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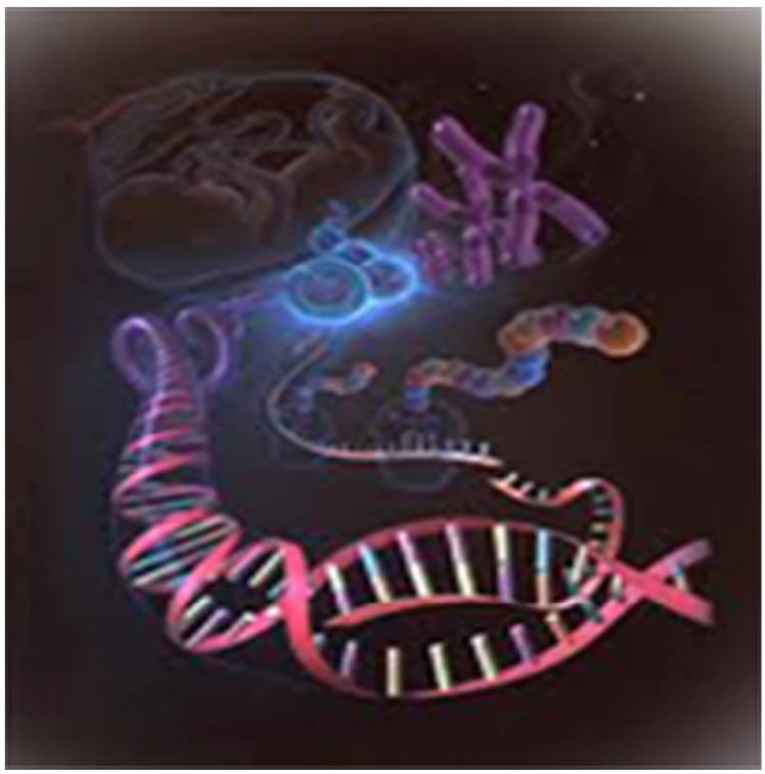

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Research Paper

ANGELMAN SYNDROME: ETIOLOGIES AND GENETIC COUNSELING

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Angelman syndrome (AS) is a neurogenetic disease involving mental retardation, dysmorphism and epilepsy. Its prevalence is 1 in 12,000. Angelman syndrome (AS) is associated with loss of function of one gene or more in the 15q11-q13 region. The mostly implicated gene is the UBE3A, subject to parental imprinting; only the maternal copy is active. We report the case of a child who's 8 years old with no family history and who has a discrete dysmorphology and epilepsy since he was 1 year old. The diagnosis of Angelman's disease has been confirmed by the presence of a deletion of the 15q11-13 region. In most cases, it is difficult to confirm the diagnosis of Angelman syndrome, especially face to the multiple etiologies, which requires a complete and methodical diagnostic strategy to inform the family about the risks of recurrence and the interest of performing prenatal diagnosis.

Keywords: Angelman syndrome, Genetic counseling, FISH, Methylation.

INTRODUCTION

Angelman syndrome (AS) is a neurogenetic disease with a prevalence of 1 in 12,000 to 20,000 (Dupont M J *et al*., 1998). It results in a set of clinical signs including mental retardation, constant disturbances of motor development (acquisition of walking, ataxia) with a very poor language, sleep disorders, a face with characteristic features, easy and unmotivated laughter with access of agitation and aggression traduced by beats of the forearms. Epilepsy, which is present in more than 80% of the cases, usually begins around the age of three years and is associated with abnormalities of the EEG. Angelman syndrome is associated with loss of function of one gene or more in the SA region (15q11-q13), subject to parental imprinting (the activity of the gene depends on its parental origin). The involved genes are expressed from the maternal chromosome. The loss of the SA region of maternal origin may involve five genetic mechanisms: maternal deletion of the 15q11-q13 region, paternal uniparental disomy (a pair of

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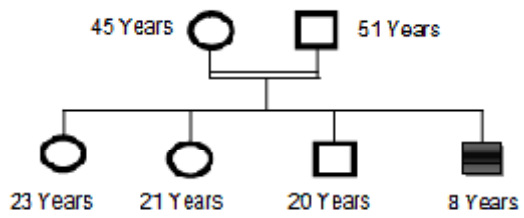
chromosomes inherited from the same parent), abnormalities of DNA fingerprinting, a mutation in the gene (UBE3A) or unknown mechanisms. Although all these mechanisms have an impact on the neurodevelopment, there are major dissimilarities between these SA genetic classes regarding the risk of disease recurrence (Dupont M J *et al*., 1998).

COMMENT

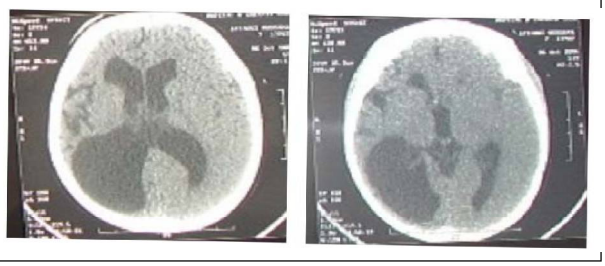
AO a boy of 8 years old, from healthy consanguineous parents; the youngest in a family of 4, no similar case in the family.

Figure 1: Pedigree of AO Family



There was no problems during the pregnancy, with a regular monitoring, the delivery was uneventful, no concept of suffering or fetal distress. Meningitis at the age of 6 months followed by a left hemiparesis has caused hypertonia of the left hand, seizures since the age of 1 year with a frequency of 3 to 4 crisis by week which are rebel to any therapy (combination: Depakine* + Gardenal*). A.O. presents unexplained seizures of laughter both daytime and night with crisis of excitability. The child is hyperactive with lack of movement's coordination, lack of language, and vigilance. Morphologically there's no clear dysmorphic features; A.O. has strabismus, thin upper lip, ears low-setted and hypopigmentation. A brain CT was performed to evaluate the effects of meningitis and eliminate an organic cause of epilepsy (tumor, cyst). It objectified a post-meningitis hydrocephalus with enlargement of the right lateral ventricle and atrophy of the right cerebral hemisphere.

