IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW OF ANGELMAN SYNDROME: A NEUROGENETIC DISORDER

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ABSTRACT

Angelman syndrome is an incurable neurodevelopmental disorder characterized by severe cognitive disability, motor dysfunction, speech impairment, hyperactivity, and frequent seizures. The maternally inherited UBE3A is rendered inactive by loss of the maternally expressed gene, which results in Angelman syndrome. The most frequent mechanism is the deletion of the maternal chromosomal region 15q11-q13. Surprisingly, duplication of the same chromosomal region, which affects >1-2% of all instances of autism spectrum disorder, is one of the few identified permanent genetic defects linked to the condition. While the general brain architecture and connection of neuronal projections in AS animal models appear to be largely normal, significant functional abnormalities are found at the level of context-dependent learning, as well as the decreased hippocampus and neocortical maturation.

KEYWORDS: Angelman syndrome, neuromuscular disorder**,** genetic disorder, UBE3A.

INTRODUCTION

Microcephaly, a severe intellectual disability, speech impairment, epilepsy, abnormalities in the EEG, ataxic movements, tongue protrusion, fits of laughter, irregular sleep patterns, and hyperactivity are all symptoms of the rare neurogenetic condition known as Angelman syndrome. The imprinted UBE3A (ubiquitin-protein ligase E3A) gene on chromosome 15q11.2-q13 is the cause of Angelman syndrome. A mutation on the maternal allele, a 5-7 Mb deletion of the maternally inherited chromosomal region, a paternal uniparental deletion of chromosome 15, or an imprinting error can all result in this loss of function. Due to the co-deletion of GABA receptor genes, chromosomal deletion tends to produce the most severe symptoms. Imprinting issues and UBE3A mutations have a significant likelihood of recurrence within families. UBE3A function in neurons appears to be disrupted.

EPIDEMIOLOGY

A rate of about 1 in 15 000 births has been regularly recorded for AS, making it a rare condition. However, recent research using alternative methodologies has indicated incidence rates between 1:10,000 and 1:62,000 based on reported figures.[1] Most of these more recent research on prevalence have calculated incidence rates relative to the general population after assessing the number of AS cases within populations of people with severe ID and/or epilepsy. These studies offer merely a sampling from the greater population, which means they may not accurately reflect the true incidence of the illness, albeit being useful for generating estimates.[2] As a result, there are probably many people with AS who have been misdiagnosed or have not yet been diagnosed. A clinical phenotype of AS is seen in 10% of people without a genetic diagnosis.[3]

SIGN AND SYMPTOMS

- Frequent laughter and smiling, often with little stimulus.
- Being easily excitable, often flapping the hands.
- Being restless (hyperactive)
- Having a short attention span.
- Trouble sleeping and needing less sleep than other children.
- A particular fascination with water.

DIAGNOSIS

If your child exhibits other indications of the illness, such as seizures, balance issues, a small head size, a pleasant disposition, and developmental delays, particularly little or missing language, you may suspect that your child has Angelman syndrome.[4]

• The parental DNA pattern. Three of the four genetic disorders that are known to cause Angelman syndrome are detected by this test, which is sometimes referred to as a DNA methylation test.

• Lack of chromosomes. If any chromosomes are missing, it can be seen by a chromosomal microarray (CMA).

• Gene alterations. When a person's maternal copy of the UBE3A gene is active but mutant, Angelman syndrome may very rarely happen. Your child's doctor might request a UBE3A gene sequencing test to search for a maternal mutation if the findings of a DNA methylation test are normal.[4]

BRAIN IMAGING

Myelination in patients 1 and 2, aged 7.5 and 8 months, respectively, was retarded and corresponded to a stage normally observed by 5–6 months.4, 5 The corpus callosum was still of a uniform size and appeared too thin for the patients' age but normal for a 5–6-month old child .[25]

