**Abstract**

**Background** Angelman syndrome is a rare neurogenetic disorder resulting in delayed neuropsychological development, intellectual disability, speech impairment, movement or balance disorder and a behavioural uniqueness. It is caused by deletion of maternal chromosome 15q11-13. The syndrome has oral manifestations such as diastemas, tongue thrusting, sucking/swallowing disorder, mandibular prognathism, and wide mouth. The dental literature on the syndrome is scarce.

**Case report** We report our approach to dental procedures in Angelman syndrome patients, and the relationship between the dental staff and the patient and his family. The purpose of this paper is to highlight the possibility of dental treatment in general anaesthesia, due to the lack of cooperation of some of these patients.

**Keywords** Angelman syndrome; Dental treatment; Rare syndrome.

**Introduction**

Angelman syndrome (AS) is a genetic neurological disorder that was first described in 1965 by Dr. Harry Angelman. The exact incidence of the syndrome is unknown but it is estimated to be between 1 in 15,000-30,000 [Murakami et al., 2008]. After the first discovery many reports and clinical experiences have been published describing the clinical phenotype of this syndrome, which comprises severe intellectual disability, epilepsy, abnormal EEG, microcephaly, lack of speech, ataxic movements, easily precipitated laughter, fair colouring in some patients, large mouth and chin. Because of the lack of a distinctive early phenotype, the age of diagnosis ranges from 2 years to adulthood [Smith et al., 1996].

Angelman syndrome patients present a characteristic “dancing puppet” gait, due to neurobehavioural disorders such as hyperactivity, also recordable by EMG [Manfredini et al., 2011, involuntary laughter and smiling; these latter features led the original title of “happy puppet syndrome” [Maguire, 2009; Espay, 2005].

The aetiology of the syndrome is due to deletion of chromosome 15 (15q11-13), which contains genes that are activated by genetic imprinting (parent-specific activation). Because the deletions seen in AS only occur on the chromosome 15 inherited from the mother, the genes responsible for the disorder were predicted to be active only on the maternal chromosome [Murakami et al., 2008].

Abnormalities of chromosome 15 at 15q11-13 associated with Angelman syndrome were identified in 1989. It is recognised that the functional absence of the UBE3A gene is responsible for the condition. There are four major categories of abnormality giving rise to functional absence of UBE3A which account for about 90% of cases; in around 10%, no genetic abnormality is identified:

1. maternal 15q11-13 deletions (65-75%);
2. paternal uniparental disomy (3-5%);
3. imprinting defects (6-10%);
4. UBE3A point mutations (4-6%);
5. unidentified (10%).

UBE3a encodes E&-AP ubiquitin E3 ligase, a component of the ubiquitin proteasome system which is involved in intracellular protein degradation. A sequence of activation, conjugation and ligation of target proteins with ubiquitins creates complexes that are degraded by proteasomes. How defective E6-AP ubiquitin E3 ligase contributes to Angelman syndrome remains unclear. In addition to UBE3A a number of other genes are found at the 15q11-13 locus, including a cluster of genes encoding γ-aminobutyric acid (GABA), receptor subunits (GABRAS, GABRB3 and GABRG3, encoding subunits α5, β3 and γ3 respectively) [Maguire, 2009]. The GABA receptor is a common channel for the action of many drugs used even for general anaesthesia [Kim et al., 2010].

Diagnosis of AS is based on results of a high-resolution chromosomal analysis and fluorescent in situ hybridisation analysis. DNA methylisation test, electroencephalogram, the patient’s medical history, and clinical features may serve as auxiliary diagnostic devices [Murakami et al, 2008; Smith et al, 1996].

A differential diagnosis should include the Rett syndrome, the Lennox-Gastaut syndrome,
nonevolutionary chronic encephalopathy, childhood autism, and alpha thalassemia associated to X-linked inheritance of intellectual disability [Murakumi et al., 2008].

Individuals with AS usually present the following clinical features.
1. Developmental delay.
2. Speech impairment with minimal or no use of word (receptive and nonverbal communication skills higher than verbal ones).
3. Movement or balance disorder (ataxia of gait and/or tremulous movement of limbs).
5. Delayed growth in head circumference, usually resulting in microcephaly by the age of 2 years.
6. Seizures, onset usually before 3 years of age.
7. Abnormal EEG, characteristic pattern with large-amplitude, slow-spike waves.

Recent studies have also reported that patients with AS caused by deletion of chromosome 15q11-13 present with early-onset epilepsy that shows an age-related improvement [Murakumi et al., 2008].

