тромбогеморрагическими осложнениями.*

***Цель*** *статьи – описание клинико-нейровизуализационных паттернов изменений вещества мозга у пациентов с МПН.*

***Материалы и методы.*** *В исследование были включены 152 пациента с установленным диагнозом МПН (согласно критериям ВОЗ 2008, 2016 гг.). Проводились клинико-неврологический осмотр, лабораторное обследование, магнитно-резонансная томография головного мозга.*

***Результаты.*** *У пациентов с истинной полицитемией и первичным миелофиброзом нейровизуализационные паттерны представлены небольшими (до 1,5 см) постинфарктными изменениями в стволе, мозжечке, области коры в зонах смежного кровоснабжения после нарушения мозгового кровообращения по типу гемореологической микроокклюзии. У пациентов с эссенциальной тромбоцитемией нейровизуализационная картина чаще представлена массивными постинфарктными изменениями вещества мозга корково-подкорковой локализации на фоне атеросклеротического поражения магистральных артерий головы, вероятно, по типу атеротромбоза. Инсульт предшествовал постановке гематологического диагноза в 30% случаев при истинной полицитемии, в 40% – при эссенциальной тромбоцитемии, в 25% – при первичном миелофиброзе.*

***Ключевые слова:*** *заболевания крови; миелопролиферативные новообразования/заболевания; тромбоз; инсульт; магнитно-резонансная томография головного мозга*

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## Introduction

Ph-negative myeloproliferative neoplasms/diseases (MPN/MPD) include the three most common clinical entities such as polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). The incidence rate is 0.5 to 4.0 cases, 1.0 to 2.0, and 0.3 to 2.0 per 100,000 person-years for PV, ET, and PMF, respectively. The etiology of MPD remains unclear, and the leading hypothesis is the influence of environmental factors. The emergence of one of the driver mutations in the *JAK2*, *MPL*, or *CALR* genes is a key factor in the development of MPN. Despite distinct clinical entities, these disorders are linked by morphological similarities and propensity to thrombotic complications and leukemic transformation [2].

The prognosis for the disease course is variable and depends on the location and grade of the thrombotic event. Thrombosis with cerebral infarction is one of the major consequences of MPN that may significantly limit life expectancy and quality of life.

The **aim** of this study was to describe clinical and neuroimaging patterns of brain changes in patients with MPN/MPD.

## Materials and methods

The study was conducted at the Research Center of Neurology and the National Medical Research Centre (NMRC) for Hematology from November 2014 to April 2024. The study included 152 patients with an established diagnosis of MPN (according to WHO criteria 2008, 2016). To confirm the diagnosis, data from clinical examination, complete blood count, core biopsy and molecular genetic testing were used, including mutation detection in *JAK2 (V617F), MPL, CALR, BCR/ABL1* genes (NMRC for Hematology).

### *Inclusion and exclusion criteria*

The study included patients with a confirmed diagnosis of one of the clinical entities of Ph-negative MPN, who signed an informed consent form and had post-infarction brain changes as assessed by magnetic resonance imaging (MRI). Exclusion criteria included missing informed consent, absence of post-infarction brain changes, presence of severe somatic comorbidities, and contraindications to MRI (e.g., pacemakers).

All patients underwent a comprehensive clinical and neurological evaluation, as well as laboratory tests including complete blood count and blood chemistry (cholesterol, triglycerides, low- and high-density lipoprotein, glucose). To confirm an ischemic brain lesion, all patients with MPN underwent brain MRI at 3 T (Magnetom Verio, Siemens) in the sagittal, coronal, and axial planes in T2, T1, T2-FLAIR, and DWI sequences.

### *Study design*

A cross-sectional, non-randomized, single-center interventional study.

The sample was formed by continuous inclusion of observations (after diagnosis, patients were offered additional examination at the Research Center of Neurology). After brain MRI, a study group was formed for further analysis (Figure 1).

### *Statistical analysis*

Data analysis was performed in the RStudio environment (v. 2023.12.1, R Programming Language v.4.2.1) using the tidyverse, finalfit, and ggalluvial packages. Non-parametric methods of descriptive statistics were used. For continuous variables, data are presented as median and lower and upper quartiles; for discrete values, data are presented as frequencies. Alluvial plots (like a Sankey diagram) are used to visualize the relationships between groups of categorical variables in the study population with MPN, with each stratum indicating the size of the relationship (in this case, the number of patients/frequency in each category). Comparisons were made using the Mann–Whitney U test for two independent groups, the ANOVA test for three independent groups, and the $\chi^2$ test for categorical variables. The null hypothesis was rejected at $p < 0.05$.

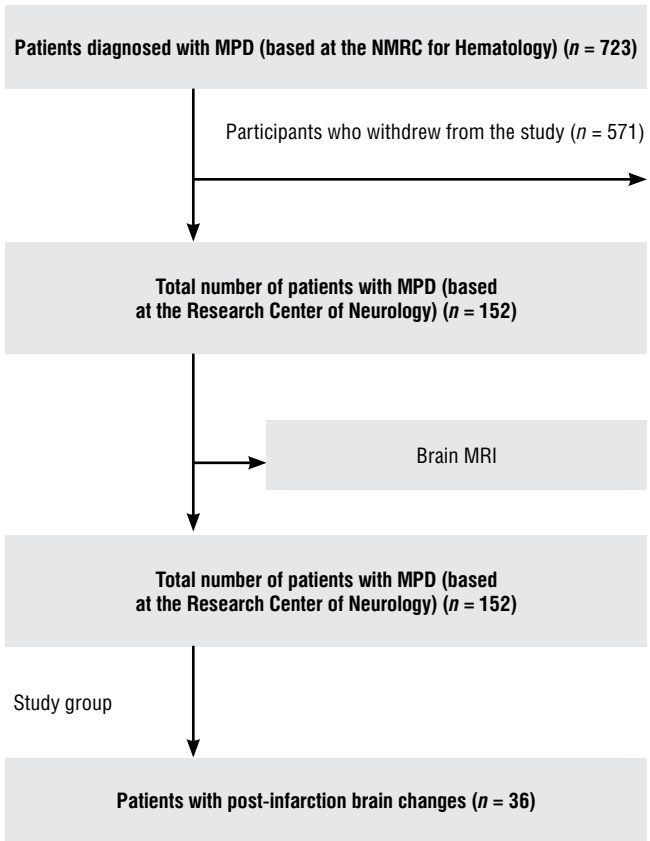


**Fig. 1. Patient selection.**

## Results

The patients were comparable in age and distribution of major risk factors for ischemic stroke. In all groups, hydroxyurea in combination with acetylsalicylic acid was the main regimen of cytoreductive therapy.

