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Angelman Syndrome: Are the Estimates Too Low?

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More than 300 cases of Angelman Syndrome (AS) have been reported. AS is still considered a clinical diagnosis because only approximately 80% of those individuals who meet the clinical criteria will have a maternal deletion of chromosome 15q11-13. Of the reported cases of AS, very few are of adults with AS. We present our findings on 11 adults with AS identified in a long-term residential care facility for persons with severe developmental disabilities. The diagnosis of AS was not recognized at the time of their admission but was established as part of our evaluation. Thus, there may be an underestimate of the true incidence of AS especially in adults with severe developmental diabilities. Am. J. Med. Genet. 80:385–390, 1998.

KEY WORDS: Angelman syndrome; severe mental retardation; associated feature; adults; unprovoked laughter; movement disorder

INTRODUCTION

AS has often been thought to be a rare disorder. Because of the lack of recognition of this syndrome, the true incidence of AS is unknown and most likely has been underestimated. AS has been reported throughout the world among all racial groups, however, in the United States most cases have been reported in Caucasians [Williams et al., 1995b]. Of the reported cases of AS, very few are of adults. Reish and King [1995] suggested that this may well be due to the fact that adults with AS were institutionalized prior to the recognition of the disorder and that adults with AS are healthy and not referred to medical specialists who may recognize the syndrome.

We present our findings on 11 adults with AS identified in a long-term residential care facility for persons with severe and profound development disabilities. The diagnosis of AS was not recognized at the time of their admission to the facility but was established as part of our evaluation of the 225 adults examined.

We think there is an underestimate of the true incidence of AS specially in adults with severe developmental disabilities. A careful history, examination, and behavior observations are crucial in the identification of this syndrome. Genetic studies are useful in confirming the diagnosis. However, lack of a confirmatory study does not rule out the diagnosis.

MATERIALS AND METHODS

We are evaluating adults with severe mental retardation (MR) at a long-term residential care facility to assess causes, including specific syndrome diagnosis not recognized at the time of admission to the facility. There are 365 residents ranging in age from 16 to 84. Many have resided in this facility for over 40 years. Thus far 225 have been evaluated, of these 11 have AS. The diagnosis of each patient was confirmed by one of the first two authors. The clinical diagnosis of AS was based on the consensus statement for the diagnostic criteria for AS [Williams et al., 1995]. All of the patients had four out of four consistent (100%) characteristics, and 8 of the 11 patients had all of the frequent (>80%) characteristics.

Clinical histories were obtained by a review of the medical records. The patients were unable to give a history themselves, and no relatives were present or could be reached at the time of evaluation, except for one. A standard physical and neurological exam was performed, and anthropometric measurements were obtained. The medical records were reviewed, and when available, EEG, CT, X-ray, and laboratory studies were reviewed. Karyotyping using high resolution banding techniques and fluorescent in situ hybridization (FISH) studies were requested on all 11 patients.

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RESULTS

The number of patients meeting each of the clinical criteria for AS is given in Tables I, II, and III. Of the 11 patients reported, nine are female and two are male. The mean age at the last visit was 47.7 years, and median age was 45 years. The age range was from 31 years to 64 years. All 11 are Caucasian.

Clinical Criteria

The number of our patients with AS who met the five criteria for the developmental history and laboratory findings are listed on Table I (Figs. 1–4). Nine of the 11 had a normal prenatal and birth history. One was reported to have intrauterine growth retardation (IUGR) with a birth weight of 2,270 grams. One had no prenatal or birth history in her record and her mother was not available for a history. There is no report of fetal exposure in any of the patients. All were spontaneous vaginal deliveries. No cesarean sections were performed. There is no record of problems in the neonatal period in any of the 11.

All 11 were documented to have delayed but forward progression of development. Eight had documentation of developmental delays evident by 12 months of age. Two had delays evident by less than two years of age. The age at which delay was evident in the remaining patient is not documented.

All had documented normal hematological, metabolic, and chemical laboratory profiles in their medical record. Five of the 11 had documented normal neuroimaging studies, one had a CT, and four had pneumoencephalograms. There is no documentation of neuroimaging performed on the remaining six.

