

Modern neuroimaging and reperfusion therapy in the management of wake-up stroke

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Wake-up stroke (WUS) remains one of the most challenging medical problems in acute cerebrovascular disease. Until recently, the unknown time of symptom onset made these patients eligible only for limited therapeutic options, thereby diminishing the likelihood of a favorable outcome. However, the development of advanced neuroimaging techniques and the revision of approaches to assessing brain tissue viability, have radically expanded treatment possibilities for this patient category.

A paradigm shift was driven by the introduction of advanced MRI and CT protocols, which enabled not only

differentiation between the ischemic core and penumbra, but also estimation of "biologic time" of the stroke. Such methods as MRI DWI-FLAIR mismatch, perfusion CT, and CT-angiography, present objective criteria for patients in order for reperfusion therapy, despite the unknown time of symptom onset.

Objective. The aim of this review is to summarize current literature on the pathogenesis, risk factors (RFs), diagnosis, and management of WUS.

Methods. This review is based on the analysis of publications by Russian and international authors from print

and online sources over the past 10 years. The following search terms were used: wake-up stroke, computed tomography, magnetic resonance imaging, thrombolysis, and thrombectomy. Studies or articles that did not meet quality standards were excluded.

Results. This review examines current evidence on the pathogenesis, RFs, diagnostic approaches, and treatment strategies for WUS. It describes the role of various MRI sequences in decision-making for reperfusion therapy. Furthermore, it provides an analysis of the literature to define indications for systemic thrombolysis and mechanical thrombectomy in cerebral vessels.

Conclusion. Pharmacological and endovascular treatment in the hyperacute phase of ischemic stroke has evolved considerably over the past two decades. This progress is attributable to improved patient selection cri-

teria, advances in diagnostic imaging, and greater availability of modern thrombectomy devices.

Keywords: wake-up stroke, computed tomography, magnetic resonance imaging, thrombolysis, thrombectomy.

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Introduction

Wake-up stroke (WUS) is a subtype of ischemic stroke in which no signs of neurological deficit are detected before the patient goes to sleep, but they become apparent immediately after awakening. Approximately 14–25% of patients with acute ischemic cerebrovascular events wake up with symptoms of stroke [1–3]. Management of patients with WUS is complicated by the inability to determine the exact time of stroke onset, which by default places them outside the standard “therapeutic window.”

According to recent studies, thrombolysis or reperfusion therapy may be an effective treatment option for this group of patients, provided that appropriate patient selection is performed [4, 5]. Selection is based on multimodal magnetic resonance imaging

and computed tomography data, which allow visualization of brain regions in which ischemic changes are potentially reversible within a certain time frame.

The aim of this study is to summarize current literature on the pathogenesis, risk factors (RFs), diagnosis, and management of WUS.

Methods

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Results

The pathogenesis and risk factors of wake-up stroke

The pathogenesis of WUS is not yet fully understood. Current research suggests that the underlying mechanisms may involve impaired cerebral perfusion and systemic hemodynamic changes due to nocturnal fluctuations in blood pressure, heart rate, oxygen desaturation, as well as sympathetic nervous system activity, slowed metabolism, and other factors [4–6]. Microvascular pathology is also considered a potential contributor. Although patients with WUS most frequently present with lacunar infarcts, the causal

relationship between cerebral microvascular disease and WUS pathogenesis requires further investigation [6]. Unusual etiologies, such as cervical spondylosis, have also been described among the diverse causes of WUS [7].

The risk factors for WUS are likely similar to those for acute cerebrovascular accidents (ACVA) in general. However, given its unique temporal profile, certain factors are hypothesized to play a more prominent role. These include obstructive sleep apnea (OSA), dyslipidemia, a sedentary lifestyle, diabetes mellitus, as well as race, age, and sex [8–10]. OSA is one of the

most common risk factors for stroke. Severe OSA may increase the likelihood of WUS by inducing hemodynamic shifts, coagulopathies, and autonomic dysfunction [4, 11-14]. Furthermore, OSA impairs the cortical respiratory drive, which may also predispose to WUS. Notably, stroke itself typically exacerbates OSA [14].

