Motor impairments, neurological signs, and developmental level in individuals with Angelman syndrome

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The aim of this study was to examine the character of motor dysfunction in individuals with Angelman syndrome (AS). Thirty-three children and adolescents (median age 6 years, range 18 months to 23 years) were consecutively investigated for learning disability*, epilepsy, and motor dysfunction to detect suspected AS. Twenty-three individuals (13 males, 10 females; median age 5 years 6 months, range 21 months to 23 years) fulfilled international consensus criteria for AS. Clinical diagnosis was supported by a positive DNA methylation test in eleven participants. Ten participants (seven males, three females; median age six years, range 18 months to 13 years) did not comply with consensus criteria for AS and were regarded as a comparison group. There was no significant difference between the AS and the comparison group regarding age or developmental level. Median developmental quotient level was 26 months (range 8 to 63 months); median gross motor developmental level in participants with AS was 24 months (range 8 to 60 months); median fine motor developmental level was 15 months (range 6 to 60 months). Muscle strength, spasticity, tremor, and coactivation were assessed: distal lower limb spasticity, ataxic like gait, stiff lower limbs, and the presence of coactivation during locomotion were significantly more frequent in participants with AS than in the comparison group ($p<0.05$). Asymmetry of muscle strength and spasticity were frequent. Neurological abnormalities were insufficient for a diagnosis of cerebral palsy and impeded function less than immaturity in both AS groups. Risk of increasing impairment needs to be anticipated to prevent negative long-term effects of muscle imbalance and motor asymmetries in individuals with AS.

*US usage: mental retardation.

Angelman syndrome (AS) was described in 1965 as a particular constellation of ataxia, learning disability, epilepsy, and certain physical and behavioural features (Angelman 1965; Table I). International consensus criteria for the clinical diagnosis of Angelman syndrome were published in 1995 (Williams et al.). Following the clinical characterization, a number of cytogenetic and molecular genetic abnormalities affecting chromosome 15q have been reported in about 80% of children with the condition. Generally, deletions are associated with the most pronounced phenotype including physical features, while uniparental disomy and point mutations are physically less obvious. Except for point mutations, most of the reported abnormalities are detected by methylation testing. Even in centres well acquainted with the condition, an accurate clinical separation of different genotypes is generally not possible (Lossie et al. 2001).

Although AS represents a clinical phenotype defined by behavioural criteria with a characteristic overall presentation, motor dysfunction is a prominent feature of the disorder. Few systematic studies have been conducted of motor function and development in this condition. Dan et al. (2001) have argued that spastic diplegia is a feature of AS. However, this view may be contested, as children with cerebral palsy (CP) have more distinct neurological and functional abnormalities. Therefore, the aim of this study was to examine the character of motor dysfunction in children and adolescents with AS.

Method

PATIENTS

The series studied consisted of 33 children and adolescents (median age 6 years, range 18 months to 23 years) who were evaluated during the period 1998 to 2001. The evaluation was made in children with learning disability, epilepsy, and motor dysfunction consecutively referred to the Queen Silvia Children's Hospital, Sweden for investigation and possible verification of the diagnosis of AS. Assessment of motor function was part of an extensive investigation including neuropaediatric, neuropsychiatric, neurophysiological, and clinical genetic examinations. This study focused on motor function and motor development.

CRITERIA FOR THE DIAGNOSIS OF AS

A simple clinical screening-score form of associated clinical Angelman features was constructed based on the International Consensus Criteria for the Diagnosis of AS (sum of scores 0–16; Kyllerman 2000; Table I). Behaviour and speech dysfunction were classified according to detailed history, findings on examination, and information obtained from medical records. At the time of the examination, DNA verification by the methylation test was available and no further genetic studies were performed. Growth charts for Swedish children were used for assessment of head circumference (Wikland et al. 2002).

DEVELOPMENTAL QUOTIENT

Development quotient (DQ) was tested in most participants using the Griffiths scale (Ålin-Akerman and Nordborg 1980). It was not possible to use the scale in two patients because of low functioning, therefore, the Vineland Social Maturity Scale (Magne and Wahlberg 1961) was applied.

MOTOR DEVELOPMENTAL LEVEL

Gross and fine motor developmental level were assessed with

the Cailler-Asuza scale (Stillman 1977), a validated motor assessment tool that measures the age of acquisition of motor milestones (Harris et al. 1983). It was developed to assess children with multiple impairments and is specially detailed in the early stages of development. The Cailler-Asuza scale has been successfully applied in clinical studies of children with learning disability (Beckung et al. 1997). To assess gross motor developmental level, the subscales for postural control and locomotion were used and for assessment of the fine motor developmental level, the subscales for fine motor development and visuomotor control were used.

