American Journal of Medical Genetics 101:59–64 (2001)

Angelman Syndrome: Mimicking Conditions and Phenotypes

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The diagnosis of Angelman syndrome (AS) can be confirmed by genetic laboratory in about 80% of cases. In 20%, the diagnosis remains clinical, but often there is uncertainty about the correctness of the clinical diagnosis and alternative diagnosis may be investigated. In evaluating individuals for AS in our center since 1989, we have encountered several mimicking conditions, and additional ones have been reported in the literature. Mimicking conditions can be grouped into the areas of chromosome, single gene, and symptom complex anomalies. Microdeletions or microduplications include chromosome regions 2,4,17, 22, and 15. Single gene conditions include methylene tetrahydrofolate reductase deficiency (MTHFR), Rett syndrome, alpha-thalassemia retardation syndrome (ATR-X), and Gurrieri syndrome. Symptom complexes include cerebral palsy, static encephalopathy, Lennox-Gastaut syndrome, autism spectrum disorder, pervasive developmental delay (PDD), and mitochondrial disorders. We present a review of these mimicking disorders to increase the awareness about conditions that can lead to an incorrect clinical diagnosis of AS. © 2001 Wiley-Liss, Inc.

KEY WORDS: Angelman syndrome; mimicking conditions; phenotype; diagnosis

INTRODUCTION

In 1965 Dr. Harry Angelman first described the syndrome that now bears his name [Angelman, 1965]. However, it was many years before the syndrome's importance was recognized, partly because the syndrome did not involve provisionally unique anomalies or malformations. Nevertheless, physicians evaluating children with severe speech delay, happy affect, epilepsy, and movement disorders were able to recognize increasing numbers of affected children. Now, the incidence of this condition appears to be about 1/12–20,000 [Clayton-Smith and Pembrey, 1992; Steffenburg et al., 1996] and AS has emerged as a prototypical genetic syndrome involving seizures and severe developmental delay.

There have been several recent reviews of the molecular mechanisms causing AS [Jiang et al., 1999; Mann and Bartolomei, 1999]. Five categories of AS can now be distinguished: 1) maternal deletions of 15q11–q13 (68–75%) (Also included in this group are rare families with unique translocations and smaller deletions within 15q11–q13.); 2) paternal UPD of chromosome 15 (2–7%); 3) imprinting center abnormalities (2–5%); 4 *UBE3A* mutations (8–11%); and 5) a group with the AS phenotype but negative genetic testing for the above four categories (10–20%). Percentages of AS individuals in each category vary somewhat depending on the clinical groups studied and the extent to which molecular investigation is pursued. Group 5 patients currently have the clinical and behavioral phenotypes of AS but have normal genetic testing. This group causes the most angst among physicians and parents for several reasons, not the least being that determination of a precise genetic mechanism can identify families at increased risk for recurrence (e.g., for those with inherited imprinting center and *UBE3A* mutations). In this paper we review our program's experience with other clinical conditions that can mimic the features of AS. We also provide a review of the literature for the purpose of identifying conditions that might be considered as alternative diagnoses in individuals suspected to have AS but who have negative AS genetic testing.

METHODS

Since 1989, our program has established a clinical and molecular repository of AS individuals, as well as atypical cases. One hundred thirty-four families are now enrolled and most have classical or near classical

Grant sponsor: State of Florida, Department of Health, Childrens Medical Services, Raymond C. Philips Unit Contract.

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Received 23 August 2000; Accepted 18 January 2001
Published online 9 April 2001

TABLE I. Consensus Criteria for Angelman Syndrome

Clinical features	
Consistent (100%)	
Developmental delay, functionally severe	
Speech impairment, none 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	
Frequent (more than 80%)	
Delayed, disproprtionate growth in head circumference, usually resulting in microcephaly (absolute or relative) by age 2 years	
Seizures, onset usually <3 years of age	
Abnormal EEG, characteristic pattern with large amplitude slow-spike waves	
Associated (20–80%)	
Strabismus	Hypopigmented skin and eyes
Tongue thrusting; swallowing disorders	Hyperactive tendon reflexes
Feeding problems in infancy	Flexed arms during walking
Prominent mandible	Increased sensitivity to heat
Wide mouth, wide-spaced teeth	Sleep disturbance
Frequent drooling protruding tongue	Fascination with water
Excessive chewing/mouthing behaviors	Flat back of head

