

Angelman Syndrome

Angelman syndrome (AS) is a behavioural disorder characterised by seizures, severe developmental delay, absent speech and ataxia.

Epidemiology

- Incidence: 1 in 12 000-40 000
- All ethnic groups
- Male = Female

Genetics

- AS results from a lack of expression of an imprinted maternal allele (SNRPN) on chromosome 15q11-13.
- Normal imprinting results in inactivation of the paternally inherited SNRPN locus. Normal development is therefore dependent on maternal allele expression.
- Lack of the required maternal expression results from a deletion of the maternal allele; paternal origin of both chromosomes 15 (uniparental disomy); an imprinting centre defect or a mutation in the E3 ubiquitin protein ligase gene (UBE3A).
- Patients with a deletion are the most severely affected whilst UPD and imprinting centre defect patients are the least affected.

Clinical Presentation

- Severe developmental delay
- Profound speech delay. Many children do not speak more than 3-4 words.
- Seizures
- Specific behaviour with excitability and inappropriate laughter.
- Movement and balance problems
- Wide based ataxic gait.
- Sleep disorder.
- Less commonly there is hypopigmentation

Physical Signs

- Microcephaly
- Jerky gait
- Increased muscle tone
- Down-turned corners of the mouth
- Wide mouth
- Deep set eyes
- Prominent chin
- Hypotonia
- Happy and sociable affect

Diagnosis

- Chromosome (FISH analysis) and DNA diagnosis demonstrating microdeletion of band 15q13-q15.
- Most often this is due to a deletion of the maternal allele (~70%); uniparental disomy, (~2-5%) or an imprinting centre defect (~2-5%). Methylation is abnormal in all three situations.
- Abnormal methylation in the absence of a deletion or UPD is indicative of an imprinting centre defect.
- Methylation analysis of the SNRPN locus on chromosome 15q detects ~80% of cases of PWS.
- AS may also result from a mutation in the UBE3A gene (20%).

Methylation is normal in this case.

- There is only a 44% pick up rate in methylation-normal, sporadic cases.
- An EEG may show characteristic 2-3Hz amplitude slow wave bursts said to be typical of AS.

Complications

- Almost all patients develop seizure (90%) with a deletion, 20% if UPD. Usual onset is by the second year.
- Scoliosis occurs in 40% of adults
- Loss of mobility and contractures

Treatment

- Monitoring for cognitive, behavioural and motor problems.
- Many children are able to learn some language by sign e.g. Makaton.
- Early motor skills are compromised by ataxia and walking is often delayed until 3-4 years.
- Most adult patients with AS require close supervision in secure environment.
- Referral to local child development centre

Genetic Counselling:

- An interstitial maternal deletion, uniparental disomy, or defective DNA methylation are sporadic events with a low recurrence risk of <1% for parents of affected children.
- Females carrying a UBE3A mutation have a 50% risk of AS in each pregnancy. Paternal transmission is silent.
- AS patients without a FISH deletion or UPD can have a recurrence risk as high as 50% due to phenocopy of an abnormal AS gene.
- Prenatal testing is possible at 12 weeks by CVS or later by 16-18 weeks by amniocentesis. A CVS can either look for abnormal methylation or a specific deletion by FISH or mutation analysis of UBE3A.
- At risk family members should be advised if an imprinting defect is suspected.

Photos?
Face