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Angelman syndrome: a review of clinical and genetic aspects

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Abstract

This paper reviews Angelman syndrome (AS) with regard to the clinical features in childhood and adulthood, epileptic seizures and EEG findings, neuroimaging studies and the present knowledge on the genetic mechanisms underlying this syndrome. Different clinical phenotypes and genotypes of AS are described, including chromosome 15q11–13 deletion, uniparental disomy, methylation imprinting abnormalities and mutations in the UBE3A gene. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Angelman syndrome; Clinical aspects; Epilepsy; Genetics; Review

1. Introduction

Angelman's syndrome (AS) has been widely reported during the past 10 years, mainly due to the newly discovered genetic mechanisms underlying this disorder. This has led to an increasing number of AS patients being diagnosed at a relatively younger age. Over 450 AS individuals have now been reported, including familial cases. The prevalence of AS is estimated to be around 1/10 000–1/20 000 [1,2]. The phenotype in children has been well described, but the adult phenotype is not well known because many adult patients with AS were already institutionalized before this syndrome was widely recognized and will, therefore, not have been diagnosed. Currently, AS is a clinical diagnosis that can be confirmed by either cytogenetic or DNA testing in about 80–85% of the cases.

This paper presents a survey of the clinical features of the syndrome, the EEG findings, results of neuroimaging studies and the genetic mechanisms involved.

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History

In 1965, Harry Angelman, an English pediatrician, reported three children with a similar pattern of mental retardation, seizures, ataxia, easily provoked laughter, absent speech and dysmorphic facial features [3]. He called them 'puppet children', because of the superficial resemblance to puppets in view of their flat head, jerky movements, protruding tongue and bouts of laughter. They reminded him of a painting in Museo di Castelvecchio in Verona by Giovanni Francesco Caroto (ca. 1480–1546) depicting a happy, young boy holding a puppet (Fanciullo con Pupazzo) [4].

His observations were confirmed over the next decade by other clinicians, and a pejorative term, 'happy puppet syndrome', was introduced, not only referring to their gait but also to their joyous facial expression and fits of inappropriate laughter [5]. Williams and Frias proposed the name 'Angelman's syndrome' because the term 'happy puppet syndrome' was considered derogatory by the majority of parents and many professionals [6]. A consensus for diagnostic criteria was established in 1995 (Tables 1 and 2) [7].

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3. Clinical features

3.1. Dysmorphic features

The features of AS frequently become apparent at 1–4 years of age, the average age at diagnosis being 6 years [8–10]. The facial features evolve over the first 5 years of life. Typical features include brachycephaly and a head circumference below the 25th centile [1]. A horizontal occipital groove is found in 35% of the patients. The mouth is large, giving rise to widely spaced but otherwise normal teeth.

The upper teeth may protrude because of persistent tongue thrusting.

Table 1
The work-up of patients with Angelman syndrome: Angelman syndrome—developmental history and laboratory findings[a]

1	Normal prenatal and birth history with normal head circumference. Absence of major birth defects
2	Developmental delay evident by 6–12 months of age
3	Delayed progression of development (no loss of skills)
4	Normal metabolic, hematological and chemical profiles
5	Structurally normal brain using MRI or CT (may have mild cortical atrophy or dysmyelination)

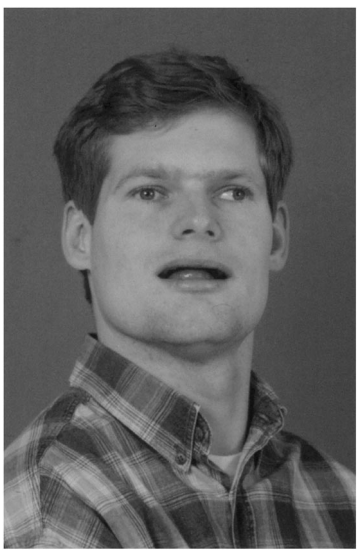
[a] These findings are useful as inclusion criteria but deviations should not exclude diagnosis (according to Williams et al. [7]).