Adapted from Williams CA, Angelman H, Clayton-Smith J, Driscoll DJ, Hendrichson JE, Knoll JHM, Magenis RE, Schinzel A, Wagstaff J, Whidden EM, Zori RT, Angelman syndrome: consensus for diagnostic criteria. Am J Med Genet 1995;56:237.

features. We have used a clinical grading system to estimate the clinical certainty of the AS diagnosis: 1 = certain, 2 = probable, 3 = questionable, 4 = unlikely, and 5 = remote possibility. The grading system does not use an obligatory point system for any particular physical or behavioral trait but rather incorporates the AS consensus criteria (see Table I) [Williams et al., 1995] in combination with the impression of the clinician; 93/134 (69%) had scores of 1 or 2 and 41/134 (31%) had scores of 3 or 4. Those with scores of 1 or 2 have been thoroughly evaluated by genetic testing and 83/93(89%) have a test-confirmed diagnosis: 63 with large deletions, 10 with *UBE3A* mutations, 7 with UPD, and 3 with imprinting center mutations; 10/93 (11%) had apparent normal genetic testing. The 41 families with diagnostic grading scores of 3 or 4 also contained test-confirmed AS cases, but most have not had *UBE3A* mutation testing. Thus, this group contained mainly individuals with an unknown diagnosis. Most in this group had extensive neurological testing at several different centers.

In the process of establishing this repository, we have had the opportunity to consider the differential diagnosis in a large number of referred families and we have encountered several conditions that mimic the clinical features of AS. Additional ones have been reported in the literature and these are also reviewed for the purpose of developing a comprehensive differential diagnosis list.

RESULTS

Mimicking conditions can be grouped into the areas of chromosome, single gene and symptom complex anomalies (Table II)

Chromosome Disorders

Of the chromosome abnormalities reported, terminal deletions of 22q11.3 appear to be the most mimicking of the AS clinical phenotype. Terminal deletion that involves 22q13.3 has been reported in about 20 cases and often presents as cryptic subtelomeric deletions not

TABLE II. Angelman Syndrome Mimicking Conditions and Phenotypes

Chromosome disorders
22q13.3 terminal deletions
Del 15q12 (Prader-Willi)
Dup 15q12
Del 2q22-q23
Others: 4q 15.2; del 4q12; del 17q23.2
Single gene disorders
Rett syndrome
Alpha-thalassemia, retardation syndrome, X-linked (ATR-X)
Methylene tetrahydrofolate reductase deficiency (MTHFR)
Gurrieri syndrome
Symptom complexes
Cerebral palsy
Lennox-Gastaut syndrome
Static encephalopathy
Childhood autism
Pervasive developmental disorder, not otherwise specified (PDD-NOS)
“Mitochondrial” encephalopathy

easily detectable by routine GTC chromosome banding [Praphanphoj et al., 2000]. Often such deletions are detected serendipitously when a 22q11.2 microdeletion FISH test is ordered (e.g., DiGeorge/Velo-cardio-facial syndrome) [Precht et al., 1998]. The telomeric control probe used in this analysis (Oncor, D22S39) is missing in such terminal deletion cases. The q13.3 critical region comprises a subtelomeric region no more than 130 kb and is often associated with a subtle unbalanced translocation [Wong et al., 1997]. Precht et al. [1998] first reported the clinical similarity to AS in two patients who had severe expressive speech delay and hypotonia; one had unstable gait. In general, patients with 22q13.3 deletions have severe expressive speech delay and mental retardation but do not appear to have any major malformations. Seizures occur in a minority. We have recently evaluated a 4-year-old girl who had a de novo 22q13.3 deletion (Fig. 1). She spoke only a few words and exhibited an excessively happy demeanor; the resemblance to a high functioning AS child was striking.

