Are there dental and medical characteristics of children with 22q11 syndrome that may impact on their oral health?

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Abstract:

2211 deletion syndrome, a collective term for Di George syndrome and velocardiofacial syndrome is the most common deletion syndrome in humans. An incidence of 1 per 4,000 live births and the fact that 85% of deletions occur de novo means that Irish general dentists will encounter this condition, although a marked phenotypic variation means that diagnosis is often missed or delayed.
This article provides an overview of the syndrome, highlighting common features and reviews the existing literature exploring medical and dental features of the syndrome which may impact upon the oral health of patients with 22q11 deletion syndrome.

Clinical Relevance:

22q11 deletion syndrome is the most common deletion syndrome in humans, its incidence of 1 per 4,000 live births means that most GDPs in Ireland may have a patient with 22q11s in their population. Due to phenotypic variability and the fact that 85% deletions occur de novo diagnosis is often delayed or missed, for this reason it is important to make practitioners aware of the syndrome as they may be ideally placed to recognise features of the syndrome in their patients.
Furthermore with improvements in medical science these children now live into adulthood; mostly with only minor learning difficulties and physical limitations. There is no reason why a GDP cannot treat such a patient, this article aims to educate practitioners about 22q11s, alleviating the ‘fear of the unknown’ which may be a barrier to the delivery of treatment.

Introduction

The WHO defines oral health as:

"A state of being free from chronic mouth and facial pain, oral and throat cancer, oral sores, birth defects such as cleft lip and palate, periodontal (gum) disease, tooth decay and tooth loss, and other diseases and disorders that affect the oral cavity."[1]

22q11 syndrome (22q11s) is a collective term for DiGeorge syndrome[2] and Velocardiofacial syndrome[3] though conotruncal anomaly face syndrome is the preferred terminology in Japan[4].

These syndromes were thought to be separate entities until the development of fluorescent in-situ hybridisation (FISH) analysis in the 1990s revealed the genetic defect of a microdeletion at chromosome 22q11.2 as the common aetiological factor. This group of disorders demonstrate marked phenotypic variability, which may explain their initial categorisation as separate clinical entities.[5]

McDonald-McGinn et al. from the Children's Hospital of Philadelphia have produced a volume of work on 22q11S and have classified the presentation into disease characteristics and additional findings:

Table 1: Disease Characteristics and Additional Findings in 22q11s.[6]

Disease Characteristics	**Additional findings**
Congenital heart disease (74%),	Hypocalcaemia (50%),
Palatal abnormalities (69%),	Renal anomalies (31%)
Learning difficulties (70-90%)	Hearing Loss
An immune deficiency (77%).	Laryngotrachealoesophageal anomalies
Characteristic facial features (demonstrated in the majority of individuals of a European lineage),	Growth hormone deficiency
	Autoimmune disorders
	Seizures
	CNS anomalies including tethered cord
	Skeletal abnormalities (scoliosis, craniosyntosis, club foot
	Opthalmic abnormalities
	Enamel hypoplasia
	Malignancies (rare)

22q11s is one of the most common syndromes of multiple anomalies.[7] Considered to be underestimated given the phenotypic variability and diversity of presentation, its incidence has been reported as 1 per 4000[8] to 1 per 5000.[9] Irish general dentists will encounter children with 22q11s, in a year such as 2012 with 17,225 births[10] there will have been 18 occurrences of 22q11s. It is autosomal dominant in inheritance although up to 85% of deletions occur de novo, penetrance is complete but a marked phenotypic variability is displayed.[11] The phenotypic variability of 22q11s combined with high proportion of de novo deletions mean that presentation can be widely varied and thus diagnosis significantly delayed.

The Evidence

The variability of phenotype and degree of genotype-phenotype discordance[5,11] results in variable presentations of 22q11s. The highly prevalent characteristics of 22q11s will be discussed along with less common characteristics which may impact on oral health.

Most cases of 22q11s are identified through paediatric cardiology units.[11] Congenital heart defects in 22q11S typically involve conotruncal defects of the outflow tract: Tetralogy of Fallot(20%), Interrupted Aortic arch – usually type B(13%) and Ventricular Septal Defect(10%).[6] Cardiac abnormalities are also the major cause of mortality from 86%[12] to over 90%.[5]

A substantial proportion of patients presenting with such cardiac anomalies demonstrated a deletion at 22q11.[13] In light of the other comorbidities seen in 22q11s, diagnosis of which may be delayed, a typical cardiac defect is sufficient grounds to investigate for 22q11 deletion.[11,13] However, studies from Europe have shown cardiac abnormalities are less frequent[11,12] demonstrating a risk of diagnostic delay if cardiac abnormalities alone are relied upon as a means of screening.

