Journal of Neurology
https://doi.org/10.1007/s00415-020-10395-4

ORIGINAL COMMUNICATION

Dystonia in Angelman syndrome: a common, unrecognized clinical finding

Edoardo Ferlazzo[1,2,3] · Michele Ascoli[1,2] · Francesca Abate[1] · Sara Gasparini[1,2] · Giovanni Mastroianni[2] · Vittoria Cianci[2] · Giulia Ferrigno[1] · Chiara Sueri[2] · Tiziana D'Agostino[2] · Umberto Aguglia[1,2,3]

Received: 23 October 2020 / Revised: 24 December 2020 / Accepted: 31 December 2020

Abstract

Introduction Angelman syndrome (AS) is a neurodevelopmental disorder characterized by cognitive disability, speech impairment, hyperactivity and seizures. Movement disorders have been reported in almost all AS subjects and they are described as "tremulous movements of limbs, unsteadiness, clumsiness or quick, jerky motions". The presence of dystonia has barely been mentioned in subjects with AS and has never been studied in detail. The purpose of this study is to evaluate the prevalence, clinical features and severity of dystonia in a series of adolescents and adults with AS.

Methods Whole body video recordings of patients with genetically confirmed AS were evaluated. Dystonia was evaluated by mean of the movement subscale of Burke–Fahn–Marsden Dystonia Rating Scale (BFM).

Results Forty-four subjects with AS were evaluated. Fourteen recordings were excluded due to poor cooperation. We finally analyzed data of 30 subjects (15 F) with a median age of 28 years (range 15–51). Dystonia was present in 28/30 (93.3%) subjects. Among these, dystonia involved the upper limbs in 28/28 (100%), lower limbs in 8/28 (28.5%), mouth in 7/28 (25%), neck in 3/28 (10.7%), trunk in 1/28 (3.6%). Severity of dystonia ranged from slight to moderate. There was a linear correlation between severity of dystonia and increasing age. There was no difference in terms of severity of dystonia among genetic subgroups.

Conclusions Dystonia is a common and previously underrecognized clinical feature of adults and adolescents with AS.

Keywords Movement disorders · Genetics · Myoclonus · Syndrome · Burke–Fahn–Marsden Dystonia Rating Scale

Introduction

Angelman syndrome (AS) is a genetic condition characterized by intellectual disability, absent speech, facial dysmorphisms, ataxia, sleep disorders, epilepsy and movement disorders [1]. These features are associated with an unusual posture of the arms (raised, with elbows flexed and hands facing down) during walking and with an apparently joyful attitude, so AS is also known as "happy-puppet syndrome". AS is caused by loss of function of the maternal copy of the ubiquitin–protein ligase E3A (UBE3A) gene, located on chromosome 15q11-q13, which encodes an ubiquitin protein ligase. Several mechanisms can support the deficient expression of the UBE3A gene: deletion in the critical region 15q11.2-q13 (60–75% of cases), point mutations (10%), paternal uniparental disomy (2–5%) and imprinting defects (2–5%). There is a well-known clinical variability among the different genetic subgroups, as patients with deletion generally show a more severe phenotype [2, 3]. Movement disorders have been reported in almost all AS subjects and they are described as "tremulous movements of limbs, unsteadiness, clumsiness or quick, jerky motions" [1]. Among movement disorders, myoclonus has been widely described [4–6], but the presence of dystonia has barely been mentioned in subjects with AS and has not been studied in detail [7]. The

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-020-10395-4.

✉ Umberto Aguglia
u.aguglia@unicz.it

[1] Department of Medical and Surgical Sciences, Magna Graecia University, Germaneto, Catanzaro, Italy

[2] Regional Epilepsy Centre, Great Metropolitan Hospital Bianchi-Melacrino-Morelli, Reggio Calabria, Italy

[3] Institute of Molecular Bioimaging and Physiology, National Research Council, Germaneto, Catanzaro, Italy

Published online: 23 January 2021

purpose of this study is to evaluate the prevalence, clinical features and severity of dystonia in a series of adolescents and adults with AS.

Subjects and methods

Subjects

We evaluated video recordings of 44 consecutive subjects with genetically confirmed AS, followed at the Regional Epilepsy Centre of Reggio Calabria (Italy) or participating to the annual national meetings of the Italian Organization for AS from 2014 to 2017. Informed consent to the study was obtained from all caregivers. We collected and tabulated demographic, clinical, neurophysiologic and genetic data.

