CASE HISTORY REPORT

Primary hyperoxaluria: Orthodontic management in a pediatric patient: A case report

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Abstract
Aims: The aim of this study is to report the case of the orthodontic treatment in a patient affected by primary hyperoxaluria type 1 and subjected to a combined liver-kidney transplant.

Methods and results: The 9-year patient was admitted to our department for the presence of facial dysmorphism. The patient was affected by primary hyperoxaluria type 1 and has undergone a combined liver-kidney transplantation. At the time of the visit, he was in treatment with immunosuppressive drugs and received a corticosteroid and an antibiotic therapy monthly. An intraoral and extraoral examination, as well as radiographic and model analysis, was performed in order to define an accurate diagnosis and a proper rehabilitation planning. An orthopedic-orthodontic treatment was performed and satisfactory final results obtained. A laser gingivectomy was also realized for eliminate the gengival hyperplasia probably induced by cyclosporine assumption. Both skeletal and dental relationships were improved by the treatment, reaching a good dental arches alignment.

Conclusion: An early diagnosis, as well as a multidisciplinary approach, is very important in patients with rare diseases. An appropriate treatment allowed us to achieve acceptable results and improve the patient quality of life.

KEYWORDS
orthodontics, pediatric dentistry, rare disorders

1 INTRODUCTION

Primary hyperoxalurias (PH) are a group of rare metabolic diseases with an autosomal recessive transmission, which causes an alteration of the glioxalate and oxalate metabolism.1 These conditions are characterized by an increased endogenous production of oxalate, a terminal metabolic product, which leads to an excessive urinary excretion of oxalate with consequent hyperoxaluria (>0.5 mmol/1.73 m² per 24h) in comparison to the normal oxalate excretion (<0.45 mmol/1.73 m² per day), and formation of insoluble calcium oxalate crystals. The kidneys undergo progressive deterioration due to calcium oxalate deposition: urolithiasis, nephrocalcinosis, and end-stage renal disease (ESRD). The parenchymal deposition of oxalate (nephrocalcinosis) induces interstitial inflammation and fibrosis that result in progressive loss of renal function.2 The renal damage is followed by an increase of oxalate concentration in blood over its sovrasaturation level (30 mmol/L).

To date, three distinct hereditary enzymatic deficiencies have been linked to PH, namely, PH type 1 (PH1), type 2 (PH2), and type 3 (PH3), and there is evidence to
speculate that further causes are yet to be identified. PH1 is the most severe and common one (incidence 1:100 000 born alive per year in Europe). It is caused by the deficit of the liver peroxisomal enzyme: alanine-glyoxylate amino transferase. PH2, rarest than the previous one, is due to a deficit of the cytosolic enzyme glyoxylate reductase/hydroxypruvate reductase. Instead, PH3, of recent identification, is caused by a deficit of the mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase. These forms should be distinguished from the secondary hyperoxalurias, caused instead by an excessive ingestion of oxalate, its precursors or ascorbic acid, vitamin B6 (or piridoxin), or by an increased intestinal absorption, a repeated use of oral antibiotics that lead to oxalate elimination, professional exposure, both to oxalic acid (workers exposed to detergents and blanchers), both to ethilenic glicole (general anesthetic), and during hemodialysis.

Around 80% of PH patients suffer PH1, characterized by systemic deposits of calcium oxalate monohydrate (ossalosis) at level of bones, heart, ocular tissue, tiroid, lymph nodes, skin, artery and venus walls, brain, meninges, and salivary glands and unless liver-kidney transplantation is performed, this condition quickly results in death in most patients. Only about 10 cases described in the literature report oral manifestations in patients with hyperoxaluria. The age of the treated patients ranged between 7 and 55 years and the most common manifestation was represented by periodontal disease. The other oral findings described in patients with oxalosis, were: 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. All these findings make the therapeutic approach more difficult than that of healthy patients. Furthermore, like stated by American Academy of Pediatric Dentistry, the most frequently documented source of sepsis in the immunosuppressed patient is the mouth. For this reasons, every patient who will receive an immunosuppressive therapy should be evaluated by dental specialists to define an appropriate approach. In particular, regarding the orthodontic appliances, the guidelines define that poorly-fitting appliances can abrade oral mucosa and increase the risk of microbial invasion into deeper tissues. Appliances should be removed if the patient has poor oral hygiene, while in patients who present good hygiene simple appliances (eg, band and loops, fixed lower lingual arches) that are not irritating to the soft tissues may be left in place. If possible, removable appliances and retainers should be preferred to the fixed ones and may be worn as long as tolerated by the patients.

