the Child Dental Patient with

22q11.2 deletion (DiGeorge Syndrome)

Pr Marie-Cécile Manière
Dr Yves Alembik (paediatrician, geneticist)

Les Hôpitaux Universitaires de STRASBOURG

European Reference Network
for rare or low prevalence complex diseases
Network
Craniofacial anomalies and ear, nose and throat disorders (ERN CRANIO)
Member
Hôpitaux Universitaires de Strasbourg — France

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Definition and epidemiology

- Also named : **DiGeorge syndrome** (1st description in 1960) or **Velocardiofacial Syndrome**
- 22q11.2 deletion syndrome (22q11.2DS) is the most common microdeletion syndrome, with an estimated prevalence of 1/3000 to 1/10 000 children
- This congenital malformation and neuropsychiatric disorder has a **variable phenotype and affects multiple systems**:
  - congenital heart disease
  - immunodeficiency
  - hypoparathyroidism
  - palatal, gastrointestinal, skeletal and renal abnormalities
  - characteristic facial features
  - developmental and speech delay
  - behavioural phenotypes
  - increased risk for psychiatric illness.

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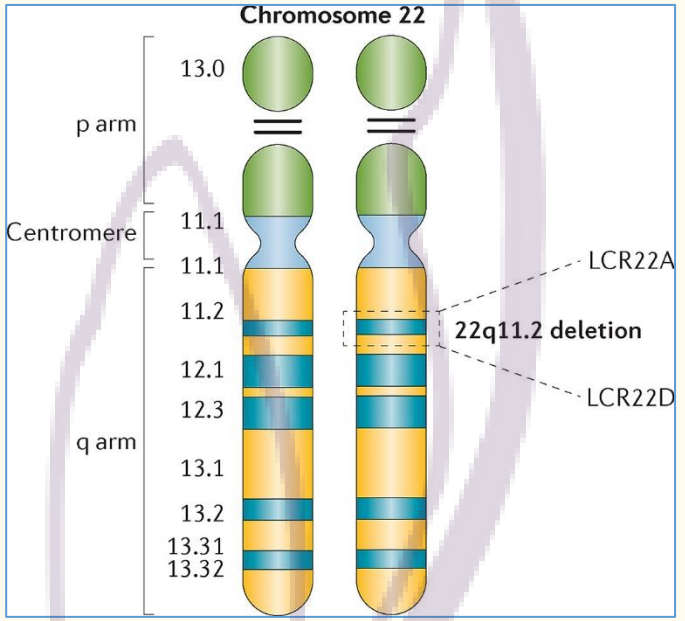
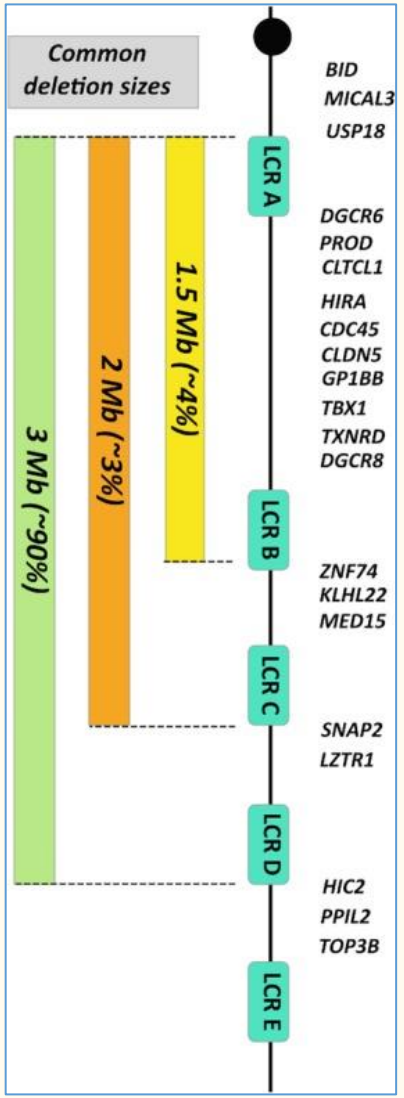
Etiology - Genetic aspects

- In most cases, the syndrome is due to a 3 million base pair (Mb) deletion on the chromosomal region 22q11.2 that is flanked by low copy number repeats.
- 90–95% newly identified patients with 22q11.2DS are found to have *de novo* deletions.
- Most deletions include the *TBX1* gene that has been shown to be implicated in cardiac, parathyroid, thymus and facial structure development.
- Early diagnosis, preferably prenatally or neonatally, could improve outcomes.
- Lack of recognition of the condition and/or lack of familiarity with genetic testing methods, together with the wide variability of clinical presentation, delays diagnosis





