THE ANGELMAN SYNDROME: A BRIEF REVIEW

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ABSTRACT

Angelman's Syndrome (AS) was described for the first time by Harry Angelman in the 1960s, based on obervation of three child patients with similar physical and behavioral features such as severe intellectual impairment, lack of language, motor disorders and happy behaviour. Many years later the typical patients' features were identified as linked to genetic abnormalities mainly characterized by neurological symptoms. Life expectancy is good although the symptoms tend to be stable and severe.

Keywords*: Angelman syndrome, behavioural abnormalities, mental retardation, UBE3A, EEG abnormalities.*

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Introduction

Angelman's Syndrome (AS) was described for the first time by British pediatrician Harry Angelman in the 1960s, based on obervation of three child patients with similar physical and behavioral features such as severe intellectual impairment, lack of language, motor disorders and happy behaviour. Many years later the typical patients' features were identified as linked to genetic abnormalities mainly characterized by neurological symptoms.

Typical clinical features

Affected children have no peculiar characteristics at birth and in prenatal, perinatal history was referred as normal.

Early signs and symptoms are usually non-specific and consisting in hypotonia and generic mealtime behavior disorders with onset near 6 months of life.

Between the first and the second year of life, different grades of psychomotor/mental retardation ten to emerge, generally severe psychomotor delay with language disruption/absence, balance disorders, tremors at the arms and ataxia. Hands movement are similar in the path and the states of excitation and such stereotypes are the same ones that are observed in the autistic spectrum subjects. The movements are generally sudden jerky. Again, behavior disorders consist in excitability, sudden laughing, happy mood and reduced attentive skills associated with hyperactivity, high social disinhibition, no fear for strangers or for dangerous situations[1-25].

In more than 80% of cases there is a decrease in the growth of the skull circumference with acquired microcephaly, around two years of age.

AS is characterized by very severe mental retardation with Intelligence quotient (IQ) < 25 with mental age not exceeding the second year of life equivalent.

Other clinical features, not always present, are plagiaroscopic (flat occiput), strabismus, hypopigmented skin, hyperephlexia and dysmorphic facial features[1-25].

In general, the AS phenotype is less marked than other genetic syndromes associated with mental retardation: dolicocephalic face, prominent jaw, large mouth and spaced teeth, protruding tongue, sunken eyes and microcephaly. Around 2/3 of AS children have blue eyes and blond hair, as effect of relevant hypopigmented skin.

About the sleep/wake cycle regulation, AS children have a marked reduction in the sleep need (about 5-6 hours per night) and abnormal sleep-wake cycles, with long or frequent waking periods during the night. Sleep problems may include starting and/or maintaining sleep and wake in the early morning[26-50].

Another neurological problem impacting the day-life is the presence of epilepsy with many types of seizures (predominantly atypical absences, myoclonic and atonic seizures) with abnormal EEG and characteristic pattern which tend to arise between the first and the third year of life with a constant incomplete antiepileptic drugs (AEDs) effects. In this picture, the severity of epilepsy is related to sleep problems, but it is still unclear whether crisis creates sleep disturbances or low sleep quality and duration may increase the epilepsy frequence[26-50].

Epileptic seizures are present in about 85 % of AS patients within three years of life, although less than 25% develops crises during the first year. The most common types are atypical absences, generalized tonic-clonic, atonic or myoclonic seizures, with multiple types of crises occurring in 50% of children. Often, febrile crises may precede the diagnosis of AS and even can emerge also for moderate temperature increasing. EEG abnormalities are relevant and important and can be not related to seizures severity, although are considered diagnostic for AS (Figure 1 and Figure 2).

In general the diagnostic criteria necessary for the definition of AS disease can be summarized in the following points:

• Prenatal history and apparently normal birth. Some babies have difficulty in feeding;

• Delay of motor development from 6-12 months, sometimes associated with trunk hypotonia;

• Delayed motor development, not associated with loss of acquired capabilities.

• Normal metabolic, hematological and chemical profiles.

• Brain structure is normal for MRI or CT analysis.

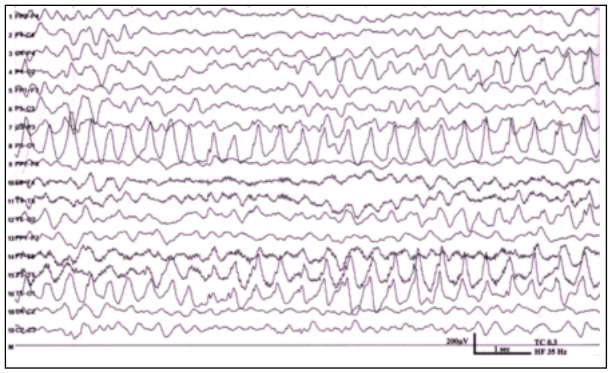

Figure 1: shows persistent rhythmic 3–4 Hz EEG activity in Angelman syndrome.