Table II lists the consistent (100%), frequent (>80%), and associated (20 to 80%) clinical criteria for the diagnosis of AS. All 11 met the four consistent clinical characteristics. All 11 had severe cognitive impairments, of those who had documented psychometric testing all tested in the severe to profound range of mental retardation. Those who did not have a documented IQ in their medical record had self help and adaptive skills commensurate with those of a 1 to 2 year old. All had severe speech impairments. Only one had any spoken language which was minimal and primarily echolalic in nature. Receptive language capabilities exceeded expressive abilities in all 11.

All were capable of ambulation for short distances, and most walk within the confines of their apartments. However, 7 of the 11 are no longer community ambulators because of their unsteady gait. For safety reasons, wheelchairs are now used for distance or community mobility. One of the 11 patients had fallen and broken his tibia. Subsequent to the fall he now refuses to walk. All 11 patients were primary ambulators during childhood and adolescence.

As described by Buntinx et al. [1995], our patients tended to be calmer with less outbursts of laughter than younger patients with AS. However, the happy disposition remains with occasional bursts of laughter. Two of the 11 had been diagnosed with bipolar disorder because their happy disposition and bursts of laughter were seen as manic behavior.

Of the frequent clinical characteristics, 10 of 11 had microcephaly at the time of admission. However, the age of onset is undetermined because of lack of documentation.

All 11 had seizures. Eight of the 11 had documented seizures prior to age 3. Age of the onset for the remaining three is unknown. The seizure type and frequency are variable among our patients. Four of the 11 patients are now seizure free for over 7 years, two of the four since childhood. Three of the four are no longer on an anticonvulsant. The fourth is still on a low-dose anticonvulsant because of the severity of her past seizures. The frequency of seizures in the remaining seven patients ranges from several per month to as few as one every other year. Virtually all types of seizures are represented in our patients, from absence to partial complex to major motor seizures. There is a consistent history of an early onset of seizures followed by a period of seizure quiescence beginning in either late childhood or after puberty with reemergence of seizures in adulthood. In two of the patients, the seizures are of greater intensity and more difficult to control than those encountered in childhood.

EEG abnormalities were present in 9 of the 11 patients. No EEG was available on the two patients who have remained seizure free since childhood. All nine of the remaining patients had evidence of slow background rhythms. Six had dysrhythmic as well as slow background rhythms. Four of the six had evidence of large amplitude slow spike waves ranging from one to five per second. The remaining three now have normal EEGs, two of which have been seizure free for over 7 years. The third still has active seizures for which she is on an anticonvulsant despite the normal EEG.

The associated characteristics seen in 50% or more of our patients were the presence of a flat occiput, protruding tongue, tongue thrusting, prognathia, wide mouth, frequent drooling, excessive chewing, hyperac-

TABLE I. Angelman Syndrome: Developmental History and Laboratory Findings*

	Patients										
Parameters	KK	MB	GW	JB	JF	ET	KH	DB	MM	JN	JH
Normal prenatal and birth Hx	+	NR	+	+	+	+	+	+	–	+	+
Developmental delay by 6 to 12 months of age	+	NR	+	+	+	+	+	+	+	–	–
Delayed but forward progression of development	+	+	+	+	+	+	+	+	+	+	+
Normal metabolic, hematologic, and chemical profiles	+	+	+	+	+	+	+	+	+	+	+
Structurally normal brain	NR	NR	NR	NR	+	+	+	+	NR	+	NR

*These findings are useful as inclusion criteria but deviations should not exclude diagnosis.
Abbreviations: +, criteria present; –, criteria absent; NR, no record or report of criteria.

