Mineral deficiency in the pathogenesis of enamel hypoplasia in prematurely born, very low birthweight children

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Abstract

Although it is well known that enamel hypoplasia commonly is observed in prematurely born, very low birthweight (VLBW) children, its pathogenesis is not understood clearly. One likely mechanism may be related to mineral deficiency, which may be diagnosed as radiological demineralization of the long bones. In this study, we compared the cortical area of the humerus as measured from neonatal radiographs in 31 VLBW children with enamel hypoplasia and 14 VLBW children without enamel hypoplasia. The results showed that children with enamel hypoplasia had a lower mean cortical area of 10.1 ± 1.9 mm² compared with 13.9 ± 1.4 mm² in children without enamel hypoplasia (P < 0.001). It was also found that intubated children with a lower cortical mass may be more predisposed to develop localized enamel hypoplasia caused by the laryngoscope (P < 0.001).

Reports on the prevalence of developmental dental defects in prematurely born, low birthweight children vary widely from 20 per cent to 100 per cent (Grahnen and Larsson 1958; Rosenzweig and Sahar 1962; Mellander et al. 1982; Johnsen et al. 1984; Seow et al. 1984a; 1984b; 1987). With increasing survival of very low birthweight (VLBW, < 1500 g) infants in recent years, studies are now available on the dentition of such children. In a controlled study, we found that the lower the birthweight of a prematurely born child, the greater is its tendency to develop enamel defects (Seow et al. 1987).

Although the pathogenetic mechanisms of these dental defects still are unclear, it is likely that both local and systemic causes are involved. An important local factor is trauma from laryngoscopy and endotracheal intubation which usually results in localized enamel hypoplasia, involving only the left maxillary anterior teeth (Seow et al. 1984a; 1987). Systemic causes associated with enamel hypoplasia include rickets of prematurity (Seow et al. 1984b), respiratory distress (Johnsen et al. 1984), neonatal asphyxia (Grahnen et al. 1969), maternal pre-eclampsia (Via and Churchill 1959), maternal diabetes (Grahnen and Edlund 1967), hyperbilirubinemia (Grahnen and Granath 1962; Funakoshi et al. 1981), and neonatal infection (Funakoshi et al. 1981).

Although significant associations have been found between individual medical conditions and enamel defects, it is difficult to isolate the relative importance of each medical condition since many of them occur concurrently in VLBW prematurely born children. Moreover, it is likely that many of these systemic disturbances act through a common mechanism of decreased mineral stores which may affect mineralization of dental tissues directly (Seow et al. 1984b; 1987). Osteopenia (or undermineralization of bone) is a well-recognized complication of prematurity (Tsaang et al. 1973; 1983; Kooh et al. 1977; Steichen et al. 1980; Chesney et al. 1981; Brooke and Lucas 1985). It is likely that factors associated with osteopenia in the VLBW prematurely born children also are those involved in the pathogenesis of enamel hypoplasia commonly seen in these children.

This comparative study was conducted to determine if mineral deficiency, as evidenced by radiological demineralization, is associated with enamel hypoplasia in a group of VLBW children.

Patients and Methods

Patients

The study patients attended the Growth and Development Clinic at the Mater Children's Hospital, established in 1978 to provide multidisciplinary longitudinal follow-up of VLBW children. Forty-five children with mean birthweight of 1149 ± 191 g, mean gestational age of 29.4 ± 2.3 weeks, and having adequate radiological records taken during the neonatal period were selected for study. The mean (± SD) ages of all the children at the
time of dental examination was 30 ± 9.1 months (range 18-42 months).

The dental examinations were performed at the University Dental School. Informed consent was obtained from parents for participation in the study. The teeth were dried, and a mirror and probe were used to detect dental caries, opacities, and enamel hypoplasia. A diagnosis of enamel hypoplasia was made if there was a break in the continuity of the enamel surface such as pitting, ridging, or other disturbances of surface contour (Commission on Oral Health, FDI, 1982). Enamel opacities were diagnosed as changes in the translucency of enamel (e.g.: white, brown, or yellow areas without breaks in the continuity of the enamel surface). If a tooth showed both opacity and hypoplasia, a diagnosis of hypoplasia was made. All tooth surfaces were examined, and all dental defects were recorded in comprehensive charts. Intraoral photographs were taken in some children. Postnatal medical and dental histories were obtained from the patients, and maternal and neonatal medical histories were obtained from hospital records.

Radiological Measurements of Cortical Bone

Mineral deficiency in the VLBW infants may be assessed by the degree of skeletal bone mineralization (Cameron et al. 1968; Garn et al. 1971; Poznanski et al. 1980). In this study, bone mineralization was determined by measuring the cortical area of the humerus according to the method of Poznanski et al. (1980). Radiological measurements were performed retrospectively by a radiologist (JPM) who was unaware of the dental examination results. Chest radiographs were taken at a mean age of 10.7 ±11.5 days (range 1-27 days). Although the radiographs were taken at varying times during the neonatal period, the values for cortical area have been shown to be fairly constant for any particular patient up to 60 days postnatal (Masel et al. 1982). For some patients, several radiographs were available. In these cases, a mean value of all the cortical areas was obtained.