The median age at initial symptoms of PH1 is 4 to 7 years in Europe. The pediatric form often presents as a life-threatening condition because of rapid progression to ESRD; at the time of the diagnosis 50% of the patients experience ESRD and 80% develop it by the age of 3 years.

The diagnosis is performed by following elements: sono-graphic examination that may show either cortical or medullary nephrocalcinosis, stone passage, nephrocalcinosis, and renal impairment. Crystalluria and infrared spectroscopy are of major interest for identification and quantitative analysis of crystals and stones.

In patients with normal or significant residual glomerular filtration rate (GFR), concomitant hyperoxaluria (urine oxalate >1 mmol/l/1.73 m2 per day, reference value 0.5 mmol/l/1.73 m2) and hyperglycoluria (urine glycolate >0.5 mmol/l/1.73 m2, reference value <0.05) are indicative of PH1, but some patients do not present hyperglycoluria.

The treatment consists in an initial conservative approach, dialysis and organ transplantation for replacing the oxalate-producing liver and the kidney with a donor organ. The strategy of liver-kidney transplantation is influenced by the stage of the disease.

Calcium-phosphate disturbances may affect the structure and metabolism of mandibular bones, promote calcification of dental pulp, and in children may cause developmental defects of teeth.

There is also a positive correlation between discoloration of the deciduous teeth and liver transplantation and between enamel hypoplasia and kidney transplantation. Pulp stones are more frequent in the kidney recipients than in liver-transplanted patients. A gingival overgrowth due to cyclosporine A (CsA) medication is widely reported in literature. CsA is ordinarily used as an effective immunosuppressive agent to prevent organ transplant rejection, as well as in the treatment of patients with adverse side effects including nephrotoxicity and hypertrichosis.

Recently, a new immunosuppressive agent, tacrolimus (TAC/FK 506), has been approved for use in solid organ transplants. The use of CsA or TAC shows no difference in enamel defects, discoloration, or caries experience.

Another complication is posttransplantation bone disease which is present in most of patients, where low bone mineral density increases the risk of fractures. Frequently, bone loss occurs in the first year after the organ transplant, due to the adverse effects of immunosuppressive drugs and, in addition, due to the long period of immobilization.

The aim of this study is to report the case of the orthodontic treatment in a small patient affected by PH1 and subjected to a combine liver-kidney transplant.

2 | CASE REPORT

The young patient, F.R., was admitted to our department in 2005 when he was 9 years old for the presence of facial
dysmorphism. In the anamnesis, the diagnosis of PH1 emerged. After the renal involvement linked to the disease, the patient has been subjected to dialysis from the age of 3 years and when he was 5 years old underwent a combine liver-kidney transplantation.

At 7 years age a cochlear implant insertion was performed, since a secondary drug-induced deafness had occurred.

At the moment of our examination, he was in therapy with immunosuppressive drugs (cyclosporine and mycophenolate mofetil), vitamin D, sodium bicarbonate, and K-based and Mg-based nutritional supplements. Moreover, he underwent a corticosteroid treatment and an antibiotic therapy monthly.

The extraoral objective structured clinical examination showed a symmetrical face with low-implant auricles and a
concave profile with upper jaw hypoplasia (Figures 1a and 1b).

