Recovery of chronic motor neuropathy due to acute intermittent porphyria after givosiran treatment in a young boy: a case report

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Abstract. – **BACKGROUND:** We describe the first case of a pediatric patient with acute intermittent porphyria and severe chronic porphyric neuropathy treated with givosiran, a small-interfering RNA that drastically decreases delta-aminolevulinic acid production and reduces porphyric attacks' recurrence.

CASE REPORT: A 12-year-old male patient with refractory acute intermittent porphyria and severe porphyric neuropathy was followed prospectively for 12 months after givosiran initiation (subcutaneous, 2.5 mg/kg monthly). Serial neurological, structural, and resting-state functional magnetic resonance imaging (MRI) evaluations were performed, including clinical scales and neurophysiological tests. Delta-aminolevulinic acid urinary levels dropped drastically during treatment. In parallel, all the administered neurological rating scales and neurophysiological assessments showed improvement in all domains. Moreover, an improvement in central motor conduction parameters and resting-state functional connectivity in the sensory-motor network was noticed. At the end of the follow-up, the patient could walk unaided after using a wheelchair for 5 years.

CONCLUSIONS: A clear beneficial effect of givosiran was demonstrated in our patient with both clinical and peripheral nerve neurophysiologic outcome measures. Moreover, we first reported a potential role of givosiran in recovering central motor network impairment in acute intermittent porphyria (AIP), which was previously unknown. This study provides Class IV evidence that givosiran improves chronic porphyric neuropathy.

Key Words:
  Acute intermittent porphyria, Chronic porphyric neuropathy, Chronic motor neuropathy, Givosiran, Delta-aminolevulinic acid, Case report.

Introduction

Acute intermittent porphyria (AIP) is an inherited metabolic disorder caused by genetic mutations that result in enzyme disfunctionalities in the heme biosynthetic pathway, leading to the build-up of non-functional and potentially neurotoxic upstream intermediate porphyrins and their precursors[1,2]. Although recovery is the rule, patients with refractory AIP may develop a chronic neuropathy. Porphyric neuropathy manifests as an acute to subacute motor-predominant axonal neuropathy, typically affecting the upper extremities. A predominantly parasympathetic autonomic neuropathy commonly precedes it. Its swift progression and concurrent dysautonomia may resemble Guillain-Barré syndrome; however, key distinctions include the absence of cerebrospinal fluid albuminocytologic dissociation, progression beyond a 4-week timeframe, and the presence of

associated abdominal pain. Chronic porphyric neuropathy (CPN) is often associated with chronic pain syndrome, represents a major source of disability and reduced quality of life (QoL), and can result in fatalities[1,2]. Among the several mechanisms proposed to explain the neurological symptoms of porphyrias, direct neurotoxicity of the heme precursor delta-aminolevulinic acid (ALA) and heme deficiency are the most convincing. Early diagnosis and timely treatment – usually carried out with intravenous heme, carbohydrate loading, and avoidance of porphyrinogenic medications – can prevent further neurological morbidity and mortality[2].

Givosiran (Givlaari, Alnylam Netherlands B.V.), a new small-interfering RNA targeting and down-regulating delta-aminolevulinic acid (ALA) synthase 1, was approved for AIP treatment in 2020. The ENVISION trial[3] demonstrated its efficacy in lowering ALA and porphobilinogen (PBG) plasma levels and reducing the frequency of porphyric attacks. Some evidence[1,2,4,5] suggests that high ALA levels in plasma may play a direct role in causing neuronal damage. Therefore, even if there is still no consistent demonstration, a beneficial effect of givosiran treatment on CPN is theoretically expected[6]. We report the case of a patient with childhood-onset refractory AIP and severe CPN treated with givosiran for 12 months and followed prospectively with serial neurological, neurophysiological, and neuroimaging assessments. To our knowledge, this is the first report of givosiran treatment in a pediatric patient with CPN.

