CASE REPORT

Successful Treatment of Refractory Landau–Kleffner Syndrome with Memantine in a Child with GRIN2A Gain-of-Function Variant

Mahmoud Mohammadi[1, 2]; Reza Shervin Badv[1], Zahra Rezaei[1, 2]; Alireza Zangooie[3, 4]; Reza Asgari[5]; Narges Mashayekhi[2]

[1]Children's Medical Center, Pediatrics Center of Excellence, Tehran University of Medical Sciences, Tehran, Iran.
[2]Pediatric and Adolescence Multidisciplinary Epilepsy Research Center (PAMERC), Tehran University of Medical Sciences, Tehran, Iran.
[3]Cellular and Molecular Research Center, Birjand University of Medical Sciences, Birjand, Iran.
[4]Hematology, Oncology and Stem Cell Transplantation Research Center, Research Institute for Oncology, Hematology and Cell Therapy, Tehran University of Medical Sciences, Tehran, Iran.
[5]Student Research Committee, Qazvin University of Medical Sciences, Qazvin, Iran.

Received: 30 Jan 2026
Accepted: 23 May 2026
Published: 1 Jun 2026

Keywords:

Landau-Kleffner syndrome
GRIN2A mutation
Memantine

ABSTRACT

Landau-Kleffner syndrome and related epilepsy-aphasia spectrum disorders are characterized by childhood-onset language regression, sleep-activated epileptiform activity, and frequently refractory seizures. This case report describe a boy with normal early development who developed progressive aphasia and non-motor seizures around age three, with electroencephalographic findings consistent with spike-wave activation during slow sleep, while neuroimaging and metabolic evaluations were normal. Standard antiseizure medications and repeated immunotherapy provided no sustained benefit. Genetic testing at age 12 identified a pathogenic heterozygous *GRIN2A* gain-of-function missense variant (p.T531M), guiding initiation of targeted therapy with memantine, and an NMDA receptor antagonist. Following memantine treatment, the patient showed marked improvement in speech and social interaction together with reduced sleep-related epileptiform discharges, although some deficits persisted. This case underscores the value of early genetic evaluation in refractory epilepsy-aphasia syndromes and supports the potential role of precision NMDA-modulating therapy in *GRIN2A*-associated epileptic encephalopathy.

How to cite this article: Mohammadi M, Shervin Badv, Rezaei Z, Zangooie A, Asgari R, Mashayekhi N. Successful Treatment of Refractory Landau–Kleffner Syndrome with Memantine in a Child with GRIN2A Gain-of-Function Variant. Iran J Child Neurol. 2026;20(3):87-93. https://doi.org/10.22037/ijcn.v20i3.51527

Introduction

Landau-Kleffner Syndrome (LKS) is a rare childhood-onset epileptic encephalopathy marked by a sudden or gradual loss of language abilities after normal development, accompanied by abnormal electroencephalographic (EEG) activity primarily in the temporoparietal regions. Seizure events, predominantly of the absence or tonic-clonic variety, exhibit a heightened nocturnal prevalence. Furthermore, these episodes are frequently associated with concurrent behavioral disruptions. While sharing certain commonalities with Sleep-Waking Activation Syndrome (SWAS), this condition remains a distinct

Corresponding Author:
Reza Shervin Badv: Email: drbadv@gmail.com
Narges Mashyekhi: Email: Nmashayekhi54@gmail.com

clinical entity, defined by its unique diagnostic markers and symptomatology (1).

The etiology of LKS remains elusive, given that structural brain lesions are rarely observed and do not appear to contribute to its underlying pathophysiology. Genetic factors, specifically mutations in the Glutamate Ionotropic Receptor NMDA Type Subunit 2A (GRIN2A) gene located at 16p13.2, may contribute, since this gene encodes the GluN2A (NR2A) protein—a key N-methyl-D-aspartate (NMDA) receptor subunit present in high concentrations in brain regions vital for speech and language. NMDA receptors broadly influence learning and memory, and GRIN2A alterations correlate with various neurodevelopmental disorders, often presenting with epilepsy as a symptom (2, 3).

