Clinical/Scientific Notes

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IMMUNOTHERAPY-REVERSED COMPULSIVE, MONOAMINERGIC, CIRCADIAN RHYTHM DISORDER IN MORVAN SYNDROME

Antibodies to voltage-gated potassium channels (VGKC-Abs) have been recognized in neuromyotonia, limbic encephalitis (LE), and Morvan syndrome (MoS),[1,2] a rare condition with insomnia, peripheral, and central and autonomic nervous system involvement. Clinical progression in MoS is variable, but potentially fatal. We describe a patient with VGKC-Abs-positive MoS who showed prominent compulsive behaviors, basal ganglia hypermetabolism, increased catecholamine and serotonin secretion, epileptic seizures, and cardiac and endocrine circadian rhythm suppression. A striking response to immunotherapy paralleled a marked reduction in VGKC-Abs over 15 months.

Case report. A 64-year-old man with idiopathic pulmonary fibrosis and polyarthrosis developed cramps, lower extremity pain, and sensory loss. Three years later, his sleep was disturbed by chewing, manual stereotypies, and sleep-talking. After an episode of tonic-clonic seizures, EEG revealed a temporal epileptic focus. He developed paroxysmal confusional episodes, with gesturing and irregular breathing, that were unresponsive to multiple anticonvulsants. He became irritable and hypomanic with overwhelming compulsive shopping and stealing. Urinary frequency, anosmia, impotence, and increased appetite appeared.

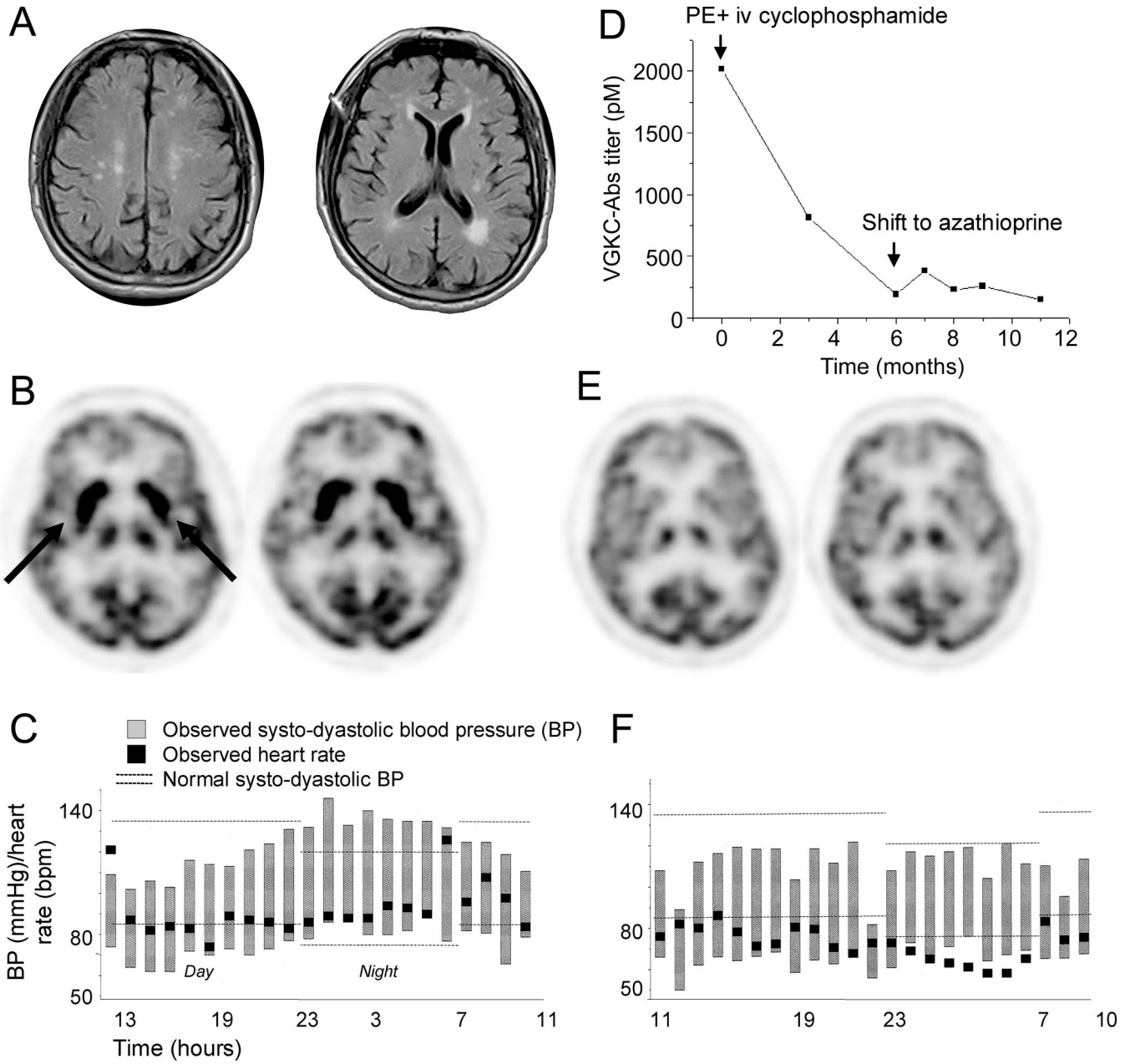
Examination showed bilateral postural tremor, multifocal myoclonus, lower extremity fasciculations, hypoesthesia, hyporeflexia, and mild proximal muscle atrophy. Laboratory investigations, including autoimmune and thyroid profile, were normal except for increased leukocytes, a raised erythrocyte sedimentation rate and creatine phosphokinase, mild hyponatremia, and antinuclear antibodies 1:160. CSF was negative for infections and 14.3.3 protein, but showed slightly increased proteins (66 mg/dL, nv <50) and matched serum/CSF IgG oligoclonal bands. Onconeural antibodies and the search for occult neoplasia proved negative. Brain MRI showed only nonspecific periventricular white matter lesions (figure, A), but brain ^{18}F-FDG-PET demonstrated markedly increased activity in the basal ganglia (figure, B). Repeated EEG showed only transient diffuse slowing.