Clinical description

- The most common **heart defects** are:
  - tetralogy of Fallot (with or without pulmonary atresia)
  - truncus arteriosus
  - aortic arch anomalies
  - ventricular septal defect
  - pulmonary artery anomalies
- **Immunodeficiency** affects up to 75% of paediatric patients with 22q11.2DS owing to thymic aplasia/hypoplasia and impaired T cell production. Manifestations of immunodeficiency include:
  - chronic infections
  - impaired humoral (antibody) immune response resulting in poor response to vaccines
  - IgA deficiency
  - allergy and asthma
  - higher risk of developing an autoimmune disease such as idiopathic thrombocytopenic purpura and juvenile idiopathic arthritis
- **Hypocalcemia** as a consequence of hypoparathyroidism is frequent in the neonatal period and usually resolves but can reappear at any age.
- **Learning difficulties** and **developmental delay** are almost always present.
- Children with 22qDS, with or without obvious palatal anomalies, are at higher risk for otitis media with effusion and eustachian tube dysfunction with resulting **conductive hearing loss** (ranging from 6.0% to 60.3%).
- **Psychiatric illness** and Parkinson's disease are more frequent than in the general population.

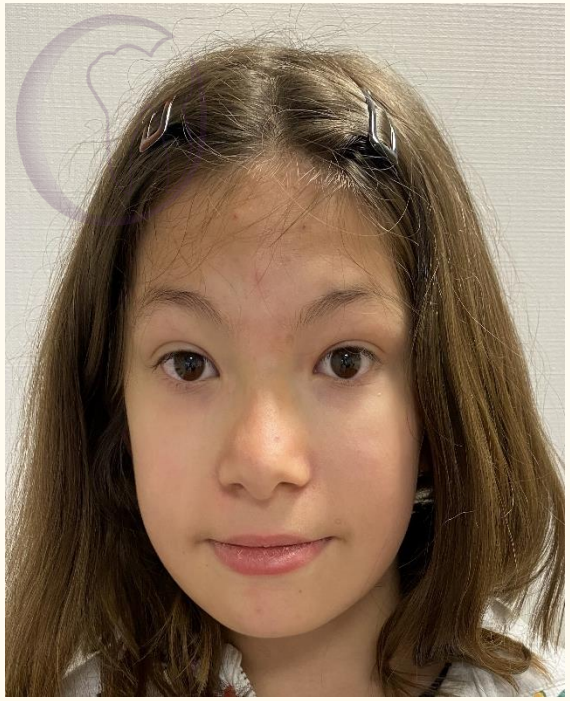
Neurocognitive and psychiatric profile

- **Complex and highly variable**, both between individuals and during the course of development.
- Infancy and early childhood:
  - gross and fine **motor delays** (often with hypotonia)
  - **speech-language deficits**
- Preschool and primary school ages:
  - **learning difficulties**
  - **impairments** in sustained attention, visual-spatial processing, working memory, arithmetic, executive functioning, abstract thinking, processing new and complex information
  - impulsivity, difficulty in psychosocial functioning
- The majority of patients with 22q11.2DS have an intellectual level that falls in the borderline range (IQ 70-84), and about one-third have mild to moderate intellectual disability (IQ: 55-75).

- **Autism spectrum disorder** and subthreshold autistic symptomatology also show increased prevalence ranging from 20% to 50%.
- In adolescence and young adulthood, **psychiatric illness** includes:
  - **anxiety disorders**
  - attention-deficit/hyperactivity disorder
  - **poor social skills** (40-50%)
  - an elevated risk of bipolar disorder and major **depression**
- A strong and specific relationship exists between the presence of the 22q11.2 deletion and **schizophrenia** (30-40%). *This risk is not associated with any other neurogenetic syndrome.*
- Social cognition is impaired in 22q11.2 DS and this observation is correlated with psychotic features.

Clinical description: mild dysmorphic facial features

- Most patients display subtle but recognizable facial features:
  - ptosis
  - hooded eyelids with upslanting palpebral fissures ± epicanthal folds
  - hypertelorism
  - malar or midfacial flatness
  - auricular anomalies including thick overfolded helices, protuberant ears, preauricular tags/pits
  - microtia and anotia
  - bulbous nasal tip with hypoplastic alae nasi ± a nasal crease or dimple
  - small mouth and micrognathia



Palatal abnormalities concern more than 65% of the patients

- Only 11% of paediatric patients have overt cleft palate, of whom 1–2% have cleft lip or cleft palate, and fewer have Pierre Robin sequence.
- **Milder malformations** are common:
  - submucous cleft palate
  - bifid uvula
  - velopharyngeal dysfunction (incompetence)
- Initial signs may only include a history of nasal regurgitation.
- **Feeding and/or swallowing disorders** are common and have been reported in 35%–68% of children.
- Later, symptoms include abnormal nasal resonance and nasal emissions.

