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Communicative and cognitive functioning in Angelman syndrome with UBE3A mutation: a case report

Marinella Zingale[1], *Rosa Zuccarello*[2], *Serafino Buono*[3], *Maurizio Elia*[4], *Antonino Alberti*[5], *Pinella Failla*[6] *& Corrado Romano*[7]

Abstract

Angelman syndrome (AS) is a neurodevelopmental disorder characterized by a severe intellectual disability, severe expressive language deficits, ataxia and a specific behavior with easy excitability excitable personality and an inappropriately happy predisposition. Phenotypical variations have been described on the basis of the underlying genetic mechanism. Several reports have suggested that individuals with AS resulting from UPD, UBE3A mutations and imprinting mutations show a milder or atypical phenotype than that observed in patients with a deletion of 15q11-q13 region. The purpose of this study is to describe cognitive and adaptive functioning in a child with AS resulting from UBE3A gene mutation, and especially the linguistic development, verbal and mimic-gestual, whose inventory and use are greater than those reported in literature.

Keywords: Angelman syndrome, Language, Phenotype, Autism Spectrum Disorders

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[1] Unit of Psychology, IRCCS Oasi Maria SS. Troina, Italy – E-mail: mzingale@oasi.en.it
[2] Pedagogy Service IRCCS Oasi Maria SS Troina Italy – E-mail: rzuccarello@oasi.en.it
[3] Unit of Psychology, IRCCS Oasi Maria SS. Troina, Italy – E-mail: fbuono@oasi.en.it
[4] Unit of Neurology and Clinical Neurophysiopatology, IRCCS Oasi Maria SS Troina, Italy – E-mail: melia@oasi.en.it
[5] Unit of Pediatric and Medical Genetics, IRCCS Oasi Maria SS Troina Italy - E-mail: aalberti@oasi.en.it
[6] Unit of Pediatric and Medical Genetics, IRCCS Oasi Maria SS Troina Italy - E-mail: pfailla@oasi.en.it
[7] Unit of Pediatric and Medical Genetics, IRCCS Oasi Maria SS Troina Italy - E-mail: cromano@oasi.en.it

1. Introduction

Angelman syndrome (AS) is a neurodevelopmental disorder, occurring with an estimated prevalence between 1:10,000 and 1:40,000 (Petersen, Brondum-Nielsen, Hansen, & Wulff, 1995; Thomson, Glasson, & Bittles, 2006; Dan, 2009). It is characterized by severe Intellectual Disability (ID), profound speech impairment with absent or minimal use of speech, ataxia, epilepsy and a characteristic behavioral profile including frequent and inappropriate laughter, a happy predisposition, an easily excitable personality, hypermotoric behavior, short attention span. Other common features include seizures, microcephaly, peculiar EEG pattern, sleep disturbances, hypopigmentation, and strabismus (Williams, Driscoll, & Dagli, 2010).

Four major molecular mechanisms are known to cause AS: maternally derived interstitial deletion of 15q11-q13 chromosome region in 65-75% of cases (Kaplan, Wharton, Elias, Mandell, Donlon, & Latt, 1987; Magenis, Brown, Lacy, Budden, & Lafranchi, 1987; Cooke, Tolmie, Glencross, Boyd, Clarke, Day *et al*., 1989; Pembrey, Fennel, Vad De Berghe, Fitchett, Summers, Butler *et al*., 1989; Williams, Gray, Hendrickson, Stone, & Cantu', 1989; Fryns, Kleczkowska, De Cock, & Vendenberghe, 1990); mutation in the UBE3A gene (10% of cases) (Kishino, Lalande, & Wagstaff, 1997; Matsuura, Sutcliffe, Fang, Galjard, Jiang, Benton *et al*., 1997); imprinting center defects (3-5 % of cases) (Nicholls, Saitoh, & Horsthemke, 1997; Young-Hui, Ting-Fen, Bressler, & Beaudet, 1998); paternal uniparental disomy (UPD) observed in 3-5 % of cases. In about 10% of patients with a clinical diagnosis, no genetic defect is found.

In particular, the cognitive and neuro-behavioral phenotype is characterized by:

- *Severe psychomotor delay* with onset around 6-12 months. Not reported, however, loss of acquired skills. Sitting autonomously is reached between six months and three years (on the average this milestone is achieved around 18 months), crawling becomes possible around 22 months, and standing without support around 7 years (Zori, Hendrickson, Woolven, Whidden, Gray, & Williams, 1992; Buntix, Hennekam, Brouwer, Stroink, & Beuten, 1995). Lossie, Whitney, Amidon, Dong, Chen, Theriaque *et al*. (2001) reported that 50% of AS patients with deletion were non-ambulatory by 5 years of age, while 95% of those with other molecular mechanisms were able to walk unassisted until 5 years of age. The study reported that children with UBE3A gene mutation walked much earlier with mean ages in the 2.4 - 2.8 years range.

- Severely compromised verbal communication with minimal or absent use of words. Expressive language is limited to 6-8 words in almost all individuals (Williams, Angelman, Clayton-Smith, Driscoll, Hendrickson, Knoll *et al.,* 1995). Lossie *et al*. (2001) did not find significant differences regarding verbal language and its evolution between patients with UBE3A mutation and those with AS by other genetic mechanisms. The patients with UBE3A gene mutations are statistically similar to the deletion patients in terms of absence of speech (Paprocka, Jamroz, Szweed-Bialozyt, Jezela-Stanek, Kopyta, & Marszal, 2007; Sartori, Anesi, Polli, Toldo, Casarin, Drigo *et al.,* 2008).

  A not homogeneous developmental profile with greater abilities in the receptive component is reported (Clayton-Smith, 1993; Williams, Zori, Hendrickson, Stalker, Marum, Whidden *et al.,* 1995; Trillingsgaard & Ostergaad, 2004; Dan, 2009). Some children with AS communicate using gestures and by pointing (Clayton-Smith, 1993; Alvares & Downing, 1998).
- *Typical behavior*, with frequent and excessive smile/laughter, inappropriately "happy" behavior, excitability often associated to "hand flapping", psychomotor instability and attention deficit (Pelc, Cheron, & Dan, 2008a). Children affected by AS seem very interested in exploring the surroundings, and manifest curiosity and specific interest for water. Hyperactivity is present in both sexes (Buntinx *et al.,* 1995; Williams *et al.,* 2010). The attention span may be so short as to interfere with social interactions.
- Intellectual Disability, often severe. Thompson and Bolton (2003) sustain that in the majority of the patients with AS the cognitive impairment is in the severe-profound range. Children with a milder form of attention deficit may have a moderate ID (Williams *et al.,* 1995); a small percentage may obtain better results in some areas, particularly in social abilities.

Several reports have suggested that individuals with AS resulting from UPD, imprinting mutations and UBE3A gene mutations show a milder or atypical phenotype than that observed in those with deletion, with a lower incidence and later onset of seizures, less severe ataxia, earlier age of walking, a greater ability to use some symbolic communication, or a lower frequency of anomalies in the facial morphology (Bottani, Robinson, DeLozier-Blanchet, Engel, Morris, Schmitt *et al.,* 1994; Smith, Marks, Haan, Dixon, & Trent, 1997;

Smith, Robson, & Buchholz, 1998; Moncla, Malzac, Livet, Voelckel, Mancini, Delaroziere *et al.,* 1999; Fridman, Varela, Kok, Diament, & Koiffman, 2000). Others, however, have argued that the supposed milder phenotype described in cases without deletion is within the range observed in all molecular classes of AS (Smith, Wiles, Haan, McGill, Wallace, Dixon *et al.,* 1996; Prasad & Wagstaff, 1997; Thompson & Bolton, 2003; Pelc *et al.,* 2008).

2. Clinical case

2.1 Personal History

The child is a male, first born of two. He was born full term by cesarean section following an uneventful pregnancy. His birth weight was 3530 gr. At birth all vital signs were normal. He had physiological jaundice, and was breast fed until four months of age. Poor growth rate and altered sleep-wake rhythm were noticed around three months.

Development was globally delayed: he controlled his head at 6 months, sat independently at 8 months and walked at 20 months. Vocalization and babbles development were normal.

Bisyllable words were present at three years of age with further gradual acquisition, up to 50 words functionally used, by age five.

Play activity was poorly organized, and inclined towards oral exploration. Significant psychomotor instability was also present, in particular during the first years of life, with gradual reduction especially in a structured learning environment, following specific rehabilitation treatment.

Diagnostic investigations were started early (the first evaluation was done at the age of seven months for a gastroesofageal reflux). Diagnosis of AS, however, was formulated at the age of four years. The patient started rehabilitation at the age of 13 months. An intensive habilitation treatment (speech therapy and physiotherapy, psychomotor and psychoeducational treatment) was carried out at the age of 36 months for a period of two months.

At the age of four, he underwent a short alternative communication treatment, interrupted voluntarily by the parents. He started kindergarten regularly.

The patient has a "de novo" duplication in exon 15 of UBE3A gene which produces a protein truncation at RNA analysis.

