What is Angelman Syndrome?

Angelman syndrome is a genetic disorder that affects the nervous system and causes severe physical and intellectual disability.

It’s relatively rare, occurring in around 1 in 15,000-20,000 people. It was first discovered in 1965 by Dr Harry Angelman. The syndrome – originally called ‘Happy Puppet Syndrome’ because of the characteristic happy demeanour and stiff jerky movements of the children – was renamed Angelman Syndrome in 1982.

Typical characteristics of Angelman syndrome include:

- delayed development (usually noticeable from 6-12 months of age)
- severe language impairment with little or no speech
- movement and balance problems (ataxia)
- frequent seizures (epilepsy) in around 85% of cases
- a small head size (microcephaly)
- sociable behaviour with frequent smiling

In most cases, Angelman syndrome isn’t inherited from your parents, and the genetic anomaly responsible for the syndrome occurs by chance around the time of conception. However, in some families, more than one child is affected (see below).

Characteristics of Angelman syndrome

The typical characteristics of Angelman syndrome aren’t usually apparent at birth.

A child with the syndrome will begin to show signs of delayed development around 6-12 months, such as being unable to sit unsupported or make babbling noises. Later, they may not speak at all or may only be able to say a few words.

Children with Angelman syndrome are very sociable and frequently smile.

The movement of a child with Angelman syndrome will also be affected. They may have difficulty walking due to problems with balance and co-ordination (ataxia), their arms may tremble or move jerkily, and their legs may be stiffer than normal.

A number of distinctive behaviours are also associated with Angelman syndrome. These may include:

- frequent laughter and smiling, with little stimulus
- being easily excitable, often flapping the hands
- being restless (hyperactive)
- having a short attention span
- sleep disturbances

By around two years of age, an abnormally small head which is flat at the back (microbrachycephaly) will often be noticeable in children with Angelman syndrome. They may also start to have seizures (fits) around this age.
Other possible features of the syndrome include:

- sticking the tongue out
- crossed eyes (strabismus)
- excessive chewing/mouthing objects
- drooling
- increased sensitivity to heat
- a wide mouth with widely spaced teeth
- walking with arms in the air
- a fascination with water
- pale skin, and light-coloured hair and eyes
- a side-to-side curvature of the spine (scoliosis)
- hyperactive lower limb tendon reflexes

Some young babies with Angelman syndrome may have problems feeding because they’re unable to co-ordinate sucking and swallowing. In such cases, a high-calorie formula may be recommended to help the baby gain weight, or they may need to be treated for reflux.

**What causes Angelman syndrome?**

The typical characteristics of Angelman syndrome are caused when a gene, known as UBE3A, is either absent or malfunctions. A gene is a single unit of DNA.

A child usually inherits one copy of the UBE3A gene from each parent. Both copies are switched on (active) in most of the body's tissues. However, in certain areas of the brain, only the UBE3A gene inherited from the mother (maternal) is active.

- **Deletion Positive**: In most cases of Angelman syndrome (about 70%), the child’s maternal copy of the UBE3A gene is missing, which means there’s no active copy of the UBE3A gene in the child’s brain.
- **UBE3A Mutation**: In around 11% of cases, the maternal copy of the UBE3A gene is altered.
- **Uniparental Disomy (UPD)**: In a small number of cases, Angelman syndrome occurs when a child inherits two copies of chromosome 15 from the father, rather than inheriting one from each parent.
- **Imprinting Centre Defect (ICD)**: It can also occur when the copy of the UBE3A gene that comes from the mother, behaves like it came from the father.
- **Clinical diagnosis**: In about 10-15% of cases, the cause of Angelman syndrome is unknown. It’s thought that some children in these unexplained cases may have different conditions involving other genes or chromosomes.

**Diagnosing Angelman syndrome**

Angelman syndrome may be suspected if a child’s development is delayed and they have the syndrome's distinctive characteristics (see above).
A blood sample can be taken to confirm the diagnosis. A number of genetic tests will be carried out on the sample.

These may include:

- **Chromosome analysis** - to see if any parts of the chromosomes are missing
- **Fluorescence in situ hybridisation (FISH)** - used to check chromosome 15 deletions
- **DNA methylation** - shows whether the genetic material on both the mother’s and father’s chromosomes is active; it can detect deletions, uniparental disomy and imprinting defects
- **UBE3A gene mutation analysis** - if the results of DNA methylation are normal, UBE3A gene sequencing can be used to see whether the maternal copy of the gene is altered. In Australia this test is only performed at the Mater Hospital in Brisbane.

For each child with Angelman syndrome, it's important to know the genetic change that caused the condition to determine the risk of it occurring again in another child.

Most children with Angelman syndrome are diagnosed between the ages of 18 months and 6 years, when the typical physical and behavioural symptoms become apparent. Diagnosis can sometimes be made by a paediatrician, but often requires a referral to a neurologist or clinical geneticist. Diagnosis is sometimes made as early as 9 months of age due to recent raised awareness of Angelman syndrome in the medical and general communities.

If your child is diagnosed with Angelman syndrome, you should be given the opportunity to discuss the genetic diagnosis and implications with a genetic doctor and/or genetic counsellor.

**Managing Angelman syndrome**

Some of the symptoms of Angelman syndrome can be difficult to manage, and you're likely to need help from a wide range of different healthcare professionals.

Your child may benefit from some of the following treatments and aids:

- **Anti-epileptic medicine** to control the seizures. Commonly used medications include Sodium Valproate (Epilim), Clobazam (Frisium), Lamotrigine (Lamictal), Levetiracetam (Keppra), Topiramate (Topamax) and Ethosuxamide (Zarontin).
- **Physiotherapy** may help to improve posture, balance and walking ability; it's also important to prevent permanent stiffening (contractures) of the joints as they get older
- **Speech therapy** may be needed to help them develop non-verbal language skills. Multi-modal forms of communication include Key Word Sign (sign language), using low-tech visual aids, using iPad applications, PODD books and dedicated speech generating devices.
- **Occupational therapy** may help with improving core muscle strength, fine motor skills, motor planning, balance, and self-care skills. Recommendations regarding specialist equipment such as chairs, car harnesses, adapted cutlery, and bathroom modifications may be made.
- **Behavioural therapy** may be recommended to help overcome challenging behaviours, hyperactivity and a short attention span
- Activities such as swimming, horse-riding, music therapy and gymnastics have also been reported as being beneficial.
• An ankle or foot orthosis (lower leg brace) may be recommended to help them walk independently
• A back brace or spinal surgery may be recommended to prevent a scoliosis from becoming worse (see treating scoliosis)

**Outlook**

While there’s currently no cure for Angelman syndrome, the results of preliminary genetic research carried out in America have been promising.

Following these studies, scientists believe that it may be possible to restore UBE3A function in the brains of people with Angelman syndrome.

Read more about the search for a cure for Angelman syndrome at (external link). http://cureangelman.org.au/

With age, people with Angelman syndrome become less hyperactive and the sleeping problems tend to improve. Most people with the syndrome will have intellectual disability and limited speech throughout their life.

In later childhood, the seizures usually improve, although they may return in adulthood. In adults, some mobility may be lost and joints may stiffen up.

A person with Angelman syndrome will have a near-normal life expectancy, but will need support for the rest of their life.