Cardiac abnormalities may impact dental management; national guidelines may necessitate prophylactic antibiotic cover for invasive treatment.[14-16]

Learning difficulties and developmental delay are the second most common route to diagnosis of 22q11s.[11] Delayed speech or walking and motor milestones are widely

reported in the early years[17] By school age a discrepancy between verbal and non-verbal intelligence develops, with reduced non-verbal IQ which may hinder learning tasks such as tooth brushing.[18,19] There are differing reports within the literature regarding the prevalence of developmental delay and learning difficulties in 22q11s with severe learning difficulties in 38%[12] but some degree of intellectual impairment in 96%.[11]

Psychiatric illness is common also, with up to 60% of patients recorded as having mental illness. Problems range from anxiety and attention deficit disorder to bipolar disorder and Schizophrenia (present in up to 25% of cases).[20] Oral health of patients with mental illness has been shown to be sub-optimal with increased DMFT scores, increased prevalence of xerostomia, periodontal disease and poor oral hygiene, compounded by barriers to attainment of oral care.[21]

DiGeorge syndrome was initially described as an immunodeficiency syndrome[22] with predominantly T cell deficiency accounting for humoral defects in 22q11s[22-24] Recurrent or severe infections are a recognised part of the syndrome, immunocompromise is present in 77%[24] to 81%[22]. The severity of the effect of immunodeficiency wanes as patients age, while many still suffer recurrent infections into young adulthood very few require active medical management of immunodeficiency.[25] Autoimmunity is also an increasingly recognised phenomenon with Juvenile Rheumatoid Arthritis and acytopaenias seen most commonly.[22,26-28]

Hypoparathyroidism is present in 30%[29] and Hypocalcaemia is reported in 17-60%.[12,30] Typically, hypocalcaemia is most serious as a neonate and normalises with growth[31] although presentations are heterogeneous and present a diagnostic challenge,[32,33] with spontaneous progression or resolution without recognised cause.[32,34] Graves' disease is also purported to be part of the clinical spectrum of 22q11s.[35]

22q11s is one of the most common syndromes associated with clefts of the secondary palate.[36] Although overt cleft lip is rare, two large scale studies found palatal abnormalities to be present in 46%[12] and 69%[30] velopharyngeal

incompetence being the most common in both. Alterations in velopharyngeal anatomy[37] in 22q11s are responsible not only for velopharyngeal dysfunction which can lead to feeding and speech problems, but a higher incidence of secondary and revision procedures following primary repair.[38] It should be noted that the link between 22q11s, feeding problems and failure to thrive is not due to palatal or cardiac abnormalities alone: 36% have feeding problems independent of the above.[30]

Nugent et al in 2010 produced a study outlining the experience of the Cleft unit in Dublin, concluding that though clefts due to 22q11s made up a small proportion of patient load, it was a significant population which benefited from early recognition and referral to other disciplines for specialist management given the diverse and complex phenotype.[38]

Dental characteristics of 22q11s are numerous, multifactorial and interrelated. Abnormalities of the dentition are common, including: Anomalies of tooth shape, number and eruption, enamel anomalies such as hypomineralisation and hypoplasia, in addition to an increased risk of caries in this patient group.[39]

The first comprehensive picture of oral manifestations of 22q11s was produced by Klingberg et al in 2002. This cross sectional study of 53 consecutive cases added much to the understanding of the oral effects of the syndrome, the study involved clinical and radiographic examination of 53 patients where previously only case reports had been published.[40,41] The results are discussed below in comparison to other data added by more recent studies.

Klingberg demonstrated a prevalence of hypodontia (not associated with cleft palate) in the primary dentition in seven cases and 5 more in the permanent dentition.[39] In comparison, a retrospective study of 45 22q11s children visiting a cleft service in Finland found tooth agenesis in 17%, mainly affecting mandibular incisors.[42] Given the percentage of 22q11 sufferers who suffer from cleft palate [12,30] one might expect that these findings are skewed by ascertainment bias.