Significant differences in hemoglobin levels, red blood cell count, and the *V617F* mutation status of the *JAK2* gene were not compared between the groups because MPD represents a heterogeneous group of clinical entities, and only PV is necessarily associated with an increase in these parameters.

**Table 1. Clinical and laboratory characteristics of the study patients**

| Parameter | All patients (*n* = 152) | With post-infarction changes (*n* = 36) | No post-infarction changes (*n* = 116) | *p* |
|---|---|---|---|---|
| Male/female, *n* (%) | 52 (34)/100 (66) | 23 (64)/13 (36) | 29 (25)/87 (75) | < 0,010 |
| Age, years, Me [$Q_1$; $Q_3$] | 48 [36; 55] | 52 [39; 57] | 47 [35; 55] | 0,080 |
| Hypertension, *n* (%) | 51 (34) | 14 (39) | 37 (32) | 0,565 |
| Diabetes mellitus, *n* (%) | 9 (6) | 3 (8) | 6 (5) | 0,765 |
| Myocardial infarction, *n* (%) | 7 (5) | 3 (8) | 4 (3) | 0,443 |
| History of venous thrombosis, *n* (%) | 19 (12,5) | 8 (22) | 11 (9) | 0,083 |
| *JAK2 V617F*, *n* (%) | 117 (77) | 27 (75) | 90 (78) | 0,924 |
| *CALR*, *n* (%) | 8 (5) | 3 (8) | 5 (4) | 0,605 |
| Cytoreductive therapy, *n* (%) | Hydroxyurea — 84; interferon — 8) (61%) | 26 (72) | Hydroxyurea — 58) (57%) | 0,147 |
| Headache | 88 (58) | 12 (33) | 76 (66) | 0,001 |
| Carotid atherosclerosis | 51 (34) | 18 (50) | 33 (28) | 0,028 |
| Hemoglobin, g/L | 141 [127; 157] | 150 [136; 163] | 140 [125; 153] | 0,014 |
| Red blood cells, × $10^{12}$ | 4,8 [4,2; 5,5] | 4,7 [4,2; 5,4] | 4,9 [4,3; 5,5] | 0,414 |
| White blood cells, × $10^9$ | 7,1 [5,7; 9,0] | 7,3 [5,5; 8,9] | 7,1 [5,7; 9,1] | 0,764 |
| Platelets, × $10^9$ | 476 [308; 594] | 429 [256; 546] | 490 [324; 601] | 0,099 |
| Low-density lipoprotein, mmol/L | 1,95 [1,42; 2,36] | 1,98 [1,40; 2,68] | 1,89 [1,42; 2,29] | 0,452 |

The following data were analyzed to evaluate potential stroke factors in patients with MPD: results of molecular genetic testing of *JAK2* and *CALR* genes, data on comorbidities, history of venous thrombosis, blood tests, cardiovascular diseases, prevalence of carotid atherosclerosis according to the presence of stroke in the general population, and post-infarction brain changes (Table 1).

No statistically significant differences were found between the two groups relative to the presence of mutations in the *JAK2* and *CALR* genes or in the prevalence of venous thrombotic events. There were no significant differences between the groups in terms of specific therapy and hypertension. Stroke was more often associated with male gender. The higher prevalence rate of cephalgic syndrome was re-

**Table 2. Clinical and laboratory characteristics of MPN patients with post-infarction brain changes**

| Parameter | PV (*n* = 17) | ET (*n* = 15) | PMF (*n* = 4) | *p* |
|---|---|---|---|---|
| Male, *n* (%) | 14 (82) | 6 (40) | 3 (75) | 0,04 |
| Age, years, Me [$Q_1$; $Q_3$] | 49 [43; 57] | 51 [38; 58] | 54 [48; 56] | 0,995 |
| Hypertension, *n* (%) | 5 (29) | 7 (47) | 2 (50) | 0,540 |
| Diabetes mellitus, *n* (%) | 1 (6) | 2 (13) | 0 (0) | 0,610 |
| Myocardial infarction, *n* (%) | 3 (18) | 0 (0) | 0 (0) | 0,160 |
| History of venous thrombosis, *n* (%) | 4 (24) | 4 (27) | 0 (0) | 0,514 |
| *JAK2 V617F*, *n* (%) | 15 (88) | 10 (67) | 2 (50) | 0,175 |
| *CALR*, *n* (%) | 0 (0) | 2 (13) | 1 (25) | 0,174 |
| Cytoreductive therapy, *n* (%) | 12 (71) | 11 (73) | 3 (75) | 0,976 |
| Headache | 5 (29) | 5 (33) | 2 (50) | 0,734 |
| Carotid atherosclerosis | 9 (53) | 9 (60) | 0 (0) | 0,097 |
| Hemoglobin, g/L | 162 [147; 174] | 131 [126; 148] | 154 [150; 158] | < 0,0001 |
| Red blood cells, × $10^{12}$ | 5,3 [4,5; 5,9] | 4,3 [3,8; 4,9] | 4,4 [4,0; 4,9] | 0,006 |
| White blood cells, × $10^9$ | 7,7 [5,7; 8,6] | 6,2 [4,7; 7,8] | 10,2 [9,3; 10,8] | 0,098 |
| Platelets, × $10^9$ | 259 [211; 499] | 436 [319; 587] | 578 [387; 746] | 0,123 |
| Low-density lipoprotein, mmol/L | 1,79 [1,35; 2,02] | 2,4 [1,4; 2,7] | 3,15 [2,67; 3,50] | 0,022 |