TABLE II. Angelman Syndrome: Clinical Characteristics

Characteristics	Patients										
	KK	MB	GW	JB	JF	ET	KH	DB	MM	JN	JH
Consistent (100%)											
Developmental delay	+	+	+	+	+	+	+	+	+	+	+
Speech impairment	+	+	+	+	+	+	+	+	+	+	+
Movement disorder	+	+	+	+	+	+	+	+	+	+	+
Behavioral uniqueness	+	+	+	+	+	+	+	+	+	+	+
Frequent (80%)											
Microcephaly	+[a]	+[a]	+[a]	+[a]	+[a]	+[a]	+[a]	+[a]	+[a]	–	+[a]
Seizures	+	+	+	+	+	+	+	+	+	+	+
Abnormal EEG	+	+	+	+	+	+	+	+	NR	NR	+
Associated (20 to 80%)											
Flat occiput	+	+	+	+	+	+	+	+	+	+	+
Occipital groove	+	–	–	+	+	–	+	–	–	–	+
Protruding tongue	+	+	+	+	+	+	+	+	–	+	+
Tongue thrusting, swallowing disorders	+	+	–	+	+	+	+	+	–	+	+
Feeding problems in infancy	NR	NR	NR	+	+	+	+	NR	NR	NR	NR
Prognathia	+	+	+	+	+	+	+	+	+	–	+
Wide mouth, wide-spaced teeth[b]	+	+	+	+	+	–	+	+	+	–	+
Frequent drooling	–	+	–	+	+	+	+	+	+	–	+
Excessive chewing/mouthing behaviors	–	+	–	+	+	+	+	+	+	+	+
Strabismus	–	+	–	+	–	+	–	–	–	–	+
Hypopigmented	+	NR[c]	NR[c]	NR[c]	–	+	NR[c]	+	NR[c]	NR[c]	–
Hyperactive DTR's	+	+	+	+	+	+	+	+	+	+	+
Uplifted, flexed arm position	+	+	+	+	+	+	+	+	+	+	+
Increased sensitivity to heat	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Attraction to water	+	–	NR	+	NR	NR	NR	NR	NR	NR	–
Sleep disturbance	+	–	NR	+	+	–	+	NR	NR	NR	–

[a]Uncertain as to time of onset but present at time of admission.
[b]All are partially or completely edentulous.
[c]Have no record of family pigmentation.

tive lower limb deep tendon reflexes, and uplifted, flexed arm position especially during ambulation. Wide spaced teeth were difficult to determine because of the number of patients who were edentulous. The anomalies least often associated with our patients were an occipital groove, strabismus, hypopigmented skin, increased sensitivity to heat, sleep disturbance, and attraction to water. Only three of the charts mentioned the presence of pigmentation in comparison with relatives, and it was noted because the patients were less pigmented than their relatives. Six of the records made no mention of the relatives pigmentation to be able to determine if the patients were more blond than their family members. Two had an olive complexion and dark hair. Behaviors such as excessive chewing may well be affected by on-going behavior management techniques by the care givers to extinguish such behaviors. Sleep disturbance may be affected by the use of anticonvulsant medications.

Table III lists the genetic testing abnormalities seen in AS. We have requested genetic testing on all 11 of our patients. Eight of the 11 have had normal high resolution G-banded chromosome studies. Of the eight, seven had FISH studies, three of which showed a deletion of 15q11-q13. These three did not have methylation studies. Two other patients had FISH studies that showed an absence of a deletion. Five of the 11 had normal methylation studies. Three of the five had FISH studies that were negative for a deletion.

Other Clinical Manifestations

There were other clinical manifestations seen in our patients that are not included in the clinical diagnostic criteria for AS. Some of these manifestations are clearly the result of aging, and others are nonspecific manifestations seen in many patients with severe developmental disabilities.

Three of the 11 had a history of cataracts. Cataracts developed between 55 and 58 years of age. Visual acuity was undetermined in most patients because of noncooperation with the examination.

There were a number of gastrointestinal manifestations, including: appendectomy (1), inguinal hernia (1), hiatal hernia (1), gastric bezoar (1), prolapsed rectum (1), ulcer disease (3), small bowel obstruction (1), vol-

TABLE III. Angelman Syndrome: Genetic Testing Abnormalities

Abnormalities	Patients										
	KK	MB	GW	JB	JF	ET	KH	DB	MM	JN	JH
Chromosome study showing deletion of 15q11-13	–	–	–	–	–	NR	–	–	NR	NR	–
FISH indicating deletion	+	+	–	+	–	NR	NR	–	–	–	–
Characteristic methylation pattern	NR	NR	NR	NR	NR	–	–	–	–	–	NR