On rare occasions a duplication, not deletion, of chromosome 15q11–13 can present with features of AS, especially if autistic-like features are present [Clayton-Smith and Pembrey, 1992]. This duplication represents the apparent reciprocal product of the deletion event and has now been described for many patients [Repetto et al., 1998; Schroer et al., 1998]. The duplication can be

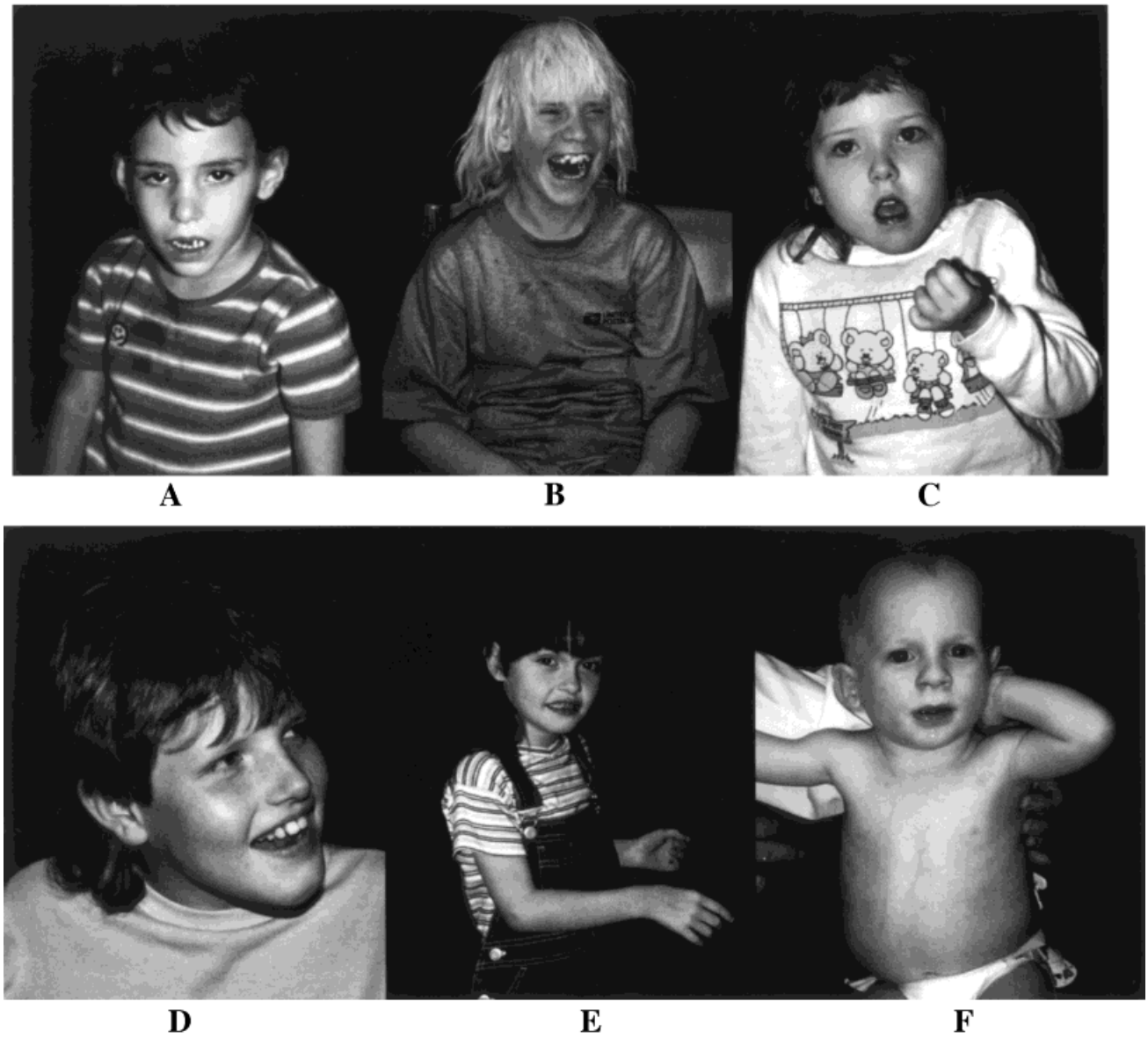

Fig. 1. Examples of mimicking conditions. **A**: Del (22) (q13). **B:** Del (4) (q12–q13). **C:** Rett syndrome. **D:** Severe methylene tetrahydrofolate deficiency. **E:** Infantile autism. **F:** Prader-Willi syndrome (PWS). This patient was misdiagnosed as PWS when FISH test showed a 15q11–13 deletion. Subsequent DNA methylation confirmed the AS diagnosis.