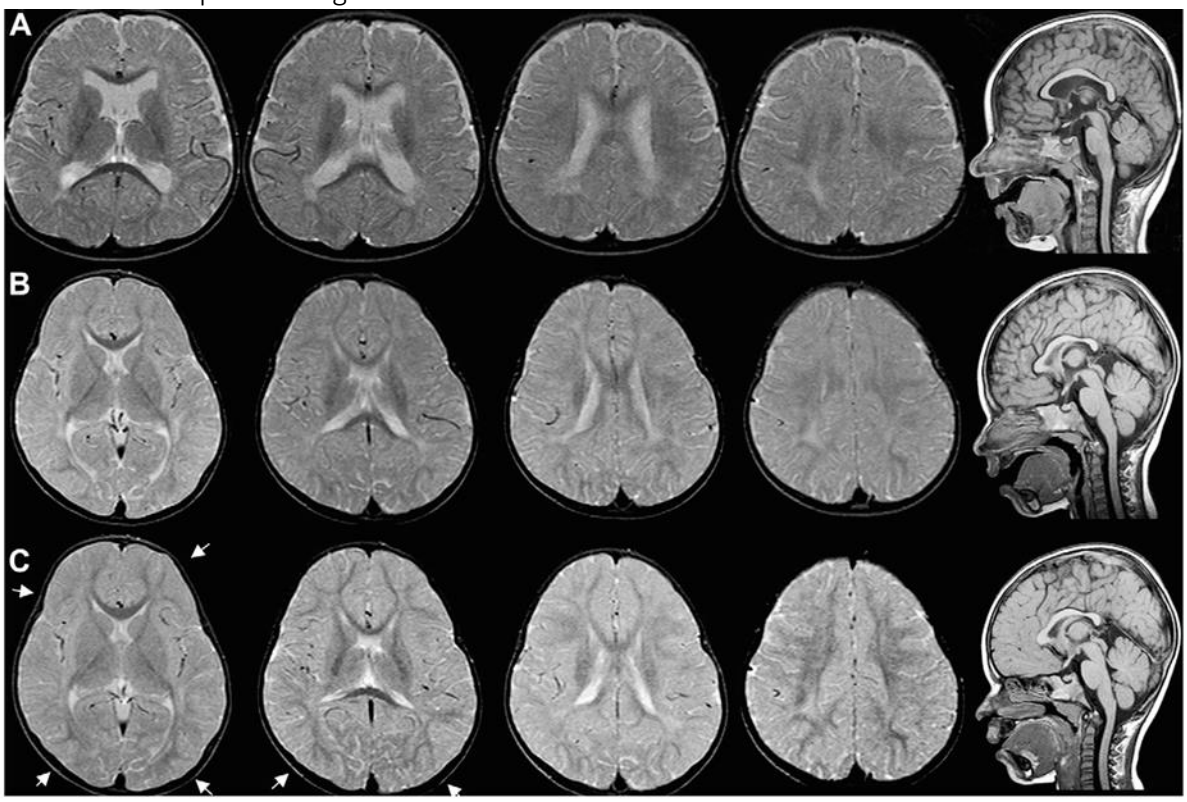

Fig no 1

The prominent, initially misleading MR finding in patient 3 was abnormal and retarded myelination which at the age of 12 months corresponded to that normally observed a MRI of patients 4 (A) and 5 (B; C) aged 17 (A), 18 (B), and corpus callosum show the normal T2 hypointense signal of my the contrast inversion between cortex and white matter has not Mild thinning of the corpus callosum and widened ventricles a lateral ventricles and irregular thinning of the splenium and an patient 5 reveals a discrete progression of myelination (arrowhe frontal lobes (C). t 8 months.[23]

PATHOGENESIS

The maternally inherited UBE3A gene, which is situated on chromosome 15q11-q13, is predominantly responsible for the condition through deletion or loss of mutations. A 100 kDa protein that serves as a transcriptional coactivator and ubiquitin ligase is encoded by the UBE3A gene. A growing body of evidence now suggests that UBE3A is crucial for both the control of activity-dependent synaptic plasticity and synaptic function[5].

