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NEUROLOGICAL AND CLINICAL ASPECTS OF ANGELMAN SYNDROME, A NEURO-GENETIC DISORDER

SATYANAND TYAGI*, MOHIT SINGLA AND SACHIN KUMAR.

K.N.G.D Modi Institute of Pharmaceutical Education & Research, Modinagar, Uttar Pradesh, India.

Corresponding Author sntyagi9@yahoo.com

ABSTRACT

Angelman syndrome (AS) is a neuro-genetic disorder characterized by intellectual and developmental delay, sleep disturbance, seizures, jerky movement's especially hand-flapping, frequent laughter or smiling, and usually a happy demeanor.Genetically, there is no way to predict this disease prior to its occurrence. There is currently no cure available for Angelman syndrome however symptoms like epileptic seizures can be controlled by the use of one or more types of anticonvulsant medications. Mild laxatives are also used frequently to encourage regular bowel movements and early intervention with physiotherapy is important to encourage joint mobility and prevent stiffening of the joints. In the present article, we have concentrated on neurological and clinical aspects of Angelman syndrome. The aim of present article is to provide in depth knowledge about Angelman syndrome and various aspects related to Angelman syndrome.

KEYWORDS

Angelman syndrome, Happy Puppet Syndrome, Genomic Imprinting and Neuro-genetic disorder.

INTRODUCTON

Angelman syndrome is genetic disorder characterized by mental retardation, movement or balance disorder, characteristic abnormal behaviors, and severe limitations in speech and language. Most cases are caused by absence of a maternal contribution to the imprinted region on chromosome 15q11-q13.

AS is a classic example of genetic imprinting in that it is usually caused by deletion or inactivation of genes on the maternally inherited chromosome 15 while the paternal copy, which may be of normal sequence, is imprinted and therefore silenced. The sister syndrome, Prader-Willi syndrome, is caused by a similar loss of paternally-inherited genes and maternal imprinting. AS is named after a British pediatrician, Dr. Harry Angelman, who first described the syndrome in 1965. An older, alternative term for AS, happy puppet syndrome, is generally considered pejorative and stigmatizing so it is no longer used, though it remains useful as a diagnostic heuristic. People with AS are sometimes known as "angels", both because of the syndrome's name and because of their youthful, happy appearance.

Dr. Harry Angelman, a pediatrician working in Warrington (then in Lancashire) first reported three children with this condition in 1965. Angelman later described his choice of the title "Puppet Children" to describe these cases as being related to an oil painting he had seen while vacationing in Italy:

"The history of medicine is full of interesting stories about the discovery of illnesses. The saga of Angelman's syndrome is one such story. It was

purely by chance that nearly thirty years ago (e.g. circa 1964) three handicapped children were admitted at various times to my children's ward in England. They had a variety of disabilities and although at first sight they seemed to be suffering from different conditions I felt that there was a common cause for their illness. The diagnosis was purely a clinical one because in spite of technical investigations which today are more refined I was unable to establish scientific proof that the three children all had the same handicap. In view of this I hesitated to write about them in the medical journals. However, when on holiday in Italy I happened to see an oil painting in the Castelvecchio Museum in Verona called . . . a Boy with a Puppet. The boy's laughing face and the fact that my patients exhibited jerky movements gave me the idea of writing an article about the three children with a title of Puppet Children. It was not a name that pleased all parents but it served as a means of combining the three little patients into a single group. Later the name was changed to Angelman syndrome. This article was published in 1965 and after some initial interest lay almost forgotten until the early eighties[1]."

Case reports from the United States first began appearing in the medical literature in the early 1980s [2, 3]. In 1987, it was first noted that around half of the children with AS have a small piece of chromosome 15 missing (chromosome 15q partial deletion) [4].

Though the prevalence of Angelman syndrome is not precisely known, there are some estimates. The best data available are from studies of school age children, ages 6–13 years, living in Sweden and from Denmark where the diagnosis of AS children in medical clinics was compared to an 8 year period of about 45,000 births. The Swedish study showed an AS prevalence of about 1/20, 0005 and the Danish study showed a minimum AS prevalence of about 1/10, 0006.

PATHOPHYSIOLOGY

All humans inherit two copies of each gene, carried on homologous maternal and paternal chromosomes. It has usually been assumed that there is no difference between normal homologous genes derived from the mother or the father. Indeed, this is true for many genes. However, it has now been established that with respect to several genes, functional differences exist between the paternal and the maternal genes. These differences arise from an epigenetic process called as genetic imprinting, where by certain genes are differentially inactivated during paternal and maternal gametogenesis.

Thus, maternal imprinting refers to transcriptional silencing of the maternal allele, where as paternal imprinting implies that the paternal allele is inactivated. Imprinting occurs in ovum or sperm and is then stably transmitted to all somatic cells derived from the zygote. The genomic imprinting is best illustrated by considering two uncommon genetic disorders: Prader-Willi syndrome and Angelman syndrome[7].

