Neurological manifestation and genetic diagnosis of Angelman, Rett and Fragile-X syndromes

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Abstract

Objective: to discuss clinical and electroencephalographic aspects and the genetic mechanisms of three neurogenic syndromes that can be related to nosologic entities in the heterogenic pathological group presenting symptoms of mental retardation and autism.

Sources: the authors carried out a bibliographic review on each syndrome involved, correlating and characterizing the neurological manifestations, as well as describing genetic mechanisms and identifying biological markers.

Summary of the findings: the authors were able to confirm that Rett Syndrome is a genetic disease resulting from the mutation of the MECP2 gene and clinical variations can be explained by different mutations in this gene. Angelman syndrome has four genetic mechanisms responsible for phenotypic variations and different risks of recurrence. In Fragile-X syndrome, the degree of cognitive impairment is related to the number of trinucleotide repeats.

Conclusions: different genetic mechanisms of the three syndromes are responsible for clinical variability. By identifying the biological markers, the diagnosis will be performed earlier and it will be possible to identify new subtle expressions of the disease.


Introduction

Some neurogenetic syndromes do not present any relevant dysmorphic alterations, having behavioral and electroencephalographic (EEG) features as the most important traits for clinical identification. This is the case of Rett syndrome, Angelman syndrome and fragile X syndrome. What these disorders have in common is their association with mental retardation and autism; however, in addition to the variability in phenotype, there are specific clinical manifestations required for the diagnosis of each of these entities, which sometimes appear only after a long time. In terms of etiological investigation, genetics offers a remarkable contribution, with the identification of biologic markers which enable early diagnosis as well as the recognition of mild or atypical forms of these syndromes.

Rett syndrome

Rett syndrome (RTT) is a neurodegenerative disease named after Austrian pediatrician Dr. Andreas Rett, the first to describe the disorder, in 1966. However, it was not until 1983 that RTT became known to the medical community, after Hagberg et al.1 published a series of 35 cases. Until
recently, the etiology of RTT was unknown, and diagnosis was based on clinical criteria only. In 1999, the identification of a methyl-CpG-binding protein 2 (MECP2) gene mutation in a large number of patients with a clinical diagnosis of RTT confirmed the genetic basis of this syndrome.\(^2,^3\)

**Epidemiology**

Initially, RTT was thought to be a rare disorder. However, several studies estimate a frequency of 1 in 10,000 to 15,000 female births.\(^4\) RTT is considered to be one of the main causes of mental retardation in girls, with manifestations of autism in its final stages. It has been described in several ethnic populations and in several parts of the world. RTT is thought to be the result of a recent mutation, with an X-linked, dominant mode of inheritance, affecting mainly females. Although RTT usually causes death in males, there have been published reports of boys with an RTT phenotype and karyotype 47, XXY. In addition, the MECP2 gene mutation has been identified in boys with severe neonatal encephalopathy.\(^5,^6\)

**Diagnosis of classic RTT**

RTT diagnostic criteria were established with the aim of achieving the required uniformity for clinical and epidemiological studies.\(^7\) Although several patients with classic RTT present most signs, if not all, clinical diagnosis is still possible in the absence of all supporting criteria, especially in younger individuals. These diagnostic criteria, first published in 1988, are restrictive and above all serve to identify patients with the classic form of RTT, with the objective of selecting a homogeneous population which could be useful for the identification of a biologic marker. Following the identification of a biologic marker, it is necessary to investigate all children presenting some of these typical features.

**Diagnostic criteria**

- apparently normal pre- and perinatal periods;
- apparently normal psychomotor development in the first six months;
- normal cephalic perimeter (CP) at birth;
- slowing down of CP increase between six months and four years (acquired microcephaly);
- temporary loss of the ability to use hands and loss of ability to communicate between six and thirty-six months;
- hand stereotypy;
- apraxia/ataxia;
- other diagnostic attempts between two and five years.

**Supporting criteria**

- breathing irregularities (hyperventilation/apneas);
- EEG anomalies;
- epileptic crises;
- spasticity and dystonias;
- scoliosis;
- delayed growth;
- limb atrophy (foot and peroneus);
- vasomotor disorders.

Although these diagnostic criteria are useful for the recognition of classic RTT, it is important to be alert for atypical forms of RTT, in which some of these signs are absent, and whose diagnosis can only be confirmed with the identification of a biological marker.

