Two cases of familial hypomagnesemia with hypercalciuria and nefrocalcinosis: dental findings

N. CETRULLO, M.G. GUADAGNI, G. PIANA

ABSTRACT. Background The authors describe dental and periodontal conditions of two Chinese sisters affected by familial hypomagnesemia with hypercalciuria and nefrocalcinosis (FHHNC). FHHNC is a rare syndrome, genetically investigated since 1999, transmitted as an autosomal recessive disease. It is related to a mutation of PCN-1 gene which encodes for a tight junction protein named paracellin. Case report Oral examination of two Chinese patients showed marked enamel hypoplasia, acute gingivitis and periodontal bone loss and severe malocclusion. The literature does not report previous investigations about the dental conditions of FHHNC patients. The syndrome is not definitely described from the clinical point of view. Conclusion Further researches are necessary to understand the linkage between bone loss and enamel structure anomalies in FHHNC and to discover the relationships between nefrocalcinosis, hypomagnesemia, hypercalciuria and amelogenesis imperfecta.

KEYWORDS: Hypomagnesemia, Nefrocalcinosis, Enamel hypoplasia, Amelogenesis imperfecta.

Introduction

Familial hypomagnesemia with hypercalciuria and nefrocalcinosis (FHHNC) is a rare syndrome (MIM 248250 and MIM 603959), first named by Praga in 1995, who cited the cases reported by Michelis as examples of the disorder [Praga et al., 1995; Michelis et al., 1972; Rodriguez-Soriano et al., 1987]. They all described patients with polyuria-polydipsia, ocular abnormalities, recurrent urinary tract infections and recurrent renal lithiasis. All the cases were affected by bilateral nephrocalcinosis.

The genome scanning of 12 kindreds with typical recessive renal hypomagnesemia demonstrated that the anomaly was located in a segment of chromosome 3q [Simon et al., 1999]. The tract was further localized to an approximately 1-cM interval flanked by loci 539-5 and D3S1288. By exon trapping, they identified the gene and called it paracellin-1. By SSCP and sequencing, the researchers found 10 different mutations in 10 of the kindreds with primary hypomagnesemia. The mutations were found in homozygous state in 8 kindreds and in compound heterozygous state in 2.

In a recent study Weber et al. [2000] confirmed the implication of paracellin-1 gene defect in the development of FNHHC and pointed out the dominant role of this protein in the paracellular reabsorption of divalent cations. FHHNC is an autosomal recessive tubular disorder and it is associated with progressive renal failure in early childhood and adolescence. All the FHHNC patients presented hypomagnesemia, hypercalciuria and nefrocalcinosis. Clinical signs are very important and can be revealed from the sixth week of life. Symptoms are reported in Table 1.

The primary defect is related to impaired tubular reabsorption of magnesium (Mg) and calcium (Ca) in the thick ascending limb of Henle’s loop. Impaired function of the paracellin-1 gene (PCLN-) leads to urinary loss of magnesium and calcium.

Limited data are available on clinical course, therapy and prognosis. Renal transplantation seems to be the definite treatment [Ram Prabahar et al., 2006].

Scientific articles reported that neither chronic oral Mg administration nor thiazide (diuretics) are able to normalize serum magnesium levels or urinary calcium excretions, respectively [Kari et al., 2003; Knohl et al., 2004]. Renal function would inevitably worsen and the progression rate of renal insufficiency is related to the severity of nephrocalcinosis.

Wolf reported that early treatment with D vitamin and Calcium are essential to promote body growth [Wolf et al., 2002]. Adequate treatment allow the
patients to reach both normal height and pubertal development but, despite calcium and magnesium substitution, normal values can not be achieved: the progression of renal failure can not be arrested [Wolf et al., 2002; Ram Prabahar et al., 2006].

Case reports about patients affected by FHHNC did not describe any dental finding that can be considered peculiar for this category of subjects.

The authors therefore present the dental features of two Chinese sisters with FHHNC referred to the Department of Dental Sciences - Special Care Unit of the University of Bologna.

**Cases report**

Two Chinese sisters of 18 and 14 years respectively, were diagnosed in March 2004 with familial hypomagnesemia with hypercalciuria and nefrocalcinosis (FHHNC). In addition the patients presented chondro-epiphisary dysplasia, growth retardation and defects (particularly the elder one).

The two girls were referred for consultation to the Department of Dental Sciences, Special Care Unit of the University of Bologna (Italy) by the Department of Paediatrics, because the paediatricians noticed their bad oral conditions.