**Note.** Comparisons were made using a one-way ANOVA test for continuous variables (the null hypothesis was that the means of all groups were equal) and Fisher's exact test without continuity adjustment for frequencies. Due to the descriptive nature of the study, no further pairwise comparisons were made at $p < 0.05$.

ported in patients without post-infarction changes. Carotid atherosclerosis was more common in stroke patients (50% vs. 28%; $p = 0.0285$). Statistically significant differences were reported in hemoglobin levels; patients with stroke had higher hemoglobin levels (150 vs. 140 g/L; $p = 0.014$) and slightly lower platelet counts (429 vs. 490; $p = 0.099$).

Given the heterogeneity of laboratory parameters, we further analyzed each clinical entity of MPD separately, including clinical and neuroimaging features of stroke (Table 2; Figures 2, 3).

### *Polycythemia vera*

Typical clinical and neuroimaging signs of stroke in PV included cortical infarct lesions in adjacent perfusion territories, brainstem, and cerebellum, corresponding to a prior hemorheological microocclusive stroke with an incidence of 65%. In a retrospective review, the clinical picture was characterized by nonspecific complaints of dizziness, sometimes vomiting, and fatigue. Patients primarily thought of food poisoning or, in the absence of vomiting, an exacerbation of the underlying hematologic disease and often did not seek medical attention. Post-infarction brain changes were found in the vertebral-basilar system (40%) and in the carotid system or adjacent perfusion territories (60%). Thrombotic occlusion of major head arteries followed by the stroke was detected in 3 patients (2 patients with thrombosis of one vertebral artery, 1 patient with internal carotid artery thrombosis). Follow-up FAT-SAT brain MRI did not confirm vascular dissection.

Two patients had concomitant ischemic stroke and hemorrhage (1 patient with the subarachnoid hemorrhage and 1 patient with the left thalamic hemorrhage). In the total group of PV patients examined, venous sinus thrombosis occurred in 1.5% of cases. In one case, thrombosis of the right transverse and sigmoid sinuses was complicated by a venous infarction on day 3.

In 30% of patients with PV, the hematologic disease was diagnosed after the stroke. Of them, one patient with moderate thrombocytosis and erythrocytosis developed a portal vein thrombosis as the first clinical event. Follow-up examination allowed diagnosing PV and specific cytoreductive and antiplatelet therapy was initiated. Considering the development of portal hypertension, it was decided to perform a mesenterico-caval anastomosis. During the 15-year follow-up period, a toxic (hepatic) encephalopathy developed, leading to cognitive decline, self-discontinuation of treatment, and subsequent recurrence of ischemic stroke.

In addition to the above cortical post-infarction changes in adjacent perfusion territories, 35% of patients with PV also had extensive hemispheric infarction lesions with severe neurological deficit (gross hemiparesis, aphasia, hemianopsia) with persistent loss of legal capacity and disability (mean age of patients was 54 years).

The main neuroimaging findings in stroke patients with PV were presented as two patterns (Figure 3):

- small (up to 1.5 cm) post-infarction lesions in the brainstem, cerebellum, deep white matter, and basal ganglia, cortical post-infarction lesions, cystic and gliotic changes without basal ganglia involvement, including adjacent perfusion territories, probably after hemorheological microocclusive stroke;
- large cortical post-infarction changes in the middle cerebral artery system and adjacent perfusion territories without basal ganglia involvement.

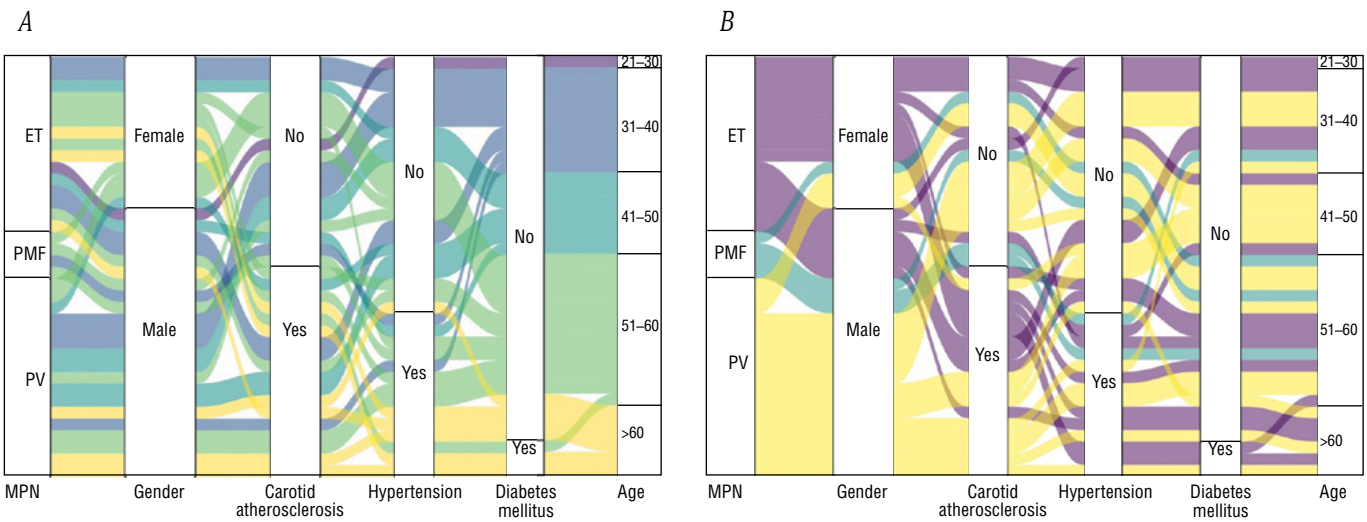


**Fig. 2. Clinical patterns in post-stroke patients with MPN (alluvial plots).**
*A*: color scheme by age category (right column); *B*: color scheme by MPN subgroup (left column).