Physicians often use empirical approaches in treating LKS due to limited data on the effectiveness and outcomes of interventions. Steroid therapy, in particular, has demonstrated improvements in language abilities for patients regardless of their EEG results. Memantine acts by blocking current flow through NMDA receptor channels, glutamate receptors essential for brain function. A previously reported GRIN2A mutation, affecting these receptors, was studied in vitro and showed varying responses to NMDA blockers (4-6).

Based on the observed altered activity of mutant GluN2A-containing NMDA receptor complexes, this study hypothesized that elucidating the functional consequences of the mutation and applying a targeted therapeutic approach could improve clinical outcomes. Therefore, the present study reports the clinical presentation, genetic findings, and treatment response of a child with early-onset epileptic encephalopathy harboring a novel GRIN2A missense mutation, who showed significant clinical and EEG improvement following memantine therapy (Figure. 1).

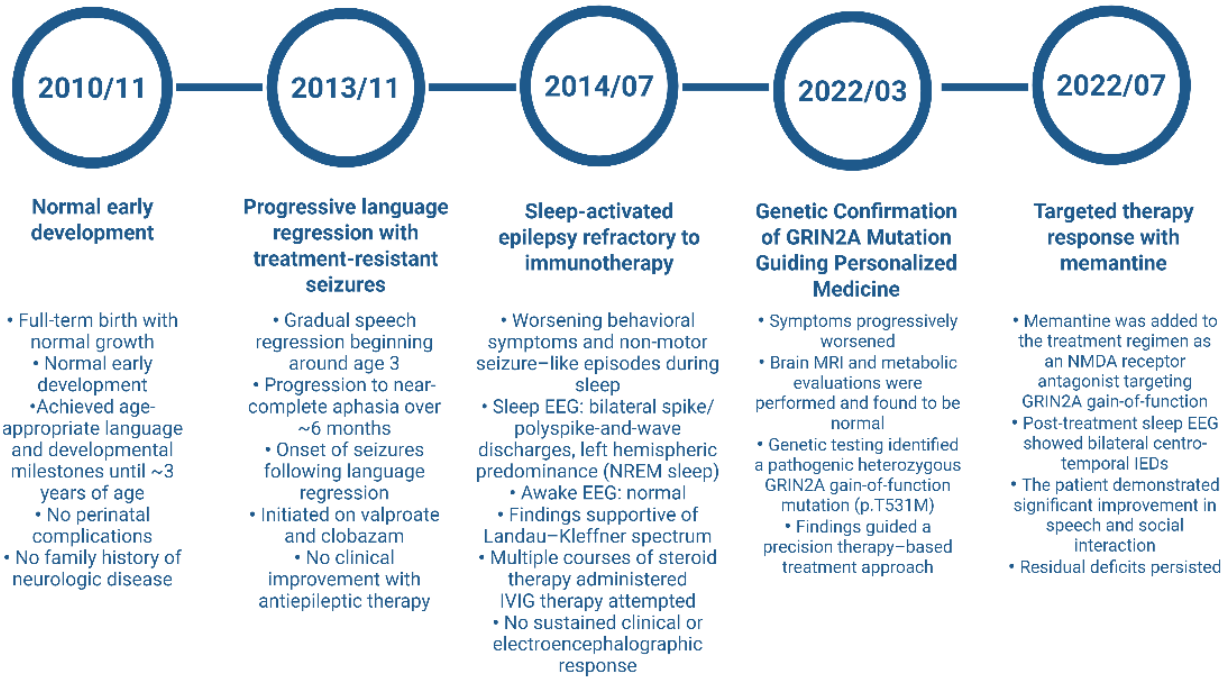

Figure 1. Clinical timeline of a patient with GRIN2A-related epilepsy–aphasia spectrum disorder

The timeline illustrates the patient's clinical progression from birth through precision-guided therapy. Following typical early development, gradual language regression emerged at around three years of age, soon accompanied by seizure onset. Sleep EEG demonstrated spike–wave activation during NREM sleep, consistent with a sleep-related epileptic encephalopathy. Multiple conventional treatments, including antiseizure medications and immunotherapy, yielded no lasting benefit. At age 12, a pathogenic heterozygous GRIN2A gain-of-function variant (p.T531M) was identified, prompting initiation of targeted therapy with memantine. Subsequent follow-up showed significant improvement in communication and social interaction, along with a reduction of epileptiform activity on sleep EEG, though some deficits remained.