On neuropsychological testing there was confusion, delusions, disorientation, confabulations, and reduplicative paramnesias with impairment in executive functions and language (table e-1 on the *Neurology*® Web site at www.neurology.org). EMG revealed peripheral neuropathy and peripheral nerve hyperexcitability, and muscle biopsy showed denervation, myopathic changes, and swollen sarcoplasmic reticulum on electron microscopy. Autonomic study, performed for persistent tachycardia and labile hypertension, demonstrated absent/inverted circadian rhythm of blood pressure, heart rate (figure, C), and temperature over 24 hours. Melatonin and prolactin circadian rhythms were also suppressed, whereas 24-hour urinary catecholamine and metabolites were increased (adrenaline 221 nmol, nv 5–110; noradrenaline 810 nmol, nv 40–600), and not inhibited by clonidine, as were urinary serotonin (2.2 μmol, nv 0–0.7) and 5-HIAA. Polysomnography demonstrated 23 critical episodes with polyspike-wave discharges corresponding to purposeless gesturing, and sleep fragmentation with REM sleep suppression (1.24%; nv ~25%). However, PRP gene analysis excluded fatal familial insomnia. He empirically received IV methylprednisone followed by oral prednisone with transient improvement, followed by neurologic deterioration and severe respiratory insufficiency. Corticosteroids were discontinued. Scaly, painful skin lesions appeared at the extremities.