Case Presentation

A 12-year-old patient was diagnosed with AIP at the age of 5 years after the first acute porphyric attack. Genetic analysis revealed a pathogenic mutation in the *HMBS* gene, confirming AIP diagnosis[7] (see **Supplementary File** for further details). Despite chronic treatment with heme arginate infusions, the patient continued to suffer from frequent porphyric attacks. About 40 days after diagnosis, he developed a subacute tetraparesis with axonal motor neuropathy at nerve conduction study (NCS), without conduction failures or signs of demyelination. Neuropathy progressively worsened, causing severe walking impairment, Achilles tendon retraction, and anterior leg atrophy. The patient has used a wheelchair since the age of 7 years. Later, mild weakness of hand

muscles appeared, with difficulties manipulating objects. Finally, a chronic pain disorder progressively developed, with tingling feet and burning legs. An extensive study ruled out other immune and metabolic causes of neuropathy (**Supplementary File**). In 2020, givosiran treatment was started at a dosage of 2.5 mg/kg monthly. Clinical assessments were performed at baseline and then 3, 6, 9 and 12 months after treatment initiation with the following rating scales: Medical Research Council scale for muscle strength; modified Inflammatory Neuropathy Cause and Treatment (INCAT) Sensory Sumscore for objective sensory impairments; INCAT Overall Disability Score, inflammatory Rasch-built Overall Disability Scale, and Norfolk Quality of Life Diabetic Neuropathy 35 items for disability and QoL[8-10]. There is no specifically validated scale for CPN; therefore, we chose the best fitting and purposely tailored instruments available, supported by recent studies[11] on similar forms of neuropathy.

Neurophysiologic evaluation at baseline and after 6 and 12 months of treatment included NCS of four limbs, electromyography (EMG) of bilateral tibialis anterior (TA) muscles, and transcranial magnetic stimulation motor-evoked potentials (MEP). All electrodiagnostic procedures were performed following published methodological standards[12-15], and the results were compared with normative values obtained internally and matched for sex and age. Neurophysiological studies were performed using a Dantec Keypoint G4™ EMG (Natus Medical Incorporated, Middleton, Wisconsin, USA) recorder and Medtronic MagPro™ (MagVenture, Inc, Alpharetta, Georgia, USA) single-coil transcranial magnetic stimulation. Functional brain connectivity changes during givosiran treatment were explored by resting-state functional magnetic resonance imaging (fMRI) seed-based correlation analysis. Specifically, we assessed longitudinal variations from baseline to 6 and 12 months after treatment initiation between two selected regions of interest (i.e., posterior cingulate and precentral cortex) and the rest of the brain (**Supplementary File**).

Informed consent was obtained from the patient's parents.