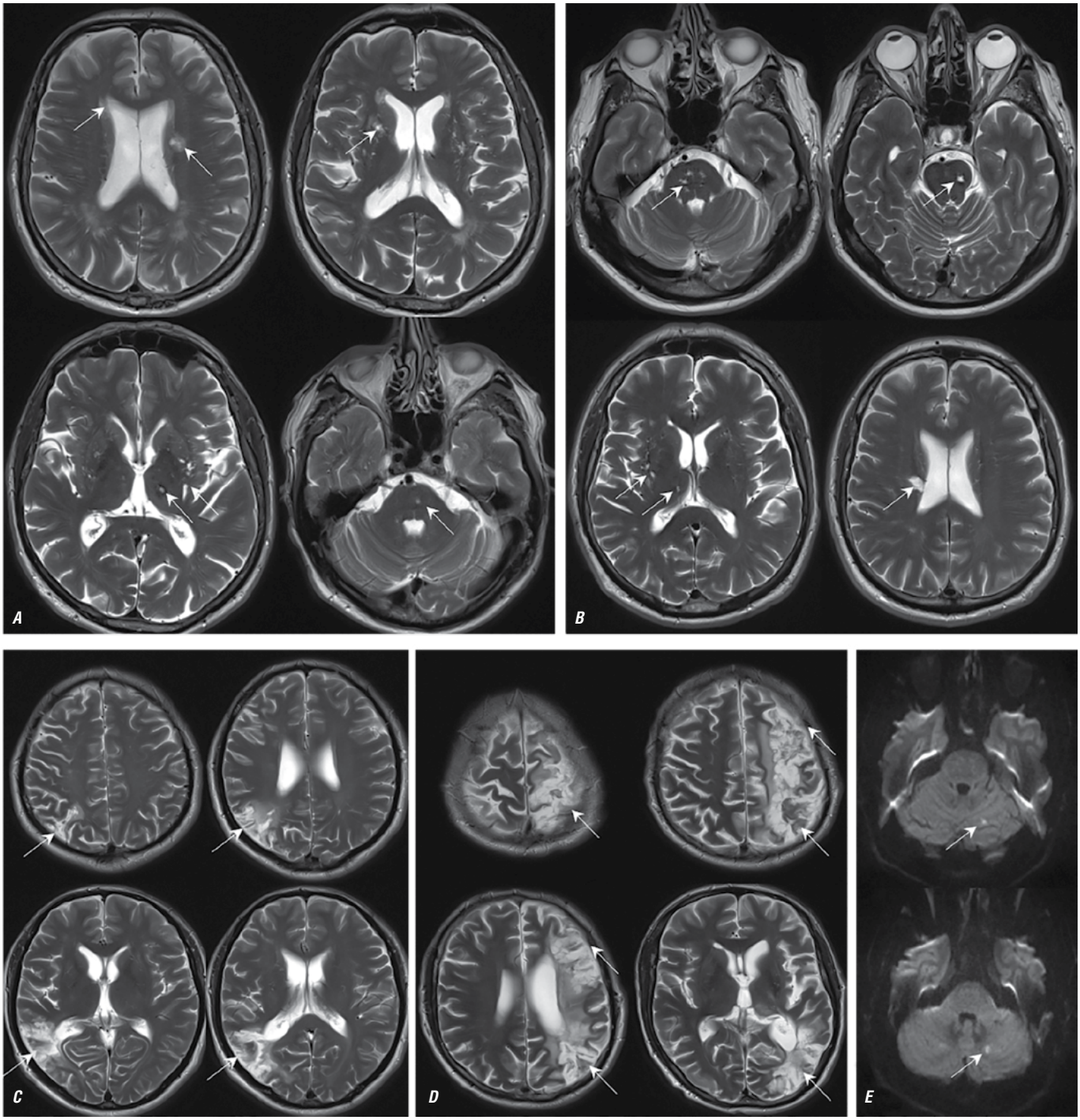


**Fig. 3. Brain MRI of patients with PV in axial T2 (*A–D*) and DWI sequences with a b-value of 1,000 s/mm² (*E*).**
Two main involvement patterns are visualized: small post-infarction lesions in the deep white matter, basal ganglia, and brainstem (*A*, *B*); one patient had lesions of acute ischemia in the left cerebellar hemisphere (*E*); large cortical post-infarction changes in the middle cerebral artery system and adjacent perfusion territories without basal ganglia involvement (*C*, *D*); post-infarction changes (*A–D*) and acute ischemic lesions (*E*) are indicated by arrows.

***Essential thrombocythemia***

Typical neuroimaging patterns of stroke in ET included massive post-infarction changes in the cortex, underlying and deep white matter, and basal ganglia with an incidence of 67%. In 26% of cases, stroke was associated with thrombotic occlusion of the internal carotid artery followed by formation of a massive ischemic lesion in the brain. Most cases were characterized by an acute onset with a gross neurological deficit. Post-infarction brain changes were found in the vertebral-basilar system (26%) and in the carotid system (74%). In 33% of the cases, the stroke resulted in permanent loss of legal capacity and disability (the mean age of the patients was 32 years).

In 1 patient with a history of right middle cerebral artery stroke followed by the left hemiparesis, the disease was complicated by thrombosis of the right jugular vein, lower extremity veins, recurrent pulmonary embolism with consequent myocardial remodeling, and persistent pulmonary hypertension.

In 40% of patients with ET, the stroke preceded the hematologic disease, including 1 patient with posterior reversible encephalopathy associated with extreme thrombocytosis (> 1 million platelets), which was the reason for the expanded hematologic examination leading to the diagnosis of ET.

An extensive cortical-subcortical lesions were the predominant neuroimaging pattern of stroke in ET (Figure 4).

