

Oral Manifestations in Scurvy Pediatric Patients: A Systematic Review and a Case Report

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Abstract: Scurvy is generated by lack of vitamin C; although it is considered a rare and past disease, scurvy continues to be detected in children with neurodevelopmental disorders and with selective diet habits. Identifying scurvy can be demanding due to the perceived rarity of the condition, and it can become a tricky diagnostic question given to the variety of nonspecific symptoms, including gingival manifestations. This study aims to identify most common clinical features in order to provide a complete picture of the signs and symptoms, and to offer clinicians the diagnostic tools for identifying patients suffering from scurvy. We present a case report of a child affected by scurvy; it has also been performed as a systematic review about scurvy in pediatric population. A search yielded 107 relevant studies since 1990. Most of the identified cases have shown oral, musculoskeletal and cutaneous manifestation that improved within a few days of starting vitamin C therapy. Identifying scurvy's characteristic clinical features allows a timely diagnosis, thus avoiding invasive investigations. Pediatric dentists should possess adequate knowledge and experience to identify the main characteristics of scurvy. This can help facilitate a prompt diagnosis in order to provide timely intervention to the patient that is relatively ease and safe.

Keywords: clinical manifestations; gingival disorders; oral scurvy; scurvy; vitamin C deficiency



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1. Introduction

Ascorbic acid (vitamin C) plays the key role of a cofactor in several metabolic reactions involved in tissue growth, development and healing [1]. In fact, ascorbic acid enables collagen's hydroxylation [2]; then, it empowers the biosynthesis of carnitine and norepinephrine, and is also involved in the metabolism of tyrosine and the amidation of peptide hormones [3]. Vitamin C performs an important function in the immune system too: scorbutic individuals usually develop a higher incidence of infections, and vitamin C auxiliary therapy is actually considered for sepsis treatment support [4]. Generally, signs of ascorbic acid deficiency begin to show after about 30 to 90 days of insufficient vitamin C intake [5]; clinical findings are directly related to the various metabolic pathway which ascorbic acid is involved in [6]. Most of characteristic disorders of vitamin C deficiency can overlap with rheumatological, infectious or hematological diseases, showing a wide range of musculoskeletal and mucocutaneous manifestations, thus mimicking other pediatric conditions [7]. Scurvy is a well-known but uncommon disease, and nowadays is considered a rare condition in developed nations [8]. Despite its low frequency in the population, cases of scurvy still occur in people at risk, including elderly populations, patients affected by malabsorption syndromes and eating disorders, and, above all, pediatric

patients with restricted or selective feeding [9]. These categories of people have chronically low levels of vitamin C, which cannot be intrinsically produced within the human body and therefore must be obtained via dietary intake [10]. The most common clinical features are hypertrophy, swelling and bleeding of the gums, follicular hyperkeratosis, lower limbs swelling and tenderness, poor wound healing [11,12]. Oral cavity signs represent peculiar characteristics in patients affected by scurvy; nevertheless, gingival overgrowth stands out as a typical manifestation of several diseases, resulting in differential diagnosis for idiopathic enlargement, drug-induced enlargement, enlargement associated with systemic diseases (such as Leukemia or Granulomatous diseases) and neoplastic enlargement (gingival tumors) [13,14]. Serological measurement of vitamin C is a readily available and widely used laboratory test; despite generally ascorbic acid serum levels accounts for the most recent food intake, they may be related to the level of reserves and predict the possibility of developing clinical signs [15]. Dietary restrictions and poor compliance with taking oral supplements appears to have brought scurvy back to the fore in the pediatric population, particularly in patients with neurodevelopmental disorders linked to highly selective diets [16]. Despite scurvy's return to clinical practice, the extreme heterogeneity of the clinical signs makes the identification of patients suffering from scurvy a very demanding challenge for the pediatric dentist [17]. The purpose of this study is to provide pediatric dentists with the means to identify clinical parameters and diagnostic tools useful for detecting patients suffering from scurvy. Here we present a case report of a patient with scurvy and a systematic review of the literature on scurvy in pediatric population.

2. Case Report

A four-year-old child presented to our department with lower limbs pain and refusal to walk, with legs fixed in flexion at hips and knees for about four months. The symptoms were partially managed with non-steroidal anti-inflammatory drugs (NSAIDs). Patient's mother did not refer fever, skin rash or weight loss. About familial history, his sister was healthy, his grandmother suffering from celiac disease and a first-grade cousin was affected from juvenile idiopathic arthritis (JIA) in therapy with NSAIDs. