Published in final edited form as:

Oral Dis. 2010 July ; 16(5): 488–495. doi:10.1111/j.1601-0825.2010.01662.x.

Craniofacial and Dental Findings in Cystinosis

CW Bassim¹, P Gautam¹, DL Domingo¹, JZ Balog², JP Guadagnini¹, WA Gahl², and TC Hart¹

¹National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD

²National Human Genome Research Institute, National Institutes of Health, Bethesda, MD

Abstract

Objectives—Cystinosis is a rare autosomal recessive lysosomal storage disorder with developmental and mineralization anomalies as part of its clinical presentation. The objective of this study was to provide the first systematic assessment of the craniofacial and dental characteristics associated with cystinosis.

Study Design—Oral and radiographic evaluations were performed on 73 patients with cystinosis. Analyses of cephalometry (n=20), taurodontism (n=47), caries (n=47), enamel defects (n=48), soft tissue anomalies (n=48), and dental age (n=41) were performed on the cystinosis group, and compared with age- and sex- comparable controls or standards.

Results—Cystinosis patients manifested relative mandibular deficiency, an increased facial height, and a reduced airway space. Taurodontism and enamel defects were significantly more prevalent in cystinosis patients compared with controls ($p<0.0001$ and $p=0.027$, respectively). Children (aged < 15 years) with cystinosis also demonstrated a significant delay, of almost 9 months, of their dental development ($p<0.001$).

Conclusion—Novel craniofacial and dental features are associated with cystinosis. Craniofacial deficiencies may influence the swallowing and respiratory complications seen in cystinosis. Renal pathology and associated mineral imbalance may explain the dental root and enamel anomalies found in cystinosis patients; the developmental delays in cystinosis include delayed dental formation.

Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disorder caused by loss-of-function mutations of the cystinosin gene (*CTNS*), leading to cellular damage from cystine accumulation (Nesterova and Gahl, 2009). The classical form of cystinosis, infantile nephropathic cystinosis, presents in the first year of life and leads inevitably to renal failure, but less severe presentations occur as late-onset or ocular cystinosis. Early clinical features of nephropathic cystinosis include renal tubular Fanconi syndrome, hypophosphatemic rickets, impaired growth, hypothyroidism, and photophobia (Gahl, 1986). Early treatment with the cystine-depleting free thiol, cysteamine, delays renal deterioration and improves long-term outcomes; along with renal transplantation, oral cysteamine therapy has lengthened and improved cystinosis patients' lives (Nesterova and Gahl, 2008).

Cystinosin normally functions to transport cystine out of intracellular lysosomes and into the cytoplasm. In cystinosis, cystine crystals form due to the poor aqueous solubility of

cystine; they are readily apparent on slit-lamp examination of the cornea from a young age (Gahl *et al.*, 2000). Heterozygotes for cystinosis exhibit approximately half of the normal cystine-transporting activity, leading to almost normal intracellular levels of cystine and no symptoms related to cystinosis (Gahl *et al.*, 1984a). In general, the severity of clinical illness corresponds to the amount of intracellular cystine accumulation, although other modifying genetic or environmental factors may influence the clinical course of cystinosis (Gahl and Tietze, 1987).

The dental and craniofacial clinical features of cystinosis remain poorly defined. Nazif and Mazloum's 1973 report on the oral manifestations of three cystinosis cases suggested that, in cystinosis, dental changes include ill-defined mucosal and tongue lesions, retardation of dental calcification age, delayed eruption of dentition, and enlarged pulp chambers (Nazif and Osman, 1973). To date, however, a systematic assessment of craniofacial, oral, and dental features has not been conducted among cystinosis patients. In this paper, we describe the craniofacial, dental, and oral findings, including cephalometric analysis, taurodontism prevalence, caries analysis, enamel defects, intraoral soft tissue findings, and dental developmental analysis, for a large group of cystinosis patients.

Materials and Methods

Seventy-three individuals with the clinical diagnosis of cystinosis were designated the cystinosis group (100% Caucasian, 39 males (53%), 34 females (47%), mean age = 13.7 ± 8.0 , median age = 12.8, age range = 2.7 to 41.1). After providing written, informed consent, each patient underwent a radiographic and oral evaluation at the National Institutes of Health Clinical Center as part of a clinical protocol, "Use of Cysteamine in the Treatment of Cystinosis." Patient studies were conducted in compliance with the Helsinki Declaration and were approved by the Institutional Review Boards of the National Human Genome Research Institute and the National Institute of Dental and Craniofacial Research. Statistical analysis was performed using the SAS 4.0 Enterprise Guide (SAS Institute Inc., Cary, NC) and two-sided p-values at the level of 0.05 were used to determine statistical significance. Continuous data are provided as means $\pm$ standard deviations (SD), and discrete data are presented as percentages. Statistical analysis to describe differences in proportions between the groups used chi-squared tests, with odds ratios, 95% confidence intervals (CI), and Fishers exact p-value reported. T-tests were used to describe continuous differences between groups.

Cephalometrics

The lateral cephalograms (Planmecca® PM 2002 CC, Helsinki, Finland) of 20 cystinosis subjects who had completed their pubertal growth spurt were analyzed for craniofacial and airway morphology (Table 1). Cephalometric analysis was performed on lateral cephalograms using imaging software (Dolphin®, Chatworth, CA) and SD from age, sex, and race standardized norms were calculated.

Taurodontism

Taurodontism occurs in multirrooted teeth where the pulp chamber of the tooth is enlarged, lowering the floor of the pulp chamber and the furcation of the roots apically (Jaspers and Witkop, 1980). The Taurodontism Index (TI, measuring pulp chamber height from the level of the pulp horns to the level of molar furcation, (Shifman and Chanannel, 1978) was used to evaluate permanent first and/or second molar pulp chamber size from panographs (Planmecca® PM 2002 CC, Helsinki, Finland) of cystinosis patients and age and sex comparable controls (Table 1). Logistic regression analysis was used to determine the

effects of TI, age, and sex on models predicting cystinosis group assignment. Panorographs were also analyzed for variations of tooth number or other root anomalies.

Caries

The number of decayed, missing, and filled permanent teeth (DMFT) per subject were calculated from clinical examination and radiographs and compared with the control group to estimate deviations from normative caries risk (Murray, 1993).

Enamel Defects

Patients with permanent maxillary central incisors and first molars were analyzed for the clinical presence of enamel defects (Table 1). The facial-incisal aspects of maxillary anterior index teeth (lateral and central incisors) and the facial-occlusal aspects of the mandibular first molars of this group were reviewed by the same dentist and assigned enamel defect scores using the Modified Developmental Defects of Enamel (DDE) Index (Clarkson and O'Mullane, 1989). A score of 0 indicates normal enamel, a score of 1–2 indicates demarcated opacities, a score of 3–6 indicates diffuse opacities or lining, and a score of 7–9 indicates hypoplasia, pitting, or missing enamel. These results were compared with an age and sex comparable control group. The proportion of subjects with at least one significant enamel defect, defined as a DDE score ≥ 3 , was compared across groups.

Soft Tissue Lesions

The subjects included in the enamel defects analysis (Table 1) were examined for intraoral soft tissue lesions and compared across groups.

Dental Development

Cystinosis subjects younger than 15 years were analyzed for dental development (Table 1). The dental ages of this group, calculated using the system of Demirjian *et al.* from panoramic assessment, were compared with their chronological ages (Demirjian *et al.*, 1973). This system assessed dental development by scoring the stage of each tooth in one dental quadrant (here, the seven teeth of the mandibular left quadrant), and then summing these scores into a dental maturity score, which was then converted into a sex-adjusted dental age (Liversidge *et al.*, 2006). The dental age of each cystinosis subject was then compared to their chronologic age, and analyzed using a paired t-test. The timing of the exfoliation of primary teeth was also assessed and compared with normal age ranges for primary teeth exfoliation (Ash and Nelson, 2002).

Results

The findings suggest that mild craniofacial anomalies, reduced posterior airway space, taurodontism, enamel defects, and dental developmental delay are associated with cystinosis. These results are discussed in detail below.

Cephalometric Analysis

Smaller values were found in the cystinosis group for the anterior cranial base (SD 1.4 to 5) and the posterior cranial base (SD -2.5 to 0.5). Higher values for the Saddle angle (N-S-Ar, SD 0.6 to 3.7) were observed in cystinosis patients compared to established age, sex, and racial norms. A reduced mandibular body length (SD -4.2 to 0) and an increased Gonial angle (SD 0.5 to 4.9) was a consistent pattern among all cystinosis patients, with most patients also showing an associated reduced mandibular ramus height (SD -2.5 to 1.2). The relationship of the mandible to the cranial base deviated from normative values, with a general tendency for increased lower anterior facial height (SD 0.1 to 2.9) and increased