Results

During the 12 months of treatment, there were no acute porphyric attacks, and ALA and PBG urinary levels consistently dropped (Figure 1). No
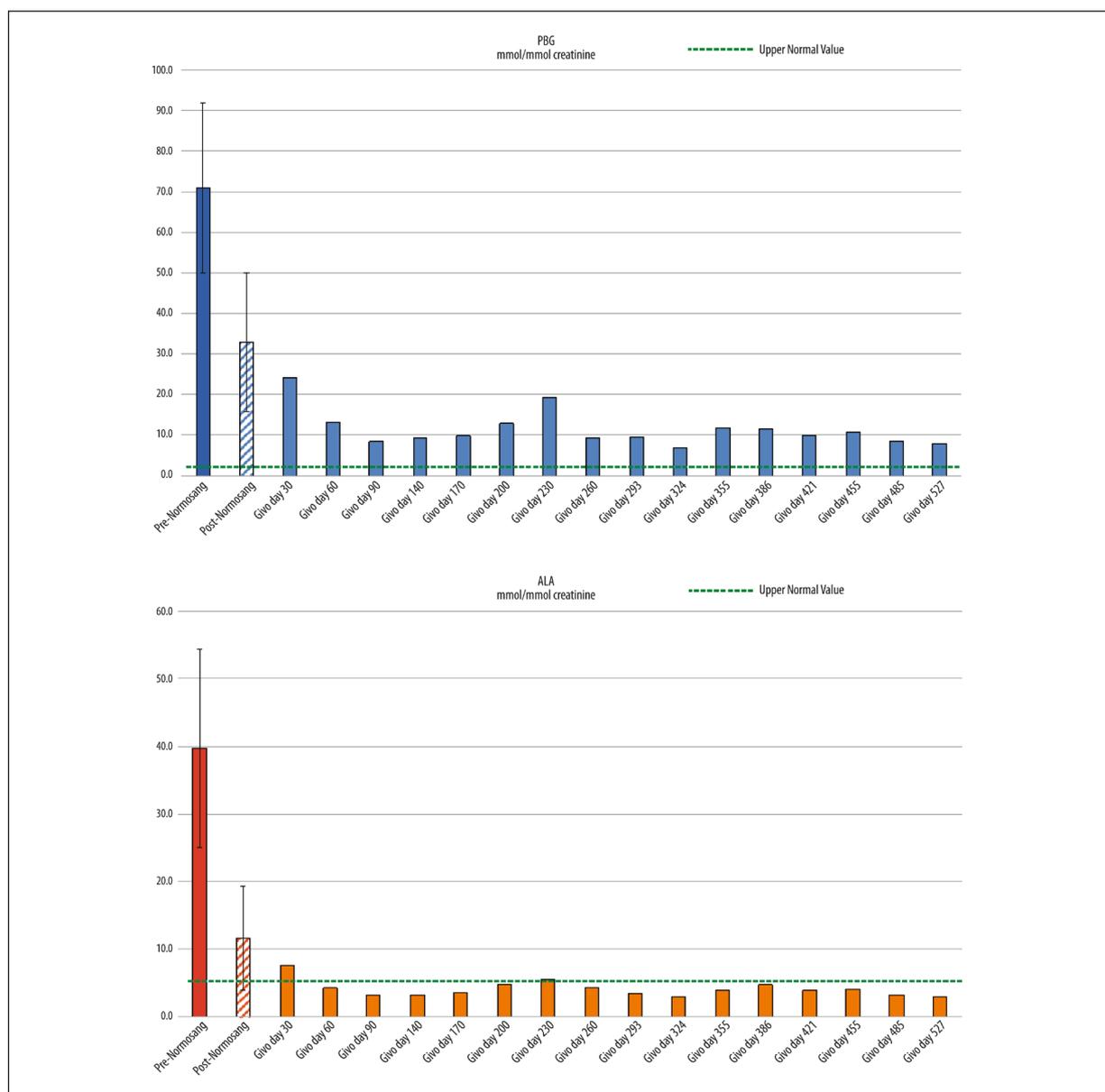
Figure 1. Aminolevulinic acid and porphobilinogen levels before and after treatment with givosiran. Levels of ALA and PBG recorded in 2013-2018 before and after treatment with heme arginate (Normosang®) are demonstrated – each of the first two columns in both panels is the average of approximately 90 measurements. After starting small-interfering RNA-based therapy, ALA and PBG values have markedly reduced; in particular, after 2 months of therapy, ALA values consistently decreased below the upper normal value. ALA=aminolevulinic acid; Givo=Givosiran; PBG=porphobilinogen.

serious adverse events were registered, and heme arginate infusions were stopped at the beginning of treatment. At the baseline evaluation, the patient was using a wheelchair with a complete deficit of ankle dorsiflexion, mild difficulties in hand movements, and diffuse chronic pain. During follow-up, all neurological scales showed relevant improvement in muscle strength, pain, disability, and QoL (Table I and Figure 2A). Apart from pain, the objective evaluation showed no sensory deficit. After 8 months of treatment, the patient could walk unaided (**Supplementary Video 1**). NCS at baseline showed a motor axonal neuropathy involving, in particular, bilateral fibular and radial nerves. EMG showed abundant denervation activity in both TA muscles with extreme poverty in motor unit recruitment. After 12 months, the mean radial nerve compound motor action poten-

Table I. Outcome measures.

