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Hereditary Hyperekplexia Overview

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Purpose

The goals of this overview on hereditary hyperekplexia (HPX) caused by dysfunction of glycinergic inhibitory transmission are the following.

Goal 1

Describe the clinical characteristics of hereditary hyperekplexia.

Goal 2

Review the genetic causes of hereditary hyperekplexia.

Goal 3

Provide an evaluation strategy to identify the genetic cause of hereditary hyperekplexia in a proband (when possible).

Goal 4

Inform genetic counseling of family members of an individual with hereditary hyperekplexia.

Goal 5

Review management of hereditary hyperekplexia.

1. Hereditary Hyperekplexia: Clinical Characteristics

Hereditary hyperekplexia (HPX), an inherited neuronal disorder caused by genetic defects leading to dysfunction of glycinergic inhibitory transmission, is characterized by the clinical core features of exaggerated startle responses to unexpected sensory stimuli and stiffness. HPX, a rare and underdiagnosed disorder, is

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manifest immediately after birth and commonly improves with age [Paucar et la 2018]. Establishing the correct diagnosis early is essential so that proper management may be initiated to alleviate stiffness and reduce the risk of complications, such as potentially life-threatening apnea during episodes of stiffness.

The term hyperekplexia is used to denote excessive or exaggerated startle that typically does not habituate. Hyperekplexia can be an acquired feature of many disorders, particularly when there is pontine pathology; it may also be observed in infants and children with complex genetic disorders associated with developmental delay/intellectual disability often resulting from an inborn error of metabolism or brain malformation (see Differential Diagnosis).

HPX Core Features

Excessive startle response (typically eye blinking and a flexor spasm of the trunk) to unexpected, innocuous (particularly auditory) stimuli, the most striking feature of HPX, is present from birth or even noted prenatally in the last trimester [Thomas et al 2013]. In contrast to a physiologic startle response, the excessive startle leads to prolonged stiffening in the neonate and young infant [Gherpelli et al 1995, Vergouwe et al 1997, Koning-Tijssen & Brouwer 2000]. Consciousness is unaltered during startle responses, and the responses do not represent epileptic seizures.

The frequency of startle responses varies considerably among individuals and over time, and often disappears or remits with medication between infancy and adolescence [Mine et al 2015].

Factors that increase the frequency of the startle responses include emotional tension (even the expectation of being frightened), nervousness, and fatigue. Holding objects or drinking alcohol reduces the intensity and frequency of startle responses.

The exaggerated head-retraction reflex (HRR) is an exaggerated startle response to tactile stimuli and is elicited by gentle taps particularly to the tip of the nose, but also to the nose ridge, the glabella, upper lip, and chin [Wartenberg 1941]. The reaction is non-habituating and comprises neck extension. Note that HRR is not specific to HPX and has also been described in acquired hyperekplexia and other disorders.

The excessive startle reflex has major implications for daily life as it cannot be suppressed and unexpected stimuli from the outside world cannot be regulated. This is a prominent problem for some infants when the simple activities of feeding or being dressed produce paroxysms of startle responses. In later life, the excessive startle reflex and associated generalized stiffness increase the risk of falls and injury.

Stiffness. The two main types of stiffness in relation to HPX are generalized continuous stiffness from birth on and stiffness induced by startle that may persist into adulthood.

- **Generalized stiffness apparent immediately after birth.** The stiffness increases with handling and disappears during sleep. Held horizontally, the baby is as "stiff as a stick" – therefore, the disorder is also called stiff-baby syndrome. The baby is alert but shows few spontaneous movements [Koning-Tijssen & Brouwer 2000]. Handling a baby, for example when changing diapers, is difficult because spreading of the legs is limited by stiffness.

  The generalized stiffness evident immediately after birth usually normalizes during the first years of life (by age 2 years; range: 0.7-5 years) [Mine et al 2015].

