CHANGES IN DENTAL DEVELOPMENT IN PAEDIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASE

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**Summary**

Dental examination of 73 paediatric patients with nephrotic syndrome and 49 with chronic renal failure revealed enamel changes of permanent teeth in about 50%. They consisted usually of white discolorations and hypoplasia of enamel. In nephrotic patients they were observed particularly after the administration of high doses of corticosteroids. In patients with renal failure enamel changes occur very early. Their location was usually compatible with an insult on enamellisation at the time of manifestation of kidney disease. The prevalence of caries was almost twice as high in patients with nephrotic syndrome than in those with renal failure.

**Introduction**

The development of permanent teeth comprises the formation of dental anlage, the production of calcified enamel and dentin and the eruption of teeth. This whole process extends from fetal life to adolescence. However, calcification of enamel is confined to the first 6–7 years. If deposition of enamel is temporarily disturbed its corresponding layers will appear hypoplastic after eruption. If the insult is removed normal enamellisation is resumed. The resultant lesion is irreversible because deficient enamel, in contrast to bone, cannot be replaced. Enamel defects in older children and adults, therefore, serve as markers of damage to ameloblasts and to dental mineralisation in the first years of life [1]. Since enamellisation of individual teeth occurs in an orderly and precise sequence, the location of enamel hypoplasia on a particular tooth after eruption allows one to estimate the age at which the insult has occurred.

It has to be expected that in young patients with chronic kidney disease, which is often accompanied by alterations of mineral metabolism [2], dental development will be disturbed. We have studied the clinical and radiographic changes of permanent dentition in paediatric patients with two different forms of chronic kidney disease, nephrotic syndrome (NS) and chronic renal failure (CRF).
Patients and Methods

The dental status was evaluated in 106 patients with NS; 33 patients were excluded from analysis because they were less than 7 years old at time of dental examination or had an onset of NS less than 2 years previously or had developed renal failure. In the remaining 73 patients (46 males, 27 females) the mean age at examination was 12.4 ± 3.3 (range 7.0 - 24.6) years. Mean age at apparent onset of NS was 4.4 ± 3.0 (range 1.0 - 13.6) years (Table I, Figure 1). All children had the

<table>
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<th>TABLE I. Enamel changes in paediatric patients with nephrotic syndrome and with chronic renal failure</th>
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<td>Number of patients</td>
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<td>Nephrotic syndrome</td>
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<td>Steroid-sensitive</td>
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<td>Total</td>
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<td>Chronic renal failure</td>
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<td>Conservative treatment</td>
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<td>SCR &lt; 5mg/dl</td>
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idiopathic form of the NS except 4 patients with symptomatic NS. Fifty-eight children were steroid sensitive (SS) and 14 were steroid resistant (SR) and were usually associated with a NS persistent up to dental examination. Renal biopsy in patients with the idiopathic NS revealed minimal glomerular changes (37, all SS); focal-segmental glomerulosclerosis (8 SR, 1 SS); membranous nephropathy (3 SR), other histological diagnoses (2 SS, 2 SR); 17 SS patients had no biopsy. Serum creatinine (SCR) was below 1.2mg/dl in all patients.

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Figure 1. Age at onset of disease in patients with nephrotic syndrome without renal failure. The patients with enamel defects are marked by different symbols.

The total amount of prednisone given up to the age of 7 years varied individually and is shown in Figure 2 for those patients in whom exact data is available. The regime of steroid therapy was also variable; since 1970 it was based mainly on the protocols of the International Study of Kidney Disease in Children and of the Arbeitsgemeinschaft für pädiatrische Nephrologie.

Twenty-nine patients had received cytotoxic agents, usually cyclophosphamide (120 cases), the majority after the age of 7 years. Tetracyclines had been given only to a few patients.

