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Acute liver failure associated with lamotrigine in children with epilepsy: A report of two cases and thoughts on pharmacogenomics

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ABSTRACT

Pediatric acute liver failure (PALF) is a rare and life-threatening clinical syndrome for which drug-induced liver injury is a cause. Lamotrigine (LTG) is generally a safe and effective antiseizure medication, and PALF related to LTG has rarely been reported. Here, we describe two cases of PALF associated with LTG in children with epilepsy. In both patients, LTG was used in combination with valproic acid at an initial dose exceeding the recommended dose, which increased the risk of adverse reactions. In addition, single nucleotide polymorphisms of genes associated with the pharmacokinetics and pharmacodynamics of LTG were selected for pharmacogenomic testing. However, the results revealed that genotypes of the patients had variable effects on the serum concentration and therapeutic responsiveness of LTG and therefore did not explain the clinical manifestations well. The findings of this case report caution clinicians to be aware of the risk of liver failure when using antiseizure medication in polytherapy, especially LTG in combination with valproic acid. When administered to children, the recommended dosage of LTG should be strictly followed. Further pharmacogenomic studies are needed to help improve the efficacy and safety of epilepsy treatment in the future.

Introduction

Pediatric acute liver failure (PALF) is a rapidly progressive clinical syndrome in which children without a history of liver disease suddenly develop liver function impairment and more than half have hepatic encephalopathy, which can be life-threatening [1]. In the United States, approximately 10 %–15 % of liver transplantations in children are due to PALF, which must be recognized and treated promptly [2]. The etiologies of PALF are classified as infectious, immunologic, metabolic, and toxin or drug-related, while more than half have no identifiable etiology [3].

Lamotrigine (LTG) belongs to the sodium channel blocking class of antiseizure medications (ASMs). LTG is widely used in patients with epilepsy and is generally safe and effective. A rare adverse effect of LTG is hepatic injury, and PALF associated with LTG has been even more rarely reported. Here, we describe two cases of PALF after LTG administration in children with epilepsy in the hope of drawing attention to the safety of the application of ASM in children.

In addition, single nucleotide polymorphisms (SNPs) in certain genes have been reported to be associated with LTG pharmacokinetics and pharmacodynamics. We selected several of these SNPs for which data from Chinese population studies were available, and we performed pharmacogenomic testing to initially explore their possible role in PALF occurrence.

Case presentation

Patient 1, a 13-year-old girl, developed seizures at the age of 10 years, which were focal to bilateral tonic-clonic seizures. In the most recent year, she was on valproate sodium (VPA) 0.4 g twice daily and clonazepam 8 mg/day, with a seizure frequency of once a week. Twenty-four days before admission, the local clinic added LTG 25 mg twice daily (2 mg/kg/day) for combination therapy. Ten days after taking LTG, she developed a fever with a maximum temperature of 40 ℃. Three days later, a rash appeared and

Abbreviations: PALF, pediatric acute liver failure; LTG, lamotrigine; DILI, drug-induced liver injury; ASM, antiseizure medication.

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spread rapidly over her body, followed by a progressive yellowish staining of her skin. Her mental state gradually deteriorated, and her seizures increased to 1–2 times/day. She had an uneventful perinatal period, delayed speech development, and no history of allergies. Her father, older brother and sister all suffered from childhood-onset drug-resistant epilepsy and epileptic encephalopathy. Furthermore, the brother died of epilepsy at the age of 15 years (Fig. 1A).

Physical examination found that the girl was lethargic, with generalized skin and scleral jaundice and a patchy, dark red rash (Fig. 1B) but no hepatomegaly or splenomegaly. Laboratory tests results were as follows: total bilirubin, 481 μmol/L (upper limit of normal, ULN = 20.5 μmol/L); direct bilirubin, 369 μmol/L (ULN = 3.42 μmol/L); alanine aminotransferase (ALT), 73.5 U/L (ULN = 29 U/L); gamma-glutamyltransferase (γGT), 920 u/L (ULN = 26 U/L); prothrombin time, 56.6 s (reference 9.4–12.5 s); activated thromboplastin time, 76.3 s (reference 25.1–38.4 s); and international normalized ratio, 4.96. The serum LTG concentration was 10.6 μg/ml 60 h after the last dose (Table 1). The results of tests for hepatitis virus were negative. Homocysteine, ceruloplasmin and alpha-fetoprotein were normal. Abdominal ultrasound showed elevated hepatic elasticity, deflation and wall thickening of the gallbladder. Abdominal CT indicated fullness of the liver and spleen with normal CT values (Fig. 1D). Cranial CT showed a deepening of the cerebral and cerebellar sulci (Fig. 1C). The results of subsequent pharmacogenomic testing are shown in Table 1.

