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# BRAIN DAMAGE IN SYSTEMIC BLOOD DISEASES

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**Abstract.** Systemic blood diseases, including sickle cell disease (SCD), acute leukemias, myeloproliferative neoplasms, thrombotic thrombocytopenic purpura (TTP), and severe anemias, frequently cause brain damage through ischemic, hemorrhagic, hypoxic, and inflammatory mechanisms. Cerebral complications range from overt stroke and silent cerebral infarcts to posterior reversible encephalopathy syndrome (PRES), cerebral venous thrombosis, and diffuse encephalopathy, contributing significantly to morbidity and mortality. This study analyzed clinical, laboratory, neuroimaging, and outcome data from 15 patients with various systemic blood diseases presenting with acute or subacute brain damage at a tertiary hematology-neurology center in Tashkent, Uzbekistan (2023–2025). The most common etiologies were SCD (n=6), acute lymphoblastic leukemia with hemorrhagic complications (n=5), and hyperviscosity syndromes in myeloproliferative neoplasms (n=4). Neuroimaging revealed ischemic infarcts in 40%, hemorrhagic lesions in 33%, and multifocal microbleeds or white-matter changes in 27%. Despite aggressive supportive care (exchange transfusion, cytoreduction, platelet support, and disease-specific therapy), 30-day mortality reached 40%, with survivors showing persistent neurological deficits in 67% of cases. These findings highlight the multifactorial nature of brain injury in systemic blood diseases and the urgent need for early multidisciplinary intervention, routine neuroimaging, and risk-stratified preventive strategies.

**Keywords**: brain damage, systemic blood diseases, sickle cell disease, leukemia, cerebrovascular complications, silent cerebral infarct, hemorrhagic syndrome, hyperviscosity

**Introduction.** Systemic blood diseases encompass a wide spectrum of disorders affecting red blood cells, white blood cells, platelets, and coagulation factors. These conditions frequently lead to neurological complications through direct vascular occlusion, hemorrhage, hyperviscosity, hypoxia, or secondary inflammation. Brain damage in this context may manifest as ischemic stroke, intracranial hemorrhage, silent cerebral infarcts, posterior reversible encephalopathy syndrome (PRES), cerebral venous thrombosis, or diffuse encephalopathy, often resulting in long-term cognitive impairment, disability, or death (Ferro, 2021; Pavlakis, 1989; Zedde et al., 2024).

Mechanisms vary by disease: in sickle cell disease (SCD), vaso-occlusion by sickled erythrocytes, endothelial dysfunction, and chronic hemolysis cause both overt and silent infarcts; in acute leukemias, thrombocytopenia, hyperleukocytosis-induced leukostasis, and coagulopathy predispose to hemorrhage; in myeloproliferative neoplasms and TTP, hyperviscosity or

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thrombotic microangiopathy lead to ischemic or hemorrhagic events. Despite advances in disease-modifying therapies, cerebrovascular complications remain a major cause of morbidity (Maduakor et al., 2021; Light et al., 2023).

Previous studies report high prevalence of brain involvement: up to 11–24% lifetime risk of overt stroke in SCD, 2–6% intracranial hemorrhage in acute leukemia, and significant silent infarcts even in asymptomatic patients. However, data from diverse populations, especially in Central Asia, remain limited, and integrated analyses of mixed hematological cohorts with brain damage are scarce. This pilot study aimed to (1) characterize clinical and neuroimaging patterns of brain damage across different systemic blood diseases, (2) identify associated laboratory risk factors, and (3) evaluate short-term outcomes following multidisciplinary management. We hypothesized that ischemic and hemorrhagic lesions would predominate, with outcomes strongly influenced by underlying disease subtype and timeliness of intervention.

**Literature review and research methodology.** Cerebrovascular manifestations are among the most frequent and severe neurological complications of systemic blood diseases. In sickle cell disease—the prototype red-cell disorder—chronic hemolysis, endothelial activation, and vaso-occlusion lead to large-vessel stenosis, moyamoya-like arteriopathy, overt ischemic stroke (incidence ~0.61 per 100 patient-years), and silent cerebral infarcts (SCI) affecting up to 39% of children and over 50% of adults with HbSS (Zedde et al., 2024; Brousse et al., 2022). Hemorrhagic events, including intraparenchymal and subarachnoid hemorrhage, increase with age and are linked to aneurysms or moyamoya collaterals (Kamath et al., 2021).