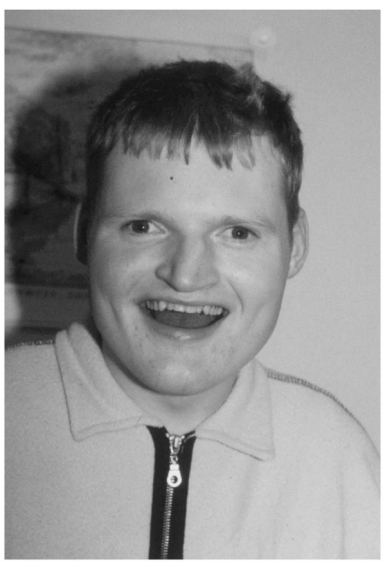
Table 2
Angelman syndrome: clinical characteristics[a]

A. Consistent (100%)	
	Developmental delay, functionally severe
	Speech impairment, no 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
B. 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 [8]
C. Associated (20–80%)	
	Flat occiput
	Occipital groove
	Protruding tongue
	Tongue thrusting; sucking/swallowing disorders
	Feeding problems during infancy
	Mandibular prognathia
	Wide mouth, widely-spaced teeth
	Frequent drooling
	Excessive chewing/mouthing behavior
	Strabismus
	Hypopigmented chin, light hair and eye color (compared to family), seen only in deletion cases
	Hyperactive lower limb deep tendon reflexes
	Uplifted, flexed arm position especially during ambulation
	Increased sensitivity to heat
	Sleep disturbance
	Attraction to/fascination with water

[a] According to Williams et al. [7].

The chin is pointed and there is mandibular prognathism. There is usually a thin upper lip and midfacial hypoplasia. The eyes are deep set and often blue. Strabismus is seen in about 40% of the patients [1]. Severe visual problems are not common. Hypopigmentation, compared to family members, is present in about 40–73% of the patients [1,11]. A coarsening of facial features with increasing age has been reported, with marked mandibular prognathism, a pointed chin, macrostomia and a pronounced lower lip [12–14]. Keratoconus is a problem of the older AS patients and appears to be related to persistent eye-rubbing over the years [6,13–16]. The oldest patient reported to date, is a 76-year-old man who demonstrated advanced keratoconus at age 46 and who became blind at age 74 following repeated intraocular hemorrhages [15].





3.2. Psychomotor development and neurological findings

Pregnancy and delivery are usually uneventful but the newborns tend to weigh 200–300 g less than their sibs [1]. They often have feeding problems, probably due to regurgitation and difficulty with sucking or swallowing, leading to weight loss and growth stagnation [1,9]. All patients have severe mental retardation and delayed motor milestones. They sit unsupported at the age of about 12 months, crawl or bottom-shuffle at the age of 18–24 months and walk at about 4 years of age (range: 18 months–7 years) [1]. Jerky movements become apparent during the first few months and motor delay is obvious by nine months of age. The jerky movements, tongue thrusting, mouthing, and hand-flapping when walking, are all characteristic.

Language does not develop with most patients having a vocabulary of only one or two words despite having reasonable comprehension of simple commands and sentences. Some have learned to communicate with sign language or other gestures. The gait is slow, ataxic and stiff-legged with the characteristic posture of raised arms with flexed wrists and elbows. There is a truncal hypotonia with hypertonia of the limbs. Reflexes are brisk. Infantile thoracic scoliosis occurs in 10% of the cases.

Walking difficulties are encountered in many adult patients due to ataxia, severe scoliosis, and limb hypertonia. In some studies the percentage of AS patients having thoracic scoliosis ranged from about 40% [12,14] to even 71% [13]. This difference is probably explained by the fact that the first two authors examined smaller adult patient groups. Scoliosis is seen both in ambulatory and non-ambulatory patients and may require orthopedic treatment by brace and sometimes by surgery [13]. General health is good and life expectancy is normal.

3.3. Behavioral characteristics

Paroxysms of easily provoked, prolonged laughter may start as early as the age of 10 weeks and become more evident in the first 6–12 months of life [1,3]. Almost all patients are 'happy' and smile frequently. Their laughter is provoked by minimal stimuli and occasionally inappropriate. Hyperactivity and sleep disturbance are common in childhood. AS children love water, have a fascination for mirrors, reflections and plastic [1]. Other favorite activities are watching television, and looking at magazines.

