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Review Article

Clinical symptoms, diagnosis and outcome of encephalopathy

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ABSTRACT

Encephalopathy comprises a range of neurological syndromes caused by several etiologies, including metabolic, toxic, structural, and infectious factors. These conditions share common clinical features such as altered mental status, seizures, and cognitive deficits, making diagnosis challenging. Subtypes include reversible forms, like hepatic encephalopathy and posterior reversible encephalopathy syndrome, and progressive forms, like chronic traumatic encephalopathy. Accurate diagnosis requires comprehensive evaluation, integrating clinical assessments and advanced imaging techniques. Management strategies vary widely, emphasizing underlying cause resolution and symptom control. Advances in diagnostic tools and tailored therapeutic strategies have improved outcomes for certain subtypes but underscore the need for early recognition and precise differentiation. Ongoing research and multidisciplinary efforts are essential to address knowledge gaps, refine management, and enhance quality of life for affected individuals. This review highlights diagnostic challenges, therapeutic approaches, and outcomes, underscoring the importance of individualized care for optimizing prognoses in these multifaceted conditions.

Keywords: Clinical symptoms, Encephalopathy, Diagnosis

INTRODUCTION

Encephalopathy is a complex neurological condition characterized by a generalized dysfunction of the brain caused by diverse etiologies, including metabolic, toxic, structural, or infectious factors. This syndrome manifests across a spectrum of severity, ranging from mild cognitive impairment to profound coma. While the etiology and pathophysiology vary depending on the subtype, common features include altered mental status, cognitive disturbances, and neurological deficits. Importantly, encephalopathy is not a single disease but rather a clinical syndrome indicative of an underlying disorder.[1]

Encephalopathy is broadly categorized into reversible and progressive types. Reversible types, such as hepatic encephalopathy (HE) and posterior reversible

encephalopathy syndrome (PRES), often resolve with prompt treatment. Conversely, progressive forms, such as chronic traumatic encephalopathy (CTE), are marked by gradual neurological decline and are often incurable. Each subtype is associated with distinct risk factors, clinical manifestations, diagnostic challenges, and prognostic outcomes. Understanding these nuances is essential for timely intervention and optimal management.[2]

The global burden of encephalopathy is substantial, reflecting its wide-ranging causes and varied clinical presentations. The incidence differs by subtype. HE is particularly common in individuals with cirrhosis, affecting 30-45% of patients with decompensated liver disease annually.[3] PRES primarily affects patients with acute hypertension, preeclampsia, or autoimmune conditions, with an incidence of 0.4% in hypertensive emergencies.[4]

In pediatric populations, acute necrotizing encephalopathy (ANE) is a rare but severe form often linked to viral infections like influenza. ANE shows higher incidence in East Asia, potentially due to genetic factors.[5] CTE, predominantly associated with athletes exposed to repetitive head injuries, has an estimated prevalence of 17% among former American football players.[6]

Despite the data available, the true prevalence and burden of encephalopathy are likely underestimated. This stems from overlapping symptoms with other neurological conditions and limited diagnostic tools in many healthcare settings.[1] These gaps highlight the need for enhanced screening, diagnostic accuracy, and public health awareness to address this pressing medical challenge.

Diagnosis of encephalopathy is inherently complex, as it lacks specific pathognomonic features and presents with overlapping symptoms. A comprehensive evaluation, including clinical examination, laboratory tests, imaging studies, and electroencephalography (EEG), is often required.[7] EEG is particularly valuable for identifying abnormal brain activity, such as generalized slowing or epileptiform discharges, which are indicative of encephalopathic states.[8] Imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) further aid in detecting structural or metabolic abnormalities, with hallmark findings such as vasogenic edema in PRES.[9]

The management of encephalopathy focuses on addressing the underlying cause, alleviating symptoms, and preventing complications, with treatment strategies tailored to the specific subtype. For HE, reducing ammonia levels using lactulose and rifaximin is central to therapy.[10] PRES requires prompt blood pressure control, discontinuation of cytotoxic agents, and supportive care.[4] ANE is managed with anticonvulsants, corticosteroids, and supportive measures, though immunoglobulin therapy shows limited evidence.[11] CTE lacks curative options, with care centered on symptomatic relief through mood stabilization and cognitive therapy.[6] Non-hepatic hyperammonemia is treated with protein restriction, ammonia-scavenging agents, or hemodialysis in severe cases.[12] General supportive measures, including oxygenation, hydration, and neurorehabilitation, are critical for all forms, with emerging therapies like neuroprotective agents offering potential but requiring further study.[13]