However, a study of 50 patients selected through the Norwegian national genetic centre and recruited to a wider scale study (i.e. a variety of presentations of 22q11s) showed tooth agenesis in 15%.[43]

This Norwegian study had a wider remit: It aimed not only to establish dental developmental disturbances, but also to explore if they could be linked to medical conditions in 22q11s.

50 candidates were studied through interview, clinical and radiographic examination and study of medical notes: 66% had enamel defects (hypomineralisation 24%, hypoplasia 8%, both 34%) the authors commented on the low prevalence of hypoplasia compared to previous work: Klingberg found hypomineralisation in 43% and hypoplasia in 30% with 19% displaying symmetrical chronological hypoplasia. The two studies used the same definition of hypomineralisation and hypoplasia, Noordgarden postulated that hypoplasia may have been masked by hypomineralisation of the same lesion, inter-observer variation may also have played a part in the discrepancy between the two studies, performed in similar samples in studies of similar design from similar geographical areas.

With regard to the link between medical problems seen in 22q11s and dental phenomena the Nordgarden study concluded:

"Hypoparathyroidism and/or hypocalcaemia are not clear aetiological factors for enamel disturbances and there were no major correlations between medical conditions and enamel disturbances". This statement is in contradiction to most of the existing literature on the subject with multiple previous studies noting a link between enamel abnormalities and disorders of calcium level,[44-47] furthermore with such low powered studies it is difficult to attain statistical significance: Absence of evidence does not constitute evidence of absence,[48] especially when using simple statistical analysis of such small samples. Other studies have used inductive models for statistical analysis; successfully demonstrating statistical inference rather than classical statistical testing of a null hypothesis, which will not be possible in low powered studies.

The authors do not publish data regarding calcium or albumin levels in their study. PTH levels, of which 11 were below normal were not identified as being one off

measurements at the time of the study, or over the course of illness and treatment for deficiency. Furthermore, PTH level is irrelevant for development of enamel if calcium supplementation is being carried out. This is not considered or mentioned at any point in the study.

The authors consider a genetic component to enamel defects in 22q11s pointing towards the TBX1 gene which is implicated in cardiac abnormalities[49] and absent in all of the common deletions of 22q11s. TBX1 is expressed in the epithelial precursors to ameloblasts,[50] animal models missing this gene display enamel hypoplasia and in foetus' homozygous for deletion of this gene there is no enamel development at all.[51] It should be noted that this research is still in animal models so may not be applicable or relevant to humans.

Klingberg identified enamel defects as described earlier and like most of the other literature[44-47] could link this to medical events in early life.

They linked hypomineralisation with diffuse medical conditions such as recurrent infections and found an association between hypoplasia and more discreet conditions such as low birth weight and congenital cardiac abnormalities. Klingberg identified an increased prevalence of caries in the study population with above average DMFT scores and impaired oral health in 28%.

Postulating initially that this may in part be due to the consumption of cariogenic foodstuffs when the child is unwell to maintain calorific intake, the team demonstrated active research in their follow up work: Hoping to explain the increased caries risk this team investigated enamel morphology and composition[52] and the properties of saliva[53] in 22q11s. These are the only studies in these areas in 22q11s.

Investigation of 38 exfoliated primary teeth from 15 subjects, with comparison of findings to medical records, found overall morphology was not different to normal enamel.[52] However, a relationship was noted between high numbers of medical events and enamel deviations: a trend of hypomineralisation and morphological aberrations around the neonatal line may signify impaired metabolism, e.g. due to

frequent infections or medical problems, these were also more common in the incisors, which mineralise earlier in life.[54]

Analysis of caries related saliva properties found a statistically significant reduction in flow and buffer capacity and a significant increase in numbers of cariogenic bacteria (*S. mutans*) in 22q11s. An increase in IgA was found to be proportional to serum levels. These findings are consistent with the findings of increased caries risk in their previous work[39,52] and the increased caries risk recognised in many special needs groups.[55-57] Furthermore coming from a sample matched to control patients of the same age, gender and caries experience this data is more robust. This study demonstrates children with 22q11s are at a higher risk of dental decay than the general population citing a plausible cause (or factor of causation) for higher caries activity.