Most of the adult AS patients also present a happy demeanor. Paroxysms of laughter still occur, although less frequently than in childhood [13,14]. Most adult patients are very curious [13]. The hyperactivity of childhood changes to quieter behavior in adult patients [12–14]. All adults are able to concentrate on one activity for a longer period of time. Almost all AS patients are capable of performing simple tasks, such as handling a spoon or a fork or (un)dressing themselves. Many adult AS patients can be (clock-)toilet-trained by day, and some of them also by night [13].

4. Epileptic seizures

Epileptic seizures occur in about 80% of the patients. Age at onset varies from one month to 5 years (mean, 2–3 years). The initial symptoms of epilepsy are febrile convulsions in infancy in about 40% of the patients [17,18]. In childhood, a diversity of seizures can be

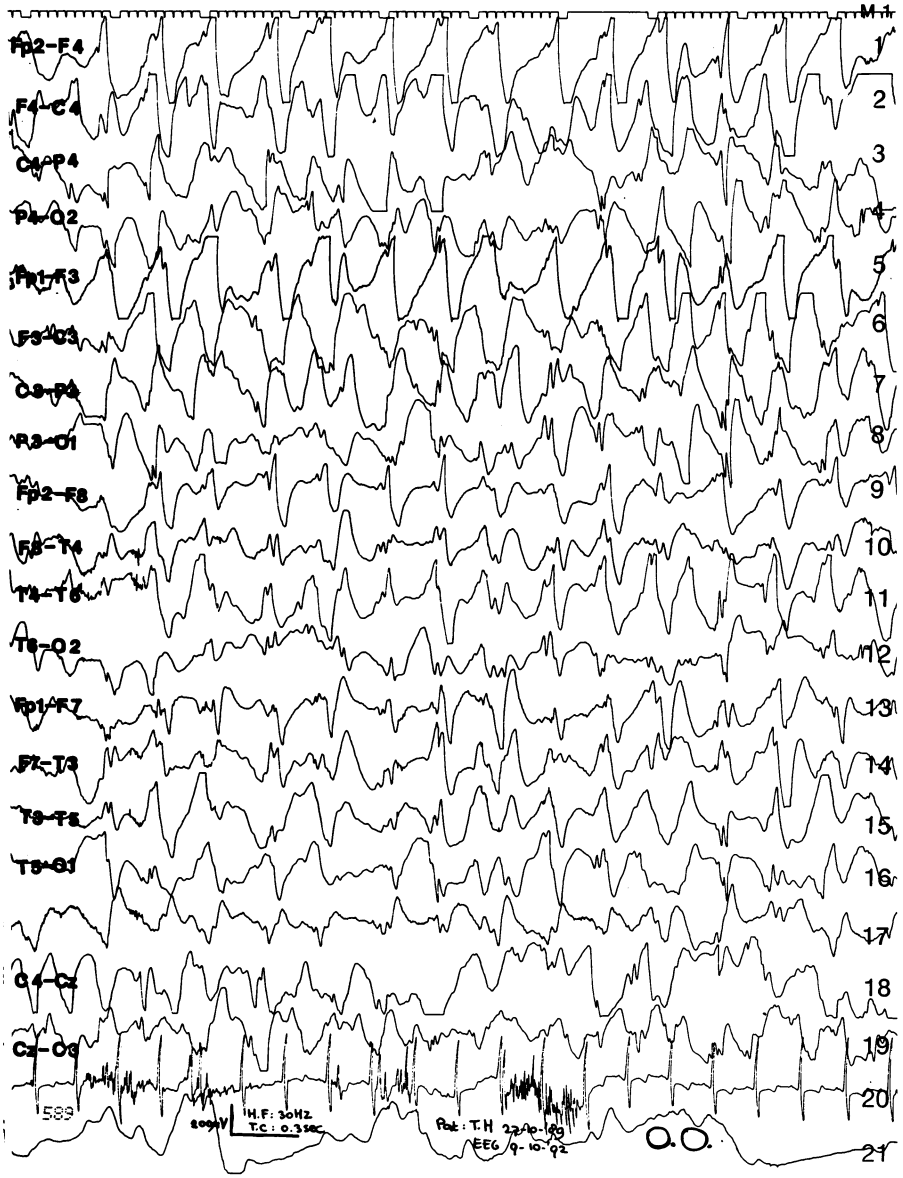


Fig. 1. Typical triphasic delta waves with a maximum over the frontal regions in a 3-year-old AS patient.