Advances in diagnostic modalities and therapeutic interventions have improved outcomes for some forms of encephalopathy, such as HE and PRES.[4,10] However, progressive and chronic types like CTE remain incurable and are associated with significant long-term morbidity.[6] This review explores the clinical presentation, diagnostic approaches, and outcomes associated with encephalopathy, synthesizing insights from recent studies to provide a comprehensive understanding of this complex condition.

LITERATURE SEARCH

This narrative review is based on a comprehensive literature search conducted on 26 November 2024 using the Medline and Cochrane databases. Medical subject headings (MeSH) and relevant keywords were employed to identify studies discussing various types of encephalopathy, including their clinical presentations, diagnostic investigations, and prognostic outcomes. To enhance the search scope, a manual search was performed through Google Scholar, and reference lists of identified articles were examined for additional relevant studies. The inclusion criteria encompassed articles across all publication dates, languages, participant demographics, and study types to ensure a broad exploration of the available literature. This methodology aimed to provide a robust foundation for a detailed comparative analysis of encephalopathy types.

DISCUSSION

In this discussion, we study different types of encephalopathy focusing on their clinical picture, diagnostic approaches, and prognostic outcomes.

Hepatic encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome resulting from liver dysfunction and/or portosystemic shunting, with presentations ranging from subtle cognitive impairments to coma. HE is categorized into minimal hepatic encephalopathy (MHE) and overt hepatic encephalopathy (OHE), with the latter associated with higher morbidity and mortality.[14]

The clinical spectrum of HE varies significantly. OHE commonly manifests with asterixis, psychomotor slowing, and confusion, progressing to lethargy, stupor, or coma in severe cases. Cognitive deficits such as impaired attention and altered sleep patterns dominate in MHE, often reported

by caregivers due to patient unawareness. Neurologic signs such as tremors, triphasic waves on EEG, and extrapyramidal symptoms may also be observed, particularly in chronic cases. Fulminant hepatic failure can lead to acute HE with rapid onset of cerebral edema and brainstem herniation.[15]

HE diagnosis requires a combination of clinical assessment and paraclinical investigations. The American association for the study of liver diseases and the European association for the study of the liver guidelines, as well as the recent French guidelines emphasized the importance of plasma ammonia levels in HE diagnosis, noting that normal levels carry an 80% negative predictive value, although elevated levels alone are not diagnostic due to limited specificity .[16,17] EEG abnormalities, such as triphasic waves, are sensitive indicators of HE severity and can help differentiate it from nonconvulsive seizures. Cerebral MRI findings, including T1 hypersignals in the basal ganglia, correlate with chronic HE and portosystemic shunting, aiding in diagnostic confirmation.[15]

MHE, often underdiagnosed due to patient unawareness, is confirmed using psychometric hepatic encephalopathy score, which assesses psychomotor speed and visuospatial ability.[18] Recently, the animal naming test has shown potential for screening MHE, with a specificity of 78% when more than 20 animals are named in one minute.[19]

HE carries significant prognostic implications. Overt HE is associated with poor survival rates in cirrhotic patients, with a Danish study indicating one-year survival rates of 35-45% following a first episode.[20] Recurrent MHE episodes worsen outcomes and necessitate a proactive approach to prevent complications such as falls, road traffic accidents, and hospitalizations.[21]

Prognosis is further complicated by precipitating factors. Gastrointestinal bleeding, infections, and hyponatremia not only trigger HE but also worsen survival prospects if not promptly managed. Patients with HE due to fulminant hepatic failure have a mortality rate exceeding 50% without liver transplantation, while post-transplant survival exceeds 70% at five years.[22]

Uremic encephalopathy

Uremic encephalopathy (UE) is a neuropsychiatric syndrome caused by the accumulation of uremic toxins in patients with advanced renal failure. The condition exhibits a broad clinical spectrum, ranging from mild cognitive dysfunction to severe neurological impairment, including coma and seizures. Early recognition and management are critical to improving patient outcomes.[23]