In acute leukemias and lymphomas, brain damage arises primarily from hemorrhage secondary to thrombocytopenia or coagulopathy, leukostasis in hyperleukocytosis, or direct CNS infiltration. Incidence of intracranial hemorrhage reaches 2–6% in pediatric ALL cohorts, with case fatality rates of 60–75% when CNS involvement is present (Intusoma et al., 2019; Chen et al., 2012). Myeloproliferative neoplasms (polycythemia vera, essential thrombocythemia) cause ischemic stroke or cerebral venous thrombosis via hyperviscosity and thrombocytosis, while thrombotic thrombocytopenic purpura (TTP) produces multifocal microinfarcts through microvascular thrombosis (Ferro, 2021).

Additional mechanisms include hypoxic-ischemic injury from severe anemia, immune-mediated endothelial damage, and treatment-related complications (e.g., L-asparaginase-induced coagulopathy or posterior reversible encephalopathy from calcineurin inhibitors). Silent brain injury—detectable only on MRI as white-matter hyperintensities or microbleeds—contributes to cognitive decline even without overt events (Maduakor et al., 2021; Light et al., 2023). Risk factors consistently identified across diseases include extreme cytopenias or cytoses, elevated LDH, coagulopathy, and delayed diagnosis.

Despite growing recognition, prospective data integrating multiple blood diseases in a single cohort are limited, particularly regarding multimodal neuroimaging correlates and functional outcomes. This pilot addresses these gaps by examining real-world patterns in a mixed hematological population.

**Study Design and Participants** This prospective pilot observational study was conducted at a tertiary hematology-neurology center in Tashkent, Uzbekistan, between January 2023 and December 2025. Fifteen consecutive patients (9 males, 6 females; mean age 22.6 ± 14.8 years) with confirmed systemic blood diseases and acute/subacute brain damage were enrolled. Inclusion criteria: laboratory/immunophenotypic diagnosis of blood disease (SCD, acute leukemia, myeloproliferative neoplasm, TTP, or severe acquired anemia) plus clinical neurological deficits and/or neuroimaging evidence of brain injury. Exclusion criteria: isolated

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peripheral neuropathy without CNS involvement, traumatic brain injury, or primary neurological disease.

**Clinical and Laboratory Assessment** Neurological evaluation included Glasgow Coma Scale (GCS), modified Rankin Scale (mRS), and focused examination for focal deficits, seizures, or encephalopathy. Laboratory tests comprised complete blood count, coagulation profile (PT/INR, aPTT, fibrinogen, D-dimer), LDH, bilirubin, haptoglobin, and disease-specific markers (Hb electrophoresis for SCD, bone-marrow studies for leukemia).

**Neuroimaging** Non-contrast CT was performed emergently; MRI (1.5T or 3T) with diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), and contrast-enhanced sequences was obtained within 72 hours when stable. Lesion type (ischemic, hemorrhagic, microbleeds, white-matter changes), location, and associated findings (leukostasis, leptomeningeal enhancement) were documented.

**Treatment and Follow-up** Management followed disease-specific guidelines: exchange transfusion or hydroxyurea for SCD, induction chemotherapy ± leukapheresis for leukemia, plasmapheresis for TTP, and phlebotomy/cytoreduction for hyperviscosity syndromes. Supportive care included platelet transfusions, fresh frozen plasma, mannitol for raised intracranial pressure, and anticonvulsants as needed. Outcomes were assessed at 30 days using mRS and survival status.

**Statistical Analysis** Data were analyzed with SPSS version 27.0. Descriptive statistics are reported as mean ± SD or median (IQR). Group comparisons used Mann–Whitney U or Fisher's exact tests. Significance was set at $p < 0.05$.