2.2 Psychometric evaluation and discussion

The child was assessed at the age of 70 months.

Neuropsychological functioning was assessed in a semi-structured environment with parents present. They were interviewed about their child's develop-

mental milestones and behavioral features. The child was assessed with (I) Leiter International Perfomance Scale (LIPS: Leiter, 1979), (II) Psychoeducational Profile Revised (PEP-R: Schopler, Reichler, Bashford, Lansing, & Marcus, 1990), (III) Griffiths Mental Development Scales (GMDS: Griffiths, 1986), (IV) Learning Accomplishment Profile (LAP: Sanford & Zelman, 1987) and (V) Vineland Adaptive Behaviour Scale (VABS: Sparrow, Balla, & Cicchetti, 1984).

The "Test di valutazione del linguaggio" (TVL, Cianchetti & Sannio Fancello, 1997), was also used to assess language evaluation.

Considering that some studies have reported a consistently high rate of autistic behavior in AS (Peters, Beaudet, Madduri, & Bacino, 2004) using Autism Diagnostic Observation Schedule (ADOS: Lord, Rutter, DiLavore, & Risi, 1999), the patient was also assessed with ADOS, module 1.

The LIPS evaluation showed a moderate ID (IQ = 43), according to ICD-10 criteria. It is to be underlined that the LIPS provides a culture-free, non verbal mean of assessing general intelligence, not influenced by the patient's expressive speech impairment.

The developmental profile, based on the results of the Griffiths scale, corresponded to a mental age of 26.3 months.

Table 1 - *Patient's scores in GMDS*

Scale	*A*	*B*	*C*	*D*	*E*	*F*	*Total*
M. A.	21	*30*	23.5	27	*30*	26	26.3
S. Q.	30	*42.85*	33.57	38.57	*42.85*	37.14	37.49

Legend: A: locomotor scale; B: personal – social scale; C: hearing & speech scale; D: eye & hand coordination scale; E: performance scale; F: practical reasoning scale; MA: mental age; SQ: subquotient.

The patient's score in GMDS showed a general developmental delay, as well as an uneven profile of abilities across different domains. A detailed analysis of the results showed a weakness in locomotor scale (MA = 21; SQ = 30), in hearing and speech scale (M.A. = 23.5; S.Q. = 33.57) and in practical reasoning scale (MA = 26; SQ = 37.14). The best results were obtained in the personal/social scale (MA = 30; SQ = 42.85) and performance scale (MA = 30; SQ = 42.85).

The test results seem to reflect the typical clinical profile of children with AS (Zori *et al.,* 1992; Williams *et al.,* 1995; Andersen, Rasmussen, & Stromme, 2001).

Although the scale does not evaluate specifically the communication skills,

it allows us to obtain some information. The related items in the two to three years age group, requires that the child recognizes and denominates some images of objects. Our patient was able to discriminate all images (33 out of 40), but nominated correctly 12 only (shoe, cup, dog, ball, train, hat, fork, flower, cat, star, child, fish), and reproduced the corresponding onomatopoeic sound to the car ("bruum"). This data seem to differ from that reported in literature as far as the number of words that a person with AS may acquire (Williams et al., 1995; Lossie *et al*., 2001).

The PEP-R profile evaluation showed greater abilities in the perceptive and fine-motor skills, whereas in other areas the performances appeared to be rather homogeneous: Development Age (DA) = about 24 months, with the exception of the cognitive verbal area where greater performance deficits are recorded (DA = 18 months). These results, reported in Table 2, seem to confirm, once again, the typical cognitive profile in children with AS.

PEP-R has been conceived by Schopler for the evaluation of children with Autistic Spectrum Disordes (ASD). It is an inventory of behaviors and abilities leading to the identification of discrepancies and idiosynchrasies throughout the items of learning. The child's profile does not fit the usual one of children with ASD (bell-shaped curve with better performances in the fine-motor and gross-motor skills, and eye-hand integration than the imitative, cognitive and verbal abilities). Notwithstanding previous reports prompting an overlap between AS and ASD, we have found differences, mainly regarding the cognitive skills.

Table 2 – *Patient's score in PEP-R*

Scale	*I*	*P*	*FM*	*GM*	*HE*	*PC*	*CV*	*Total*
Total	7	*12*	*12*	14	4	11	2	62
D. A.	22	*48*	*38*	30	24	24	18	24

Legend: I = Imitation; P = Perception; FM = Fine-motor Skill; GM = Gross-motor Skills; OM = Hand-eye coordination; PC = Cognitive performance; CV = Cognitive-verbal performance; DA = Developmental age.