UE presents with both mental and motor symptoms. Early manifestations include confusion, irritability, and sleep disturbances, progressing to delirium, psychosis, and severe cognitive dysfunction. Asterixis, a characteristic motor sign, along with myoclonus and tremors, is frequently observed. Severe cases may involve seizures, stupor, or coma, particularly in patients with untreated or inadequately managed renal failure. Chronic UE often includes subclinical symptoms such as depression, emotional lability, and impairments in memory and executive function.[24]

The pathogenesis of UE is multifactorial, involving an imbalance of excitatory and inhibitory neurotransmitters, accumulation of guanidino compounds, and disruption of monoamine metabolism. Secondary hyperparathyroidism and the buildup of middle molecules, such as beta-2 microglobulin and indoxyl sulfate, contribute to neurotoxicity. Oxidative stress and inflammation further exacerbate the condition, as demonstrated in experimental models of chronic kidney disease.[25]

UE is a clinical diagnosis supported by the exclusion of other causes of encephalopathy, such as infections, drug toxicity, or metabolic imbalances. EEG often reveals diffuse slowing with theta and delta waves, reflecting cortical dysfunction. Triphasic waves may also appear, particularly in advanced stages. Brain imaging, while generally unremarkable, may show cortical atrophy or ventricular enlargement in chronic cases. Lumbar puncture is not typically diagnostic but may be used to rule out alternative causes.[25]

Prognosis of UE is favorable if promptly treated with renal replacement therapy, such as hemodialysis/ peritoneal dialysis. Most neurological symptoms resolve within days to weeks of initiating RRT. However, persistent cognitive deficits may remain in some patients, particularly those with prolonged untreated uremia/ concurrent vascular/ inflammatory brain damage. Combined peritoneal and hemodialysis approaches have been effective in cases refractory to single-modality treatments, highlighting the importance of adequate toxin removal.[24]

Severe cases associated with prolonged uremia or comorbidities like malnutrition inflammation atherosclerosis (MIA) syndrome carry a poorer prognosis, with increased risks of recurrent encephalopathy or long-term cognitive impairment. Successful renal transplantation generally leads to complete resolution of UE symptoms, underscoring the role of definitive treatment in advanced kidney disease.[24]

Septic encephalopathy

Septic encephalopathy (SE) is the most common form of encephalopathy in intensive care settings, with reported prevalence rates ranging from 9% to 71%, often remaining undiagnosed due to its diverse symptomatology.[26] It is characterized by diffuse cerebral dysfunction resulting from the inflammatory response to infection, without direct central nervous system (CNS) involvement. Clinical manifestations include neurological symptoms in up to 70% of septic patients, ranging from mild lethargy to coma, with sepsis-associated delirium (SAD) being the

most frequent presentation. SAD is often undiagnosed, despite its prevalence, due to limited awareness and overlapping symptoms with other conditions.[27]

Diagnostic tools for SAD include the confusion assessment method for the ICU (CAM-ICU), with high specificity (97%), and the intensive care delirium screening checklist (ICDSC), with greater sensitivity (99%).[28,29] For non-ICU settings, the 3D-CAM provides robust sensitivity (95%) and specificity (94%).[30] Differentiating SE from conditions like sepsis-associated meningitis or encephalitis requires thorough neurological examinations and the recognition of focal neurological signs absent in SE.[31] Neuroimaging, though not routine for SAD, becomes critical in cases with persistent altered consciousness or focal signs.[32] While CT scans help exclude acute structural abnormalities, MRI offers superior sensitivity for small ischemic lesions, white matter changes, and posterior reversible encephalopathy syndrome (PRES).[33] Advanced imaging modalities like PET and MR spectroscopy provide insights into SE pathophysiology but face clinical application challenges due to difficulties of conducting prolonged imaging studies in critically ill, delirious, or comatose patients.[34]