- **Generalized stiffness following the startle response** means that for a short period, affected individuals become stiff and voluntary movements are impossible [Bernasconi et al 1996]. Startled individuals may fall "like a log," with the stiffness preventing them from putting out their arms to safeguard themselves, resulting in an increased risk of injuries [Tijssen et al 2002, Thomas et al 2013, Mine et al 2015, Lee et al

2017]. This may persist into adult life. Affected individuals may have a cautious, stiff-legged, broad-based gait (but without signs of ataxia; see video at Zhang et al [2019]; full text).

Other complications of severe attacks of stiffness:

- Episodes of tonic neonatal cyanosis (i.e., attacks of apnea in neonates with HPX) [Vergouwe et al 1997, Miraglia Del Giudice et al 2003, Rees et al 2006, Rivera et al 2006]. Akin to the generalized stiffness, attacks of tonic neonatal cyanosis often resolve during infancy [Rees et al 2006]. The association with sudden infant death syndrome underlines the importance of early diagnosis and treatment [Nigro & Lim 1992].
- Frequent occurrence of inguinal, umbilical, or epigastric hernias, paralytic ileus, and congenital dislocation of the hip [Mine et al 2015]

Associated features that may be present include the following:

- In some children, delayed motor milestones and mild developmental delay or learning difficulties (particularly speech acquisition); children later catch up [Thomas et al 2013].
- Periodic limb movements in sleep (PLMS) and hypnagogic myoclonus (myoclonus occurring when falling asleep)
- Epilepsy; estimated prevalence in hyperekplexia of 7%-12% [Thomas et al 2013]

Differential Diagnosis

The differential diagnosis of abnormal startle can be divided into the following:

- Conditions with an abnormal, exaggerated startle including:
  - Complex genetic neurodevelopmental disorders
  - Acquired causes

  Note: It is this group of disorders that is most likely to be confused with hereditary hyperekplexia resulting from dysfunction of glycinergic inhibitory transmission.
- Conditions in which the startle response per se is normal, but the startle is triggering the actual disease-defining symptoms
- Neuropsychiatric syndromes, in which startle may be excessive and can be followed by additional manifestations

Conditions with an Abnormal, Exaggerated Startle

Complex genetic neurodevelopmental disorders in which an excessive startle response in infants and children can be associated with developmental delay/intellectual disability often resulting from an inborn error of metabolism or brain malformation (with or without microcephaly and/or epilepsy) (Table 1) are distinct from hereditary hyperekplexia and will not be discussed further in this overview.

Table 1. Complex Genetic Neurodevelopmental Disorders with an Excessive Startle Response

Gene	Disorder	MOI	Distinguishing Clinical Features	Reference [1]
ARHGEF9	Early-infantile epileptic encephalopathy 8	XL	• Severe ID • Epilepsy (often intractable focal seizures or febrile seizures) • Dysmorphic features	OMIM 300607

Table 1. continued from previous page.