The girl was diagnosed with epilepsy, acute liver failure, and stage II hepatic encephalopathy. LTG and VPA were immediately discontinued and replaced with levetiracetam. She received intravenous reductive glutathione and ornithine aspartate to protect hepatic function in combination with oral ursodeoxycholic acid to promote bilirubin excretion. In addition, she was administered vitamin K1 intramuscularly and fresh frozen plasma infusion to improve coagulation function. However, the parents abandoned the treatment 2 days later due to financial difficulties, and the girl died a few days later.

Patient 2, a 3-year-7-month-old boy, presented with seizures at 6 months old, which were focal clonic seizures, mostly during fever, with recurrent episodes of status epilepticus. The initial administration of oxcarbazepine aggravated the seizures, therefore oxcarbazepine was changed to a combination of VPA, clonazepam, levetiracetam and topiramate. At the age of 3 years, a suspected epileptogenic focus was resected at a local hospital. However, he still had 1–2 episodes of status epilepticus per month. Two weeks before admission, LTG 12.5 mg once daily (0.7 mg/kg/day) was added by a local clinic. After taking LTG for one week, the boy developed a fever with a maximum temperature of 39.5 ℃. Two days later, elevated transaminases were detected, so LTG was discontinued, but he developed impaired consciousness and frequent seizures with vomiting and diarrhea. He had mild mental and motor retardation, no history of allergies, and no relevant family history (Fig. 2A).

Physical examination found a Glasgow coma score of 8 and no jaundice or rash but hepatomegaly and splenomegaly. Laboratory tests results were as follows: ALT, 7267.7 U/L (ULN = 30 U/L); aspartate aminotransferase, 4834.7 U/L (ULN = 45 U/L); γGT, 296