***Primary myelofibrosis***

In most of PMF patients examined, the typical clinical signs of stroke included recurrent transient numbness in arms/legs, fine motor clumsiness that resolved spontaneously within a few hours, depending on the type of transient ischemic attack (TIA). Some patients described having TIAs several weeks or months before the stroke. Several patients reported episodes of significant, atypical headache with aura (visual snow, abnormal color perception), followed by focal changes (for several weeks).

The mean age of PMF patients with stroke was 50 years; there were no cases with post-infarction changes leading to persistent disability with significant motor deficit.

One patient did not receive cytoreductive antithrombotic therapy after PMF diagnosis (no history of thrombosis, age < 60 years), but developed a stroke in the right middle cerebral artery system 7 years after PMF diagnosis. In another patient, stroke preceded diagnosis of asymptomatic hematologic disease.

The predominant neuroimaging pattern of post-infarction changes in patients with PMF included small lesions in the deep brain substance, most likely after the hemorheological microocclusive stroke (Figure 5).

## Discussion

Arterial and venous thrombosis of various locations is the leading cause of mortality and disability in ET, PV, and PMF [3, 4]. The diagnosis of Ph-negative MPN is based on the clinical picture and clinical laboratory data (peripheral blood tests, histology features in bone marrow core biopsy, and molecular genetic markers such as *JAK2*, *CALR*, *MPL*).

The goal of PV and ET therapy is to inhibit disease progression and preserve patients' quality of life. With proper management, the life expectancy of patients with PV and ET should not differ from that of the general population. The goal of PMF treatment is to increase life expectancy and prevent complications that can severely impact a patient's quality of life. All Ph-negative MPNs are treated using a risk-adapted strategy.

Arterial thrombosis accounts for two-thirds of thrombotic complications in patients with MPD, with stroke, TIA, and coronary thrombosis being the most clinically relevant [5–7]. Recent recommendations use objectively validated thrombotic risk factors [8]. On the one hand, such an approach reduces the long-term toxic effects of cytoreductive, anticoagulant, and antiplatelet therapies. On the other hand, existing thrombotic risk scales mainly consider only age, prior thrombotic events, cardiovascular diseases (hypertension), and mutation status (*V617* in the *JAK2* gene), and do not include factors such as the presence of atherosclerotic lesions in the major head arteries, cardiac pathology (atrial fibrillation, valve disorder, coronary atherosclerosis), obesity, oral contraceptive use, thrombophilia, low physical activity, and alcohol abuse.

J. Bogousslavsky first described cerebrovascular compli-cations in MPN patients in 1983, emphasizing that early diagnosis is essential to prevent the development and progression of cerebrovascular disease [9]. Subsequently, several publications described stroke, myocardial infarction, extensive atherosclerosis, deep vein thrombosis, and pulmonary embolism as the most common causes of death in MPN patients. The main factors of thrombotic complications have also been identified, such as the *V617F* mutation in the *JAK2* gene, leukocytosis, age, and vascular factors (hypertension) [10, 11].

In the European population, the cumulative incidence of ischemic stroke (mean follow-up of 3 years) was 25% in the PV group and 21% in the ET group [12]. This is generally comparable to our results, where the incidence of ischemic stroke was 24% in PV and 25% in ET.

A population-based cohort study by M. Hultcrantz et al. showed that patients with MPN have an approximately 1.5 times