Moursi took a wider view of lifestyle factors affecting oral health in children with special healthcare needs, citing the following as factors which contribute to poor oral health: decreased appetite and increased nutritional risk (i.e. risk of malnourishment in the hypermetabolic state of illnesses); increased frequency of food intake to maintain calorific intake (often of highly cariogenic foodstuffs); parental overindulgence, poor oral hygiene and prevention; long-term use of cariogenic medications and xerostomia.[58]

To consider the full impact of 22q11s upon oral health it is necessary to look beyond medical and dental characteristics of the syndrome. Without consideration of psychological and social barriers to oral health for patients and families it would not be possible to gain a holistic picture of the challenges faced.

Qualitative work based in grounded theory with information taken from open interview provides useful insights into the perspectives of the parents of 22q11s[59] and other orofacial handicaps.[60] Parents shape and mould the health behaviours of children and in the case of disabled children for more prolonged periods of time. The study of 22q11s found oral health was of concern to parents but many children did

not understand the importance of oral hygiene. Parents felt often there were other conditions both medical and psychological which were perceived as more important than oral health issues. In both studies parents admitted to supplying cariogenic foods to their children when unwell to boost calorific intake or as a comfort.[59] The parents of children with more severe orofacial handicaps considered the oral health problems of their children to be based around feeding and communication, the only mentioned dental condition was of malocclusion (no mention of caries or gingivitis) and even then in relation to feeding or speech problems.[59]

Many studies have outlined the problems of access to care for the disadvantaged or patients requiring special care dentistry and socially constructed barriers to receipt of care.[61-63]

Discussion

The evidence above demonstrates that phenotypic features of 22q11s can affect oral health. Furthermore, it is recognised that the culmination of several disabilities judged to be 'mild' can have severe effects.[64]

Dental characteristics include: Anomalies of tooth shape, number and eruption; enamel anomalies such as hypomineralisation and hypoplasia in addition to an increased risk of caries which is multifactorial. Cleft palate and other intra-oral anatomical abnormalities can result in pathological or poorly co-ordinated oral mechanisms; deficiencies in chewing, swallowing and oral cleansing which can jeopardise both oral and systemic health.[65]

Medical problems can affect the dentition itself, its development, the maintenance of oral health and the risk of oral diseases and caries. Medical and dental factors of 22q11s which impact upon oral health do not occur in isolation:

The hypermetabolic state of congenital heart disease can necessitate highly cariogenic foodstuffs or supplements to maintain calorific intake.[58] Hypoxia and illness during early development has been purported to affect ameloblasts and linked to developmental deficiencies of enamel.[47] Abnormalities of PTH and hypocalcaemia have been linked to enamel defects also.[44-47]

While immunodeficiency in 22q11s has been demonstrated to be subclinical and not commonly severe enough to necessitate treatment, abnormalities in salivary immunoglobulins have been reported and require further investigation.[53] Discussion with physicians on an individual basis is advised to ascertain if antibiotic cover is required for dental treatment in immunodeficiency.[66]

Patients with intellectual disability have poorer oral hygiene and higher plaque levels than the general population[67] developmental delay, poor motor skills and reduced nonverbal IQ[17-19] contribute to difficulties in co-ordination which may jeopardise the ability of patients to perform oral hygiene tasks.[68] Musculoskeletal problems such as Juvenile Rheumatoid Arthritis or hypotonia with poor co-ordination may exacerbate this. Anxiety is common in 22q11s and has been demonstrated as a significant barrier to the attainment of dental care in special needs groups.[69]

Oral health needs are the second most likely to be unmet in children with chronic systemic disease after psychological support.[70] In addition it can be difficult for families to find a local dentist to provide treatment.[65] Difficulties in access may be compounded by attitudes of patients with special needs toward oral health[21] or the common conception amongst carers that oral health is superseded by other health problems.[59]

Conclusion

Many phenotypic features of 22q11s impact upon oral health either directly or indirectly through multifactorial, interrelated and sometimes complex actions.

Biological factors of 22q11s may impair oral anatomy and physiology, the development and maintenance of the dentition and oral tissues in addition to the cardiovascular, immune, exocrine, endocrine, neuro-psychiatric and musculoskeletal systems. Effects upon speech, communication, metabolism and nutritional state are also implicated in poor health, developmental delay, and limited function. No system in the body acts in isolation or is unaffected by dysfunction elsewhere; the

cumulative effect of multiple disabilities can result in profound functional deficit. However, it is important not to focus singularly upon the biological effects of the syndrome when considering impaired oral health; psychological and social effects of 22q11s also impact upon the oral health of the individual and the provision of oral care.

Word Count: 2,698

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