	Baseline	6 months	12 months
Clinical evaluation			
MRC score (0: worst - 60: best)	48	52	54
mISS (0: best - 33: worst)	0	0	0
INCAT ODS (0: best - 10: worst)	6	5	4
I-RODS (0: worst – 100: best)	37	42	47
Norfolk QoL-DN 35 (-4: best - 136: worst)	79	56	41
Nerve conduction study			
Radial cMAP amplitude (mV) (nv: >4.5 mV)	3.81	4.36	5.77
Fibular cMAP amplitude (mV) (nv: >2.0 mV)	0.94	0.29	0.49
Motor-evoked potentials			
Upper limbs:			
• Mean central conduction time (ms) (nv: <7.7 ms)	10.5	10.5	9.0
• Mean cortical silent period (ms) (nv: <230 ms)	220	235	213
Lower limbs:			
• Mean central conduction time (ms) (nv: <11.2 ms)	13.1	12.9	10.0
• Mean cortical silent period (ms) (nv: <230 ms)	248	275	190

All NCS and MEP results were expressed as mean values between the left and right sides since no significant difference was noted. Nv: normal values. The patient's height did not change during the follow-up time. cMAP: Compound motor action potential; I-RODS: Inflammatory Rasch-built Overall Disability Scale; INCAT ODS: Inflammatory Neuropathy Cause and Treatment Overall Disability Scale; mISS: modified Inflammatory Neuropathy Cause and Treatment Sensory Sum score; MRC: Medical Research Council; QoL-DN: Quality of Life, Diabetic Neuropathy. In brackets, it is reported the direction of the score.

tial (cMAP) amplitude was higher than baseline, while fibular cMAP was unchanged (Table I). EMG of TA muscles showed sporadic residual denervation activity with a slight increase in motor unit density compared with baseline.

MEP study showed normal motor threshold, amplitude, and absolute mean cortical latency times. However, mean central motor conduction time (CMCT) and mean cortical silent period (CSP) were significantly increased for lower limbs (about three standard deviations longer than normal values). At 6 and 12 months follow-up, mean CMCT was notably shorter than baseline for both upper and lower limbs (-14% and -24%, respectively). Similarly, a remarkable reduction in mean CSP (-23%) was noted for lower limbs (Table I and Figure 2B-C). Precentral cortex seed-based fMRI analysis at baseline lacked a recognizable motor resting-state network (RSN) architecture in an otherwise structurally normal brain. After 12 months of treatment, cortical maps differed dramatically, restoring a normal configuration of motor RSN. As a control, the default mode network cortical architecture (seed: posterior cingulate cortex) was preserved at baseline and did not change during treatment (**Supplementary Figure 1**). Similarly, connectivity analysis demonstrated a wide increase in active functional connections between the precentral cortex and many different cortical and subcortical areas during treatment (Figure 2D).

Discussion

Up to 40% of AIP patients develop CPN, but no specific treatment has been validated. Evidence suggests that ALA may cause neural damage in different ways. It can penetrate the blood-nerve barrier and act as a partial agonist or antagonist on gamma-aminobutyric acid and L-glutamate receptors due to the structural similarities between ALA and these neurotransmitters[2,4]. Furthermore, ALA self-reacts to oxidant species, causing mitochondrial dysfunction[4]. Finally, previous studies[5] demonstrated altered membrane depolarization in motor neurons of AIP patients due to a specific deficit in inward rectifying conductance as a result of impaired neuronal metabolism.

