Prolidase deficiency: dento-facial aspects in a paediatric patient

ABSTRACT

Background Prolidase Deficiency (PD) is a rare hereditary disease consisting in developmental delay, mental retardation, facial dysmorphosis, splenomegaly, recurrent pulmonary infections and skin lesions.

Case report The present study reports a case of PD treated in the Paediatric Section of the Department of Dentistry and Surgery at the University of Bari. A special diagnostic and clinical approach to the patient was useful to improve his quality of life and identify some new aspects of this systemic disease. In particular, clinical features never described before are reported: low hairline, decreased osteotendinous reflexes, long upper lip, microrhinia, dentoskeletal Class III, dental age (Proffit) older than chronological age, fusion of 2nd and 3rd cervical vertebrae, incomplete atlanto-occipital fusion.

Keywords Hyperiminodipeptiduria; Hyperprolinemia; Prolidase deficiency; Skin lesions.

Introduction

Prolidase Deficiency (PD), first described in 1968, is a rare autosomal recessive disease that belongs to monogenic human inborn errors of metabolism of L-proline along with hyperprolinemia type I (HPI), hyperprolinemia type II (HPII), D1-pyrroline-5-carboxylic acid (P5C) synthetase deficiency, ornithine aminotransferase (OAT) deficiency, hydroxyprolinemia, and iminoglycinuria [Mitsubuchi et al., 2008; Shrinat et al., 1997]. PD prevalence rate is lower than 1:1,000,000: about 100 cases have been diagnosed all over the world, of which 10 in Italy

[Bissonette et al., 1993; Cabrera et al., 2004; Milligan et al., 1989; Ogata et al., 1981; Pedersen et al., 1983; Powell et al., 1974].

Prolidase is a ubiquitous cytosolic enzyme with a major role in the recycling of proline released during the degradation of collagen and dietary proteins: actually it hydrolyses dipeptides with carboxy-terminal proline or hydroxyproline [Endo et al., 1989; Palka et al., 1996; Phang et al., 1995]. Therefore, PD causes an accumulation of dipeptides, then secreted in urine and definable by capillary electrophoresis. The prolidase gene (PEPD) has been localised to chromosome 19q12-q13.2 and currently 17 causative mutations have been reported. Moreover, marked phenotypic variability, including intrafamilial, has been documented. Considering both the amount of molecular defects and the highly variable phenotype, we could expect a wide clinical spectrum of PD [Falik-Zaccai et al., 2009].

The clinical manifestations of PD include developmental delay, mental retardation, facial dysmorphosis, splenomegaly, recurrent pulmonary infections and skin lesions [Falik-Zaccai et al., 2009; Freij and Der Kaloustian, 1986]. Accessory signs are vasculitis and hepatitis-like symptoms. Typical features of systemic lupus erythematosus (SLE) and hyper-IgE syndrome have also been documented [Shrinat et al., 1997]. Affected patients could even apparently remain asymptomatic. Hyperiminodipeptiduria is the characteristic biochemical abnormality. Reduced prolidase activity in leukocytes, erythrocytes, cultured fibroblasts, or amniocytes confirms the diagnosis [Falik-Zaccai et al., 2009].

We report a case of PD treated in the Paediatric Section of the Department of Dentistry and Surgery at the University of Bari.

Case report

The patient CS, a 10-year-old male, was admitted to our Department in January 2000 with a diagnosis of PD. The consent was obtained from the patient’s parent for publication of the case and related images. Anamnesis resulted negative for any hereditary diseases. Deficiencies of language and learning, pharyngotonsillitis, ulcerated scab lesions of feet and glutes during the first years of life were reported [Aysin K et al., 2002; Monafo et al., 2000].