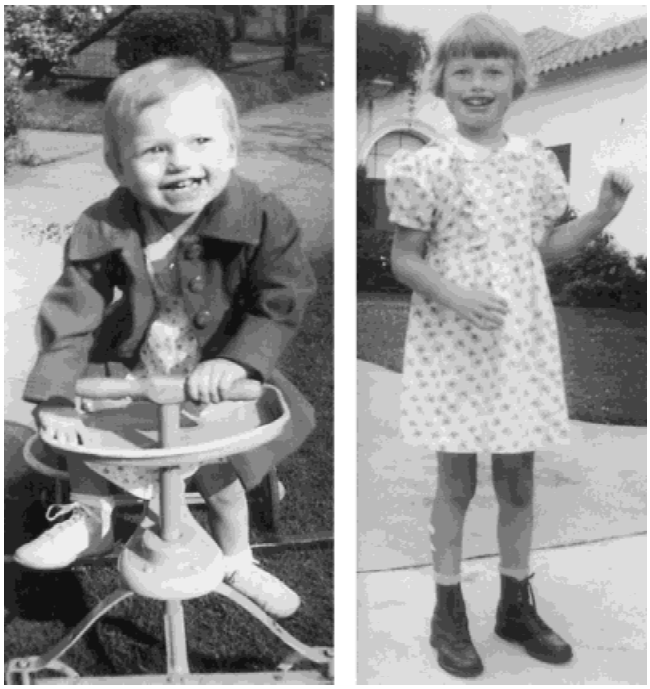

Fig. 1. **Left:** K.K., age 2 years. **Right:** K.K., age 8 years.

vulus of the colon with resulting colonostomy (1), gastroesophageal reflux (2), esophagitis (1), GI bleeding (2), and chronic constipation (4). Three of the 11 required placement of a gastrostomy tube as an alternate pathway for feeding and medications.

There were two reported fractures secondary to falls caused by an unsteady gait, one of the tibia and one of the hand. Six patients had scoliosis, one with spina bifida occulta. All had some degree of spasticity and some with subsequent skeletal deformities. Five of the 11 were noted to have small hands smaller than the 3%. All patients were noted to have a very smooth, velvet-like skin texture.

Several cardiac defects were noted, one ventricular

Fig. 2. M.B. (left), age 57 years, and K.K., age 60 years.

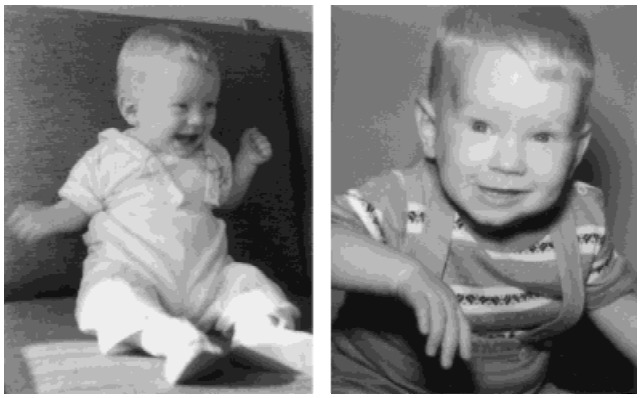

Fig. 3. **Left:** J.B., age approximately 8 months. **Right:** J.B., age 12–14 months.

septal defect (VSD) that closed spontaneously and one bicuspid aortic valve. Two patients have mitral valve prolapse, and one has tricuspid valve regurgitation.

Two are reported to have hypothyroidism and are on Synthroid. One has type 2 diabetes mellitus that is controlled with diet and oral medications. One has a history of Graves disease, and one had an ovarian cyst.

One patient was diagnosed with depression and two with bipolar disorder. The happy personality was interpreted as manic behavior.

This group has had relatively few infections. There are three patients with histories of pneumonia and two patients with a history of urinary tract infections (UTIs). One of the two had frequent UTIs, but evaluation of her renal system was normal. One had reports of frequent upper respiratory tract infections, and one had sinusitis. Two have asthma, and one has allergic rhinitis.

DISCUSSION

The estimate of the incidence of AS is most likely low [Buntinx et al., 1995; Petersen et al., 1995; Reish and King, 1995; Williams and Frias, 1982; Williams et al., 1995b]. There are very few reports in the literature of adults with AS [Buntinx et al., 1995; Clayton-Smith, 1993; Penner et al., 1993; Reish and King, 1995; Williams et al., 1989]. This is primarily caused by the lack of

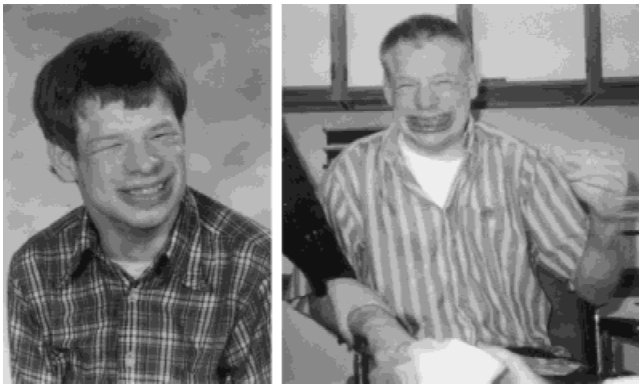

Fig. 4. **Left:** J.B., age 35 years. **Right:** J.B., age 43 years.