EEG remains a sensitive tool for detecting brain dysfunction in SE, with delta-predominant activity and non-reactivity linked to increased mortality. A systematic review of 17 studies highlighted the widespread presence of EEG abnormalities in patients with SAD, with the type and extent of abnormalities correlating with disease severity.[35] Continuous EEG is particularly valuable for identifying nonconvulsive status epilepticus, a complication in some SE cases.[36]

Other diagnostic modalities, such as transcranial Doppler ultrasonography, can assess cerebral blood flow changes that correlate with the clinical severity of SE within the first 24 hours, but lack routine applicability.[37] Cerebrospinal fluid (CSF) analysis, in some SE cases, may reveal a mild elevation in protein levels while cell counts, and glucose levels typically remain within normal ranges, supporting SE diagnosis.[38]

The prognosis of SE is poor, with mortality rates between 10% and 30%, influenced by age, sepsis severity, and pre-existing conditions. Survivors frequently experience long-term cognitive deficits, including impaired memory and executive dysfunction, significantly impacting quality of life. Cognitive rehabilitation, encompassing mental health support and structured cognitive training, is essential for improving outcomes in SE survivors and addressing the prolonged effects of SE.[38]

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is a clinical and radiological entity characterized by acute cerebral endotheliopathy leading to vasogenic edema, most commonly affecting the parieto-occipital regions of the brain. This syndrome results from disruptions in cerebrovascular autoregulation and blood-brain barrier integrity.[39]

Clinical manifestations of PRES are diverse and typically present acutely. Non-descript encephalopathy, observed in up to 94% of patients, is one of the most common features, ranging from mild confusion to deep coma. Seizures are another hallmark, occurring in approximately 75% of cases, with some progressing to status epilepticus in up to 18%. Headaches, described as dull and diffuse, are reported in about half of the cases, though thunderclap headaches are also documented in association with reversible cerebral vasoconstriction syndrome (RCVS).[40]

Visual disturbances, occurring in 20-39% of patients, include visual field deficits, cortical blindness, and hallucinations. In many cases, these symptoms correlate with occipital lobe involvement on imaging. Focal neurological deficits, such as hemiparesis or aphasia, are less common but may occur depending on the extent and location of brain involvement.[39] In children, seizures are even more prominent, reported in up to 90% of cases, with similar clinical presentations as seen in adults.[41]

Diagnosis of PRES relies on clinical assessment combined with neuroimaging findings. Magnetic MRI is the gold standard, as it provides detailed visualization of vasogenic edema, which predominantly involves the parieto-occipital regions. This edema appears as bilateral hyperintensities on fluid-attenuated inversion recovery (FLAIR) and T2-weighted sequences. However, atypical patterns affecting the frontal lobes, basal ganglia, cerebellum, or brainstem are increasingly recognized, emphasizing the variability in PRES presentations.[4]

Advanced imaging techniques like diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping are critical in differentiating vasogenic edema, which typically shows increased ADC values, from cytotoxic edema, which indicates irreversible brain injury. In some cases, angiographic studies may reveal cerebral vasoconstriction, highlighting an overlap with RCVS. However, the lack of specific diagnostic criteria for PRES often necessitates ruling out other conditions, including posterior circulation stroke, autoimmune encephalitis, and infectious or toxic encephalopathies.[42]

PRES generally has a favorable prognosis when recognized and treated promptly. Most patients experience a resolution of clinical symptoms and radiological abnormalities within weeks to months. Studies report recovery in 70-90% of cases, particularly when underlying triggers, such as hypertension, renal failure, or exposure to immunosuppressants, are managed effectively.[43] For example, cessation of calcineurin inhibitors in transplant patients and aggressive blood pressure control in hypertensive emergencies significantly improve outcomes.[44]

Despite the overall reversibility, complications such as intracranial hemorrhage, ischemia, or cytotoxic edema may occur, leading to residual neurological deficits or increased mortality. Hemorrhage, identified in 10-25% of cases, has been strongly associated with poor outcomes, with studies reporting a pooled odds ratio of 4.9 for adverse prognosis in patients with hemorrhagic PRES. Mortality rates range from 8% to 17%, influenced by factors such as older age, comorbid conditions, and the severity of underlying disease processes. For instance, patients with eclampsia-associated PRES tend to have better outcomes compared to those with chemotherapy-related PRES or severe renal failure.[43,45]

