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Angelman Syndrome in Adulthood

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We studied the clinical and EEG-findings in 28 adult patients (aged 20–53 years) with Angelman syndrome (AS). Twenty-three showed a maternal chromosome 15q11–13 deletion; in 5, the diagnosis was based on a combination of typical clinical findings. Compared to the clinical manifestations present in childhood, "coarsening" of facial traits (100%), thoracic scoliosis (71%), and being wheelchair-bound (39%) were found more frequently. Paroxysms of laughter were still observed in adulthood (79%), but less frequently than in childhood. Most adult patients could feed themselves, but needed help with many daily activities. The majority (82%) had epileptic seizures. Abnormal EEG-activity consisting of 2–3/s rhythmic triphasic waves of high amplitude with a maximum over the frontal regions, which has been identified in many AS children, was found in 67% of these adult patients.

KEY WORDS: Angelman syndrome, adulthood, epilepsy

INTRODUCTION

Since the first description of Angelman syndrome (AS) by Angelman [1965], more than 400 cases have been reported. Most studies have described AS in infancy or childhood, and only a few have mentioned adult AS patients [Williams and Frias, 1982; Bjerre et al., 1984; Williams et al., 1989; Ganji and Duncan, 1989; Magenis et al., 1990; Imaizumi et al., 1990; Kirkilionis et al., 1991; Jay et al., 1991; Matsumoto et al., 1992; Clayton-Smith, 1993; Smith et al., 1994; Buntinx et al., 1995]. Little is known about the evolution of the clinical symptoms into adulthood. Here we report on the clinical data and EEG findings in 28 adult AS patients.

PATIENTS AND METHODS

All known adult AS patients from eight institutions for the mentally disabled (total number of residents: 3,961) were included in the study. AS patients were identified as such by the primary physician of these institutions. Each patient was personally examined by the first author, and a detailed clinical history was taken. A clinical data system for each of these patients was completed (Table I). Epileptic seizures, if present, were classified according to the Commission on Classification and Terminology of the International League Against Epilepsy [1981]. The frequency and type of seizures were described and noted by the nursing staff in clinic records, and explained in a personal interview to the first author. All EEG examinations performed in these patients were reviewed by the first author. Cytogenetic or molecular studies or both had been performed in all patients. In patients without a proven chromosome 15q11–13 deletion the diagnosis was confirmed clinically by at least two of the authors, using the criteria described by Williams et al. [1995].

RESULTS

Twenty-eight patients (12 females, 16 males; mean age, 32 years; range, 20–53 years) entered the study. A chromosome 15q11–13 deletion of maternal origin, determined by RFLP analysis or cytogenetic analysis, was found in 23 patients. The other 5 showed no deletion. No case of paternal uniparental disomy was found. The main clinical findings of the adult AS patients are compared to those found in children [Clayton-Smith, 1993], and are summarized in Table I. There was no difference of clinical findings between the patients with and without a chromosome 15q11–13 deletion.

Face

Facial characteristics in the adult cases were more pronounced than in children. Examples are reported in Figures 1–3. A marked prognathism, with pointed chin and macrostomia, was found in all patients; the lower lip was more pronounced than in childhood. The tongue protruded in 20 of 28 patients. Two patients, aged 36

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TABLE I. Clinical Findings in 28 Adult Angelman Patients Compared to Those in Children as Reported in the Literature

	Adult AS patients		AS Children[a]
	Number of patients in which finding was present/total number of examined patients	%	%
Face			
Macrostomia	28/28	100	
Mandibular prognathism	26/27	96	95
Flat occiput	14/15	93	
OFC <50th centile	23/28	82	98
OFC <2nd centile	10/28	36	25
Blue eyes	23/28	82	88
Good visual acuity (without glasses)	20/25	80	89
Blond hair	22/28	79	65
Brachycephaly	18/28	64	
Strabismus	16/28	57	42
Occipital groove	14/27	52	
Widely-spaced teeth	13/25[b]	52	
Keratoconus	2/28	7	
Neurological findings			
Raised flexed arms (when walking)	20/20	100	
Ataxic puppet-like gait	27/28	96	100
Limb hypertonicity	26/28	93	
Hyperreflexia	25/28	89	
Tremor	11/13	85	
Epileptic seizures	23/28	82	86
Scoliosis	20/28	71	11
Truncal hypotonia	13/26	50	
Behavior			
Happy facial expression	28/28	100	
Absent speech (≤3 words)	28/28	100	100
Sad facial expression (sometimes)	25/27	93	
Paroxysms of laughter	22/28	79	96
Drooling	20/26	78	
(Excessive) chewing/mouthing	15/20	75	
Tongue protrusion	20/28	71	
Hyperactivity	14/28	50	
Ability to cry with tears	10/25	40	
Fixation on food	6/18	33	
Obesity	4/27	15	