Givosiran demonstrated high efficacy in reducing porphyric attacks by lowering ALA and PBG levels[3]. In our patient, the expected benefit of givosiran on CPN was confirmed since all clinical, neurophysiological, and neuroimaging outcome measures scored significantly better after 12 months of treatment, with major improvements for pain syndrome, distal limb muscle strength, disability, and QoL. Notably, the patient could walk unaided for short distances after using a wheelchair for 5 years. When asked to share his perspective on the treatment received, the patient stated: "After starting givosiran therapy, it was a continuous improvement.
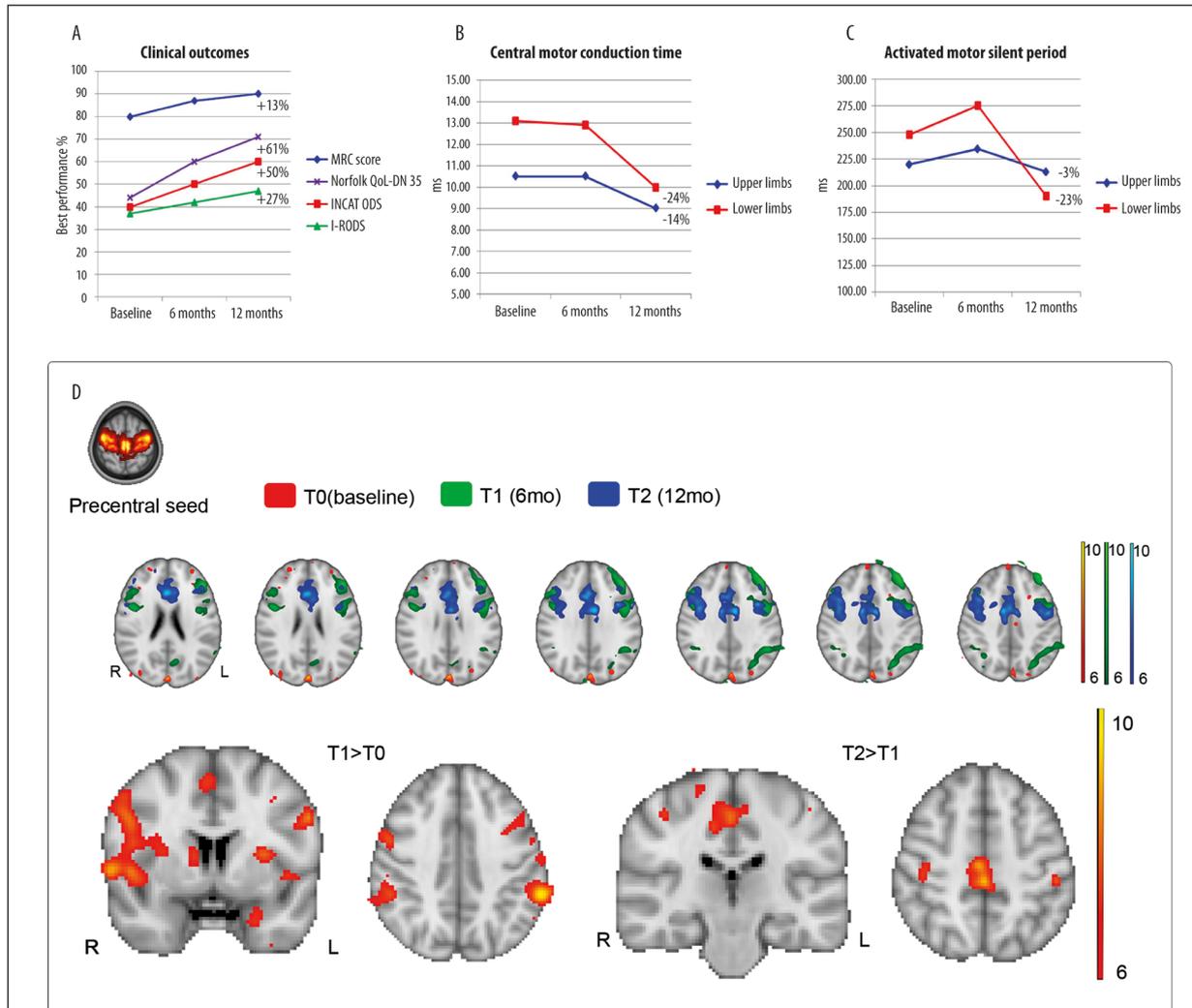
Figure 2. Clinical (**A**) and neurophysiological (**B-C**) outcome measures at baseline and after 6-12 months of givosiran treatment. **A**, All scores are expressed as normalized (percentage on maximum score) and inverted, when necessary, in order to compare them: higher values correlate with better performance. Tags with percentage values represent the variation of each outcome measure since the baseline evaluation. **B-C**, motor-evoked potential results were expressed as mean values between the left and right sides since no significant difference was noted. The patient's height did not change during the follow-up time. Functional MRI findings (**D**) Upper images: correlation map related to the precentral cortex seed overlaid onto the canonical template, axial slices [Montreal Neurological Institute (MNI) 152, 2 mm] as implemented in femtosecond laser (FSL) eyes. The correlation maps are shown in different colors corresponding to the different time points (baseline, T0=red; 6 months after givosiran start, T1=green; 12 months after givosiran start, T2=blue). Bottom images: comparison of precentral-related functional connectivity between baseline and T1 and T1 *vs.* T2. The precentral functional connectivity resulted in an increase from T0-T1 at the left precentral and postcentral gyrus, right inferior parietal lobuli, bilateral middle and superior frontal gyrus, and right temporal regions (uncus and superior temporal gyrus). When comparing T2 and T1, the connectivity from the precentral region of interest was increased over a complex cortical and subcortical network that included left basal ganglia, right thalamus, pre- and post-central regions and premotor cortex (middle and superior frontal gyrus), inferior and superior parietal lobuli bilaterally and left and right temporal regions (parahippocampal cortex and superior temporal gyrus). cMAP: Compound motor action potential; I-RODS: Inflammatory Rasch-built Overall Disability Scale; INCAT ODS: Inflammatory Neuropathy Cause and Treatment Overall Disability Scale; L=Left; MRC: Medical Research Council; QoL-DN: Quality of Life, Diabetic Neuropathy; R=Right.