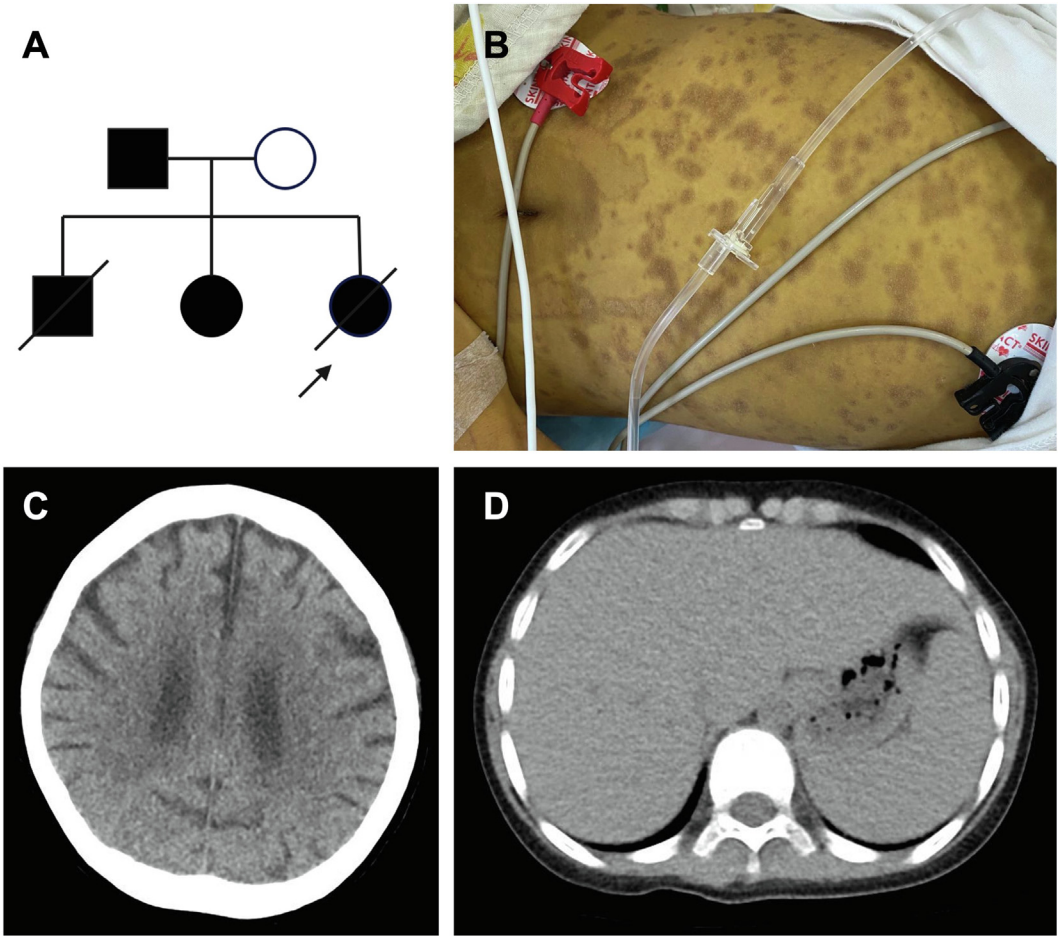

Fig. 1. Case 1. **(A)** Family pedigree of case 1. Solid black represents a family member with epilepsy. **(B)** Picture of abdomen showed skin jaundice with dark rashes. **(C)** Cranial CT showed a deepening of the cerebral sulci. **(D)** Abdomen CT indicated fullness of the liver and spleen.

Table 1
Features of the two patients with acute liver failure.

		Case 1	Case 2
Primary disease		Epilepsy	Epilepsy – Dravet Syndrome
Age/Sex		13y /F	3y7m/ M
Dose of LTG		2 mg/kg/day	0.69 mg/kg/day
Concurrent medications		VPA, CZP	VPA, LEV, CZP, TPM
Clinical manifestations	Latency time	10 days	7 days
	Impaired consciousness	+	+
	Fever	+	+
	Rash	+	–
	Jaundice	+	–
	Hepatomegaly	–	+
Laboratory tests	Worst liver function	AST 111.9 U/L	AST 4834.7 U/L
	abnormality	ALT 73.5 U/L	ALT 7267.7 U/L
		γGT 920 U/L	γGT 296 U/L
		TBil 481 μmol/L	TBil 22.27 μmol/L
		DBil 369 μmol/L	DBil 14.42 μmol/L
		TBA 119 μmol/L	
		ALP 846 U/L	ALP 374 U/L
		ALB 30 g/L	ALB 27 g/L
		Ammonia 71 μmol/L	Ammonia 143 μmol/L
	Coagulation function	PT 56.6 s	PT 23 s
		APTT 76.3 s	APTT 42 s
		INR 4.96	INR 2.03
		FIB 2.42 g/L	FIB 1.18 g/L
		D-Dimer 0.077 mg/L	D-Dimer 2.67 mg/L
	Complete blood count	WBC 3.53 × 10^9/L	WBC 3.36 × 10^9/L
		Lym 29.7 %	Lym 12.8 %
		Eo 0.3 %	Eo 0 %
		Hb 87 g/L	Hb 123 g/L
		PLT 65 × 10^9/L	PLT 79 × 10^9/L
	Serum concentration of LTG	10.6 μg/ml (60 h after last dose)	0.2 μg/ml (1 week after last dose)
Pharmacogenomic testing	LTG pharmacokinetics	*UGT1A4* rs2011425 TT	*UGT1A4* rs2011425 TG
		UGT2B7 rs7668258 CT	
		ABCG2 rs3114020 CC	
		SLC22A1 rs628031 GG	
	LTG pharmacodynamics	*SCN1A* rs2298771 AG	
		SCN2A rs2304016 AG	
	LTG allergy	*HLA-B*15:02* TT	*HLA-B*15:02* TT
Outcome		Died	Recovered