Prader-Willi syndrome is characterized by mental retardations, short stature, hypotonia, obesity, small hands and feet, and hypogonadism. In 65% to 70% of cases, an interstitial deletion of band q 12 in the long arm of chromosome 15, del (15) (q11.2q13), can be detected[8]. It is striking that in all the cases the deletion affects the paternally derived chromosome 15. In contrast with Prader-Willi syndrome, patients with the phenotypically distinct Angelman syndrome are born with a deletion of the same chromosomal region derived from their mothers. Patients with Angelman syndrome are also mentally retarded, but in addition they present with ataxic gait, seizures, and inappropriate laughter. Because of their laughter and ataxia they are also called as “happy puppets” [9].

Angelman syndrome is caused by the loss of the normal maternal contribution to a region of chromosome 15, most commonly by deletion of a segment of that chromosome. Other causes include uniparental disomy, translocation, or single gene mutation in that region. A healthy person receives two copies of chromosome 15, one from the mother, the other from the father. However, in the region of the chromosome that is critical for Angelman syndrome, the maternal and paternal contributions express certain genes very differently. This is due to sex-related epigenetic imprinting; the biochemical mechanism is DNA methylation. In a normal individual, the maternal

allele is expressed and the paternal allele is silenced. If the maternal contribution is lost or mutated, the result is Angelman syndrome. (When the paternal contribution is lost, by similar mechanisms, the result is Prader-Willi syndrome.) It should be noted that the methylation test that is performed for Angelman syndrome (a defect in UBE3A) is actually looking for the gene's neighbour SNRPN (which has the opposite pattern of methylation)[10].

Angelman syndrome can also be the result of mutation of a single gene. This gene (*UBE3A*, part of the ubiquitin pathway) is present on both the maternal and paternal chromosomes, but differs in the pattern of methylation (Imprinting). The paternal silencing of the *UBE3A* gene occurs in a brain region-specific manner; in the hippocampus and cerebellum, the maternal allele is almost exclusively the active one. The most common genetic defect leading to Angelman syndrome is an ~4Mb (mega base) maternal deletion in chromosomal region 15q11-13 causing an absence of *UBE3A* expression in the paternally imprinted brain regions. *UBE3A* codes for an E6-AP ubiquitin ligase, which chooses its substrates very selectively and the four identified E6-AP substrates have shed little light on the possible molecular mechanisms underlying the human Angelman syndrome mental retardation state[11].

Initial studies of mice that do not express maternal *UBE3A* show severe impairments in hippocampal memory formation. Most notably, there is a deficit in a learning paradigm that involves hippocampus-dependent contextual fear conditioning. In addition, maintenance of long-term synaptic plasticity in hippocampal area CA1 *in vitro* is disrupted in *Ube3a*$^{-/-}$ mice. These results provide links amongst hippocampal synaptic plasticity *in vitro*, formation of hippocampus-dependent memory *in vivo*, and the molecular pathology of Angelman syndrome.

The bio chemical basis of imprinting in Angelman syndrome is still not clear. Methylation of DNA is known to affect gene expression, and in many cases, imprinting is associated with differential pattern of DNA methylation. Other mechanisms include histone H4 deacetylation and methylation. Regardless of the mechanism, it is believed that the marking of paternal and maternal chromosomes occurs during gametogenesis, and thus it seems that from the moment of conception some chromosomes remember where they came from. In the Angelman syndrome, the affected gene is a ubiquitin protein- ligase that has a role in the ubiquitin- proteosome proteolytic pathway. The gene, called UBE3A, maps within the 15q12 region, is imprinted on the paternal chromosome, and is expressed from the maternal allele primarily in specific regions of the normal brain. The imprinting is tissue- specific in that UBE3A is expressed from both alleles in most tissues. In approximately 10% of cases, Angelman syndrome occurs, not due to imprinting but due to a point mutation in the maternal allele, thus establishing a firm link between the UBE3A gene and Angelman syndrome. In contrast to Angelman syndrome, no single gene has been implicated in Prader-Willi syndrome. Instead, a series of genes located in the 15q11.2-13 interval (which are imprinted on the maternal chromosome and expressed from the paternal chromosome) are believed to be involved. These genes are being characterized[12].

CLINICAL FEATURES AND SYMPTOMS OF ANGELMAN SYNDROME

The following list features of Angelman Syndrome and their relative frequency in affected individuals.

Consistent (100%)

- Developmental delay, functionally severe
- Speech impairment, none or minimal use of words; receptive and non-verbal communication skills higher than verbal ones
- Movement or balance disorder, usually ataxia of gait and/or tremulous movement of limbs
- Behavioral uniqueness: any combination of frequent laughter/smiling; apparent happy demeanor; easily excitable personality, often with hand flapping movements; hypermotoric behavior; short attention span.

Frequent (more than 80%)

- Delayed, disproportionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2 .
- Seizures, onset usually < 3 years of age .
- Abnormal EEG, characteristic pattern with large amplitude slow-spike waves.

Associated (20 - 80%)

- Strabismus
- Hypopigmented skin and eyes
- Tongue thrusting; suck/swallowing disorders
- Hyperactive tendon reflexes
- Feeding problems during infancy
- Uplifted, flexed arms during walking
- Prominent mandible
- Increased sensitivity to heat
- Wide mouth, wide-spaced teeth
- Sleep disturbance
- Frequent drooling, protruding tongue
- Attraction to/fascination with water
- Excessive chewing/mouthing behaviors
- Flat back of head
- Enlarged toes
- Smooth Palms[13, 14].