observed, ranging from tonic-clonic seizures, atypical absence seizures, myoclonic seizures, and tonic seizures to status epilepticus. Absence status and myoclonic status epilepticus may also occur. Seizures are often difficult to control, especially in early childhood. Some reports [1,17,19] suggest a decreasing frequency of epileptic seizures with age, but we found that more than 90% of the adult patients still have epileptic seizures [18]. In adulthood, atypical absence seizures, myoclonic seizures, or a combination of the two are most prominent [18]. Epileptic seizures are more difficult to control with antiepileptic drugs (AEDs) in patients with a chromosomal deletion [20,21].

The most effective AEDs are valproate (VPA) in combination with clonazepam (CZP) or other benzodiazepines, whereas carbamazepine (CBZ) sometimes has an adverse effect [17,18,21]. In adult AS patients phenobarbital (PB) is also effective. Experience with vigabatrin and lamotrigin is very limited.

5. EEG findings

There are specific EEG patterns in AS patients, which may appear in isolation or in various combinations, either in the same EEG recordings or at different times in the same patient (Fig. 1) [5,8,18,19,22]. Boyd et al. [8] described EEGs of 19 AS children in detail and found the following EEG abnormalities: (1) Persistent rhythmic 4–6/s activities reaching more than 200 μV not associated with drowsiness. (2) Prolonged runs of rhythmic 2–3/s activity (200–500 μV) often more prominent anteriorly, sometimes associated with discharges (ill-defined spike/wave complexes). (3) Spikes mixed with 3–4/s components usually more than 200 μV mainly posteriorly and facilitated by, or only seen with, eye closure. The high voltage 4–6/s activity is only seen in childhood. Rhythmic triphasic 2–3 Hz activity of high amplitude (200–500 μV), mixed with spikes or sharp waves with a maximum over the frontal regions, present intermittently or sometimes continuously, usually persists in adulthood. These EEG features are characteristic in AS and can occur before a clinical diagnosis AS is considered in about 45% of these children [18]. The eye-closure test is seldom possible in these hyperactive, severely retarded children. Therefore, the findings of Boyd et al. could not be confirmed in EEG examinations by other authors. The EEG findings are similar in patients with and without seizures [18,21,23]. There is no correlation between any particular EEG pattern and the paroxysms of laughter [8]. Prolonged video-EEG recordings showed that the paroxysms of laughter were not epileptic in nature [24]. EEG examination can play an important diagnostic role in the appropriate clinical context. The rhythmic triphasic waves of high amplitude with a maximum over the frontal regions have been mentioned as hypsarrhythmia or Lennox-Gastaut status in the literature, but are in fact different from the above-mentioned triphasic 2–3 Hz activity with spikes or sharp waves over the frontal regions.

6. Neuroimaging

Two studies mentioned computerized tomography (CT scan) findings. They were normal or showed cerebral atrophy and ventricular dilatation in a minority of the patients [1,12]. One report described an abnormally convoluted surface area of the cortex in the parietal lobe of the Sylvian fissure in the supramarginal gyrus, using specific techniques in magnetic resonance imaging (MRI) [25]. One study found abnormalities in 80% of AS patients, varying from enlarged insular cisterns, small temporal opercula, enlarged frontal interhemispheric fissure, enlarged temporal horns and hypoplasia of the frontal lobes, indicative of atrophy of the frontal and temporal lobes [63]. Imaging studies in adult patients did not show more atrophy than those in children, suggesting a non-progressive underdevelopment of the frontal and temporal lobes in AS. CT/MRI findings in patients with a deletion of chromosome15q11–13, epileptic seizures or microcephaly did not differ from those without these features [63]. In our opinion the abnormalities on CT and MRI scans, although aspecific, have a characteristic distribution pattern, which as such may be of diagnostic help in those patients who cannot be identified by genetic methods.

7. Pathology

Two neuropathological studies have been published with different findings [26,27]. The first describes mild cerebral atrophy and cerebellar degeneration in one patient, the second mentions relatively small frontal and temporal lobes with an abnormal convolutional pattern in another single case. Both studies mention an irregular distribution of neurons in layer 3 of the cerebral cortex. Jay et al. found this phenomenon also in layer 5.