vertical growth seen among the patients, along with short (SD 3.2 to 10.2) facial depth (indicated by Nasion-Gonion distance). The analysis of antero-posterior relationship revealed retropositioning of both maxilla (SNA: SD -2.1 to 1.2) and the mandible (SNB: SD -3.5 to 2.8) in most of the cystinosis patients, with 2 individuals demonstrating Skeletal Class III pattern as a result of mandibular prognathism. The analysis of the airway revealed smaller values (SD: -11 to -7.4) of posterior airway space. The hyoid bone position was found to be more inferiorly and posteriorly located, as suggested by the mandibular plane to hyoid bone distance (MP-H) (SD: -6.6 to 4.4). A reduced length of the soft palate (SD: -10.9 to 0.9) was consistently observed among the cystinosis patients.

The SD values reported here were derived from the Dolphin database for comparative norms. Figure 1 illustrates these cephalometric variables for one cystinosis subject.

Taurodontism

All three classifications of taurodontism (hypo-, meso-, and hypertaurodontism) were significantly more prevalent in cystinosis patients than in controls (Table 2). Figure 2 (radiographs of molars from a control subject (A) and various cystinosis subjects (B-F)) illustrates the spectrum of taurodontism seen in the cystinosis group. Using the TI as a continuous variable, the cystinosis group had a significantly higher individual TI than controls (18.83 ± 5.73 vs. 14.73 ± 2.91 , $p < 0.001$). The individual TI remained a significant independent modelling variable of cystinosis group assignment in a logistic regression analysis (OR = 1.29, 95% CI = [1.16 to 1.44], $p < 0.001$), even after adjusting for age and sex (OR = 1.34, 95% CI = [1.19 to 1.52], $p < 0.001$).

The cystinosis group also had a significantly greater individual prevalence of bifurcated mandibular premolars than controls ($p = 0.042$), and a greater prevalence, albeit non-significantly, of congenitally missing permanent teeth than controls ($p = 0.117$) (Table 2). Missing teeth for the cystinosis group were as follows: 1 individual missing tooth #24 (mandibular left lateral incisor); 1 missing tooth #20 (mandibular left second premolar); 1 missing teeth #4 (maxillary right second premolar), #12 (maxillary left first premolar), #13 (maxillary left second premolar), #20, and #29 (mandibular right second premolar); and 2 missing teeth #20 and #29. The two control individuals with missing teeth were missing teeth #20 and #29.

Caries

DMFT scores were not significantly different for the cystinosis group compared to the control group (2.28 ± 4.82 vs. 2.81 ± 2.29 , $p = 0.380$, Table 2).

Enamel Defects

Enamel defects (diffuse opacities or hypoplasia, as coded by DDE > 3) among cystinosis patients were found in 27% (79 of 288) of the index teeth examined, compared to 7% (20 of 288) in the control group, a significant difference (OR = 5.06, 95% CI = [3.02 to 8.50], $p < 0.0001$). Furthermore, the cystinosis group had a significantly greater percentage of individuals with at least one index tooth with an enamel defect coded DDE > 3 (36%) when compared with controls (6%, OR = 8.31, 95% CI = [3.07 to 22.36], $p < 0.0001$) (Table 2). Enamel defects of diffuse opacities and of non-carious localized circular defects were most commonly seen (Figure 3).

Soft Tissue Lesions

Tongue lesions consistent with mild benign migratory glossitis were noted for a greater percentage of cystinosis subjects compared with controls, however, this difference was not statistically significant (Table 2). No other anomalies of intraoral soft tissue were found.

Dental Development

Dental age was found to be significantly delayed, by a mean of 8.86 months (8.69 ± 3.33 dental years old vs. 9.43 ± 3.62 chronological years old, 95% CI of the difference in mean = [5.16 to 12.72 months], $p < 0.001$). Retention of primary teeth past standardized exfoliation ages were found in 34% (14 of 41) of cystinosis patients. Figure 4 demonstrates various cystinosis subjects with age matched controls showing dental developmental delay.

Discussion

This study characterized craniofacial and dental anomalies associated with cystinosis. Cephalometric analysis revealed variables suggestive of a mildly altered craniofacial morphology in cystinosis patients. Cystinosis is frequently associated with early growth retardation, hypophosphatemic rickets due to renal tubular Fanconi syndrome, and decreased muscular function due to poor nutrition or development (Gahl, 1997; Gahl *et al.*, 2002). Normal muscular function and its resultant biomechanical stress are important for proper craniofacial development (Kiliaridis and Katsaros, 1998). Consequently, poor muscular development, along with general growth retardation during the active growth period, may have contributed to altered craniofacial morphological development in cystinosis patients.

