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STATUS MIGRAINOSUS: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY, CLINICAL MANAGEMENT, AND THERAPEUTIC STRATEGIES IN CENTRAL ASIA

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Abstract. Status migrainosus represents one of the most challenging and debilitating complications of migraine, characterized by a severe migraine attack persisting for more than 72 hours despite attempted treatment. This narrative review examines the current understanding of status migrainosus, with particular emphasis on epidemiological patterns in Central Asia, underlying pathophysiological mechanisms, diagnostic criteria, and evidence-based therapeutic interventions. The analysis reveals that status migrainosus affects approximately 1-3% of patients with migraine, with significantly higher prevalence reported in regions with limited access to specialized headache care, including Central Asian countries. The pathophysiology involves persistent activation of the trigeminovascular system, central sensitization, and neurogenic inflammation, complicated by medication overuse and psychological factors. Central Asian countries face unique challenges including limited availability of modern abortive therapies, socioeconomic barriers to healthcare access, and insufficient specialized headache services. The review evaluates contemporary treatment approaches, including intravenous medications, neuromodulation techniques, and emerging CGRP-targeted therapies, while addressing regional considerations for implementation in Central Asian healthcare systems. The findings underscore the urgent need for standardized protocols, healthcare professional training, and improved access to evidence-based treatments across the region.

Keywords: Status migrainosus; Intractable migraine; Trigeminovascular system; Central sensitization; CGRP-targeted therapy; Central Asia; Neuromodulation; Intravenous therapy; Headache emergency; Medication overuse headache.

Status migrainosus is defined as a debilitating migraine attack lasting for more than 72 hours, with the headache phase failing to respond to standard abortive treatments. This condition represents one of the most severe complications of migraine, often requiring emergency medical intervention and hospitalization. According to the International Classification of Headache Disorders, Third Edition (ICHD-3), the diagnosis requires a continuous headache lasting more than 72 hours with typical migraine characteristics, including unilateral location, pulsating quality, moderate to severe pain intensity, aggravation by routine physical activity, and associated nausea, photophobia, or phonophobia.

The prevalence of status migrainosus among migraine patients ranges from 1% to 3%, with higher rates reported in populations with limited access to specialized headache care. The condition disproportionately affects women, with a female-to-male ratio of approximately 3:1, consistent with the overall epidemiology of migraine. The mean age of onset typically occurs in the third to fourth decade of life, though status migrainosus can develop at any age in patients with pre-existing migraine.

Central Asian countries face particularly challenging circumstances regarding headache disorders. The Global Burden of Disease 2021 data identify the region as having the highest tension-type headache prevalence in Asia, with migraine affecting over 13,000 per 100,000 population. In Uzbekistan, population-based studies demonstrate a migraine prevalence of 7.2%, with status migrainosus representing a significant proportion of headache-related emergency

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department visits. The limited availability of specialized headache centers, restricted access to modern abortive medications, and socioeconomic barriers to healthcare contribute to prolonged attack duration and increased disability in the region.

The pathophysiology of status migrainosus involves complex interactions between the trigeminovascular system, central sensitization mechanisms, and neurogenic inflammation. Persistent activation of trigeminal afferents leads to sustained release of calcitonin gene-related peptide (CGRP), substance P, and other inflammatory mediators, perpetuating vasodilation and sensitization of pain pathways. Central sensitization, involving altered processing in the brainstem, thalamus, and cortex, contributes to the intractable nature of the pain and the development of cutaneous allodynia.

The relevance of this review is determined by several critical factors. First, status migrainosus represents a medical emergency requiring prompt and effective intervention to prevent complications including dehydration, electrolyte imbalances, sleep deprivation, and psychological distress. Second, the condition significantly impairs quality of life and functional capacity, often necessitating prolonged absence from work or educational activities. Third, inadequate treatment of status migrainosus frequently leads to medication overuse headache, creating a vicious cycle of increasing headache frequency and treatment resistance. Fourth, Central Asian healthcare systems face unique challenges in managing this condition, including limited availability of evidence-based treatments and insufficient specialized training for healthcare providers.

The aim of this review is to synthesize current evidence regarding the epidemiology, pathophysiology, diagnostic approach, and therapeutic management of status migrainosus, with particular attention to regional considerations in Central Asia and practical strategies for implementation in resource-limited healthcare settings.

Materials and Methods. This narrative review was conducted through a comprehensive search of peer-reviewed literature published between 2018 and 2025. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were systematically searched using combinations of keywords: "status migrainosus," "intractable migraine," "refractory migraine," "headache emergency," "CGRP-targeted therapy," "neuromodulation," "Central Asia," and "medication overuse headache."