Hashimoto's encephalopathy

Hashimoto's encephalopathy is a rare and poorly understood autoimmune neurological condition. It is characterized by a broad spectrum of neurological symptoms and is often associated with elevated levels of antithyroid antibodies. The disease predominantly affects middle-aged women but has been reported across all age groups.[46]

Hashimoto's encephalopathy manifests with diverse and often non-specific neurological symptoms. Common presentations include encephalopathy with altered mental status, seizures, myoclonus, hallucinations, and psychosis. Patients may also exhibit neuropsychiatric symptoms such as depression and cognitive impairment. Some patients experience relapsing and remitting episodes, while others have progressive symptoms resembling dementia. Stroke-like episodes, tremors, and movement disorders are additional features reported in some cases. Rarely, Hashimoto's encephalopathy presents as pure cerebellar ataxia or limbic encephalitis. Seizures, seen in up to two-thirds of patients, may be focal, generalized/refractory to standard antiepileptic therapy.[47]

Diagnosis of Hashimoto's encephalopathy is challenging and relies on the exclusion of other causes of encephalopathy, including infections, metabolic derangements, and other autoimmune encephalitides. Elevated antithyroid peroxidase (anti-TPO) and antithyroglobulin antibodies are central to diagnosis, although their levels do not correlate with disease severity. Thyroid function is often normal or shows subclinical hypothyroidism.[48]

Imaging findings are typically nonspecific. Brain MRI may be normal or show abnormalities such as ischemic lesions, demyelination, or edema. CSF analysis often reveals mildly elevated protein levels, but these changes are not diagnostic. EEG commonly demonstrates diffuse slowing and may assist in monitoring response to corticosteroid therapy.[49]

The prognosis of Hashimoto's encephalopathy is generally favorable with appropriate treatment. Most patients respond well to corticosteroids, showing clinical improvement within weeks to months. Some patients require prolonged immunosuppressive therapy with agents such as azathioprine, cyclophosphamide, or rituximab for relapse prevention or steroid intolerance. Intravenous immunoglobulin has also shown efficacy in some cases.[47]

Delayed diagnosis or untreated Hashimoto's encephalopathy can lead to permanent cognitive deficits, but most patients remain disease-free after treatment tapering. Spontaneous remission has been reported in rare cases.[47] The presence of IgG4-related thyroiditis has been identified as a potential marker for a more aggressive disease course in some patients.[50]

Chronic traumatic encephalopathy

Chronic traumatic encephalopathy (CTE) is a neurodegenerative condition associated with repetitive traumatic brain injury (TBI). It is most commonly observed in athletes participating in contact sports such as boxing, American football, soccer, and rugby, as well as in military veterans exposed to repetitive concussive or subconcussive impacts.[51]

CTE manifests as a progressive syndrome characterized by a triad of cognitive, behavioral, and mood disturbances, often accompanied by motor symptoms in advanced stages. Cognitive impairments include memory loss, executive dysfunction, and visuospatial deficits, typically appearing later in life. Behavioral symptoms such as impulsivity, explosivity, and aggression often emerge earlier and are more pronounced in younger patients. Mood symptoms, including depression, anxiety, hopelessness, and suicidality, are common and may precede cognitive decline.[52]

CTE is categorized into clinical subtypes: a behavioral/mood variant, a cognitive variant, a mixed variant, and a dementia variant. Motor symptoms, including tremors, ataxia, and parkinsonism, can occur in any subtype but are more common in the dementia variant. Onset and severity are influenced by the frequency and intensity of head injuries, with a latency period of years to decades between exposure and symptom onset. CTE diagnosis remains a significant challenge as it currently relies on postmortem neuropathological findings. The pathognomonic lesion of CTE consists of phosphorylated tau aggregates in neurons and astrocytes at the depths of cortical sulci, particularly around small blood vessels. These lesions distinguish CTE from other tauopathies such as Alzheimer's disease.[53]