recognition of the syndrome in the severe to profound mentally retarded adult population. Of the 225 patients examined, 11 were diagnosed with AS, giving an incidence of 4.8 per 100. Obtaining an estimate for the incidence among the disabled population at large is difficult, primarily, because of the lack of data. Most of the data bases available, such as the Census Bureau or the Department of Health and Human Services, do not keep information on the severity or type of disability or even on all age groups. If we use the accepted estimate, mental retardation makes up approximately 3% of the general population, and 3% to 5% of the mentally retarded population are severely to profoundly retarded [American Association on Mental Retardation, 1992]. Based on the July 1997 Census Bureau estimate of the population of Washington state, we would expect a population of approximately 5,050 severely, developmentally disabled persons in the state. Among this population, the incidence of AS would be approximately 50:1,000 and for the general population approximately 1:20,000. This is the same incidence quoted by Clayton-Smith and Pembrey in 1992 but not as high as the 1:10,000 quoted by Petersen et al. in 1995.

Although the clinical findings of adults with AS may be more subtle, as seen in our patients, they still met the clinical criteria put forth in the consensus statement. In many of the adults with AS, the movement and balance disorder may be difficult to assess as they are placed in wheelchairs for perceived safety reasons because of their unsteady gait. The behavior of our adults with AS was still unique, and they maintained their happy demeanor but were much calmer, less excitable, and had fewer outbursts of laughter than is reported in the younger population [Buntinx et al., 1995; Fryburg et al., 1991; Hersh et al., 1981; Williams et al., 1995b].

All of our patients had a history of seizures. All but two had documented abnormal EEGs. Four still demonstrated evidence of large amplitude slow-spike waves, and three now have normal EEGs. Buntinx et al. [1995] postulated that the EEG pattern in patients with AS improves over time. This would appear to be true in our patients. However, because EEGs from childhood were not available on our patients, we are unable to confirm that the present EEG patterns seen in our patients represent an improvement over time. The adherence to a strict EEG pattern with large amplitude slow-spike waves [Boyd et al., 1988] appears to be less useful in making the diagnosis of AS in adults. Although the seizure type and frequency are variable in our patients, the life time pattern of an early onset of seizures followed by seizure quiescence and reemergence of seizure in adulthood is a very consistent pattern.

All of the associated clinical criteria were seen with the exception of increased sensitivity to heat. As in younger patients, the associated features are seen in varying degrees and frequency in the adults.

Although our observations were of adults in a long term residential care facility and may differ from AS adults living in the community, the overall health of our adults with AS is good. It would appear that there are no specific health issues unique to adults with AS. With the exception of seizures, they have no more serious health issues than the general population. However, they are at risk for health problems frequently seen in other adults with severe developmental disabilities, specifically the development of skeletal contractures and scoliosis caused by the decreased mobility and dependence on wheelchairs for ease of care. Maintaining mobility for as long as possible may help to prevent these problems in future adults with AS. As with other adults with developmental disabilities, our patients had frequent gastrointestinal complaints, none of which are specific for AS. Psychiatric illnesses do not appear common in our patients. However, a diagnoses of bipolar disorder in an adult with a severe developmental disability may be a flag for the consideration of AS.

Although not as consistent a finding as seen in Prader-Willi Syndrome, many of our patients have small hands. In addition, the texture of the skin was velvet like to the touch. This appears to be somewhat unique to this population and could be considered as an additional associated feature seen in adults with AS.

Our observations do not predict the outcome for the present cohort of young children diagnosed with AS who are enrolled in early intervention services (EIS) previously not available to our patients. Early recognition of the syndrome is crucial in initiating appropriate EIS. With a normal life expectancy and the present push for community versus institutional living, EIS should be vigorously pursued in patients with AS, especially in the area of communication and self help skills. Patients with AS have far better receptive than expressive language abilities. It is hoped that with recent advances in augmentative communication techniques, equipment, and early intervention, future patients with AS may develop better communication. Improvements in self-help skills and maintained mobility may decrease the number of secondary complications and the health care cost over the life span of the patient with AS.

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