The anterior cranial base and the posterior cranial base appears smaller in cystinotic patients. The larger Saddle angles suggest inadequate cranial base flexure, which has been associated with mandibular deficiency, possibly adding to baseline mandibular hypoplasia in cystinosis patients. The increased lower anterior facial height along with a short facial depth (Nasion-Gonion distance) may indicate a backward and downward mandibular growth rotation. The craniofacial features of cystinosis patients could be attributed to the inter-relationship of altered vertical craniofacial growth and possible involvement of the surrounding musculature, i.e., masticator muscles and perhaps the less affected suprahyoid musculature (Pepicelli *et al.*, 2005). This oro-facial muscle involvement may also contribute to a lowered tongue position in cystinosis patients, which could compromise the tongue's counterbalancing forces developed during the lowering of the mandible by the stretched facial musculature. This may affect the teeth transversely, decreasing the width of the palate and causing a lowered position of the mandible. The involvement of oro-facial muscles and subsequent swallowing dysfunction in cystinosis has been reported in the literature (Sonies *et al.*, 2005).

An increased vertical facial pattern and mandibular deficiency (absolute and relative), as seen in cystinosis patients, has been associated with upper airway constriction (Freitas *et al.*, 2006). These features are consistent with our findings of a reduced posterior airway space in cystinosis patients. Furthermore, the postero-inferior positioning of the hyoid bone observed in our study has been associated with reduced airway patency (Johal *et al.*, 2007). As a result, the tongue may be positioned further posteriorly, which may contribute to the restriction of airway dimensions in cystinotic patients. Respiratory insufficiency caused by overall respiratory muscle myopathy is a severely debilitating complication of cystinosis (Anikster *et al.*, 2001; Edens *et al.*, 2006). Restricted airway dimensions caused by involvement of oro-pharyngeal muscles and altered craniofacial morphology could further complicate the pulmonary insufficiency resulting from respiratory muscle atrophy.

Enamel defects have been associated with many pediatric systemic illnesses that occur during the critical period of enamel formation, including kidney disease (Bassim *et al.*, 2009; Bhat and Nelson, 1989; Lucas and Roberts, 2005; Pindborg, 1982; Russell *et al.*, 1996). In humans, calcification of permanent anterior teeth commences at 3–12 months. Formation of enamel is complete at 4–7 years of age, with enamel remaining biologically inert and non-responsive after development (Ash and Nelson, 2002; Hu *et al.*, 2007). The

presence of enamel defects, therefore, is highly dependent on conditions occurring during the critical time of enamel formation and mineralization.

Cystinosis accounts for approximately 5% of chronic renal failure in children, with renal Fanconi syndrome generally presenting before the age of one (Nesterova and Gahl, 2008). Proximal renal tubule atrophy and decreased resorption of phosphate may lead to rickets in cystinosis patients (Nesterova and Gahl, 2008). Taurodontism and severe hypoplastic enamel defects are well-characterized dental features in patients with rickets, and have been suggested to be associated with altered tooth mineralization (Goodman *et al.*, 1998; Murayama *et al.*, 2000; Seow *et al.*, 1995; Zambrano *et al.*, 2003).

Cystinosis-associated hypophosphatemic rickets, with a high fractional excretion of phosphate, normal vitamin D levels, hypocalcemia, and elevated levels of serum alkaline phosphatase, is characterized by osteomalacia, bone deformities, and delayed ambulation (Gahl, 1986; 1997). Hereditary hypophosphatemic vitamin D resistant rickets manifests a similar metabolic picture and has distinct dental findings of hypoplastic and pitted enamel, dentin weakness, poorly defined lamina dura, enlarged pulp chambers, and shortened dental roots (Murayama *et al.*, 2000). As a result, rickets patients often show increased caries, dental attrition and pulp exposure with ensuing odontogenic abscesses and periapical radiolucencies (Seow *et al.*, 1995).