RTT is a progressive encephalopathy with four different clinical stages determined by age at onset and predominance of some clinical traits. The development in stages and the duration of each stage do not follow a regular pattern in all children. Some individuals reach puberty without presenting clinical features beyond stage III; others evolve quickly from stage II to IV. The classification of RTT in clinical stages, proposed by Witt-Engerstrom in 1990,\(^8\) differs from the previous classification\(^9\) especially because it places emphasis on the child’s ability to walk.

**Stage I or early onset stagnation period:**

- between five and 24 months;
- lasts for months;
- characterized by delay or absence of acquisition of new stages of motor development, loss of interest in games or play, poor social interaction, change in personality and slowing down of cranial growth.

**Stage II or rapid developmental regression**

- begins between age one and three years, until age four to five years;
- lasts for weeks or months;
- characterized by loss of previously acquired abilities, autistic manifestations, severe dementia, loss of language, hand stereotypy (Rett-type), loss of the ability to use hands (hand apraxia), irregular breathing and periods of hyperpnea.

**Stage III or pseudostationary period**

- begins at preschool or school age;
- lasts for years;
- may or may not evolve to the next stage;
- characterized by slow progression of signs and symptoms, discrete improvement of social interaction and expression of emotional aspects, severe mental retardation, signs of motor dysfunction (hyper-reflexia, spasticity), hand stereotypy, hyperventilation episodes, prominent ataxia/apraxia, weight loss, bruxism, and epileptic crises.
Stage IV or late motor impairment:
- begins after loss of ability to walk;
- lasts for decades;
- characterized by major motor impairment, with tetra or paraparesis and postural deformities (equine foot) which prevent or restrict walking. Scoliosis and trophic or vasomotor disturbances are frequent.

Clinical diagnosis
Due to the variability in clinical presentation, the main aspect to be considered in the clinical diagnosis of RTT is disease evolution, which depends on age and stage of the disease at the moment of evaluation.

The most striking features of RTT are not present at initial stages, and children are often misdiagnosed as carriers of autism and/or delay in psychomotor development.

Infantile autism is the most common diagnosis made in girls with RTT between one and three years of age, when there is a predominance of autistic features and the pattern of stereotypy is not specific to RTT. Although the characteristics of autism are not among the diagnostic criteria for RTT, certain manifestations, such as lack of socialization, isolation, absence of verbal and non-verbal communication, occur until four or five years (start of stage III, pseudostationary), when they become attenuated or disappear. However, some peculiar behavioral characteristics of RTT help distinguish this disorder from infantile autism. RTT must be considered in all girls diagnosed with autism who maintain eye contact and smile, have an expressive gaze, do not roll or grasp small objects, or do it for short periods of time only.

With the development of the disease, after four years, on average, more specific features of RTT appear and a differential diagnosis can be reached without difficulty. Rett-type hand stereotypy, characterized by movements of washing or wringing hands; tendency to keep the hands close to the mouth (mouthing); and periods of apnea and hyperventilation; help the recognition of children with RTT. Hand stereotypies mark the beginning of stage II, and precede the loss of the ability to use the hands, one of the most striking features of RTT. Although these signs are very common in RTT and this should be the main diagnostic hypothesis if they are present in girls, they are not specific only to RTT, and are also observed in children with mental retardation due to other causes.

Starting at four-five years until the beginning of adolescence, children with Rett syndrome develop with slow progression of clinical manifestations, and some improve in terms of social interaction; however, from a cognitive point of view, they behave as a severe case of mental deficiency. There are striking stereotypies and worsening of gait features, with an ataxic-apraxic pattern and a tendency to tip-toeing. At this stage, called pseudostationary, epileptic crises frequently appear.

Epilepsy occurs in 50 to 80% of the children affected. There is variability in the presentation and severity of epileptic crises. The most frequent are partial motor and psychomotor crises, tonic and generalized atypical absent spells. West syndrome may be the first sign in RTT with early onset epilepsy. Children with RTT present episodes of apnea and dystonic posture which may be interpreted as epileptic crises. Such episodes may frequently precede true crises, and should not be interpreted as a critical manifestation. With advancing age and the progression of the disease, at stage IV the crises often subside, and sometimes the epilepsy becomes inactive.