Analysis of lipid profiles in WUS patients has shown a tendency toward elevated levels of low-density lipoproteins and cholesterol [9]. A sedentary lifestyle is another widespread risk factor for WUS [3, 5]. Diabetes mellitus also increases WUS risk, highlighting the role of cerebral microvascular injury as a key pathogenetic mechanism [11].

Epidemiological data indicate that WUS is more common among black individuals and younger adults [2]. In younger patients, the presence of a patent foramen ovale and OSA elevates WUS risk [15]. Sex also contributes to the risk profile: a history of OSA is more frequently reported in men with WUS than in women [9], although current evidence in this area remains insufficient.

The therapeutic window in wake-up stroke

The first 3-4.5 hours from symptom onset represent the optimal window for thrombolysis. Although the exact time of "disease onset" is never known in WUS, evidence suggests that most ACVA causing WUS occur within a relatively short period before awakening. The demographic characteristics, clinical presentation, and neuroimaging findings in patients with WUS do not differ from those in patients with a precisely known time of ischemia that falls within the therapeutic window [16].

Barreto A.D. et al. published a multicenter prospective study on thrombolysis outcomes in WUS patients treated within 3 hours of awakening. The results of this work also demonstrated the safety and efficacy of intravenous thrombolysis in this population [17].

Current literature also addresses the treatment of patients with Unwitnessed Stroke (UWS), a broader category encompassing both WUS and daytime strokes with an unknown onset time. This combined category differs somewhat in terms of risk factors, etiology, and clinical presentation, necessitating careful analysis in clinical practice. In diagnosing and treating WUS, the concept of "last known well" (LKW) time, which is the last time the patient was seen without a neurological deficit, has become standard, used as a substitute for the unknown exact time of ischemia. A single-center retrospective study of 206

patients divided into a WUS group and a group with witnessed stroke onset within the previous 8 hours concluded that the outcomes of endovascular therapy were comparable between the groups [18].

WUS patients presenting within 9 hours of the midpoint of sleep were also included in the EXTEND trial, which established that their outcomes could be improved by timely thrombolysis when significant penumbra was present on imaging [19]. These results are promising, as they suggest a potential expansion of the conventional therapeutic window.

Determining the exact time of stroke onset is crucial, as it typically dictates the extent of salvageable brain tissue at risk. Frequently, this very question becomes a major obstacle in defining treatment strategy. Technological advances in MRI and CT have provided a solution. Modern advanced neuroimaging protocols can identify patients with potentially viable ischemic tissue, thereby pushing the boundaries of the standard time-based therapeutic window. Today, the paradigm is shifting from a rigid "time window" to a "tissue window," representing an area of active investigation. A substantial body of evidence confirms that the most justified approach is to base treatment decisions on whether imaging findings meet specific criteria for viability, rather than on elapsed time alone [20].

Thrombolysis in patients with wake-up stroke

Due to the uncertain time of symptom onset, only 8-27% of patients with WUS receive thrombolytic therapy, even though many could be good candidates for this procedure given careful patient selection [21, 22].

Non-contrast CT of the brain remains the preferred initial imaging modality in the routine diagnosis and management of acute stroke to exclude intracranial hemorrhage. However, its use in isolation is not recommended for treatment decisions in WUS. CT perfusion (CTP) imaging, a technique for assessing cerebral blood flow using CT, can provide crucial information on cerebral hemodynamics and enable identification of the ischemic penumbra.

A recent retrospective analysis of 22 WUS patients demonstrated the efficacy of systemic thrombolytic therapy in patients selected for reperfusion treatment based on CTP findings, compared to conservative management, which supports the conclusion that thrombolysis can significantly improve functional outcomes in these patients [23, 24].