The combination of subacute encephalopathy, insomnia, and neuromuscular involvement, however, led us to suspect MoS. This was supported by raised VGKC-Abs (2,016 pM, nv <100). Alternate day plasma exchange was performed for 2 weeks and then at monthly intervals for 8 months, with the addition of IV cyclophosphamide followed by azathioprine. After 15 months, VGKC-Abs had fallen to 130 pM (figure, D); the psychiatric abnormalities, fasciculations, and seizures disappeared and there was dramatic improvement in executive, logic, and linguistic functions (table e-1), paralleling ^{18}F-FDG brain PET normalization (figure, E). Peripheral neurotransmitters also normalized, while cardiac (figure,

Supplemental data at www.neurology.org

Figure VGKC-Abs, imaging, and cardiac rhythms before and after immunotherapy



(A) Axial brain MRI FLAIR images showing multiple nonspecific white matter lesions. (B) Pretreatment ^{18}F-FDG brain PET showing pathologically increased metabolism in basal ganglia. (C) Pretreatment 24-hour blood pressure and heart rate monitoring showing disruption of the circadian rhythm, with inversion of the physiologic nocturnal dipping. (D) Drop of VGKC-Abs titer over time after treatment with plasma exchange (PE) and IV cyclophosphamide shifted to azathioprine after 6 months. (E) Normalization of basal ganglia hyperactivity after 15 months of immunotherapy. (F) Post-treatment control showing normalization of the heart rate circadian rhythm and improvement of the blood pressure profile.

F), endocrine, and sleep rhythms improved substantially as well as olfaction.

Discussion. Neurohormonal abnormalities have been described in MoS.[2] We found a marked increase in peripheral catecholamines but also in serotonin which was reversed by immunotherapy. The observed neurochemical abnormalities might result from VGKC-Abs mediated neuronal hyperexcitability and neurotransmitter release.

Interestingly, some of the clinical MoS manifestations are reminiscent of serotoninergic[3] and catecholaminergic overstimulation. Monoaminergic brainstem nuclei project to different interconnected limbic-paralimbic subcortical regions (diencephalon, amygdala, hippocampus, basal ganglia, and suprachiasmatic nuclei) and frontal cortex. They may be involved in the disruption of behavior, REM sleep, neuroendocrine function, and rhythmicity,[4] dramatically responsive to im-

munotherapy in our patient, suggesting a likely role in MoS pathogenesis.

Basal ganglia hypermetabolism, unreported in MoS or LE, is reminiscent of PET findings in compulsive and psychotic disorders, with which our patient shared several features.[5,6] Nevertheless, drug-resistant seizures, not observed in MoS, but common in LE, confirm a continuum between these two conditions.

The clinical spectrum of VGKC-Abs-related disorders is rapidly expanding. They can mimic different neurodegenerative and psychiatric disorders, infectious, paraneoplastic, and nutritional encephalopathies, drug intoxications, and CNS lupus. Complex presentations including neurologic but also psychiatric, endocrine, and cardiac disturbance, should lead the clinician to consider an autoimmune, potentially treatable etiology, even in the presence of nonspecific brain imaging and CSF analysis, and apparent corticosteroid unresponsiveness.

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FETAL ACETYLCHOLINE RECEPTOR INACTIVATION SYNDROME AND MATERNAL MYASTHENIA GRAVIS

The fetal acetylcholine receptor (AChR) is present until 33 weeks gestation, when the fetal (γ) subunit is replaced by the adult (ε) subunit. Most infants of myasthenic mothers are asymptomatic despite intrauterine exposure to AChR antibodies (AChR Ab). A higher fetal to adult AChR Ab ratio can lead to transient neonatal myasthenia gravis (TNMG) in 10–15% of infants or rarely to arthrogryposis multiplex congenita (AMC). Here we report three brothers with facial diplegia, highly arched palate, velopharyngeal incompetence, conductive hearing loss, and cryptorchidism. The maternal fetal AChR Ab were elevated. We propose the term fetal acetylcholine receptor inactivation syndrome and suggest this phenotype results from inactivation of the fetal subunit during a critical period of fetal muscle development.