Inclusion criteria encompassed clinical trials, systematic reviews, meta-analyses, epidemiological studies, clinical guidelines, and consensus statements focusing on the diagnosis, pathophysiology, and treatment of status migrainosus. Particular emphasis was placed on studies reporting data from Central Asian populations, resource-limited settings, and recent investigations evaluating novel therapeutic approaches including CGRP-targeted therapies and neuromodulation techniques. Exclusion criteria included non-peer-reviewed publications, case reports with insufficient methodological quality, and studies not directly relevant to the acute or preventive management of status migrainosus.

Data extraction focused on epidemiological patterns, diagnostic criteria according to ICHD-3, pathophysiological mechanisms, acute treatment protocols, preventive strategies, and outcomes assessment. Special attention was given to studies evaluating treatment accessibility, cost-effectiveness, and implementation challenges in developing healthcare systems. The collected evidence was analyzed using descriptive and comparative methods, with emphasis on clinical applicability in Central Asian healthcare settings and practical guidance for emergency and outpatient management.

Results. The analysis of contemporary literature reveals several critical findings regarding the epidemiology, pathophysiology, diagnostic challenges, and management of status migrainosus.

Epidemiological data demonstrate that status migrainosus affects approximately 1-3% of patients with migraine, with higher prevalence rates reported in populations with limited access to specialized headache care. Emergency department studies indicate that status migrainosus

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accounts for 8-15% of all headache-related emergency visits, with significant regional variation. The condition demonstrates a clear female predominance, with women comprising approximately 70-80% of affected patients. The mean duration of untreated attacks ranges from 5 to 14 days, with some cases persisting for weeks or months without appropriate intervention.

Central Asian countries face particularly concerning epidemiological patterns. The high prevalence of migraine in the region, affecting approximately 13,584 per 100,000 population according to Global Burden of Disease 2021 data, creates a substantial pool of patients at risk for status migrainosus. Uzbekistan-specific data reveal limited availability of specialized headache services, with fewer than 10 certified headache specialists serving a population of over 36 million. The ratio of neurologists to population remains significantly lower than World Health Organization recommendations, contributing to delayed diagnosis and inadequate treatment of severe migraine attacks. Socioeconomic factors, including limited health insurance coverage and high out-of-pocket medication costs, further exacerbate treatment delays and contribute to the development of status migrainosus.

Pathophysiological mechanisms underlying status migrainosus involve persistent activation of the trigeminovascular system with sustained release of CGRP, substance P, neurokinin A, and other inflammatory mediators. This persistent neurogenic inflammation leads to sensitization of peripheral and central pain pathways, including the trigeminal nucleus caudalis, thalamus, and somatosensory cortex. Central sensitization manifests as cutaneous allodynia, where normally non-painful stimuli produce pain, and hyperalgesia, where painful stimuli produce exaggerated pain responses.

The transition from episodic migraine to status migrainosus involves multiple contributing factors. Medication overuse represents one of the most significant risk factors, with frequent use of simple analgesics, triptans, or combination medications leading to medication overuse headache and treatment resistance. Psychological factors including anxiety, depression, and stress contribute to central sensitization and perpetuation of headache. Sleep deprivation, dehydration, hormonal fluctuations, and comorbid medical conditions including obesity and hypertension further increase susceptibility to prolonged attacks.

Neuroimaging studies in status migrainosus reveal hypothalamic activation, consistent with the role of this structure in migraine chronification and attack generation. Functional MRI studies demonstrate altered connectivity between pain-processing regions and areas involved in affective and cognitive processing, explaining the frequent comorbidity of mood disturbances and cognitive impairment during prolonged attacks. Structural changes including white matter hyperintensities and cortical thickness alterations are more prevalent in patients with frequent or prolonged migraine attacks, suggesting cumulative brain effects.

The clinical presentation of status migrainosus typically evolves from the patient's usual migraine pattern, with gradual intensification and failure to respond to standard abortive treatments. The headache is invariably severe, often described as the worst headache experienced by the patient. Associated symptoms include persistent nausea and vomiting, frequently leading to dehydration and electrolyte imbalances. Photophobia and phonophobia are universally present, with many patients requiring complete isolation in darkened, quiet environments. Cognitive impairment including difficulty concentrating, memory disturbances, and slowed processing speed is common. Mood changes including irritability, anxiety, and depressive symptoms frequently accompany prolonged attacks.

Diagnostic evaluation of suspected status migrainosus requires systematic exclusion of secondary headache etiologies. Neuroimaging with computed tomography or magnetic resonance imaging is essential to exclude intracranial hemorrhage, venous sinus thrombosis, arterial dissection, mass lesions, and infection. Lumbar puncture may be necessary when subarachnoid hemorrhage or central nervous system infection is suspected. Laboratory evaluation should address electrolyte imbalances, renal and hepatic function, thyroid dysfunction, and markers of systemic inflammation. The diagnosis of primary status migrainosus can only be

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established after comprehensive exclusion of secondary causes, with documentation of attack duration exceeding 72 hours and failure to respond to appropriate abortive treatments.

