SSBP Syndrome Sheets

Angelman Syndrome

Alternative names

Although the term ‘happy puppet syndrome’, proposed by Bower and Jeavons in 1967 was widely used until the early 1990’s, the eponym ‘Angelman’ syndrome is generally preferred by families and professionals.

First description

In 1965, Doctor Harry Angelman, a general paediatrician in Warrington, described three children with severe developmental delay, ataxia, prolonged bouts of laughter, seizures and similar craniofacial features. He referred to these patients as ‘puppet children’.

Genetic aspects

Angelman syndrome is caused by a disruption of the maternally inherited proportion of chromosome 15q11.2-13 (Clayton-Smith & Laan, 2003; Knoll et al., 1989) via four known genetic mechanisms (Jiang et al., 1998). Approximately 70% of cases are caused by a de novo deletion (Knoll et al., 1989). The deletion can be further categorised as a ‘Class I’ or ‘Class II’ depending on the amount of information missing (Sahoo et al., 2006), with Class I deletions representing a larger deletion, encompassing Class II. The majority of deletions in Angelman syndrome are Class II, with an estimated prevalence of between 55 and 60% of de novo deletions (Christian et al., 1995). 2-7% of cases are caused by uniparental disomy (UPD; Engel, 1993; Prasad & Wagstaff, 1997), where two copies of the paternal chromosome are inherited, 2-8% of cases are caused by a mutation in the UBE3A gene (Kishino, Lalande, & Wagstaff, 1997) and 2-5% of cases are caused by an imprinting centre defect (ICD; Bürger et al., 1997). In around 40-50% of ICD cases caused by an epimutation, mosaicism is identified (Buiting, 2010; see Le Fevre et al., 2017 for case reports). Between 5-20% (dependent upon sample and extent of molecular investigations) of individuals with the physical and behavioural features of Angelman syndrome show no identifiable abnormalities in the 15q 11-13 region (Clayton-Smith & Laan, 2003; Williams, Lossie, & Driscoll, 2001). Explanations for when no abnormality can be detected can be that there are currently unidentified mechanisms that affect the expression of UBE3A or there is a misdiagnosis of another syndrome that is phenotypically similar to Angelman syndrome (Bird, 2014). There are several syndromes that phenotypically overlap with Angelman syndrome which can result in misdiagnosis (for reviews of ‘Angelman-like’ syndromes see Tan, Bird, Thibert, & Williams, 2014; Williams, Lossie, & Driscoll, 2001). The genetic association between Angelman syndrome and Prader-Willi syndrome has evok ed interest in genomic imprinting (see Brown & Consedine, 2004; Haig & Wharton, 2003 for an excellent discussion).

Many of the features of the syndrome are thought to result from impaired expression of UBE3A. This gene is found throughout the brain and has a role in proteic scavenging processes. This expression is normally determined epigenetically by a methylation pattern which is specific to the maternally inherited chromosome. Abnormal imprinting in various regions of the brain and the cerebellum are probably responsible for most of the phenotype.

Incidence/prevalence

Prevalence rates vary between 1 in 10,000 and 1 in 40,000 live births (Buckley, Dinno, & Weber, 1998; Clayton-Smith, 1993; Petersen, Brøndum-Nielsen, Hansen, & Wulff, 1995). Reports on the male to

female ratio of Angelman syndrome are inconsistent, with estimates given between 1:1 to 1:2 (Saitoh etal., 1994; Smith et al., 1996).

Physical phenotype

Craniofacial features include microbrachycephaly, short, hooked nose, prognatism, wide smiling mouth, widely spaced teeth and hypopigmentation (Williams et al., 2006). Facial change with age, with a 'coarsening' of facial characteristics into adulthood (Sandanam et al., 1997).

Clinical phenotype

Children and adults are reported to have difficulties with movement and balance (Williams et al., 2006) and ataxic gait thought to be caused by cerebellar dysfunction (Chéron, Servais, Wagstaff, & Dan, 2005). Scoliosis may develop, especially in less mobile patients. Axial hypotonia is present from birth. Limb hypertonia predominating at the lower extremities appears in infancy. As individuals with Angelman syndrome get older, they tend to become less mobile, although the majority do remain independently mobile (Larson, Shinnick, Shaaya, Thiele, & Thibert, 2015; Prasad, Grocott, Parkin, Larson, & Thibert, 2018).

Early onset of seizures in Angelman syndrome (< 3 years) is reported in over 80% of individuals (Williams et al., 2006) and seizures persist into adulthood (Laan, den Boer, Hennekam, Renier, & Brouwer, 1996; Larson et al., 2015; Thibert et al., 2009). Abnormal EEG is found in most cases of Angelman syndrome (Boyd, Harden, & Patton, 1988) regardless of the presence of seizures (Laan & Vein, 2005).