Case report. A 33-year-old woman developed ptosis, facial weakness, generalized fatigue, and elevated AChR Ab (>1,000, normal <0.4). Thymectomy, pyridostigmine, prednisone, and plasmapheresis improved her symptoms. Subsequently, she had three successive pregnancies with polyhydramnios and normal fetal movements while continuing prednisone. Each son was born at term by C-section with no respiratory distress.

During her first pregnancy, the mother received no plasmapheresis. At birth, the infant (figure, A) had hypotonia, poor suck, and inability to swallow. He remained in the neonatal intensive care unit (NICU) with TNMG for 5 weeks and improved with IV immunoglobulin (IVIg) and nasogastric (NG) tube feedings. At 5 years he has microcephaly, facial diplegia with inability to close mouth or eyes completely, excessive drooling, and hypernasal poorly intelligible speech. Brain MRI, serum CK, and repetitive median and accessory nerve stimulation at 3 Hz are normal.

During the second pregnancy, the mother received plasmapheresis biweekly after the first trimester. At birth, the infant (figure, B) had hypotonia and poor suck and swallow. He remained in the NICU with TNMG for 5 weeks and improved with NG tube feedings and IVIg. At 3 years he has facial diplegia, incomplete mouth and eye closure, excessive drooling, and hypernasal speech.

The third child (figure, C) is the least severely affected. The mother received plasmapheresis biweekly throughout pregnancy. At birth, he was hypotonic and sucked poorly but swallowed. He remained in the NICU with TNMG for 3 weeks,

Figure First child at age 6 years 10 months (A), second child at age 5 years (B), and third child at age 3 years 10 months (C)

The three brothers share the following characteristics, with decreasing severity from the eldest to the youngest: facial diplegia with incomplete mouth closure, highly arched narrow palate, excessive drooling, dysarthria, lingual weakness, bilateral middle ear effusion managed with myringotomy tubes, intact extraocular movements, and surgically corrected cryptorchidism and inguinal hernias; the second child has a bone conduction hearing aid.

improving with NG tube feedings. At 2 years he has mild facial diplegia, full mouth and eye closure, and mild speech difficulties.

All three siblings have normal neurobehavioral milestones, intact axial and limb muscle strength, pes cavus deformities, areflexia, no joint contractures, surgically corrected cryptorchidism and inguinal hernias, and middle ear effusions with conductive hearing loss managed with myringotomy tubes. The second child required bone conduction hearing aid. Serum, obtained from the mother when asymptomatic after her third pregnancy and assayed by radioimmunoassay,[1] was positive for AChR antibodies. The titer was 1,890 nM against fetal AChR and 157 nM against adult AChR (normal values <0.5 nM).

Discussion. We found nine other reported cases with persisting bulbar and facial weakness following TNMG.[2-6] In one report[6] maternal antibodies selectively inhibited the fetal AChR subunit. His mother had six further pregnancies all affected by lethal AMC while she remained clinically asymptomatic.

The maternal fetal/adult AChR Ab ratio is a stronger predictor of severity in offspring than the total AChR Ab. In our case, the maternal fetal AChR Ab titer was 10 times higher than the adult titer. More aggressive plasmapheresis treatment in the second and third pregnancies correlated with decreasing phenotypic severity. Another case report supports plasmapheresis therapy.[7] A myasthenic mother had two successive pregnancies culminating in AMC and neonatal death. Prednisone and plasmapheresis during her third pregnancy resulted in a newborn with TNMG only.

The persistent weakness of selective muscle groups in these children suggests a differential vulnerability during fetal development. Bidirectional signaling between the muscle and nerve modulates the maturation of the postsynaptic membrane. Fast and delayed synapsing muscle groups have heterogeneous synaptic maturation rates and distinct response patterns to disturbances in the agrin-MuSK pathway. Fetal AChR inactivation impairs fetal movements and neuromuscular development as seen with gamma mutant mice and humans with the lethal and Escobar variants of multiple pterygium syndrome. A fetal akinesia sequence model, developed by injecting plasma from a myasthenic mother with affected babies into pregnant mice, also has been reported.[1]

Mothers with a previously affected child have a risk for future pregnancies approaching 100% irrespective of their clinical symptomatology. These findings should be considered during prenatal counseling of myasthenic mothers. Long-term follow-up of infants with TNMG may identify previously unrecognized speech impairment and hearing loss.

