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TITOLO TESI

GUIDELINES OF SPECIAL CARE DENTISTRY IN PATIENTS WITH CHROMOSOMAL AND GENETIC SYNDROMES

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Chapter 1.

INTRODUCTION

Special Need Dentistry has been defined as that branch of dentistry that provides oral care services for Special Health Care Need (SHCN) patients by Special Care Dentistry Association (SCDA). SHCN patients are people with physical, medical, developmental, or cognitive conditions which limit their ability to receive routine dental care.

Special Need Dentistry involves treatment of patients affected with chromosomal and genetic syndromes. Those syndromes are congenital disorders that may cause physical, developmental, mental disability and are considered as rare diseases because their incidence rate is lower than 5 over 10.000 citizens. The typical features of chromosomal and genetics syndromes may include craniofacial and dental anomalies, which require early dental intervention, because of their great impact of on the quality of life.

DEFINITION OF DISABILITIES

The American Academy of Paediatric Dentistry (AAPD) considers special health care needs as “any physical, developmental, mental, sensory, behavioural, cognitive, or emotional impairment or limiting condition that requires medical management, health care intervention, and/or use of specialized services or programs. The condition may be congenital, developmental or acquired through disease, trauma, or environmental cause and may impose limitations in performing daily self-maintenance activities or substantial limitations in a major life activity. Health care for individuals with special needs requires specialized knowledge acquired by additional training, as well as increased awareness and attention, adaptation, and accommodative measures beyond what are considered routine” [1].

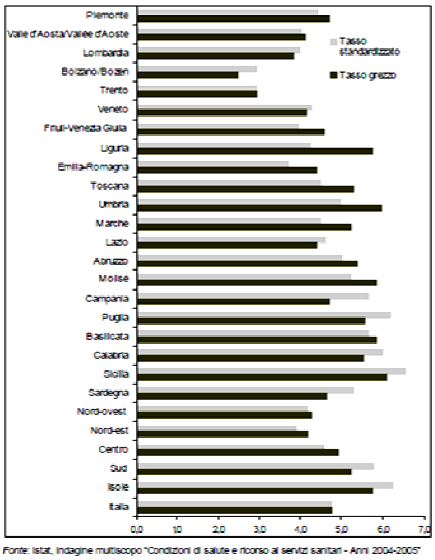
The rem disability may include several conditions: orthopaedic , visual, speech and hearing impairments, cerebral palsy, mental retardation, autism and specific learning disabilities. It includes also reversible or irreversible conditions, such as epilepsy, cancer, heart disease and other systemic diseases may be a cause of disability [2].

Generally, disabilities can be divided into two major groups: congenital/developmental and acquired. Congenital/developmental disabilities occur in developing body organs: the onset can be before birth, at birth or before the age of 22 years and usually last a lifetime. Patients with congenital syndromes often have several impairments and systemic diseases. These conditions may cause limitations in learning,

communication and usually subjects are unable to live independently without assistance. On the other hand, acquired disabilities are the result of diseases, trauma or injuries[3]. Both categories of disabilities may require the aid of a caregiver.

RARE DISEASES

"A rare disease (RD) is a disease that occurs infrequently or rarely in the general population". In Europe a disease or disorder is rare when it affects less than 1 in 2,000 citizens (Orphan Drug Regulation 141/2000). In order to be considered as rare, each specific disease cannot affect more than a limited number of people out of the whole population, with a prevalence rate of 5 rare disease patients out of 1000 citizen. "About 30 million people have a RD in the 25 EU countries"[4]. In the EU, 6% to 8% are rare disease patients. The number of RD patients varies considerably from disease to disease, most people suffer from even rarer diseases, affecting only one in 100,000 people or less. It is worth noting that most cancers, including all cancers affecting children, are rare diseases [5]. People affected by MR are considered as SHCN patients.



Fonte: Istat, Indagine multiscopo "Condizioni di salute e ricorso ai servizi sanitari - Anni 2004-2005"

Table 1. Prevalence of SNHC people in each Italian region.

STATISTICS

According to the Italian National Institute of Statistics (Istat), in 2004 approximately 2.6 million of italians (aged >6 years) had a disability, corresponding to 4.8% of total population. In 2014, Censis (Centro Studi Investimenti Sociali) recorded an increased number of people affected with disability of about 4.1 million. This number corresponds to 6.7% of total population, and it is estimated to increase to 4.8 million (7.9%) for the year 2020 and 6.7 million (10.7%) for the year 2040 [6].

Prevalence of disability in Italian territory is heterogeneous: in Sicily and Sardinia disabled people are in percentage the 5.7% of the total population, while the percentages are 5.2% and 4.1% in southern and northern Italy, respectively (Table 1).

DISABILITY AND ITS PUBBLIC IMPACT

An increase of the number of disabled people is expected, however they are considered as a minory. This results in difficulties in their integration, creating problems and with difficulties in the full integration into society. The management of the problems related to disabled patients requires introducing environmental

modifications to allow the full participation of these subjects and their involvement in all areas of social life. This has to be considered a collective responsibility of society at large [7].

Percent of CSHCN Needing Specific Health Services	
Prescription drugs	86.4%
Preventive dental care	81.1%
Routine preventive care	77.9%
Specialty care	51.8%
Eyeglasses/vision care	33.3%
Mental health care	25.0%
Other dental care	24.2%
Physical, occupational, or speech therapy	22.8%
Disposable medical supplies	18.6%
Durable medical equipment	11.4%
Hearing aids/hearing care	4.7%
Home health care	4.5%
Mobility aids/devices	4.4%
Substance abuse treatment	2.8%
Communication aids/devices	2.2%

Table 2. Services in percentage required by SNHC patients in USA.

Furthermore, disabled people require a broad range of medical services, from primary and specialty medical care to prescription medications, medical equipment and therapies; which may have a great financial impact on society. Like all children, people with disability and RD need preventive health care and prompt care when they are sick; in addition to a variety of other services to manage their conditions, maintain their abilities, and promote their development.

The required services are shown in Table 2: preventive dentistry measures are needed by 81,1% of SHCN patients and other dentistry services are needed by 24.2% . In Italy, the National Health Service (Servizio Sanitario Nazionale) provides health services and benefit for free to SHCN people affected by specific RD. Those services are called the Essential Levels of Health care (LEA). The list of specific RD having access to LEA is published online on Ministry of Health website [8]. This service warrants priority to patients affected with RD for preventive medicine to actual therapy [9].

ORAL DISEASES AND DISABILITIES

Special Health Care Need people can be at a high risk for oral diseases [10, 11, 12, 13]. Oral pathologies may have a direct and devastating impact on the health and quality of life of subjects with certain systemic health problems or conditions. Patients with compromised immunity (eg, leukemia or other malignancies, human immunodeficiency virus) or cardiac conditions associated with endocarditis may be especially vulnerable to the complications of oral diseases [14]. Patients with mental, developmental, or physical disabilities who do not have the ability to understand and cooperate with preventive oral health practices are patients considered high risk as well [15].

RD and congenital syndromes include disorders or conditions in the oro-cranio-facial complex which can manifest orally as:

- delay in teeth eruption;
- anomalies or variations in number, size and shape of teeth;

- anomalies of tooth structure, such as enamel defects, that may be caused by high fever or medications or the cause may be unidentified;
- low levels of dental hygiene due to inability in tooth-brushing as a consequence of movement impairment or uncooperation;
- traumatic injuries of the facial structures and/or teeth frequently associated to poor muscle coordination or seizures;
- higher risk of bleeding during surgery procedures due to anticoagulants therapy or congenital coagulation defects;
- adverse reaction to medication such as antiepileptic drugs which are the cause of gingival overgrowth, known as gingival hyperplasia, resulting in interference with chewing and speech, gingival bleeding, and periodontal disease;
- dental structure anomalies such as tooth severe dyscromie due to tetracyclines taken by the mother during pregnancy or by the baby himself at young age (less than 3 years);
- dental and skeletal malocclusions due to muscle hypotonia or hypertonia, hypodevelopment of maxillary bones and oral breathing.

The aim of this review is to identify and describe the dental and craniofacial alterations typical of genetic and chromosomal syndrome examined. The review is based on data found in literature and our clinical observation in a sample of patients affected by Down Syndrome, Noonan Syndrome, Williams Syndrome, Turner Syndrome, Hypophosphatemic Rickets and Muscular Dystrophies. For each single patients a preventive and treatment plan to guarantee a good oral health has been defined. Finally, customized guidelines for each syndrome will be presented at the end of the work.

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Chapter 2.

CHROMOSOMAL AND GENETIC SYNDROMES

Definition and classification

The term "syndrome" refers to a group of specific features which appear to be unrelated, but which define a number of disorders when they develop together. A syndrome can be defined as a disease or disorder which has more than one peculiar feature or symptom. Each genetic syndrome will include many typical features, which depends on which stage of development are affected by abnormal genes or chromosomes.

A genetic disorder is a disease caused in whole or in part by a change in the DNA sequence away from the normal sequence. Genetic disorders can be caused by a mutation in one gene (monogenic disorder), mutations in multiple genes (multifactorial inheritance disorder), a combination of gene mutations and environmental factors or by damage to chromosomes (changes in the number or structure of entire chromosomes, the structures that carry genes)(Figure 1).

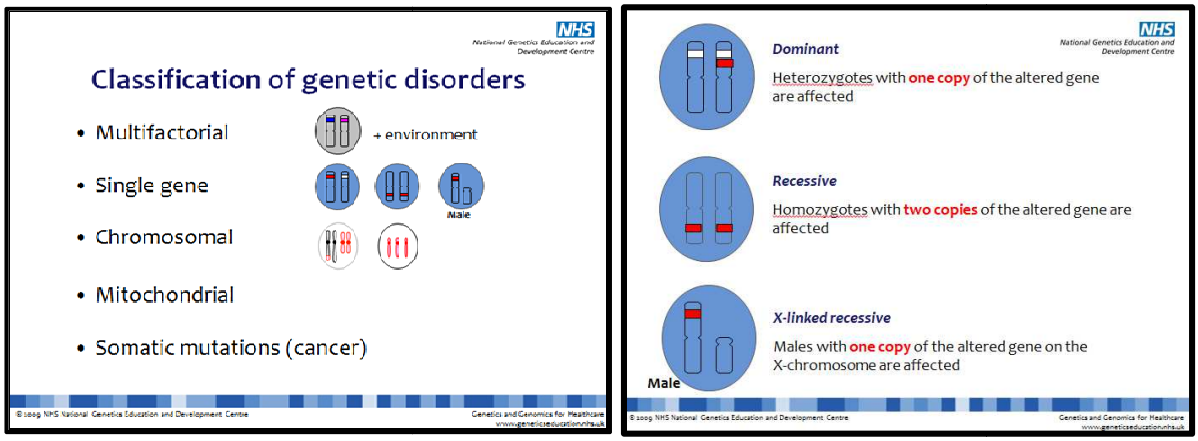

Figure 1. Gene

Multifactorial inheritance disorders are caused by a combination of small inherited variations in genes, often in presence of interac with environmental factors. Heart disease, diabetes, and most cancers are examples of such disorders [1].

- *Chromosomal disorders* are caused by an excess or deficiency of the genes that are located on chromosomes, or by structural changes within chromosomes. Down syndrome, for example, is caused by an extra copy of chromosome 21: although all the chromosomes are normal, in the case of Down syndrome no individual gene on the chromosome is abnormal. Williams syndrome, on the other hand, is caused by the absence or non-expression of a group of genes on chromosome 7[1].

- *Monogenetic disorders* are caused by a mutation in a single gene. The mutation may be present on one or both parental chromosomes. A major distinction among monogenic disorders is between "dominant" and "recessive" diseases. Dominant diseases are caused by the presence of the disease gene on just one of the two inherited parental chromosomes. In dominant diseases, the chance of a child inheriting the disease is 50 percent. Recessive diseases require the presence of the disease gene on both of the inherited parental chromosomes. The result will be a 25% chance of the child inheriting the diseases [1] (Figure 1).

Diagnosis

Genetic disorders may manifest at birth with obvious body deformities, abnormal organ function, or neurological problems. However, many syndromes symptoms can be noticed only once the baby is born and starts to feed and grow or even later. The late onset causes great difficulties in early diagnosis and treatment. Genetic testing is the only means for an accurate genetic disease diagnosis. However, clinical diagnosis, based on observing the patient's signs and symptoms, remains the first step in the detection of the pathologies.

Genetic testing can be performed on infant and children, as well as on adults and it is used to diagnose a disease in an individual with symptoms or to help measure risk of developing a disease. Adults can undergo preconception testing before deciding to become pregnant, and prenatal testing can be performed during a pregnancy.

There are three main types of genetic testing:

1. *Gene tests* evaluate individual genes or relatively short lengths of DNA or RNA taken from a person's blood, other body fluids like saliva, or tissues. These tests can look for large changes, such as a gene that has a section missing or added, or small changes, such as a missing, added, or altered chemical base (subunit) within the DNA strand.

2. *Chromosomal tests* look at features of a person's chromosomes, including their structure, number and arrangement. These tests look for changes, such as pieces of a chromosome being deleted, expanded, or being switched to a different chromosomal location.
    a) *Karyotype* - This test gives a picture of all of a person's chromosomes from the largest to the smallest. This type of testing can identify changes in chromosome

number and large changes in DNA structure (for example it identifies the presence of an extra copy of chromosome in Down syndrome)(Figure 2).

b) *FISH analysis (fluorescent in situ hybridization)* – it can find small pieces of chromosomes that are missing or have extra copies. These small changes can be missed by the overall karyotype test (Figure 3).

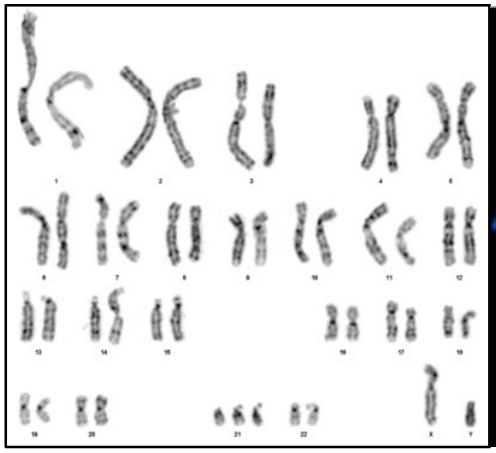

Fig. 2. Karyotype analysis

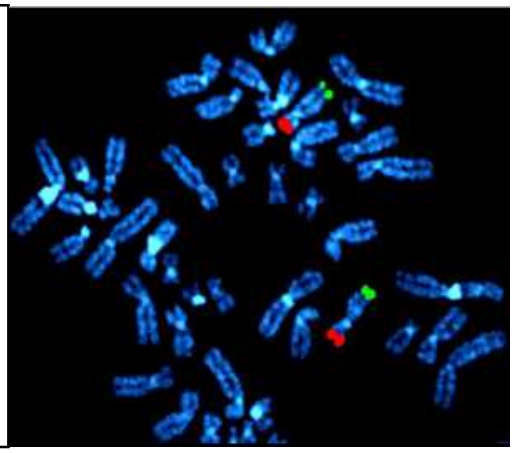

Fig. 3. FISH analysis of chromosomes

3. *Biochemical tests* look at the amounts or activities of key proteins. Since genes contain the DNA code for making proteins, abnormal amounts or activities of proteins can detect abnormal genes. These tests are often used for newborn screening.

Clinical management

Treatment and management strategies are designed to reduce the morbidity associated with the signs and symptoms associated with the diseases. The approaches vary and are specific to the individual's health needs. For example, a genetic disorder associated with a heart defect depending on the disorder might be treated with surgery to repair the defect or with a heart transplant. For genetic conditions which cause abnormalities in production of specific enzymes or hormones, treatment strategy may include dietary changes or replacement of the missing enzyme/hormone.

The symptomatic treatment may improve quality of life and life expectancy but it doesn't cure the diseases. Researchers are studying the *gene therapy* which is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow to treat a disorder by inserting a gene into a patient's cells instead of using pharmacologic therapy or surgery. Gene therapy includes several approaches

such as replacing a mutated gene that causes disease with a healthy copy of the gene, inactivating a mutated gene that is functioning improperly and introducing a new gene into the body to help fight a disease.

Gene therapy is a promising treatment option for a number of diseases (e.g. inherited disorders, some types of cancer, and certain viral infections), however the technique remains risky and is still being studied to increase its affectiveness and reduce or prevent any side effects. [2]

Oral care management

Oral health and overall systemic health are strongly linked, which proves the presence of oral health implications linked to systemic disease and pharmacological therapy. [3] The prevalence and severity of caries and periodontal disease in the disabled population is significantly higher than the rest of the population. Furthermore, genetic syndromes also include disorders or conditions which manifest only in the orofacial complex such as, amelogenesis imperfecta, dentinogenesis imperfecta, cleft lip/palate, oral cancer. Poor oral health has an important impact on systemic health but also on learning, communication and self-esteem which affects activities in school, work and home. [4] General guidelines for special care dentistry are the following:

1) **Especially trained dentists**

   Special Care Dentistry requires specially trained dentists, who are able to manage with uncooperative patients, and able to use a multi-disciplinary approach in treatment planning.

2) **Barrier–free environment**

   The creation of a barrier–free environment in the dental office for patients with movement impairments, adding handrails to hallways and grab bars in restrooms, changing door knobs to a lever type, rearranging furniture in the reception area with various chair heights including space for a wheelchair and a portable ramp into the building entrance. [5]

3) **Patient compliance**

   This especially important with young children and patients with mental retardation, because of dental anxiety children with disabilities may exhibit resistant behaviours that can interfere with the safe delivery of dental treatment. The aid of the parents/caregiver usually allows dental procedures under local anaesthesia in the dental office with most of the physically and mentally disabled patients. In case of a bad collaboration, parents/caregivers may help clinician to hold the patient, this is known as “soft constraint”(Figure 4). Whenever the bad compliance doesn’t allow safe procedures, in-office sedation/general anaesthesia treatment can be considered [6].

Fig. 4. Example of “Soft Constraint”.

4) Informed consent

All patients or their legal representative must provide signed informed consent for dental treatment [7].

5) Accurate medical anamnesis and multi-disciplinary team approach

Information regarding the chief complaint, history of present illness, medical conditions and/or illnesses, medical care providers, hospitalizations/surgeries, anaesthetic experiences, current medications, allergies/sensitivities, immunization status, review of systems, family and social histories, and thorough dental history should be obtained. When indicated, the physician should be consulted regarding medications, contraindications to sedation or general anaesthesia. A thorough review regarding special restrictions that may be required to ensure the safe delivery of oral health care. The dentist and staff always should be prepared to manage a medical emergency.

6) Dental examination and oral disease-risk assessment

An extra-oral examination including the head and neck, in addition to intra-oral examination should be performed on all patients. A oral diseases-risk assessment should be performed by caries, oral hygiene, gingivitis, periodontitis, traumatic injuries evaluation. An individualized preventive program, including period recall visits are recommended and planned with the treating physician of the patient together with physicians[8].

7) Oral health preventive strategies

- Education of parents/caregivers to appropriate and regular supervision of daily oral hygiene: brushing with a fluoridated dentifrice at least twice a day to help in caries and periodontitis prevention. Electric toothbrushes and floss holders may improve patient compliance. Caregivers should provide the appropriate oral care when the patient is unable to do so adequately.
- A non-cariogenic diet is recommended for long term prevention of dental disease, with a reduced consumption of sweetened-products (snacks, candies, cola, juices…etc).
- Topical fluorides are indicated in patients in high risk for caries. Fluoride varnish (NaFV 22.500 ppm) and foam may be applied on all the teeth after the professional hygiene by dentist. High concentration fluoride gel (12.500 ppm) may be used at home once a week by positioning gel on tooth with enamel defects [9].
- For all the patients, pit and fissure sealants are recommended to reduce the risk of caries in primary and permanent teeth, especially for those with deep fissure and those who are affected by enamel abnormalities;
- In cases of gingivitis and periodontal disease, chlorhexidine mouth rinse may be indicated. For patients who might swallow a rinse, a toothbrush can be used to apply the chlorhexidine gel (1%) [10].
- Preventive strategies for patients with lack of motor skills and motor coordination deficiency, traumatic injuries can be prevented with a mouthguard.

8) Patients with developmental or acquired severe orofacial conditions

Developmental defects such as hereditary ectodermal dysplasia, epidermolysis bullosa, cleft lip/palate frequently require an interdisciplinary team approach to their care.

Especially patients with ectodermal dysplasia, where most teeth are missing or malformed, cause lifetime problems that can be devastating to children and adults require an interdisciplinary team approach to their care. Removable or fixed prostheses (including complete dentures or over-dentures) and/or implants may be indicated.

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Chapter 3.

MATERIALS AND METHODS

Participants

All the examined subjects were affected by chromosomal and genetic syndromes and were referred from the Pediatric and Auxology Department in Sant'Orsola Hospital and Nigrisoli Hospital in Bologna for an oral examination in the Dentistry for Special Needs patients, Department of Oral Sciences (DIBINEM, University of Bologna).

The total sample consist in 195 patients, 137 females and 58 males, most of Italian ancestry, with an age range of 3 to 40 years:

- Down syndrome: 133 patients(72 males and 61 females). Mean age is 13.4 ± 9.7 years.
- Williams syndrome: 10 patients (3 males and 7 females). Mean age is 12.1 ± 6.7 years.
- Turner syndrome: 17 females. Mean age is 16.8 ± 9.1 years.
- Noonan syndrome: 13 patients (9 males and 4 females). Mean age is 14.1 ± 6.7 years
- Hypophosphatemic rickets: 10 patients (8 females and 2 males). Mean age is 9.8 ± 4.3 years
- Muscular Dystrophies: 12 patients (8 males and 4 females). The main age is 16.9 ± 7.7 years.

Questionnaire

A questionnaire regarding detailed medical and dental history, oral health and dietary habits, was filled by parents/caregivers, or patients themselves when possible.