Case Presentation

A 14-year-old boy was born at term after an uneventful pregnancy and delivery, with no perinatal complications or prior hospitalizations. He is the first child of healthy, non-consanguineous parents, with no family history of neurological or genetic disorders, and he currently attends a special education school.

His early developmental milestones were normal until approximately three years of age, when he began to experience gradual speech regression, eventually leading to complete loss of speech within six months. Subsequently, seizures were noted, and he was initially treated with sodium valproate and clobazam without clinical improvement.

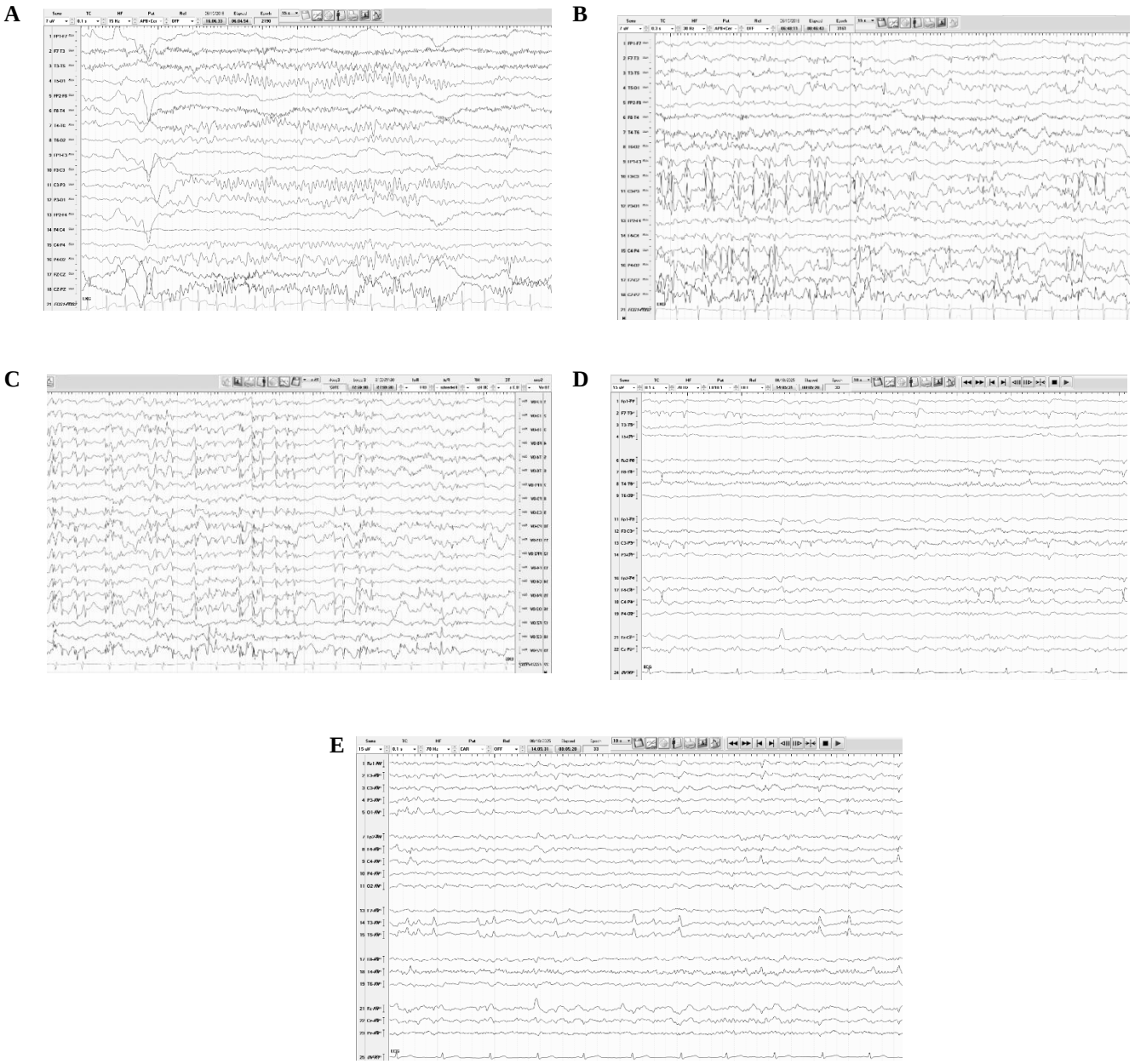

Figure 2. Electroencephalogram (EEG) recordings demonstrating treatment progression and response
(A) Bipolar montage; Normal PDR, No epileptiform discharges during wakefulness. **(B)** AP Bipolar montage; Bilateral spike/poly-spikes and wave with more predominance at left hemisphere (NREM-Sleep). **(C)** Average montage; Bilateral spike/poly-spikes and wave (NREM-Sleep). **(D)** Bipolar montage; Bilateral Centro-temporal IEDs (NREM-Sleep). **(E)** Average montage; Bilateral Centro-temporal IEDs with Left temporal predominance (NREM-Sleep). NREM: Non rapid eye movement

The patient was subsequently referred to the Children's Medical Center, Tehran, Iran. Although he did not exhibit overt clinical (motor) seizures, he progressively developed speech regression accompanied by psychiatric and behavioral disturbances that were more evident during sleep. These clinical presentations were indicative of non-convulsive status epilepticus, primarily observed during sleep, and manifested as non-motor seizures that correlated with significant behavioral and language impairments Based on this gradual regression pattern and EEG findings demonstrating a normal awake EEG (Figure. 2A),and Bilateral spike/poly-spikes and wave with more predominance at left hemisphere (NREM-Sleep) (Figure. 2B,C) , a preliminary diagnosis of LKS or epileptic encephalopathy with spike-wave activating during slow sleep (SWAS)was established.

Due to inadequate clinical response, he underwent repeated hospitalizations for additional IVIG therapy. Over time, he developed drooling, involuntary tongue protrusion movements, and episodes of unresponsiveness suggestive of non-convulsive seizures, leading to further evaluations and hospital admissions.