F, female; M, male; y, year; m, month; LTG, lamotrigine; VPA, valproate acid; CZP, clonazepam; LEV, levetiracetam; TPM, Topiramate; +, positive; -, negative; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGT, γ-glutamyl transpeptidase; TBil, total bilirubin; DBil, direct bilirubin; TBA, total bile acid; ALP, alkaline phosphatase; ALB, albumin; PT, prothrombin time; INR, international normalized ratio; FIB, fibrinogen; APTT, activated partial thromboplastin time; WBC, white blood cell; Lym, lymphocyte; Eo, eosinophile granulocyte; Hb, hemoglobin; PLT, platelet.

U/L (ULN = 19 U/L); and ammonia, 143 μmol/L (ULN = 74 μmol/L) (Table 1). There was no specific abnormality in blood or urine screening for congenital metabolic disorders, and the results of tests for hepatotropic viruses were negative. The serum concentration of VPA was 83.75 μg/ml. Toxicological examination detected residues of LTG one week after its withdrawal, with a serum concentration of 0.2 μg/ml. Abdominal ultrasound demonstrated an enlarged liver with rough parenchymal echogenicity and cholecystic bed edema. Brain MRI showed postoperative gliosis around the resected lesion in the left frontal lobe (Fig. 2C). Electroencephalogram recorded slowed background activity and epileptiform discharges predominantly in the right temporal and frontal leads (Fig. 2D). A gene panel testing for epilepsy identified a de novo heterozygous variant c.971A > C (p.His324Pro) of *SCN1A*, which was interpreted as likely pathogenic (Fig. 2B). The results of pharmacogenomic testing are shown in Table 1.

The boy was diagnosed with epilepsy (specifically, Dravet syndrome), acute liver failure, and stage III hepatic encephalopathy. Respiratory support was provided by nasal continuous positive airway pressure. He received intravenous reductive glutathione and ornithine aspartate, combined with oral gluconolactone and bicyclol to protect hepatic function; intravenous arginine to reduce ammonia; and intravenous prothrombin complex to improve coagulation function. All ASMs were discontinued and replaced with intravenous pumped midazolam. After 2 weeks of treatment, his liver function returned to normal. The ASMs were switched to VPA, levetiracetam, topiramate and nitrazepam, after which the seizures decreased. The boy has been followed up for 2.5 years to date and has had one seizure every 1–2 months, with cluster attacks during fever.

According to the Roussel Uclaf causality assessment method (RUCAM), the scores of the two patients were 5 and 8, so that the degree of causality between hepatotoxicity and LTG was possible and probable, respectively (Table 2). However, the score for case 1 was low due to the lack of recheck data, which did not match her severity and prognosis. In conclusion, we suggest that these two cases of PALF were likely to be drug-induced liver injury (DILI) associated with LTG.

Discussion

Liver failure induced by LTG is rare and life-threatening. In 1995, Makin et al. reported the first case [4], and Arnon et al. first reported a pediatric case in 1998 [5]. From 2004 to June 2022, the Food and Drug Administration Adverse Event Reporting System recorded 211 cases of LTG-related liver failure, with 59 (28.0 %) deaths, of which 39 (18.5 %) of the patients were younger than 18 years of age and 2 (5.1 %) died. The mechanism of LTG-related liver failure is not well understood and is currently considered to