The questionnaire regarded the following information (patients or guardians filled the gap requested or ticked when the disease was present):

1) Medical history
   a) gender, age (years and months), height and weight;
   b) birth and prenatal stage information: physiological pregnancy, smoke and drugs taken by the mother during pregnancy, weight at birth;
   c) diseases occurred and drugs taken in first two years.

2) Medical anamnesis
   a) *Nervous system diseases*: epilepsy, migraines, cerebral palsy, autism, mental retardation;
   b) *Heart diseases*: congenital or acquired hearth disease, rheumatic fever, requiring of antibiotic prophylaxis;
   c) *Respiratory diseases*: tonsillitis, otitis, bronchitis, pneumonia, rhinitis, sinusitis, asthma, tonsillectomy, adenoidectomy;

d) *Blood diseases*: leukaemia, anaemia, coagulation pathologies;

e) *Endocrine diseases*: diabetes, thyroid deficiency or pathologies, growth-hormone deficit;

f) Muscular dystrophies;

g) *Infectious diseases*: HIV, Hepatitis B, Hepatitis C, others (specify which one);

h) *Digestive diseases*: celiac disease, Chron's morbus, others (specify which one);

i) *Anorexia and bulimia;*

j) *Rheumatic diseases;*

k) *Kidney and Liver diseases;*

l) *Sight and hearing problems;*

m) *Specific Syndromes.*

3) Current therapy (specify medications and dose/day)

4) Allergies to drugs (antibiotics and FANS), local anaesthesia, latex, dietary products, metals, others, etc…

5) Dental history

a) Dental previous experiences: first visit, dental trauma, extractions, restorations, hygiene, orthodontic treatment;

b) Previous oral diseases: pain, swelling, fistula, caries, trauma to deciduous/permanent dentition, aphtas;

c) Level of compliance;

d) Tooth brushing habits: times per day, ability or inability to self-tooth brushing with or without caregiver supervision, type of toothbrush used (manual or electric), type of toothpaste (fluoridated or not), dental floss, mouthwash;

e) Fluoride prophylaxis: tablets or drops (dosage).

f) Tooth brushing habits: how many times/day, ability or inability to self-tooth brushing with or without caregiver supervision, type of toothbrush used (manual or electric), type of toothpaste (fluoridated or not), dental floss, mouthwash;

g) Dietary habits: sweetened food consumption (sweets, snacks, biscuits, juices, cola…) how many times/day;

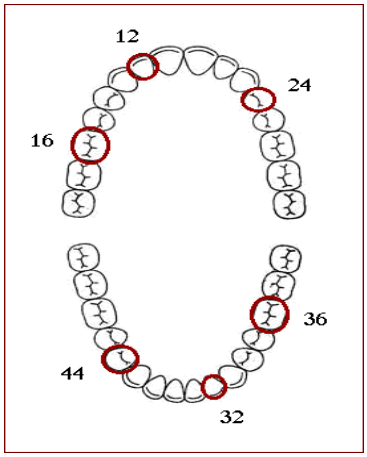
h) Pacifier, finger, tongue sucking and nail biting;

i) Oral breathing.

Dental visit

1) Extraoral examination
   a) Evaluation of facial asimmetries;
   b) Extraoral swelling or fistulas;
   c) Temporomandibular joint examination.

2) Intraoral examination
   a) Dentition stage (deciduous, mixed, permanent) and dental formula;
   b) Tooth shape anomalies present:
      - Microdontia: reduced tooth dimension;
      - Taurodontism defined as increased tooth dimension, enlarged pulp chamber, apical displacement of the pulpal floor [1];
      - Conoid teeth (which particularly affect lateral incisors, screw drive incisors, Hutchinson's incisors):
   c) Tooth structure anomalies present:
      - Enamel hypoplasia present: developmental disturbances as an incomplete or defective formation of the organic enamel matrix of teeth [2];
      - Molar Incisors Hypomineralization (MIH) are discoloured opacities or a total absence of enamel, commonly affecting the first permanent molars (FPMs) with or without involvement of the permanent incisors.[3]
      - Amelogenesis imperfecta: a group of genetic conditions involving the quality and/or the quantity of dental enamel [4]. Tooth number anomalies
      - Tooth agenesis, or hypodontia: it is defined as the congenital absence of one or more teeth; it is the most common developmental anomaly in the human dentition. Oligodontia is the congenital absence of 6 or more permanent teeth, excluding third molars. Anodontia is the absence of all teeth. Tooth agenesis may be present as part of a syndrome or as a familiar form: the familiar form provides evidence of a genetic contribution [5], the syndromic form is likely due to chromosome anomalies, teratogenes, or uncategorized syndromes, the causes of which remain unknown [6]. The diagnosis of tooth agenesis can be made only with radiographical examination.
      - Supernumerary teeth: it's an additional tooth to the normal series and can be found in almost any region of the dental arch. The most common supernumerary tooth which appears in the maxillary midline is called a mesiodens [7]. Others form of supernumerary teeth are conical, tuberculate, supplemental, odontome.



d) Presence of carious lesions: the prevalence of caries is evaluated by using DMFT/dmft index.

DMFT index is the most commonly used measure of caries experience in epidemiological studies and it is applied to the permanent dentition and is expressed as the total number of teeth or surfaces that are decayed (D), missing (M), or filled (F) in an individual[8].

The calculation of "individual DMFT" is the sum of D + M+ F:

- Decayed Teeth (D)- when carious lesions or both carious lesion(s) and a restoration are present;
- Missing Teeth (M)- when a tooth has been extracted due to caries;
- Filling teeth (F)- when a permanent or temporary filling is present, teeth restored for reasons other than caries are not counted.

The scores per individual can range from 0 to 32, depending on whether the third molars are included in the scoring.

"Group average DMFT" is calculated by dividing the sum of each individual DMFT by total number of individual in the group.

When written in lowercase letters, the **dmft index** is a variation that is applied to the primary dentition. The caries experience for a child is expressed as the total number of teeth or surfaces that are decayed (d), missing (m), or filled (f). The dmft index expresses the number of affected teeth in the primary dentition, with scores ranging from 0 to 20 for children [9].

e) **Plaque Index**: the measurement of the state of oral hygiene by Silness-Löe plaque index is based on recording both soft debris and mineralized deposits on specific teeth (permanent dentition: shown on Figure 1; deciduous dentition: 55, 52, 64, 72, 75, 84). Each of the four surfaces of the teeth (buccal, lingual, mesial and distal) is given a score from 0-3. The scores from the four areas of the tooth are added and divided by four in order to give the plaque index.

0 No plaque

1 A film of plaque adhering to the free gingival margin and adjacent area of the tooth. The plaque may be seen by using the probe on the tooth surface.

2 Moderate accumulation of soft deposit s within the gingival pocket, or the tooth and gingival margin which can be seen with the naked eye.

3 Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

ich Plaque

f) Orthodontic evaluation

The American Association of Orthodontists recommends that the initial orthodontic evaluation should occur at the first sign of orthodontic problems or no later than age 7. At this early age, orthodontic treatment may not be necessary, but vigilant examination can anticipate the most advantageous time to begin treatment.

Orthodontic evaluation considers the dental and skeletal relationships between the maxilla and the mandible.

Angle classification

The classification of Edward Hartley Angle is based on the relationship of the mesiobuccal cusp of the maxillary first molar and the buccal groove of the mandibular first molar (Figure 2)[10].

- NORMAL OCCLUSION - The mesiobuccal cusp of the maxillary first molar is aligned with the buccal groove of the mandibular first molar. There is alignment of the teeth, normal overbite and overjet and coincident maxillary and mandibular midlines.
- CLASS I MALOCCLUSION - A normal molar relationship exists but there is crowding, misalignment of the teeth, cross bites, etc.
- CLASS II MALOCCLUSION - A malocclusion where the molar relationship shows the buccal groove of the mandibular first molar distally positioned when in occlusion with th mesiobuccal cusp of the maxillary first molar.

  Class II Division 1- the maxillary anterior teeth are proclined and a large overjet Is present.

  Class II Division 2 - the maxillary anterior teeth are retroclined and a deep overbite exists.
- CLASS III MALOCCLUSION - A malocclusion where the molar relationship shows the buccal groove of the mandibular first molar mesially positioned to the mesiobuccal cusp of the maxillary first molar when the teeth are in occlusion.

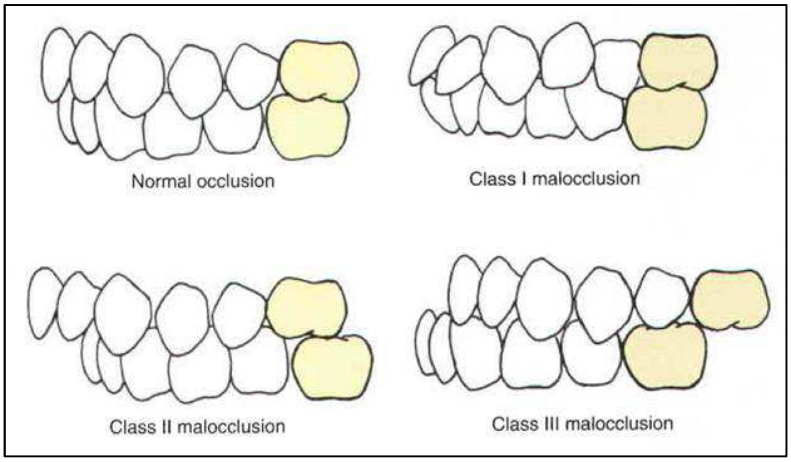


Figure 2. Normal occlusion and Angle class malocclusions

Skeletal pattern

The patients can be classified through cephalometric analyses into three skeletal patterns (Figure 3):

- Skeletal Class I Pattern
- Skeletal Class II Pattern
- Skeletal Class III Pattern

These patterns may or may not correspond with the Angle Classification.

Understanding the skeletal pattern is essential for choosing the proper treatment mechanics [11,12].

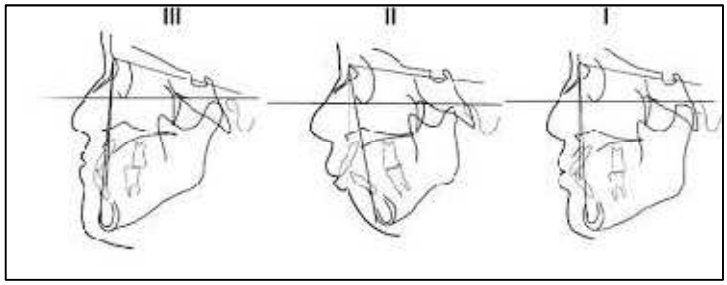


Figure 3. Skeletal pattern classification

Incisal relationship

Overbite is the amount of the vertical overlap of the mandibular anterior teeth by the maxillary anterior teeth measured perpendicular to the occlusal plane [13](Figure 4).

An open bite is present when there is no vertical overlap of the maxillary and mandibular anterior teeth or no contact between the maxillary and mandibular posterior teeth.

A deep bite is present when the vertical overlap exceeds 2mm (Figure4c).

Overjet is a term used to describe the horizontal distance between the labial surfaces of the mandibular incisors and the incisal edge of the maxillary incisors (Figure 5).

Anterior Crossbite is a present when the maxillary and mandibular teeth when they occlude with the antagonistic tooth in the opposite relation to normal.

Figure 4. Incisal relationship (overbite)

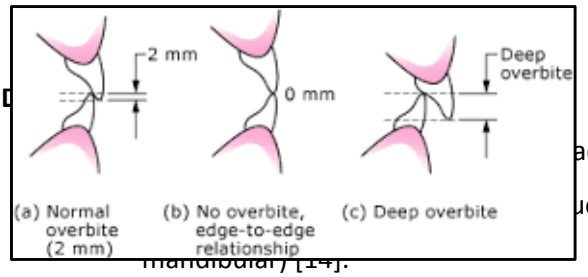
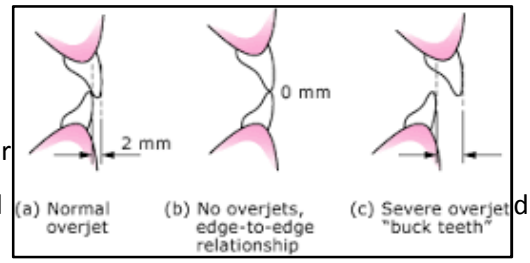


Figure 5. Incisal relationship (overjet)



g) D

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mandibular) [14].

h) Radiographic examination

All the dental radiographic records were executed in Oral Radiology Department, Dental Clinic, Dibinem, University of Bologna.

a) Intraoral radiography: used in case of trauma or for caries and endodontic lesion detection.
a) Bitewings: for interproximal caries detection
b) Ortopantomography (OPT): it's a 2D comprehensive view of dentition, maxillary and mandiblular jaws. It's fundamental for tooth agenesis detection.
c) Skull teleradiography (TLL): for skeletal malocclusion detection.

The choice of X-ray dental examination depends on patient's age (usually OPT and TLL is not recommended in patients from 0 to 6 years), and compliance: in young patients OPT sometimes is preferred to intraoral radiographies for its easy execution.

The radiographic records taken depended on the need and the age of each specific patient and level of compliance.

i) Dental impressions

a) Diagnostic study models of the maxillary and mandibular arches for appropriate orthodontic diagnosis.

b) Alginate impressions were taken for patients for diagnosis of malocclusions while Polyvinylsiloxane impressions have been taken only for specific research protocols (study of enamel alteration in patients affected by Hypophosphatemic Rickets).

REVIEW OF LITERATURE

A thorough analysis of literature was performed regarding about genetic diagnosis, epidemiology, medical and dental and cranio-facial manifestations for each specific syndrome.

The obtained data about each specific syndrome was compared to the result of our research and to data about general population, parameters such as DMFT index, Plaque Index and prevalence of malocclusions. General population was considered as a control group of non-syndromic population.

Prevalence of caries in healthy vs SHCN population.

Decayed Missing Filled index has been widely used for caries prevalence epidemiology.

The World Health Organization (WHO) from 1980 to 2003 show the prevalence of caries in different countries of the world. According to the WHO Oral Health Data Bank in 1980, DMFT values were available for 107 of 173 countries, of these, 51% had 3 DMFT or less, while the remaining 49% had higher values. In the year 2000, data were available for 184 countries as recorded in the WHO Oral Health Country/Area Profile Programme: in 68%, a DMFT of <3 was reported(Figure 5) [15].

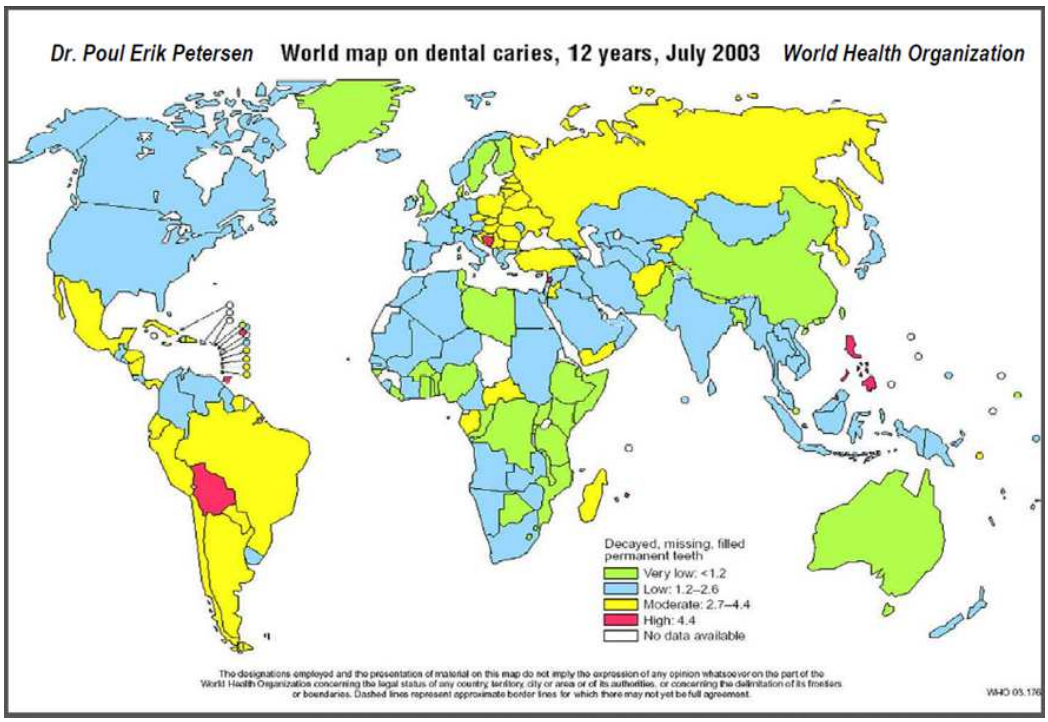

Figure 5. World map on dental caries survey in 12 years- July 2003- by WHO.

1.

In a study conducted in Italy, in 5342 subjects aged 12 years showed a prevalence of caries in 43.1% of the sample and an average DMFT of 1.09 [16]. In 2007,a twelve-years-old population showed an average DMFT of 1.44 and 55.1% of the sample was caries free [17]. In Saudi Arabia, a sample of 360 students of 12 years evidenced a caries prevalence of 57.2% and an average DMFT of 1.53 [18]. In Portugal 661 adolescents with a mean age of 13 years, showed an average DMFT score of 2.23, a result relatively high related to a previous study conducted in Portugal in 2005/2006 that evidenced a DMFT of 1.48, and related to other European countries average DMFT: Spain (2005) 1.33, Denmark (2005) 0.8, Germany and UK (2010) 0.7.

In SHCN patients affected by disabilities, the DMFT/dmft index was calculated to highlight differences between special care need patients and the general population. In literature a study conducted in Turkey in 2010, 136 disabled subjects scored an average DMFT of 1.58 and dmft of 1.18 [19]; a similar study in Iran in a sample of 1621 disabled subjects showed an average DMFT of 2.68 and dmft of 2.27 [20] , in Iran a sample of 237 disabled subjects scored an average DMFT of 5.14 [21].

Analysis of literature about oral hygiene status in general population and SHCN population.

Tooth brushing, using of dental floss and mouthwashes require manual ability and collaboration, for those reasons frequently SHNC people, if not assisted by parents or guardian during these procedures, may have a poor oral hygiene status.

Plaque index (PI) proposed by Silness&Löe in 1964 evaluate the presence of plaque/tartar on tooth surfaces: In Italy Plaque index levels evaluate on general population sample (average age 38 years) is about 0.8-1.1.[22] and in a sample of children (3-6 years) is about 0.3±0.5[23].

Comparing PI scores of SHCN people are usually higher than non-SHCN: in literature, for example, in an indian study SHCN population showed a higher PI scores (average PI among disabled population groups: 1.1±0.4) compared to non-disable population (PI : 0.6±0.5)[24].

Analysis of literature about prevalence of malocclusions in general population and SHCN population.

In a population of children and adolescents, the prevalence of dental and skeletal malocclusions was studied in order to evaluate the incidence of each Angle class malocclusion.

In an epidemiological study conducted in Tirana (Albania) on 2617 non-SHCN subjects aged from 7 to 15 years, evidenced a greater prevalence of I Class crowding malocclusion of 40.4% on other malocclusions, II class, III class malocclusion and asymmetries with a prevalence of 29.2%, 3.2% and 27.1% of the sample, respectively [25]. Similar studies conducted in Germany [26]and India are shown on Table 1 [27].

Reference	Sample (n)	I class crowding	II class	III class	Asymmetries	Open bite	Deep bite	Scissor bite
Laganà G et al., 2013. Albany	2617	40.4%	29.2%	3.2%	27.1%	/	/	/
Tausche E et al.,2004. Germany	1975	14.3%	31.4%	3.2%	/	17%	46%	0.5%
Kumar CP et al., 2013. India	1200	75.2%	23%	1.8%	/	/	/	/

Table 1. Results of three studies about malocclusion prevalence on non-SCHN subjects.

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Chapter 4.

DOWN SYNDROME

Definition and epidemiology

Down syndrome (DS) is a genetic disorder that affects more than 5.8 million individuals and occurs in approximately one in every 700 live births. It's considered the most prevalent chromosomal disorder in the world [1]. Down Syndrome accounts for 8 per cent of all registered congenital anomalies in Europe [2]. It's not considered a rare disease due to its relatively high prevalence.

The majority of individuals with DS have an extra copy of chromosome 21, however a small proportion may have other genetic aberrations such as mosaicism and translocations [3, 4]. Delays in physical and intellectual development are common in DS subjetcs [5]. The median age at death of individuals with DS has risen significantly in the US, from 25 years in 1983 to 49 years in 1997. Congenital heart defects (CHD) and respiratory infections are the most frequently reported medical disorders on death certificates for individuals with DS [6].

Diagnosis

The incidence of fetal trisomies is directly related to maternal age [7]. The risk of having a child with Down syndrome increases in a gradual, linear fashion until about age 30 and increases exponentially thereafter. The risk of having a child with Down syndrome is 1/1,300 for a 25-year-old woman; at age 35, the risk increases to 1/365. At age 45, the risk of a having a child with Down syndrome increases to 1/30 [8]. Prenatal screening tests for Down syndrome are noninvasive and provide an estimate of the risk of an affected pregnancy, while definitive prenatal diagnosis is made by karyotyping cultured fetal cells obtained via an invasive procedure such as chorionic villus sampling (CVS) or amniocentesis. Trisomy 21 can be detected in 30% of pregnant women of age 35 years or more through amniocentesis [9]. Women younger than 35 years give birth to about 70 percent of infants with Down syndrome (Figure 1) [10].

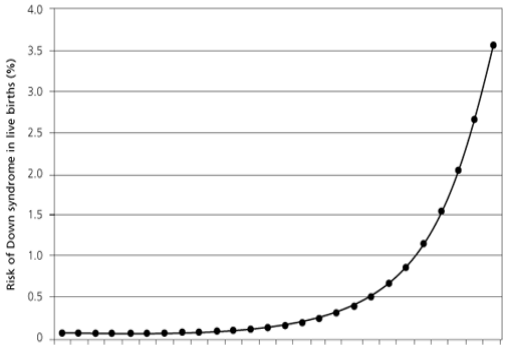

Figure 1. Risk of having a baby with DS related to maternal age.