[a]Percentages reported by Clayton-Smith [1993] (82 patients, almost all children).
[b]Three patients had no teeth.

and 37 years, respectively, showed a keratoconus. In both patients this was diagnosed at age 25 years. Persistent eye-rubbing was observed in both patients. None of the others had any eye abnormalities, although the eyes were more deep-set in adult AS patients as compared to children.

Behavior

All 28 patients were of a happy disposition. Paroxysms of laughter still occurred in 22. Although 93% of patients could display a sad facial expression, crying was only observed in 45%. Most adults (93%) were very curious; the hyperactivity of childhood had given way to quieter behavior in 50% of the patients. Fifty percent were still hyperactive, but to a lesser degree than in childhood. All adults were able to concentrate on one activity for a longer period of time. Favorite activities were playing in or with water, watching television, and looking at magazines. None of the patients has ever been able to speak more than a few words, but 86% could, to a certain extent, express their will nonverbally, using gestures (Table II). They could be quite stubborn. Their receptive ability was sufficient to allow them to understand simple commands, especially "everyday-life" situation-bound commands, supported nonverbally. Eighty-five percent were capable of performing simple tasks, such as handling a spoon or a fork or helping to (un)dress themselves (50%). Sixteen patients became (clock-)toilet trained by day, and 3 of 28 patients also by night.

Neurological Findings

All patients were severely mentally retarded. They walked with a slow, stiff, awkward gait and with the characteristic posture of raised arms with flexed wrists and elbows. They frequently flapped their hands when excited or while walking. Walking had become more difficult as they grew older; 11 patients had become wheelchair-bound. Thoracic scoliosis was found in 20 of 28 patients at examination in the standing position (71%); this represented 92% of female AS patients and 56% of male patients. In 5 cases (4 females), the scoliosis ne-

