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## **Craniofacial disorders in the course of Angelman syndrome - a review of the literature**

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### **Abstract**

Angelman syndrome is a neurogenetic disorder with an estimated prevalence of 1 in 10.000 to 1 in 40.000 cases. Clinical presentation is based on characteristic neurobehavioral and emotional disorders, a function of the nervous and pulmonary system as well as dysmorphic features within craniofacial and neurocranium. The aim of the study is an evaluation based on the literature reviewing disorders in the craniofacial region in patients with Angelman Syndrome, with particular emphasis on the oral cavity. Literature from the PubMed base and the Main Medical Library from the last 30 years was analysed. sixteen items were obtained; after verification, the requirements were met by 16 publications, which together contained a description of the craniofacial and oral cavity disorders in 226 patients. Disorders associated with Angelman syndrome affected many aspects related to health, basic life functions and interpersonal relationships. Proper substantive preparation for working with such a patient enables effective prevention and health monitoring, adjustment of the treatment plan, as well as readiness for any unexpected situations.

**Key words: Dento-facial deformities Angelman Syndrome**

## Introduction

Angelman syndrome is a neurogenetic disorder with an estimated prevalence of 1 in 10.000 to 1 in 40.000 cases [1,2,3]. For the first time, it was described in 1965 by Harry Angelman, who called three children as puppets [1,4]. Clinical presentation is based on characteristic neurobehavioral and emotional disorders, a function of the nervous and pulmonary system as well as dysmorphic features within craniofacial and neurocranium [2]. Dysfunctions contribute to the occurrence of specific neurological, orthopaedic, pulmonary and stomatological disease [5]. The development of neurological disorders is affected by the loss of the enzyme encoded by the UBE3A gene - ubiquitin ligase within the brain, which in consequence may result in ataxia as well as epilepsy, the first symptoms of which can be observed before 3 years of age [2,7]. Seizure disorders occur as a result of a GABA receptor gene deficiency [8].

The aetiology is based on four genetic mechanisms within chromosome 15 that condition the UBE3A gene disorder. There are material 15q11-13 deletions, paternal uniparental disomy, imprinting defects, UBE3A point mutations. In 10% of cases, genetic abnormalities are not taken into account [1,4].

Patients with diagnosed Angelman Syndrome manifest severe intellectual disability and motor disorders in maintaining balance as well as conscious control of arm and shoulder movements [8]. Behaviorally, patients exhibit hyperactivity, uncontrollable bouts of laughter as well as concentration and attention problems.

The diagnosis of Angelman Syndrome is based on fluorescent in situ analysis (FISH). The incidence of the genetic mechanism that conditions Angelman Syndrome is around 70% [9]. Characteristic clinical features suggesting the need for cytogenetic testing are revealed before 2 years of age [2]. During the prenatal, perinatal and early postnatal period, there are no deviations from the norm [3]. The biggest intensity of symptoms is present in patients with the 15q11-13 deletions [10].

The aim of the study is an evaluation based on the literature reviewing disorders in the craniofacial region in patients with Angelman Syndrome, with particular emphasis on the oral cavity.

## Material and methods

A question was asked what disorders in craniofacial and oral cavity morphology occur in patients with AS. Literature from 1990-2020 from the PubMed database, Google Scholar, was analyzed, entering the terms: Angelman syndrome, dentofacial deformities Angelman syndrome, oral manifestation Angelman syndrome. Account has been taken of publications in English that describe patients with genetically confirmed AS, special attention has been paid to craniofacial developmental disorders and oral abnormalities.

Inclusion criteria: research works and case reports of AS patients with craniofacial development and oral abnormalities were selected. A description of the craniofacial abnormalities was required in these works. The above requirements were met by 16 publications, which together contained a description of the craniofacial and oral cavity disorders in 226 patients.

After a full review of the work, the content of selected articles was re-evaluated and the data obtained were presented in tabular form [Table 1].