The significance of a family history of Down syndrome depends on the karyotype of the affected person (proband). If the proband has trisomy 21, the likelihood of a trisomy 21 pregnancy is minimally increased for family members other

than the parents. The risk of recurrence in presence of a previous history of DS pregnancy. Diagnosis of a chromosome-21 translocation in the fetus or newborn is an indication for karyotype analysis of both parents. If both parents have normal karyotypes, the recurrence risk is 2 to 3 percent. If one parent carries a balanced translocation, the recurrence risk depends on the sex of the carrier parent and the specific chromosomes that are fused [11].

Maternal serum screening (multiple-marker screening) can allow the detection of trisomy 21 pregnancies in young women. Alpha-fetoprotein (AFP), unconjugated estriol and human chorionic gonadotropin (hCG) are the serum markers most widely used to screen for Down syndrome. This combination is known as the "triple test" or "triple screen"[12]. Second-trimester ultrasound assessment may be helpful for predicting the likelihood of trisomy 21 in pregnancies at increased risk. The most common ultrasonographic finding associated with trisomy 21 is increased nuchal fold thickness (nuchal translucency), which is caused by subcutaneous edema at the base of the occiput [13]. Post natal diagnosis of DS may be based on physical findings, but the diagnosis is confirmed only by chromosome analysis.

Systemic features

When a baby affected with DS is born, parents should be aware of the probable medical problems and recommended therapies. Focus on the baby, there are many medical conditions that require immediate attention (i.e., hypotonia, feeding difficulties, heart defect, and referral for early intervention). In addition to other co-morbidities that manifest beyond the pediatric period. Congenital cardiac anomalies may be corrected with surgery during infancy [14]. Congenital hypothyroidism is traced by neonatal screening, and often thyroid treatment is recommended.

Congenital heart diseases- The prevalence of CHD in neonates with DS is about 44–58% worldwide. Atrioventricular septal defect and ventricular septal defect are the most common forms of CHD, constituting up to 54% for ASD and to 33% for VSD, of all CHDs in children with DS. Down syndrome, early recognition of CHD is necessary as it can lead to the optimal management of the defect and can sometimes prevent the development of pulmonary hypertension. The surgical correction of significant defects usually takes place at the age of 2–4 months, though it is sometimes performed earlier (e.g. in cases of Tetralogy of Fallot) [15].

Motor skills - The motor-skeletal system of children with DS is characterized by ligamentous laxity, joint hypermobility and hypotonia.

Gastro-intestinal defects- Congenital defects of the gastrointestinal tract are present in 4–10% of DS children and play an important role in morbidity during the first year of life. These defects include oesophageal atresia/trachea-oesophageal fistula (0.3–0.8%), pyloric stenosis (0.3%), duodenal stenosis/atresia (1–5%), Hirschsprung disease (1–3%) and anal stenosis/atresia (<1–4%) [16]. Coeliac disease (CD) is another DS specific disorder and is seen in 5–7% of children with DS, a rate that is ten times higher than in the normal population [6].

Haemato-oncological disorders - Newborns with DS may have thrombocytopenia (up to 66%) and polycythaemia (up to 33%). The first must be differentiated from pre-leukaemia while the latter may be symptomatic and may cause hypoglycemia or respiratory problems. Children with DS have an increased risk of developing both acute myeloid as well as lymphoblastic leukaemia [17].

Thyroid disorders have been reported in up to 28–40% of children with DS, and the frequency increases up to 54%, as the children age. Thyroid abnormalities in DS children range from congenital hypothyroidism (1.8–3.6%) to primary hypothyroidism, autoimmune (Hashimoto) thyreoiditis (0.3–1.4%) and compensated hypothyroidism (25.3–32.9%) [18]. The follow-up of length and weight in children with DS should be part of the regular medical screening and special attention for the weight should be paid because children with DS are prone to overweight. Their lack of feeling of satisfaction and their unlimited food intake, as well as their moderate exercise pattern, need special attention [19].

Cognitive profile - Children with Down syndrome have a smaller brain volume than other children. Previously unreported reductions in parietal cortex, reductions in the temporal lobe and improper neural development might be responsible for the particular features of mental retardation that in some way result from trisomy 21 [20]. Most children with DS function in the low range of typical development, and their intelligence quotient decreases in the first decade of life. In adolescence, cognitive function may reach a plateau that persists in adulthood. Mental development shows a deceleration between the ages of 6 months and 2 years [21]. IQ values vary, usually ranging from 35 to 70, indicating mild to moderate mental impairment; severe mental impairment is only occasionally seen in children with DS [22]. Counterproductive behaviour and avoidance tactics can impede learning, and language production is often substantially impaired. Delayed verbal short-term memory and expressive language indicate the need for a special approach to teaching these children to speak (for example, learning to speak by first learning to read) [23]. Furthermore, impaired oral motor function can influence articulation.

Craniofacial and oral features

The craniofacial and oral features involved in Down syndrome include brachycephaly (condition where the head is disproportionately wide), usually small nose associated with a low nasal bridge, small maxilla, ogival palate and tongue with fissures and papillary hypertrophy [24].

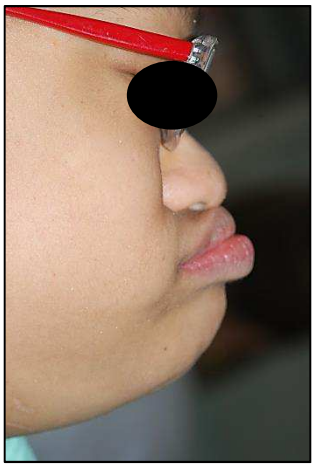

Figure 2. Middle third of the face bones hypoplasia in DS subject.

These individuals have a hypoplastic middle third of facial bones with reduced nasal protrusion and a smaller lower facial third (mandible) than non-syndromic subjects (Figure 2) [25] . The teeth of these patients present complete mineralization, but with a great variation in the eruption pattern, however the sequence and symmetry of eruption are rarely affected. It is common to find cases of periodontal disease, and lower incidence of caries in Down syndrome patients [26]. The higher prevalence of periodontal disease is probably related to the impaired host response rather than to specific periodontal pathogens [27]. The low caries prevalence seems to be due to immune protection caused by the elevated salivary S. mutans specific IgA concentrations [28]. The literature indicates low prevalence of caries [29]. Dental anomalies are common in both deciduous and permanent dentition [30]. As the development of individuals with DS is delayed in most aspects, dental eruption in both dentitions is usually late [31]. Nevertheless, the sequence of this eruption is similar to that of non-syndromic individuals. As regards dental maturation, however, in the literature it is not clear whether the chronology is delayed in DS.

Dental anomalies are very common, both in the primary and permanent teeth, and in the patients with Down syndrome, dental anomalies occur with an incidence five times greater than in the normal population [32].

DATA COLLECTION

The patients affected with DS were referred from the Pediatric and Auxology Department in Sant'Orsola Hospital in Bologna for a dental examination in the Dentistry for Special Needs patients, at the Department of Oral Sciences (DIBINEM, University of Bologna). Most significant data were collected in the following table (Data Collection Table in Down Syndrome) (page 31-35).

DATA COLLECTION TABLE IN DOWN SYNDROME SUBJECTS

	G	*Name*	*Age*	*Clinical features*		*Alimentary and oral hygiene habits*			*Dental features*						*Orthodontics features*					
				Systemic diseases	CHD	Sweetened/die	Brushing/die	SF	PI	dmft	DMFT	Tooth number anomalies	Structure anomalies	Shape anomalies	O. Br.	Oral habits	Dental maloc	Skelet maloc	OB	OJ
1	F	A.A.	16	Hypothiroidism	no	1	2	yes	1.3	-	0	no	no	no	no	Atypical swallowing	III	III	0	-3
2	M	A.S.	6	no	yes	0	2	no	0.8	0	-	no	no	no	no	/	-	-	0	0
3	M	A.A.	6	Renal dysfunctions	no	1	2	no	2.1	0	0	no	no	no	no	Atyoical swallowing	I	-	3	2
4	M	A.T.	16	no	yes	2	2	no	1.9	-	2D	-1	no	no	yes	Atypical swallowing	II	II	-3	4
5	M	A.F.	4	Hypothiroidism	yes	2	1	no	1.3	0	-	-1	no	no	no	Pacifier	-	-	0	0
6	F	B.C.	25	no	no	1	2	yes	1.1	-	9F	no	no	no	no	no	III	III	-1	0
7	F	B.G.	7	no	no	2	3	yes	1.4	0	0	no	no	no	yes	no	II	II	-2	3
8	M	B.C.	4	Sd. West	no	0	1	no	1.8	0	-	no	no	Fusion71-72	no	Pacifier	II	-	-3	4
9	F	B.A.	5	no	yes	0	2	no	1.2	0	-	no	no	Conoid 82	no	Pacifier	-	-	0	1
10	M	B.F.	8	no	yes	1	1	no	2.1	0	1D	no	no	no	no	Atypical swallowing	III	-	-2	0
11	M	B.E.	12	Celiac disease	no	0	2	no	2.8	0	0	no	no	no	yes	Atypical swallowing	III	III	1	0
12	M	B.T.	4	no	no	0	1	no	0.2	0	-	-2	no	no	no	Pacifier	-	-	1	-1
13	F	B.M.	19	no	no	1	1	no	2.6	-	0	no	no	no	no	no	III	III	1	1
14	M	B.Q.	19	Recurrent respiratory infections	no	1	1	no	2.8	-	7D2M3F	-2	no	no	yes	Atypical swallowing	III	III	1	0
15	M	B.F.	9	no	no	0	1	yes	1.3	0	0	0	no	no	no	no	II	-	3	4
16	F	B.C.	7	Recurrent respiratory infections	yes	2	0	no	2.7	3d2f	0	-2	no	no	yes	no	-	-	2	0
17	F	B.E.	21	Hypothiroidism	yes	1	2	yes	2.8	-	2D	-6	no	no	no	Atypical swallowing	III	III	-1	0
18	F	B.S.	13	no	yes	1	1	no	2.9	0	2	-1	no	Conoids	yes	no	III	III	0	-2
19	M	B.R.	16	Duodenal atresia	yes	0	2	no	1.7	-	2D	no	no	no	yes	Atypical swallowing	III	III	2	0
20	F	B.F.	17	Hypothiroidism	no	0	1	yes	2.7	-	0	-1	no	no	no	no	III	III	2	2
21	F	B.T.E.	8	anemia	yes	0	2	yes	0.9	0	0	no	no	no	no	no	III	III	2	-3
22	M	B.L.	11	no	yes	1	2	yes	1.6	2f	2D	-1	no	Microdontia	no	no	III	III	1	-4

25	M	B.R.	3	no	yes	0	1	no	0.8	0	-	-2	no	no	no	Finger sucking	-	-	-	-
26	M	B.M.	3	Hypothyroidism	no	2	1	no	0.5	0	-	no	0	no	no	Tongue Protrusion	-	-	-	-
27	M	B.G.	11	no	no	1	1	no	2.1	0	2F	no	no	no	yes	pacifier	III	III	1	-3
28	M	B.L.	14	no	no	0	2	no	1.5	0	1D2M	-2	no	no	no	no	III	III	0	-2
29	F	B.M.	8	Hypothyroidism	yes	0	2	yes	0.9	0	0	-2	no	no	no	no	I	III	2	1
30	M	C.G.	8	no	yes	0	2	no	1.7	0	0	no	no	no	no	pacifier	III	-	1	-2
31	F	C.A.	40	no	no	0	2	no	2.1	-	1D2M1F	no	no	no	no	no	III	-	0	-4
32	M	C.M.	10	no	yes	1	2	no	1.4	3f	0	no	no	no	No	no	III	III	0	-1
33	F	C.P.	4	Cardio-respiratory disease	no	1	1	no	1.6	0	-	no	no	no	yes	pacifier	-	-	-3	3
34	M	C.E.	6	Tonsillitis	yes	0	1	no	1.8	0	-	no	no	no	no	no	I	-	0	0
35	M	C.M.	4	no	yes	1	2	no	0.9	0	0	no	no	no	no	Finger sucking	II	III	2	2
36	F	C.G	10	no	yes	2	2	no	1.1	0	0	no	no		yes	no	III	-	1	0
37	F	C.S.	5	Celiac disease	no	1	3	yes	0.4	0	-	no	no	no	no	no	II	-	3	4
38	M	D.M.	8	Hypothiroidism	yes	0	2	yes	2.1	7f	0	no	Enamel hypoplasia	no	yes	no	II	-	2	4
39	M	D.M.	20	Respiratory apneas	no	1	1	no	2.7	-	3D11F	no	no	no	yes	no	III	-	1	-3
40	M	D.C.	6	Kidney agenesis	yes	0	1	no	1.7	0	-	no	no	no	no	no	I	-	1	0
41	M	D.D.	15	no	no	1	1	yes	1.9	-	2D1M	-1	no	Conoid 22	no	no	II	II	-2	2
42	F	D.M.	10	no	yes	2	2	yes	1.2	1f	0	-14	no	Conoid 12	no	no	I	-	2	1
43	F	D.B.	8	no	no	2	2	no	2.8	0	0	no	no	no	yes	Atypical swallowing	II	-	0	4
44	F	D.C.	5	Hypothyroidism	no	1	1	no	2.5	0	-	-2	no	no	yes	no	III	-	0	0
45	M	E.M.	3	Hypothyroidism	yes	2	1	no	1.9	0	-	no	no	no	no	Atypical swallowing	-	-	-	-
46	M	E.M.	7	Hypothyroidism	yes	1	1	yes	2.6	0	-	no	no	no	yes	no	II	-	0	3
47	M	E.K.	3	Hypothyroidism	yes	0	0	no	2.8	0	0	no	no	no	no	Tongue protrusion	-	-	-	-
48	F	E.C.	22	autism	no	0	2	no	1.6	-	2D	-1	no	no	no	no	III	III	-3	0
49	M	E.F.	7	Respiratory infections	no	1	2	yes	2.1	3f	-	no	no	no	yes	Atypical swallowing	III	-	-3	-1
50	M	F.F.	31	Hypothyroidism, recurrent respiratory infections	yes	1	2	no	1.3	-	1	no	no	no	no	Tongue protrusion	III	-	1	-4

51	M	F.E.	14	Hypothyroidism	no	0	2	no	1.8	0	0	-5	no	no	no	Atypical swallowing	III	-	2	-6
52	M	F.G.	9	Recurrent Bronchitis	no	0	1	no	2.1	0	0	no	no	no	no	no	III	III	1	-5
53	M	G.F.	7	no	no	2	1	no	1.8	0	1D1M	-4	no	no	no	no	I	-	0	1
54	M	G.G.	4	Hypothyroidism	yes	1	2	no	0.7	0	-	no	no	no	yes	pacifier	-	-	-3	0
55	M	G.F.	6	no	no	0	2	yes	0.8	0	-	-2	no	no	no	Finger sucking	III	-.	0	-1
56	F	G.G.	4	Hyperthyroidism	no	1	1	no	1.1	0	-	no	no	no	no	Tongue protrusion	-	-	3	1
57	F	G.B.	25	no	yes	0	2	no	2.5	2f	0	-2	no	no	no	no	I	-	3	2
58	M	G.A.	5	no	no	0	1	yes	1.3	0	-	no	no	no	no	no	I	-	1	1
59	M	G.G.	9	no	no	0	2	no	0.8	0	0	no	no	no	yes	Atypical swallowing	III	-	-2	3
60	M	G.M.	36	no	no	0	3	no	1	-	6F	no	no	no	no		III	III	1	-4
61	M	H.D.	7	no	yes	1	1	no	1.2	1f	0	-3	no	no	no	no	II	-	4	3
62	M	H.A.	5	no	yes	2	1	no	0.7	0	-	no	no	no	yes	Atypical swallowing	-	-	-3	2
63	M	L.R.	13	Recurrent bronchitis and tonsillitis	no	0	1	no	1.9	0	0	no	no	Conoid 11	no	no	III	-	0	-4
64	F	L.L.	16	Hypothiroidism	yes	3	3	yes	1.3	1f	4F	-2	no	no	yes	Tongue protrusion	III	III	-4	-2
65	F	L.S.	8	no	no	0	1	no	2.2	8f	0	-3	no	no	no	Pacifier	III	-	-2	1
66	F	L.M.	33	Hypothiroidism	yes	2	1	no	2.7	-	0	no	no	no	no	no	III	III	0	-4
67	F	L.F.	16	Hypothiroidism	no	1	1	no	2.3	-	0	no	no	no	yes	Atypical swallowing	III	-	-3	1
68	M	L.F.	17	no	yes	0	2	yes	0.6	4f	0	-6	no	no	no	no	III	III	0	-2
69	M	M.M.	34	no	no	0	2	yes	1.3	-	3F	no	no	no	no	no	III	III	1	-6
70	M	M.A.	5	Hypothiroidism	no	1	1	no	1.4	0	-	no	no	no	no	pacifier	-	-	4	3
71	F	M.D.	37	no	yes	0	3	no	0.7	-	1D 3F	-2	no	no	no	no	III	III	0	-4
72	F	M.S.	13	Recurrent respiratory infections	no	0	1	yes	0.6	0	0	-2	no	Conoid 12,22	yes	Atypical swallowing	II	-	1	6
73	F	M.L.	11	Leukemia	yes	1	3	no	0.4	0	1D	no	no	no	no	Finger	III	III	1	-4
74	F	M.S.	14	no	yes	2	2	yes	1.7	-	0	no	no	no	no	no	I	III	2	1
75	F	M.E.	16	no	yes	2	1	no	2.1	-	2D	no	no	no	no	no	III	III	-3	2
76	F	M.B.	18	Recurrent tonsillitis, otitis	yes	1	2	no	0.9	-	3F	no	no	no	no	pacifier	II	II	4	1

77	F	M.S.	6	Hypothiroidism	no	1	2	no	2.3	0	-	no	no	no	yes	pacifier	-	-	0	0
78	F	M.G.	18	bronchitis	yes	1	1	no	1.8	1d	2D	-4	no	no	no	no	III	III	2	-4
79	M	M.N.	8	bronchitis	yes	2	1	no	1.6	0	0	no	no	no	no	Finger sucking	III	-	2	0
80	M	M.G.	10	Recurrent bronchitis	yes	1	1	no	2.1	3d	0	no	no	no	no	Finger sucking	III	-	-3	1
81	F	M.C.	11	Hypothyroidism	yes	0	1	no	1.8	0	0	no	no	no	yes	Pacifier	III	III	-2	0
82	F	M.H.	5	no	yes	1	0	yes	2.6	0	-	no	no	no	no	Tongue protrusion	III	-	-2	2
83	F	M.S.	4	Hypothiroidism	yes	2	1	no	1.9	0	-	no	no	no	no	Finger sucking	-	-	0	0
84	M	M.D.	8	no	yes	0	2	no	1.5	1d	1D	no	no	no	no	Finger sucking	III	-	2	-5
85	F	M.C.	8	Alopecia	yes	1	1	no	2.4	0	1D	no	MIH	no	no	no	II	-	4	2
86	F	M.L.	11	no	no	1	0	no	1.2	0	1F	no	no	no	no	no	II	II	3	4
87	M	M.B.	6	no	no	1	1	yes	1.5	1	-	no	no	no	yes	Finger sucking	III	-	-4	0
88	F	N.F.	7	no	yes	0	2	no	1.8	0	-	-2	no	no	no	no	-	-	0	0
89	M	N.P.	9	Recurrent respiratory infections	no	2	2	no	2.1	0	2	no	no	no	yes	Pacifier	III	-	0	2
90	F	N.S.	7	no	yes	1	2	yes	0.8	0	0	no	no	no	no	no	III	-	1	-4
91	F	N.I.	4	Hypothiroidism	no	0	1	no	0.9	0	-	no	no	no	no	Tongue protrusion	-	-	0	2
92	F	P.L.	14	Recurrent respiratory infections	yes	2	2	no	2	2f	4D	-4	no	no	no	no	III	III	2	-4
93	F	P.L.	10	no	yes	1	2	yes	1.7	4f	0	-2	no	no	no	no	I	-	2	2
94	F	P.M.	7	Sd West	no	0	1	yes	0.6	0	-	-2	no	no	no	no	II	-	3	2
95	M	P.B.	11	no	no	0	1	no	0.8	0	0	no	no	no	no	no	I	-	2	2
96	F	P.L.	10	Recurrent bronchitis	yes	0	1	no	1.2	0	0	no	no	no	no	no	III	III	0	0
97	M	P.A.	8	Hypothiroidism	no	1	2	no	0.5	0	0	no	no	no	yes	Atypical swallowing	III	-	-3	0
98	M	P.M.	49	no	no	1	2	no	2.4	-	6D	no	no	no	no	no	III	-	1	-2
99	M	P.L.	38	no	no	0	2	no	2.1	-	2M3F	-2	no	no	no	no	III	III	0	-3
100	M	P.E.	33	Asthma	no	1	1	no	1.9	-	2D	-1	no	no	no	no	III	III	1	-4
101	F	P.A.	15	no	yes	2	1	yes	1.8	0	0	-2	no	no	no	Atypical swallowing	II	-	-4	1
102	F	P.C.	13	Recurrent bronchitis	yes	1	2	no	1.5	2f	3D	no	no	no	no	Atypical swallowing	II	II	-3	2
103	M	P.P.	9	no	yes	2	1	no	0.8	6f	1F1D	no	Amelogenesis imperfecta	no	no	Pacifier	III	-	-4	2
104	F	R.E.	11	Recurrent	no	0	3	no	2.4	3f	1D1F	no	no	no	yes	no	II	I	1	4