The LAP has been designed for the assessment of psychomotor development in young children. Table 3 lists the resuls of LAP test in our boy. Our child showed 30-month skills in the pre-wri-ting and autonomy, lower scores in the gross-motor and fine-motor skills, and strengthenesses in the communication and social abilities.

Table 3 – *LAP test results*

Areas	*Gross Motor*	*Fine Motor*	*Pre-writing*	*Cognitive*	*Language*	*Self-Help*	*Personal-Social*
M. A.	21	27	30	30	36	30	36

Legend: MA: = mental age.

Furthermore, some items, out of the fine-motor and autonomy's areas, were compatible with to a 36-month psychomotor development.

Such scores are coherent with the other administered tests, highlighting the weaknesses and strengths of people with AS, with the exception of the Language area (MA = 36 months).

The results obtained from the VABS, reported in Table 4, indicated an overall level of adaptive functioning equivalent to 19 months.

Table 4 – *Patient's scores in VABS*

	Subscale	*Equivalent Age*
Communication	Receptive	17
	Espressive	18
	Written	18
	Total	*17*
Daily Living Skills	Personal	27
	Domestic	21
	Community	21
	Total	*24*
Socializzation	Interpersonal	21
	Play and leisure time	19
	Coping Skill	20
	Total	*19*
Motor Skills	Gross	18
	Fine	24
	Total	*20*

No further evaluation of the communication's skills was been possible, due to the child's severe impairments in this area, and the lack of adequate tools in children with low functioning, attention deficits and hyperactivity. The administration of the above-mentioned developmental scales, the TVL score, and

video-recorded observations in free situations, where the child has spoken words spontaneously or after stimulus, lead to the total count of 54 spoken words. All the words reported from the mother during the personal history, but not heard by us, were omitted, for the lack of objective confirmation.

The patient's ADOS scores, reported in Table 5, excluded the diagnosis of Autism and ASD.

Although verbal communication was severely impaired, the patient was observed to use a number of other means to communicate, including pointing, gesturing, and directing facial expressions. Verbalizzation was also observed to be well coordinated with eye contact.

The patient showed some appropriate pleasure in interaction with the examiner, answered to joint attention, with delayed spontaneous onset.

He was observed to engage in some functional play with objects, but imaginative play was more limited.

Repetitive or stereotyped behaviors did not occur during the ADOS evaluation.

Table 5 – *Patient's score in ADOS*

ADOS	*Autism spectrum cut-off*	*Autism cut-off*	*Patient's scores*
Communication (CO)	2	4	2
Reciprocal Social Interaction (RSI)	4	7	3
RSI + CO	7	12	5

3. Conclusions

Data collected by us seem to confirm a less severe phenotype in patients with UBE3A mutations (Bottani *et al.,* 1994; Smith *et al.,* 1997, 1998; Moncla *et al.,* 1999b; Fridman *et al.,* 2000).

The age of acquisition of autonomous walking in our patient (20 months) seems to confirm the report from Lossie *et al.,* (2001) averaging at 2.8 years the age of spontaneous walking in children with UBE3A mutations, earlier than the children with AS due to deletions. Our results show a nonhomogeneous profile, peaking his weaknesses in the gross-motor, understanding, speech,

and practical reasoning areas, and his strengths in the personal/social, eye-hand coordination, and performance areas.

Such results seem to overlap with those authors (Williams *et al.,* 1995; Andersen *et al.,* 2001) reporting on a peculiar profile in AS. Our child scores 25.8 months at the Mental Age (MA) evaluation following the GMDS developmental scale administration. This disagrees with that reported from Andersen *et al.,* (2001), who administered the same test to 20 children (age range 2-14 years, mean age 7 years) with AS, averaging their MA at 10 months, with only two 7-year-old children peaking at 23 months. On the contrary, our results overlap with those of Williams *et al.* (2010).

In our case, the global functioning is compatible with a moderate degree of ID, while previous reports (Thompson & Bolton, 2003) usually have found severe or profound degree of ID. However, other studies (Williams *et al.,* 1995) have pointed out that the less impaired the attention, the more probable is the reaching of a moderate ID.

No differences regarding the development of communication among genetic subgroups are evident in people with AS, according to Lossie *et al.,* (2001).

Several reports (Clayton-Smith, 1993; Williams *et al.,* 1995; Andersen *et al.,* 2001) maintain in the 6-8 words range the language portfolio of people with AS. However, our patient speaks out 54 different words in a communicative functional way. Currently, it is unclear why this boy has reached such performance, and if the early stimulation has played a role in this achievement, but this is conceivable. Only a longitudinal follow-up will tell about the global functioning reached by this boy.

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