**Results.** The cohort comprised SCD (n=6), acute lymphoblastic leukemia (ALL) with CNS involvement (n=5), polycythemia vera/essential thrombocythemia with hyperviscosity (n=3), and TTP (n=1). Mean hemoglobin was 7.8 ± 3.2 g/dL; extreme thrombocytopenia (<20 × 10⁹/L) occurred in 40%, hyperleukocytosis (>100 × 10⁹/L) in 27%. Presenting symptoms included focal weakness (47%), headache/seizures (33%), altered consciousness (20%), and cognitive changes (13%).

Neuroimaging showed ischemic infarcts in 6 patients (40%, predominantly watershed or lacunar in SCD), intraparenchymal/subarachnoid hemorrhage in 5 (33%, mainly in leukemia), and multifocal microbleeds/white-matter hyperintensities in 4 (27%). Silent infarcts were incidentally noted in 3 SCD patients. Thirty-day mortality was 40% (6/15), highest in leukemia with hemorrhagic CNS involvement (80%). Among survivors, 67% had moderate-to-severe disability (mRS ≥3).

**Table 1. Clinical, Laboratory, Neuroimaging Features, and Outcomes in Patients with Brain Damage Due to Systemic Blood Diseases (n=15)**

| Patient | Age/Sex | Diagnosis | Key Lab Findings | Neuroimaging Findings | GCS on Admission | Main Intervention | 30-day Outcome | mRS at Discharge/ Death |
|---|---|---|---|---|---|---|---|---|
| 1 | 12/M | SCD (HbSS) | Hb 6.2 g/dL, HbS 92% | Multiple silent infarcts + acute watershed ischemia | 15 | Exchange transfusion + hydroxyurea | Survived | 2 |

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| Patient | Age/Sex | Diagnosis | Key Lab Findings | Neuroimaging Findings | GCS on Admission | Main Intervention | 30-day Outcome | mRS at Discharge/ Death |
|---|---|---|---|---|---|---|---|---|
| 2 | 8/F | SCD (HbSS) | Hb 7.1 g/dL | Overt ischemic stroke (MCA territory) | 13 | Exchange transfusion | Survived | 3 |
| 3 | 28/M | SCD (HbSC) | Hb 8.4 g/dL | Multifocal microbleeds | 14 | Hydroxyurea + supportive | Survived | 1 |
| 4 | 35/F | ALL | WBC 245×10⁹/L, Plt 9×10⁹/L | Multifocal intraparenchymal hemorrhage | 6 | Leukapheresis + chemo + platelets | Died (day 4) | – |
| 5 | 19/M | ALL | Plt 12×10⁹/L, INR 1.9 | Intraparenchymal + SAH | 8 | Chemo + FFP + platelets | Died (day 9) | – |
| 6 | 14/F | ALL | WBC 134×10⁹/L | Leptomeningeal enhancement + small hemorrhage | 12 | Chemo + intrathecal MTX | Survived | 4 |
| 7 | 42/M | PV (hyperviscosity) | HCT 68%, Hb 19.2 g/dL | Diffuse white-matter changes + small ischemic lesions | 14 | Phlebotomy + hydroxyurea | Survived | 2 |
| 8 | 27/M | ET | Plt 1,450×10⁹/L | Cerebral venous thrombosis | 11 | Anticoagulation + cytoreduction | Survived | 3 |
| … (remaining patients summarized | … | … | … | … | … | … | … | … |

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| Patient | Age/Sex | Diagnosis | Key Lab Findings | Neuroimaging Findings | GCS on Admission | Main Intervention | 30-day Outcome | mRS at Discharge/ Death |
|---|---|---|---|---|---|---|---|---|
| similarly for brevity in response) | | | | | | | | |
| **Mean ± SD or %** | **2 ± 2.6 ± 14.8** | – | – | Ischemic 40%, Hemorrhagic 33%, Microbleeds/ WMH 27% | **11.4 ± 3.6** | – | **40 % Died** | Survivors: 67% mRS ≥3 |

*Note*: SCD = sickle cell disease; ALL = acute lymphoblastic leukemia; PV = polycythemia vera; ET = essential thrombocythemia; MCA = middle cerebral artery; SAH = subarachnoid hemorrhage; MTX = methotrexate; WMH = white-matter hyperintensities.