				Pneumonia															
105	M	R.M.	12	Hypothiroidism, diabetes	yes	0	1	yes	1.7	2f	2D	-5	no	no	yes	no	III	-	1	0
106	M	R.J.	7	Recurrent Otitis, Osas	yes	0	2	no	2.7	1d	0	no	no	no	yes	Atypical swallowing	II	-	0	4
107	F	R.E.	28	Recurrent bronchitis, Anaemia	no	1	3	no	1.3	-	2D1F	no	no	no	no	no	III	III	0	-2
108	M	S.F.	6	Bronchitis	yes	1	1	yes	0.7	1d	0	-1	no	Conoid 21	no	Atypical swallowing	II	-	4	1
109	F	S.G.	5	Hypothiroidism	no	0	2	no	0.8	0	-	no	no	no	no	no	-	-	1	1
110	F	S.A.	13	Celiac disease	yes	0	3	yes	1.6	1f	2D	no	no	no	yes	Finger sucking	III	-	1	-2
111	M	S.I.	10	no	no	0	1	no	2.3	4f	1D	no	no	no	no	no	III	-	2	0
112	M	S.V.	13	Growth disturbances	no	1	2	yes	1.8	1f	0	-4	no	Conoids	no	no	III	III	1	-4
113	F	S.E.	8	Gastric reflux	no	1	2	no	1.1	0	0	no	no	no	no	no	II	-	4	3
114	F	S.E.	18	no	no	0	3	yes	2.1	3f1d	6D	-4	no	no	yes	Atypical swallowing	III	-	-3	2
115	F	S.N.	9	Hypothiroidism	no	0	1	no	1.6	0	1D	-1	no	no	no	no	II	-	0	4
116	M	S.L.	10	no	no	0	2	yes	1.9	2d1 m2f	2D	no	no	Conoid 42	no	Atypical swallowing	III	-	1	-3
117	M	S.C.	11	no	no	1	1	no	2.4	2m	3F	no	no	no	no	Pacifier	III	III	-3	0
118	F	S.E.	5	Hypothiroidism	yes	0	2	yes	2.5	0	-	no	no	no	no		I	-	0	2
119	M	T.L.	13	no	no	1	3	no	1.7	2f	2D	-5	no	no	no	no	III	-	0	-2
120	F	T.A.	48	Hypothiroidism	no	1	1	no	0.8	-	2M11F	no	no	no	no	no	III	III	0	-3
121	M	T.A.	6	no	no	0	1	yes	1.3	0	-	no	no	Conoid 12,22	no	no	I	-	1	1
122	F	T.E.	22	Celiac disease	yes	0	1	no	2.1	-	0	-2	no	no	no	no	III	III	1	-4
123	M	T.A.	6	No	no	0	1	yes	1.6	0	-	no	no	no	no	Pacifier	I	-	0	0
124	F	T.F.	11	Growth disturbances	no	1	1	no	1.1	2f	2D	-2	no	no	si	no	III	-	2	-3
125	F	T.O.	32	no	yes	1	2	no	2.3	9f	4F	-10	no	no	no	Atypical swallowing	III	III	-3	0
126	M	V.D.	13	no	no	1	2	yes	0.7	0	0	no	no	Conoid 13,23	no	no	II	-	4	5
127	M	V.A.	12	no	yes	0	3	yes	1.9	0	3F	no	no	no	yes	no	II	-	-2	4
128	M	V.N.	8	no	no	1	1	no	1.4	2d	1F	no	no	no	no	no	III	-	0	0
129	M	Z.R.	5	no	yes	0	1	no	1.8	0	-	no	no	no	no	no	I	-	0	1
130	M	Z.E.	8	Recurrent bronchitis	yes	1	0	no	2.1	0	0	no	no	no	yes	no	I	-	1	1
131	F	Z.C.	48	no	no	1	2	no	1.6	-	5D3M	no	no	no	no	no	III	III	0	-3
132	F	Z.C.	6	no	no	0	3	yes	0.8	0	-	no	no	no	no	Pacifier	III	-	2	-3
133	F	Z.C.	14	Hypothiroidism	yes	2	2	yes	1.3	4f	8F	no	no	Microdontia	no	Atypical swallowing	II	-	-3	4

Table Legend: - (not evalualable), G (gender), CHD (congenital heart disease), SF (Systemic Fluoride), PI (Plaque Index), O.Br. (Oral breathing), Dental malocc (Dental malocclusion-Angle classification), Skeletal maloc (Skeletal malocclusion), OB (over bite), OJ (overjet).

RESULTS

The sample consist of 133 subjects with DS (72 males and 61 females). The mean age is 13.4 ± 9.7 years (age range 3-49) .

Medical History

In accordance to what is reported in the literature, 64 subjects (48%) were affected with congenital heart diseases, many of them requiring antibiotic prophylaxis for bacterical endocarditis during surgical procedures or professional dental hygiene. The percentage of subjects with hypothyroidism was 21,8% (29 subjects), only one subject had hyperthyroidism and none evidenced autoimmune diseases interesting thyroid gland. Thirty-eight had other systemic diseases (28.5%) such as recurrent respiratory system infections (rhinitis, tonsillitis, bronchitis, pneumonia), celiac disease and growth disturbances. Two subjects displayed a combination of SD and West syndrome.

The parents/caregivers declared through questionnaire that all the patients showed mild to severe mental retardation: 17 had severe mental retardation, 109 moderate and 7 mild mental retardation.

In order to evaluate the correlation between dental anomalies and general anamnesis, the sample was divided into four groups:

- Subgroup A: DS only (n=33);
- Subgroup B: DS and congenital heart disease (n=64);
- Subgroup C: DS and hypothyroidism (n=29)
- Subgroup D: DS and other systemic diseases (pulmonary diseases, celiac disease, etc.)(n=38).

Alimentary habits and oral hygiene

Fifty-three subjects consumed sweetened food and beverage everyday one time/day, 22 two times/day. All the subjects of the sample, excluding five subjects affected by severe mental retardation, brushed their teeth every day, with an average frequency of tooth brushing/day of 1.6 ± 0.7. One hundred-four subjects had taken tablets or lozenges of fluoride, the others used fluoride toothpastes.

Dental visit

The average Plaque Index was 1.6±0.7. The dmft index, calculated on deciduous dentition, was evaluated in 104 subjects: average dmft was 0.9±1.8. The average DMFT index was calculated on permanent dentition and evaluated considering 100 subjects, was 1.9±1.8.

Age of eruption. The age of teeth eruption was recorded only in 97 subjects of the sample, the others did not remember with accuracy the age of the eruption of the first deciduous tooth. The average age of eruption for the sample evaluated was 13.4±4.8 months (range: 6-18 months).

Dental agenesis. An orthopantomogram (OPT) was taken for subjects older than 7 years (n=98), in order to evaluate dentition stage and tooth agenesis. Subjects with tooth agenesis, evaluated in 120 subjects (more than 5 years old) were 42 (35%): permanent agenesis, deciduous agenesis and both permanent and deciduous agenesis are 40, 9 and 2, respectively. The average number of congenitally missing teeth on the total sample was 0.9±2. On the 42 patients with tooth agenesis the average number of missing teeth was 2.9±2.5.

Permanent teeth - This data was registered for subjects more than 7 years-old (n=98). Hypodontia, of 103 permanent teeth, was confirmed in 40 out of 98 patients, representing 40.8% of the group. Prevalence in percentage of each tooth agenesis on the total sample (98 patients) was: maxillary right and left lateral incisors 15.6% and 19.2% respectively; 7.2% of maxillary right and left second premolars were missing; mandibular right and left second premolars: 7.2% and 9.6%, respectively; maxillary left second molar: 4.8%; Mandibular right and left lateral incisors: 7.2% and 8.4% respectively; mandibular right and left incisors: 2.4% and 3.6% .

Deciduous teeth - Deciduous teeth agenesis was recorded for subjects in subjects in an age range of 5-14 years (n=82). Deciduous hypodontia was found in 9 out of 82 patients (10.9%). The percentages of each deciduous tooth agenesis on the total sample (n=9) was: left mandibular central incisors and right lateral mandibular incisors were absent in 3.7%; left mandibular central incisor and right maxillary lateral incisor: 2.5%; others tooth missing (53, 55, 61, 62, 63, 65 and 72) in 1.2% . Seven patients had agenesis of both the deciduous and their corresponding permanent teeth.

One way analysis of Variance (ANOVA) and Bonferroni t-test were used in order to detect differences in dental agenesis in the different subgroups A, B, C and D. Significant difference ($p<0.05$) were present between subgroup A and B, while no significant differences were detected among other subgroups.

Dental form anomalies. Dental shape and structure anomalies were recorded considering total sample of patients in deciduous, mixed and permanent dentition (n=133). Shape abnormalities were found in 10.5% of

the sample (n=14): 11 subjects had conoid-shaped teeth, 2 subjects evidenced microdontia, and one subject crown fusion.

Malocclusion were evaluated in 122 subjects: 16 subjects with class I malocclusion (13.1%) someone associated to tooth crowding; 26 subjects with class II malocclusion (21.3%) associated to open bite and deep bite, in 9 and 15 subjects respectively; 70 subjects had class III malocclusion (57.4%) associated to open bite and anterior cross-bite, in 18 and 39 subjects respectively. Oral habits have been recorded in 88 subjects on 133: oral breathing in 34 (25%), atypical swallowing in 25 (19%) and pacifier or finger sucking in 29 (22%). Seven young subjects revealed severe facial muscle hypotonia with tongue protrusion.

DISCUSSION

Considering the high percentage of patients affected by congenital heart diseases (48%), careful investigation on the indication for antibiotic prophylaxis is needed. It's also required to give to parents/caregivers oral hygiene instruction, and to insist on the importance of oral health on general health: the average frequency of toothbrushing/day (1.6) is too low compared to what recommended. Comparing results of our WS sample to non-syndromic population, Plaque Index results reveal a poorer oral hygiene level respect to non-syndromic population: probably manual dexterity in toothbrushing is not so proper to eliminate all the plaque from tooth surfaces. Many subjects, especially adults, have gingivitis and periodontitis with a higher risk to develop severe periodontitis and tooth loss: those patients require professional scaling every 3 months.

Figure 3. Oral hygiene instructions to a DS little boy and his family.

Dmft/DMFT index average values seem to be similar to the non-syndromic population [29]. Anyway the use of fluoride toothpaste is advised.

Delayed growth is a typical feature of DS [33]. This delay is also expressed as a delay in primary dentition eruption: in our sample the mean age of first tooth eruption is 13.4 months, which clearly showed a 5-

months delay compared to non-syndromic italian population [34]. The prevalence of tooth agenesis in our sample is relatively high: considering that in non-syndromic subjects a prevalence of 4.6% dental agenesis was reported, it can be noticed that its prevalence in DS is 10-times higher.

The statistical analysis demonstrated a significant correlation between dental agenesis and cardiac diseases: literature confirms that poor terminal vascularization can lead to a complete or partial odontoblastic degeneration, which leads to dental agenesis [35]. Another hypothesis about dental agenesis in DS is that an altered growth process of the peripheral nervous system and to the abnormal development of chondral elements can lead to dental agenesis: recent researches suggested that dental morphogenesis could be linked to trigeminal nerve fibers development. Hypothyroidism usually leads to a delayed and prolonged proliferation of cells of the trigeminus nerve, resulting in a decreased rate of neuron production [36]. Failure of the nerve to establish the lingual branch results in the absence of the mesenchymal dental follicle and, therefore, in a congenital missing tooth [37]. Our sample consisted of 29 patients with hypothyroidism: they presented a 6-month delay in tooth eruption compared to non-syndromic subjects. From a statistical point of view, significant correlations between dental agenesis and hypothyroidism were not present.

The prevalence of class III malocclusion is higher than 50% on the total population and it may be related to maxillary hypoplasia which is a typical feature of DS. The maxilla resulted underdeveloped in all the three spaces (sagittal, transversal and vertical) and this is the cause of a “relative prognathism” [38, 39]. Maxillary hypoplasia and facial- masticatory muscles hypotonia are related to the DS-typical face with open bite and tongue protrusion.

The hypotonic tongue results in a pseudomacroglossia which is related to undersized bones [40]. The oral breathing tendency could be related to tongue position, usually laying low in the floor of the mouth, associated with a narrow palate and underdeveloped nasal cavities[41]. In subjects affected with DS, the class III malocclusion tends to worsen with time for the ligament laxity of temporo-mandibular joint, therefore it’s important to act preventively with orthopedic treatment [42].

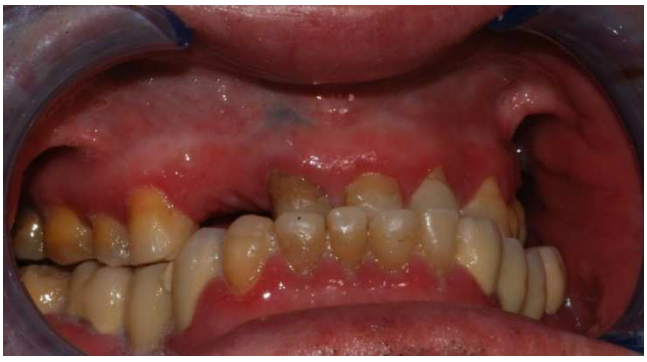

Figure 4. Class III malocclusion associated with severe anterior cross-bite, in an adult DS subject.

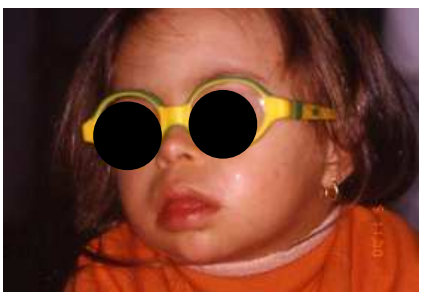

Figure 5. Little DS girl with tongue protrusion, “pseudomacroglossia”.

PREVENTION AND TREATMENT PLAN

An individual and intensive prevention and/or treatment plan was elaborated for each subject based on his own clinical feature.

General guidelines:

1) Oral hygiene instruction and correct dietary advices to parents/guardian and patients affected by DS (e.g. to recommend the use of fluoride toothpaste, with the correct fluoride concentration in according to the patient age, for a topical domiciliary fluoride prophylaxis);
2) Psychological approach in order to gain patient's confidence, when possible. "Soft Constraint": in case of poor collaboration, parents/guardians may help clinicians in containing patient during dental procedures.
3) Professional oral hygiene and recall visit every 3-6 months;
4) Fissure sealants of permanent molars (first and second permanent molars);
5) Interceptive and/or comprehensive orthodontic treatment in patients with optimal oral hygiene levels. Rapid maxillary expanders (REP)(Figure 7) are usually used to correct narrow palates; while bite blocks or functional activators are used to correct open bite and skeletal malocclusions, respectively.

Special guidelines for DS:

1) First dental visit in subjects with DS should be at 6 months;
2) In cases of muscle hypotonia in babies the use of pacifier is advised to train the facial muscles. In those cases physiotherapist (from 6 months) and speech therapist (from 3 years) play an important role;
3) In cases of muscles hypotonia and tongue protrusion, devices stimulating the right position of tongue (Castillo-Morales appliance) may be applied on the baby palate from the age of 2-3 months (Figure 6);

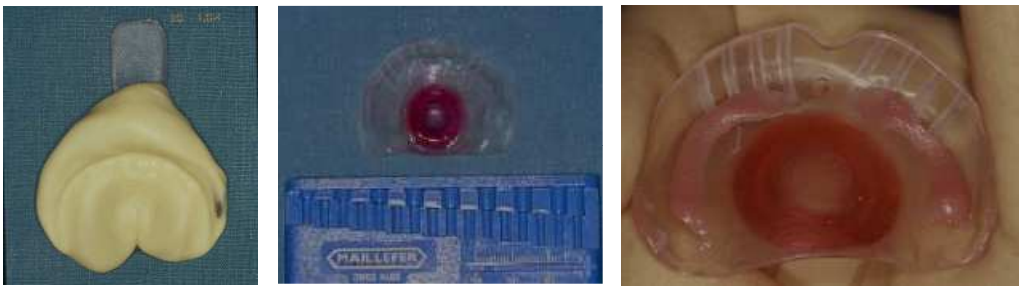

Figure 6. Palate impression taken in a baby with DS; Castillo- Morales appliance; prosthesis adhesive may help in wearing the appliance.

4) In case of poor collaboration and severe anxiety, patients affected by congenital heart diseases should be treated with sedation or general anaesthesia, also “soft containing” may stress patients causing hypertension and heart rate increasing;
5) Antibiotic prophylaxis for endocarditis, when required;
6) Prompt caries therapy, especially in patients affected by congenital heart diseases or in cases of dental agenesis;
7) In cases of permanent teeth agenesis, try to maintain deciduous tooth as long as possible;
8) Orthopaedic-orthodontic treatment of early detected malocclusions;
9) In cases of maxilla hypoplasia, the orthopaedic treatment is advised with the appliance of Rapid Maxillary Expander (Figure 7) to correct transversal underdevelopment, and Delaire’s Mask (Figure 8) to correct sagittal and vertical underdevelopment;

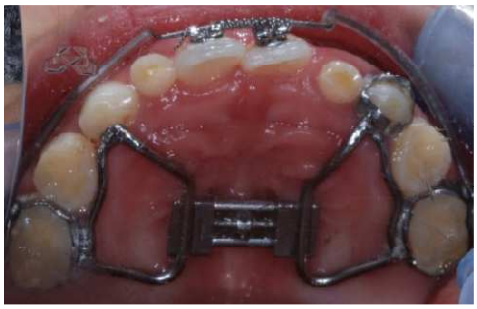

Figure 7. Rapid Maxillary Expander.

Figure 8. Delaire’s Mask: an intra-extra oral appliance for Class III malocclusion correction.

10) After orthopaedic treatment, the fixed orthodontic treatment may correct dental malocclusion;
11) Orthodontic treatment plan should consider dental agenesis management in young patients or implant/prosthetic treatment plan in adults.

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Chapter 5.

HYPOPHOSPHATEMIC VITAMIN D-RESISTANT RICKETS

Definition and epidemiology

Hypophosphatemic vitamin D-resistant rickets is a group of hereditary metabolic diseases caused by alterations in either vitamin D receptive system or in phosphate and calcium metabolism [1]. The different forms of Hypophosphatemic Rickets were classified according to their mode of inheritance into autosomal dominant (ADHR), autosomal recessive (ARHR) and X-linked dominant (XLH) forms [2]. XLH is the most frequent form of infantile rickets and of vitamin-D resistant rickets and it has a prevalence of approximately 1/ 20,000. The disease affects both sexes equally.

Diagnosis

X-linked Hypophosphayemic rickets is caused by a mutation of Phosphate-regulating gene with Homologies to Endopeptidases on the X chromosome (PHEX) gene. This gene is expressed in structures such as osteoblasts, osteocytes, odontoblasts and parathyroid glands, resulting in abnormal osteogenesis and odontogenesis [3]. PHEX mutation causes renal loss of phosphate, increased alkaline phosphatase activity, normal serum calcium levels . XLH symptoms can vary from one subject to another owing to several factors: family history, the degree of hypophosphatemia and the age of the patient at the start of systemic treatment [4].

Diagnosis is based on clinical and biochemical findings, and typical rickets/osteomalacia radiographic features (in children: fraying and cupping of metaphyseal regions; in adults: pseudofactures and enthesopathies). The most common laboratory findings usually include normal calcium and parathyroid hormone serum levels, normal or raised 25(OH) vitamin D levels, with low or undetectable levels of 1,25(OH) 2 vitamin D [5, 6]. Iliac bone biopsy may reveal osteomalacia and hypomineralized periosteocytic lesions. Molecular genetic testing confirms the diagnosis [7].

Clinical features

Phosphate wasting leads to hypophosphatemia and numerous consequences including mineralization defects. The main clinical features are characterized by growth disturbances and skeletal abnormalities: immature skeletal bone calcification and an increased tendency towards bone fractures, bowing of the legs, short stature, thickened wrists and ankles, beading of the ribs (rachitic rosary), craniotabes with frontal bossing of the skull, enlargement of the costal cartilages and spinal stenosis (Table 1, Figure 1a,b). Affected

subjects also report muscle weakness, decreased muscle tone, muscle cramps and rarely tetany associated to normal or low serum levels of vitamin D [8].

In children, XLH results in variable degrees of delayed walking, waddling gait, leg bowing, enlarged cartilages, bone pain, craniostenosis and growth failure (Figure 1). If undiagnosed during childhood, hypophosphatemia is suspected when adolescent/adult patients evidence bone and/or joint pain, fractures, mineralization defects such as osteomalacia, entesopathy, severe dental anomalies, hearing loss and fatigue [9]. A radiograph of an adult affected with XLH tends to present in a classic way: bowing of the legs (outward curve of long bone of the legs) and a deformed chest. Changes in the skull also occur causing a distinctive "square headed" appearance. These deformities persist into adult life if not treated.

XLH clinical features	
Bone pain or tenderness	Increased tendency to fracture (especially greenstick fractures). Craniotabes. Harrison's groove
Dental problems	Enamel defects, dentine defects, spontaneous abscesses, enlarged pulp chamber.
Muscle weakness	Lack of muscle tone in babies ("floppy baby syndrome")
Skeletal deformities	Bowed legs (toddlers). Cranial, spinal, and pelvic deformities. Rachitic rosary. Squared head.
Tetany	Uncontrolled generalized muscle spasm due to hypocalcemia.

Table 1. Most common clinical manifestation of XLH.

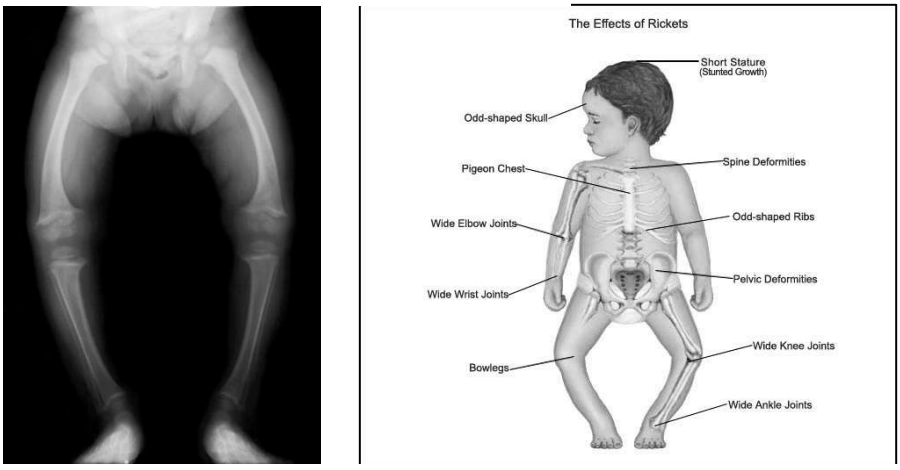

Fig 1. Skeletal anomalies in XLH , in particular bowing of the legs radiography (on the left).