The dental status was examined in 49 patients (25 males, 24 females) with CRF. Mean age at time of evaluation was 12.3 ± 1.0 (range 7.2–19.1) years. Mean age at which CRF (serum creatinine > 1.5mg/dl) was first observed was 9.1 ± 4.1 (range 0–17.6 years). The following primary kidney disorders were noted: glomerulonephritis (13), urinary tract malformations (11), juvenile nephronophthisis (7), renal hypoplasia (5), segmental renal hypoplasia (3), tubular disorders (4), haemolytic uraemic syndrome (2), others and unknown (4). At the time of dental examination 28 patients were on conservative treatment (CT), 12 on regular haemodialysis (HD) for 0.5 – 18 (mean 3) months and 9 had cadaver graft functioning between 5 and 54 (mean 31) months. Drug therapy in CRF patients included early application of vitamin D, aluminium hydroxide and calcium supplements, usually from the time when CRF was first diagnosed.

The dental examination included a standard oral inspection and dental photography with emphasis on the detection of enamel changes. The frequency of caries
Figure 2. Teeth with enamel defects in percent of all teeth present in patients with nephrotic syndrome, compared to the total dose of prednisone given up to the age of 7.0 years. Each dot, representing dental discolouration, corresponds to an individual patient. If the dot is related to a triangle both discolouration and hypoplasia of enamel were present in the same patient. Dots on the bottom line (without corresponding vertical line) indicate absence of enamel changes. Up to a total dose of 10g/m² of prednisone only 11 of 20 patients, and above a dose of 20g/m² 7 of 8 patients were affected by alterations of enamel

was determined by the DMF-T index [3]. In addition a standard X-ray of the lower incisors and a separate panorama view of the maxilla and mandible were taken. Radiographic examination of the teeth was performed in most patients with NS and in all patients with CRF. The state of eruption (dental age) was also estimated [1]. An X-ray of the left hand and wrist was usually obtained at the same time for assessment of skeletal age according to Greulich and Pyle.

Results

Dental inspection

Table I and Figure 1 demonstrate that in about half of all patients with NS some enamel defects were found. These changes consisted either of white or yellowish discolorations or of hypoplasia. Only 4 – 6% of normal subjects of similar age show hypoplastic changes of enamel [4]. The enamel defects had a similar incidence in SS and SR patients. They were not related to the age at start of the NS.
However, some relation was found between positive dental findings as expressed by the proportion of teeth affected by discoloration or enamel hypoplasia and the total amount of prednisone given prior to the age of 7 years when enamellisation is usually completed (Figure 2). It appears from our data that with increasing doses the proportion of patients and of teeth affected rises; above a dose of 21g/m² of prednisone all patients were affected.

In CRF the percentage of patients with discoloured teeth or with enamel hypoplasia was similar to that in NS (Table I). No relations existed between the presence of these changes and the age of onset of CRF. However, enamel changes appeared to be more frequent in those patients with an early manifestation of kidney disease. In congenital nephropathies enamel changes were slightly more frequent (15/30 cases) than in acquired kidney disorders (7/18). No significant differences were observed between different treatment groups (Table II), although in the presence of serum creatinine values below 5mg/dl, including some patients with a very early onset of renal symptoms, alterations of enamel appeared more prevalent than in more advanced degrees of CRF (Table I). Enamel changes were also observed in some adolescent patients examined at a very early stage of CRF.

The location of discolourations and enamel hypoplasia was generally compatible with an insult on enamellisation of permanent teeth at the time of onset of the NS; exceptions to this rule were found mainly in the SR group. Ten of 15 patients with enamel changes of first or second incisors had an onset of the NS between the age of 1 and 3.5 years; 5 cases in this group started later, between 5.5 and 13.5 years and 4 of these were SR. Enamel changes of first or second premolars, present in 8 cases of NS, were found in patients older than 6 years at time of first symptoms with only two exceptions. Among the patients with CRF the first or second incisors were generally affected in the presence of congenital nephropathies (9/11 children) whereas 3/7 patients with involvement of first and second premolars had acquired kidney disease.