Gene	Disorder	MOI	Distinguishing Clinical Features	Reference [1]
ASNS	Asparagine synthetase deficiency	AR	• Profound DD & progressive encephalopathy • Microcephaly • Hypotonia followed by spastic quadriplegia • Seizures	Asparagine Synthetase Deficiency
CACNA1A	Early-infantile epileptic encephalopathy 42	AD	• Epileptic encephalopathy w/myoclonic epilepsy • Myoclonic seizures provoked by tactile stimuli & spontaneous & reflex seizures to noise & touch	OMIM 617106
CLPB	CLPB deficiency (3-methylglutaconic aciduria)	AR	• Congenital or infantile cataracts • Neutropenia • Other neurologic signs: hypotonia, spasticity, ataxia, dystonia, epilepsy, or ID	CLPB Deficiency
CRLF1	Crisponi syndrome	AR	• Dysmorphic features, camptodactyly • Facial & bulbar weakness	Cold-Induced Sweating Syndrome Including Crisponi Syndrome
CTNNB1	*CTNNB1*-related syndrome	AD	• Hyperekplexia is rare in this entity (single case report) • Later onset of hyperekplexia (not congenital but in childhood) & atypical pattern (no generalized stiffness induced by startle) • No congenital stiffness • Progressive neurologic involvement w/ additional signs (ID, ataxia, spasticity) • Microcephaly	CTNNB1 Neurodevelopmental Disorder
GPHN	Molybdenum cofactor deficiency, complementation group C	AR	• Intractable seizures • Severe psychomotor retardation • Hypotonia combined w/hyperreflexia • Usually lethal in infancy	Molybdenum Cofactor Deficiency
HEXA	Tay-Sachs disease	AR	• DD or regression • Visual impairment • Epilepsy • Later: macrocephaly, decerebrate posturing, dysphagia, progression to unresponsive vegetative state	Hexosaminidase A Deficiency
RPS6KA3	Coffin-Lowry syndrome	XL	• ID • Facial dysmorphism, tapering digits, & skeletal deformity • Besides hyperekplexia, there may be other types of stimulus-induced drop attacks (e.g., cataplexy-like episodes)	Coffin-Lowry Syndrome
SCN8A	Early-infantile epileptic encephalopathy 13	AD	Epileptic encephalopathy w/DD & ID	*SCN8A*-Related Epilepsy with Encephalopathy
SLC6A9	GLYT1 encephalopathy	AR	• Hypotonia > hypertonicity • Arthrogryposis • Respiratory failure • Dysmorphic features • Encephalopathy	GLYT1 Encephalopathy

Table 1. continued from previous page.

Gene	Disorder	MOI	Distinguishing Clinical Features	Reference [1]
SUOX	Isolated sulfite oxidase deficiency	AR	• Progressive epileptic encephalopathy • Other neurologic features: opisthotonus, spastic quadriplegia, pyramidal signs • Microcephaly, dysmorphic features	Isolated Sulfite Oxidase Deficiency
TRAK1	Early-infantile epileptic encephalopathy 68	AR	• Hypotonia • Progressive epileptic encephalopathy	OMIM 618201
TSEN54	Pontocerebellar hypoplasia type 2	AR	• Generalized clonus ("jitteriness") • Delayed developmental (motor & cognitive) milestones • Other neurologic signs: spasticity, chorea, visual impairment, epilepsy	*TSEN54*-Related Pontocerebellar Hypoplasia

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. OMIM phenotype entry or citation is provided if a related *GeneReview* is not available

Acquired causes of excessive startle

- **Structural and other causes of brain stem dysfunction** can include post-anoxic reticular myoclonus, infarct, hemorrhage, medullary compression, posterior fossa malformations, neurodegeneration (multisystem atrophy, lateral sclerosis), and infectious or autoimmune encephalitis (reviewed in Balint et al [2018]) including multiple sclerosis [Abboud et al 2019].
- **Infection.** The most important infectious cause is tetanus, a potentially lethal disorder caused by the toxin of *Clostridium tetani* which degrades synaptobrevin and thereby prevents neurotransmitter release for glycinergic inhibition. The latter is the common end route with HPX, explaining the phenotypic similarities.
- **Glycine receptor antibodies** (targeting the same protein affected by pathogenic variants in *GLRA*) are an autoimmune cause of exaggerated startle and stiffness [Hutchinson et al 2008] and may manifest as brain stem encephalitis or a variant of stiff person spectrum disorder (SPSD), such as progressive encephalomyelitis with rigidity and myoclonus [Balint & Bhatia 2016]. However, SPSD is also seen with glutamic acid decarboxylase, amphiphysin, or DPPX antibodies. They share as core features stiffness, spasms, and hyperekplexia (in varying degrees and body distribution). Onset is typically in adulthood, although infantile onset has been described by Damásio et al [2013]. Other features distinguishing SPSD from HPX are the mostly continuous and prominent muscle stiffness, sometimes co-occurring neurologic signs, and often a strong association with other autoimmune diseases.
- **Strychnine** is a competitive inhibitor of the postsynaptic glycine receptor. Strychnine poisoning causes acute onset of stiffness, spasms, and hyperekplexia.