Craniofacial and oral features

Histological and radiographic maxillary bone alterations in both primary and permanent teeth in subjects with XLH are described in literature as osseous structure abnormalities such as thin bony trabeculations and absence of lamina dura [10]. Teeth display short roots, large pulp chambers and high pulp horns [11]. The dominant tooth feature in XLH patients is the occurrence of spontaneous infections of the dental pulp tissue, resulting in tooth abscesses. In contrast with common endodontic infections, these abscesses develop in teeth without any signs of trauma or decay, affecting both the deciduous and permanent dentition [12]. Histologic investigations generally show a normal or slightly hypoplastic enamel morphology [3, 13]. However thinner or poorly calcified areas with long microcracks may also be present [16]. The dentin exhibits dysplastic histologic characteristics: large tubular clefts or lacunae reaching the dentino-enamel junction. The lack of fusion of calcospherites in the circumpulpal dentin leads to the formation of large interglobular spaces which are filled with a non-mineralized organic matrix while the mantle dentin is usually unaffected [14, 15]. These defects in the anatomy and histology of enamel and dentin facilitate the bacterial invasion into the pulp without a substantial tubular matrix destruction, causing spontaneous periapical infections. Dental abscesses in non-carious teeth and in absence of trauma or fracture histories are considered typical oral finding in patients affected by XLH [16].In literature, no studies about maxillary bones growth pattern and malocclusion in XLH are detectable.

Treatment

During childhood medical treatment decreases phosphate wasting and aims to normalize serum alkaline phosphatase (ALP) levels and radiological signs. Treating rickets will promote growth, correct leg deformities progressively and facilitate tooth mineralization. In infants diagnosed before they even show signs of rickets, the treatment goal is to stop the development of rickets. Generally oral phosphorus supplementation with multiple daily intakes to compensate for renal phosphate wasting and active vitamin D analogs (alfacalcidol or calcitriol) to counteract the 1,25- diOH-vitamin D deficiency is advised [17]. Surgery treatment of skeletal deformities during childhood should be avoided because of open epiphyses, patients present a significant risk of recurrence. When necessary, due to major bone deformities, surgery should be combined with adjusted doses of phosphate supplements and vitamin D analogs in order to prevent recurrence as previously evoked. The actual place of the surgery is the correction of residual deformities at the end of growth.

Dental treatment

To allow normal amelogenesis and dentinogenesis process, sufficient levels of vitamin D and phosphorous are needed. Since they both occur between the fourth month of intrauterine life and 11 years, structural defects in deciduous teeth usually cannot be prevented by systemic therapy. On the other hand, alterations in permanent teeth can be prevented through calcitriol and phosphate administration. Patients born from mothers affected by XLH, under systemic therapy during pregnancy, could have a reduced risk of enamel and dentin defects compared to patients with sporadic forms of XLH. In order to avoid the onset of spontaneous abscesses in patients affected by XLH, preventive dental procedures are recommended; including professional cleaning of teeth, topical fluoride application, pit and fissure sealants of permanent molars, and premolars, composite resin veneers on incisor teeth and stainless steel crowns on molars [18]. In order to avoid the onset of spontaneous abscesses, particularly in the presence of crater-shaped depressions, the best prevention measures are the prophylactic sealing or the application of a low viscosity composite resin material in association with a self-etching system on the entire crowns of all the teeth present [16]. The treatment options of spontaneous abscesses are either extraction or endodontic therapy.

DATA COLLECTION

The patients affected with XLH were referred from the Pediatric and Auxology Department in Sant'Orsola Hospital in Bologna for a dental examination in the Dentistry for Special Needs patients, at the Department of Oral Sciences (DIBINEM, University of Bologna). Most significant data were collected in the table (Data Collection Table in X-linked Hypophosphatemic Ricket) (page 49).

RESULTS

The sample consist of 10 patients, 2 males and 8 females. The main is 9.8 ± 4.3 years (age range 5-19).

Medical

Generally all the patients have mild skeletal deformities such as bowed legs, but other severe skeletal deformities were not evident. All the patients were treated with Calcitriol (0,25-0,75 mcg/die), in association with Phosphates (anhydrous Phosphate) or Sodium phosphate dibasic/potassium phosphate monobasic. Only one subject had a mild congenital heart disease, not requiring antibiotic prophylaxis before surgical procedure. Two subjects manifested growth disturbances such as growth delay, treated with GH therapy.

Alimentary habits and oral hygiene

Four subjects consumed sweetened food one time/day. All the subjects brushed their teeth every day, with an average frequency of tooth brushing/day of 1.8 ± 0.6. No one took any kind of fluoride prophylaxis.

DATA COLLECTION TABLE IN X-LINKED HYPOPHOSPHATEMIC RICKETS

	G	Name	age	*Clinical features*		*Alimentary and oral hygiene habits*			*Dental features*						*Orthodontics features*					
				Systemic diseases	CHD	Sweetened/die	Brushing/die	SF	PI	dmft	DMFT	Tooth Number anomalies	Structure anomalies	Shape anomalies	O.Br.	Abitudini viziate	Dental malocc	Skelet malocc	OB	OJ
1	M	A.G.	9	Growth disturbances	no	1	1	no	1.2	0	0	no	Enamel anomalies	no	no	no	II	II	3	3
2	F	A.P.	15	Growth disturbances	no	0	2	no	0.9	-	1F	no	Enamel anomalies	no	yes	Atypical swallowing	I right II left	II	3	4
3	F	B.A.	7	no	yes	0	2	no	0.7	0	-	no	Enamel anomalies	no	no	no	I	-	2	2
4	F	C.A.	19	no	no	0	3	no	1.1	-	1D2F	no	Enamel microcrack	no	no	no	I	I	2	2
5	F	D.S.	8	no	no	1	2	no	1.3	0	0	no	Enamel anomalies	no	no	no	II	-	2	4
6	F	G.M.	6	no	no	1	1	no	0.4	0	-	no	Enamel anomalies	no	no	no	I	-	1	2
7	F	I.C.	12	no	no	1	2	no	0.6	4f	0	no	Enamel anomalies	no	no	no	III	III	0	-4
8	F	M.A.	9	no	no	0	1	no	2.3	0	0	no	Enamel anomalies	no	yes	Atypical swallowing	II	-	-3	3
9	F	M.A.	5	no	no	0	2	no	0.6	0	-	no	Enamel anomalies	no	no	no	I	-	1	1
10	M	S.C.	8	no	no	0	2	no	0.4	0	0	no	Enamel anomalies	no	no	no	I	-	2	3

Table Legend: - (not evalualable), G (gender), CHD (congenital heart disease), SF (Systemic Fluoride), PI (Plaque Index), O.Br. (Oral breathing), Dental malocc (Dental malocclusion-Angle classification), Skeletal maloc (Skeletal malocclusion), OB (over bite), OJ (overjet).

Dental visit

The average Plaque Index was 0.9 ± 0.6. The dmft index was calculated in 7 subjects in the deciduous or mixed dentition, with an average dmft of 0.6±1.5, with a higher prevalence of decayed teeth compared to filled or missing teeth. The average DMFT index calculated in 7 subjects in the mixed and permanent dentition was 0.6±0.4, with an average prevalence of multiple caries of 28%.

The presence of malocclusions was evaluated in all the subjects: 50% of them displayed malocclusions, 40% showed a class II malocclusion, 10% showed a class III malocclusion. One subject had open bite (OB <0) and another one anterior cross-bite (OJ<0).

No one evidence dental agenesis or dental shape anomalies.

In orthodontic evaluation, all the subjects were included. Malocclusions were found in 5 subjects (50%): II class-malocclusion had an higher prevalence in the sample (40%) than III class-malocclusion (10%).

Enamel structural defects are visible in all the patients by observing enamel replicas with Scanning Electron Microscope, as explained in the following study.

Study about enamel defect in XLH subjects [16]

Methods

All the patients have been enrolled in a study conducted by our Department, Dentistry for Special Need Patients, DIBINEM, University of Bologna.

In order to remove the bacterial biofilm and food material, all the teeth were cleaned with an ultrasonic scaler and then polished using Nupro prophylaxic paste for 1 min with a rubber cup mounted on a slow-speed handpiece. The teeth were thoroughly rinsed and dried for at least 30 s using an air– water syringe. Moisture control was performed using cotton rolls placed in the labial and buccal vestibules. Then a twolayered polyvinylsiloxane impression was taken of the buccal surfaces of the teeth. The first layer of the impression material was loaded on teeth surfaces and high-pressure air with an air–water syringe was used to ensure its full penetration into enamel anfractuosities, then the second layer of polyvinylsiloxane was loaded on top of the first. The material was allowed to set for 6 min following the manufacturer's instructions.

The impressions were poured using an epoxy resin material in order to obtain replicas of the teeth to be examined. Electrodeposition of a layer of 300A of palladium and gold with Sputter Coater SC7620 was performed for each arch replica. The surfaces of the replicas were analysed using a scanning electron microscope (SEM) using magnifications of 35x, 200x, 500x, 1,000x, and 5,000x.

An orthopantomogram (OPT) was taken for 7 out of the 10 subjects of the study group, the other three patients were too young (<6-yearold) for X-ray exposure.

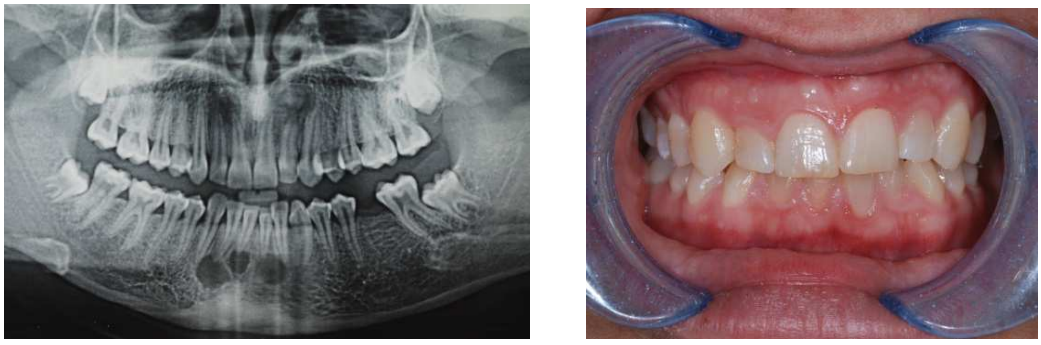

Figure 2. Patient 4 OPT examination (left) and frontal teeth picture (right).

Results

Radiographic results - No significant abnormalities are evidenced apart from 2 patients. One patients, patient 4 (Data collection Table), evidenced 7 periapical lesion, without teeth showing carious lesions or fractures. Patient 1 (Data collection Table), showing enlarged pulp chamber in lower first permanent molars.

SEM results – In all the 20 replica analysed, enamel surfaces normally show an irregular structure and pit depressions (Figure 2).Increasing the enlargement to 1000x and 2000x, the microstructure displayed irregularly distributed prisms with undefined margins and a non-parallel direction. Particular findings were observed in Patient 4: numerous crater-shaped depressions on enamel surfaces.

Discussion

In our sample all the enamel surfaces showed structure anomalies such as surface irregularities and enamel prisms defects but only in Patient 4, affected by numerous spontaneous abscesses, deep microclefts were present. A correlation between enamel structure of permanent teeth and spontaneous periapical infections is strongly hypothesized. Enamel defects may be also related to the age: adults affected by XLH may have more severe and symptomatic enamel defects than younger subjects.

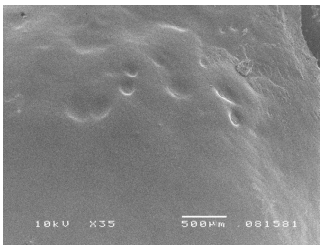

Figure 3a

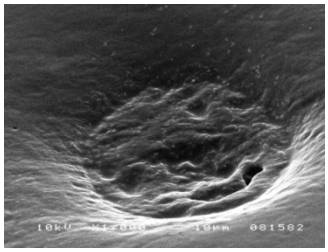

Figure 3b

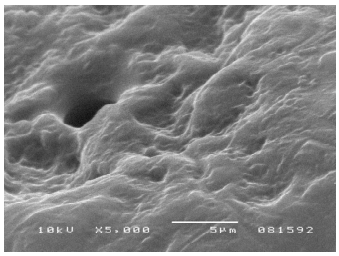

Figure 3c

Figure 3. Patient 3. SEM image showing crater-shaped depressions on the surface: 35x magnification (a), 1000x magnification (b), 5000x magnification (c).SEM image of one of the pit visible on Figure 3a. Deep microcleavages penetrated into the enamel thickness are visible inside each pit. Microcleavage's dimensions reached a diameter of 4.2mm (1,000x magnification) on Figure 3b,c.

DISCUSSION

Considering general health, the patients with XLH of our sample, did not show a severely compromised health status: only two were affected by growth disturbances, associated to XLH. No one had severe congenital heart diseases, requiring antibiotic prophylaxis before surgical procedures. None of the patients was at risk for bacterial endocarditis showed mental retardation or problems in collaboration during dental treatment.

Dmft/DMFT, Plaque Index and frequency of toothbrushing are similar to non-syndromic population. Oral hygiene levels are also good.

Class II skeletal malocclusion associated with maxillary jaw underdevelopment and a narrow palate had the highest prevalence in the sample. Only one subject displayed class III malocclusion associated with an anterior cross-bite.

PREVENTION AND TREATMENT PLAN

An individual and intensive prevention and/or treatment plan was elaborated for each subject based on his own clinical needs.

General guidelines:

1) Oral hygiene instruction and correct dietary advices to parents/guardian and patients affected by XLH (e.g. to recommend the use of fluoride toothpaste, with the correct fluoride concentration in according to the patient age, for a topical domiciliary fluoride prophylaxis);
2) Psychological approach in order to gain patient's confidence, when possible. "Soft Constraint": in case of poor collaboration, parents/guardians may help clinicians in containing patient during dental procedures.
3) Professional oral hygiene and recall visit every 3-6 months;
4) Fissure sealants of permanent molars (first and second permanent molars);
5) Interceptive and/or comprehensive orthodontic treatment in patients with optimal oral hygiene levels. Rapid maxillary expanders (REP)are usually used to correct narrow palates; while bite blocks or functional activators are used to correct open bite and skeletal malocclusions, respectively.

Special guidelines for XLH:

1) Even if XLH subjects usually have a good collaboration during dental procedures, in young patients psychological approach in order to gain patient's confidence is advised;
2) In order that normal amelogenesis and dentinogenesis occur, sufficient levels of vitamin D and phosphorous are needed. Enamel alterations in permanent teeth can be prevented through calcitriol and phosphate administration.
3) Advise mothers affected by XLH to continue calcitriol and phosphate systemic therapy during pregnancy, to have a reduced risk of enamel and dentin defects in children;
4) Topical fluoride application every 6 months;
5) Fissure sealants of permanent molars and premolars;
6) Application of a low viscosity composite resin material in association with a self-etching system on the entire crowns of all the teeth present, to fill the cracks can be and create a mechanical barrier to microorganisms invasion;
7) Orthodontic treatment plan considering oral hygiene levels: subjects with high PI and DMFT scores are not advised to start an orthodontic treatment for the high-risk caries and periodontal disease high risk.

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Chapter 6.

MUSCULAR DYSTROPHIES

Definition and epidemiology

Muscular dystrophy (MD) is a group of diseases that affect the musculoskeletal system and progressively reduce locomotion ability and respiratory system activity. Nine types of MD (Table1) are recognized as major form of MD, but other several minor MD-like conditions have also been identified.

DM Types	**Prevalence (born alive/year)**	**Trasmission mode**	**Gene locus**	**Altered protein**
DUCHENNE	1:3.300	X-linked recessive	Xp21	dystrophin
BECKER	1:18.000 – 1:31.000	X-linked recessive	Xp21	dystrophin
EMERY-DREIFUSS	1:300.000	X-linked recessive/ autosomal dominant	Xq28 / 1q11	emerin / laminin AC
CONGENITAL MUSCULAR DYSTROPHY	1:30.000	autosomal recessive/ dominant	6q22 / 9q31/ 12q13 / 9q34/ 21q22.3	laminin α2/ fukutin/ α7 integrin/ protein-O-mannosyltrasferase/ α1type VI collagen
MYOTONIC DYSTROPHY TIPE I/II	1:20.000/ 1:100.000	autosomal dominant	19q13/ 3q21.3	myotonic protein kinase/ Zinc finger protein (ZNF)

Table 1. Muscular dystrophies: types, prevalence, transmission mode, genes involved and altered proteins.

Common symptoms to all the forms of MD are progressive muscular loss, muscular weakness and inability to walk, scoliosis, respiratory difficulties, cardiomyophathy. The mode of inheritance, the age of onset, the involvement of particular skeletal muscle types and the overall progression have been used to classify different forms of muscular dystrophy [1].

DUCHENNE and BECKER

Duchenne and Becker muscular dystrophy (DMD/BMD) comprise a spectrum of devastating X-linked muscle wasting disease accounting for over 80% of all cases of muscular dystrophy.

DMD and BMD are severe forms of progressive muscular dystrophy. It is an X-linked recessive disorder that affects 1 in 3500 live born males, the defect affecting the short arm of the X chromosome in the p21-2 position [2]. This gene codes for dystrophin, a protein which is present in the sarcolemma of the muscular cell, are absent or hardly
detectable in DMD. The absence of dystrophin causes alterations in dystrophin-glycoprotein complex (DGC) which is an integral component of the skeletal muscles [3]. The DGC is a proteins complex which connects the extracellular matrix with the cytoskeleton [4]: the disruption of this link, caused by mutations of dystrophin or the sarcoglycans, causes sarcolemmal instability, which in turn may render the muscle fibers susceptible to necrosis, the major event in muscular dystrophies [5]. The absence of dystrophin renders the sarcolemma vulnerable to damage-inducing factors so that, as the affected organism grows in size, increased amounts of stress will be imposed on the sarcolemma as a result of increased load and force generation. The continuous degeneration and regeneration of muscle tissue as a result of stress factors has been suggested to be responsible for elevated levels of fibrosis [6].

Diagnosis and clinical features

Duchenne muscular dystrophy (DMD) is detected clinically at an average age of 3.5 years, but in the majority of the subjects, the parents recognize an earlier delay in motor function [7]. The muscular proprioceptive reflexes disappear at an early stage, and 5 to 10 years after the onset of the disease the patients become wheelchair-bound: sign such as calf muscle pseudohypertrophy [8] and the characteristic Gowers' sign (weakness of the proximal muscles, particularly those of the lower limb) [9] are early present. In patients with DMD mental QI at early age retardation is quite rare, an intellectual function reduction may occur in 20-30% of the subjects, with a score reduction to 70. Respiratory complications, including sleep-disordered breathing and apnoea, arise during the teenage years and result in headaches, nausea, fatigue and poor appetite[10]. Life expectancy is about 16-18 years, only 25% can survive until 25 years old: most patients die from recurrent upper airway infections or heart failure.

In Becker Muscolar Dystrophy (BMD), the disease is milder and more clinically heterogenous than DMD. Muscle weakness often is first noticed in adolescence or young adulthood. Cardiac decline in BMD patients may surpass skeletal muscle decline, with death from cardiomyopathy often occurring before age 60 [11].

Therapy

Numerous different therapeutic strategies have been advised to correct the various deleterious consequences of dystrophin absence. These strategies can be divided into the following four categories: cell

therapy (myoblast transplantation and stem cell therapy); gene replacement therapy; mutation-specific approaches (exon skipping and suppression of premature termination codons); and utrophin upregulation [12, 13, 14].

Craniofacial and oral features

During post-natal growth, bones continue their modelling process to maintain a form that is appropriate to their biomechanical function. Muscle function exerts an influence on skeletal growth and also on the facial skeleton [15]. Generally vertical dentofacial aberrations have been observed in patients with reduced muscle function: a high prevalence of malocclusions has been noted in DMD patients, such as anterior open bites and posterior crossbites, which appear to be strongly related to the involvement of the orofacial muscles in the disease. DMD affects muscles at various stages of the evolution of the disease: the weakening of the masseter muscles occurs at an earlier stage compared with the labial muscles [16]. Due to the imbalance between lateral and anterior forces combined with the increased lingual volume, lateral dentoalveolar effects are more significant than frontal effects and take the form of an increased transverse diameter; in turn, this causes buccal tipping of the teeth, as well as a lateral open bite and crossbite [17].
The studies conducted by Morel – Verdebout et al. (2014) [18] and Matsumoto et al.2002 [19] show that DMD patients have a tendency towards a skeletal Class III relationship with dental compensation. A clear skeletal Class III relationship was found in DMD patients in the permanent dentition, in contrast to DMD patients who were in the mixed dentition and showed only a tendency to a Class III skeletal relationship. In the vertical dimension, the high frequency of anterior and lateral open bites is characteristic of DMD patients: anterior and lateral open bites are more frequent in the older than in the younger patients.

CONGENITAL MUSCULAR DYSTROPHIES

Congenital muscular dystrophies (CMDs) are a group of hereditary myopathies with a predominant autosomal recessive mode of inheritance, characterized by an early onset congenital muscular hypotonia, progressive muscle weakness and difficulties in movement.

Nine different types and 20 subtypes of CMDs have been recognized and classified considering mode of inheritance, autosomal dominant (AD) or recessive (AR), and genes involved: Merosin deficient CMD (AR), CDM and abnormal glycosylation of dystroglycan (AR), Fukuyama CMD (AR), Walker-Warburg syndrome

(AR), Muscle-eye-brain disease (AR), Rigid spine syndrome (AR), Ullrich syndrome (AR), Bethlem myopathy (AD), CMD with integrin deficiency (AR)[20, 21].