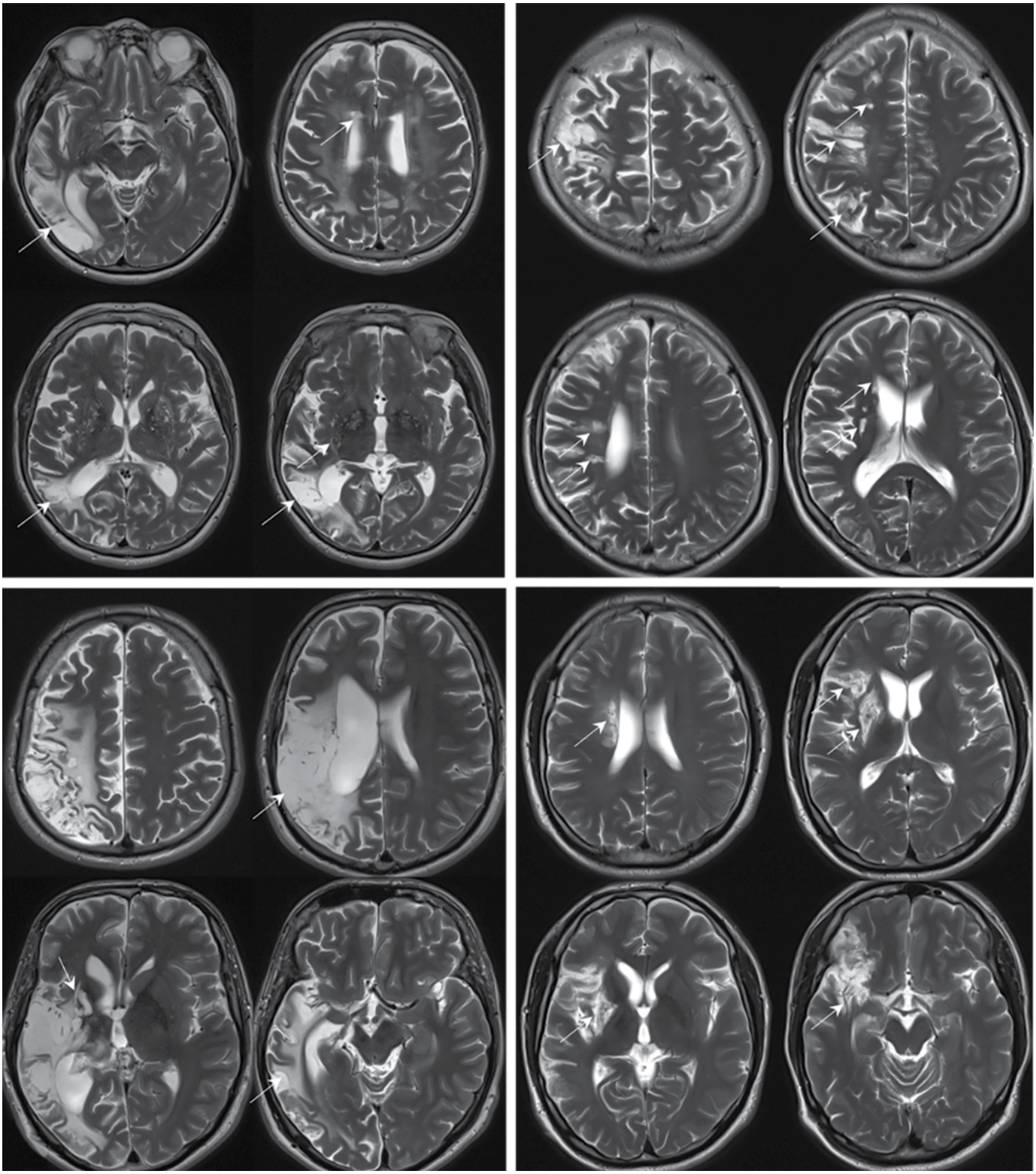

**Fig. 4. Brain MRI of patients with ET; axial plane T2-weighted images.**
In all cases, massive post-infarction changes are found in the cortex, underlying and deep white matter, and basal ganglia (post-infarction changes are indicated by arrows).

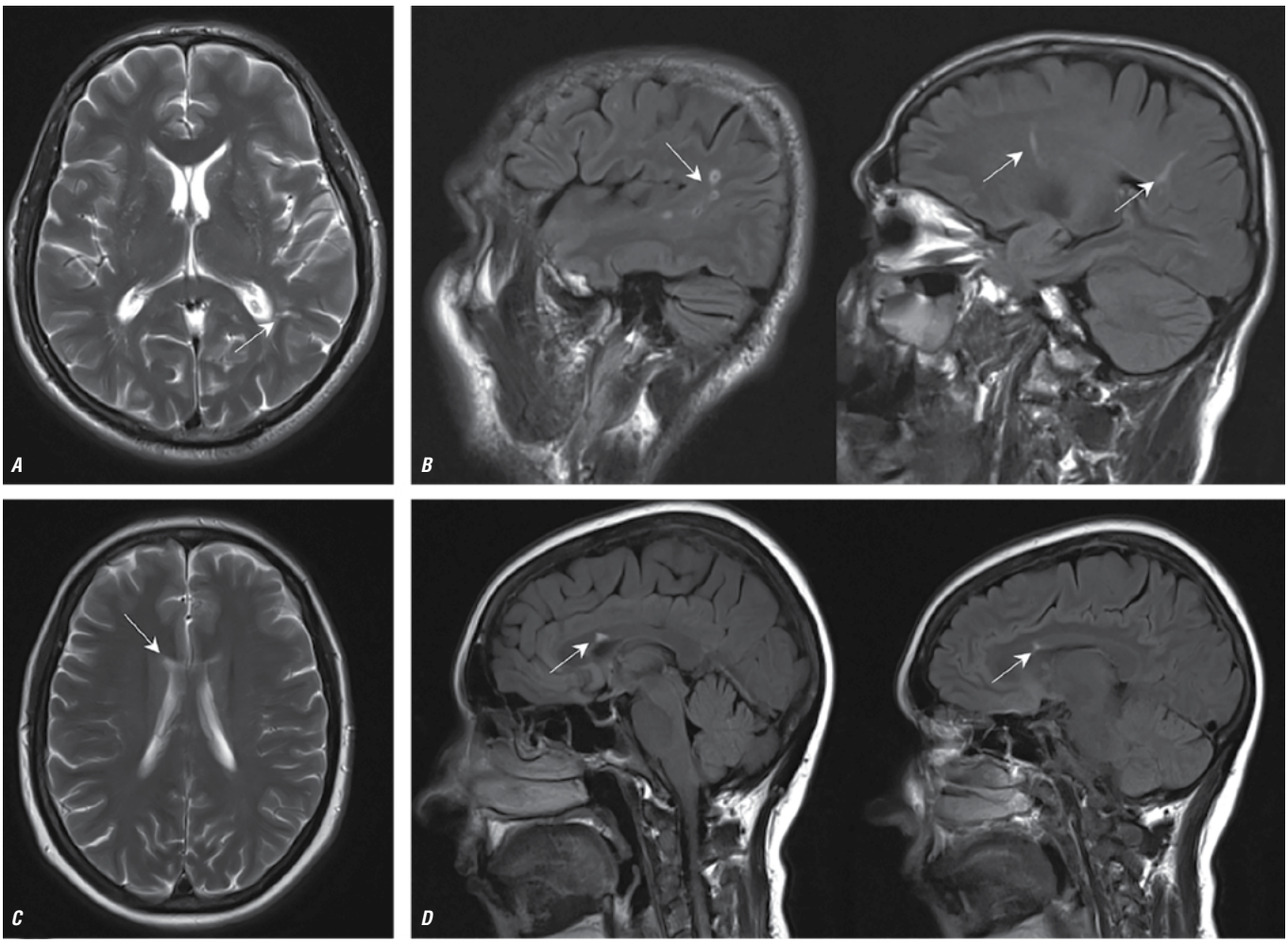


**Fig. 5. Brain MRI of patients with PMF in axial T2 images (*A*, *C*) and in sagittal T2 FLAIR images (*B*, *D*).**
Small post-infarction periventricular lesions are visualized (as indicated by arrows).

higher risk of ischemic stroke 5 years after diagnosis compared to age- and gender-matched controls [13]. These data support MPN as a group of diseases that require more careful monitoring and control of the underlying disease.