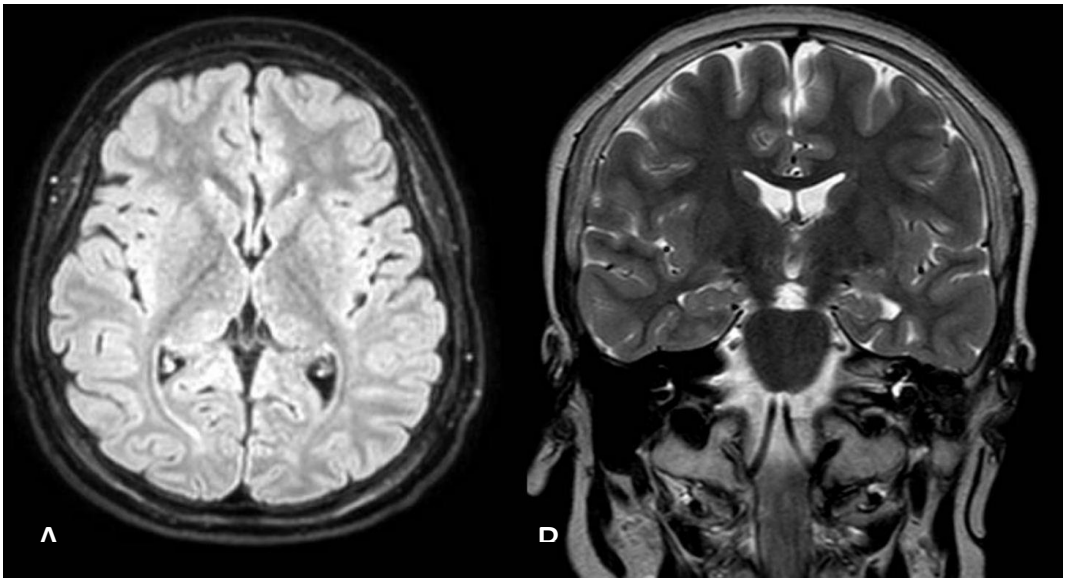

Figure 3. (A) Brain MRI, including axial FLAIR and (B) coronal T2-weighted sequences, reveals no significant structural abnormalities

At 12 years of age, following an increase in seizure frequency and decreased level of consciousness, he was admitted for comprehensive evaluation, including metabolic studies, brain MRI, and genetic testing. The metabolic and MRI results were normal (Figure. 3). However, genetic analysis revealed a pathogenic heterozygous variant in the GRIN2A gene (transcript NM_001134407), specifically c.C1592T, resulting in an amino acid substitution p.T531M. This variant is located in exon 7 of the gene and corresponds to reference SNP ID rs397518468 at chromosome 16:9934563 (GRCh37), with an autosomal dominant inheritance pattern.

Based on these findings, high-dose memantine was added to his treatment regimen, already included prednisolone, clobazam, sodium valproate, and carbamazepine. Follow-up EEGs demonstrated that the sleep EEG after treatment with antiseizure medications (ASM) and before memantine showed Bilateral spike/poly-spikes and wave with more predominance at left hemisphere (NREM-Sleep) (Figure. 2B, C), the awake EEG before and after memantine and ASM was normal (Figure. 2A), and the sleep EEG after adding memantine to ASM showed Bilateral Centro-temporal IEDs with Left temporal predominance (Figure. 2D, E). After starting memantine, the patient's speech and social interaction improved markedly.

In summary, this case represents a GRIN2A-related epileptic encephalopathy with a LKS/SWAS phenotype, characterized by speech regression, behavioral and non-convulsive seizure features, and demonstrates the potential clinical benefit of memantine as adjunctive therapy in GRIN2A-associated epilepsy-aphasia spectrum disorders.

Discussion

Epileptic encephalopathy syndromes represent a group of severe epileptic disorders characterized by frequent and often drug-resistant seizures, abnormal EEG patterns, and progressive cognitive and developmental impairment. Well-known syndromes in this category include West syndrome (infantile spasms), Lennox–Gastaut syndrome, Dravet syndrome, Ohtahara syndrome, LKS, and Epilepsy with SWAS. These conditions have diverse etiologies, including structural brain abnormalities, metabolic disturbances, genetic mutations, and immune-mediated mechanisms. Early and accurate identification of the specific syndrome is crucial, as it guides targeted management strategies and influences long-term outcomes. Advances in next-generation sequencing and high-resolution neuroimaging have significantly improved diagnostic precision, allowing for more personalized therapeutic approaches. Despite these advances, seizure control and neurodevelopmental outcomes remain suboptimal in many patients, emphasizing the urgent need for novel treatments, disease-modifying therapies, and early multidisciplinary interventions (7, 8).

Among these, LKS is an electroclinical syndrome of childhood, typically manifesting between the ages of three and eight years. This disorder is characterized by language regression, various seizure types, and striking EEG abnormalities during sleep, with variable neurocognitive outcomes depending on the timing of diagnosis and response to treatment (9, 10).

LKS is classically defined by acquired aphasia, specifically receptive language regression, often following a period of normal language development. Clinical manifestations may include behavioral disturbances, drooling, neuromotor dysfunction, and a spectrum of seizure types, most commonly focal or generalized tonic-clonic seizures. EEG findings are critical in diagnosis; the hallmark is paroxysmal epileptiform discharges during non-REM sleep, often demonstrating a pattern of electrical status epilepticus during sleep (ESES) or SWAS, with spike-wave activity occupying > 85% of non-REM sleep. While MRI is typically normal in LKS, neuroimaging helps exclude structural or acquired lesions (11-13).