Diagnosis and clinical features

Early diagnosis of CMDs is favoured by a birth or in infancy onset (hypotonia and weakness, and delay in walking) and a muscle biopsy which is usually compatible with the presence of a dystrophic myopathy.
Differential diagnosis among all the types and subtypes of CMDs starts with family history and physical examination, creatinine-kinase (CK) levels analysis and peripheral neurophathy evaluation by electromyography. Consequently auxiliary procedures such as brain and muscle magnetic resonance imaging (MRI) [22], muscle biopsy histology and immunochemistry and skin biopsy can be helpful in differential diagnosis [23].

The typical presentation of a "floppy baby", unable to walk unassisted, can be observed; however, in some patients with milder symptoms, antigravity movements may be preserved. Even though cardiomyopathy can develop during the course of disease in a patient with CMD, it is particularly evidenced in the second decade of life: sudden cardiac death has been reported almost exclusively in LMNA-related CMD [24].

Brain involvement can simply manifest as mental retardation (MR) without MRI structural abnormalities. While respiratory failure, particularly at night, is usually a common symptom in most CMDs during the advanced stages of the disease when the patient has lost his/her ability to walk, this symptom might unexpectedly become apparent when patients are still ambulant, particularly in Rigid Spine Muscular dystrophy and Ullrich syndrome [25]. Rapid progression of symptoms is not common in CMDs: it has been observed in Laminin α2 related CMD and Laminin A/C CMD[26].

Craniofacial and oral features

In literature dento-cranio-facial characteristics of patients affected by CMDs are not reported, the only feature reported is that facial muscle weakness is unlikely in CMDs subjects, differently from other congenital myopathies, apart from Merosin-deficient CMDs [27].

MYOTONIC DYSTROPHIES

Myotonic dystrophy (DM) is the most common adult muscular dystrophy, characterized by autosomal dominant progressive myopathy, myotonia and multiorgan involvement [28]. The two major types of myotonic muscular dystrophy (MMD), MMD1 and MMD2, are both caused by genetic defects: MMD1, the most common type, results from an abnormal DNA expansion in the DMPK gene on chromosome 19. MMD2 is caused by an abnormal expansion of DNA in the ZNF9 gene on chromosome 3 (Table 1)[29, 30].

Diagnosis and clinical features

After family history and clinical examination, the typical DM1 and DM2 diagnostic method is mutation verification by genetic tests [31]. In the case of DM1, symptoms and family history are often clear and distinctive enough to make a clinical diagnosis, on the contrary, the wide clinical spectrum of DM2 phenotype makes the clinical diagnosis more difficult. However in DM1 and DM2 the mutation can be confirmed by PCR and Southern Blot analysis [32, 33].

MD1 is characterized by the phenomenon of anticipation, by which the disease has an earlier onset and more severe course in subsequent generations. Patients with DM1 can be divided into three main subtypes, each presenting specific clinical features and management problems:

- congenital-onset MMD1 — begins at or around the time of birth and is characterized by severe muscle weakness, cognitive impairment and other developmental abnormalities [34];
- juvenile-onset MMD1 — begins during childhood (after birth but before adolescence) and is characterized by cognitive and behavioural symptoms, muscle weakness, myotonia (difficulty relaxing muscles after use) and other symptoms [35];
- adult-onset MMD1 — begins in adolescence or early adulthood and is characterized by slowly progressive weakness, myotonia, cardiac abnormalities and, sometimes, mild to moderate cognitive difficulties [36].

MMD2 rarely begins in childhood and its clinical presentation includes myotonia, muscular dystrophy, cardiac conduction defects, posterior iridescent cataracts, cerebral involvement and endocrine disorders.
It involves the proximal muscles (close to the center of the body) rather than the distal muscles (far from the center of the body) that are the first to be affected in MMD1. Usually MMD2 is not as severe as MMD1 [37].

Subjects born with congenital MMD, both MMD1 and MMD2, may have serious cognitive impairment: this condition seems to be related to abnormal development of parts of the brain, presumably caused by genetic abnormalities.

Craniofacial and oral features

In literature dento-cranio-facial characteristics of patients affected by MMDs are not reported, the only feature reported is facial muscles and tongue weakness associated to inability to suck, and difficulties in talking, chewing and swallowing in both MMD1 and MMD2 [38].

DATA COLLECTION

The sample consist in 12 patients affected by Muscular Dystrophies, aged from 7 to 31 years, referred from the Nigrisoli Hospital in Bologna for a dental examination in the Dentistry for Special Needs patients Division (DIBINEM, University of Bologna). Most significant data were collected in the table (Data Collection Table in Muscular Dystrophies subjects) (page 63).

RESULTS

The sample consist of 12 patients, 8 males and 4 females. The mean age is 16.9 ± 7.7 years (age range 7-31 years).

Medical history

The 8 males of the sample were all affected by Duchenne muscular dystrophy (DMD), two females (sisters) by Myotonic dystrophy tipe 1 (MMD1), and the remaining two females by Congenital muscular dystrophy (CMD), one affected by (MCD1A).

None of the subjects was affected with had congenital heart diseases, on the other hand, all the DMD subjects were treated for hypertension and prevention of congestive heart failure (ace-inhibitors) and for cardiac arrhythmias (β-blockers). One of them was under bisphosphonate and calcium treatment for osteoporosis.

Two subjects with DMD, showed both mild to severe mental retardation.

Alimentary habits and oral hygiene

Eight subjects consumed sweetened food and beverages 1 time/day, the other 4 subjects declare to avoid eating or drinking sugary food or beverage. Three subjects of the sample are able to brush their teeth

DATA COLLECTION TABLE IN MUSCULAR DYSTROPHIES SUBJECTS

	G	*Name*	*age*	*Clinical features*		*Alimentary and oral hygiene habits*			*Dental features*						*Orthodontics features*					
				Type of DM	CHD	Sweetened /die	Brushing/ die	SF	PI	dmft	DMFT	Tooth Number anomalies	Structure anomalies	Shape anomalies	Oral Breath	Oral habits	Dental malocc.	Skelet maloc	OB	OJ
1	M	A.A.	17	Duchenne	no	0	2	no	3.5	-	6F	no	no	no	no	Atypical swallowing	III	III	1	-3
2	M	B.G.	18	Duchenne	no	1	2	yes	2.7	0	2D	no	no	no	yes	Atypical swallowing	II	II	-4	4
3	F	B.E.	7	Myotonic 1	no	1	2	yes	2.6	2d	0	no	no	no	no	no	-	-	0	1
4	F	B.L.	9	Myotonic 1	no	1	2	yes	2.8	1m	0	no	no	microdontia	yes	no	III	III	-3	-1
5	M	B.M.	21	Duchenne	no	0	1	no	2.8	0	7F	-2	no	no	yes	no	III	III	-4	2
6	M	C.F.	31	Duchenne	no	0	2	no	3.6	-	6D	no	no	no	no	no	III	III	0	0
7	M	D.F.	13	Duchenne	no	1	0	yes	2.7	0	0	-2	no	no	yes	Atypical swallowing	I	III	2	1
8	F	F.A.	11	Congenital (MCD1A)	no	1	1	no	1.2	0	1D	no	no	no	no	Atypical swallowing	III	III	1	0
9	M	P.D.	7	Duchenne	no	1	2	no	1.6	0	0	no	no	no	yes	Atypical swallowing	-	-	-2	3
10	M	R.R.	20	Duchenne	no	1	0	no	3.8	3d	8D2M	-4	no	no	no	no	III	III	0	0
11	M	S.S.	26	Duchenne	no	0	2	no	1.9	-	8D1F	no	no	no	no	no	I	I	3	1
12	F.	S.F.	23	Congenital	no	1	2	yes	1.5	-	0	no	no	no	yes	no	II	II	-3	6

Table Legend: - (not evalualable), G (gender), CHD (congenital heart disease), SF (Systemic Fluoride), PI (Plaque Index), O.Br. (Oral breathing), Dental malocc (Dental malocclusion-Angle classification), Skeletal maloc (Skeletal malocclusion), OB (over bite), OJ (overjet).

individually, the other 9 subjects can't brush their teeth without someone else assistance. Three subjects/parents declared not to brush teeth every day, two of them due to poor compliance. The others

brushed their teeth every day, with an average frequency of tooth brushing/day of 1.5 ± 0.8. Four subjects had taken tablets or lozenges of fluoride, the others used fluoride toothpastes.

Dental visit

The average Plaque Index was 2.6 ± 0.8. The dmft index, calculated on deciduous dentition, was evaluated in 8 subjects: average dmft was 0.7±1.2. The average DMFT index was 3.4±3.9 and it was calculated on permanent dentition and evaluated in all the subjects.

Dental agenesis was found in 3 subjects (25%) had multiple dental agenesis of permanent teeth (more than 1 dental agenesis), with 8 missing teeth totally. Shape and structural anomalies were not found in the sample, apart from one subject evidencing microndontia, with undersized tooth crowns and short roots.

Malocclusion were evaluated in 10 subjects (2 subjects were excluded for the young age). Malocclusions were found in 8 subjects (80%). Class III malocclusion had a higher prevalence in the sample (60%) than class II malocclusion (20%). Class III malocclusion is associated to deep palate, discrepancy between upper and lower jaws with underdevelopment of the maxilla, causing bilateral posterior cross-bite. Open bite (OB <0) was found in five subjects, which is frequently related to oral breathing and atypical swallowing.

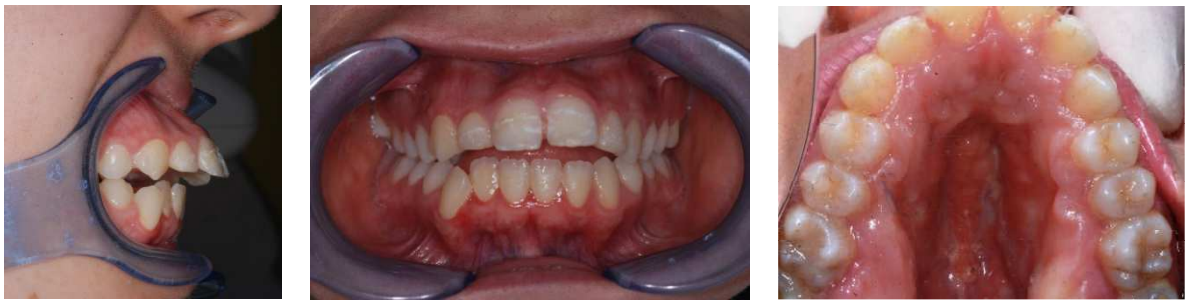

Figure 1. Severe II class malocclusion in a subject with congenital DM: open bite with increased overjet, transversal hypodeveloped maxilla and narrow palate.

DISCUSSION

The prevalence of Duchenne Muscular Dystrophies on other forms is evident also in our limited sample. No special contraindication to dental treatment are reported. Beside of complications of bisphosphonate

therapy in case of surgical procedures. In cases of poor cooperation, when general anaesthesia intervention is needed, there can be a risk of respiratory failure and malignant hyperthermia. For all those reasons, parents/caregivers should be educated and motivated to brush properly patients teeth.

From our results, oral hygiene habits and a high plaque index score reveal lack in oral hygiene measures at home, which could be attributed to a bad compliance and inability in motor skill. The consequence is a high prevalence of caries, challenging conditions for the clinician during therapy. The high incidence of caries in DMs is also associated to lack in masticatory function and in swallowing, which is slow and inefficient,: food remains for a longer time in contact to tooth surfaces [39].

Dental agenesis associated to deciduous teeth ankylosis may occur: in those cases prompt deciduous teeth extraction is needed to avoid infections and cysts.

According to data found in literature, the 80% of patients have malocclusions, due to temporal and facial muscle hypotonia or atrophy. Many of them have difficulties in speaking and swallowing (atypical swallowing. Class III malocclusion associated to underdeveloped maxillary bones, ogival palate and posterior cross-bite are common (60%). An incorrect posture of tongue, atypical swallowing and oral breathing may be at the origin of open bite and an increased overjet.

PREVENTION AND TREATMENT PLAN

An individual and intensive prevention and/or treatment plan was elaborated for each subject based on his own clinical feature.

General guidelines:

6) Oral hygiene instruction and correct dietary advices to parents/guardian and patients affected by DMs (e.g. to recommend the use of fluoride toothpaste, with the correct fluoride concentration in according to the patient age, for a topical domiciliary fluoride prophylaxis);
7) Psychological approach in order to gain patient's confidence, when possible. "Soft Constraint": in case of poor collaboration, parents/guardians may help clinicians in containing patient during dental procedures.
8) Professional oral hygiene and recall visit every 3-6 months;
9) Fissure sealants of permanent molars (first and second permanent molars);
10) Interceptive and/or comprehensive orthodontic treatment in patients with optimal oral hygiene levels. Rapid maxillary expanders (REP) are usually used to correct narrow palates; while bite blocks or functional activators are used to correct open bite and skeletal malocclusions, respectively.

Special guidelines for DMs:

6) Parents/guardians should help subjects with DMs in oral hygiene for their difficulties in movement coordination and poor dexterity;
7) Prompt caries therapy especially in patients taking bisphosphonate, endodontic infection can be at the origin of maxillary bones necrosis;
8) In surgery procedures planning, clinician should be involved for the risks of bisphosphonate therapy: in some cases, the therapy could be suspended for 6 months;
9) Also in case of poor collaboration and severe anxiety, local anaesthesia procedures are preferred to general anaesthesia for an increased risk of respiratory failure. General anaesthesia procedures should be planned evaluating risk & benefit ratio;
10) In patients with severe muscles weakness, physiotherapy and orthopaedic devices are advised;
11) In orthodontic-orthopaedic treatment plan, life expectancy and “biological” cost & benefit ratio should be considered.

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Chapter 7.

NOONAN SYNDROME

Definition and epidemiology

Noonan syndrome (NS) is a common genetic disorder with multiple congenital abnormalities. It is characterized by mildly unusual facial characteristics, short stature, heart defects, bleeding problems, skeletal malformations and other signs and symptoms. Noonan syndrome is an autosomal dominant, variably expressed, multisystem disorder with an estimated prevalence of 1 in 1000–2500 [1].

Diagnosis

Seven gene mutations (PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF and MEK1 genes) are identified in 75 % of the cases, the other 25% of cases are due to ex novo mutations. The implicated genes encode for functionally related proteins implicated in a common signal transduction pathway. Noonan syndrome was linked to the chromosomal band 12q24.1 and PTPN11—that encodes protein SHP2 which is located within this region[2]. However, it is important to remember that not all patients with NS carry a detectable alteration in one of these genes. There are likely to be additional, undiscovered genes that play a role in the development of Noonan syndrome for the remaining 25-30 percent of patients. Therefore, the failure to identify an alteration in one of these genes does not exclude the diagnosis of NS.

Multiple developmental disorders are clinically and genetically related to NS. Among them, LEOPARD syndrome (PTPN11, RAF1 and BRAF), Noonan-like syndrome with loose anagen hair (SHOC2), neurofibromatosis- Noonan syndrome (NF1), cardio-facio-cutaneous syndrome (BRAF, KRAS, MEK1 and MEK2), and “CBL mutation associated” syndrome (CBL) are the most close [3].

Noonan syndrome is characterized by marked variable expressivity, which makes it difficult to identify mildly affected individuals. In familial cases, autosomal dominant inheritance is confirmed. The risk of Noonan syndrome developing in the sibling of an affected person is 50% if the parent is affected, but is less than 1% if the parent is unaffected. Risk of transmission to the offspring of an affected individual is 50%. Most cases of NS are sporadic: until recently, diagnosis was made solely on the basis of clinical features, but nowadays molecular genetic testing can provide confirmation in 70% of the cases [4].

Clinical features

Noonan syndrome is characterized by congenital heart disease, short stature, a broad and webbed neck, sternal deformity, variable degree of developmental delay, cryptorchidism, increased bleeding tendency, and characteristic facial features that evolve with age. As NS patients require monitoring for a large number of potential health conditions, age-appropriate guidelines for the management of Noonan syndrome are available to support clinicians in their daily practice [5].

Noonan syndrome is the second most common syndromic cause of congenital heart disease, exceeded in prevalence only by trisomy 21[6]. The most common heart defect is a pulmonary valve stenosis affecting from 32 to 74% of the subjects, related in 8-33% of the cases to hypertrophic cardiomyopathy [7, 8]. Almost 25% of patients die because of heart failure in the first year, although the rate of sudden death is lower than that for familial hypertrophic cardiomyopathy [9].

Approximately 50 to 70 % of individuals with Noonan syndrome have short stature. At birth, they are usually of normal height and weight, but growth slows over time. Growth hormone deficiency, neurosecretory dysfunction, and growth hormone resistance can occur in NS contributing to the slow growth [10]. In 2007, the US Food and Drug Administration approved treatment of short stature in NS with recombinant human growth hormone in doses of up to 0·066 mg/kg per day. This treatment is still controversial because of different treatment results even if data are difficult to compare because of differing protocols and outcome criteria [11]. In a report of final adult height of 73 patients with a clinical diagnosis of Noonan syndrome, only 21 had an adult height in the normal range [12].

Characteristic chest deformities consist of pectus carinatum superiorly and pectus excavatum inferiorly. These sternal abnormalities are present in 70-95% of cases. The thorax is broad, and the internipple distance is large. Other common orthopedic features include cubitus valgus (50%), radioulnar synostosis (2%), clinobrachydactyly (30%), joint hyperextensibility (50%), and talipes equinovarus (12%). Giant cell lesions of the jaw, similar to those seen in cherubism, have been reported in several patients [13].

Adolescent males with Noonan syndrome typically experience delayed puberty. Affected individuals go through puberty starting at age 13 or 14 and have a reduced pubertal growth spurt. Most males with Noonan syndrome have undescended testicles (cryptorchidism), which may be related to delayed puberty or to infertility (inability to father a child) later in life [14]. Females with Noonan syndrome typically have normal puberty and fertility.

A variety of bleeding disorders have been associated with Noonan syndrome. Some people may have excessive bruising, nosebleeds, or prolonged bleeding following injury or surgery. Women with a bleeding disorder typically have excessive bleeding during menstruation (menorrhagia) or childbirth [15].

Cranio-facial and oral features

People with Noonan syndrome have distinctive facial features such as a deep philtrum, widely spaced eyes that are usually pale blue or blue-green in color, and low-set ears that are rotated backward (Fig.1).

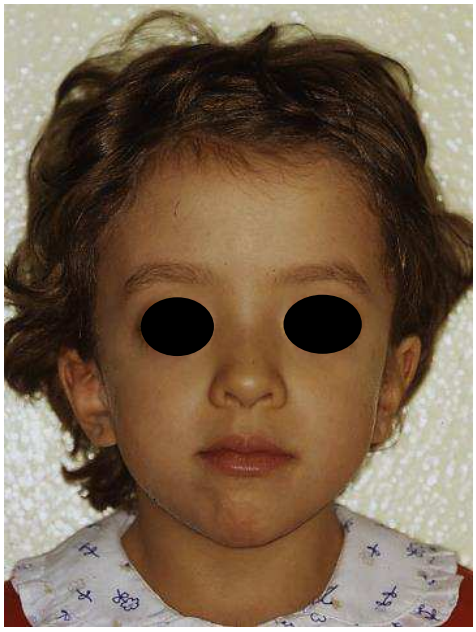

Figure 1. Young girl affected by NS: characteristic facial features.

Affected individuals may have high-arched palate, crowding of teeth and a small lower jaw (micrognathia). Many children with Noonan syndrome have a short neck and both children and adults may have excess neck skin (also called webbing) and a low hairline at the back of the neck [16].

The literature lacks reports on dental features of NS. A high prevalence of caries in deciduous and permanent dentition, associated to bad dietary habits and difficulties in motor skills, was described [17,18].

In NS subjects, giant cell multiple lesions located usually in the mandible and rarely in the maxilla have been described: this condition has been called " Noonan-like/ multiple giant cell lesions syndrome" [19].

The orthodontic features include class II malocclusion, a clock-wise facial growth pattern, underdevelopment maxilla and mandible and narrow palate. Tooth crowding, posterior cross-bite and cases of open bite or deep bite are also reported [20, 21, 22].

DATA COLLECTION

The sample consist of 13 patients affected by Noonan Syndrome referred from the Pediatric and Auxology Department in Sant'Orsola Hospital in Bologna for a dental examination in the Dentistry for Special Needs patients Division (DIBINEM, University of Bologna). Most significant data were collected in the following table (Data collection Table in Noonan Syndrome subjects)(page 73).

RESULTS

The sample consist in 13 patients, 9 males and 4 females. The mean is 14.1 ± 6.7 years (age range 6-22).

Medical history

DATA COLLECTION TABLE IN NOONAN SYNDROME SUBJECTS

		Name	*Age*	*Clinical features*		*Eats and oral hygiene habits*			*Dental features*						*Orthodontic features*					
				Systemic features	CHD	Sweetened /die	Brushing/die	FS	PI	dmft	DMFT	Tooth number anomalies	Structure anomalies	Shape anomalies	O.Br	Oral habits	Dental malocc	Skeletal maloc	OB	OJ
1	F	B.M.	12	Growth disturbances Coagulation defects	yes	0	1	no	2.8	0	1F	no	no	no	no	Atypical swallowing	III	-	1	-2
2	F	B.G.	14	no	no	1	2	no	1.2	-	0	no	no	no	no	Atypical swallowing	III	II	-4	-1
3	M	B.F.	10	no	yes	1	2	no	1.6	0	0	-1	no	no	yes	no	III	-	2	0
4	F	B.V.	6	no	no	2	2	no	0.9	0	0	no	no	no	si	Atypical swallowing	II	II	-3	3
5	M	C.L.	20	Growth disturbances	yes	0	1	no	2.9	-	4D	no	no	no	no	no	III	III	0	0
6	M	D.P.	13	Growth disturbances Mild mental retardation	no	0	0	no	2.7	0	no	no	no	no	no	Atypical swallowing	II	II	1	2
7	M	E.L.	14	no	no	1	1	yes	2.6	2f	0	+1	no	no	yes	no	I	II	2	2
8	M	F.I.	18	Growth disturbances	no	2	2	yes	2.8	0	2F	no	no	no	no	no	III	III	1	-1
9	M	M.M.	15	no	no	1	1	no	3	-	7D3F	no	no	no	no	no	III	III	1	-3
10	F	P.A.	6	Growth disturbances	no	0	3	yes	0.6	0	n.v.	no	no	no	no	Pacifier	II	-	2	4
11	M	P.L.	17	Hypothyroidism	yes	1	2	no	2.7	-	2D5F	no	no	no	yes	Atypical swallowing	I	I	2	1
12	M	P.H.	17	no	no	1	2	no	1.8	-	4F	-2	MIH	macrodontia	no	no	I	II	2	2
13	M	X.K.	22	Giant-cell lesion	yes	1	1	no	1.7	-	2F6D	no	no	no	no	no	III	III	2	-2

Table Legend: - (not evalualable), G (gender), CHD (congenital heart disease), SF (Systemic Fluoride), PI (Plaque Index), O.Br. (Oral breathing), Dental malocc (Dental malocclusion-Angle classification), Skeletal maloc (Skeletal malocclusion), OB (over bite), OJ (overjet).