Cerebral and especially carotid atherosclerosis are known to play a key pathogenetic role in the development of ischemic stroke [14]. A. Drofenik et al. showed comparable prevalence and characteristics of carotid atherosclerosis in patients with ET and in the control group. However, the level of coronary calcium was higher in patients with ET [15], indicating greater vessel wall stiffness in these patients and therefore a potentially higher embolic risk. S. Kwon et al. described the epidemiology of cerebral atherosclerosis in patients with MPD associated with chronic inflammation (including *JAK2*-mediated) and demonstrated a higher neutrophil-lymphocyte ratio and carotid plaque burden compared to the general population [16]. The authors concluded that inflammation probably plays a critical role in the pathogenesis of MPD and that proinflammatory factors not only induce a prothrombogenic activity of blood, but also contribute to the progression of atherosclerosis, increasing cardiovascular risk. Abnormal activation of leukocytes, platelets, and vessel walls in ET and PV may lead to earlier development of atherosclerosis.

In our study, the higher detection rate of carotid athero-sclerosis was reported in stroke patients with ET (60%). However, extensive cortical-subcortical post-infarction changes were observed in patients with ET, indicating an atherothrombotic pathogenetic stroke, whereas brain tissue involvement was more likely in the PV and PMF groups, corresponding to a hemorheological microocclusive stroke.

In the study by M. Burattini et al., ischemic stroke was the presenting manifestation of PV in 16.2% of cases. The overall incidence of cerebrovascular complications was 5.5 per 100 persons per year, and stroke accounted for 8.8% of all PV-related deaths. The main risk factors were age, mutations, and history of thrombosis [17]. In our study, the incidence of stroke as the first manifestation of PV was 30%,

which can be explained by the characteristics of the population; some patients with hemorheological microocclusive stroke had no history of neurological symptoms, and only brain MRI according to the study protocol detected post-infarction changes.

Strokes associated with PV often remain unrecognized, in part due to the low prevalence of this clinical entity. Early diagnosis can lead to more effective treatment (with the use of phlebotomy, cytoreduction, and low-dose aspirin) and can reduce the risk of recurrence.

Data on the prevalence of stroke associated with ET as the first sign of an underlying hematologic disease are often limited to case series. T. Kato et al. described 10 patients with ET and ischemic stroke. In 8 patients (80%), the stroke preceded the diagnosis of ET [18]. In our study, stroke was the first manifestation of ET in 40% of cases.

M.I. Stefanou et al. at the University of Tübingen in 2014-2017 studied the medical records of 3,318 patients with cerebrovascular diseases, including 17 patients with MPD and ischemic stroke. In 58% of cases, stroke/TIA was the first manifestation of MPD [19].

Such variability in the available data may be explained by limitations in patient recruitment and enrollment. However, despite the variability of the parameters used, this underscores the relevant issue of the prevalence of stroke in patients with MPD, especially at a young age.

Sinus thrombosis has also been described in the literature as the first manifestation of MPD [20]. In our study, the incidence of venous sinus thrombosis was 7% (all patients had PV), but no hematologic disease was subsequently diagnosed.

One of the steps in this study was to evaluate erythrocyte/platelet aggregation parameters and their association with cerebrovascular disease in patients with MPD, which we have previously described [21, 22]. The neuroimaging pattern in hematologic patients is characterized by a relatively high frequency of so-called silent cerebral infarction lesions in addition to symptomatic stroke. Despite the absence of clinical manifestations, the consequences of previous silent MRI infarction lesions in patients with MPD may significantly and directly affect cognitive function and increase the risk of dementia in future [23, 24].

The rare hemorrhagic strokes described in this study are the subject of debate regarding the appropriateness of continuing aggressive antiplatelet therapy, particularly in cases of unrecognized resistance to certain antithrombotic drugs.

Management strategies, clinical outcomes, and life expectancy may be significantly affected in patients with established hematologic disease with or without adequate cytoreductive therapy when neurologic manifestations (headache, fatigue, transient hemi-/monoparesis of extremities, dysarthria, mild coordination disorders, cerebral ischemic lesions on MRI, sometimes silent) are present and the major features of MPD are underestimated. MPD should be recognized as a risk factor for stroke by all clinicians, not just neurologists. An expanded hematologic and neurologic examination may reduce the incidence of cryptogenic stroke.

Limitations of the study A relative limitation of this study is the recruitment of patients from a single clinical center; this cannot exclude a low representativeness of the sample.

## Conclusion

A heterogeneous group of MPDs with persistent blood abnormalities is an important risk factor for cerebrovascular disease. The described clinical, laboratory, and neuroimaging patterns of cerebrovascular diseases in MPD may guide further examination of patients with unexplained and/or cryptogenic stroke.