I went from being continuously ill and hospitalized three/four times a year to being perfectly healthy, allowing me not to miss school." Therefore, although we have described a single case report, these findings sound encouraging and require a wider validation on a larger population to demonstrate givosiran effectiveness on porphyric neuropathy.

To our knowledge, there are no reports in the literature about MEP and fMRI studies in patients affected by AIP and CPN. Interestingly, baseline MEP in our patient showed abnormal CMCT and CSP duration. Similarly, the fMRI study showed disruption of motor RSN at baseline. After givosiran treatment, MEP parameters improved, and fMRI restored motor RSN connectivity compared with baseline. All these data suggest a previously unknown role of central motor pathway involvement in AIP that may be partially responsible for motor disability, which further investigations need to confirm.

Conclusions

Givosiran treatment resulted in improvements in clinical and peripheral nerve neurophysiologic outcome measures in a young patient with refractory AIP and severe CPN. After 12 months of treatment, the patient could walk unaided after using a wheelchair for 5 years. We also report a previously unknown potential role of givosiran in recovering central motor network impairment in AIP. This study provides Class IV evidence that givosiran improves CPN.

Informed Consent

Written informed consent was obtained from the patient and the patient's parents.

Ethics Approval

The present case report did not require ethical approval or notification in accordance with national and institutional guidelines.

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Conflict of Interest

Paolo Ventura and Matteo Marcacci received grants for consulting and lectures from Alnylam Pharmaceuticals, Inc. The other authors have no conflicts of interest to declare.

Authors' Contributions

Marco Mazzoli, study design; data collection; neurophysiological study; data analysis; manuscript drafting. Andrea Ricci, study design; data collection; data analysis; manuscript drafting. Anna Elisabetta Vaudano, data collection; fMRI study; data analysis; manuscript drafting. Matteo Marcacci, study design; data collection; data analysis; manuscript drafting. Stefano Marchini, data collection. Stefano Marchini, data collection. Patrizia Bergonzini. study design; manuscript revision for intellectual content. Elena Di Pierro, data collection; manuscript revision for intellectual content. Elena Pischik, manuscript revision for intellectual content. Lorenzo Iughetti, manuscript revision for intellectual content. Antonello Pietrangelo, study design; manuscript revision for intellectual content. Stefano Meletti, study design; manuscript revision for intellectual content. Paolo Ventura, study design; manuscript revision for intellectual content.

Availability of Data and Materials

Anonymized data are available for sharing upon request by any qualified investigator to the corresponding author.

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