Five subjects had congenital heart diseases (38%), and all of them need antibiotic prophylaxis during surgical procedures or professional dental hygiene. Five subjects showed growth disturbances (38%) and one mild mental retardation, one subject has hypothyroidism and one coagulation defects. One patient reported to have been affected by giant cell multiple lesions in the mandible.

Alimentary habits and oral hygiene

Two subjects ate and drank sweetened food everyday more than one time/day, 7 one time/day and the other 4 subjects declare to avoid eating or drinking sugary food or beverage. Twelve subjects of thirteen (92%) brushed their teeth every day, with an average frequency of tooth brushing/day of 1.5 ± 0.8. Only three subjects had taken tablets or lozenges of fluoride, the other nine used fluoride toothpastes. One subject brushed rarely their teeth and didn't take any kind of fluoride prophylaxis.

Dental visit

The average Plaque Index was 2.1 ± 0.8. The dmft index, calculated on deciduous dentition, was evaluated considering 7 subjects: average dmft was 0.3±0.7, with a higher prevalence of decayed teeth respect to filled or missing teeth. The average DMFT index, calculated on permanent dentition and evaluated considering 11 subjects, was 2.6±3.5, with an average prevalence of multiple caries of 64%.

Dental agenesis was evaluated on 11 subjects, 2 were too young for panoramic x-ray exposure: two subjects (18%) had dental agenesis of permanent teeth, with 3 missing teeth totally. One subject showed one sovranumerary tooth. One subject showed enamel hypoplasia and another one showed macrondontia of deciduous dentition, associated to microstomia.

In orthodontic evaluation, all the subjects were included. Malocclusions were found in 11 subjects (84%): class III malocclusion had an higher prevalence in the sample (61%) (Figure 2) than class II malocclusion (15%). Open bite (OB <0) was found in two subjects. Narrow palate associated to atypical swallowing was detectable in 5 subjects (38%).

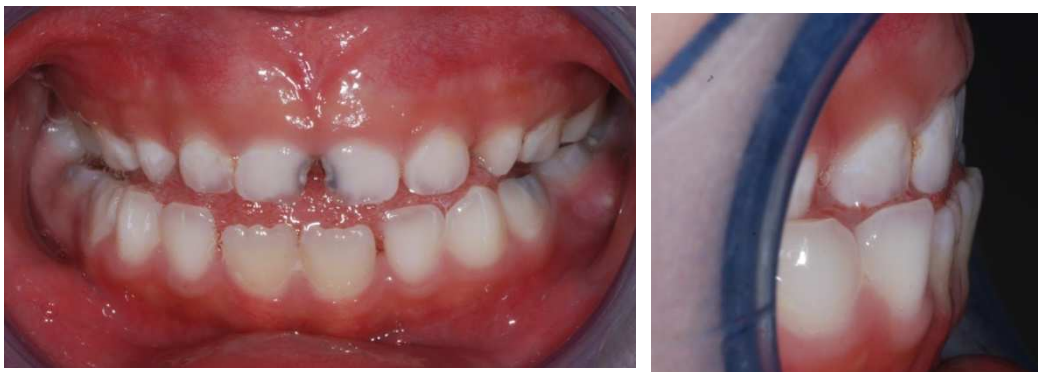

Figure 2. Patient 1. Class III malocclusion associated with anterior cross-bite (negative overjet).

DISCUSSION

Considering the high prevalence of patients affected by congenital heart diseases, it's advised to make sure if antibiotic prophylaxis before surgical procedure for each patient. It's also required to give to patients and parents/caregivers oral hygiene instruction, and to insist on the importance of oral health on general health: the average frequency of toothbrushing/day (1.5) is too low compared to what usually is recommended. When the results of NS are compared to the non-syndromic population Plaque Index results reveal a poorer oral hygiene levels: probably due to a lack of manual dexterity inability to perform proper oral hygiene. Almost all the patients showed inflamed gum, bleeding on probing. Caries prevalence and Dmft/DMFT index average scores are higher than non-syndromic population, related to bad oral health and dietary habits. In the sample, high PI scores were associated to multiple caries lesions.

According to data found in literature, II class malocclusion associated to maxillary bones underdevelopment and narrow palate has the higher prevalence in the sample. Only one subject has III class malocclusion associated to anterior cross-bite.

PREVENTION AND TREATMENT PLAN

An individual and intensive prevention and/or treatment plan was elaborated for each subject based on his own clinical feature.

General guidelines:

12) Oral hygiene instruction and correct dietary advices to parents/guardian and patients affected by NS (e.g. to recommend the use of fluoride toothpaste, with the correct fluoride concentration in according to the patient age, for a topical domiciliary fluoride prophylaxis);
13) Psychological approach in order to gain patient's confidence, when possible. "Soft Constraint": in case of poor collaboration, parents/guardians may help clinicians in containing patient during dental procedures.
14) Professional oral hygiene and recall visit every 3-6 months;
15) Fissure sealants of permanent molars (first and second permanent molars);
16) Interceptive and/or comprehensive orthodontic treatment in patients with optimal oral hygiene levels. Rapid maxillary expanders (REP) are usually used to correct narrow palates; while bite blocks or functional activators are used to correct open bite and skeletal malocclusions, respectively.

Special guidelines for NS:

17) Be careful to subject with coagulation defects: antifibrinolytics, desmopressin, blood products factors replacement might be taken before dental procedures. To those subjects FANS should not be prescribed;
18) After surgical procedure, use wraps of tranex acid on the wound, tight suture, and application of ice. Excessive bleeding during pulp theraphy can be controlled through the use of sodium hypochlorite and hydrogen peroxide.

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Chapter 8

TURNER'S SYNDROME

Definition and epidemiology

Turner's syndrome (TS) is one of the most common types of aneuploidy in humans and it's evidenced in 1:2000 newborn females corresponding to approximately 1.5 million women worldwide [1,2]. Turner's syndrome affects approximately 3% of female foetuses: there appears to be a high foetal abortions with only 1% of these embryos surviving to term [3]. It is responsible for 7–10% of all spontaneous abortions.

Turner's syndrome is the result of complete or partial X chromosome monosomy, associated with characteristic clinical features, such as short stature and gonadal dysgenesis. Affected women are exposed to a higher risk to develop cardiovascular disease, osteoporosis, and other endocrine, gastrointestinal, and renal disorders. Women with TS need an all-life-long follow-up so that early medical intervention may reduce morbidity and improve life expectancy [4].

Diagnosis

TS is cytogenetically characterized by X chromosome monosomy, but various from of this monosomy have been shown: the presence of an abnormal X chromosome (45 X) or mosaicism of a 45X cell line with another cell line. Mosaicisms might be 46XX, 46XY or have an abnormal sex chromosome rearrangement. Pure 45X monosomy is the most common karyotype (50-60%) and is associated with the most abnormal phenotype, 45Xmosaicisms are evident in 30%, other Y chromosome anomalies in 10% [2]. The monosomy of X chromosome is due to a nondisjunction of the sex chromatids during meiosis in the parental gamete or in the early embryonic divisions. The latter usually results in mosaicisms that usually have a less severe phenotypical features [5]. Women with 45X/46,XY mosaicism have an increased risk of developing gonadoblastoma, and a minority of these women are masculinized [2].

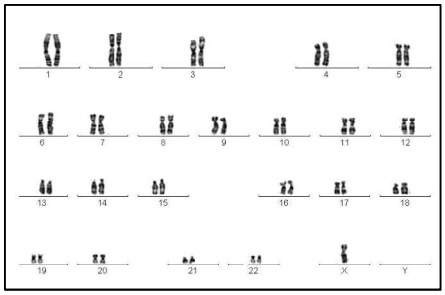

Figure 1. 45 X kariotype

The diagnosis of TS may be delayed until adulthood in up to 10% of women: especially in those cases of TS females who enter puberty spontaneously and consequently evidence amenorrhea (primary or secondary) or infertility. Usually the clinical diagnosis is confirmed by a chromosomal analysis [6]. In rare cases of

mosaicism the classic cytogenic technique was diagnostically inclusive because large number of cells.The use of molecular techniques such as fluorescence in situ hybridization (FISH) and the polymerase chain reaction (PCR) had improved the detection of low-frequency cell lines and possible structural abnormalities [7].

Karyotype	**Phenotype**
45,X	Most severe phenotype. Highest incidence of structural cardiac and renal abnormalities
46,Xi(Xq)	Structural abnormalities uncommon. Increased risk of autoimmunity, particularly thyroiditis and IBD, and deafness
45,X/46,XX	Least severe phenotype. Increased mean height. Spontaneous puberty and menses in up to 40%
46,Xr(X)	Spontaneous menses in 33%. Congenital abnormalities uncommon. Cognitive dysfunction in those with a small ring chromosome
45,X/46,XY	Increased risk of gonadoblastoma
45,X/46,X,idic(Y)	Increased risk of gonadoblastoma
46,XXp-	Similar phenotype to 45,X monosomy
46,XXq-	Variable phenotype

Table 1. Cytogenetics of TS women and correlation with phenotype [3]

Clinical features (Figure 2)

Short stature - It is the first common feature in women with TS: it's present in all with monosomy X and in more than 96% of mosaic females or those with a structurally abnormal X chromosome. The mean final adult height was 143-147 cm in untreated TS Caucasian women[8, 9]. Genes responsible for short stature have been localized to the distal part of short arm of the X (Xp11–22) and Y (Yp11) chromosomes. Treatment during childhood consists of early growth hormone (GH) therapy in supraphysiological doses and estrogen replacement around the normal age of puberty. An average gain of 10 cm(range 3.9–24.8 cm) in final height may be achieved by the early introduction of growth-promoting therapies. In the past, girls with TS who did not receive growth hormone (GH) therapy achieved an average adult stature approximately 20 cm shorter than normal [10, 11].

Gonadal dysfunction - In a normal fetus, the number of germ cells rises progressively to 600,000 by 2 months post conception to a maximum of 7,000,000 at about 5 months of gestation. The number of germ cells then decreases so that at full gestation only 50% of the germ cells remain. There is then a progressive germ cell degeneration up until the age of menopause[12]. The gonads in TS differentiate normally until the third month of gestation. After this period, the absence of part, or the whole, X chromosome in the germ cells results in an accelerated degeneration of oocytes and an increase in ovarian stromal fibrosis [13]. Most females with TS do not enter puberty spontaneously because of the early gonadal failure and subsequent estrogen deficiency. Spontaneous breast development is either minimal or does not occur, and primary amenorrhea usually occurs. However, this is not inevitable, as indicated by a recent study from Italy in which the incidence of spontaneous puberty in women with TS was found to be as high as 16% [14]. Only 8% of those with 45,X karyotype and 10% of those with a structural X chromosome abnormality entered puberty spontaneously, as opposed to 47% of females with 45,X/46,XX mosaicism. However, few women with TS will maintain ovarian function and fertility consequent. Spontaneous pregnancy occurs in less than 5% of women [15], the majority occurring in those with mosaicism. Additionally, the outcome of these pregnancies is often poor. Approximately 40% of conceptions end in spontaneous abortion or perinatal death. In the liveborns there is a 37% risk of chromosomal abnormalities, particularly Down's or Turner's syndrome, and congenital malformations, especially congenital heart and neural tube defects.

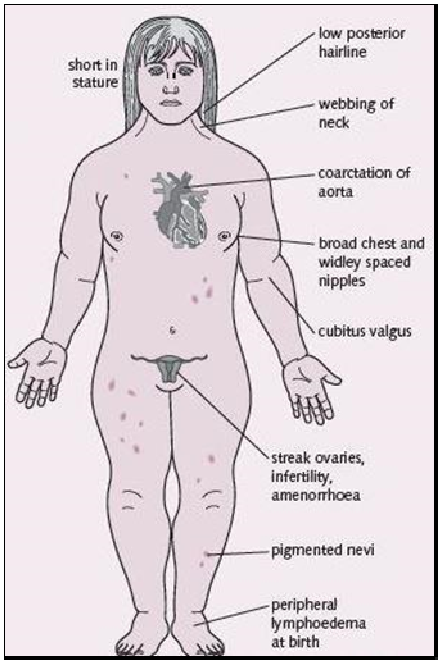

Figure 2. Clinical features in TS

Bone abnormalities - Many of the physical problems of TS are a result of structural bone defects. Typically, females with TS have disproportionately short legs and an abnormal upper-to-lower segment ratio. This results in the appearance of a squarely shaped chest and widely spaced nipples. Cervical vertebral hypoplasia contributes to the short stature and the short neck often seen in females with TS. Scoliosis may be present in approximately 10% of females, and it may or may not be associated with vertebral abnormalities [2]. The molecular defect has not yet been characterized, although it has been hypothesized that deletion of a gene on the X chromosome may be responsible for the connective tissue abnormalities [16].

Osteoporosis - There is a reduction in peak bone mass by 25% in women with TS [17,18]. There remains a great deal of speculation as to whether the reduction in bone mass seen in TS is a result of poor bone mineralization, and thus increases the risk of fractures, or is solely a consequence of delayed skeletal maturation and small bones. Prepuberal girls with TS show a significantly decreased bone density compared to chronological and bone age-matched controls and also had a fracture incidence that was 3 times that of normal controls [19]. Bone density remains low even after correction of height and skeletal maturation [17]. After adolescence, estrogen replacement therapy seems to be the single most important factor in maintaining peak bone mass. Since bone mass is improved but not normalized after hormonal therapy, an intrinsic bone defect is likely [20].

Cardiovascular abnormalities - The increased mortality in TS is primarily a result of its cardiovascular complications [21]. Congenital cardiac anomalies are common in females with TS, with a prevalence estimated to be between 23 and 40%: bicuspid aortic valve is the most common congenital malformation affecting the heart, it can occur as isolated or in combination with other congenital heart anomalies such as aortic coarctation, partial anomalous venous drainage and mitral valve prolapse [22]. Coarctation of the aorta affects approximately 10% of women with TS and is an important cause of hypertension: it may be the result of the abnormal lymphatic flow in TS altering intracardiac blood flow by compressing the ascending aorta. Aortic coarctation, providing it is the only cardiac abnormality, is usually surgically corrected in childhood with excellent results [23]. Aortic root dilatation is thought to occur with a prevalence estimated to be between 8 and 42%: sometimes it can be the cause of aortic dissection and sudden death in TS females [24].

The risk of hypertension is increased 3-fold in women with TS. It is estimated to occur in 7–17% of girls and 24–40% of women with TS. There does not appear to be an association with karyotype, and it is hypothesized that hypertension is secondary to small vessel renovascular disease [2], as elevated renin activity has been shown in hypertensive girls with TS before estrogen therapy is initiated. Estrogens seem to reduce hypertensive tendency [25].

Women with TS may be twice as likely to develop coronary artery disease compared with the general population. Women with TS have several risk factors for ischemic heart disease and atherosclerosis that include, in addition to hypertension, insulin resistance (affecting 10-34%) [26] and hyperlipidemia (up to 50% of TS women as hypercholesterolemia) [27].

Cognitive profile - Turner syndrome has also been shown to have a typical neurocognitive profile characterized by average to low-average full-scale intelligence quotient (IQ) scores with a significant disjunction between verbal and performance IQ, as well as the frequent occurrence of atypical social traits.

Most patients with TS have normal intelligence and identify as females. Many girls and women with TS have difficulties with visual-motor skills (i.e., writing and copying designs), visual-spatial skills (i.e., visual imagery, directional sense, map reading), visual attention, executive functioning, planning, and problem solving. Some individuals have difficulty interpreting non-verbal communication resulting in difficulties with socialization and coping with new situations. These findings tend to be more common among patients with 45,X karyotype [28, 29].

Immunological dysfunctions and other systemic diseases - The incidence of auto-immune disorders is increased among females with TS. Specific manifestations include auto-immune thyroid disease (both Hashimoto's thyroiditis and Grave's disease), celiac disease, inflammatory bowel disease, rheumatoid arthritis, and diabetes mellitus [30] The incidence of autoimmune thyroid disease in females with TS increases with age. Studies demonstrated a doubling in the prevalence of autoimmune thyroid disease from the first to the third decade of life [31]. Hypothyroidism should be treated promptly to avoid associated morbidity, particularly obesity and hypercholesterolemia. Also the risk of inflammatory bowel diseases (IBD), Crohn's disease and celiac diseases is doubled in women with TS. Women with the isochromosome Xq karyotype are particularly susceptible, accounting for 52% of the reported cases of IBD in women with TS. The causes of Crohn's disease and ulcerative colitis are not known, but immunological dysfunction is thought to play an important role [32].

The prevalence of structural renal abnormalities in TS between 25% and 43%. These abnormalities do not usually result in significant morbidity but they can increase the risk of urinary tract and renal infections [33].

The congenital craniofacial malformations and consequent distortion of the eustachian tubes and impaired ventilation of the middle ear predispose girls with TS to middle ear infections [34].

Malignancy - Abnormalities in gonad organogenesis can lead to the development of gonadal tumors,38 especially in patients with dysgenetic gonads [35]: cryptorchidism and gonadal dysgenesis were identified as risk factors for gonad germ-cell tumors. The precursor lesion for gonad cells tumors is gonadoblastoma who has the potential to progress towards invasive germ-cell tumors, particularly dysgerminoma in 50%, and, less frequently (10%) towards other tumors, such as embryonic carcinoma, teratoma, yolk sac tumor and choriocarcinoma [36]. Hyperandrogenism is a phenomenon commonly associated with gonadoblastoma, especially in cases of coexistence with dysgerminoma [37]: studies have demonstrated the presence of a specific gene associated with the development of gonadoblastoma on Y chromosome. Gonadoblastomas may produce sexual hormones such as androgens or estrogens, resulting in virilisation or feminization, respectively. The prophylactic excision of the gonads is indicated in all Turner mosaics with Y chromosome.

Craniofacial and oral features

The characteristic facies of a female with TS is also primarily due to skeletal malformations. These result in micrognathia, a high arched palate, hypertelorism (increased distance between eyes), epicanthus (a downward drop of the outer corner of the eyes) and low-set ears (Figure 1). A primary defect in bone formation is thought to exist in TS because of the numerous skeletal dysplasias associated with the syndrome propensity for osteoporosis [2]. In patients with DS tendency to develop a class II skeletal malocclusion associated with a clock-wise rotation of the mandible, is reported [38]. High arched palate and posterior monolateral/bilateral cross-bite are related to oral breathing and frequent respiratory infections [39].

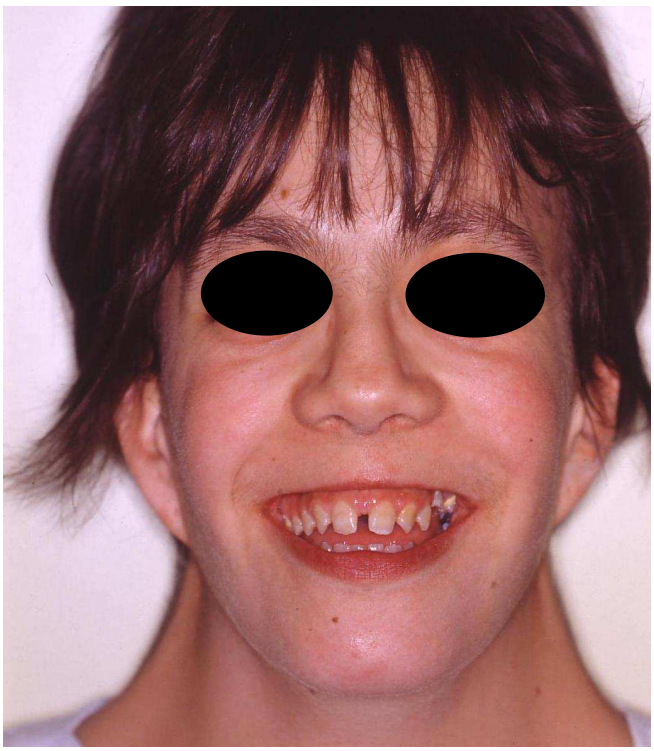

Figure 1. Typical TS face: hypertelorism epicanthus, low-set ears and large neck.

Dental anomalies are a typical feature of TS: regulator genes of odontogenesis are located on short arm of chromosome X (locus 22), resulting in alteration of the amelogenin gene (AMGX). Amelogenin is the enamel structural protein, and it is normally produced by odontoblasts. TS women can show quantitative and qualitative enamel anomalies such as shape anomalies (microdontia) and structural anomalies (enamel hypoplasia) [40]. In patients with TS, dental caries index (DMFT) results to be higher, such as parodontal disease, gingivitis associated to high plaque index levels (PL) are frequent features[41].

DATA COLLECTION

The sample consist in 17 patients affected by Turner's Syndrome, aged from 5 to 35 years, referred from the Pediatric and Auxology Department in Sant'Orsola Hospital in Bologna for a dental examination in the Dentistry for Special Needs patients Division (DIBINEM, University of Bologna). Most significant data were collected in the following table (Table Data Collection in Turner Syndrome girls) (page 84).