Although CT-based technologies are often more practical in the hyperacute phase of stroke, the advent of multimodal MRI has significantly increased the diagnostic value of the method. Studies note that a salvageable penumbra is clearly visualized on MRI in more than half of WUS patients within the first 3 hours of stroke onset. Available data indicate that MRI utilizing sequences such as DWI (Diffusion-Weighted Imaging), FLAIR (Fluid-Attenuated Inversion Recovery), PWI (Perfusion-Weighted Imaging), and SWI (Susceptibility-Weighted Imaging) can not only extend the therapeutic window but also help exclude contraindications for specific treatments and assess the contribution of certain risk factors. Several studies have shown that MRI-guided thrombolytic therapy is safer and more effective compared to treatment decisions based solely on CTP [25].

The DWI-FLAIR Mismatch

The DWI-FLAIR mismatch refers to a discrepancy where an acute ischemic lesion is visible on DWI but appears normal on FLAIR sequences. This finding indirectly suggests that the stroke likely occurred within a relatively short time frame. DWI is highly sensitive to cytotoxic edema, while FLAIR detects vasogenic edema [25].

Data from multicenter studies involving ACVA patients presenting within 4.5 hours of symptom onset show that the DWI-FLAIR mismatch can identify patients within this time window with an accuracy of 0.78 and a positive predictive value (PPV) of 0.83 [26].

A study utilizing artificial intelligence to analyze DWI and FLAIR scans for the presence of this mismatch demonstrated that such technologies can also be applied to the diagnostic workup of WUS patients [27].

In the WAKE-UP trial, the DWI-FLAIR mismatch was used to justify thrombolytic therapy for patients with UWS. Treatment outcomes in the thrombolysis group were significantly better than in the placebo group [28].

The DWI-FLAIR mismatch concept has limitations. For instance, it may overestimate the actual time of stroke onset due to its low sensitivity and negative predictive value (NPV), potentially excluding candidates who could still benefit from reperfusion therapy [29].

In nearly 80% of ACVA patients, a salvageable penumbra is visible within the first 3 hours of ischemia. This represents brain tissue with less severe perfusion reduction than the ischemic core, where neu-

ronal damage remains reversible if effective treatment is initiated promptly. In such patients, DWI-PWI mismatch-based thrombolysis can lead to favorable functional outcomes [25].

It is anticipated that a favorable MRI profile (a DWI-PWI mismatch in the absence of a FLAIR signal hyperintensity) will eventually become a widely accepted screening standard. This approach would allow clinicians to analyze scans more rapidly than waiting for software processing that matches imaging findings to the ASPECTS (Alberta Stroke Program Early CT Score) scale [30]. MRI-ASPECTS could make thrombolytic therapy considerably more effective and safer for WUS patients by substantially reducing diagnostic decision-making time.

Additional MRI-based screening approaches

Several other MRI-based diagnostic methods for ACVA have been proposed. In a retrospective study, Guo et al. utilized a DWI-T2-weighted image mismatch to justify thrombolytic therapy, reporting satisfactory outcomes in WUS patients [31]. Furthermore, a machine learning model has been developed to estimate stroke onset time from MRI data. This method demonstrated superior accuracy compared to the qualitative assessment of DWI-FLAIR mismatch [32].

Legrand L. et al. suggested that a discrepancy between FLAIR vascular hyperintensity (FVH) and DWI lesions could serve as a criterion for selecting patients likely to benefit from thrombolysis. This FVH-DWI mismatch is defined as FVH signals present outside the DWI-delineated lesion area [33]. Whether this mismatch is more suitable than DWI-FLAIR for screening WUS patients requires further investigation. It has been established that quantitative FLAIR analysis can identify patients within 6 to 8 hours of symptom onset [34].

According to research by Cheng B. et al., FLAIR signal intensity correlates with time from symptom onset: greater signal intensity indicates a longer elapsed time since ischemia and is associated with worse clinical outcomes [35].

A discrepancy between findings on Magnetic Resonance Angiography (MRA) and DWI has also been shown to correlate with the extent of the DWI-PWI mismatch and can serve as a patient selection criterion. This mismatch may also indicate the presence of a proximal intracranial internal carotid artery

or M1 segment middle cerebral artery occlusion with a DWI lesion volume of less than 50 ml [36].