Table 1. Morphological features in the craniofacial region in patients with AS

Extraoral manifestation	
Microbrachycephaly	N=118; 52,21%
Mandibular Prognathism	N=76; 33,63%
Hipopigmented skin	N=118; 52,51%
Thin blond hair	N= 78; 34,51%
Light Eyes	N= 73; 32,3%
Deeply set eyes	N= 6; 2,65%
Strabismus	n= 76; 33,63%
Upslanting palpebral fissures	n= 4; 1,77%
Infraorbital cyanosis	n= 3; 1,33%
Macrostomia with thin upper lip	N= 55; 24,34%
Excessive chewing behavior	n= 3; 1,33%
Hypotonia of lips	n=2; 0,88%
Hypoplasia of the maxillary bones	n=1; 0,44%
Intraoral manifestation	
Tongue protrusion	N=56; 24,78%
Widely spaced teeth	N= 5; 2,21%
Open mouth	N= 4; 1,77%
High arched palate	n=1; 0,44%

## Results

After analyzing the obtained material, we find that the most common associated features in the case of Angelman's syndrome within the craniofacial area are: hipopigmented skin 52,51%; microbrachycephaly, 52,21%; mandibular prognathism, 33,63%; Strabismus 33,63%; macrostomia with thin upper lip, 24,34%; Tongue protrusion 24,78%; thin blond hair 34,51%; light eyes 32,3%.

Features such as deeply set eyes, upslanting palpebral fissures, infraorbital cyanosis, hypotonia of lips, maxillary hypoplasia, widely spaced teeth, open bite and high arched palate, have been reported in individual cases.

## Discussion

A common problem when describing patients with rare defects is a short description of the irregularities that occur in a given disease. When describing a patient, researchers often focus on disorders that directly relate to their interests or specialization, ignoring those features that may be of interest to other researchers. Our work aimed to describe craniofacial disorders. When analyzing the literature, particular attention was paid to the lack of an accurate description of the craniofacial morphology. Obtained pieces of information were short, inaccurate, often did not include information about the oral cavity. Usually, the examined patients were examined just by a neurologist, so there was no description of the intraoral examination. This fact constituted the main limitation of this study.

Diagnostics of Angelman syndrome and knowledge of the characteristic neurobehavioral disorders (on the one hand close to autism, on the other hyperactive), motor, paroxysmal (epilepsy) and pulmonary, plays a key role in working with the patient [2,3]. It is necessary to bear in mind a severe intellectual disorder that significantly affects interpersonal relationships,

awareness of activities performed as well as motor coordination. As a consequence, patients don't understand the essence and necessity of basic nursing activities and are unable to do it with full awareness and motor control. The role of a guardian who takes responsibility for maintaining cleanliness within his body is crucial in caring for the sick. At every stage of the mentee's life and development, he should be educated in the selection of appropriate hygiene measures, adapted to the condition of the oral cavity and skin, care techniques, as well as building interpersonal relationships with the intellectually disabled. Lack of knowledge regarding the management of patients, conducting a properly balanced diet and incorrect cooperation on the doctor-guardian-patient line contributes to the occurrence of numerous carious cavities within the oral cavity, which if left untreated, affect the functioning of the whole organism over time. Many factors contribute to effective anti-caries prophylaxis in patients with Angelman syndrome. Early adaptation to a new place - a dental office - is crucial, in which multi-coloured objects that affect the dispersion and excitement of the subject should be avoided. All reflective surfaces, such as mirrors and water, will help the patient to focus [11]. According to Murakami et al. [11], people with diagnosed Angelman syndrome should participate in regular consultations (preferably every 4 months), which help patients to keep in touch with the dental team, the surgery and to remember all activities used to perform medical procedures. Correct cooperation enables systematic control of the condition of the oral cavity, early diagnosis, treatment, as well as preventive use of fluoride in primary and permanent dentition. According to Gallo et al. [4], the lack of patient-physician cooperation leads to the need for general anesthesia for the safe course of dental treatment. The use of such a solution should be a last resort. Comorbidities may be a contraindication to general anesthesia. Facial malformations impede or prevent intubation of the patient. In epilepsy patients, it is important to gather a detailed history of the types, frequency of seizures, medications taken and doses, as well as the opinion of the treating physician. There is a risk of convulsive seizures as well as peripheral muscle atrophy during general anesthesia of patients with Angelman syndrome. As a result of taking antiepileptic drugs, increased bleeding may occur during the procedure. It is important to avoid the use of drugs that lower the seizure threshold during anesthesia. The first step is to try to carry out medical procedures under local anesthesia, which has fewer complications. If, due to existing comorbidities, it is not possible to introduce anesthetic drugs and the patient does not cooperate, it is necessary to apply direct coercion during the procedure. This type of form involves holding with the use of physical force or immobilizing the patient with the use of belts or a straitjacket [13]. To keep the patient's mouth open and maintain full access to the treatment area, it is advisable to use a retractor. Such procedures allow you to increase safety for both the patient and medical staff.