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STROKE FOLLOWING PULMONARY ARTERIOVENOUS FISTULA EMBOLIZATION IN A PATIENT WITH HHT

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant disorder involving the vascular system. Two clinically indistinguishable forms are described, HHT1 and HHT2, caused by mutations in the *ENG* and *ALK1* genes.[1] Diagnosis is based on the presence of at least three of the four following symptoms: spontaneous epistaxis, cutaneous telangiectases, arteriovenous malformations in internal organs, and positive familial history. The main complications are severe anemia, portal and pulmonary hypertension, hypoxemia, brain abscesses, and stroke.[1,2]

Case report. A 17-year-old boy, with HHT for only past medical history, was admitted in the emergency department for an acute isolated aphasia. Neurologic examination was normal apart from the aphasia, which spontaneously resolved in 10 hours. A general examination was normal. This neurologic event occurred 48 hours after endovascular treatment of a pulmonary arteriovenous malformation (PAVM) identified 6 months before, following the occurrence of an abnormal dyspnea. The consecutive pulmonary investigations (chest X-ray and CT scan with angiography) had led to the detection of three PAVMs. Because of severe hypoxemia, endovascular treatment of the most important PAVM had been planned (figure, A and B). Embolotherapy was performed using first three mechanical detachable coils to ensure no migration before coil detachment, and then using several pushable coils with microfibers. Pretherapeutic brain MRI and MR angiography had ruled out a cerebral arteriovenous malformation and a previous cerebral ischemic event. No neurologic symptoms were reported during the procedure and until the patient was discharged 24 hours after PAVM embolization.

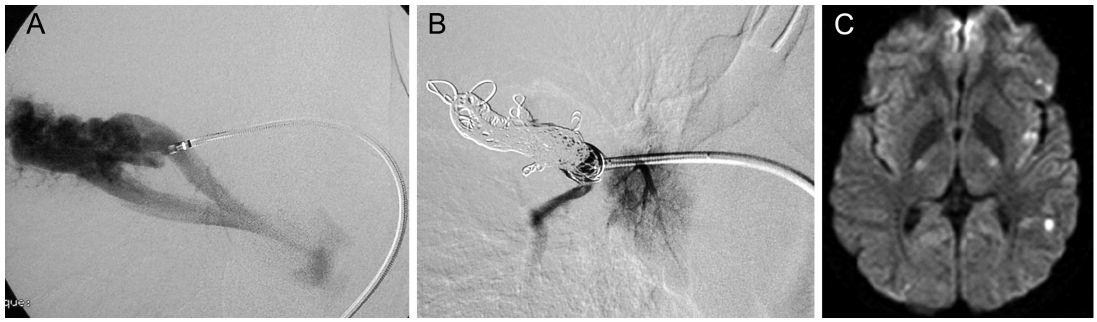
Brain diffusion MRI demonstrated several hyperintense cortical lesions (figure, C) in the territory of the left middle cerebral artery with low apparent diffusion coefficient values. MR angiography was normal. Standard biologic investigations were normal. Assessment of thrombophilia, including antithrombin III, C protein, S protein, factor VIII, and homocystinemia measurement, was negative. EKG and Holter EKG were normal. Transthoracic contrast echocardiography and transesophageal echocardiography (TEO) found a right-to-left shunt, and a patent foramen ovale (PFO) was evoked. PFO was ruled out during cardiac catheterization, and the right-to-left shunt was determined to be related to a persistent untreated PAVM.