8. Genetic mechanisms

8.1. Background

Cytogenetically visible deletions of the proximal long arm of chromosome 15q11–13 were first associated with Prader-Willi (PWS) syndrome [28]. In 1987, apparently the same deletion was also reported in 60% of AS

Table 3
Angelman syndrome: genetic testing abnormalities[a]

A	High resolution G-banded chromosome study showing deletion of 15q11–13. Because of the possibility of false positive and negative results from this study, G-banding should not be used as a stand-alone test but should be extended by fluorescence in situ hybridization (FISH), polymorphism, or methylation analysis
B	Abnormal FISH indicating a deletion of cloned 15q11–q13 DNA sequences that are included in the Angelman syndrome critical region. Use of a pericentromeric FISH probe enhances ability to detect subtle translocation
C	DNA polymorphism analysis showing absence of maternal alleles at 15q11–q13 loci, which may result either from maternal deletion or from paternal uniparental disomy
D	Characteristic DNA methylation pattern (i.e. paternal imprint only) of 15q11–q13 cloned DNA sequences using methylation-sensitive restriction endonucleases. An abnormal methylation pattern in individuals without 15q11–q13 deletion is not a stand-alone test for uniparental disomy
E	UBE3A mutation analysis to detect mutations in the E6-AP ubiquitin-protein ligase gene on chromosome 15q11–13

[a] According to Williams et al. [7,56,57].

patients [9,29,30]. PWS is characterized by hypotonia and failure to thrive in infancy, variable mental retardation, hypogonadism, narrow bifrontal diameter, decreased retinal pigmentation, short stature, small hands and feet in later childhood and hyperphagia leading to obesity and is thus phenotypically different from AS.

In 1989, it was shown that the deleted chromosome was of paternal origin in most PWS patients [31] and of maternal origin in AS patients [32,33]. The combination of classical cytogenetic analysis and fluorescence in situ hybridisation (FISH), can detect smaller deletions in the same region in about 70–80% of AS patients [34–38] (Table 3).

AS is a disorder in which genetic imprinting plays a role [38]. The term imprinting implies that genetic material (chromosome regions or individual genes) is 'marked' or designated in some way depending upon whether it is inherited from the mother or the father. Imprinting most likely occurs during meiosis. During this stage the genes that a woman inherited from her father must be redesignated as 'maternal' so that they will act in a maternal manner as she passes them on to her own offspring. Similarly, the genes that a man inherits from his mother must be changed to 'paternal' [39]. Imprinting must, therefore, be reversible (i.e. it must switch when the germline sex changes). Within chromosome 15q11–13, multiple genes have been identified that are regulated by imprinting. DNA methylation represents at least part of the mechanism of this somatic and germline regulation [38,40]. In 5% of the

Table 4
Genetic etiology

Deletion of chromosome 15q11–13	75%
Paternal uniparental disomy	2–3%
Methylation imprinting mutation	2–3%
UBE3A Mutations	2–3%
Unknown	15–20%