The prevalence of taurodontism and enamel defects in the cystinosis group is highly suggestive of rickets-related dental development anomalies. In the cystinosis group, 36% of subjects exhibited at least one of the more severe types of taurodontism (meso- and hypertaurodontism), compared with 6% for controls ($p<0.0001$); 33% of cystinosis subjects had an enamel defect compared with 13% of controls ($p=0.27$). However, a predisposition to pulpitis, abscesses, or periapical radiolucencies was not apparent from our dental evaluations of cystinosis patients. Though an occasional cystinosis patient did present with the generalized dental hypoplasia characteristic of rickets (Figure 5) most exhibited diffuse opacities or discrete enamel pitting defects, more closely resembling the clinical appearance of pediatric renal failure (Figure 3). Enamel defects in renal failure have been suggested to result from altered dental mineralization due to hypocalcemia and elevated serum phosphate, parathyroid hormone, and fluoride levels (Victoria and Roberts, 2005).

It is also possible that the taurodontism and enamel defects observed could be the direct result of an anomaly in the epithelial development of the tooth structures or secretion of mineral during dental development. Taurodontism may reflect a developmental effect on the invagination of Hertwigs epithelial root sheath, which determines root shape and is derived from the enamel organ during tooth development (Jafarzadeh *et al.*, 2008). Taurodontism has been associated with many conditions affecting epithelial-derived tissues; this is not surprising, since abnormal epithelial root sheath function has been implicated as the cause of taurodontism (Wright, 2007). Further, other glandular functions are reduced in cystinosis, including sweating (Gahl *et al.*, 1984b) and salivation (Gahl, 1986). Because the mineralization of enamel and dentin during dental development is a secretory process involving lysosome-like organelles (Gahl *et al.*, 2001), it is possible that a direct effect of cystinosis on the transport of mineral to develop enamel and dentin may play a role in dental developmental anomalies seen in cystinosis patients.

In this study, caries burden for the cystinosis group was equivalent to or less than that of the control group. While enamel defects and a lowered caries risk have generally been associated with pediatric chronic renal failure (Davidovich *et al.*, 2005; Nunn *et al.*, 2000; Wolff *et al.*, 1985), these findings are not universally supported (Martins *et al.*, 2008). The protective buffering influence of the high amount of urea in the saliva of chronic renal

failure patients is hypothesized to account for the lowered caries rate among renal failure patients (Nowaiser *et al.*, 2003). This, or other salivary changes that lead to alterations in oral microflora or salivary pH, may help explain the normal caries burden in the cystinosis group (Bassim *et al.*, 2009; Lucas and Roberts, 2005).

Chronic renal failure directly influences pediatric growth and development, and has been associated with delayed dental maturity (Jaffe *et al.*, 1990). Familial hypophosphatemic rickets, though, has not been shown to affect the rate of dental development (Seow *et al.*, 1995). Children with cystinosis demonstrate profound growth retardation and delayed bone age due to renal damage, acidosis, hypophosphatemic rickets, nutrient losses, and hypothyroidism due to glandular atrophy (Gahl, 1997). The significant delay in dental development, almost 9 months, may be part of the spectrum of generalized growth retardation seen in cystinosis. Compared with control values in the literature (Mitchell *et al.*, 2009; Tunc and Koyuturk, 2008), this delay is significant ($p < 0.0001$); in fact, 63% of our cystinosis children had significantly delayed dental development.

Conclusion

This study presents novel findings involving mildly altered craniofacial morphology and reduced airway dimensions in cystinosis. Delayed dental development and delayed eruption of permanent teeth were also found in the cystinosis group. Cystinosis associated variations in tooth root morphology and enamel defects were found; these may be part of the disease spectrum affecting mineralized tissues. The observed altered craniofacial growth may reflect a complex interaction of morphological and functional aspects of the skeleton and the surrounding soft tissues. These findings provide insight into craniofacial morphology and oro-dental development in cystinosis, and highlight the need for craniofacial and dental characterization of complex diseases.

Acknowledgments

This study was supported through the Divisions of Intramural Research of the NHGRI and NIDCR/ IRP, NIH, DHHS.