Following this ischemic stroke an antiplatelet drug treatment (aspirin) was started; the initial dose of 250 mg PO daily was reduced to 75 mg because of epistaxis. This treatment was maintained for 6 months without side effects. No stroke recurrence was observed during this period. The patient is currently waiting for a new PAVM embolization.

The diagnosis of HHT was molecularly confirmed by identifying a heterozygous deletion of exon 2 to 10 of *ALK1* in this patient using quantitative multiplex PCR of short fragments.[1]

Discussion. Acute ischemic stroke, cerebral hemorrhages, bacterial meningitides, and cerebral abscess

Figure Pulmonary angiography showing a pulmonary arteriovenous malformation before (A) and after (B) embolization of endovascular material before stroke, and brain diffusion MRI demonstrating recent cerebral infarcts in the left middle cerebral artery territory (C)



are the main neurologic complications of HHT.[2] Among them, ischemic stroke and cerebral abscess are strongly related to the presence of PAVMs. During the last decade, PAVM embolization, a well-validated procedure, has demonstrated its ability to reduce the frequency of these complications. Nevertheless, this treatment can be associated with severe side effects such as infections, lung infarction, pleural pain and effusion, air embolism, cardiac arrhythmia, transient angina, and paradoxical embolization with cerebral infarction.[3]

In the present report, the short interval (48 hours) between PAVM embolization and stroke occurrence and the absence of any other stroke etiologic factor (large artery disease, PFO, thrombophilia) strongly suggest a potential link between these events.

The location of the lesions observed on MRI, the presence of a right-to-left shunt found on TEO, and the persistence of two PAVMs support the hypothesis of a paradoxical embolism through an unclosed PAVM or the treated PAVM itself in case of partial occlusion. In this context, clot, gas, or coil embolization can be evoked. Gas or coil embolisms are directly related to the procedure and therefore can be ruled out due to the delayed stroke occurrence.[2,3]

Several factors can contribute to increase the risk of paradoxical clot embolism following PAVM endovascular treatment in patients with HHT. First, patients with HHT have an increase of procoagulant factors such as factor VIII, D-dimer, and thrombin-antithrombin complex serum levels directly related to their disease.[4,5] Second, PAVM can induce a shunt-related hypoxemia that leads to polyglobulia and hyperviscosity. Third, endovascular treatment itself is associated with an increased plasma level of prothrombotic factors.[6] The combination of these factors increases the risk of thrombus formation whereas PAVM occlusion modifies the pressures in persistent PAVM, therefore increasing the risk of clot embolization.

In this context, antiplatelet drug use, such as low-dose aspirin, as primary stroke prevention during the days following endovascular PAVM embolization in patients with HHT should be evaluated. Defective platelet aggregation by adenosine diphosphate (ADP) and collagen adrenalin has been previously reported in HHT patients with severe bleeding.[7] Thus, checking platelet function with ADP- and collagen-induced platelet aggregation tests before using antiplatelet drugs seems to be mandatory in HHT.

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From the AAN History Library Collection
Gowers' *A Manual of Diseases of the Nervous System* (1888)

William Richard Gowers' (1845–1915) two-volume textbook, *A Manual of Diseases of the Nervous System* (1886, 1888), was often referred to as the "Bible of Neurology" and was one of the most influential and important neurology texts of the nineteenth century. The second volume, first published in 1888, consists of approximately 1,000 pages addressing the structure and function of the brain, cerebral localization, and various diseases of the cranial nerves, meninges, and brain. A considerable portion of the second volume was devoted to movement disorders, including a thorough and accurate description of the resting tremor and other clinical features of Parkinson disease, as well as detailed and insightful clinical descriptions of chorea, torticollis, tetanus, and writer's cramp. This sketch, from the second volume (1888) of Gowers' textbook,[1] shows the typical posture of "paralysis agitans" (Parkinson disease), a condition which had been described by his countryman, James Parkinson, some seventy years before in *An Essay on the Shaking Palsy* (1817).[2]

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