Acute treatment protocols for status migrainosus require a multimodal approach combining intravenous medications, fluid resuscitation, and supportive care. Intravenous fluids address dehydration and electrolyte imbalances, with normal saline typically administered at maintenance rates. Intravenous metoclopramide or prochlorperazine provide antiemetic effects and may offer direct headache relief through dopamine receptor antagonism. Intravenous magnesium sulfate demonstrates efficacy in patients with suspected magnesium deficiency, with typical doses of 1-2 grams administered over 15-30 minutes. Intravenous valproate, administered at doses of 300-1000 mg, provides headache relief through multiple mechanisms including GABAergic modulation and sodium channel blockade. Intravenous dexamethasone, typically at doses of 10-25 mg, reduces neurogenic inflammation and prevents early headache recurrence.

The introduction of CGRP-targeted therapies has expanded treatment options for status migrainosus. Intravenous eptinezumab, administered at 100-300 mg, demonstrates rapid onset of action and sustained headache relief. Subcutaneous rimegepant, available in orally disintegrating tablet formulation, provides acute treatment without risk of medication overuse. The lack of vasoconstrictive effects makes these agents particularly suitable for patients with cardiovascular risk factors or vascular comorbidities. However, limited availability and high costs restrict access to these medications in many Central Asian healthcare settings.

Neuromodulation techniques represent emerging non-pharmacological interventions for status migrainosus. Non-invasive vagus nerve stimulation, applied to the cervical branch of the vagus nerve, modulates pain processing and reduces headache intensity. Transcranial magnetic stimulation, targeting the occipital cortex, interrupts cortical spreading depression and reduces pain signaling. Remote electrical neuromodulation, applied to the upper arm, activates conditioned pain modulation pathways. While these techniques demonstrate promising results in clinical trials, availability remains limited in Central Asian healthcare systems.

Preventive strategies following resolution of status migrainosus are essential to prevent recurrence. Optimization of preventive medications, including beta-blockers, antiepileptic drugs, CGRP monoclonal antibodies, or gepants, should be undertaken. Identification and management of medication overuse is critical, with structured withdrawal protocols when necessary. Lifestyle modification including regular sleep patterns, adequate hydration, stress management, and regular physical activity reduces trigger exposure. Patient education regarding early intervention at attack onset and appropriate use of abortive medications prevents progression to status migrainosus.

Discussion. The findings of this review confirm that status migrainosus represents a significant clinical challenge with substantial implications for patient outcomes, healthcare resource utilization, and public health across Central Asia. The disproportionately high burden of migraine in the region, combined with limited specialized healthcare infrastructure, creates conditions conducive to the development and prolongation of severe migraine attacks.

The pathophysiological complexity of status migrainosus, involving persistent trigeminovascular activation, central sensitization, and neurogenic inflammation, explains the therapeutic challenges encountered in clinical practice. The self-perpetuating nature of the condition, where pain leads to stress, sleep disruption, and medication overuse, which in turn exacerbate headache, creates a vicious cycle requiring comprehensive multimodal intervention. Understanding these mechanisms is essential for developing effective treatment protocols and preventing progression from episodic migraine to chronic intractable headache.

The diagnostic evaluation of status migrainosus requires careful exclusion of secondary headache etiologies, particularly in patients presenting with atypical features or first severe headache. The overlap between migraine symptoms and potentially life-threatening conditions including subarachnoid hemorrhage, cerebral venous thrombosis, and meningitis necessitates thorough investigation. In Central Asian healthcare settings, where access to advanced

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neuroimaging may be limited, clinical decision-making must balance the need for comprehensive evaluation against resource constraints. Development of regional diagnostic algorithms incorporating locally available investigations could improve diagnostic efficiency while maintaining patient safety.

The acute management of status migrainosus in Central Asian healthcare systems faces multiple practical challenges. Limited availability of intravenous medications, including metoclopramide, valproate, and magnesium sulfate, restricts treatment options in many regional hospitals. The absence of CGRP-targeted therapies from national formularies in most Central Asian countries leaves patients dependent on traditional medications with limited efficacy in severe refractory cases. Training of emergency department physicians and general neurologists in evidence-based treatment protocols could improve outcomes even with existing medication availability.