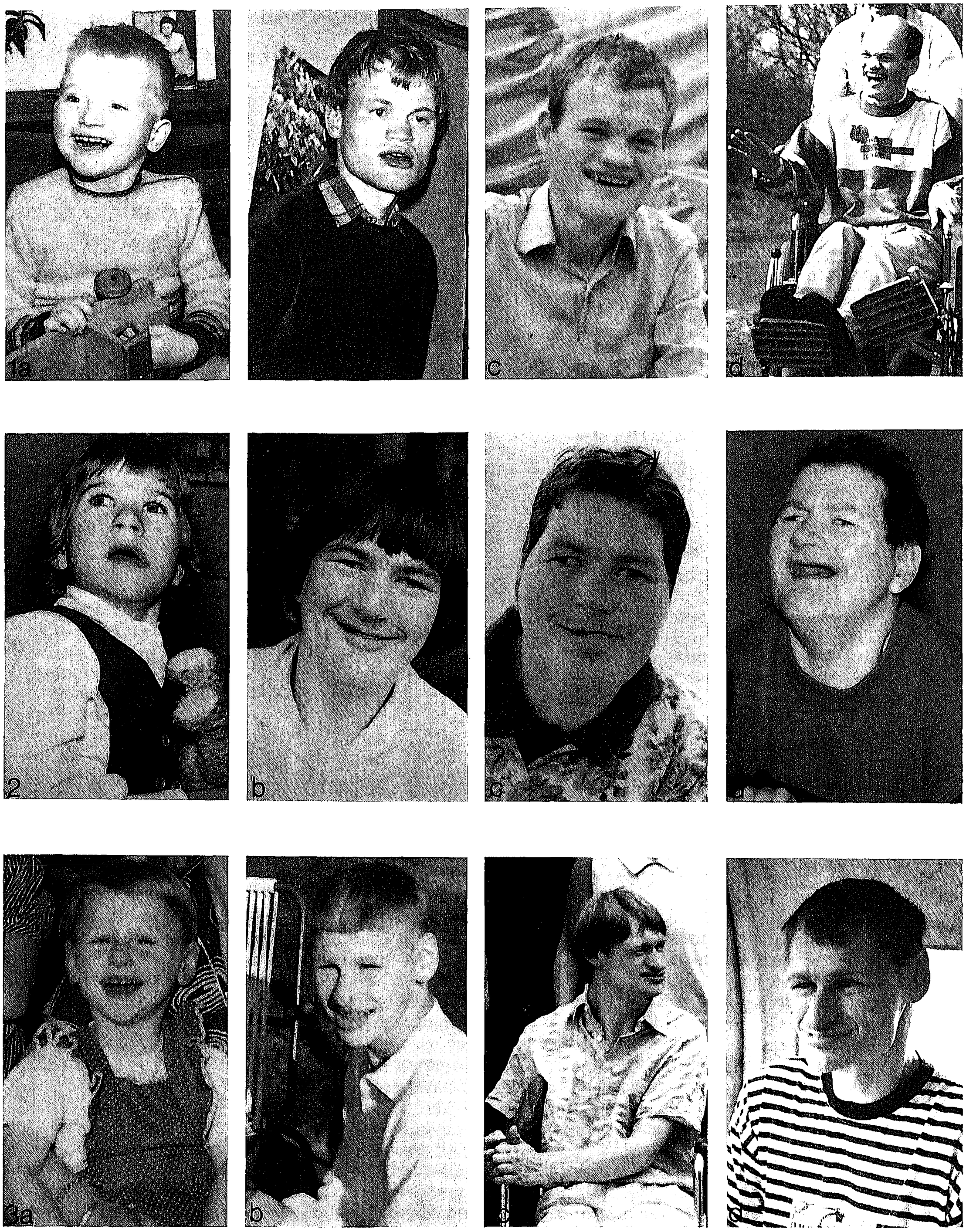

Fig. 1. Patient 1. AS patient at age 5 years (**a**); age 18 years (**b**); age 22 years (**c**); age 40 years (**d**).
Fig. 2. Patient 2. AS patient at age 5 years (**a**); age 16 years (**b**); age 34 years (**c**); age 40 years (**d**).
Fig. 3. Patient 3. AS patient at age 3 years (**a**); age 15 years (**b**); age 36 years (**c**); age 43 years (**d**).
All patients had a chromosome 15q11–13 deletion.

TABLE II. Daily Life Activities in Adult AS Patients

	Adult AS patients	
	Number of patients in which feature is present/ total number of examined patients	%
Love to watch TV	24/24	100
Handle spoon or fork	23/27	85
Ability to express their will to some extent	23/27	85
Understanding of simple commands	22/28	79
Attraction to water	21/27	78
Use of simple gestures (e.g., pointing)	21/27	78
Cooperative in (un)dressing	19/28	68
Ability to walk	17/28	61
Daytime continence for urine	16/28	57
Undress themselves	14/28	50
Dress themselves	3/28	11
Wash themselves	0/28	0

cessitated orthopedic treatment by brace (3 patients) or surgery (2 patients). For the other 15 patients with thoracic scoliosis, 6 had scoliosis prior to our exam; in the other 9, mild scoliosis was found for the first time. Three of the 11 nonambulatory patients showed severe scoliosis. Scoliosis was found in 13 of 17 ambulatory patients, which was severe in 2 cases. Hypertonicity and brisk reflexes, especially of the legs, were seen in 85% of patients. The general state of health of all cases remained good.

Epileptic Seizures

Three patients had never had an epileptic seizure. None had a deletion of chromosome 15q11–13. Two other patients, aged 21 and 45 years, had been seizure-free without antiepileptic drugs (AEDs) for 14 and 5 years, respectively. In 23 patients (82%), epileptic seizures had started in infancy or childhood and had continued into adulthood. The seizures consisted of myoclonic seizures (3 patients), atypical absence seizures (6 patients), or a combination of the two (4 patients); a combination of atypical absence seizures and tonic-clonic seizures (2 patients); a combination of myoclonic seizures and tonic-clonic seizures (1 patient); atonic seizures (1 patient); tonic-clonic seizures (1 patient); and three or more different seizure types (5 patients). Best results were obtained with monotherapy using valproic acid (4 patients), phenobarbital monotherapy (1 patient), a combination of valproic acid or phenobarbital with benzodiazepines (3 patients), or ethosuximide (5 patients). The other patients used different combinations of AEDs. In 4 patients, the frequency and duration of epileptic seizures became worse in adulthood. Adding another antiepileptic drug (ethosuximide) resulted in fewer seizures in 2. Three patients had become seizure-free on AEDs; decreasing the dosage had led to recurrence of seizures. One patient, without AEDs, had atypical absence seizures.