At intraoral examination (Figures 2a and 2b), the following findings were identified: a widespread enamel hypoplasias, Class III canine and molar dental relationship, upper diastema of the incisors, crowding in the lower arch, and generalized gengival hyperplasia, probably induced by cyclosporine assumption.

Panoramic radiograph (Rx-OPT) showed the absence of external radicular resorption as well as parodontal or bone lesions (Figure 3a). The latero-lateral rx (Figure 3b) and the relative cephalometric analysis according to Giannì (Table 1) revealed the presence of a skeletal Class I tending to Class III (subspinale(A)-nasion(N)-suprmanetae(B) angle (ANB) = 1), skeletal deep-bite, normo-divergence, and normal mandibular growth with horizontal growth pattern.

An interesting finding was constituted by a particular conformation of the hands, presenting short phalanges (Figure 4).

The aims of the treatment were: to correct the skeletal relationship between the upper and lower jaws, to resolve the crowding in the lower arch, to reach a dental Class I, and to reduce the gingival hyperplasia.

After a plurispecialized medical examination and an oral hygiene and prophylaxis program with recurrent medical examination, the patient was subjected to a treatment divided in three steps:

- orthopedic treatment with Delaire Mask for three and a half years;
- orthodontic treatment of the lower arch with Straight Wire technique. In order to decrease the accumulation of dental plaque, we opted for key techniques of orthodontic management, such as: to avoid molar bands and to involve only the crowded teeth bonding from 3.3 to 4.3 (orthodontic archwire sequence: NiTi .014, .016, .018 and steel .014), to use small-sized brackets, to remove carefully the excessive composite, to plan frequent follow-up, the final upper and lower removable retainers; and
- laser gingivectomy (Figures 2c and 2d) with laser diodes (super pulsed, 4 Watt, fibre 400 μm).

Final extraoral (Figures 1c and 1d) and intraoral photos (Figure 5a-e) were acquired. Rx-OPT (Figure 3c) and lateral teleradiography (L-L rx) (Figure 3d) were performed.

At the end of orthodontic treatment, esthetic reconstructions of the upper central incisors to close midline diastema using composite resin materials were performed (Figure 5f).

3 | RESULTS

The orthopedic/orthodontic treatment has improved both skeletal and dental relationships (orthodontic camouflage), reaching a good dental arches alignment. The laser surgery solved the gingival hyperplasia. The observance of a proper domestic oral hygiene by the patient contributed to the
Table 1  Cephalometric analysis according to Jarabak

<table>
<thead>
<tr>
<th>Cephalometric L-L study</th>
<th>Normal value</th>
<th>11 years</th>
<th>17 years</th>
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<tr>
<td>Sagittal skeletal relationships (°)</td>
<td></td>
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<tr>
<td>SNA</td>
<td>82 ± 2</td>
<td>77</td>
<td>79</td>
</tr>
<tr>
<td>SNB</td>
<td>80 ± 2</td>
<td>76</td>
<td>78</td>
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<tr>
<td>ANB</td>
<td>2 ± 2</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Vertical skeletal relationships (°)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ar-S-N</td>
<td>122 ± 5</td>
<td>124</td>
<td>130</td>
</tr>
<tr>
<td>S-Ar-Go</td>
<td>143 ± 6</td>
<td>145</td>
<td>137</td>
</tr>
<tr>
<td>Ar-Go-Me</td>
<td>120 ± 5</td>
<td>124</td>
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<tr>
<td>Ar-Go-N</td>
<td>50 ± 2</td>
<td>53</td>
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<tr>
<td>N-Go-Me</td>
<td>70 ± 3</td>
<td>71</td>
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<tr>
<td>S+Ar+Go</td>
<td>396 ± 2</td>
<td>393</td>
<td>394</td>
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<tr>
<td>S-N/Go-Me</td>
<td>32 ± 5</td>
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<td>Vertical skeletal relationships (mm)</td>
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<tr>
<td>N-Me</td>
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<tr>
<td>S-Go</td>
<td>65</td>
<td>81</td>
<td></td>
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<tr>
<td>% Jarabak</td>
<td>59%–63%</td>
<td>55%</td>
<td>58%</td>
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<td>Sagittal plane (mm)</td>
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<tr>
<td>S-N</td>
<td>71 ± 3</td>
<td>70</td>
<td>78</td>
</tr>
<tr>
<td>Go-Me</td>
<td>71 ± 5</td>
<td>60</td>
<td>78</td>
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<tr>
<td>Cranial base length (mm)</td>
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<tr>
<td>S-N</td>
<td>71 ± 3</td>
<td>70</td>
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<tr>
<td>S-Ar</td>
<td>32 ± 2</td>
<td>31</td>
<td>38</td>
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<td>Mandibular component (mm)</td>
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<tr>
<td>Ar-Go</td>
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<tr>
<td>Go-Me</td>
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<td>Dentoalveolar component (°)</td>
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<tr>
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<td>Interincisal angle</td>
<td>130 ± 5</td>
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<td>140</td>
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</table>