The last stage is defined only by the inability to walk because the capacity to do so was progressively lost or because adolescence was reached without this capacity being acquired. About 20% of the children do not lose their ability to walk and therefore remain in the pseudostationary stage. Eighty percent lose their ability to walk or never acquire it. These present a poorer prognosis with a rapid evolution from stage II to IV.

EEG features
The EEG is the only ancillary exam that is frequently abnormal in RTT. Although not specific to RTT, EEG alterations are sufficiently characteristic to contribute towards a diagnosis of RTT. At initial stages, for example, when the most typical features of RTT have not yet appeared, the presence of EEG abnormalities may suggest the possibility of RTT in girls diagnosed with autism.

The most frequent EEG abnormalities observed are epileptiform discharges, which may or may not precede epileptic crises. In most children, they appear starting at three years of age, but they may also occur earlier. Frequently, these are spikes or multifocal sharp waves; however, there is a predominance in central regions, and sometimes in centrotemporal regions in one or both brain hemispheres. The frequency increases during light sleep, and in young children they are restricted to sleep stages I and II. The discharges may be asymmetric in distribution, sometimes affecting predominantly one of the hemispheres. They are either infrequent and low-frequency, or frequent and repetitive, in this case usually presenting high amplitude. This same EEG pattern is also found in several other diseases, such as, for example, in benign epilepsy of childhood with centrotemporal (rolandic) spikes. Discharges of the spike-and-slow wave complex (2-3 cycles/second) have also been described. In central regions, spikes may be evoked by tactile stimulation of the hands and blocked by passive moving of the hands.

In addition to epileptiform discharges, other EEG findings may be observed in RTT patients. With the development of the disease, there is a progressive disorganization of the base activity during wake-sleep periods, with disappearance of the alpha rhythm and sleep...
phases, sometimes predominantly in one of the hemispheres. The presence of rhythmic activity is also frequently observed in RTT, at the frequency of 3 to 5 Hz, during wake periods, sleepiness and sleep (more frequent during sleepiness); and slower activity (2-4 c/s) is observed during sleep.10

EEG alterations are associated with RTT clinical stages. An evolving EEG pattern can be recognized: usually, EEG is normal in RTT stage 1; in stage 2, disorganized base rhythms are observed, with excessively slow activity and epileptiform discharges, frequent and maximal in central regions; stage 3 is associated with more marked deterioration of the base activity, frequent multifocal spikes and rhythmic activity during wake and sleep periods; and stage 4 is associated with low voltage background activity.12

**RTT variants**

The RTT phenotype in girls is more heterogeneous than what was originally described. Current knowledge suggests the existence of a clinical spectrum for the syndrome, which varies from severe cases, with the classic presentation, to milder variants. Clinical variants are identified in patients who present some of the classic RTT signs/symptoms, but which show considerable variation in terms of type and age at onset, severity of clinical manifestations, and clinical course. These phenotypic variations of RTT include the forme fruste, early onset epilepsy, congenital RTT, late onset RTT, and the preserved speech variant.14 These conditions can be characterized as subgroups of a “Rett complex,” with the classic form (80% of the cases) and the preserved speech form being the most frequent.15 However, the hypothesis that the elevated frequency of these forms is related to the fact that they are more easily recognizable must be considered.

**Physical therapy**

Although RTT is a progressive neurodegenerative disease, affected children respond to physical therapy with acquisition of motor functions. The training of walking is one of the objectives of physical therapy. With adequate therapy, most patients are able to acquire, maintain or recover the ability to walk.

**Genetic mechanisms**

RTT is an X-linked inherited disorder. The mutation is located on the long arm of the X chromosome (Xq28).16,17,19 In 1999, an MECP2 gene mutation was identified in patients with classic RTT.19 Since then, over 20 mutations have been described,20 and the variability of clinical presentation has been associated with the allele variation.21 The diagnosis of RTT may be reached using PCR techniques to identify the molecular alteration.