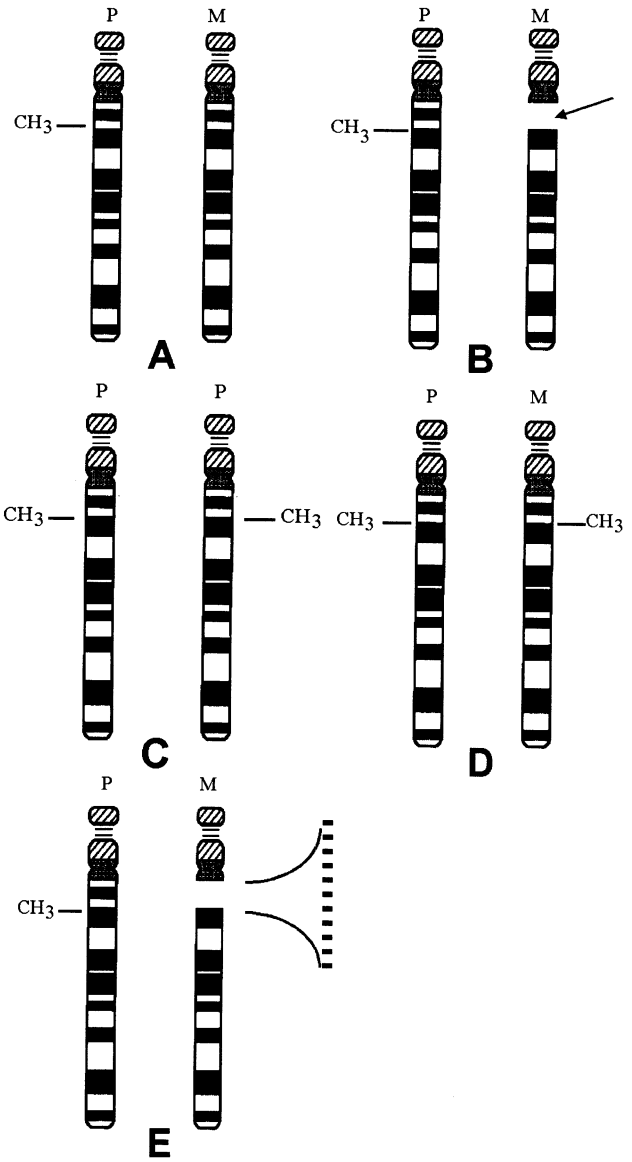


Fig. 2. Schematic representation of chromosome 15 and the relevant genetic etiologies. P, paternal; M, maternal; CH3, methylated gene (inactive); A, normal situation; B, deletion of chromosome 15q11–13; C, uniparental (paternal) disomy; D, imprinting mutation (methylation); E, UBE3A mutations.

AS and PWS families, mutations are found in the imprinting process. About 50% of these cases have microdeletions in the gene sequence which can encode an alternative transcript or the promotor of the imprinted SNRPN gene, respectively, defining an element which is called the imprinting center. The imprinting center elements mutated in these AS and PWS patients appear to control resetting of the primary imprint during gametogenesis (paternal → maternal imprint switch in oogenesis and maternal → paternal imprint switch in spermatogenesis, respectively). A translocation family has been described in which patients with Prader-Willi syndrome as well as patients with Angelman syndrome shared the same abnormal karyotype but differed in phenotype because they inherited the unbalanced translocation through parents of opposite gender [41].

Genetic etiology of AS can be categorized into five main groups (Table 4; Fig. 2):

8.1.1. Cytogenetic and molecular deletion of chromosome 15q11–13

Most AS cases are caused by large maternally inherited deletions in chromosome 15q11–13. These can be detected by high resolution banding analysis in approximately 60% of AS patients [42,43] and with molecular techniques (fluorescence in situ hybridisation (FISH) and methylation analysis) in about 80% of AS patients [34,44]. Genes encompassed in this deletion include three γ-aminobutyrate-A ($GABA_A$) receptor subunit genes, candidate genes for epilepsy. $GABARB_3$ especially, the most centromeric of the three GABA receptor genes, is suspected to play a role in AS and some researchers hypothesized that deletion of $GABARB_3$ results in severe epilepsy in the group of AS patients with a deletion of chromosome 15q11–13 [21]. There is only one AS family described, in which three sibs carried a maternally derived, submicroscopic deletion [45]. Such mutations may be inherited in an autosomal-dominant manner, influenced by genomic imprinting.

The recurrence risk of AS in subsequent children in families with a child with a de novo deletion is approximately 2 = 1% [46].

8.1.2. Uniparental disomy

In 1991, Malcolm described uniparental paternal heterodisomy (UPD) in two AS patients. In these cases, both chromosomes 15 are inherited from the father [36]. The chromosomes themselves are normal. Later on, another child with UPD was reported, using DNA markers [47]. UPD occurs in about 2–3% of AS patients [47,48]. The most likely explanation is a trisomic concept followed by loss of the maternal chromosome 15 [36]. Of course other mechanisms can also take part as monosomic rescue [49]. Nicholls and colleagues have found that Prader-Willi syndrome may arise when both of the apparently normal chromosomes 15 have been inherited from the mother because of uniparental maternal heterodisomy or isodisomy [31]. This finding confirms that this region of chromosome 15 is subject to imprinting. It also indicates that a maternal contribution at the Angelman's locus is essential for normal development and that two normal paternally derived chromosomes are not sufficient [36]. The AS phenotype tends to be milder in patients with UPD as compared to AS patients with a deletion [50]. UPD is detectable by methylation tests and polymorphism analysis. The recurrence risk is likely to be extremely low.