MOTOR FUNCTION TESTS

Gross motor function level was classified according to the Gross Motor Function Classification System (GMFCS; Palisano et al. 1997). The GMFCS was developed to classify gross motor function in children with CP (Palisano et al. 1997) and has proven to be a reliable and valid instrument (Wood and Rosenbaum 2000).

Muscle strength was examined in functional movements such as the ability to sit up from lying, bending and raising, gait, and climbing stairs (Hinderer and Hinderer 1993). Range of movement was examined with goniometry (Norkin and White 1995). The position of the feet was studied when the participants were standing on a mirror box. The ability to walk down a slope was studied using the Sloping Plane Test. Participants were asked to walk down a 2.3m long slope from a height of 40cm down to floor level. This functional test allowed a composite assessment of perception and sensorymotor integration.

NEUROLOGICAL SIGNS

Spasticity was defined as 'a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon reflexes resulting from hyperexcitability of the stretch reflex as one component of the upper motor syndrome' (Lance 1980, p 45). Spasticity was assessed in the arms, hands, legs, and feet with fast passive movements through the range of joint motion, according to the modified Ashworth scale (Bohannon and Smith 1987). The sign ataxia was classified by performance and considered to be present when there was a uncoordinated movement pattern comprising broad-based gait, stiff lower limbs on ambulation, jerky motor function, and a disturbed sense of equilibrium in the upright position with compensating arm movements. The presence of tremor was observed during the fine motor function tests for each participant. Coactivation of agonist–antagonistic muscles was observed when there was a disturbance of muscle control resulting in an abnormal muscle pattern with stiff leg movements. General muscle tone and trunk hypotonus were assessed empirically from observation of the child during locomotion and during passive and active movements.

Table I: Associated clinical features (n=16) in Angelman syndrome (Kyllerman 2000)

Flat occiput
Occipital groove
Prognathia
Wide mouth
Infant feeding problems
Tongue protrusion and thrusting
Suck–swallow disorder
Frequent drooling
Excessive chewing, mouthing behaviours
Strabismus
Hypopigmented skin, blond hair, blue eyes
Hyperactive lower limb reflexes
Uplifted, flexed arm position on ambulation
Sleep disturbance
Attraction to water
Increased sensitivity to heat

STATISTICAL METHODS

Non-parametric statistical methods were used for statistical analysis: the Kruskal Wallis test for one way analysis of variance for three groups; the Mann–Whitney U test for comparison of two groups; and the Spearman's rank correlation test.

This study was approved by the ethics committee of Göteborg University. Informed consent was obtained from parents of the children.

Results

Twenty-three children and adolescents (13 males, 10 females; median age 5 years 6 months, range 21 months to 23 years) fulfilled the four clinical inclusion criteria for AS (learning disability, speech impairment, movement–balance disorder, and behavioural peculiarity) and at least two of the three consistent criteria (head circumference >2SD below the mean of normally developing Swedish children, epilepsy, and electroencephalogram abnormality with epileptiform discharges). The remaining 10 participants did not fulfil any of the four inclusion nor the three consistent criteria for AS and, therefore, made up a comparison group.

In 11 of the 23 patients with AS, the diagnosis was confirmed by chromosome or DNA studies. No one in the comparison group had a positive methylation test.

There was no significant difference in the sum of associated clinical features (Table I) between AS group 1 with DNA methylation test (range 5–13, median 10) and AS group 2 with only criteria-supported diagnosis (5–14, median 9). Both AS groups had significantly higher scores than the comparison group (2–8, median 5; $p<0.001$).

DEVELOPMENTAL QUOTIENT

Distribution of DQ showed no significant difference among the three groups (Table II). All 33 participants had learning disability, with a DQ<70; median DQ level was 26, (range 8 to 63). Thirteen participants had profound learning disability (DQ<20), 10 had severe learning disability (DQ 20–34), six had moderate learning disability (DQ 35–49), and four participants had mild learning disability (DQ 50–69).

MOTOR DEVELOPMENTAL LEVEL

Gross motor developmental age was generally low (median 24 months, range 8–60 months; Fig. 1). Median fine motor developmental level was 15 months (range of 6–60 months). There was no significant difference among the groups.

MOTOR FUNCTION TESTS

Distribution of GMFCS levels showed no significant difference among the three groups (Table III). The majority of all participants were ambulant without assistive devices. Ten participants had limited self-mobility and were classified at

GMFCS level IV.

Eight participants had restricted range of motion in upper and lower limbs with contractures in their lower limbs. Asymmetries in muscle strength and spasticity were found in 19 participants. Valgus feet in the standing position were present in 23 individuals. There was no significant difference in motor function between groups.

NEUROLOGICAL SIGNS

Mild or moderate spasticity (Ashworth scale 1–2) was present distally in the lower extremities in 11 participants, combined with ataxia in nine, and it was significantly more common in the two AS groups (10/23) than in the comparison group (1/10, $p<0.05$; Table IV).