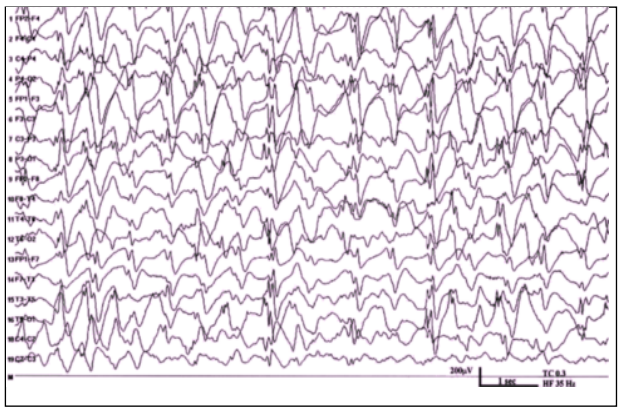

Figure 2: shows the rhythmic 2 Hz activity (triphasic activity) most prominent over the frontal regions, mixed with spikes and sharp waves typical of Angelman syndrome.

Etiology

AS is due to changes in the expression of the UBE3A gene located in the chromosomal region 15q11-13. The disease develops in the presence of the maternal allele of the gene in 70% of cases, with disomy unipolar such paternal chromosome 15, 2.5% of cases and imprinting defect and UBE3A intragenetic deletions in 10% of cases. This syndrome is mainly due to the lack of expression of the maternal copy of the E3 ubiquitin-protein

(UBE3A) gene in the fetal brain and the frontal cortex of affected adult. Observing AS patients, it can be deduced that there are many mechanisms through which this can occur and this is deducible by numerous molecular results, for the existence of an abnormal pattern of methylation at chromosome 15 level[51-75].

About 50% of subjects with defective imprinting exhibit mutations in an area outside the genomic region 15q11-q13 (imprinting center; IC). The imprinting center regulates the chromatin structure, DNA methylation, and the gene expression in 15q11-q13 region through regulatory genetic and cromosomal elements. In the remaining 50% of cases, IC alterations don't yet have precise causes for methylation defects. A high percentage of cases of AS (about 10% of cases), both familiar and non-existent, still remain today without an apparent molecular explanation. Point-to-point alterations to the MECP2 gene appear to be responsible for a number of cases (about 3%) where no abnormalities have been found. The UBE3A gene occupies about 120 kb and is transcribed in telomer-centromere direction. The gene consists of 10 coding exons (exons 7-16) and 6 non-coding exons located in 5 'untranslated (5'UTR). The region 3'UTR occupies about 2 kb. The 5' end of the gene is subject to alternative splicing that generates 9 different products in the adult and 2 in the fetus.

These various mRNAs encode three isoforms of Ube3a protein using different start ATGs and thus differ with respect to their N-terminal portion (Figure 3)[51-75].

Figure 3: shows the UBE3A gene structure.

Evolution in adulthood

In AS patients the severe cognitive disabilities and limited expressive language are permanent, and in 70-80% of cases, subjects develop epileptic seizures. In AS adults epilepsy is the main health problem forced to frequent hospitalization periods. The most significant epileptic severity period is childhood, followed by a period of improvement around the first 15 years of life. After 20 years of age, patients have a new epileptic severity and thus acute all symptoms and problems related to the disease. With ageing an improvement in sleep-wake cycle problems may be verified, although important residual troubles tend to remain. The AS's pathophysiological impact on pulmonary, endocrine and gastrointestinal systems remains important, and AS patients report high rates of pneumonia, episodes of asphyxia during eating, behavior resistant to drinking fluids[76-85].

Obesity is a major health problem for adults with AS, in fact more than 30% of the observed population is overweight or obese. At the orthopedic level the most important problem remains the scoliosis and the increased probability of a diagnosis of severe osteoporosis[76-85].

Finally, subjects with this pathology, in adulthood, develop multiple language modalities in support of verbal, which appears rather limited. The use of signs or gestures, the use of sounds with meaning are the two most significant modes. This probably promotes or reinforces aggressive and self-inducing behavior, resulting in significant morbidity, which is conducive to poor social involvement. It is important to note, however, that aggressive behaviors do not have the intent of hurting, but rather have social aim (i.e. communication method for protest or creating relationships).

Life perspective

Life expectancy for AS patients can be considered normal, although some patients must follow a life-threatening disease-like pathology and the administration of supplements such as betaine, folate and others may increase the expression of the sleeping allele in UBE3A, although this is still under experimentation. Another element of interest is the weight control, considering that AS subjects ongoing research food despite of lower energy expenditure linked to the lack of physical activity. The resulting obesity, which occurs mainly on the abdomen, buttocks and thighs, is the major cause of mortality, so the control of this condition allows the average length of life suggesting that AS has been known for over 50 years, but still has no effective treatment and current therapies are auxiliary, which

helps to mitigate symptoms and increase the quality of life[76-85].

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