Methods

Dystonia was defined as a sustained muscle contraction that causes torsion of a body segment with abnormal postures [8]. We assessed the presence, distribution and severity of dystonia through the movement subscore (range, 0–120) of Burke–Fahn–Marsden Dystonia Rating Scale (BFM) [9]. The presence of other disabling symptoms such as intellectual disability, ataxia and speech impairment did not allow us to evaluate the disability subscale of BFM.

Three independent observers (E.F., F.A. and U.A.) reviewed the whole-body video recordings of a series of AS patients. We assessed dystonia at rest (when possible, due to the poor patients' cooperation), during voluntary movements and activation manoeuvres (grasping of an object). For each district (eyes, mouth, speech/swallowing, neck, arms, trunk, legs) we measured the severity of dystonia. The severity scores were obtained from individual assessments of each district in terms of severity and provoking factors such as writing and walking. Both severity and provoking factors were rated from 0 to 4, with higher scores denoting more severe dystonia. The individual score for each region was the product of the two factors (provoking factor and severity factor) multiplied for a "weight" factor (0.5 or 1) according to the involved district [9]. The total BFM score ranged from 0 to 120 [9].

Statistical analysis

We evaluated the relationship between the severity of dystonia and the type of genetic mutation through one-way analysis of variance (ANOVA). The relationship between severity of dystonia and age was assessed using Pearson's correlation coefficient.

Results

We evaluated the video recordings of 44 subjects with AS. Fourteen recordings were excluded due to poor cooperation (patients' hands kept by parents or caregivers to allow the execution of video recordings). We finally analysed data of 30 subjects (15 F) with a median age of 28 years (range 15–51). The main clinical features of patients with AS are reported in Table 1. All patients a typical AS phenotype including impairment of adaptive behaviour with a very low mental age, absent speech, facial dysmorphisms and ataxia.

Dystonia was present in 28/30 (93.3%) subjects, involving the upper limbs in 28/28 (100%), the lower limbs in 8/28 (28.5%), the mouth in 7/28 (25%), the neck in 3/28 (10.7%), the trunk in 1/28 (3.6%) (Fig. 1a, b) (video, as supplementary material).

The severity of dystonia ranged from slight to moderate in all involved body districts. The total scores ranged from 0 to 30 in single patients. There were no differences in dystonia severity scores among the different genetic subtypes ($p = 0.678$). Conversely, there was a linear correlation between increasing patients' age and dystonia severity scores (r correlation coefficient $= 0.41$, $p = 0.02$). A scatter diagram is reported in Fig. 2.

Discussion

Dystonia is a common, unrecognized clinical finding in AS. Ninety-three percent of our subjects had dystonia. International Parkinson and Movement Disorder Society Task Force did not report dystonia as a neurological feature of AS [6]. No study evaluated in detail the presence of dystonia in subjects with AS. Guerrini et al. described cortical myoclonus in AS patients [4]; in some, myoclonus was reported as associated with "dystonic postures" whose features (site, severity, etc.) were not detailed [4]. In our series, dystonia mainly affected the upper limbs or, more rarely, lower limbs or mouth. In all subjects, intensity of dystonia ranged from slight to moderate.

The severity of dystonia did not appear to correlate with genotype, differently from literature data suggesting a more severe phenotype in patients with UBE3A deletion [2, 3]. Conversely, we demonstrated a linear correlation between age and the severity of dystonia. The cross-sectional nature of the present study does not allow to establish whether dystonia worsens with age or it is simply a late manifestation of AS. The notion that most clinical features of AS improve with age may support the latter hypothesis. Longitudinal studies are needed to validate this hypothesis.

Table 1 .