Our data shows that about 24,78% of the patients analyzed had tongue protrusion [13, 14, 17, 18, 20, 22, 26]. Musculo-functional disorders in the oral cavity and face in people with Angelman Syndrome adversely affect normal growth as well as development in the jaw, mandible and soft tissues. Depending on the position the tongue takes, it can contribute to specific deformations. When resting between dental arches, it causes improper or stopped tooth eruption, which in turn contributes to the formation of an open bite. The excessive leaning of the tongue on the teeth leads to their incorrect deflection, which people with Angelman Syndrome are particularly vulnerable to. An additional influence on this may have a thin upper lip, which was described in 31.56% of patients analyzed. Dental treatment is very difficult for people with Angelman syndrome. In the absence of proper doctor-patient cooperation, treatment of this type of disorder may be complicated or impossible depending on the patient's state of health.

The clinical picture of patients with Angelman syndrome analyzed by us consisted of hypopigmentation in the skin, hair and eyes (52,51%) [13, 14, 18, 22, 23, 25, 26]. In infants with

psychomotor retardation, the coexistence of these types of lesions may suggest the need for cytogenetic testing. Hypopigmentation in Angelman syndrome is caused by hemizygosity or defects in the P gene located in the vicinity of UBE3A on chromosome 15, determining oculocutaneous albinism of tyrosine-positive (OCA2), as well as the lack or deficiency of the UBE3A gene that reduces the expression of MC1R protein responsible for regulation and production of pigment. The blue or yellow-brown coloring of the iris (32,3%) and the yellow-brown hair color (34,51%) are characteristic. Congenital hypopigmentation promotes the development of skin cancer, so patients should avoid high exposure to sunlight, use special protective clothing, protective filters and regularly undergo ophthalmological and dermatological assessment to detect malignant lesions early.

## Conclusion

Disorders associated with Angelman syndrome affected many aspects related to health, basic life functions and interpersonal relationships. Proper substantive preparation for working with such a patient enables effective prevention and health monitoring, adjustment of the treatment plan, as well as readiness for any unexpected situations.

## References

1. M. Maguire, Anaesthesia for an adult with Angelman syndrome, *Anaesthesia*, 2009;64(11):1250-3.
2. Bo Sung Kim, Jin Seok Yeo, Si Oh Kim, Anesthesia of a dental patient with Angelman syndrome-A case report-, *Korean J Anesthesiol.*, 2010;58(2): 207–210.
3. Rohit Sachdeva, Sarah J. Donkers, Soo Y. Kim, Angelman Syndrome: A Review Highlighting Musculoskeletal and Anatomical Aberrations, *Clin Anat.*, 2016;29(5):561-7.
4. C. Gallo, A. Marcato, M. Beghetto, E. Stellini, Dental treatment in Angelman syndrome patients. 8 Case reports, *Eur J Paediatr Dent*, 2012;13(4):345-8.
5. M. Felicitas Domínguez-Berjón, Ana Clara Zoni, María D Esteban-Vasallo, Juan Manuel Sendra-Gutiérrez, Jenaro Astray-Mochales, Main causes of hospitalization in people with Angelman syndrome, *J Appl Res Intellect Disabil.*, 2017;31(3):466-469.
6. Aleksandra Čalic , DMD/Borut Peterlin, MD, PhD, Epigenetics and Bruxism: Possible Role of Epigenetics in the Etiology of Bruxism, *Int J Prosthodont.*, 2015;28(6):594-9.
7. Laurie E. Seltzer, Alex R. Paciorkowski, Genetic Disorders Associated With Postnatal Microcephaly, *Am J Med Genet Part C*, 2014;9999:1–16.
8. Nagore Elu, Nerea Osinalde, Javier Beaskoetxea, Juanma Ramirez, Benoit Lectez, Kerman Aloria, Jose Antonio Rodriguez, Jesus M. Arizmendi, Ugo Mayor, Detailed Dissection of UBE3A - Mediated DDI1 Ubiquitination, *Front Physiol.*, 2019;10: 534.
9. Fukiyama Y, Tonari M, Matsuo J, Oku H, Sugasawa J, Shimakawa S, Ogihara T, Okamoto N, Ikeda T, A case of Fundus Albinoticus Diagnosed as Angelman Syndrome by Genetic Testing, *Case Rep Ophthalmol*, 2018;9:102–107.
10. Kristin A. Bakke, Patricia Howlin, Lars Retterstø, Øivind J. Kanavin, Arvid Heiberg, Terje Nærland, Effect of epilepsy on autism symptoms in Angelman syndrome, *Mol Autism.*, 2018;9: 2.
11. Christiana Murakami, Maria Salete Nahás Pires Corrêa, Fernanda Nahás Pires Corrêa, José Paulo Nahás Pires Corrêa, Dental treatment of children with Angelman syndrome: a case report, *Spec Care Dentist.*, 2008;28(1):8-11.
12. Sarkar PA, Shigli A, Patidar C., Happy Puppet syndrome. *BMJ Case Rep.*, 2011:bcr0920114747.