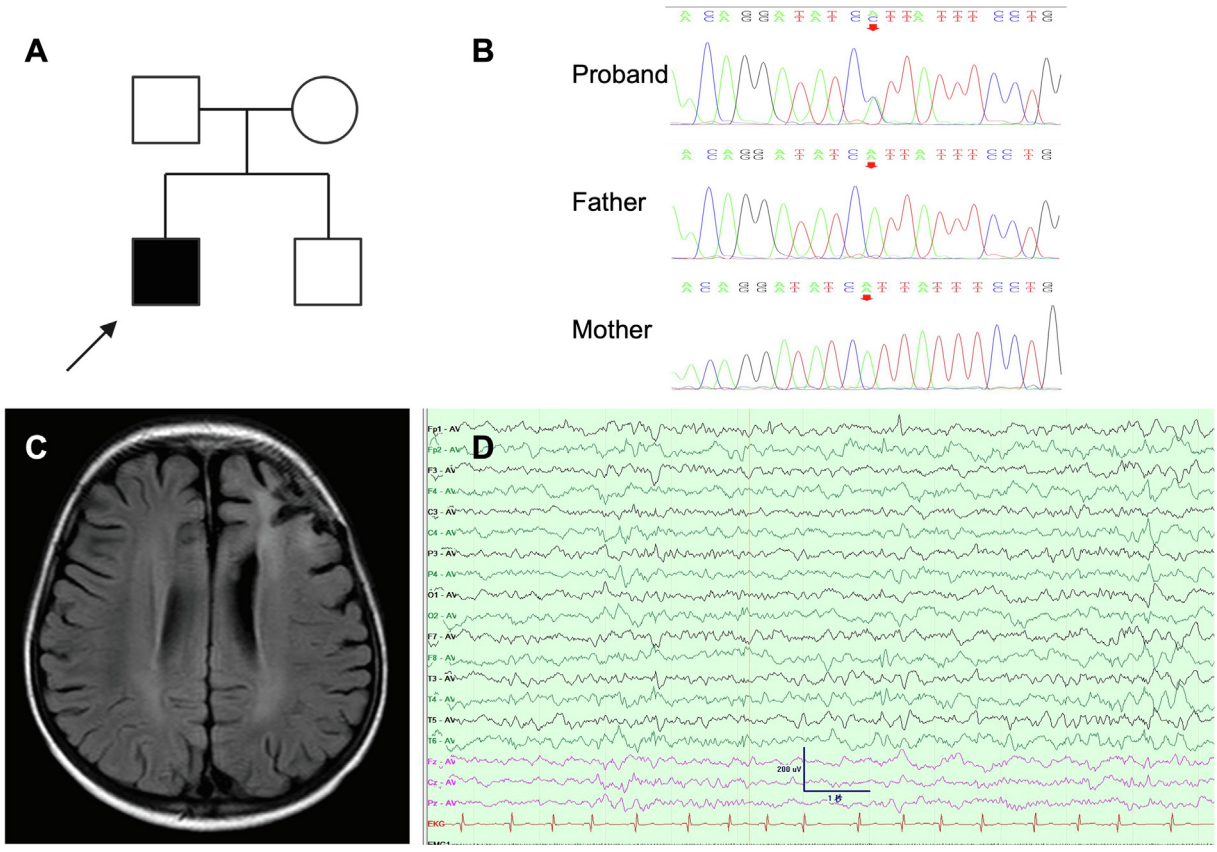

Fig. 2. Case 2. **(A)** Family pedigree of case 2. **(B)** Sanger sequencing confirmed a de novo heterozygous variant c.971A > C (p.His324Pro) of the *SCN1A* gene. **(C)** Axial, FLAIR brain MRI showed postoperative gliosis around the resected lesion in the left frontal lobe. **(D)** Electroencephalogram showed interictal epileptiform discharges predominantly in right temporal and frontal leads.

Table 2
RUCAM for the hepatotoxicity with LTG of the two cases.

Patterns of hepatotoxicity	Case 1: Cholestatic		Case 2: Hepatocellular
1. Time to onset from the beginning of the drug			
5–90 days	2	5–90 days	2
2. Course of ALP/ALT after cessation of the drug			
No information	0	Decrease ≥ 50 % within 8 days	3
3. Risk factors			
Alcohol use	0	Alcohol use	0
Age < 55 years	0	Age < 55 years	0
4. Concomitant use of drug			
Concomitant drug with incompatible time to onset	0	Concomitant drug with incompatible time to onset	0
5. Search for alternative causes			
Group I: HAV, HBV, HCV, HEV, Hepatobiliary sonography/CT, Alcoholism, Acute recent hypotension history		Group I: HAV, HBV, HCV, HEV, Hepatobiliary sonography, Alcoholism, Acute recent hypotension history	
Group II: CMV, EBV, HSV, Complications of underlying disease		Group II: CMV, EBV, HSV, Complications of underlying disease	
Evaluation of groups I and II: The 7 causes of group I ruled out	1	Evaluation of groups I and II: The 7 causes of group I ruled out	1
6. Previous hepatotoxicity of the drug			
Reaction labelled in the product characteristics	2	Reaction labelled in the product characteristics	2
7. Response to unintentional reexposure			
Other situations	0	Other situations	0
Total score	5		8
Causal relationship	Possible		Probable