Around 45% of individuals with Angelman syndrome have sleep difficulties (Agar et al., 2021). A range of sleep difficulties are reported in Angelman syndrome, the most common of which is insomnia affecting all phases of sleep (i.e. initiation, maintenance, morning awakening) (Agar et al., 2021; Bruni et al., 2004; Trickett, Heald, Oliver & Richards, 2018). Other difficulties reported are sleep disordered breathing (Bruni et al., 2004; Miano et al., 2005, Trickett et al., 2018), reduced total sleep time, sleep bruxism (teeth grinding) sleep enuresis (bed wetting), sleep-related movement disorders and excessive daytime sleepiness (Agar et al., 2021; Spruyt, Braam & Curfs, 2018).

Behavioural aspects

The behavioural phenotype of Angelman syndrome is characterised by heightened levels of laughing andsmiling, a happy demeanour, excessive sociability, aggression, impulsivity and sleep disorders (Horsler &Oliver, 2006a). Early work suggested that frequent laughing and smiling was neurologically driven, and therefore environmental factors were not influential (Williams, Frias, & Opitz, 1982). However, careful experimental manipulation of the environment identified that both the frequency and duration of these behaviours are related to environmental context, namely adult interaction (Horsler & Oliver, 2006b; Oliver,Demetriades, & Hall, 2002). Increased prevalence of aggression, not self-injury, is reported (Arron, Oliver,Moss, Berg, & Burbidge, 2011), with typical topographies including hair pulling and skin grabbing (Summers, Allison, Lynch, & Sandier, 1995). Although it has been suggested that social motivation underpins the heightened aggression in Angelman syndrome, this is not shown consistently in the literature (Allen et al., 2010; Radstaake et al., 2013; Strachan et al., 2009).

Other behaviours that have been related to the behavioural phenotype of Angelman syndrome include sensory processing impairments, particularly sensory seeking behaviours, reported in 74% of individuals (Heald et al., 2019; Walz & Benson, 2002), and a specific profile of repetitive and stereotyped behaviours most notably hand-flapping (Moss et al., 2009; Summers et al., 1995; Walz & Benson, 2002). There have also been reports of abnormal eating and feeding behaviour in around 36% of cases (Horsler & Oliver, 2006a). These behaviours consist of overeating and a narrow range of food preferences (Clarke & Marston, 2000), and when compared to other genetic syndromes, individuals with Angelman syndrome scored higher for taking and storing food,

preoccupation with food, and impaired satiety, which overlaps with the profile seen in Prader-Willi syndrome (Welham et al., 2015). Recent reports have indicated that anxiety may be prevalent in Angelman syndrome, with estimates between 26-92% (dependent on measures used and age of sample) (Grebe et al., 2022; Keary et al., 2021; Wheeler et al., 2019; Prasad et al., 2018). In particular, separation from a primary caregiver is reported as a frequent cause of anxiety (Keary et al., 2021; Wheeler et al., 2019).

Cognitive aspects

Angelman syndrome is associated with a severe to profound intellectual disability, with deficits found in allareas of adaptive behaviour and cognition (Gentile et al., 2010; Peters et al., 2004). Comparisons across cognitive skills suggest relative strengths in socialisation (Peters et al., 2004) and deficits in learning and attention (Jiang et al., 2010; Walz & Benson, 2002). Although broad communication difficulties are shown (Clayton-Smith & Laan, 2003), Angelman syndrome is associated with a particular communication phenotype characterized by a near universal absence of speech that is dissociated from receptive and non-verbal communicative abilities (Pearson et al., 2019). Some individuals with Angelman syndrome are successful at using alternative and augmentative communication (AAC) to communicate with others (Calculator, 2013a,b; Roche et al., 2020).

Genotype x phenotype correlations

Genotype x phenotype correlations have been reported with agreement that a de novo deletion results in a more severe and 'classical' phenotype than non-deletion mechanisms (Fridman, Varela, Valente, Marques-Dias & Koiffmann, 2002; Gentile et al, 2010; Lossie et al., 2001; Mertz et al., 2014). UBE3A pathogenic variants, UPD and ICD are associated with lower severity, frequency and later onset of seizures, earlier achievement of developmental milestones and development of obesity (Fridman et al., 2002; Lossie et al., 2001). Non-deletion mechanisms are also related to a higher cognitive ability and receptive language skills and greater likelihood of acquiring a few spoken words (Gentile et al., 2010; Lossie et al., 2001; Mertz et al.,2014).

Differences in the phenotype between the non-deletion aetiologies are less researched and results are inconsistent, but a larger scale study suggests that UBE3A pathogenic variants and ICD present a milder phenotype than UPD (Keute et al., 2021). Comparisons across the deletion classes (Class I and Class II) highlight Class I deletions (larger amountof information missing) as being associated with lower levels of adaptive and cognitive functioning, including expressive language (Sahoo et al., 2006; Varela, Kok, Otto, & Koiffmann, 2004).

Life expectancy

It is estimated that life span may be 10-15 years shorter (Williams, Driscoll, & Dagli, 2010), although this has not been examined directly.

Key references

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Updated May 2022 (Previous version: August 2017)
