

Angelman Syndrome

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Definition

Angelman Syndrome is a complex of recognizable clinical findings due to abnormal function in the UBE3A gene located on chromosome 15. It was originally called the "happy puppet syndrome" because of the puppet-like jerky gait, hand-flapping, and the tendency to smile and laugh almost continuously.

Introduction

Dr. Harry Angelman first described Angelman syndrome in 1965. Three different children with similar characteristics were admitted to the children's ward at the hospital in which he worked. All three had a stiff, jerky gait, absent speech, seizures, and excessive laughter. Initially it was presumed to be rare, but now it is believed that thousands of cases have gone undiagnosed, or misdiagnosed as cerebral palsy, autism, or other childhood disorders. The incidence is not known, but is estimated at 1 in 15,000 to 1 in 30,000 individuals. The majority of known cases seem to be of Caucasian origin. Males and females are equally affected.

In 70% of individuals with Angelman Syndrome, a small deletion on chromosome 15 is detected on genetic studies. The deleted region on chromosome 15 is known to contain genes that are activated or inactivated depending on the chromosome's parent of origin. This process is known as imprinting. Imprinting selectively inactivates either the gene from the mother or the gene from the father. Individuals with Angelman syndrome are born with a deletion of the chromosomal region derived from their mothers. (In contrast, individuals with Prader-Willi syndrome are born with a deletion of the same chromosomal region derived from their fathers.)

There are several other rare causes of Angelman syndrome, which have been discovered, each involving the portion of chromosome 15 that contains the UBE3A gene. UBE3A is an enzyme in a complex protein degradation pathway, but we do not yet know what proteins the UBE3A enzyme is supposed to be degrading.

Angelman Syndrome is not usually recognized at birth, and prenatal and birth history is normal. Developmental delay becomes apparent by 6-12 months of age, with delayed forward progress, but no loss of skills. The hematologic and metabolic lab work is normal, and brain is structurally normal by MRI or CT scan. Individuals with Angelman Syndrome have speech impairment, with verbal expressive language more severely affected than receptive or non-verbal communication. They also exhibit a movement disorder, with tremulousness of the limbs and/or ataxic gait. The unique finding is the happy demeanor, frequent smiling or laughter, excitability, often with hand flapping movements, short attention span, and hypermotoric behavior.

Delayed head growth usually results in microcephaly by age two. Most individuals with Angelman syndrome have seizures, usually with onset before age three, and the EEG is abnormal.

If the individual has a large deletion of chromosome 15, skin and eye hypopigmentation usually results, because the pigment gene is normally located near the AS gene. Thirty–sixty percent have strabismus, and this is more common in the children with eye hypopigmentation, since pigment in the retina is crucial to the development of the optic nerve pathways.

Feeding problems are frequent in infancy, and include uncoordinated sucking and swallowing, frequent spitting up, gastroesophageal reflux, and poor weight gain in infancy or even failure to thrive. Many children with AS have tongue protrusion, and most have difficulty with persistent drooling.

Diagnosis

Genetic testing makes the diagnosis.

Prevention and Treatment

There is no available treatment or prevention at this time.

Genetic counseling is available, but about 70-75% of cases are caused by spontaneously occurring abnormalities. Routine prenatal testing often misses these abnormalities since they are too small or require specialized testing looking specifically for Angelman syndrome. Fetal ultrasound is also not helpful, as the affected fetus is well formed.

Treatment is directed towards the specific developmental and health problems that may occur.

Seizures

Seizures may be difficult to recognize or distinguish from the individual's usual tremulousness, attention deficits, and the EEG is often more abnormal than expected. Children with AS are at risk for over medication because their movement abnormalities or inattention can be misinterpreted as seizure activity. Single medication use is preferred, but seizure breakthrough is common. Children with uncontrollable seizures have been placed on ketogenic diet in an attempt to better control their seizures.

Gait and Movement Disorders

Physical therapy is helpful in improving ambulation, and sometimes bracing or surgical intervention may be needed to properly align the legs.

Hyperactivity

Essentially all young children with Angelman syndrome have a component of hyperactivity. Attention span can be so short that social interaction and communication is adversely affected. Persistent and consistent behavior modification can help decrease these behaviors. Observations in young adults suggest that hyperactivity decreases with age. Most children with Angelman syndrome do not receive drug therapy for hyperactivity, although some may benefit from the use of medications such as methylphenidate (Ritalin). Use of sedating agents is not recommended.

Hypopigmentation

Individuals with hypopigmentation or relatively lighter skin than family members are sun sensitive, so use of protective sunscreen is important.

Strabismus

Management of strabismus requires evaluation by an ophthalmologist, correction of any visual deficit, and where appropriate, patching or surgical correction of the eye muscle imbalance.

Emergency Situations – What can go wrong?

Status epilepticus – prolonged seizure activity such as a seizure that lasts for more than 10 minutes or several seizures that occur one after another for 20-30 minutes.

Injury – including bruising, concussion, fractures or even drowning if the seizure occurs during a bath.

Trouble breathing – individual’s lips may turn blue.

What to Do:

1. Clear the area around the individual, stay with him/her to prevent injury; DO NOT put anything in his/her mouth.
2. Try to write down what happened before, during and after the seizure and how long the seizure lasts.
3. Notify agency nurse/supervisor as soon as possible.
4. Call 911 if the seizure lasts longer than 5 minutes, if individual is injured or if he/she stops breathing.
5. Begin rescue breathing if you are certified to do so.

Conclusion

Angelman syndrome is a genetic disorder caused by an abnormality on chromosome 15 characterized by developmental delay, impaired communication, movement disorder, seizures and a unique behavioral pattern of happy demeanor, laughter, hyperactivity and short attention span. Individuals with Angelman syndrome need the same preventative health care measures that are provided to everyone. Individuals with this syndrome can benefit from consistent behavioral therapy and adaptive communication techniques. Because of their interest in people, and their ability to understand language, they are able to participate in group activities, assist with the responsibilities of daily living and establish rewarding friendships.

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