Startle-Induced Manifestations in Other Disorders

In this diverse group of disorders, the startle reflex itself is not excessive, but rather induces another clinical feature that is more prominent and characteristic than the startle response [Dreissen & Tijssen 2012]. Examples include the following:

- Startle epilepsy (normal startle triggers seizures)
- Paroxysmal kinesigenic choreoathetosis (See *PRRT2*-Associated Paroxysmal Movement Disorders; startle can be one of many triggers of sudden movements.)
- Creutzfeldt-Jakob disease (See Genetic Prion Disease.)
- Subacute sclerosing panencephalitis

Neuropsychiatric Startle Syndromes

In addition to excessive startling, behavioral and/or psychiatric findings are observed in the following groups of disorders:

- Culture-specific syndromes, in which an exaggerated startle response, evoked by auditory, sensory, or visual stimuli occurs within a community [Meinck 2006]. The initial brief component of the startle reflex is normal, but the secondary orientating response includes abnormal behaviors such as jumps, echopraxia, or echolalia, spontaneous vocalizations including coprolalia, and automatic execution when startled with vigorous commands ("forced obedience").
- Anxiety disorders, functional neurologic disorders
- Tics and Gilles de la Tourette syndrome, in which an exaggerated startle reflex has been described in some, but not all, affected individuals

2. Hereditary Hyperekplexia: Causes

To date, three genes are known to be associated with hereditary hyperekplexia (HPX): *GLRA1*, *GLRB*, and *SLC6A5*. Genetic defects in these genes result in dysfunction of glycinergic inhibitory transmission. The relative contribution of each of these three genes to HPX (based on data on 97 individuals with confirmed *GLRA1*-, *GLRB*-, or *SLC6A5*-HPX [Thomas et al 2013]), the modes of inheritance, and methods of pathogenic variant detection are summarized in Table 2.

Table 2. *GLRA1*, *GLRB*, and *SLC6A5*-Related Hereditary Hyperekplexia: Modes of Inheritance and Methods of Variant Detection

Gene	Proportion of HPX Attributed to Mutation of Gene	MOI [1]	Proportion of Probands with a Pathogenic Variant Detectable by Method [2]	
			Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]
GLRA1	61%-63%	AD & AR	~95%	See footnote 5.
GLRB	12%-14%	AD & AR	11/12	1/12 [6]
SLC6A5	25%	AR (rarely AD [7])	24/24	None reported

AD = autosomal dominant; AR = autosomal recessive; HPX = hereditary hyperekplexia; MOI = mode of inheritance

1. ~85% were AR and ~15% were AD [Thomas et al 2013].

2. Since the study of Thomas et al [2013], additional affected individuals have been reported, many as case studies. For additional reported variants, see Human Genome Mutation Database [Stenson et al 2020].

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications

5. Deletion of exons 1 through 7 is common in the Turkish population [Thomas et al 2015]. Deletion of exons 1 through 6 [Brune et al 1996] and of 4 through 7 have also been reported [Chung et al 2010].

6. Chung et al [2013]

7. Rees et al [2006]

Phenotype Correlations by Gene

The following were observed in the study of Thomas et al [2013]:

- Individuals with *GLRB*-HPX or *SLC6A5*-HPX were more likely to have developmental delay (RR1.5 P<0.01; RR1.9 P<0.03) than those with *GLRA1*-HPX, whereas 92% of individuals reported with *GLRB*-HPX had mild-to-severe delay in speech acquisition.

- Children with *SLC6A5*-HPX were significantly more likely to have had recurrent infantile apnea (RR1.9; P<0.005) than those with *GLRA1*-HPX.
- Individuals without a molecularly confirmed diagnosis of HPX compared to those with a molecular diagnosis were more likely to have first clinical manifestations after age one month (P<0.001). In contrast, the characteristic "stiffness, startles, and stumbles" of hyperekplexia, apnea attacks (50 of 89), and delayed development (47 of 92) were frequently reported in both groups.
- Individuals with a molecularly confirmed diagnosis of HPX typically are not dysmorphic and brain imaging reveals a structurally normal brain.