**Angelman syndrome**

**Clinical manifestations**

Angelman syndrome (AS), named after British pediatrician Harry Angelman, was first described in 1967, but its clinical features were not established until 1995. The clinical features observed in all children with AS are: a marked delay in psychomotor development since childhood, severe language and mental impairment, gait ataxia, myoclonic-type involuntary movements in association with a peculiar happy behavior, with unexplained laughs, puppet-like swinging of hands, hyperactivity and attention deficit. Around 80% of the patients present epileptic crises, characteristic EEG patterns and microcephaly. The dysmorphic alterations are discrete and extremely variable in frequency. The most common are: triangular face, prognathism, macrostomia, widely spaced teeth, protruding tongue, and hypopigmentation. Sleep disturbances and hypersensitivity to heat have also been described.22

As in RTT, the development of the most marked features in AS, which allow clinical identification, takes some time. There is also age-related phenotypical variation in AS. It is not until the second and third years of life that the most common dysmorphic features, such as the peculiar behavioral profile, become evident.23 However, highly characteristic EEG alterations precede the clinical manifestations and epilepsy, and may contribute towards the early diagnosis of AS, which currently can also be reached through laboratory assays.

In AS, epilepsy does not present a specific pattern, and several types of crises may occur. The most frequent are crises with myoclonal jerks and atypical absence and partial crises. The age at onset is also variable (four months to five years), and remission may occur at any age. Febrile convulsions occur in 30% of the patients.23,24

Similarly to RTT, AS is a cause of mental retardation that is frequently unrecognized. The diagnosis of AS should be considered in all patients with severe mental retardation associated with epilepsy. These two syndromes present an overlapping clinical presentation whose most common manifestation, in addition to the severe mental retardation, include autism, microcephaly, speech disorders, ataxia/apraxia, hand stereotypes, and occasionally a similar physical appearance.

**Genetic mechanisms**

AS (similarly to Prader-Willi syndrome, PWS), is a striking example of genomic imprinting involving deletion of the long arm of chromosome 15 (15q11-q13). When the chromosome carrying the deletion is inherited from the father, SPW develops. In these children, the genetic information in 15q11-q13 is derived only from the maternal chromosome. On the contrary, when the chromosome carrying the deletion is inherited from the mother, the offspring will develop AS, with genetic material derived only from the paternal chromosome. This clearly shows that
the parental origin of the genetic material will deeply influence clinical expression in the affected child.

As with genetic imprinting, studies of AS and PWS have contributed towards increasing the knowledge about uniparental disomy, suggesting that normal human development requires that the genes in the 15q11-q13 region be inherited from both parents.

In AS, the great majority of cases are sporadic, but there are a few rare familial cases. In 75 to 80% of the cases, the deletion of the 15q11-q13 band of maternal chromosome 15 can be observed at a molecular level. This deletion may also be shown at a cytogenetic level, using FISH, in 50% of the cases.25 In all other patients, the disease results from mutations in the UBE3A gene, which encodes a ubiquitin protein ligase (20%), altering the imprinting through deletion/mutation in the imprinting center (2 to 6%), or through uniparental disomy of paternal chromosome 15 (rare).

Since AS has multiple causes, some aspects must be considered for genetic counseling. The cases resulting from deletion and uniparental disomy have a low recurrence rate (1%); in cases resulting from a UBE3A gene mutation and from mutation of the imprinting center, inherited from the mother, the risk of recurrence may be as high as 50%.26 The potential risk for recurrence and the association between severity of clinical presentation and molecular alteration have already been demonstrated,27 as well as the correlation between phenotype and genotype.28

The diagnosis of AS can be made through molecular studies, using the FISH technique or high-resolution karyotype.

**Alterations on EEG**

EEG is an integral part of AS diagnosis. Currently, three EEG patterns are recognized as supporting the diagnosis of AS when correlated with specific clinical features.

The delta pattern is the earliest EEG pattern in AS, described as starting at the age of four months. It consists of mostly anterior bursts of delta waves (2-2.5 Hz), of great amplitude, with or without interposition of small spikes. Initially, the spikes have an irregular pattern, resembling a hypsarhythmic pattern. With age, there is progressive organization of the tracing, with greater regularity of slow waves and a predominance of spikes in the downward side of slow waves, in anterior regions, resulting in a typical EEG pattern, with frontal triphasic delta waves (trihpasic AS complex). This pattern persists during adulthood, when the behavioral and dysmorphic features are no longer as evident.24

The theta pattern, the second EEG pattern found in AS, is age-dependent and disappears after adolescence. It is characterized by semi-rhythmic 4-6 Hz theta activity with an amplitude of 50-200 μv, diffuse activity or projection in posterior quadrants during wake periods and sleepiness, not influenced by the opening and closing of the eyes.