Figure 2: Brain CT of AO Showing Post-meningitis Hydrocephalus With Enlargement of the Right Lateral Ventricle and Atrophy of the Right Cerebral Hemisphere



The EEG (Electro Encephalo Gram) shows the occurrence of left tips while VEPs (Visual Evoked Potentials) are strictly normal. The standard karyotype, which was performed to detect a deletion and seek the presence of associated chromosomal aberrations, revealed no abnormality. The methylation stady, for confirmation of the diagnosis, showed the absence of the maternal copy.

DISCUSSION

Epilepsy is a very common manifestation of AS (up to 96% of patients present with seizures at the age of 3 years with consistent signs on EEG) (3). In our case, the diagnosis of AS was confirmed by methylation test in contrast with an inconclusive clinical profile, mainly a normal EEG and the concept of meningitis at the age of 6 months with hydrocephalus which could explain the epilepsy that occurred at the age of 1 year, as a post meningitis sequelae. Unfortunately, a karyotype of the parents, essentially of the mother, couldn't be done. It's primordial and allow us to give an adequate genetic counseling.

In the case of a microdeletion, it is imperative to seek a chromosomal rearrangement in the

mother, especially that the microdeletion of 15q11-q13 region on the chromosome of maternal origin present 75% of cases of AS (Lossie A C *et al*., 2001) (Table 1).

Table 1: Genetic etiologies of Angelman Syndrome (AC Lossie *et al*. 2001)

Genetic Etiologies of Angelman Syndrome	Frequency (%)
Microdeletion of the 15q11-q13 region	75
Paternal disomy of chromosome 15	2–3
Mutations in the imprinting center	2–3
Mutations in the gene UBE3A	2–3
Unknown	15–20

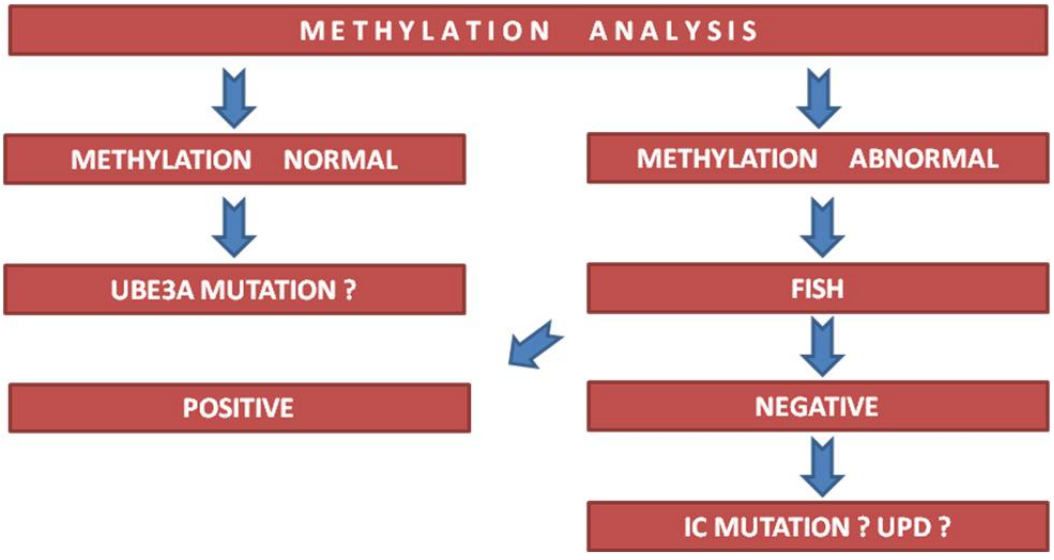
Given the frequency of Angelman Syndrome etiologies, a systematic diagnostic strategy is needed to guide the investigation in a practical and logical way (Figure 3).

In general, there are two opposing strategies: one is to seek first a disturbance of methylation in order to confirm the diagnosis and then search the etiology. The second one is based on the frequency of microdeletions to give priority to a cytogenetic test to have both diagnostic and etiological confirmation, but in case of normality, we must complete the review by searching for other etiologies (Moncla A *et al*., 1994). Once the etiology found, it determines the genetic counseling and recurrence risk for future pregnancies, this recurrence is very low in case of de novo deletion or uniparental disomy and may increase to 50% if the mother presents a deletion of the 15q11-q13 region, a UBE3A gene mutation or a mutation of the imprinting center (Wevvs *et al*., 1993).

CONCLUSION

Angelman Syndrome is a good example of genetic disease related to several genetic abnormalities; chromosomal abnormalities (deletion), single gene defect (mutation in the gene UBE3A) and an unconventional transmission (uniparental disomy). It also involves one of the 30 genes subject to parental imprinting. When dealing with Angelman Syndrome, it is important to lead a prudent diagnostic with a complete etiological

Figure3: Diagnosis Strategy of Angelman Syndrome



survey, both in children and the mother, to estimate the risk of recurrence and elaborate an adequate genetic counseling.

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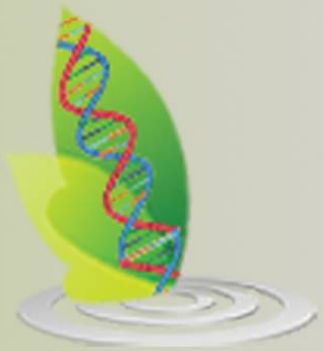

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