3. Hereditary Hyperekplexia: Evaluation Strategy to Identify the Genetic Cause in a Proband

Establishing a specific genetic cause of HPX can aid genetic counseling (see Section 4). Establishing the genetic cause of HPX in a proband usually involves family history and genomic/genetic testing.

Family history. A three-generation family history should be obtained, with attention to relatives with HPX and documentation of relevant findings through direct examination or review of medical records including results of molecular genetic testing. Identify "sudden infant deaths" that may have been caused by apnea.

Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel or single-gene testing) and comprehensive genomic testing (exome sequencing, exome array, or chromosomal microarray analysis [CMA]). Some pathogenic variants are more common in some geographic regions and population groups [Thomas et al 2015]. Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **Serial single-gene testing** can be considered if family history indicates that pathogenic variants in a particular gene are most likely (see Table 2). Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis in the following order: *GLRA1*, *SLC6A5*, and *GLRB*. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *GLRA1*, *GLRB*, and *SLC6A5* is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 2).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

4. Hereditary Hyperekplexia: Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

GLRA1- and *GLRB*-related hereditary hyperekplexia (HPX) can be inherited in an autosomal recessive or, less commonly, an autosomal dominant manner (Table 2). *SLC6A5*-HPX is inherited in an autosomal recessive manner (autosomal dominant inheritance of *SLC6A5*-HPX has been reported in one family). General genetic counseling issues regarding autosomal dominant and recessive inheritance are discussed in this section.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of a child with autosomal recessive HPX are obligate heterozygotes (i.e., presumed to be carriers of one *GLRA1*, *GLRB*, or *SLC6A5* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for an autosomal recessive HPX-causing pathogenic variant and to allow reliable recurrence risk assessment. (*De novo* variants are known to occur at a low but appreciable rate in autosomal recessive disorders [Jónsson et al 2017].)
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing hyperekplexia.

Sibs of a proband

- If both parents are known to be heterozygous for an autosomal recessive HPX-causing pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive HPX are obligate heterozygotes (carriers) for a pathogenic variant.

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the pathogenic variants in the family.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant HPX have an affected parent.
- In rare cases, an individual diagnosed with autosomal dominant HPX has the disorder as the result of a *de novo GLRA1* or *GLRB* pathogenic variant [Miraglia Del Giudice et al 2003, James et al 2013, Horváth et al 2014].
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.

- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant; another possible explanation is germline mosaicism in a parent (though theoretically possible, no instances of parental germline mosaicism have been reported).

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of having the same pathogenic variant is 50%. However, because autosomal dominant hereditary hyperekplexia is not 100% penetrant, sibs who inherit a pathogenic variant may or may not manifest features of HPX [Sprovieri et al 2019].
- If the proband has a known pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for hereditary hyperekplexia because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant HPX has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, the parent's family members may be at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the HPX-causing pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Library of Medicine Genetics Home Reference**
  Hereditary hyperekplexia

5. Hereditary Hyperekplexia: Management

Treatment of Manifestations

Clonazepam is the treatment of choice for HPX [Tijssen et al 1997, Tsai et al 2004, Thomas et al 2013, Mine et al 2015]. The stiffness in the neonatal period and stiffness related to startle diminish with the treatment. Suggested daily doses are 0.01 to 0.1 mg/kg for children and 0.8 mg/d for adults [Mine et al 2015].

Other drugs, mostly described in case reports, which have shown variable results include: carbamazepine, clobazam, phenytoin, diazepam, valproate, 5-hydroxytryptophan, piracetam, and phenobarbital. For an overview see Bakker et al [2006].

Physical and cognitive therapy to reduce the fear of falling and thereby improve walking can be considered; no randomized trials have assessed the effectiveness of such treatment.

Attacks of tonic neonatal cyanosis can be stopped by the Vigevano maneuver, consisting of forced flexion of the head and legs towards the trunk [Vigevano et al 1989].

Chapter Notes

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