DATA COLLECTION TABLE IN TURNER SYNDROME GIRLS

	G	Name	age	Clinical features		Alimentary and oral hygiene habits			Dental features						Orthodontics features					
				Systemic diseases	CHD	Sweetened/die	Brushing /die	Systemic Fluoride	PI	dmft	DMFT	Tooth number anomalies	Structure anomalies	Shape anomalies	O.Br.	Oral habits	Dental malocc	Skelet malocc	OB	OJ
1	F	A.A.	5	no	yes	1	2	no	0.9	0	-	no	no	no	no	ciuccio	I	-	0	1
2	F	A.A.	14	delayed growth	yes	0	2	no	0.6	-	0	no	no	no	yes	Atypical swallowing	II	II	-1	2
3	F	B.N.	14	delayed growth	no	0	2	no	0.8	0	0	no	no	no	no	Atypical swallowing	III	III	4	1
4	F	B.S.	8	no	no	1	2	no	0.4	1f	0	no	no	no	yes	Atypical swallowing	II	II	-2	3
5	F	B.E.	16	no		0	2	no	1.7	-	3D4F	no	Enamel hypoplasia	no	no	Atypical swallowing	III	III	-1	
6	F	C.E.	18	delayed growth	no	1	2	no	1.6	-	7F	no	Enamel hypoplasia	no	yes	no	II	II	-3	5
7	F	D.A.	35	delayed growth; rheumatoid arthritis	no	0	2	no	2.1	-	8F	no	no	no	no	no	II	-	1	2
8	F	G.A.	15	otitis; tonsillitis	no	1	1	no	2.8	0	0	no	no	no	no	Atypical swallowing	II	II	2	4
9	F	G.L.	33	Severe mental retardation	no	2	0	no	0.5	-	3D	no	no	no	yes	Atypical swallowing	II	-	-2	6
10	F	M.M.	20	delayed growth; otitis; tonsillitis	no	0	2	no	2.6	-	0	no	no	no	yes	Atypical swallowing	II	II	3	3
11	F	M.L.	7	delayed growth otitis; tonsillitis	no	2	1	yes	0.3	1d	-	no	no	no	no	Atypical swallowing	II	-	3	6
12	F	P.E.	28	no	no	0	2	no	0.4	-	3F	no	no	no	no	no	I	-	2	1
13	F	P.P.	12	delayed growth	yes	0	2	no	0.8	0	0	no	no	no	no	no	II	II	2	3
14	F	S.M.	11	Otitis; bronchitis	no	1	2	no	0.9	2f	0	no	no	no	no	no	III	III	0	0
15	F	S.G.	8	delayed growth; otitis	yes	0	3	yes	1.2	0	0	no	no	no	no	Atypical swallowing	II	II	3	4
16	F	T.S.	28	delayed growth; otitis; tonsillitis; sinusitis	no	0	2	no	1.1	-	4F	no	Enamel hypoplasia	no	no	no	I	I	3	2
17	F	T.C.	13	delayed growth Down Syndrome	no	1	1	no	0.7	-	0	no	no	no	yes	Atypical swallowing	II	II	3	4

Table Legend: - (not evalualable), G (gender), CHD (congenital heart disease), SF (Systemic Fluoride), PI (Plaque Index), O.Br. (Oral breathing), Dental malocc (Dental malocclusion-Angle classification), Skeletal maloc (Skeletal malocclusion), OB (over bite), OJ (overjet).

RESULTS

The sample consist in 17 females with TS (TS type is not specified). The main is 16.8 ± 9.1 years (age range 5-35).

Medical history

At the time of the visit eleven subjects (64.7%) declare to have had or actually have growth dysfunctions: 8 subjects were currently under growth hormone (GH) therapy; three subjects (more than 28 years old) had already completed GH therapy. Four subjects had congenital heart diseases (23.5%), and all of them need antibiotic prophylaxis during surgical procedures or professional dental hygiene. Five subjects (29%) had recurring otitis associated to upper respiratory system infections (sinusitis, tonsillitis, bronchitis). One subject showed severe mental retardation, one subject had rheumatoid arthritis and one girl was also affected with Down syndrome.

Alimentary habits and oral hygiene

Eight subjects consumed sweetened food and beverage 1-2 times/day, the other subjects declare to avoid eating or drinking sugary food or beverage. All the subjects of the sample, excluding the one affected by severe mental retardation, brushed their teeth every day, with an average frequency of tooth brushing/day of 1.8 ± 0.7. Only two subjects had taken tablets or lozenges of fluoride, the other fifteen used fluoride toothpastes.

Oral examination

The average Plaque Index was 1.1 ± 0.8. The dmft index, calculated on deciduous dentition, was evaluated considering 8 subjects: average dmft was 0.5±0.7. The average DMFT index, calculated on permanent dentition and evaluated considering 15 subjects, was 2.1±3.0.

Dental anomalies were rarely found in our sample. Dental agenesis or shape abnormalities were not observed. Three subjects on total sample (17%) showed enamel defects: a mild enamel hypoplasia diffused almost to all teeth, without structural severe enamel loss. Those subjects revealed a higher DMFT result respect to other subjects of the sample (DMFT>4).

Dental and skeletal malocclusions were found in 15 subjects (82%): class II malocclusion had an higher prevalence in the sample (64%) than class III malocclusions (17%). Malocclusions are all associated to underdeveloped maxillary bone and narrow palate. Bilateral posterior cross-bite were occasionally present. Open bite (OB <0) was found in five subjects.

DISCUSSION

The collected data regarding systemic clinical features are in line with the literature: 65% girls of the sample have or had had growth disturbances in therapy with GH, 23.5% are affected by congenital heart diseases and 29% by recurrent respiratory infections. Also eating and tooth brushing habits, PI results are similar to non-syndromic population. The reason could be that TS girls usually do not present mental retardation or difficulties in collaboration in oral hygiene and dental procedures. On the contrary, the average DMFT scores results higher than non-syndromic population: it's important to underline that the average score is increased in those subjects who presented with severe enamel defects and was associated to DMFT higher than 4.

Malocclusions affected the 85% of the sample and were mainly of the skeletal and dental class II type, characterised by maxilla underdevelopment, mandibular clockwise rotation, narrow palate and an open bite. Oral breathing related to recurrent respiratory infection may have a role in worsening the open bite.

PREVENTION AND TREATMENT PLAN

An individual and intensive prevention and/or treatment plan was elaborated for each subject.

General guidelines:

1) Oral hygiene instruction and correct dietary advices to parents/guardian and patients affected by TS (e.g. to recommend the use of fluoride toothpaste, with the correct fluoride concentration in according to the patient age, for a topical domiciliary fluoride prophylaxis);
2) Psychological approach in order to gain patient's confidence, when possible. "Soft Constraint": in case of poor collaboration, parents/guardians may help clinicians in containing patient during dental procedures.
3) Professional oral hygiene and recall visit every 3-6 months;
4) Fissure sealants of permanent molars (first and second permanent molars);
5) Interceptive and/or comprehensive orthodontic treatment in patients with optimal oral hygiene levels. Rapid maxillary expanders (REP) are usually used to correct narrow palates; while bite blocks or functional activators are used to correct open bite and skeletal malocclusions, respectively.

Special guideline for TS:

1) GH therapy may speed up growth process: in those case orthopaedic-orthodontic treatment should be planned considering each single patient response to GH therapy.

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Chapter 9

WILLIAM'S SYNDROME

Definition and epidemiology

Williams syndrome (WS), also known as Williams-Beuren syndrome, is a multisystem disorder involving the cardiovascular, connective tissue and central nervous systems; resulting in mild to moderate mental retardation [1]. It's considered a "rare disease" for its very low incidence: it occurs approximately in 1 over 10.000 live births [2].

Diagnosis

The microdeletion of q.11.23 region on chromosome 7 is responsible of WS syndrome, and it causes the loss of 26-28 genes, including ELN gene coding for protein elastin [3]. Hemizygosity of the ELN is responsible for the vascular pathology in WS, the remaining 25 to 27 deleted genes contribute to other phenotypic findings in patients with WS [4]. The first diagnosis of Williams–Beuren syndrome is usually made by the clinician who recognizes signs and symptoms in babies and children. In 95% of the cases, fluorescence in situ hybridization (FISH) establishes the diagnosis of Williams–Beuren syndrome, only in 5% of the cases the microdeletion is so minimal to be invisible to this test [5]. Prenatal screening is possible by amniocentesis and villocentesis ,however these tests are recommended only for familiar risk.

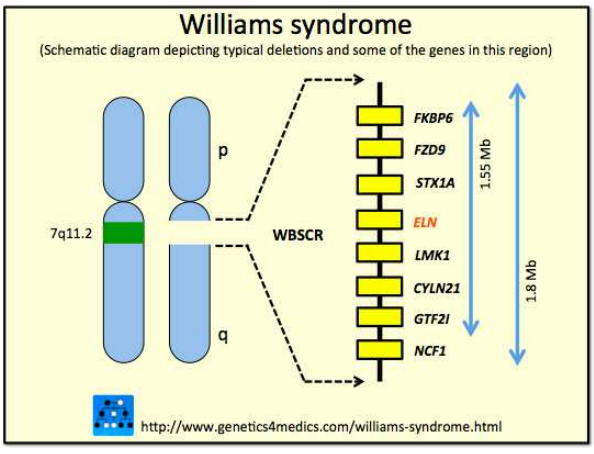

Figure 1. Genes involved in WS on chromosome 7.

Clinical features

As a result of the size of the deletion, WS has numerous clinical findings: cardio-vascular abnormalities, endocrine abnormalities, characteristic facial features ("elfic face") (Figure 2) and a typical behavioural profile are the most common features.

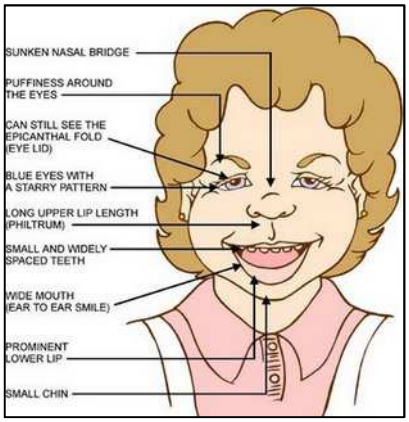

Figure 2. Characteristic "elfic face".

Cardiovascular anomalies such as vascular stenosis, valve abnomarmalities and hypertension are common findings. Supravalvular aortic stenosis occurs in almost 70% of patients affected by WS [6]. Hypertension, in 50% of adults appears as idiopathic hypertension and it rarely appears in childhood. Hypertension is due to renovascular stenosis, in which is surgically repairable [7, 8].

Among endocrine disorders, the most frequent findings are hypercalcemia, diabetes mellitus and hypothyroidism. Hypercalcemia has been reported in 5 to 50% of patients with WS: it's usually mild (calcium levels up to 11,5 mg/dl) but it can be more severe in infancy. Hypercalcemia can be asymptomatic or associated to nonspecific symptoms [9, 10]. Glucose intolerance and diabetes mellitus- type II was reported in several adults, which can be related to obesity because many subjects with WS have a body-mass-index (BMI) greater than 25 [11]. Newborns may have feeding difficulties due to sickness, vomiting and gastro-esophageal reflux [12].

In the recognition of the syndrome, the characteristic "elf-like" facial appearance, can be helpful: children show full prominent cheeks, a small upturned nose with prominent flat nasal bridge, periorbital puffiness, long philtrum, whereas older patients have slightly coarse features, with full lips, a wide smile, and a full nasal tip (Figure 1,2) [13].

General muscular hypotonia causes difficulties in motor skills, movement coordination and serious growth delays resulting also in microcephaly and short stature (in adulthood men average height is 159 cm and women 147 cm) [14]. Young children have delays in acquisition of early motor skills and in achievement of language. Standardized testing in older children and adults demonstrates a full-scale IQ averaging 50 to 60 (ranges from 40 to 100), indicative of mild-to-moderate intellectual disability [15].

Subjects with WS have a distinctive cognitive profile, strength in language and face-processing and very weak in visuospatial and problem solving abilities [13]. The behavioural profile is characterized by a "hypersocial attitude", extremely confidential, sometimes intrusive, also with unknown people [16].

Craniofacial and oral features

Dental (Class II and III) and skeletal malocclusions occur in 85% of subjects with WS. Due to masticatory muscles and tongue hypotonia, frequently tongue has a low posture causing growth-deficit of the maxilla, arched palate, mouth breathing, open bite and lip incompetence (Figure 3) [17]. Dental eruption is usually delayed and it's related to a general growth delay [18]. The 40,5% of subjects with WS are affected by dental agenesis, 40.5% with more than one tooth missing, 11.9% with more than 6 teeth missing [19]. Dental shape anomalies, as conoid-shaped teeth or microdontia (short and thin dental roots) , are described in 12.5% of deciduous teeth and 40.7% permanent teeth of WS subjects. Enamel defects in tooth in the deciduous and permanent dentition are also common [18].

Dental caries incidence in WS is higher compared to non-WS population: gastro-esophageal reflux and enamel hypoplasia can be risk factors [18].

Periodontal diseases is hypothesized to be related to elastin protein abnormalities. Periodontal disease is described in many WS subjects affected by WS. Elastin is the main gingival structural component and is the major component of the parodontium to allows parodontal tissue resistance to trauma. In cases of low level of dental hygiene and plaque accumulation, gingival hypertrophy and periodontal pocket are described [20].

DATA COLLECTION

The sample consist of 10 patients affected by Williams-Beuren Syndrome referred from the Pediatric and Auxology Department in Sant'Orsola Hospital in Bologna for a dental examination in the Dentistry for Special Needs patients Division (DIBINEM, University of Bologna). Most significant data were collected in the table (Data Collection Table in Williams Syndrome subjects).

RESULTS

The sample consist in 10 patients, 3 males and 7 females. The mean is 12.1 ± 6.7 years (age range 5-27 years).

Medical history

Seven subjects had congenital heart diseases (70%), and all of them were indicated for antibiotic prophylaxis during surgical procedures or professional dental hygiene. Five subjects showed mild to moderate mental retardation, one subject was affected with hypothyroidism and one subject affected with celiac disease.

Alimentary habits and oral hygiene

DATA COLLECTION IN WILLIAMS SYNDROME SUBJECTS

	G	Name	Age	Clinical features		Alimentary and oral hygiene habits			Dental features						Orthodontic features					
				Systemic features	CHD	Sweetened /die	Brushing/die	FS	PI	dmft	DMFT	Tooth number anomalies	Structure anomalies	Shape anomalies	O. Br.	Oral habits	Dental maloccl	Skeletal maloc	OB	OJ
1	M	C.D.	5	no	yes	2	no	No	1.8	4d	-.	-	no	no	no	pacifier	I	-	3	2
2	F	C.C.	13	no	yes	2	3	No	1.1	2f	1F	no	no	no	no	Atypical swallowing	II	I	-2	2
3	F	D.R.	18	no	yes	0	1	No	0.4	-	2F	-3	no	no	no	no	II	II	1	9
4	F	G.E.	8	Hypothiroidism	yes	0	2	No	2.7	0	0	-2	no	no	no	no	I	-	0	0
5	M	M.R.	27	Mild mental retardation	yes	3	2	yes	1.7	-	3D	-2	no	microdontia	no	no	III	III	3	-3
6	F	M.C.	15	Respiratory infections	yes	2	3	No	0.8	-	0	no	no	no	yes	Atypical swallowing	I	III	2	2
7	F	N.A.	10	Mild mental retardation	no	No	1	yes	0.6	0	0	-2	no	no	no	no	I	I	2	2
8	F	T.E.	6	Mild mental retardation	no	No	1	no	0.9	0	0	-1	no	no	no	pacifier	III	-	0	1
9	M	T.F.	12	Severe mental retardation	no	No	1	no	2.8	0	0	no	no	no	no	no	III	-	0	0
10	F	T.C.	7	Mild mental retardation Celiac disease	yes	2	no	no	2.3	1d	-	-	yes	no	no	pacifier	III	-	-2	0

Table Legend: - (not evalualable), G (gender), CHD (congenital heart disease), SF (Systemic Fluoride), PI (Plaque Index), O.Br. (Oral breathing), Dental malocc (Dental malocclusion-Angle classification), Skeletal maloc (Skeletal malocclusion), OB (over bite), OJ (overjet).

Five subjects consumed sweetened food and beverages more than 2 time/day. Eight subjects of ten, brushed their teeth every day, with an average frequency of tooth brushing/day of 1.4 ± 1.1. Only two subjects had taken tablets or lozenges of fluoride, the other six used fluoride toothpastes. Two subjects rarely brushed their teeth and didn't take any kind of fluoride prophylaxis.

Oral examination

The average Plaque Index was 1.5 ± 0.9. The dmft index, calculated on deciduous dentition, was evaluated considering 7 subjects: average dmft was 1.0±1.5, with a higher prevalence of decayed teeth compared to filled or missing teeth. In eight subjects with permanent dentition, the DMFT index was 0.75±1.16 on average.

Dental agenesis was evaluated in 8 subjects: two of the patients were too young for panoramic x-ray exposure. Five subjects (62.5%) had dental agenesis of permanent teeth, with 10 missing teeth totally. One subject showed just one congenitally missing tooth, the others multiple missing teeth. Among all teeth upper and lower second premolars and lower lateral incisors were missing in 70% and 30% respectively. One subject showed enamel hypoplasia and another showed microndontia, with thin tooth crowns, short roots and diastemas.

Malocclusion were evaluated in 9 subjects, one subject (age 3 years) was excluded for the young age. Seven subjects (78%) showed a skeletal class III malocclusion (44%) while showed a skeletal class II malocclusion(22%). Open bite (OB <0) was found in two subjects and anterior crossbite in 3 subjects with dental and skeletal class III malocclusion.

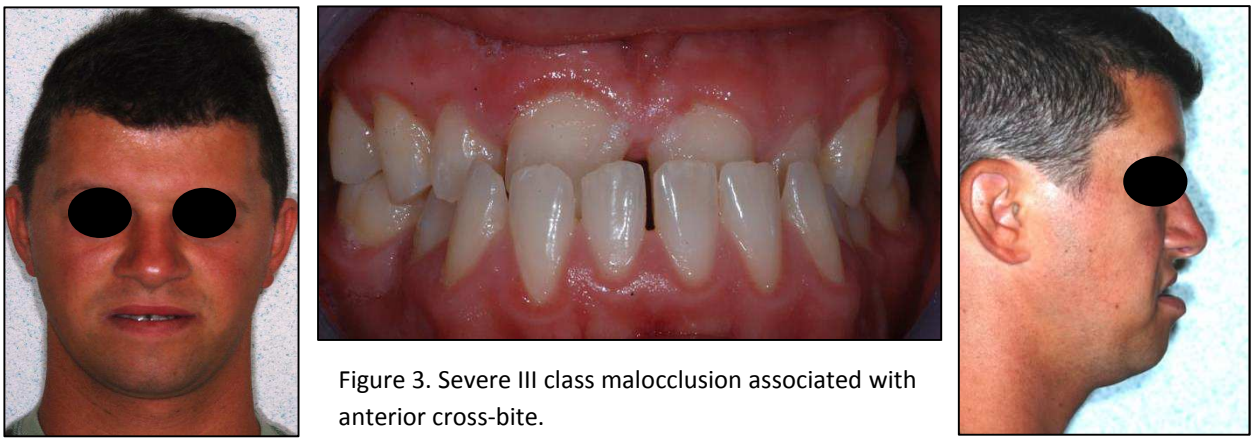

Figure 3. Severe III class malocclusion associated with anterior cross-bite.

DISCUSSION

The data of our sample, due to its limited number was compared to data from literature. Considering the high percentage of patients affected by congenital heart diseases, antibiotic prophylaxis is indicated before surgical procedure for every patient. Oral hygiene instructions and motivation is indicated for every and the patients themselves: the average frequency of toothbrushing/day (1.4) is too low respect to the 2-3 times a day advised. Comparing results of our WS sample to non-syndromic population, Plaque Index results reveal a poorer oral hygiene level compared to non-syndromic population probably due to a lack in manual dexterity. Dmft/DMFT index average values seem to be similar to the non-syndromic population. Tooth agenesis have a high prevalence (62.5%) and usually lateral incisors and premolars are congenitally missing leading to spaced dentitions.

Similarly to data found in literature, malocclusions occurred in 78% of WS patients. A skeletal class III malocclusion associated with to underdeveloped maxillary bones and anterior cross bitewas the most common finding. Early detection and treatment of malocclusion is strongly recommended.

PREVENTION AND TREATMENT PLAN

An individual and intensive prevention and/or treatment plan was elaborated for each subject based on his own clinical features.

General guidelines:

1) Oral hygiene instruction and correct dietary advices to parents/guardian and patients affected by WS (e.g. to recommend the use of fluoride toothpaste, with the correct fluoride concentration in according to the patient age, for a topical domiciliary fluoride prophylaxis);
2) Psychological approach in order to gain patient's confidence, when possible. "Soft Containing": in case of poor collaboration, parents/guardians may help clinicians in containing patient during dental procedures.
3) Professional oral hygiene and recall visit every 3-6 months;
4) Fissure sealants of permanent molars (first and second permanent molars);
5) Interceptive and/or comprehensive orthodontic treatment in patients with optimal oral hygiene levels. Rapid maxillary expanders (REP) are usually used to correct narrow palates; while bite blocks or functional activators are used to correct open bite and skeletal malocclusions, respectively.

Special guidelines for WS:

1) Also in case of poor collaboration and severe anxiety, local anaesthesia procedures are preferred to general anaesthesia for an increased risk of respiratory failure. General anaesthesia procedures should be planned evaluating risk & benefit ratio;
2) Prompt caries therapy especially in patients to avoid endocarditis and extractions, especially in cases of congenitally missing teeth;
3) In patients with enamel defects or erosion due to gastro-oesophageus reflux, professional application of fluoride varnish every 3 months, fluoride toothpaste and fluoridated gel or foam on tooth surfaces with defects;
4) Orthodontic treatment plan considering dental agenesis management in young patients or implant/prosthetic treatment plan in adults.

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