REFERENCES

- Anikster Y, Lacbawan F, Brantly M, Gochuico B, Avila N, Travis W, et al. Pulmonary dysfunction in adults with nephropathic cystinosis. *Chest*. 2001; 119:394–401. [PubMed: 11171714]
- Ash, M.; Nelson, S. *Wheeler's Dental Anatomy, Physiology, and Occlusion*: Saunders. 8 edition. 2002.
- Bassim C, Wright J, Guadagnini J, Muralidharan R, Sloan J, Domingo D, et al. Enamel defects and salivary methylmalonate in methylmalonic acidemia. *Oral Diseases*. 2009; 15:196–205. [PubMed: 19143946]
- Bhat M, Nelson KB. Developmental enamel defects in primary teeth in children with cerebral palsy, mental retardation, or hearing defects: a review. *Adv Dent Res*. 1989; 3:132–142. [PubMed: 2701156]
- Clarkson J, O'Mullane D. A modified DDE Index for use in epidemiological studies of enamel defects. *J Dent Res*. 1989; 68(3):445–450. [PubMed: 2921385]
- Davidovich E, Schwarz Z, Davidovitch M, Eidelman E, Bimstein E. Oral findings and periodontal status in children, adolescents and young adults suffering from renal failure. *J Clin Periodont*. 2005; 32:1076–1082.
- Demirjian A, Goldstein H, Tanner J. A new system of dental age assessment. *Hum Biol*. 1973; 45(2): 211–227. [PubMed: 4714564]
- Edens M, Son Wv, Greef Md, Levchenko E, Blijham T, Wijkstra P. Successful treatment of respiratory dysfunction in cystinosis by nocturnal non-invasive positive pressure ventilation. *Clin Nephrol*. 2006; 66:306–309. [PubMed: 17064000]

- Freitas, Md; Alcazar, N.; Janson, G.; Freitas, K.; Henriques, J. Upper and lower pharyngeal airways in subjects with Class I and Class II malocclusions and different growth patterns. *Am J Orthod Dentofacial Orthop.* 2006; 130(6):742–745. [PubMed: 17169736]
- Gahl W, Bashan N, Tietze F, Schulman J. Lysosomal cystine counter-transport in heterozygotes for cystinosis. *Am J Hum Genet.* 1984a; 36:77–82.
- Gahl W, Hubbard V, Orloff S. Decreased sweat production in cystinosis. *J Pediatr.* 1984b; 104:904–905. [PubMed: 6726525]
- Gahl W. Cystinosis coming of age. *Adv Pediatr.* 1986; 33:95–126. [PubMed: 3541536]
- Gahl W, Tietze F. Lysosomal cystine transport in cystinosis variants and their parents. *Pediatr Res.* 1987; 21:193–196. [PubMed: 3822600]
- Gahl W. Nephropathic cystinosis. *Pediatr Rev.* 1997; 18:302–304. [PubMed: 9286148]
- Gahl W, Kuehl E, Iwata F, Lindblad A, Kaiser-Kupfer M. Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eyedrops. *Mol Genet Metab.* 2000; 71:100–120. [PubMed: 11001803]
- Gahl, W.; Thoene, J.; Schneider, J. Cystinosis: A Disorder of Lysosomal Membrane Transport. In: Scriver, ABCR.; Sly, WS.; Valle, D.; Vogelstein, B., editors. *The Metabolic and Molecular Bases of Inherited Disease.* 8th ed.. Vol. 199. New York: McGraw-Hill; 2001. p. 5085–5108.c.
- Gahl W, Thoene J, Schneider J. Cystinosis. *N Engl J Med.* 2002; 347:111–121. [PubMed: 12110740]
- Goodman J, Gelbier M, Bennett J, Winter G. Dental Problems associated with hypophosphataemic vitamin D resistant rickets. *Int J Paediatr Dent.* 1998; 8:19–28. [PubMed: 9558542]
- Hu JC, Chun YH, Hazzazzi TA, Simmer JP. Enamel formation and amelogenesis imperfecta. *Cells Tissues Organs.* 2007; 186:78–85. [PubMed: 17627121]
- Jafarzadeh H, Azarpazhooh A, Mayhall J. Taurodontism: a review of the condition and endodontic treatment challenges. *International Endo J.* 2008; 41:375–388.
- Jaffe E, Roberts G, Chantler C, Carter J. Dental maturity in children with chronic renal failure. *J Int Assoc Den Child.* 1990; 20:54–58.
- Jaspers M, Witkop C. Taurodontism, an isolated trait associated with syndromes and x-chromosomal aneuploidy. *Am J Hum Genet.* 1980; 32:396–413. [PubMed: 6992564]
- Johal A, Patel S, Battagel J. The relationship between craniofacial anatomy and obstructive sleep apnoea: a case-controlled study. *J Sleep Res.* 2007; 16:319–326. [PubMed: 17716281]
- Kiliaridis S, Katsaros C. The effects of myotonic dystrophy and Duchenne muscular dystrophy on the orofacial muscles and dentofacial morphology. *Acta Odontol Scand.* 1998; 56:369–374. [PubMed: 10066119]
- Liversidge H, Chaillet N, Mörnstad H, Nyström M, Rowlings K, Taylor J, et al. Timing of Demirjian's tooth formation stages. *Ann Hum Biol.* 2006; 33:454–470. [PubMed: 17060069]
- Lucas S, Roberts G. Oro-dental health in children with chronic renal failure and after renal transplantation: a clinical review. *Pediatr Nephrol.* 2005; 20:1388–1394. [PubMed: 15947987]
- Martins C, Siqueira W, Primo LG. Oral and salivary flow characteristics of a group of Brazilian children and adolescents with chronic renal failure. *Pediatr Nephrol.* 2008; 23(4):619–624. [PubMed: 18228044]
- Mitchell J, Roberts G, Donaldson A, Lucas V. Dental age assessment (DAA): Reference data for British caucasians at the 16 year threshold. *Forensic Sci Int.* 2009 epub.
- Murayama T, Iwatsubo R, Akiyama S, Amano A, Morisaki I. Familial hypophosphatemic vitamin D-resistant rickets: dental finding and histologic study of teeth. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000; 90:310–316. [PubMed: 10982952]
- Murray J. Efficacy of preventive agents for dental caries. Systemic fluorides: water fluoridation. *Caries Res.* 1993; 27:2–8. [PubMed: 8500120]
- Nazif M, Osman M. Oral manifestations of cystinosis. *Oral Surg Oral Med Oral Pathol.* 1973; 35(3): 330–338. [PubMed: 4510605]
- Nesterova G, Gahl W. Nephropathic cystinosis: late complications of a multisystemic disease. *Pediatr Nephrol.* 2008; 23:863–878. [PubMed: 18008091]