Statistical scores for cortical areas

Because the patients differed in their birthweights and gestational ages, it was necessary to compute a statistical score of cortical area for each patient in relation to the standard curve for his/her gestational age. The scores were as follows: 9 for > +2 SD; 8 for +1.5 SD; 7 for +1 SD; 6 for +0.5 SD; 5 for mean, 4 for -0.5 SD; 3 for -1 SD; 2 for -1.5 SD; and 1 for <-2 SD

Statistical Analysis

Student’s t-tests and X² tests were used for statistical analysis of the data.

Results

Prevalence of enamel hypoplasia

Of the 45 children examined, 31 (68.9%) demonstrated enamel hypoplasia (Table 1, see next page). Thirteen of these 31 children (28.9%) had enamel hypoplasia localized to the left primary maxillary central and/or lateral incisor and canine. A further 18 (40.0%) showed generalized enamel hypoplasia usually involving all the primary maxillary incisors, and occasionally the canines. In 14 (31.1%) children, no enamel defects were evident.

Prevalence and type of enamel hypoplasia observed in intubated and nonintubated children

Although it had been previously established that laryngoscopy and endotracheal intubation are associated with localized enamel hypoplasia (Seow et al. 1984a; 1987), the prevalence of each type of defect in intubated and nonintubated children has not been described. This was therefore analyzed in the present study.

As shown in Table 1, 41.9% of intubated children showed localized enamel hypoplasia, 25.9% showed generalized enamel hypoplasia, and 32.2% showed no defect. In contrast, in the nonintubated group of children, none showed localized enamel hypoplasia, 71.4%
had generalized enamel hypoplasia, and no defect was observed in 28.6%. These differences were statistically significant ($X^2 = 10.9, df = 2$), indicating that children with enamel hypoplasia tended to have lower mean cortical areas compared to children without enamel defects.

**Correlation of enamel hypoplasia with bone cortical area**

The mean humeral cortical areas in the groups of children with and without enamel hypoplasia were compared. As shown in Table 2, there were no statistically significant differences in the mean birthweights or gestational ages in these two groups of children. Hence it is appropriate to compare their mean cortical areas directly (Poznanski et al. 1980). As shown in Table 2, children with enamel hypoplasia (either localized or generalized) tended to have lower mean cortical areas compared to those children without enamel hypoplasia. Children with the generalized type of enamel hypoplasia had a mean cortical area of $9.9 \pm 2.0 \text{ mm}^2$ and those with the localized type of enamel hypoplasia had a mean value of $10.4 \pm 1.7 \text{ mm}^2$. In contrast, the children without enamel hypoplasia had a much higher mean cortical area of $13.9 \pm 1.4 \text{ mm}^2$. This difference was statistically significant ($P < 0.001$), indicating that children with enamel hypoplasia tended to have lower cortical areas compared to children without enamel defects.

**Comparison of children with localized and generalized enamel hypoplasia**

Although localized enamel hypoplasia has been associated with local etiological factors, it is of interest to compare children with this form of enamel hypoplasia with those showing the generalized form to determine if there are differences in systemic susceptibility. No significant differences can be detected between these two groups of children in their gestational ages and birthweights (Table 2). More importantly, their mean cortical areas do not differ significantly ($9.9 \pm 2.0$ vs. $10.4 \pm 1.7$) with both statistical scores for cortical mass at about 1 SD below the mean. These results indicate that both localized and generalized enamel hypoplasia are associated with a significantly lower mean cortical mass.

**Comparison of cortical areas in intubated children with and without enamel hypoplasia**

Since not all intubated children demonstrate enamel hypoplasia, the question posed was whether children with enamel hypoplasia also have lower mean cortical areas compared to those without enamel defects. The results (Table 3, see next page) show this to be true, indicating that children with lower cortical masses are those most susceptible to the local traumatic effects of intubation.

**Discussion**

The VLBW prematurely born infant usually suffers a
multitude of serious illnesses during the neonatal period such as respiratory distress, apnea, hypoglycemia, intracranial hemorrhage, cardiac defects, and infections. The high prevalence of enamel hypoplasia in this group of children has been associated with many such conditions individually (Grahnen and Granath 1962; Funakoshi et al. 1981; Johnsen et al. 1984). However, significant associations of individual medical conditions and enamel hypoplasia are not difficult to obtain from statistical computations when low birthweight children with enamel hypoplasia are compared with healthy full-term control children without any enamel defects. The difficulty, therefore, lies in defining the relative importance of these conditions in the pathogenesis of enamel defects. Multivariate analyses often are difficult in these cases, since nearly all the conditions occur concurrently in patients showing enamel defects.