ALP, alkaline phosphatase; ALT, alanine aminotransferase; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus; HSV, herpes simplex virus.

be idiosyncratic DILI [6]. Active drug metabolites, genetic susceptibility and environmental factors are involved in the development of DILI, with complex interactions among them [7].

Higher dose, rapid titration, and combination with VPA have been linked with higher incidence of LTG hepatotoxicity [8]. When used in combination with VPA, the blood concentration of LTG is approximately doubled, and the half-life is prolonged more than twice [9]. In both cases, VPA had been taken for more than 2 years before the addition of LTG. In patients receiving VPA, the starting dose of LTG must be less than half of that without combined VPA, and the recom-

mended initial dose of LTG for children aged 2–12 years is 0.15 mg/kg/day. However, the initial dose in case 1 exceeded the recommended dose by 13.3 times, while in case 2 by 4.6 times, significantly increasing the risk of adverse drug reactions.

With recent advances in pharmacogenomics, genetic factors have been revealed to contribute significantly to the high variability in the response to ASMs across people with epilepsy [10,11]. Individual responses to drugs are associated with variations in a range of gene categories affecting pharmacokinetics and pharmacodynamics [12]. LTG is cleared by the glucuronidation pathway associated with uridine diphosphate glycosyltransferase (UGT). LTG transport is associated with *ABCG2*, which encodes ATP-binding cassette subfamily G member 2, and *SLC22A1*, which encodes the solute carrier family 22 member 1. Pharmacogenetic testing for these genes may be useful in assessing individual metabolism of LTG [13]. In addition, certain SNPs of genes encoding voltage-gated sodium channels were suggested to be involved in LTG responsiveness and resistance [14]. Case 1 carried *UGT1A4* rs2011425 TT and *ABCG2* rs3114020 CC, both of which may lead to a possible increase in serum LTG concentration [15,16], but she also had *SLC22A1* rs628031 GG which may decrease the concentration, and *UGT2B7* rs7668258 CT, which does not affect the concentration in Han Chinese individuals [17,18]. She carried *SCN1A* rs2298771 AG, which does not play a significant role in influencing the response to LTG, and *SCN2A* rs2304016 AG, which may lead to resistance to LTG in the Chinese population [19]. Case 2 carried *UGT1A4* rs2011425 TG, which has a frequency of 26 % in the southern Chinese population and has no significant effect on LTG blood concentrations [15,20,21]. The results showed that genotypes of the patients had variable effects on the serum concentration and therapeutic responsiveness of LTG, which could not explain their clinical manifestations well. Therefore, we cannot determine the role of any SNP in causing liver injury at present.

In terms of allergic reaction, as an aromatic ASM, a risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in LTG is associated with the *HLA-B*15:02* allele [22]. The fact that in both patients HLA-B*15:02 was found to be negative and there was no eosinophilia does not support that their liver failure was a simple allergic reaction.

Conclusion

LTG has the potential to induce life-threatening PALF and requires cautious use. Clinicians should be aware of risk of DILI when a patient is considered for polytherapy, especially including VPA and LTG in polytherapy and should be monitored accordingly. The initial dose and titration scheme should strictly follow the recommendations of the instructions and guidelines, to reduce the risk of drug-related adverse reactions. Pharmacogenomic testing is expected to serve as a reference that may help to individualize therapy involving antiseizure medications and improve both efficacy and safety of medications in the future. To date, however, the data from pharmacogenomic studies are relatively limited and preliminary. Large case-cohort studies based on different populations are needed to understand the relationship between genotype and phenotype and to determine the functional impact of the type and frequency of genetic variants.

Ethical statement

The authors confirm that the work was conducted in accordance with the Declaration of Helsinki and the ethical standards of the institutional research committee. The authors have obtained informed consent for publication from the patients' parents.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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