detected with the FISH probes that are used to detect deletions but often the duplication can be found on routine GTC chromosome preparations. In most cases, patients with duplication 15q11–13 have an autistic spectrum presentation, often in the higher function range and most have some expressive speech. Most cases can be easily differentiated from AS on clinical grounds. Although AS has been reported to manifest autism-like traits, AS individuals are definitely not autistic, especially in their ability to engage in appropriate social reciprocity and personal interactions. Deletions of 15q11–13 can be misdiagnosed as PWS in infancy if care is not taken to distinguish the clinical differences between AS and PWS [Dupont et al., 1999] (Fig. 1). In such situations, DNA methylation testing can distinguish between the two.

Mowat et al. [1998] recently described a syndrome characterized by mental retardation, severe speech delay, happy demeanor, and Hirschsprung disease. Four of the six developed Hirschsprung disease before age 6 weeks; two of the six had agenesis of the corpus callosum. Facial anomalies were subtle. Composite photographs showed many features of AS, including open mouth with visible tongue, prognathism, and a prominent columella with mild tapering of the nasal tip. One patient had an interstitial deletion on chromosome 2 in region q21–q23, but the other five children had normal chromosomes. Normal microsatellite studies of 2q21–23 region in them ruled against presence of a subtle microdeletion. The occurrence of brain malformations and/or Hirschsprung disease should easily distinguish this syndrome from AS, but cases without these abnormalities could conceivably be quite similar.

A child with an interstitial deletion of 17q23.2 has been reported to have AS-like features of excessive laughter, hand flapping, absence seizures, abnormal EEG, and global developmental delay [Mickelson et al., 1997]. The features that were not like AS were a 35 word spoken vocabulary and proximally placed thumbs. The authors advised high-resolution chromosome studies in all AS cases with normal genetic testing. Interstitial 4p deletion has been associated with AS-like features of excessive laughter, no intelligible words, excessive drooling, unsteady movements, blond hair, and fair skin [Innes et al., 1999]. Although AS was initially suspected, *SNRPN* methylation was normal but then high-resolution chromosome study showed a deletion of 4p15.2–16.1. We have evaluated a 13-year-old girl referred for hypopigmentation, hyperactivity with happy affect, wide-based gait, and severe speech impairment (could speak only a few words) who was referred to rule out AS. Upon review of records, it was evident that she had been previously diagnosed to have a 4q12–13.1 deletion (Fig. 1.). Interstitial deletions of bands 4q12–q13.1 have been noted to cause mental retardation, short stature, and nonspecific, typically minor physical anomalies [Slavotinek and Kingston, 1997]. The presence of piebald trait appears due to deletion of the c-kit oncogene that maps to 4q12 and is a distinctive clinical finding [Schinzel et al., 1997] but, as in our case, not all children have piebald trait.

Single Gene Disorders

Rett syndrome (RS) is probably the most common mimicker during the infant and toddler ages [Ellaway et al., 1998]. Muscular hypotonia, seizure disorder, unstable or awkward gait, and mild microcephaly may be the main presenting features of RS girls between 1 and 3 years of age. During this time, developmental regression and stereotypical midline movements characteristic of RS may not have emerged. There is also a significant group of RS "variants" who never exhibit sufficient diagnostic criteria for RS and who do not have obvious neurological regression [Clarke, 1996]. The higher cognitive ability in AS serves to easily distinguish them from RS, but the distinction may be less apparent in more profoundly impaired AS children who have a severe seizure disorder (Fig. 1.). The identification of a DNA methyl binding protein gene, *MECP2*, as the cause of RS now enables mutation testing. Mutation sensitivity is currently at about 50% [Amir et al., 1999; Xiang et al., 2000]. Nevertheless, molecular diagnosis may now be possible in some cases during early infancy, when confusion with AS can occur.