In vivo diagnosis remains elusive. Advanced neuroimaging modalities such as tau PET have shown promise in detecting tauopathy in symptomatic patients with a history of repetitive head trauma. Structural MRI may reveal cortical atrophy or cavum septum pellucidum, but findings are non-specific. Emerging blood and cerebrospinal fluid biomarkers, including neurofilament light chain and tau, are under investigation but lack diagnostic reliability. Differential diagnosis includes conditions with

overlapping features, such as behavioral variant frontotemporal dementia, Alzheimer's disease, and Lewy body dementia. Comprehensive clinical evaluations, including detailed history of repetitive head trauma and cognitive, mood, and motor assessments, are crucial for identifying probable cases.[54]

CTE has a progressive course with variable outcomes depending on the clinical subtype and severity. Behavioral/mood variants may remain relatively stable for years, whereas the cognitive and dementia variants often show relentless progression. Symptom severity correlates with neuropathological stage, with advanced cases exhibiting widespread tauopathy and significant brain atrophy.[53]

Prognosis is also influenced by coexisting neurodegenerative pathologies such as Alzheimer's disease, TDP-43 proteinopathy, or amyloid plaque deposition, which may exacerbate symptoms. There is currently no curative treatment for CTE; management focuses on symptomatic relief and minimizing further head trauma. Preventative strategies, including stricter regulations for contact sports and improved protective equipment, are critical in reducing CTE incidence.[55]

Acute necrotizing encephalopathy

Acute necrotizing encephalopathy (ANE) is a rare, rapidly progressive, and often fatal neurological condition primarily associated with viral infections. It is characterized by widespread necrotizing lesions in the brain, predominantly affecting the bilateral thalami, and is mediated by a cytokine storm rather than direct viral invasion. The condition affects children more frequently but has also been reported in adults.[56]

ANE typically presents in three stages: a prodromal viral infection, an acute encephalopathy phase, and recovery (if survival occurs). The prodromal stage is marked by fever, cough, vomiting, or diarrhea. Neurological symptoms, including sudden altered mental status, seizures, focal deficits, and rapid progression to coma, often emerge within 1-3 days of the prodromal illness. Systemic symptoms such as disseminated intravascular coagulation, organ failure, or shock are also common during the acute phase. While some patients fully recover, most survivors have long-term neurological sequelae, such as cognitive or motor impairments.[57]

Diagnosis is primarily radiological, with brain MRI showing bilateral symmetric lesions in the thalami, brainstem, cerebellum, and white matter. These lesions exhibit a "trilaminar" appearance on DWI and ADC imaging, with central necrosis, cytotoxic edema in the periphery, and vasogenic edema at the outermost layer. Gadolinium-enhanced MRI may detect blood-brain barrier disruptions in early stages, aiding in prompt diagnosis.[56]

Laboratory findings are nonspecific. CSF analysis typically shows normal or mildly elevated protein levels without pleocytosis, distinguishing ANE from viral encephalitis. Serum biomarkers, including elevated cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), reflect the cytokine storm central to its pathogenesis. Genetic testing for RANBP2 mutations is indicated in recurrent or familial cases, where autosomal dominant inheritance is suspected.[58]

The prognosis of ANE remains poor, with a reported mortality rate of approximately 30%. Survivors often experience significant neurological sequelae, including cognitive deficits, epilepsy, or motor impairments. Early treatment, including high-dose corticosteroids and cytokine-blocking agents such as tocilizumab (targeting IL-6), has been shown to improve outcomes in some cases. Supportive measures, such as therapeutic hypothermia and intensive care management, may mitigate complications like cerebral edema and systemic organ failure.[59]

Although recovery in ANE is possible, many survivors exhibit residual changes, including brain atrophy, hemosiderin deposition/cyst formation. Early diagnosis and timely intervention are critical to reducing the mortality and long-term disability associated with ANE.[60]

CONCLUSION

Encephalopathy represents a heterogeneous group of neurological syndromes with distinct etiologies, presentations, and outcomes. While reversible forms benefit from timely interventions, progressive types remain challenging due to limited treatment options. Advances in diagnostic tools and tailored therapeutic strategies have improved outcomes for certain subtypes but underscore the need for early recognition and precise differentiation. Ongoing research and multidisciplinary efforts are essential to address knowledge gaps, refine management, and enhance quality of life for affected individuals. Future priorities should focus on expanding access to diagnostic modalities and developing innovative treatments to mitigate global impact of these disorders.

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