EEG Findings

EEG studies had been performed in 26 of 28 patients (total, 107 EEGs; 49 EEGs in adulthood). In 7 patients, EEGs were only obtained in childhood. A review of the EEGs obtained in adult patients showed that EEG-findings typical of childhood AS, such as large amplitude 4–6/s slow-wave activity, were not present. The EEGs of those patients for whom both childhood and adult data were available (n = 19) demonstrated a maturation of background activity from childhood into adulthood. Rhythmic triphasic 2–3/s delta activity of high amplitude (200–500 μV), mixed with spikes or sharp waves with a maximum over the frontal regions, was seen in 40 of 49 adult EEGs (19 patients); this activity was present in 49 of 58 childhood EEGs. This pattern was seen continuously in the EEGs of 3 adult AS patients and intermittently in 14. Two patients did not show this typical pattern (only one EEG of each could be examined), although they still have epileptic seizures. The EEGs from the 5 patients without a deletion of chromosome 15 (3 had never had an epileptic seizure) also showed this pattern.

DISCUSSION

The most prominent findings in our group of adult AS patients, compared to those reported in children [Clayton-Smith, 1993], are the typical AS face, with more pronounced traits, thoracic scoliosis, and decreased mobility. In addition, we found a persistence of epileptic seizures despite AED treatment, and characteristic EEG phenomena in most patients. A similar coarsening of facial traits with increasing age has been reported by other authors [Buntinx et al., 1995]. The cause of the coarsening of the face is unknown. It was found in patients both with and without chronic AED use. Paroxysms of laughter still occurred, although less frequently than in childhood. Many patients used simple gestures to communicate rather than speaking. Visual problems were seen in 2 patients with a keratoconus, as described in 2 other cases [Williams and Frias, 1982; Bjerre et al., 1984]. The keratoconus appears to be related to persistent eye-rubbing over the years, as was the case in our patients. This has been reported by other authors [Koenig and Smith, 1993].

Scoliosis was a major problem in 71% of the adult AS patients. Clayton-Smith [1993] and Buntinx et al. [1995] reported scoliosis in 11% and 38.8% of their patients, respectively, mostly children. Scoliosis tended to increase in adolescence and adulthood [Clayton-Smith, 1993; Buntinx et al., 1995]. It is not known whether scoliosis is related to the hypertonicity generally found in these patients. Loss of ambulation does not seem to be a causative factor, as scoliosis was found in both ambulatory and nonambulatory patients. Ascertainment bias seems not to play a role in our study group with respect to the high prevalence of scoliosis, as nearly all Dutch AS patients are institutionalized at a relatively young age. Perhaps early recognition and physiotherapy might prevent orthopedic intervention in these patients. Walking difficulties were found in many adult patients, due to ataxia, severe scoliosis, or limb hypertonicity.

Although epilepsy has been described in some individual adult cases [Williams and Frias, 1982; Bjerre et al., 1984; Williams et al., 1989; Ganji and Duncan, 1989; Imaizumi et al., 1990; Kirkilionis et al., 1991; Jay et al., 1991; Matsumoto et al., 1992; Smith et al., 1994; Buntinx et al., 1995], generally it has been stated that epileptic seizure activity decreases after adolescence [Clayton-Smith, 1993; Buntinx et al., 1995]. We found, however, that 82% of adult AS patients still suffer from epileptic seizures. It was remarkable that 3 patients without a chromosomal deletion did not have epileptic seizures. In contrast to Boyd et al. [1988], we also found characteristic EEG phenomena in adult AS patients.

This study describes the clinical course of AS from childhood into adulthood. It aims at improving recognition of adult AS patients in institutions for the mentally retarded.

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