Contraindications and risks of thrombolysis in wake-up stroke

The primary contraindication to thrombolysis is intracranial hemorrhage (ICH). While non-contrast head CT was traditionally used for all suspected stroke patients to rule out ICH, the development of multimodal MRI has revealed superior alternatives for this purpose, such as Gradient Echo (GRE) and DWI sequences. SWI also exhibits high sensitivity for intracranial hemorrhages, particularly chronic microbleeds. Additionally, DWI on low-field scanners can visualize acute hemorrhage within infarct zones.

MRI also facilitates bleeding risk assessment. For instance, thrombolysis is not recommended for patients with a DWI lesion volume (VDWI) > 100 ml or a Tmax ≥ 8 sec perfusion lesion volume (VTmax>8s) ≥ 100 ml due to the unacceptably high risk of symptomatic intracranial hemorrhage [25].

Thrombectomy in patients with wake-up stroke

Another treatment option for WUS patients is mechanical thrombectomy. Numerous clinical observations and observational studies have demonstrated that interventions guided by CT and MRI findings are becoming increasingly common [37, 38].

An observational study, using a CTP mismatch (defined as NIHSS ≥ 4 and a TTP/CBF ratio ≥ 2) in combination with large vessel occlusion (LVO) as the primary criterion, recommended endovascular treatment for ten WUS patients. Their outcomes were deemed favorable in 33.3% of cases, with a 3-month modified Rankin Scale (mRS) score of ≤ 2. Thrombectomy based on DWI-PWI mismatch proved effective for treating both WUS and strokes with a known onset time [39].

Another study conducted in Brazil enrolled WUS patients with an ASPECTS > 6 and a last known well time < 24 hours for endovascular therapy, also reporting satisfactory outcomes [40].

Interventions based on ASPECTS score were further analyzed in another retrospective study, whose conclusions also confirm their positive impact on clinical outcomes. The authors of the DAWN trial screened patients for a mismatch between clinical severity and ischemic core volume, assessed using RAPID software [41]. In this trial, patients were stratified into

three cohorts: Cohort A – patients aged ≥80 years with NIHSS ≥10 and core volume <21 mL; Cohort B – patients aged <80 years with NIHSS ≥10 and core volume <31 mL; Cohort C – patients aged <80 years with NIHSS ≥20 and core volume <51 mL. After analyzing 90-day functional outcomes (mRS) and stroke-associated mortality, the authors concluded that thrombectomy combined with standard medical therapy yields better outcomes than medical therapy alone. A post-hoc analysis indicated that baseline non-contrast CT findings and ASPECTS directly influence treatment results in DAWN patients [42].

A clinical-imaging mismatch (defined as NIHSS ≥ 12 and ASPECTS ≥ 7) was established. Santos T. et al. used this criterion in their work, leading them to conclude that thrombectomy is safe and effective in WUS patients [43].

A recent re-analysis of the DAWN trial data demonstrated that endovascular therapy was equally effective regardless of the witnessed nature of the stroke onset [44, 45], reinforcing the importance of basing the decision for endovascular intervention on perfusion imaging findings.

Conclusion

Pharmacological and endovascular treatment of ACVA in the hyperacute phase has evolved considerably over the past two decades. This progress is attributable to improved patient selection methods, advances in diagnostic imaging, and greater availability of modern thrombectomy devices. The presence of a skilled multidisciplinary team, an optimized workflow, rapid diagnostics, and effective treatment strategies enables the delivery of early, targeted therapy. This approach aims to minimize final infarct volume and reduce the likelihood of persistent disability.

Recent evidence indicates that approximately one in five acute ischemic strokes is a wake-up stroke. According to current guidelines, this patient group has traditionally been ineligible for thrombolysis. However, findings from recent studies suggest that advanced MRI (DWI-FLAIR mismatch) and CT perfusion imaging are pivotal in extending the therapeutic window for this stroke subtype. The use of these modalities contributes to improved functional outcomes. Nevertheless, convincing evidence supporting the routine application of this approach specifically in WUS management is still lacking, highlighting the need for further research in this field.

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