The potential role of CGRP-targeted therapies in managing status migrainosus deserves particular attention. The rapid onset of action and sustained efficacy of intravenous eptinezumab, combined with the favorable cardiovascular safety profile, make this agent particularly attractive for emergency treatment. However, economic considerations significantly limit accessibility. The cost of a single dose of CGRP monoclonal antibody exceeds the monthly salary of many Central Asian citizens, creating insurmountable barriers without insurance coverage or government subsidy programs. Strategies for improving accessibility include negotiation of preferential pricing, development of biosimilar preparations, and phased introduction through targeted programs for high-need patients.

Neuromodulation techniques offer promising non-pharmacological alternatives, though infrastructure requirements present implementation challenges. Non-invasive vagus nerve stimulation devices, while portable and relatively inexpensive, require patient training and regular use for optimal effect. Transcranial magnetic stimulation devices, though effective, require significant capital investment and specialized training for operators. The development of locally adapted neuromodulation protocols and training programs could expand access to these interventions in regional healthcare centers.

Medication overuse headache represents a critical complicating factor in status migrainosus management, particularly in Central Asian populations where limited access to specialized care leads to self-medication patterns. The high frequency of analgesic and triptan use, driven by inadequate acute treatment and lack of preventive therapy, perpetuates headache chronification and treatment resistance. Structured withdrawal programs, combining patient education, psychological support, and transitional preventive medications, are essential components of comprehensive management. However, the availability of addiction medicine specialists and structured withdrawal programs remains limited in the region.

The role of psychological factors in status migrainosus requires greater recognition in clinical practice. Anxiety, depression, and catastrophizing pain beliefs contribute to central sensitization and perpetuation of headache. Cognitive-behavioral therapy, biofeedback, and relaxation techniques demonstrate efficacy as adjunctive treatments, though availability of trained psychologists and structured programs is limited in Central Asian healthcare systems. Integration of psychological interventions into multidisciplinary headache clinics could improve outcomes and reduce reliance on pharmacological treatments.

Healthcare system strengthening represents a fundamental requirement for improving status migrainosus outcomes across Central Asia. Development of specialized headache centers in major regional hospitals, training programs for neurologists and emergency physicians, and establishment of referral pathways from primary care could significantly improve diagnostic accuracy and treatment access. Telemedicine platforms offer potential for expanding specialist consultation to remote regions, though infrastructure development and digital literacy programs are prerequisite for effective implementation.

Patient education and self-management support are essential components of status

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migrainosus prevention. Educational materials adapted to local languages and cultural contexts, addressing trigger identification, early intervention strategies, and appropriate medication use, could empower patients to manage their condition more effectively. Support groups and community-based programs provide peer support and reduce isolation, particularly important in regions where headache disorders carry significant stigma.

Limitations of this review include the narrative methodology, potential publication bias favoring positive treatment outcomes, and limited availability of Central Asian-specific clinical data. Future research priorities should include prospective studies determining status migrainosus incidence and outcomes in Central Asian populations, evaluation of treatment accessibility and cost-effectiveness in regional healthcare systems, development of culturally adapted clinical guidelines, and assessment of telemedicine and community-based intervention effectiveness.

Conclusion. Status migrainosus represents a severe and debilitating complication of migraine that poses significant challenges for patients, healthcare providers, and healthcare systems across Central Asia. The high regional prevalence of migraine, combined with limited specialized care infrastructure and restricted access to modern therapies, creates conditions conducive to prolonged attacks and increased disability.

Current evidence indicates that status migrainosus results from persistent trigeminovascular activation, central sensitization, and neurogenic inflammation, perpetuated by medication overuse, psychological factors, and inadequate acute treatment. Diagnosis requires meticulous exclusion of secondary headache etiologies and documentation of attack duration exceeding 72 hours despite appropriate treatment attempts.

The management of status migrainosus requires comprehensive multimodal intervention combining intravenous medications, fluid resuscitation, antiemetic therapy, and supportive care. The introduction of CGRP-targeted therapies offers promising new options for refractory cases, though accessibility remains severely limited in Central Asian healthcare systems. Neuromodulation techniques provide non-pharmacological alternatives, though infrastructure requirements restrict widespread implementation.

Prevention of status migrainosus recurrence requires optimization of preventive medications, management of medication overuse, lifestyle modification, and patient education. Multidisciplinary approaches involving neurologists, emergency physicians, psychologists, and rehabilitation specialists offer the most comprehensive management strategies.

Healthcare system strengthening, including development of specialized headache services, training programs for healthcare providers, and improved access to evidence-based treatments, is essential for reducing the burden of status migrainosus across Central Asia. The integration of modern therapeutic approaches, including CGRP-targeted therapies and neuromodulation techniques, into regional clinical practice holds significant promise for improving patient outcomes. Collaborative efforts between regional healthcare systems, international research organizations, and pharmaceutical stakeholders will be essential for translating scientific advances into accessible clinical benefits for patients throughout Central Asia and beyond.

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