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Case report

Oral findings associated with primary hyperoxaluria type I

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ABSTRACT

In the present paper we report the oral findings of a patient who was diagnosed with hyperoxaluria. Hyperoxalurias can basically be classified as primary and secondary, with the first being inborn errors of metabolism and the second a result of excessive oxalate intake.

Primary hyperoxalurias form a rare group of metabolic diseases that are inherited in the autosomal recessive fashion. The affected genes code for specific hepatic enzymes that are involved in glyoxylate metabolism and their deficiency results in overproduction of oxalate.

Two different types are described: Primary hyperoxaluria type I results from a deficiency of peroxisomal enzyme alanine–glyoxylate aminotransferase and the more rare type II from a deficiency of cytosolic enzyme D-glycerate dehydrogenase.

Since oxalate is primarily excreted through the kidneys, abnormally high concentration of oxalate in the urine occurs. This can in turn result in recurrent kidney stones and parenchymal renal damage and end-stage renal disease (ESRD). Inability to further excrete oxalate through the kidneys leads to its deposition in various organs (oxalosis).

Several oral findings have been described in patients with oxalosis, most important of whose are bone resorption in the jaws, external root resorption and rapidly progressive dental mobility, as well as dental pain associated with deposition of oxalate in the dentine and the pulp.

1. Introduction

Oxalate is an end product of the metabolism and is excreted primarily by the kidneys (Hoppe and Langman, 2003; Raju et al., 2008; Hoppe et al., 2009).

Hyperoxaluria, as is suggested by its name is defined as excretion of oxalate in the urine above the normal levels, that is above 0.5 mmol/1.73 m^2 per day (Hoppe and Langman, 2003; Hoppe et al., 2009). The high concentration of oxalate leads to supersaturation of the urine in calcium oxalate and subsequent aggregation of calcium oxalate crystals into stones. Crystals also accumulate inside the renal tubule cells and into the renal parenchyma (Hoppe and Langman, 2003; Hoppe et al., 2009).

The resulting renal damage and the decline of GFR leads to inability of the kidneys to further excrete oxalate and a rise in blood oxalate concentration above the level of calcium oxalate supersaturation (30 mmol/L) and the resulting calcium oxalate deposition in various organs, thus leading to systemic complications (Bobrowsky and Langman, 2008).

This deposition of calcium oxalate crystals in extrarenal tissues was first named oxalosis by *Chaplin* in 1977.

The initial rise in oxalate concentration in the blood that leads to hyperoxaluria can either be due to inborn errors of metabolism (primary hyperoxaluria) or to increased dietary uptake and absorption of oxalate in the GI tract (secondary hyperoxaluria) (Chaplin, 1977; Hoppe and Langman, 2003; Cochat et al., 2006; Bobrowsky and Langman, 2008; Raju et al., 2008; Hoppe et al., 2009; Panis et al., 2010).

Dietary factors such as excessive consumption of rhubarb or ethylene glycol as well as Klinefelter syndrome, liver cirrhosis, sarcoidosis and intestinal bypass surgery with the aim of weight reduction, steatorrhea or any other indigestion with malabsorption were assumed to have an aetiopathogenic relationship with secondary hyperoxaluria (Glass, 1973; Fantasia et al., 1982; Lapointe and Listrom, 1988). The common factor in all the above-mentioned condition is the absence of the binding of oxalate to insoluble calcium-oxalate that normally takes place in the intestine (Glass, 1973).

Primary hyperoxaluria was first described by *LePoutre* in 1925 and its genetic character was recognised in the fifties (LePoutre, 1925; Dunn, 1955). Two main genetic forms are recognised, with respective mutations in two enzymes in the glyoxylate pathway

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(Milliner et al., 2001; Hoppe and Langman, 2003; Cochat et al., 2006). However, other forms of primary hyperoxaluria that do not fall in the two basic categories have been described (Monico et al., 2002; Hoppe and Langman, 2003).

Today we know that primary hyperoxaluria (PH1) is an autosomal-recessive deficiency of peroxisomal alanine:glyoxylate aminotransferase (AGT) within hepatocytes. This enzymatic deficiency may be partial or complete, leading respectively to different severity of the disease. The enzyme can be completely absent, inactive or incorrectly sited in mitochondria instead of in the peroxisome due to mistargeting (Danpure, 1995; Danpure et al., 1994, 1996; Leiper et al., 1996). Recent studies of the molecular basis of these enzyme defects have allowed the identification of many of the underlying genetic mutations and their structural effects on the enzyme (Danpure, 1998; Basmaison et al., 2000; Rumsby, 2000; Santana et al., 2003; von Schnakenburg et al., 2003; Zhang et al., 2003; Yuen et al., 2004). In patients with PH1 a failure to follow the normal metabolic pathway of conversion of glyoxylate to glycine within the peroxisome results in glyoxylate instead being metabolised in the cytosol to form oxalate and glycolate (Gibbs and Watts, 1973; Hoppe and Langman, 2003; Bobrowsky and Langman, 2008; Hoppe et al., 2009).

In Europe PH1 has an incidence of $1/10^7$ population/year and a prevalence of $1–3/10^6$ (Cochat et al., 1995; van Woerden et al., 2003).