DIAGNOSIS

The diagnosis of Angelman syndrome is based on:

- A history of delayed motor milestones and then later a delay in general development, especially of speech
- Unusual movements including fine tremors, jerky limb movements, hand flapping and a wide-based, stiff-legged gait.
- Characteristic facial appearance (but not in all cases).
- A history of epilepsy and an abnormal EEG tracing.
- A happy disposition with frequent laughter
- A deletion on chromosome 15 [15].

Diagnostic criteria for the disorder were initially established in 1995 in collaboration with the Angelman Syndrome Foundation (USA); these criteria have undergone revision in 2005[16].

TREATMENT AND PROGNOSIS

There is currently no cure available. The epilepsy can be controlled by the use of one or more types of anticonvulsant medications. However, there are difficulties in ascertaining the levels and types of anticonvulsant medications needed to establish control, because AS is usually associated with having multiple varieties of seizures, rather than just the one as is normal cases of epilepsy. Many families use melatonin to promote sleep in a condition which often affects sleep patterns. Many individuals with Angelman Syndrome sleep for a maximum of 5 hours at any one time. Mild laxatives are also used frequently to encourage regular bowel movements and early intervention with physiotherapy is important to encourage joint mobility and prevent stiffening of the joints.

Those with the syndrome are generally happy and contented people, who like human contact and play. People with AS exhibit a profound desire for personal interaction with others. Communication can be difficult at first, but as a child with AS develops, there is a definite character and ability to make themselves understood. It is widely accepted that their understanding of communication directed to them is much larger than their ability to return conversation. Most afflicted people will not develop more than 5-10 words, if any at all[17]

Seizures are a consequence, but so is excessive laughter which is a major hindrance to early diagnosis.

The severity of the symptoms associated with Angelman Syndrome varies significantly across the population of those affected. Some speech and a greater degree of self-care are possible among the least profoundly affected. Unfortunately, walking and the use of simple sign language may be beyond the reach of the more profoundly affected. Early and continued participation in physical, occupational (related to the development of fine-motor control skills), and communication (speech) therapies are believed to improve significantly the prognosis (in the areas of cognition and communication) of individuals affected by AS. Further, the specific genetic mechanism underlying the condition is thought to correlate to the general

prognosis of the affected person. On one end of the spectrum, a mutation to late to the least affected, whereas larger deletions on chromosome 15 are thought to correspond to the most affected [18].The clinical features of Angelman syndrome alter with age. As adulthood approaches, hyperactivity and poor sleep patterns improve. The seizures decrease in frequency and often cease altogether and the EEG abnormalities are less obvious. Medication is typically advisable to those with seizure disorders. Often overlooked is the contribution of the poor sleep patterns to the frequency and/or severity of the seizures. Medication may be worthwhile in order to help deal with this issue and improve the prognosis with respect to seizures and sleep. Also noteworthy are the reports that the frequency and severity of seizures temporarily escalate in pubescent Angelman Syndrome girls but do not seem to affect long-term health. The facial features remain recognizable but many adults with AS look remarkably youthful for their age.Puberty and menstruation begin at around the average age. Sexual development is thought to be unaffected, as evidenced by a single reported case of a woman with Angelman syndrome conceiving a female child who also had Angelman syndrome[19].The majority of those with AS achieve continence by day and some by night. Angelman Syndrome is not a degenerative syndrome. Many people with AS improve their living skills with support. Dressing skills are variable and usually limited to items of clothing without buttons or zippers. Most adults are able to eat with a knife or spoon and fork and can learn to perform simple household tasks. General health is fairly good and life-span near average. Particular problems which have arisen in adults are a tendency to obesity (more in females), and worsening of scoliosis if it is present. The affectionate nature which is also a positive aspect in the younger children may also persist into adult life where it can pose a problem socially, but this problem is not insurmountable [20].

CONCLUSION

It may be concluded that Angelman syndrome is a complex genetic disorder that primarily affects the nervous system. Characteristic features of this condition include developmental delay, intellectual disability, severe speech impairment, and problems with movement and balance (ataxia). Most affected children also have recurrent seizures (epilepsy) and a small head size (microcephaly). Delayed development becomes noticeable by the age of 6 to 12 months, and other common signs and symptoms usually appear in early childhood. Genetically, there is no way to predict this disease prior to its occurrence. Although the disease's progression cannot be stopped or reversed, therapies and support can partially alleviate symptoms and improve quality of life. There is no standard course of treatment for Angelman syndrome. Physical therapy and adaptive devices may help patients with jerky gait. Early language evaluation and intervention is often recommended. Anticonvulsant medications may be prescribed for epilepsy; further consultations of CNS specialist, child brain specialist, child neurosurgeon, nerve specialist, muscle specialist, bone specialist, stroke & vascular specialists, senior health specialists (geriatrics), may be required time to time.

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