ANB: subspinale(A)-nasion(N)-supramentale(B) angle; SNA, sella(S)-nasion(N)-subspinale(A) angle; SNB, sella(S)-nasion(N)-supramentale(B) angle.

4 | DISCUSSION

PH and complications resulting from its management can lead to severe impairments of different organs.23

The first discussion of the oral manifestation of the PH was performed by Glass in his case report (1973), regarding oral findings in a patient diagnosed with PH (postmortem).24

To date, few papers have described the oral complications of this disease.8,10,25–31 Oral manifestations of hyperoxaluria are rare. Among the main complications: hypodontia and microdontia, dental pain,26,30 root resorption,31 periodontal diseases8,10 and bone alterations such as radiolucencies in the jaws32 are described.22 These alterations are due to both the primary disease and to secondary parathyroidism due to the chronic renal failure, as well as to the transplantation sequelae and protracted pharmacological treatments.20 Bone and tooth resorption may be the result of chronic inflammation and the presence of osteoclastic cells surrounding the oxalate crystal deposits.33

The management of these patients requires a multidisciplinary approach and, as early as possible, a dental intervention. Besides the complications mentioned above, in consideration of an orthodontic treatment in such patients, some observations should be made. In particular, an important consideration with orthodontic implication is the altered Ca/P metabolism and bone turnover linked to the kidney-liver transplantation and the related immunosuppressive therapy. Moreover, dialyzed and transplanted patients demonstrate a premature loss of the osseous tissue (compact alveolar lamina, alveolar bone), which may lead to gomphosis, and impaired bone trabeculation and demineralization resulting in resorption of the periodical tissue, and even fracture of the maxilla and mandible22 as well as in other rare diseases.34 Our pediatric patient was under corticosteroid treatment which, in animal studies, has been shown to interfere with orthodontic tooth movement rate and tissue reaction.35 Furthermore, it was observed that chronic steroid ingestion leads to an increased biological reaction to mechanical perturbation indicating that the orthodontic force level should be reduced and controlled more frequently in patients on chronic steroid treatment.36

For these reasons, frequent and accurate orthodontic examinations were necessary in order to check the dental movements and the hard tissues alterations31 as well as for other rare diseases characterized by altered Ca/P metabolism.57–39 Furthermore, the gingival hyperplasia due to cyclosporine therapy had to be treated, as put at risk the periodontum status.

5 | CONCLUSIONS

It is clear that this kind of patient requires an accurate anamnesis, a well-timed intervention, a careful dental-periodontal evaluation, good oral health standards, and an appropriate
management of the orthodontic strengths in order to reach positive and stable in time results.

Early diagnosis and consequent early intervention are very important, especially in patients with rare diseases.

Our multidisciplinary approach allowed us to achieve acceptable results, avoiding the recourse to invasive surgical techniques and increasing at the same time the small patient compliance and his quality of life.

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CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

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INFORMED CONSENT
Informed consent was obtained from all individual participants included in the study.

DECLARATION OF PATIENT CONSENT
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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