Patients	Sex, age	Genetics	Main clinical finding	Burke–Fahn–Marsden Movement Scale						
				Provoking factor	Arms	Legs	Mouth	Neck	Trunk	Score (max = 120)
1	M, 50	Del	E, S, M	3	0	R:2; L:2	0	0	0	12
2	F, 36	Del	E, S, M	3	R:1; L:1	R:2; L:2	2	0	0	19
3	M, 35	P.U.D.	E, S, M	3	0	R:3; L:3	0	0	0	18
4	F, 25	Del	E, S	0	0	0	0	0	0	0
5	F, 30	Del	E, M	3	0	R:2; L:2	0	0	0	12
6	F, 32	P.U.D.	E, M	3	0	R:1; L:1	0	0	0	6
7	F, 33	Mut	E, S, M	3	R:1; L:1	R:3; L:3	2	0	0	25
8	F, 24	Mut	E, S, M	3	0	R:1; L:1	1	0	0	6,5
9	M, 37	Del	E, S, M	3	R:1; L:1	R:1; L:0	0	1	0	9,5
10	F, 19	Del	E, S, M	3	0	R:0; L:1	2	0	0	4
11	F, 21	Del	E, S, M	3	0	R:3; L:3	2	0	0	19
12	M, 51	P.U.D.	E, S, M	3	0	R:2; L:2	1	0	0	12,5
13	M, 23	Del	S, M	3	0	R:0; L:2	0	0	0	6
14	F, 34	Mut	E, M	3	0	R:2; L:2	0	1	1	13,5
15	F, 19	Del	E, S, M	3	0	R:1; L:1	1	0	0	6,5
16	F, 24	Del	E, S, M	3	0	R:1; L:0	0	0	0	3
17	M, 20	P.U.D.	E, S	3	R:1; L:1	R:1; L:0	0	0	0	9
18	F, 22	P.U.D.	E, M	3	0	R:0; L:1	0	0	0	3
19	M, 29	Imp	E, M, P	3	0	R:3; L:3	0	0	0	18
20	F, 30	Del	E, M	0	0	0	0	0	0	0
21	F, 21	Del	S, E	3	R:2; L:2	R:3; L:3	0	0	0	30
22	M, 31	Del	S, M	3	R:1; L:1	R:3; L:3	0	1	0	24,5
23	M, 25	Del	E, S	3	0	R:0; L:1	0	0	0	3
24	M, 43	Del	E, S, M	3	0	R:3; L:3	0	0	0	18
25	M, 40	Del	E, S, M	3	R:1; L:1	R:3; L:3	0	0	0	24
26	M, 19	Del	E, M, P	3	0	R:1; L:0	0	0	0	3
27	M, 37	Del	E, S	3	R:2; L:2	R:0; L:1	0	0	0	15
28	M, 23	Del	E, S, P	3	0	R:0; L:1	0	0	0	3
29	F, 22	Del	E, S	3	0	R:0; L:1	0	0	0	3
30	M, 15	Del	E, S. M	3	0	R:1; L:0	0	0	0	3

Del deletion, *E* epilepsy, *Imp* imprinting defects, *L* left, *M* myoclonus, *Mut* point mutations, *P.U.D.* paternal uniparental disomy, *P* pyramidal signs, *R* right, *S* scoliosis, *0* absent, *1* slight, *2* mild, *3* moderate, *4* severe

The poor attention to this clinical feature in literature may be due to the habitually mild intensity of dystonia and the prominence of other more disabling neurological disorders (cognitive disability, myoclonus, epilepsy, sleep disturbances, etc.) in AS subjects. Moreover, as dystonia appears to be a more prominent feature with advancing age, many studies focusing on paediatric patients may have missed this phenomenon. Finally, dystonia might have been misidentified with atypical stereotyped postures commonly observed in neurodevelopmental disorders such as Rett syndrome. Dystonia in our AS subjects, usually occurred in the context of immature and poorly organized movements [10].

Convergent evidences from clinical investigation and experimental models supports the view that dystonia is due to basal ganglia–thalamo–cortical and cerebello–thalamo–cortical pathways disorders [11]. UBE3A is involved in targeting proteins for degradation within cells and is highly expressed in different brain areas including basal ganglia and cerebellum. Notably, loss of UBE3A appears to have a definite impact on neurons leading to intrinsic changes in membrane properties, including increased length of the axon initial segment [12]. We hypothesize that neuronal changes of the above-mentioned circuits could be involved in the pathogenesis of dystonia in AS subjects.