Rather than attempting to discern which individual medical conditions are most important, we have examined a possible central mechanism by which many of these conditions may operate to cause enamel hypoplasia in VLBW children. This is mineral deficiency (or osteopenia) which is diagnosed in our study by measurements of the radiological cortical area of the humerus. Direct measurements of blood calcium levels as indicators of mineral loss usually are not useful, since blood calcium levels tend to remain fairly constant even in cases of extreme calcium deficiency (Binstadt and L'Heureux 1978; Masel et al. 1982) with mineral being removed from calcified tissues to maintain serum homeostasis.

The results of the present study show that children with the lowest mineral stores in bone (i.e., those with cortical areas below the mean for gestational age) are most predisposed to enamel hypoplasia. From these results, it is reasonable to hypothesize that in the presence of mineral deficiency, calcification in dental tissues may be decreased or even halted in an attempt to achieve mineral balance in serum. This hypothesis is substantiated by the observation that children with various types of congenital and acquired forms of calcium balance disorders all show enamel hypoplasia (Hinrichs 1956; Purvis et al. 1973; Garfunkel et al. 1979).

The difference between the 2 groups of intubated children is statistically significant, $P < 0.001$. ($t = 3.75$, df = 30).

In addition, the extreme sensitivity of the ameloblasts to calcium change of even short periods of time is evidenced by the finding that neonatal hypocalcemia of just a few hours duration is associated with enamel hypoplasia (Purvis et al. 1973; Stimmler et al. 1973).

Also of interest is the finding from this study that intubated children with enamel hypoplasia had smaller cortical areas compared with intubated children without enamel defects. These findings indicate that low mineral stores further predispose intubated children to the effects of local trauma from the laryngoscope.

Metabolic bone disease, manifesting as decreased mineralization of bone in prematurely born children (Fig 2) is gaining increasing recognition with improving survival figures for infants weighing less than $1000$ g (Lewin et al. 1971; Davies et al. 1978). However, the pathogenesis still is unclear and in any one infant is likely to be multifactorial in nature. The main cause of metabolic bone disease is probably inadequacy of mineral supply to these infants whose requirements for calcium and phosphate are large. Unsupplemented breast milk which supplies only a fraction of the estimated fetal accretion rate of calcium and phosphorus for the last trimester of pregnancy has been thought to
be a contributory factor (Abrams et al. 1988). However, many VLBW infants fed on a special preterm formula with twice the phosphorus and calcium concentration of human milk and receiving a high intake of vitamin D still developed biochemical evidence of metabolic bone disease (McIntosh et al. 1983; Senterre et al. 1983).

Hence other factors apart from mineral supply also may be involved. One of these may be immaturity of hepatic and kidney vitamin D metabolism (Seino et al. 1981; Kovar et al. 1982); however, there is little evidence that vitamin D deficiency is an important problem. Inadequate placental transfer of calcium and phosphorus also may be a contributory factor, since osteopenia has been found to be more prevalent in neonates with maternal histories of pre-eclampsia (Bosley et al. 1980).

For prophylaxis against metabolic bone disease, it is now common practice to supplement all preterm infants with extra calcium and phosphate, and in some instances vitamin D. All the patients in the present study had been placed on these regimes, yet evidence of osteopenia and enamel hypoplasia still were observed.

Whatever the causes, metabolic bone disease is now considered a common problem of prematurity of birth and low birthweight. Dental defects associated with it also should be recognized so that early dental referral and management of accompanying clinical problems may be instituted.

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Did you know...

- Two recent surveys have ranked dentists second in ethical behavior, echoing a Gallup poll taken several years ago.
  The 795 business persons polled by the Penncle Group ranked 16 professions on the basis of their ethical behavior, with accountants first and dentists second.
  One thousand and ninety-three high school students also ranked dentists second, with doctors chosen first.
- Fewer workers are getting free health insurance benefits and more are having to pay for some or all of their coverage because of rising health insurance costs.
  In 1981, 46% of U.S. workers received free medical insurance, while 37% got free life insurance. Today, those percentages are 40 and 29.
- The percentage of dentists using in-house computers for their bookkeeping system is growing. In 1987, 17.9% of dentists responding to the Dental Economics Annual Practice Survey said they were using computers; in 1988, 23.6% of respondents were using computers; and in 1989, 29.1% of respondents were using in-house computers for bookkeeping purposes.
- American Druggist, a publication for the nation's pharmacists, reported the most commonly dispensed prescription drugs in retail pharmacies for 1988:
  1. Amoxil—Infections
  2. Lanoxin—Arrhythmia/congestive heart failure
  3. Xanax—Anxiety
  4. Zantac—Ulcers
  5. Premarin—Menopause
  6. Dyazide—Hypertension
  7. Tagamet—Ulcers
  8. Tenormin—Hypertension/angina
  9. Naprosyn—Pain/arthritis
  10. Cardizem—Angina