The third EEG pattern presents spike paroxysms or sharp waves followed by slow waves (3-4 cycles/second) in occipital regions, triggered by the closing of the eyes.

Just like some of the clinical alterations (dysmorphic features and epilepsy), EEG abnormalities are more evident in patients with deletion.29 This correlation between the genetic mechanism and phenotype has been explained by a greater involvement of the decoding genes in the beta 3 subunit of GABA A receptors. The preservation of these genes would lead to a smaller number of EEG alterations, and to a less evident clinical presentation.30 In patients without deletion, especially those with paternal disomy, there is a greater proportion of normal EEG examinations, or EEGs with less characteristic patterns (such as the delta pattern), with shorter bursts or absence of the theta pattern.

**Treatment of epileptic crises**

The most efficacious antiepileptic drugs in the control of crises in AS are valproate (VPA), clonazepam (CZP) and lamotrigine (LTG), administered in isolation or in combined therapies associating VPA and CZP, or VPA and LTG.31 Topiramate, a new drug which increases GABAergic transmission, is also effective to control crises.32 The use of carbamazepine and vigabactrin should be avoided because these drugs induce or increase the frequency of crises.31,33

**Fragile X syndrome**

Fragile X syndrome (FXS) is the most common cause of inherited mental retardation worldwide, and the second most common genetic cause of mental deficiency, after Down syndrome. It affects 1 child in 1,000 male births, and 1 in 2,000 female births. In Brazil, the frequency of FXS among institutionalized individuals has been estimated at 8% for males and 4% for females.34 FXS occurs in all ethnic groups, and must be considered in the differential diagnosis of any child with developmental delay, mental retardation, and learning disabilities.

FXS results mainly from a trinucleotide expansion, with CGG repeats in the promoter region of the FMR-1 gene. In normal individuals, this region presents from 5 to 52 repeats. In FSX patients, the region is considerably expanded, with over 200 repeats. The great expansion causes methylation of the promoter region, and consequent gene inactivation. A few FXS patients present FMR-1 gene mutations.

**Clinical signs**

Just as in the other syndromes described above, the dysmorphic features in FXS are subtle and appear late, and therefore they are of little diagnostic value in children. Behavioral features and cognitive deficit are the earliest and most common signs of FXS.

Cognitive impairment is always present in male patients with FXS. However, the expression of this disorder varies...
widely, ranging from learning disability (3.6% of the cases) to severe mental impairment. Most patients are in the moderate mental retardation range (about 50%). There is a correlation between molecular and cognitive findings. In carriers of large CGG inserts, the IQ is lower; in individuals with smaller inserts, the IQ is higher. Several studies report a decline in intellectual function with age, more accentuated in individuals with higher IQ, especially during puberty. There is controversy concerning whether there is a progressive decline of cognitive functions or whether the discrepancy found at different ages results from a slowing down or interruption in cognitive development which is more evident at more advanced ages, when there are more requirements for abstract thinking. In heterozygous women, about 34% present borderline or subnormal levels of intelligence.

Speech impairment is another striking feature. There is a delay in the acquisition of speech, with articulatory difficulties (substitution and omission of phonemes), alterations in rhythm (oscillating rhythm and inadequate pauses) and fluency. Repetitive speech, with palilalia-type repetitions, is more frequently observed in FXS carriers than in Down syndrome and autism patients.

FXS carriers present a behavioral profile that is similar, in some aspects, to that of autistic individuals. However, most patients do not meet all the criteria for a diagnosis of autism. As a result, and adding to the variability in terms of symptom intensity in autism, which is dependent on the degree of cognitive impairment, there is controversy in the literature concerning the association between autism and FXS. However, some of the features of autism are extremely frequent and characteristic of the carriers of FXS. Avoiding eye contact, with a shift of the head or trunk when looked at, repetition of words and sentences with echolalia, stereotypies such as waving and biting hands and an exaggerated tendency to take objects to the mouth, when found in association, signal a behavioral profile that is consistent with FXS, and in a way may serve to distinguish this disorder from others in the group of diseases that present the clinical spectrum of autistic behavior. Other behavioral problems are also frequently observed: hyperactivity with or without attention deficit, irritability, aggressiveness, abnormal response to stimuli, especially hypersensitivity to sounds.