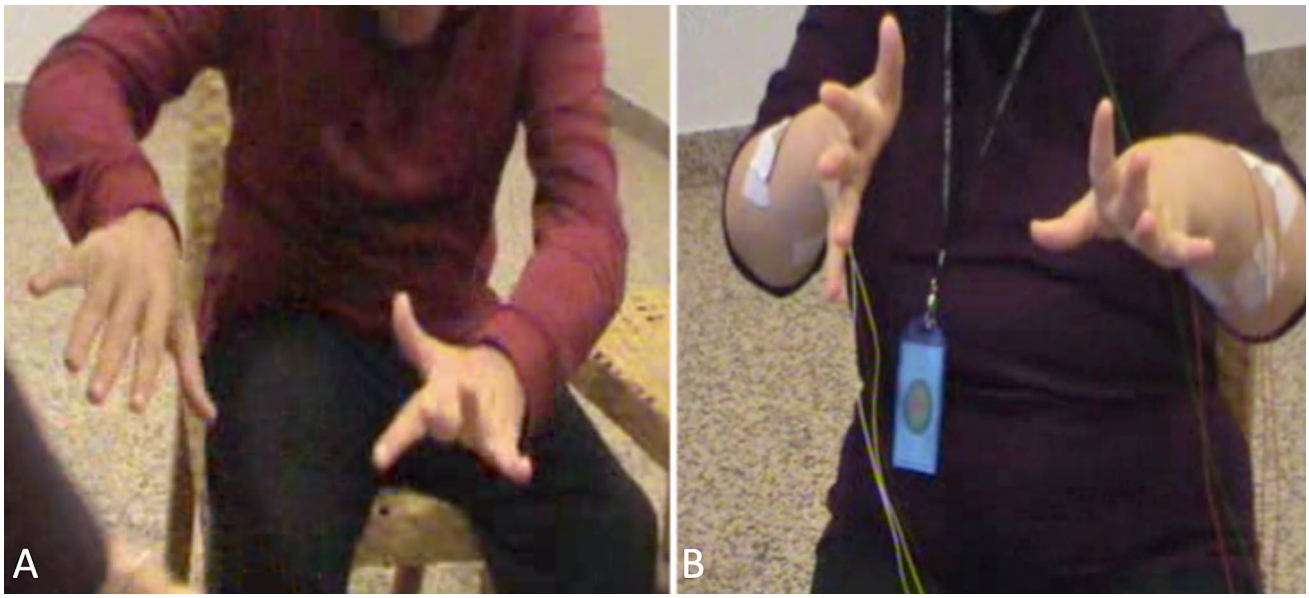

Fig. 1 Bilateral upper limb dystonia evident during posture maintenance (**a** and **b**)

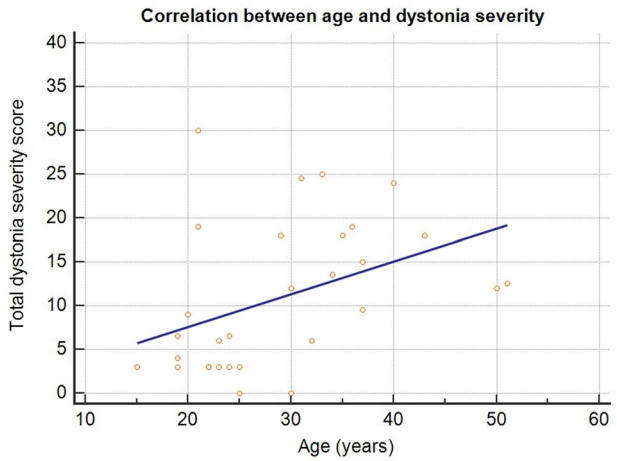

Fig. 2 The scatter diagram showing linear correlation between increasing patients' age and dystonia severity scores

Our study has some limits. First, the lack of blindness of examiners could have led to an overestimation of the presence of dystonia. Secondly, the absence of a control group consisting of subjects with Rett syndrome or other neurodevelopmental disorders presenting hand stereotypies could have caused an overestimation of the presence of dystonia. Lastly, it was not possible to perform a neurophysiological assessment of dystonia by mean of blink reflex recovery cycle, due to the subjects' lack of cooperation [13].

In conclusion, dystonia is common in movement disorder of AS, often involving the upper limbs. The impact of dystonia on global motor performances may not be assessed due to the presence of ataxia and intellectual disability in AS subjects.

Acknowledgements We are grateful to the patients' parents and caregivers for their cooperation and to the Italian Organization for AS (OrSA) for giving us the chance to attend their meetings and to involve AS families in this study.

Author contributions UA and EF: conceptualization of the study, interpretation of the data, drafting the manuscript and revision. MA: conceptual contribution, interpretation of the data, drafting the manuscript and revision. FA: analysis and interpretation of the data, contributed to manuscript draft. SA: conceptual contribution, analysis and interpretation of the data and revising the manuscript for intellectual content. GM: interpretation of the data and revising the manuscript for intellectual content. VC: interpretation of the data and revising the manuscript for intellectual content. GF: interpretation of the data and revising the manuscript for intellectual content. CS: conceptual contribution, interpretation of the data, and revising the manuscript for intellectual content. TD: conceptual contribution. All authors read and approved the final manuscript.