Airway and voice

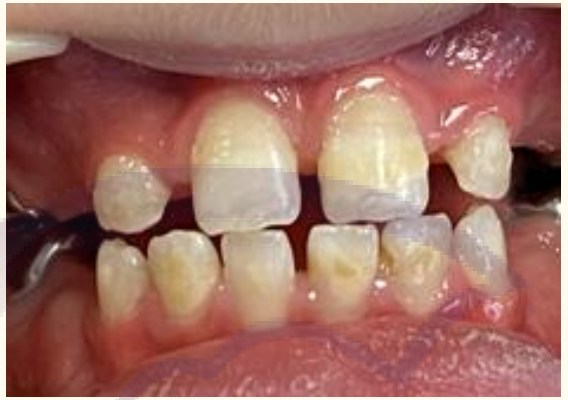
- The palatal anomalies may lead to hypernasal speech.
- Disorders of the upper and lower airway, often seen in children with 22qDS, include vocal nodules, unilateral vocal fold paralysis, laryngeal web, subglottic stenosis, laryngotracheomalacia, and vascular ring.
- Voice disorders, such as decreased loudness, hoarseness, breathiness, tension, vocal fatigue, strained–strangled voice, and high pitch, are relatively common.

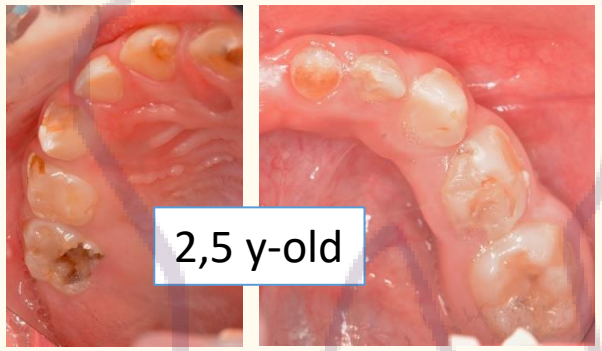
Medical management

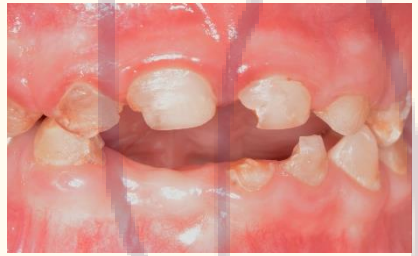
- Management is symptom-based and requires a **multidisciplinary approach** involving paediatrics, general medicine, surgery, dentistry, psychiatry, psychology, interventional therapies and genetic counselling.
- It may consist of:
  - heart and/or palate surgery
  - nasogastric feeding
  - calcium supplementation
  - occupational, physical, and speech, language therapy
  - educational and behavioral therapy
  - support and treatment for psychiatric disease
  - tonsillectomy is not recommended unless indicated by a center of expertise
  - a regular surveillance of calcium, thyroid function and blood cell count is necessary
  - immune function must be evaluated before administering live vaccines.
- **Speech-language pathologists** may be among the first professionals to be consulted in children with 22qDS because of the high prevalence of feeding difficulties, speech-language delays, and disorders in infants and young children.
- Cognitive remediation is a promising tool for treating neuro- and social cognitive deficits in 22q11.2DS.
- The prognosis is variable and depends on the severity of the disease and on the degree of autonomy.

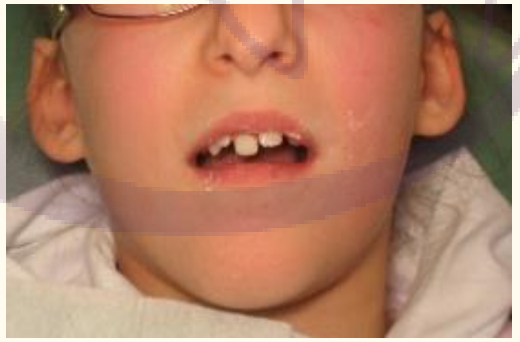
Oro-dental features

- Oral features are common to most patients with 22q11.2DS, including:
  - higher prevalence of tooth agenesis: the mandibular incisors, maxillary lateral incisors and maxillary second premolars as the main teeth affected
  - delayed tooth formation and eruption have also been reported
  - defects in the quality and quantity of enamel are also common findings, with a predominance of hypomineralisation, particularly in permanent teeth
- Oral manifestations include a high prevalence of dental caries and of gingival inflammation.
- Mouthbreathing is common, contributing to gingivitis.