Caries or filling of teeth was found in 63/73 (86%) subjects with NS and in 32/49 (65%) patients with CRF. The mean value of the DMF-T index was almost twice as high in NS (0.190) than in CRF (0.107), compared to 0.153 in a normal population with a similar age distribution [3].

**Radiographic findings**

Alterations of the lamina dura were frequently encountered in both renal conditions. The number of patients with partial and complete erosions of the laminae durae was 26 and 2 of 40 (70%) NS patients and 25 and 5 of 37 (78%) CRF patients respectively. Absence of dental anlage was observed in only 2 patients with CRF and one with NS, which corresponds to a similar incidence in the normal children [1]. In a few cases the teeth and the roots appeared small (cone-shaped), but mobilisation of the roots was never noticed.

Dental eruption was delayed by more than 1.5 years from the corresponding chronological age in 4 of 47 (8%) patients with CRF but never in those with NS. Retardation of skeletal maturation by more than 15 years was observed in 26 of 47 cases (55%) with CRF and never in NS.
Discussion

Formation of permanent dentition may be disturbed by a number of pathological states, e.g. malnutrition, severe infections, hypothyroidism and other metabolic alterations present during the first years of life. Our study demonstrates that chronic kidney disease starting during this vulnerable period is associated with persisting enamel defects. Similar observations have been made earlier in NS [5-7] and in CRF [7,8]. In contrast to other authors [6] we have found that in children with NS the involvement of enamel is not dependent on the age at onset of the disease. We observed a number of patients with enamel defects in whom the NS was manifest only after the 7th year of life; in some of them (mainly SR cases) the disease may have been present previously in a subclinical state. On the other hand it appears from our data that discolourations and hypoplastic changes of enamel in NS are related to the dose of corticosteroids given during the critical period of enamellation.

The pathogenesis of enamel changes in NS as well as in CRF remains unclear. Besides exogenous influences such as corticosteroids and tetracyclines (applied only in a few of our patients) malnutrition, alterations in mineral metabolism, hormonal changes and perhaps congenital amelogenesis imperfecta may be considered as causal factors.

The clinical significance of these changes in dental development have still to be explored. In the NS they seem to be associated with an increased prevalence of caries, as reported also by others [7], although in individual cases this association is often absent. In CRF caries seems to be less frequent, even when compared to the normal population. Other reports support this impression [7,8]. This relative resistance to the development of caries could be attributed to the antibacterial properties of high salivary urea levels.

Delayed eruption of permanent teeth has been observed only in a few of our patients with CRF. This may indicate that vitamin D deficiency in the early course of chronic kidney disease is not severe enough to delay the eruption of teeth.

Acknowledgments

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Open Discussion

CHANTLER (London) It seems to me that the changes you are describing are similar to those described in neonates with hypocalcaemia and I wonder if you would comment on that. The other point I would like to make is that we have also found this relative resistance to caries in our children with chronic renal failure.

SCHÄRER I think we should not go into the subject of neonatal hypocalcaemia at this meeting but I am sure that the dentists would confirm that hypoplastic enamel after neonatal hypocalcaemia as well as after rickets, hypothyroidism or malnutrition during the first years of life are very similar to the changes presented.

DONCKERWOLCKE (Utrecht) When I compare the data with our own patients, you have a large number of patients with anomalies. What is the incidence of patients with congenital disease in this series of patients with chronic renal failure? Are they all patients with congenital disease?

SCHÄRER No, about a third of our patients with renal failure had acquired kidney disease.

DRUKKER (Jerusalem) Have you seen changes in the cement of the teeth of your patients? In one of our paediatric patients on dialysis, who had spontaneous exfoliation of teeth we have histological evidence with both light microscopy and with electronmicroscopy of local disappearance of cement of the teeth. I do not know how to explain it, unless it is a part of secondary hyperparathyroidism. There is only one short report in the dental literature which refers to this.

SCHÄRER I am not aware that in any one of our patients changes of cement were observed.