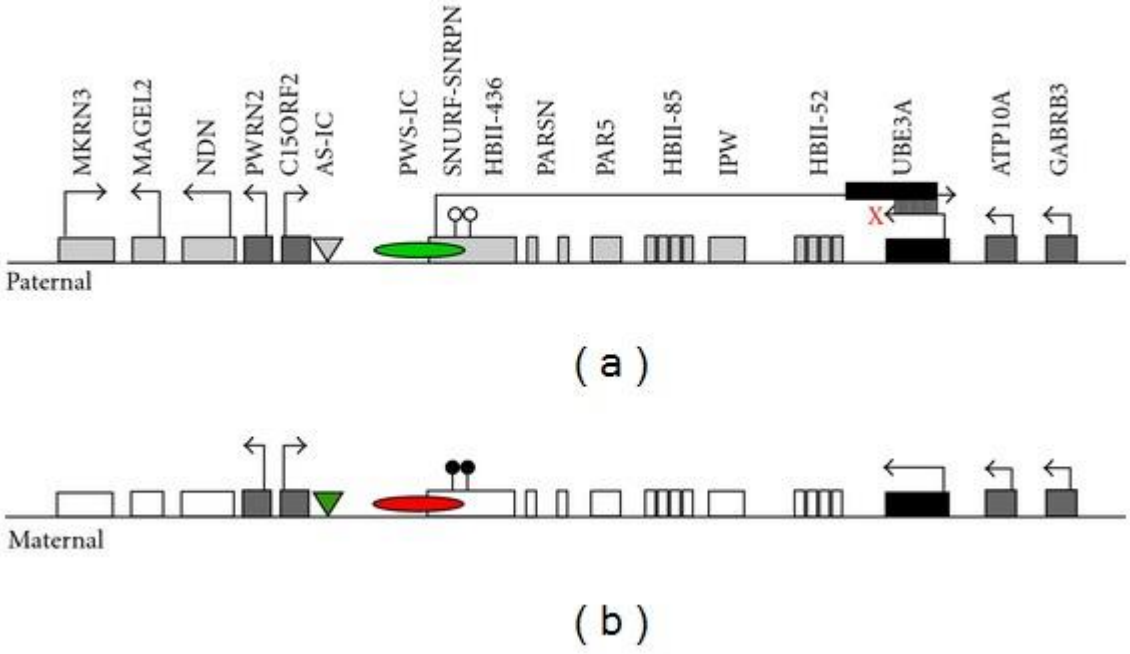

Fig no 2

Human chromosomal 15q11–13 area imprinting map around AS imprinting center (AS-IC). (A) and (B) respectively show the maternal and paternal chromosome 15q11-13 areas around AS-IC and PWS-IC. Arrows designating transcription start sites are used to depict genes that are maternally repressed (white boxes), biallelically expressed (dark grey boxes), paternally expressed (grey boxes), and maternally expressed (black boxes). Gene transcription on the "+" strand is shown by the right arrow, whereas transcription on the "strand is indicated by the left arrow. Depending on the level of histone modification in the region, AS-IC (triangle) and PWS-IC (ellipse) are shaded.[7-8] On the paternal chromosome, AS-IC is inactive (grey triangle), whereas, on the maternal chromosome, it is acetylated and methylated at H3-lys4 (green triangle), making it active. Since PWS-IC is also acetylated and methylated at H3-lys4, it is active on the paternal chromosome (green ellipse).[8] PWS-IC on the maternal chromosome, however, is suppressed and methylation at H3-lys9 (red ellipse). SNRPN exon 1's differentially CpG methylated region (DMR1) largely overlaps with PWS-IC. Be aware that DMR1 on the maternal chromosomes is methylated but not the paternal one (black pin). Upstream of SNRPN, UBE3A-ATS (antisense transcript) can either form a biodegradable complex with UBE3A transcript or stop the UBE3A transcript from extending.[10]

MANAGEMENT

The use of special nipples may improve feeding in newborn AS babies with feeding difficulties. Gastroesophageal reflux is often present and requires upright positioning or specific motility medications. As the majority of patients develop seizures at a very young age early attention should be given to this possible complication, which needs anticonvulsant medications.[11] As children may develop ocular problems, visual assessment is important to encourage interactions and diminish autistic and self-mutilative tendencies. Ocular surgery can be offered in patients with strabismus. A diet rich in fibers or laxative agents can be helpful in patients with constipation. Drooling in mentally retarded patients is often present but difficult to treat, and behavioural treatment should be considered[13]. New surgical techniques on salivary duct reimplantation or ligation in this improving treatment area are valuable alternatives. Orthopaedics problems, such as subluxed or pronated ankles, tight Achilles tendons or scoliosis may be treated by bracing or even surgery. The vigilance of cardiac rhythm during anaesthesia and the perioperative period is required.[15]

Physical therapy is needed for unstable or non-ambulatory children and extremely atactic children with adaptive chairs or positioners. With advancing age, adults become less active and the use of activity schedules may be helpful to prevent the extent of scoliosis and obesity.[16]

As decreased mobility leads to difficulties in walking, prevention should be focused on severe neurological instability by providing rehabilitative, early intervention, and psychosocial services. Occupational therapy is needed to stimulate fine motor and oral motor control skills.[18] Speech therapy including nonverbal methods of communication, picture cards, or communication boards should be introduced as active communication in this group of children is poorly developed. Patients that exhibit excessive hypermetric activity require a secure, tailored setting or maybe medicated, although frequently patients gain from both choices.[20] In cases of severe sleep issues, a sedative medicine may be prescribed. Melatonin may help AS patients sleep better, yet it was shown that for most AS patients, its favourable effects wore off within a few weeks.[22]

CONCLUSION

Microcephaly, maxillary hypoplasia, neurological issues with a puppet-like stride, ataxia, and epileptic seizures are all symptoms of AS, along with nonexistent speech, inappropriate laughing spells, severe mental impairment, and particular EEG abnormalities. Currently, there is no particular treatment for Angelman syndrome. The best course of action is to reduce seizures, anxiety, and digestive problems while increasing sleep. While sleep disorders are managed with sedatives and sleep training, seizures are treated with drugs and nutritional therapy.

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