At the age of 9 years, the patient had been addressed to the Department of Dermatology at the University of Bari because the lesions had worsened. The presence of chronic ulcers on upper and lower limbs during infancy aroused the suspicion of a metabolic disease (Fig. 1). Then, on the basis of prolidase dosage in erythrocytes and the presence of hyperiminodipeptiduria, Prolidase Deficiency was diagnosed. Extra-oral examination showed good facial proportions, hypertelorism, depressed nasal saddle,
Delaire’s cephalometric analysis showed that line C2 (height of the cranial vault) was not tangent to the posterior edge of the condylus but it was anterior; the anterior crus CF1 (front line of the craniofacial balance) was set at the base of apex of condylus and the posterior crus CF3 (rear line of the craniofacial balance) showed an anteroposition of the lower jaw ramus [Delaire, 1978]. At the wrist X-ray the skeletal age was less than the chronological one (growth period II, phase III of skeletal growth according to Giannì’s auxological

Giannì’s cephalometric analysis revealed a dentoskeletal Class III in a hyperdivergent subject with upper jaw anteinclination and a lower jaw postrotation, skeletal open bite, further vertical growth could be expected. The linear dimensions of the cranial base, upper and lower jaw revealed: long anterior cranial base, lower jaw dimensions below average, long mandibular ramus. The cranial base angle was reduced with an anterior and lower position of glenoid fossa. Therefore, the dentoskeletal Class III was not caused by a dimensional imbalance between the jaws but by a positional one (Table 1).

A complete radiographic assessment was made (orthopantomography, latero-lateral, antero-posterior and axial teleradiography, wrist radiography X-rays) in order to perform the orthodontic evaluation (Fig. 4). Both cephalometric analysis according to Giannì and Delaire were considered (Fig. 5).

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The patient was enrolled in periodontal therapy sessions consisting in scaling and fluoroprophylaxis, to promote oral hygiene. In addition, a restorative dental treatment and interceptive orthodontics were performed: a rapid palatal expander was fabricated and bonded to the first upper molars to increase the palatal transverse diameter.

At the two-year follow-up the patient showed a stable correction of transverse dentoskeletal maxillary relationships (Fig. 7), though the skeletal Class III was unchanged (Fig. 8, Table 2).

**Discussion**

PD is a rare autosomal recessive disorder. Although there is considerable knowledge concerning the putative roles of the prolidase enzyme, the pathophysiology of PD is still unknown.
It is a multisystem disorder in which skin ulcerations are the most prominent findings. Other common features include characteristic facies, mental retardation, splenomegaly, and susceptibility to infections. Skin ulcers are usually long standing and difficult to heal. Scarring and pitting are common. Eczematous lesions, telangiectasia, and purpura are other dermatological features. Pruritus, photosensitivity, and hyperkeratosis have also been described. Other reported clinical findings include a high arched palate, simian creases, wasting of the small muscles of the hand, joint laxity, short stature, osteoporosis, talipes equinovarus, deafness, and ocular keratitis [Shrinat et al., 1997].

The present study reports the case of a 10-year old male child affected by PD, without any history of hereditary diseases in his family. The patient presented some clinical features never described before (Table 3), such as low hair line, osteotendinous reflexes on lower limbs hardly evoked, long upper lip, microrhinia, dentoskeletal Class III, dental age (according to Proffit) older than chronological age, a pathological fusion of the 2nd and 3rd cervical vertebrae, pathological malformation of the cervico-occipital hinge (uncomplete atlanto-occipital fusion). This deformity could be the reason of the low cranial base angle width and skeletal Class III relationship (according to Gianni’s cephalometric analysis).

Delaire’s cephalometric analysis revealed the presence of an architectural imbalance of the cranial structures with a predominance of rachidial portion compared to cranial one. According to Delaire [1978], the mandibular position is influenced both by the relationship with the maxilla and the cervical posture; therefore, in this patient the shortening of the cervico-occipital hinge and forward displacement of the odontoid process are the factors causing the counterclockwise rotation of the occiput with fulcrum on the sphenio-occipital synchondrosis, forward displacement of the mandible and Class III malocclusion.

**Conclusion**

This report confirms the importance of cooperation among specialists, such as dermatologists and dentists, especially when treating rare syndromes.
The early diagnosis of a rare pathology as PD in this young patient meaningfully improved his quality of life. Above all, this work points out some dental features not described before, except for multiple caries, and it shows that patients with rare diseases and craniofacial deformities exhibit an alteration of the normal growth pattern. Consequently, for these patients not only conventional analysis referring to statistical averages should be used, but also cephalometric analysis on craniofacial balance and individual proportions.

References