Ataxic-like gait with hand flapping was found in 20 children and adolescents and it was significantly more frequent in the two AS groups than in the comparison group ($p<0.05$). Stiff lower limbs and the presence of coactivation during locomotion were found in 24 individuals; this was more common in both AS groups than in the comparison group ($p<0.01$; Table IV).

Spasticity without signs of ataxia occurred in two participants, one from each AS group. Ataxic signs only were found in 11 participants (AS group 8/23; comparison group 3/10, $p<0.05$). Difficulty with walking down a slope in the Sloping Plane Test was significantly more often present in both AS groups than in the comparison group ($p<0.01$). Hand tremor during fine motor activities was found in eight individuals with AS but not in the comparison group (Table IV).

Abnormal muscle tone was common. Muscle tone was normal in 12 participants, low in 11 participants, and high with general hypertonus in 10 participants. Trunk hypotonus was present in 17 participants; muscle weakness was present in 21 participants. Distribution of muscle tone, muscle strength, range of motion, asymmetries, and the presence of valgus feet showed no statistically significant difference between groups.

Correlations were found between spasticity and contractures ($r=0.7$, $p<0.0001$), spasticity and coactivation ($r=0.6$, $p<0.01$), and contractures and weakness ($r=0.5$, $p<0.001$). Associations were also seen between coactivation of mus-

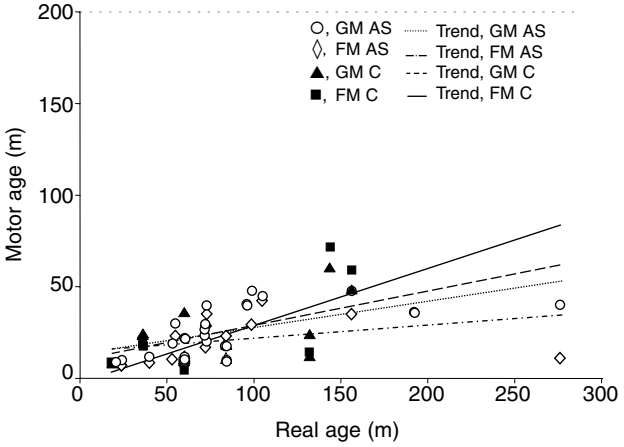

Figure 1: *Gross (GM) and fine motor(FM) developmental level in Angelman syndrome (AS) (n=23) and comparison (C) groups (n=10). Trends are statistically calculated from individual scores.*

The associated clinical features of AS in this study showed a comparable distribution between AS group 1 (with positive methylation tests) and group 2 (with only criteria-supported diagnosis), supporting the similarity in this study between the two AS groups. The comparison group, on the other hand, had much lower scores. In a previous study of 144 children investigated for AS, a strong association between high scores and the AS phenotype was found which was corroborated by DNA studies (Kyllerman 2000). The AS score seemed to be a fairly robust and reliable support for the diagnosis. The phenotypic variation in AS has been described in several studies (Saitoh et al. 1994, Bottani et al. 1995, Burger et al. 1996, Moncla et al. 1999, Fridman 2000, Lossie et al. 2001). Patients with deletion appear to be the most severely affected while uniparental disomy and imprinting centre mutations present a generally milder phenotype. Regardless of the genetic abnormality, both AS groups in this study had equal clinical screening scores. The comparison group were not, by clinical criteria, patients with AS.

Significant differences between the participants with AS and the comparison group were the presence of neurological

Table II: Distribution of DQ level according to ICD-10)

Group	*DQ*			
	<20	*20–34*	*35–49*	*50–69*
AS 1, $n=11$	3	5	2	1
AS 2, $n=12$	6	3	3	–
Comparison group, $n=10$	4	2	1	3
Total, $n=33$	13	10	6	4

AS 1, positive methylation test ; AS 2, only criteria-supported diagnosis.

Table III: Level of locomotion according to Gross Motor Function Classification System (GMFCS; Palisano et al. 1997)

Group	*GMFCS levels*				
	I	*II*	*III*	*IV*	*V*
AS 1, $n=11$	–	8	–	3	–
AS 2, $n=12$	–	8	–	4	–
Comparison group, $n=10$	–	7	–	3	–
Total, $n=33$	0	23	0	10	0

AS 1, positive methylation test ; AS 2, only criteria-supported diagnosis.