We have previously reported that methylene tetrahydrofolate reductase deficiency (MTHFR) can present with seizures, ataxia, happy affect, and absent speech [Arn et al., 1998]. The resemblance of this case to AS was striking but DNA methylation and FISH studies were normal (Fig. 1). Since this report, subsequent *UBE3A* mutation screening has been normal. Protruding tongue and profound mental retardation can be prominent in the syndrome of alpha-thalassemia and X-linked mental retardation (ATR-X) [Gibbons et al., 1995]. Families with an X-linked pattern of inheritance can easily be excluded from AS consideration. Cases of ATR-X without a positive family history however can be difficult to diagnose and these children often have nonspecific severe mental retardation and no laboratory evidence for alpha-thalassemia. Mutation testing for the ATR-X gene (X-linked Nuclear Protein: *XNP*) offers hope of improved diagnosis [Guerrini et al., 2000; Villard et al., 1999].

Early onset seizures and absent speech have been reported to mimic a recently described autosomal recessive mental retardation syndrome, Gurrieri syndrome, that also exhibits radiographic changes such as hypoplasia of the iliac alae and relatively tall vertebral bodies [Battaglia and Gurrieri, 1999]. These authors concluded that individuals with AS should be studied for possible bone dysplasias that might resemble that observed in the Gurrieri syndrome.

Symptom Complexes

Misdiagnosis can occur when children with cerebral palsy exhibit AS-like traits. These infants may have muscular hypotonia, feeding difficulty, and a happy affect. They can also present with ataxia and/or unstable gait or tremulous movements. Their prenatal and birth history may be unrevealing (as in AS) and the MRI, as often seen in AS, may be normal or show only the nonspecific changes of mild atrophy. Infants with spastic diplegia may also be considered to have AS, but

as they develop, higher cognitive functioning and emergence of expressive speech usually distinguish them from AS. Children with cerebral palsy have considerable etiologic heterogeneity [Bass, 1999]. Sometimes, however, the correct diagnosis of AS is often made in a child previously considered having nonspecific cerebral palsy.

Epilepsy in infancy, in association with mental retardation, can mimic the seizures and developmental delay of AS. Abnormal EEG's may lead to the diagnosis of Lennox-Gastaut syndrome (LGS), a syndrome that consists of slow spike-wave activity in the EEG, mental retardation, and intractable seizures of various types (e.g., tonic-clonic, absence, atonic, and tonic atypical) [Markand, 1977]. However, the EEG in LGS is grossly abnormal and has a characteristic pattern with diffuse slow spike/wave activity and fast recruiting rhythms during sleep. More often, undiagnosed AS children may be misdiagnosed as having LGS. However, some children with LGS who have vestigal speech and profound mental retardation can have AS-like traits and can be misdiagnosed as atypical AS. Most cases of LGS can be distinguished from AS on clinical grounds [Boyd et al., 1988]. Also a significant percentage of LGS have an earlier history of infantile spasms (i.e., hypsarrhythmia) [Rantala and Putkonen, 1999]. Infantile spasms, with onset usually before 6 months, is rare in AS.

Childhood autism may be misdiagnosed as AS, especially during the age of 2–4 years (Fig. 1). With advancing age, the pervasive features of autism serve to distinguish these children from AS, since AS children are usually social seeking and have good social reciprocity. Pervasive developmental disorder, not otherwise specified (PDD/NOS) is a general diagnostic label that is extraordinarily nonspecific and typically refers to children with pervasive disabilities who do not otherwise have autism, Rett syndrome, etc. [Volkmar et al., 1999]. PDD/NOS diagnosis may be a more appropriate diagnosis for many AS-like children who have negative AS genetic testing

We have also evaluated two children with mild lactic acidosis and encephalomyopathy who subsequently had resolution of their lactic acidemia and had positive genetic testing for AS. Some children with mitochondrial diseases will present in infancy with seizures, hypotonia, and a movement disorder. Most cases are easily distinguished from AS on the basis of neurological regression but some cases of apparent mitochondrial dysfunction appear to have static encephalopathy [Nissenkorn et al., 2000]. These cases seem more likely to be confused with other epilepsy syndromes like AS.

ACKNOWLEDGMENTS

We would also like to thank the families who have participated in the Angelman Syndrome Clinical and DNA Repository.

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