- Nesterova, G.; Gahl, W. Cystinosis in: GeneReviews at GeneTests: Medical Genetics Information Resource [database online] Copyright, University of Washington, Seattle. 1997–2009. 2009. Available at <http://www.genetests.org> <<http://www.genetests.org>>
- Nowaiser AA, Roberts G, Trompeter R, Wilson M, Lucas V. Oral health and oral streptococcal flora of children with chronic renal failure. *Pediatr Nephrol.* 2003; 18:39–45. [PubMed: 12488989]
- Nunn J, Sharp J, Lambert H, Plant N, Coulthard M. Oral health in children with renal disease. *Pediatr Nephrol.* 2000; 14:997–1001. [PubMed: 10975315]
- Pepicelli A, Woods M, Briggs C. The mandibular muscles and their importance in orthodontics: a contemporary review. *Am J Orthod Dentofacial Orthop.* 2005; 128:774–780. [PubMed: 16360920]
- Pindborg JJ. Aetiology of developmental enamel defects not related to fluorosis. *Int Dent J.* 1982; 32:123–134. [PubMed: 6749692]
- Russell BG, Russell MB, Praetorius F, Russell CA. Deciduous teeth in tuberous sclerosis. *Clin Genet.* 1996; 50:36–40. [PubMed: 8891384]
- Seow W, Needleman, Holm I. Effect of familial hypophosphatemic rickets on dental development: a controlled longitudinal study. *Pediatr Dent.* 1995; 17:346–350. [PubMed: 8524683]
- Shifman A, Chananel I. Prevalence of taurodontism found in radiographic dental examination of 1,200 young adult Israeli patients. *Community Dent Oral Epidemiol.* 1978; 6(4):200–203. [PubMed: 278704]
- Sonies B, Almajid P, Kleta R, Bernardini I, Gahl W. Swallowing dysfunction in 101 patients with nephropathic cystinosis: benefit of long-term cysteamine therapy. *Medicine (Baltimore).* 2005; 84(3):137–146. [PubMed: 15879904]
- Tunc E, Koyuturk A. Dental age assessment using Demirjian's method on northern Turkish children. *Forensic Science Internatl.* 2008; 175:23–26.
- Victoria S, Roberts G. Oro-dental health in children with chronic renal failure and after renal transplantation: a clinical review. *Pediatr Nephrol.* 2005; 20:1388–1394. [PubMed: 15947987]
- Wolff A, Stark H, Sarnat H, Binderman I, Eisenstein B, Drukker A. The dental status of children with chronic renal failure. *Int J Paediatr Neph.* 1985; 6:127–132.
- Wright T. The molecular control of and clinical variations in root formation. *Cells Tissues Organs.* 2007; 186:86–93. [PubMed: 17627122]
- Zambrano M, Nikilaos N, Sanchez-Quevedo M, Sauk J, Sedano H, Rivera H. Oral and dental manifestations of vitamin D-dependent rickets type I: Report of a pediatric case. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2003; 95:705–709. [PubMed: 12789152]

Figure 1.
Cephalometric findings for a cystinosis subject: 1: smaller Anterior Cranial Base, 2: higher Saddle Angle, 3: higher Total Anterior Facial Height, 4: higher Lower Anterior Facial Height.