13. Alexandra Mussolino de Queiroz, Talitha de Siqueira Melara, Paula Dariana Fernandes Ferreira, Marília Pacífico Lucisano, Andiará De Rossi, Paulo Nelson-Filho, Raquel Assed Bezerra Silva, Dental findings and special care in patients with Angelman syndrome: a report of three cases, *Spec Care Dentist.*, 2013;33(1):40-5.
14. Chunawalla Yusuf, Morawala Abdul, Jain Kapil, Naqiyah Khandwawal, Angelman Syndrome: a case report, *International Journal of Current Research*, 2018;10, (01), 63993-63996.
15. Çelebi Kocaoğlu, Two Sisters with Angelman Syndrome: A Case Series Report, *J Pediatr Neurosci.*,2017; 12(4): 383–385.
16. Farah Ashrafzadeh, Arianeh Sadrnabavi, Javad Akhondian, Mehran Beiraghi Toosi, Mohammadhassan Mohammadi, Kazem Hassanpour, Angelman Syndrome: Case Report, *Iran J Child Neurol.*, 2016;10(2): 86–89.
17. Jagath C. Ranasinghe, Damitha Chandradasa, Sanjaya Fernando, Uditha Kodithuwakku, D.E.N. Mandawala, Vajira HW Dissanayake, Angelman Syndrome presenting with a rare seizure type in a patient with 15q11.2 deletion: a case report, *Journal of Medical Case Reports*, 2015; 142.
18. Cintia Fridmanaib, Monica C Varela, Robert D Nicholls Celia P Koiffmann, Unusual clinical features in an Angelman syndrome patient with uniparental disomy due to a translocation 15q15q, *Clinical Genetics*,1998;54(4):303-308.
19. Andrea Van Lierde, Maria Gabriella Atza, Daniela Giardino, Francesco Viani, Angelmans Syndrome in the First Year of Life, *Dev Med Child Neurol.*, 1990;32(11):1011-6.
20. Ana Teresa Hernandez Teodoro, Daphyne Yachel Chaves, Patrícia Abreu Pinheiro Crenitte, Simone Rocha de Vasconcellos Hage, Dionísia Aparecida Cusin Lamônica, Language, neurodevelopment, and behavior in Angelman syndrome: a case report, *CoDAS*, 201931(4):e20180177.
21. K. R. Ramanathan D. Muthuswamy B. J. Jenkins, Anaesthesia for Angelman syndrome, *Anaesthesia.*, 2008;63(6):659-61.
22. Saitoh S1, Harada N, Jinno Y, Hashimoto K, Imaizumi K, Kuroki Y, Fukushima Y, Sugimoto T, Renedo M, Wagstaff J, et al., Molecular and clinical study of 61 Angelman syndrome patients., *Am J Med Genet.*, 1994;52(2):158-63.
23. Smith A1, Wiles C, Haan E, McGill J, Wallace G, Dixon J, Selby R, Colley A, Marks R, Trent RJ., Clinical features in 27 patients with Angelman syndrome resulting from DNA deletion., 1996;33(2): 107–112
24. Sabrina Buoni, Salvatore Grosso, Lucia Pucci, Alberto Fois, Diagnosis of Angelman syndrome: clinical and EEG criteria, *J Med Genet.*, 1999;33(2):107-12.
25. Jill Clayton-Smith, Clinical Research on Angelman Syndrome in the United Kingdom: Observations on 82 Affected Individuals, *Am J Med Genet.*, 1993;46(1):12-5.
26. Bai JL, Qu YJ, Jin YW, Wang H, Yang YL, Jiang YW, Yang XY, Zou LP, Song F., Molecular and clinical characterization of Angelman syndrome in Chinese patients., *Clin Genet.*, 2014;85(3):273-7.
27. Amy Lawson-Yuen, Bai-Lin Wu, Va Lip, Trilochan Sahoo, Virginia Kimonis, Atypical Cases of Angelman Syndrome, *Am J Med Genet A.*, 2006;140(21):2361-4.