The deposition of oxalate crystals is most prominent in kidneys and bone, but may also be observed in other organs such as the teeth. In those cases where the diagnosis is made before the establishment of renal impairment, there is a gradual decline in renal function over a period of years with the onset of chronic renal failure occurring in late childhood or early adult life.

An infantile form is also recognised with an early rapid progression, but the correlation between genotype and phenotype in terms of disease course varies greatly and, even within the same family, quite different clinical patterns are observed with apparently the same genetic defect (Shapiro et al., 2001; Pirulli et al., 2003). Once the patient is in established renal failure, oxalate can no longer be excreted and systemic oxalosis rapidly develops with progressive clinical deterioration.

Implied therapeutic measures, which include careful dietary management, high fluid intake (with the goal of maintaining a constant high urine output and secretion of low osmolality urine, thus reducing the risk of crystallisation and stone formation) (Scheinman, 1991) and pharmacological manipulation (citrate, pyridoxine) (Leumann et al., 1986, 1995; Milliner et al., 1994; Hoppe and Langman, 2003), may delay or prevent the development of stone disease. These measures along with optimal management of calculi are the essential features of treatment but can only be initialised when the diagnosis is established. Unfortunately diagnosis is often established late in the natural history of the disease and patients often present with renal failure (Cochat et al., 1995; Milliner et al., 1998; van Woerden et al., 2003).

Intensive haemodialysis may at best be able to remove oxalate effectively in a sufficient degree, so as to slow the rate of accumulation but the rate of production cannot be matched (Hoppe et al., 1996; Yamauchi et al., 2001). Renal transplantation alone cannot obviously correct the underlying metabolic defect but, in selected cases, when there are living donors available, so that an optimal early graft function is ensured, and with appropriate careful post-operative medical management a good outcome can be expected (Milliner et al., 1998; Scheinman, 1998; Monico and Milliner, 2001). Nonetheless the general renal transplant survival (particularly with cadaveric grafts) in PH1 patients has been disappointing (Broyer et al., 1990; Hoppe and Langman, 2003).

In 1987, Watts and co-workers described a new treatment involving both liver and kidney transplantation in an effort to achieve more normal enzymatic conditions for oxalate metabolism (Watts et al., 1987). The method has been quite successful and has taken a central role in the management of PH1 (Cochat et al., 1999; Millan et al., 2003; Jamieson, 2005).

A milder but not benign second type of primary hyperoxaluria has also been described. Here the deficient enzyme is glyoxylate reductase/hydroxypyruvate reductase (GPHPR). The course of the disease is slower and patients can be asymptomatic for many years. Stone formation is less severe and renal function is better preserved overtime (Kemper et al., 1997; Hoppe et al., 2009). Patients with PH2 do not benefit from pyridoxine and there has not been demonstrated that liver transplantation is helpful. Therefore, kidney transplantation alone remains the appropriate therapy and patients tend to respond relatively well (Hoppe et al., 1996, 2009; Bobrowsky and Langman, 2008).

Oral findings associated with hyperoxaluria are rarely described. The fact that worldwide less than a dozen case reports with information about effects of oxaluria on teeth and oral tissue have been published, could either be attributed to the more dominant constitutional symptoms like nephrolithiasis, joint and muscular pain as a result of accumulation of oxalate crystals with foreign body reactions. More reports have come up recently, which can be attributed since the introduction of dialysis and the implementation of novel therapeutical approaches that led to the higher life expectancy, allowing oral findings to manifest (Bunte et al., 1977).

2. Case report

A 23-year-old male patient, who was being prepared for liver and kidney transplantation was referred to our department for assessment, due to extensive dental mobility. The patient reported that kidney transplantation due to nephrolithiasis has been performed twice before. Failure of the last transplantation despite of immunosuppressant therapy forced again the patient to undergo haemodialysis for a period of sixth months. Three years ago, the patient was submitted to parathyroidectomy due to osteoporosis. A family history (four half brothers and sisters) of consanguinity was ruled out, whereupon his father is not acquainted with him.

On referral the patient presented complaining of arthralgia in the right wrist joint, which was strongly attenuated by his job as a bookbinder. A body height of 168 cm and a weight of 52 kg were documented. Laboratory findings revealed pathological aberrance concerning both serum test and differential blood count.

On oral examination the clinical picture was dominated by generalized gingivitis in combination with dental mobility due to severe periodontitis. There were no missing teeth in the maxilla, whereas the second mandibular premolar was absent on both sides, with an existing gap the width of a molar.

As far as imaging was concerned, the orthopantomograms (Fig. 1) taken at three months' intervals show a severe root resorption of the middle maxillary incisors and an initial resorption of the apical part of the root of the right central mandibular incisor. There was also a marked resorption of the mesial roots of the lower first molars whereas the sensitivity of the above-mentioned teeth was preserved. Distal to the last right lower molar the X-ray, a radiolucency concerning the ventral part of the ascending ramus up to the incisura was shown. The lesion was well demarcated, but without a sclerotic borderline, which is typical of cysts. 12 weeks later (Fig. 2) the resorption of the roots of the above-mentioned teeth has clearly progressed and involvement of other teeth was now noticed. Particularly impressive was the loss of bone in the region of the diastema in the lower jaw on both sides and of the left ascending ramus, where now osteolysis started.