Figure 2.

A control subject's panograph (A) with a series of cystinosis subject's panographs (B–F) to show the taurodontism seen in the cystinosis group (black arrows indicate meso- and white arrows show hypertarodontism).

Figure 3.

A control subject's enamel photograph (A) with a series of cystinosis subject's enamel photographs (B–F) to show the enamel defects (arrows indicate diffuse opacities or pitting defects) seen in the cystinosis group.

Figure 4. Panoragrams of cystinosis subjects (A1, B1, C1, D1, E1) compared with age-matched control subjects (A2, B2, C2, D2, E2) to illustrate dental developmental delay in cystinosis (subject A1 is 13.02, A2 is 12.72, B1 is 12.75, B2 is 12.49, C1 is 9.07, C2 is 8.21, D1 is 8.04, D2 is 8.16, E1 is 6.85, E2 is 6.67 years old).

Figure 5. Severe enamel defects seen in cystinosis subjects (each row shows facial and mandibular occlusal plane views of a subject with cystinosis).

Table 1

Summary statistics comparing cystinosis group with control group.

	Cystinosis Group	Control Group	<i>p</i> value
Taurodontism [‡] and Caries Analysis (By Panographic Radiograph)			
Number of Subjects	47	94	-
Mean age ± SD	19.07 ± 7.25	18.22 ± 4.69	0.401
Age Range	10 to 41 years old	10 to 42 years old	-
Males / Females	24 / 23	37 / 57	0.210
Enamel Defect and Intraoral Soft Tissue Analysis (By Clinical Examination)			
Number of Subjects	48	48	-
Mean age ± SD	16.05 ± 6.29	18.17 ± 6.43	0.106
Age Range	9 to 41 years old	8 to 42 years old	-
Males / Females	23 / 25	27 / 21	0.281
Cephalometric Analysis (By Lateral Cephalometric Radiograph)			
Number of Subjects	20	Compared to cephalometric standards [‡]	
Mean age ± SD	16.80 ± 3.42		
Age Range	15.60 to 20.30		
Males / Females	10 / 10		
Dental Development Analysis (By Panographic Radiograph)			
Number of Subjects	41	Calculated dental age [‡] compared to chronologic age	
Mean age ± SD	9.43 ± 3.62		
Age Range	2.67 to 14.93		
Males / Females	23 / 18		

[‡] As measured using taurodontism analysis of Shifman and Chanannel, 1978.

^{‡‡} Individual patient's parameters compared with age, gender and race matched normative data from Dolphin®.

[‡] As measured using dental age analysis system of Demirjian et. al., 1973.

Table 2

Prevalence differences between the cystinosis and control group for radiographic and clinical dental anomalies.

	Cystinosis Group	Control Group	<i>p</i> value	Odds Ratio (95% CI of OR)
Taurodontism	59% (28 of 47)	16% (15 of 94)	< 0.001	7.76 (3.50 to 17.21)
Hypotaurodontism	23% (11 of 47)	10% (9 of 94)	0.039	2.89 (1.13 to 7.40)
Mesotaurodontism	25% (12 of 47)	4% (4 of 94)	< 0.001	7.71 (2.44 to 24.21)
Hypertaurodontism	11% (5 of 47)	2% (2 of 94)	0.041	5.48 (1.17 to 25.39)
Bifurcated Mandibular Premolars	15% (n = 7 of 47)	4% (n = 4 of 94)	0.042	3.94 (1.16 to 13.32)
Congenitally Missing Teeth	11% (n = 5 of 47)	3% (n = 3 of 94)	0.117	3.61 (0.91 to 14.32)
DMFT[‡]	2.28 ± 4.82 (n = 47)	2.83 ± 2.29 (n = 94)	0.356	NA
Enamel Defects	33% (n = 16 of 48)	13% (n = 6 of 48)	0.027	3.50 (1.26 to 9.66)
Benign Geographic Tongue	13% (n = 6 of 48)	2% (n = 1 of 48)	0.111	6.71 (0.99 to 43.81)

[‡]Decayed, missing, filled teeth.