Epilepsy in FXS has been described in several studies, with a frequency between 13% and 45%. This wide variation results mainly from methodological issues. The time for the onset of crises varies from two to nine years of age. The most frequent crises are simple or complex partial crises. In general, patients respond to treatment with conventional antiepileptic drugs, which allow total control of the crises.

The most frequent EEG pattern is similar to that of rolandic epilepsy, with discharge of sharp waves projected in centrotemporal regions, activated by sleep. Although unspecific, such a pattern, when found in children with mental retardation of unknown etiology, is suggestive of FXS. The frequency of epilepsy is lower in FXS women, who present unspecific EEG findings. Rolandic discharges have been recently reported in a woman carrier of asymptomatic FXS, and in her two daughters with FXS presenting mental retardation and epilepsy. A relationship between the FMR-1 gene mutation and the occurrence of epilepsy has been discussed.

Several of the dysmorphic features of SXF carriers become evident only after puberty. The long face, prognathism, a large and square forehead, macrocephaly, large ears and macro-orchidism are the most common features and at least one of them is present in 80% of pre-pubertal patients. Some of these features seem to be related to alterations in connective tissue; other features include joint laxity (especially in metacarpal-phalangeal joints), mitral valve prolapse, myopia, strabismus, pectus excavatum, flat foot and high palate.

**Genetic mechanisms**

In 1969, Lubs showed the fragile site in the X chromosome (FRAXA) for the first time, in a family with X-linked mental retardation. Since then, FRAXA located at 1.3Xq27 has been identified in several families with mental retardation. FRAXA is present in all males affected by FXS; however, the rate of identification varies widely, and it is rarely above 50% in classic cytogenetic examinations. Male carriers of a pre-mutation, with normal intelligence, like most of the women who carry the pre-mutation, test negative for the fragile site in classic cytogenetic examinations, which indicates that chromosomal studies are not efficacious to identify these individuals.

In 1991, the mutation in the fragile mental retardation I (FRM-1) gene which causes FXS was identified. The FMR-1 gene is found in several species, expressed in the human encephalon and placenta. It has 17 exons, with an extension of 38 Kb, and 4.4 Kb transcribed RNA. The first exon contains a CGG repeat whose alteration in size affects gene function and expression. The sequencing of the FMR-1 gene region revealed that the mutation is an increase in the size of a region containing tandem repeats of a CGG sequence, located in the 5' region of the first exon of the gene. Several authors have shown that the number of copies of this trinucleotide is polymorphic in the normal population, and may reach up to 52 copies with stability. In the presence of more copies, the individual is considered as carrier of a pre-mutation (about 52 to 200 copies), which may progress until reaching the number of copies that characterize a complete mutation (more than 200 copies).

FSX is the most common isolated case of mental retardation. It is an X-linked dominant condition, with a penetrance of 80% in males and only 30% in females. Women inherit the defective gene from their fathers, but carry only the pre-mutation and are not affected. Male sons...
may be affected. This pattern is known as Sherman’s paradox, and it is a peculiar example of genetic inheritance.

Due to the high frequency of FSX and its hereditary character, it is important that diagnosis be made especially in high risk groups without a definitive diagnosis, that is, individuals with learning disabilities, autistic manifestations, and hyperactivity.

The diagnosis of a child with FXS provides an invaluable opportunity for genetic counseling aimed at identifying other individuals, both affected and carriers, and at preventing new cases. Since 1992, there are molecular tests available to diagnose FSX. DNA testing, combining Southern-blotting with PCR, enables an accuracy higher than 99%.

Currently, molecular tests, especially PCR, can be used for screening in all children with mental retardation who are suspected of FXS, or without a specific diagnostic suspicion.

Conclusions
In general terms, it is possible to conclude that:
- There is phenotypical variability in the three syndromes described. That has been explained by the different genetic mechanisms that determine these syndromes.
- The screening process for referral to genetic investigation, due to the high cost of this procedure, must be based on EEG examination as an ancillary tool, due to the characteristic patterns which may be observed.
- These syndromes may present mild and atypical forms, which require special attention for identification.

References

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