Funding None.

Data availability Video available as supplementary material. Datasets analyzed may be obtained from the corresponding author upon request.

Code availability Code used for statistical analysis may be obtained from the corresponding author upon request.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard statement All human studies must state that they have been approved by the appropriate ethics committe and have therefore been performed in accordence with the ethical standards laid down in the 1964 Declaration of Helsinki.

References

1. Williams CA, Beaudet AL, Clayton-Smith J, Knoll JH, Kyllerman M, Laan LA, Magenis RE, Moncla A, Schinzel AA, Summers JA, Wagstaff J (2006) Angelman syndrome 2005: updated consensus for diagnostic criteria. Am J Med Genet A 140:413–418. https://doi.org/10.1002/ajmg.a.31074
2. Guerrini R, Carrozzo R, Rinaldi R, Bonanni P (2003) Angelman syndrome etiology, clinical features, diagnosis and management of symptoms. Pediatr Drugs 5:647–661. https://doi.org/10.2165/00148581-200305100-00001
3. Bird LM (2014) Angelman syndrome: review of clinical and molecular aspects. Appl Clin Genet 16:93–104. https://doi.org/10.2147/TACG.S57386
4. Guerrini R, De Lorey TM, Bonanni P, Moncla A, Dravet C, Suisse G, Livet MO, Bureau M, Malzac P, Genton P, Thomas P, Sartucci F, Simi P, Serratosa JM (1996) Cortical myoclonus in Angelman syndrome. Ann Neurol 40:39–48. https://doi.org/10.1002/ana.410400109
5. Ferlazzo E, Franceschetti S, Gasparini S, Elia M, Canafoglia L, Pantaleoni C, Ascoli M, D'Agostino T, Sueri C, Ferrigno G, Panzica F, Cianci V, Aguglia U (2019) Connectivity measures suggest a sub-cortical generator of myoclonus in Angelman syndrome. Clin Neurophysiol 130:2231–2237. https://doi.org/10.1016/j.clinph.2019.08.031
6. Sueri C, Ferlazzo E, Elia M, Bonanni P, Randazzo G, Gasparini S, D'Agostino T, Sapone AR, Ascoli M, Bellavia MA, Cianci V, Gambardella A, Labate A, Aguglia U (2017) Epilepsy and sleep disorders improve in adolescents and adults with Angelman syndrome: a multicenter study on 46 patients. Epilepsy Behav 75:225–229. https://doi.org/10.1016/j.yebeh.2017.07.041
7. van der Veen S, Zutt R, Klein C, Marras C, Berkovic SF, Caviness JN, Shibasaki H, de Koning TJ, Tijssen MAJ (2019) Nomenclature of genetically determined myoclonus syndromes: recommendations of the International Parkinson and Movement Disorder Society Task Force. Mov Disord 34:1602–1613. https://doi.org/10.1002/mds.27828
8. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK (2013) Phenomenology and classification of dystonia: a consensus update. Mov Disord 28:863–873. https://doi.org/10.1002/mds.25475
9. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J (1985) Validity and reliability of a rating scale for the primary torsion dystonias. Neurology 35:73–77. https://doi.org/10.1212/wnl.35.1.73
10. Goldman S, Temudo T (2012) Hand stereotypies distinguish Rett syndrome from autism disorder. Mov Disord 27:1060–1062
11. Downs AM, Roman KM, Campbell SA, Pisani A, Hess EJ, Bonsi P (2019) The neurobiological basis for novel experimental therapeutics in dystonia. Neurobiol Dis 130(104):526. https://doi.org/10.1016/j.nbd.2019.104526
12. Rotaru DC, van Woerden GM, Wallaard I, Elgersma Y (2018) Adult Ube3a gene reinstatement restores the electrophysiological deficits of prefrontal cortex layer 5 neurons in a mouse model of Angelman syndrome. J Neurosci 12(38):8011–8030. https://doi.org/10.1523/JNEUROSCI.0083-18.2018
13. Nisticò R, Pirritano D, Salsone M, Valentino P, Novellino F, Condino F, Bono F, Quattrone A (2012) Blink reflex recovery cycle in patients with dystonic tremor: a cross-sectional study. Neurology 78:1363–1365. https://doi.org/10.1212/WNL.0b013e3182518316