**Case 1**

XHX, 18 years old (Fig. 1). The subject’s dental examination revealed a full permanent dentition, severe enamel hypoplasia with fissures and pits and brown stained enamel (Fig. 2, 3). Oral hygiene was poor: significant plaque accumulation (Periodontal Index = 2), gingivitis (Gingival Index = 2), bleeding and periodontal pocketing, mobility affecting most of the teeth. Periodontal acute inflammation of teeth 3.6 and 4.6. She referred pain in the left side of the mandible and discomfort while chewing.

The X-ray examination confirmed generalised alveolar bone loss; lower incisors and first molars were severely affected by periodontal disease (Fig. 5).

From the orthodontic point of view the patient showed: severe Class III malocclusion with Class III molar and canine relation, midline deviation (inferior to the right: 6 mm), anterior open and cross-bite and left posterior open bite, overjet -3, overbite +2 (Fig. 4).

Antibiotic therapy was immediately administered to treat infection and pain caused by the apical lesion. Oral hygiene instructions were given to the patient. Scaling and root planing were performed and frequent hygiene recalls were suggested to monitor the periodontal tissues conditions. Conservative therapy to improve aesthetics, of the front teeth in particular, was scheduled together with topical fluoride applications to protect the enamel tissue.

A combined orthodontic surgical treatment plan was outlined, but the surgical team advised against surgery because of the severe periodontal condition.
Case 2
LX, 14 years old (Fig. 6). The patient had full permanent dentition except for the element 1.3., retained. Oral examination revealed: marked enamel hypoplasia, periodontal disease, abundant dental plaque, severe gingivitis, bleeding on probing (Periodontal Index = 2, Gingival Index = 2), caries of 1.7, 2.6, 3.6, 3.7 and 4.6. (Fig. 7, 8). The x-ray examination showed the canine impaction and signs of horizontal bone loss (Fig. 10).
Orthodontic evaluation showed: skeletal Class III malocclusion with Class III molar and canine relation, anterior open and cross-bite, bilateral posterior cross-bite, overjet -3, overbite -0.5 (Fig. 9).
Scaling and root planing were performed. The decayed elements underwent conservative treatment and oral hygiene maintenance programme was scheduled.

Prognosis
Both sisters were advised about the importance of maintaining a good dental hygiene and regular dental check ups.
The two cases described have been both scheduled for a long term follow up in order to support dental and periodontal healthy conditions, to promote a good oral function and avoid pain, with the awareness that the
systemic disease will proceed towards renal failure and renal transplantation will be definite treatment.

**Discussion**

FHHNC is a very rare disease and there is no description of dental condition of these patients in literature. Furthermore, the syndrome is not definitely described and there are several clinical variants of hypomagnesemia associated with other symptoms. For example, chondrocalcinosis and growth defects are described in Gitelman’s variant of Bartter’s Syndrome (characterized by hypomagnesemia associated with calcium-pyrophosphate dehydrate crystal -CPPD- deposition, hypokaliemia and hypercalciuria); hence hypomagnesemia cannot be considered typical of FHHNC strictly speaking [Bettinelli et al., 2003, Normand de la Tranchade, 2003]. We found reports of amelogenesis imperfecta and nefrocalcinosis in a rare autosomal recessive inherited syndrome described first by Mc Gibbon in 1972 and then by Lubinsky et al. in 1985, defined as Enamel-Renal Syndrome (ERS) (MacGibbon, 1972; Lubinsky et al., 1985).

Another case of this syndrome was described by Normand de la Tranchade et al. in 2003. The author reported the case of a patient with enamel agenesis of the primary and permanent dentition, delayed or absent eruption of the permanent dentition, coronal intra-alveolar resorption and gingival enlargement [Normand de la Tranchade et al., 2003]. Renal symptoms included medullary nephrocalcinosis with no apparent cause and evolution to renal failure.

The pathogenesis of this disease has been correlated to vitamin K-dependent calcium binding protein, although the authors recognised that the findings could represent secondary changes [Lubinsky et al., 1985]. Abnormalities in calcium-phosphate metabolism are supposed to lead to dental structural defects and periodontal anomalies.

Dent’s disease is an X-linked disorder characterised by hypercalciuria. It is associated with gene mutations that disrupt the function of a voltage-gated chloride channel and impair the filtered proteins reabsorption, as well as other transport functions of proximal tubules. Therefore the genetic defect leads, apparently indirectly, to hypercalciuria and renal failure [Knohl et al., 2004].

No description of dental conditions of these patients is available in the literature.

Comprehensive researches are necessary to understand the linkage between renal dysfunction/bone loss and enamel structure anomalies in FHHNC in order to find the possible relation...
between nefrocalcinosis and amelogenesis imperfecta.

It is interesting to notice that the eldest of the two sisters has a worse periodontal condition than the younger one and that the enamel defects are not similar. The large amount of dental plaque and the age could explain the severe gengivitis of case 1; X-ray examination showed aspects similar to juvenile periodontitis.

References