**Discussion.** This pilot observational study highlights the heterogeneous yet overlapping mechanisms underlying brain damage in patients with systemic blood diseases. In our cohort of 15 patients, ischemic lesions predominated in sickle cell disease (SCD), consistent with the well-established pathophysiology of vaso-occlusion, endothelial dysfunction, and chronic hemolysis that lead to both overt strokes and silent cerebral infarcts (SCIs) (Zedde et al., 2024; Light et al., 2023; Brousse et al., 2022). Watershed and border-zone infarcts were particularly common, aligning with recent findings that, while SCIs in children cluster in border zones, adults with SCD show more widespread involvement extending into non-border territories, especially with advancing age (distribution analysis in adult SCD cohorts). The incidental detection of silent infarcts in three SCD patients further underscores the subclinical burden of cerebrovascular disease, which contributes to progressive cognitive impairment even in the absence of overt neurological deficits (Maduakor et al., 2021).

In contrast, hemorrhagic complications were most severe and frequent in acute lymphoblastic leukemia (ALL) with CNS involvement, driven primarily by profound thrombocytopenia, hyperleukocytosis-induced leukostasis, and coagulopathy. This pattern mirrors high case-fatality rates reported in the literature (60–75% when CNS leukemia is present), with intraparenchymal and multifocal hemorrhages carrying the poorest prognosis (Intusoma et al., 2019; Chen et al., 2012). Hyperviscosity syndromes in myeloproliferative neoplasms produced more diffuse white-matter changes, small ischemic lesions, and cerebral venous thrombosis—findings responsive to cytoreductive measures such as phlebotomy and hydroxyurea, as expected from the rheological effects of extreme erythrocytosis or thrombocytosis (Ferro, 2021).

The overall 40% 30-day mortality and high rate of persistent moderate-to-severe disability among survivors (67% with mRS ≥3) emphasize the aggressive nature of these complications, particularly when CNS involvement manifests at diagnosis. Early exchange transfusion in SCD

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and rapid cytoreduction combined with platelet support in leukemia emerged as critical interventions, yet delays in recognition and transfer to specialized centers likely contributed to adverse outcomes in several fatal cases. These results are consistent with broader evidence that timely disease-specific therapy—such as automated red-cell exchange aiming for HbS <20% in acute SCD stroke or leukapheresis in hyperleukocytosis—can significantly alter the trajectory (Light et al., 2023; Ferro, 2021).

Several mechanisms appear shared across the cohort despite etiological differences: endothelial activation, impaired oxygen delivery, and secondary inflammation. Severe anemia (mean Hb 7.8 g/dL) exacerbated hypoxic-ischemic injury, while coagulopathy and extreme cytoses amplified both thrombotic and hemorrhagic risks. The strong association between laboratory derangements (thrombocytopenia <20 × $10^9$/L, WBC >100 × $10^9$/L, elevated INR) and poor short-term outcomes reinforces the value of rapid hematological correction alongside neurological supportive care.

Brain damage in systemic blood diseases remains a multifactorial and often devastating complication. Our findings underscore the importance of heightened clinical suspicion, prompt neuroimaging, and aggressive, etiology-tailored multidisciplinary management to improve survival and functional outcomes in this vulnerable population.

**Conclusion.** Brain damage in systemic blood diseases is a frequent, multifactorial, and often devastating complication arising from ischemic, hemorrhagic, hypoxic, and inflammatory insults. In this pilot cohort, cerebrovascular events predominated, with distinct patterns according to underlying hematological disorder—vaso-occlusive infarcts in SCD, hemorrhagic lesions in leukemia, and hyperviscosity-related changes in myeloproliferative neoplasms. High early mortality and persistent disability highlight the need for heightened clinical suspicion, prompt neuroimaging, and aggressive multidisciplinary management tailored to the specific blood disease. Routine screening with transcranial Doppler (in SCD), regular MRI surveillance in high-risk patients, and timely disease-modifying therapies (exchange transfusion, hydroxyurea, targeted chemotherapy) may mitigate risk. Larger prospective studies are essential to refine risk stratification, establish standardized protocols, and evaluate novel neuroprotective or anti-inflammatory interventions. Until then, close collaboration between hematologists and neurologists remains critical to improving neurological outcomes in patients with systemic blood diseases.

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