## References / Список источников

1. Shallis R.M., Zeidan A.M., Wang R., Podoltsev N.A. Epidemiology of the Philadelphia chromosome-negative classical myeloproliferative neoplasms. *Hematol. Oncol. Clin. North Am.* 2021;35(2):177–189. DOI: 10.1016/j.hoc.2020.11.005
2. Greenfield G., McMullin M.F., Mills K. Molecular pathogenesis of the myeloproliferative neoplasms. *J. Hematol. Oncol.* 2021;14(1):103. DOI: 10.1186/s13045-021-01116-z
3. Barbui T., Thiele J., Gisslinger H. et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J.* 2018;8(2):15. DOI: 10.1038/s41408-018-0054-y
4. Schwarz J., Ovesná P., Černá O. et al. Thrombosis in thrombocythemic Ph-myeloproliferations is associated with higher platelet count prior to the event: results of analyses of prothrombotic risk factors from a registry of patients treated with anagrelide. *Eur. J. Haematol.* 2016;96(1):98–106. DOI: 10.1111/ejh.12554
5. Duangnapasatit B., Rattarittamrong E., Rattanathammethee T. et al. Clinical manifestations and risk factors for complications of Philadelphia chromosome-negative myeloproliferative neoplasms. *Asian Pac. J. Cancer Prev.* 2015;16(12):5013–5018. DOI: 10.7314/apjcp.2015.16.12.5013
6. Rungjirajittranon T., Owattanapanich W., Ungprasert P. et al. A systematic review and meta-analysis of the prevalence of thrombosis and bleeding at diagnosis of Philadelphia-negative myeloproliferative neoplasms. *BMC Cancer.* 2019;19(1):184. DOI: 10.1186/s12885-019-5387-9
7. Carandina A., Lazzeri G., Villa D. et al. Targeting the autonomic nervous system for risk stratification, outcome prediction and neuromodulation in ischemic stroke. *Int. J. Mol. Sci.* 2021;22(5):2357. DOI: 10.3390/ijms22052357
8. Barbui T., Barosi G., Birgegard G. et. al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J. Clin. Oncol.* 2011;29(6):761–770. DOI: 10.1200/JCO.2010.31.8436
9. Bogousslavsky J., Regli F., Rousselle J., Schmidt P.M. Cerebrovascular complications of thrombocytosis. *Schweiz. Med. Wochenschr.* 1983;113(14):493–496.
10. Casini A., Fontana P., Lecompte T.P. Thrombotic complications of myeloproliferative neoplasms: risk assessment and risk-guided management. *J. Thromb. Haemost.* 2013;11(7):1215–1227. DOI: 10.1111/jth.12265
11. Танашян М.М., Кузнецова П.И., Лагода О.В. и др. Миелопролиферативные заболевания и ишемический инсульт. *Анналы клинической и экспериментальной неврологии.* 2014;8(2):41–45.
Tanashyan M.M., Kuznecova P.I., Lagoda O.V. et al. Myeloproliferative diseases and ischemic stroke. *Annals of Clinical and Experimental Neurology.* 2017;8(2):41–45. DOI: 10.17816/psaic181
12. Kaifie A., Kirschner M., Wolf D. et al. Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry. *J. Hematol. Oncol.* 2016;9:18. DOI: 10.1186/s13045-016-0242-9
13. Hultcrantz M., Björkholm M., Dickman P.W. et al. Risk for arterial and venous thrombosis in patients with myeloproliferative neoplasms: a population-based cohort study. *Ann. Intern. Med.* 2018;168(5):317–325. DOI: 10.7326/M17-0028
14. Parish S., Arnold M., Clarke R. et al. Assessment of the role of carotid atherosclerosis in the association between major cardiovascular risk factors and ischemic stroke subtypes. *JAMA Netw. Open.* 2019;2(5):e194873. DOI: 10.1001/jamanetworkopen.2019.4873
15. Anžič Drofenik A., Vrtovec M., Božič Mijovski M. et al. Progression of coronary calcium burden and carotid stiffness in patients with essential thrombocythemia associated with JAK2 V617F mutation. *Atherosclerosis.* 2020;296:25–31. DOI: 10.1016/j.atherosclerosis.2020.01.001
16. Kwon S.S., Yoon S.Y., Jeong S.Y. et al. Neutrophil-lymphocyte ratio and carotid plaque burden in patients with essential thrombocythemia and polycythemia vera. *Nutr. Metab. Cardiovasc. Dis.* 2022;32(8):1913–1916. DOI: 10.1016/j.numecd.2022.04.013
17. Burattini M., Falsetti L., Potente E. et al. Ischemic stroke as a presenting manifestation of polycythemia vera: a narrative review. *Rev. Neurosci.* 2021;33(3):303–311. DOI: 10.1515/revneuro-2021-0066
18. Kato Y., Hayashi T., Sehara Y. et al. Ischemic stroke with essential thrombocythemia: a case series. *J. Stroke Cerebrovasc. Dis.* 2015;24(4):890–893. DOI: 10.1016/j.jstrokecerebrovasdis.2014.12.012
19. Stefanou M.I., Richter H., Härtig F., et al. Recurrent ischaemic cerebrovascular events as presenting manifestations of myeloproliferative neoplasms. *Eur. J. Neurol.* 2019;26(6):903–e64. DOI: 10.1111/ene.13907
20. Arai M, Sugiura A. Superior sagittal sinus thrombosis as first manifestation of essential thrombocythemia. Rinsho. Shinkeigaku. 2004;44(1):34–38.
21. Танашян М.М., Шабалина А.А., Ройтман Е.В. и др. Тромбогенность у больных ишемическим инсультом на фоне истинной полицитемии. *Вестник Российского государственного медицинского университета.* 2020;(4):49–55.
Tanashyan M. M., SHabalina A. A., Rojtman E. V. et al. Thrombogenicity in patients with ischemic stroke and pre-existing polycythemia vera. *Bulletin of RSMU.* 2020;(4):49–55. DOI: 10.24075/vrgmu.2020.052
22. Kuznetsova P.I., Raskurazhev A.A., Shabalina A.A. et al. Red blood cell morphodynamics in patients with polycythemia vera and stroke. *Int. J. Mol. Sci.* 2022;23(4):2247. DOI: 10.3390/ijms23042247
23. Kuznetsova P.I., Raskurazhev A.A., Lagoda O.V. et al. Covert brain infarcts in patients with Philadelphia chromosome-negative myeloproliferative disorders. *J. Clin. Med.* 2021;11(1):13. DOI: 10.3390/jcm11010013
24. Меликян А.Л., Суборцева И.Н., Ковригина А.М. и др. Национальные клинические рекомендации по диагностике и лечению Ph-негативных миелопролиферативных новообразований (истинной полицитемии, эссенциальной тромбоцитемии, первичного миелофиброза) (редакция 2024 г.). *Клиническая онкогематология.* 2024;17(3):291–334.
Melikyan A.L., Suborceva I.N., Kovrigina A.M. et al. National clinical guidelines on diagnosis and treatment of Ph-negative myeloproliferative neoplasms (polycythemia vera, essential thrombocythemia, and primary myelofibrosis) (Edition 2024). *Clinical oncohematology.* 2024;17(3):291–334. DOI: 10.21320/2500-2139-2024-17-3-291-334

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