Dental management – Risk assesment

If the child has	Risk management – What to do?
Cardiopathy with endocarditis risk Immunodeficiency	Contact the cardiologist or the referent specialist Assessment if the dental treatment is not contra-indicated and if specific precautions are necessary
Auto-immune disease (ex: idiopathic thrombocytopenic purpura) Hematologic disease	Determine if the dental treatment include a bleeding risk Apply the usual precautions to control the bleeding complications
Obtructive sleep apnoea	Obtain sleep history, consider polysomnography/referral to sleep center Evaluate the oral function and occlusion Orthodontic management could be necessary Sedation with midazolam could be contra-indicated
Clefts lip/ Cleft lip and palate/submucous cleft palate	Assess for nasopharyngeal reflux Refer to Cleft Palate Team if necessary Management of the cleft or velopharyngeal insufficiency need healthy dental supports (orthodontic or surgery treatment, speech therapy)
Modification of the salivary flow and/or of the composition of the saliva	Reinforce the preventive measures Recommend fluoride toothpaste use, fluoride varnishes application Diet recommendation
Dental anomalies: enamel defects, hypoplasia, hypomineralization	Assess the hypersensibility Protect the enamel (sealants, composite, pediatric crowns…) Early esthetic restorations should be proposed
In all cases, enforce a preventive program in order to limit the infectious complications of dental origin	

Behavior management

- To **reduce the behavioral problems in the dental setting**, the dentist should :
  - understand the psychopathological changes: intellectual disability, language deficits, poor responsiveness to simple questions, impulsivity, autism spectrum disorders, self-injuries…
  - know the medication taken (*antidepressant and ADHD medication for example*)
  - simplify the “dental” language
  - ensure instructions are understood
  - emphasise nonverbal communication
  - use a picture exchange communication system for certain patients
  - collaborate with the speech-language pathologist.
- Behavior management with **sedatives** could be considered.

Behavior management - GA considerations

- **General anesthesia** should be indicated in case of extensive caries, poor cooperation and to control the oral infection:
  - complications such as seizures and difficult intubation may arise more frequently in patients with 22q11.2DS than in typical patients when GA is administered
  - careful perioperative and postoperative monitoring of ionised calcium, oxygen levels and heart rate as well as the use of smaller intubation equipment should be regularly practised
  - before indicating a sedation or GA, a close consultation with specialists and anesthesiologists is essential.

Dental management - Prevention

- Patients with 22q11.2DS have an increased risk of dental caries and gingival inflammation. Therefore, preventive strategies and therapeutic interventions should be **planned early** for such patients.
- First dental visit as early as possible:
  - thorough clinical history
  - assessment of oral diseases and of caries risk
  - evaluation of ability to cooperate
- Observation of basic prevention guidelines from the first year of life:
  - good levels of oral hygiene
  - application of topical fluoride varnishes
  - low sugar diet
  - frequent preventive dental appointments.

Conclusion

- The combination of persistent language deficits, social communication impairment, speech disorders, cognitive and behavioral disorders makes the communicative profile of this syndrome unique and treatment especially challenging.
- Dental care is an essential part of the multidisciplinary therapeutic approach of children with deletion 22q11.
- Being in contact with a parents' association may be very helpful for dental management.

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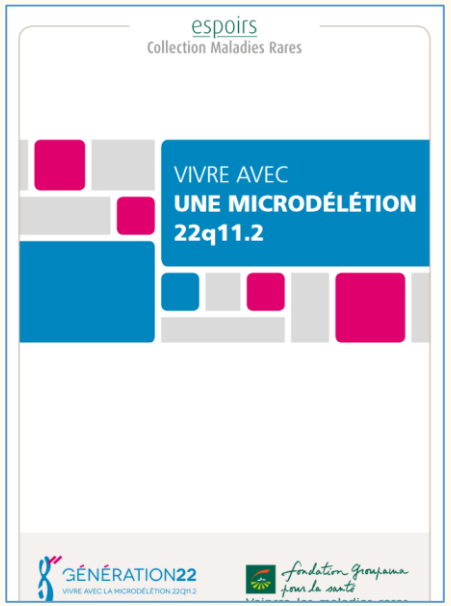

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