Table IV: Distribution of neurological signs

Group	*Spast.*	*Ataxia*	*Coact.*	*SPT*	*Tremor*
AS 1, $n=11$	4[b]	8[a]	10[b]	9[b]	3
AS 2, $n=12$	6[b]	8[b]	10[a]	11[b]	5
Comparison group, $n=10$	1	4	4	3	0
Total, $n=33$	11	20	24	23	8

Spast., spasticity;Coact., coactivation; SP, Sloping Plane Test; AS 1, positive methylation test; AS 2, only criteria-supported diagnosis.
[a]$p<0.05$; [b]$p<0.001$.

signs, spasticity, ataxia, and tremor. This was also true for coactivation of muscles, muscle weakness, and sensorymotor integration problems, as seen in the Sloping Plane Test. Hypotonus, however, was more likely to appear in the comparison group. These results indicate that the pathophysiology in individuals with AS is somewhat similar to that described in those with CP and other upper motor neuron syndromes, and at the same time differs from what is seen in children with learning disability from other causes.

Recently, a kinematic and kinetic study of a standardized squatting movement was performed by Dan et al. (2001) in a group of children with spastic diplegic CP and children with AS compared with normally developing controls. Children with spastic CP and AS were described as sharing some clinical features, such as trunk hypotonus and lower limb hypertonus which was more marked distally and increased with active mobilization. The children with AS displayed no anticipatory changes in muscle activity. These results showed lower extremity stiffening, agonist–antagonist muscle coactivation patterns, and non-conservative postural reactions of trunk, head, and arms in both patient groups. Lack of movement selectivity, which was observed in children with AS, is consistent with a hypothesis of reduced presynaptic inhibition in the spinal cord and cerebral cortex, as well as with recent views on the cerebellar selection of dynamic movement. Thus their results indicated a combined corticospinal and cerebellar dysfunction in the children with AS (Dan et al. 2001).

In our opinion, motor problems in individuals with AS mainly represent immature uncoordinated movement patterns, similar to what is seen in the early stages of motor development. All the participants of this study functioned at a very immature gross and fine motor developmental level. There was no significant difference between the two AS groups. The comparison group demonstrated a tendency towards more advanced motor function in the higher ages, which was much less apparent in the AS groups. Signs of ataxia and spasticity were more prevalent in AS than the comparison group, which may indicate that there are additional dysfunctions specific to individuals with AS. We also found that the movement pattern was ataxic-like, but differed from the dysmetria and dyssynergia seen in cerebellar ataxia syndromes (Hagberg et al. 1972). The neurological abnormalities were mild and, in our opinion, do not qualify for the diagnosis of CP syndromes.

Median age of the participants in this study was 6 years and we found that mean motor developmental age was less than half of that age or 24 months. Immaturity of the participants may explain the fact that one third of the participants in this study were classified at GMFCS level IV. We found no child from either group on GMFCS levels I, III, nor V. The GMFCS was developed to classify motor function in children with CP, a heterogeneous group of children. The distribution of the GMFCS levels for children with CP has recently been described in two population based studies (Nordmark et al. 2001, Beckung and Hagberg 2002). Children with ataxic diplegia were in both studies predominately classified at GMFCS levels I and II. Children with spastic diplegia were distributed on all levels. Motor dysfunction in participants with AS in this study was more homogeneous and the GMFCS appeared not to be a suitable classification for this group, mainly because of the inability of those who could not walk to make use of assistive devices. The validity of the GMFCS for the children with AS was difficult to evaluate in this small sample. Although motor impairment is obvious in participants with AS, gross motor function is one of their best skills.

The Sloping Plane Test was a qualitative, composite test of sensory input and motor output functions comprising vision, perception, and motor execution. Participants were not able to anticipate balance disturbances but used late compensatory strategies with coactivation and distal-to-proximal stiffening of the legs to increase stability.

The difficulties these participants had in the test probably resulted from central uncoordination with difficulties in the positioning of the body and the interaction between body and environment. The participants seemed to have problems in sensorimotor integration, i.e. deficient interaction between multiple spinal and supraspinal systems.

Scoliosis was not investigated but asymmetric motor function and the presence of trunk weakness was observed in several individuals. Decreasing mobility with age, increasing joint contractures in the lower limbs, and scoliosis has been described by Clayton-Smith (2001). We observed that in young adults with AS, the ataxic-like gait became less pronounced and the posture became more crouched with flexion of the hips, knees, and feet.

When investigating the complete clinical picture for a child with AS, motor function should also be taken into consideration. The risk of increasing impairments needs to be anticipated by therapists in order to prevent the most devastating long-term effects of hypertonus and motor asymmetries. In our opinion, most children with AS need an early, active, and individualized intervention programme. This should aim at correcting foot position with adequate shoes, stretching for the lower limbs, and castings, orthoses, or botulinum toxin injections while the contractures are still dynamic.

DOI: 10.1017/S0012162204000398

Accepted for publication 10th October 2002.

Acknowledgements
Gudrun Hagberg MD Hon for constructive advice and Anna Söderholm, Project Nurse, for coordinating patient contacts.

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