8.1.3. *Methylation imprinting mutations*

Imprinting mutations causing AS are characterized by biparental inheritance and a paternal methylation pattern on both chromosomes 15q11–13 (Fig. 2). They are also rare [44,51]. These cases are frequently associated with small deletions in the imprinting center. They are detectable with a methylation test. The risk to subsequent children can be as high as 50% and sibs of the same sex as the carrier parent have the same risk for their children if they also carry the deletion [52]. A number of familial cases can be explained by this mechanism [53].

8.1.4. UBE3A mutations

In 1997, two groups described mutations in the E6-AP ubiquitin–protein ligase gene (UBE3A) in AS patients, located within the 15q11–13 region [54,55]. Two de novo truncating mutations were identified in exon 3, a two base pair deletion (1344delAG) and a nonsense mutation (Arg417stop). Two missense mutations were identified. In addition, a 4bp deletion in the coding region was identified in a large family with inherited AS. A 5-bp de novo tandem duplication was also found and a heterozygous mutation in two brothers, an A to G transition. These mutations can each lead to a premature stop codon and therefore to a complete lack of UBE3A function, which plays an obligatory role in ubiquitin-mediated proteolysis during normal brain development. Since then, other mutations in UBE3A have been found. Recent studies have shown that the UBE3A gene inherited from the mother is active at a much higher level than the gene inherited from the father. These results indicate that AS is caused by loss of maternal expression for UBE3A [56]. Recurrence risk to subsequent children varies from nearly 0 (when there is a new mutation in the proband) to 50% (when it is inherited from a mother, who has a new mutation or from a mother, who inherited it from her father). Mutation analysis is important for genetic counseling of these families. There are several families where affected siblings but the mother does not have the mutation so she must be a genetic mosaic and this means, that even if you have a sporadic single case where the child has the mutation and the mother doesn't, there is still a significant risk that this mother is a germline

mosaic [57]. It has been demonstrated that some families with affected siblings have imprinting defects but none is present in the mother. We assume that the mother is a germline mosaic and also in those families there is a recurrence risk of 0–50% [62].

8.1.5. The 'quadruple-non' group

The remaining 15–20% of AS patients show none of the genetic abnormalities mentioned above and are, therefore, also named the 'quadruple-non' group. These quadruple-non AS patients may have other specific mutations. This group includes a significant number of familial cases in which the recurrence risk is probably high (up to 50%).

9. Differential diagnosis

The diagnosis of Angelman syndrome is based on the history, clinical features, behavior, EEG findings, and the presence of genetic abnormalities in about 80% of patients. In the remaining 20% no genetic abnormality can be found. Girls with Rett syndrome have overlapping clinical features. The main characteristic of having a history of regression with loss of acquired skills in Rett syndrome distinguishes them from Angelman syndrome children who never acquire the skills from the beginning [58]. The recently delineated syndrome of X-linked alpha thalassemia and mental retardation has many phenotypic features in common with Angelman syndrome [59]. The facial features of these severely mentally retarded boys include microcephaly, marked hypertelorism, epicanthus, a small, triangular, upturned nose with marked hypoplasia of the nasal bridge, and a flat face. Other particular characteristics are genital abnormalities (undescended testis, shawl scrotum). This diagnosis has been confirmed in a boy who was previously thought to have Angelman syndrome [60]. Non-progressive encephalopathy with mental retardation, infantile autism and non-specific cerebral palsy may also mimic the features of AS [7].

10. Therapy

At present there is no specific therapy for AS patients. Epileptic seizures often need AEDs and good results are achieved with valproic acid and clonazepam. Physiotherapy is very important for AS patients to keep them mobile as long as possible and to minimize orthopedic interventions. The use of non-verbal communication is potentially useful for them, but attempts to train the use of signing to augment their speech may be unsuccessful due to their poor imitation skills and possible motor organisational difficulties [61].

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