Some associated clinical features of children with AS are of extreme importance for dentists. For instance, tongue thrusting, mandibular prognathism, diastemas, a thin upper lip, micro- or brachycephaly, and excessive chewing behaviour are characteristic that may require direct or indirect intervention by the dentist, with treatment such as orthodontics. The accuracy of radiological analysis is very important for the planning of the therapy [Tomasi et al., 2011].

Other characteristics like hyperactive tendon reflexes, frequent drooling, sucking/swallowing disorders, increased sensitivity to heat, sleep disturbances, and fascination with water and reflective surfaces may be helpful or disruptive during dental treatment. As a health professional, the dentist must also be aware that strabismus, hypopigmentation of skin and eyes, uplifted and flexed arms during walking, and a flat back of the head may be present in patient with AS [Murakumi et al., 2008; Espay et al., 2005].

As with any other child, it is essential to consider the psychological aspects of the dental treatment. Developmental delay, speech impairment, hyperactivity, and a short attention span are characteristic of children with AS, which make behaviour management extremely challenging. For this reason, if dental procedures are invasive such as teeth extractions, children with AS are usually addressed to general anaesthesia, as for those affected by Scleroderma [Trainito et al., 2012] which offers a safe approach for the child and the dentist, too. During the general anaesthesia, the dentist offers all dental treatment that the child needs. If the behavioural management, instead, offers the possibility to treat child with AS without general anaesthesia, and/or dental procedures are not too invasive, the dentist has to use the correct techniques and psychological approach, to establish communication, and to obtain compliance even if in more visits.

### Cases report

In this paper we present and describe the oral health status and the dental treatment approach in a group of 8 children (5 females and 3 males) affected by A.S., which came to the Special Care Dental Unit of the Hospital of Piove di Sacco - Padua (Italy) for dental evaluation. The average age of the first dental visit was 6.8 years.

Not all cases presented the characteristic hypopigmentation of fair hair and blue eyes (Fig. 1, 2). In fact, according to recent literature, it is now clear that the clinical spectrum of AS is much broader than was originally thought by Harry Angelman.

The main reason for the first dental exam was usually the acute toothache with infection (frequent dental abscess treated with antibiotic therapy), increasing salivary, sleep disorder and worsening restlessness. Dental private offices refuse to treat this kind of patients for the complexity of approach and usually address them to the public dental service. In almost all cases the cooperation was scarce or absent. Common dental features were: wide mouth and jaws, diastemas, insertion of the tip of the tongue between the front teeth and front open bite, frequent drooling, sucking, eating and drinking difficulties and enamel erosions [Lucchese et al., 2011]. The anamnesis revealed difficult oral hygiene practice and frequent consumption of sweet soft drinks to ease assumption of liquids. These bad habits led to incipient and painful tooth lesions, requiring urgent dental treatment (Fig. 3, 4).

After specific assessment, 5 patients underwent general anaesthesia for dental treatment. Medical evaluation revealed a level 2 anaesthetic risk (ASA2) in 4 of the 5 patients undergoing general anaesthesia for lack of cooperation (Fig. 5-10). No particular intra-operative complications were reported. In 2 patients bronchospasm happened during the post-operative phase resolved with cortisone drugs.

The dental treatment included:
- tooth extraction in primary and permanent dentition;
- dental restoration with adhesive technique (composite resins);
- professional teeth cleaning.

The other three cases (females) underwent periodic dental checkups and two of them showed orthodontic problems (disturbancies in tooth eruption, and mandibular prognathism with anterior cross bite).

In all cases, the medical history revealed severe difficulties in oral hygiene practices, but frequent appointments for dental control and reinforcement of positive message of correct hygiene and dietary habits, greatly improved the dental status and oral symptoms.
Moreover, we taught simple miofunctional exercises to strengthen the orbicular oris muscles to contrast tongue interposition between the jaws, anterior open bite and contain drooling.
Discussion and conclusion

In the majority of cases of children affected by AS, the lack of cooperation requires the use of general anaesthesia for dental treatment. Early dental visits are crucial to inform parents on oral hygiene and dietary habits to prevent dental diseases, in order to improve the quality of life of children with A.S.

Even if the syndrome is rare, knowledge of the main features of the disease and these patients’ needs, is necessary for the dentist. It is important, however, to establish a relationship between the dentist and the dental staff and the patient’s family, to control oral hygiene and prevent oral diseases.

References