In the presented case, the child experienced normal early development followed by speech regression, increased seizure frequency, and EEG findings consistent with SWAS, all compatible with the LKS phenotype.

Advances in genetic testing have revealed that mutations in GRIN2A, encoding the GluN2A subunit of the NMDA receptor, are one of the most common monogenic causes of epilepsy-aphasia spectrum disorders, including LKS and SWAS. Recent studies estimate that GRIN2A variants account for up to 15–20% of LKS and related phenotypes. These mutations are typically inherited in an autosomal dominant fashion with variable penetrance, though many cases are de novo (14, 15).

At the cellular and molecular levels, GluN2A subunits play a crucial role in regulating glutamatergic synaptic transmission and synaptic plasticity, particularly during critical periods of cortical language network development. Gain- or loss-of-function mutations can disrupt NMDA receptor kinetics, leading to hyperexcitability of cortical networks, particularly in perisylvian language regions. This aberrant excitatory-inhibitory balance manifests clinically as epileptiform discharges during sleep, speech regression, and cognitive impairment (9, 14, 15).

Management of LKS involves seizure control and modulation of the underlying encephalopathic process. First-line therapies typically include benzodiazepines (e.g., clobazam & diazepam), valproate, and high-dose corticosteroids or ACTH, which can suppress epileptiform activity and sometimes lead to language improvement. Intravenous immunoglobulin (IVIG) has been used in refractory cases with variable success (16, 17).

In patients with GRIN2A-related epilepsies, targeted therapy using NMDA receptor modulators has gained interest. Memantine, a non-competitive NMDA receptor antagonist, has shown promise in several case series and reports, particularly for gain-of-function GRIN2A mutations, by normalizing receptor overactivity and improving both seizure control and language function. In this patient, following a genotype-specific treatment algorithm, memantine was introduced and gradually dose-adjusted as an adjunct to ASMs (9, 18, 19).

Other potential treatments in refractory cases include ketogenic diet, epilepsy surgery (e.g., multiple subpial transections), or novel precision therapies targeting NMDA receptor dysfunction. However, the response is variable and strongly influenced by age at onset and duration of epileptic activity (18).

The clinical course of GRIN2A-related epileptic encephalopathy is heterogeneous. Earlier onset, prolonged ESES, and delayed initiation of appropriate treatment are associated with poorer language and cognitive outcomes. Regular follow-up with serial EEG, neurocognitive assessments, and individualized therapy adjustment is essential (11, 20). In the presented case, despite aggressive therapy, the patient continues to exhibit persistent seizures and cognitive-

linguistic impairment, reflecting the refractory nature of GRIN2A-related LKS in some individuals.

In Conclusion

This case highlights the significance of incorporating genetic testing into the diagnostic evaluation of children with refractory epilepsy-aphasia spectrum disorders. Identifying a pathogenic GRIN2A gain-of-function variant enabled the application of a personalized and mechanism-based therapy using memantine, resulting in clinically meaningful improvement in speech abilities, social interaction, and sleep-related EEG abnormalities. Although residual deficits remain, the positive response supports the growing evidence that targeted NMDA receptor modulation may offer therapeutic benefit in selected GRIN2A-associated epileptic encephalopathies. Early recognition and precision treatment interventions may improve long-term neurodevelopmental outcomes in this challenging patient population.

Ethics statement

Ethical review and approval were not required for this case report in accordance with local legislation and institutional guidelines, as all clinical procedures were part of routine patient care. Written informed consent was obtained from the patient's legal guardians for participation and for the publication of any potentially identifiable clinical information and images contained in this article.

Acknowledgement

We would like to express our sincere gratitude to the Children's Medical Center (Tehran, Iran) for their exceptional care and support in the diagnosis and treatment of this patient. We also extend our thanks to BioRender (https://BioRender.com) for providing the tools that enabled us to create the figure used in this article.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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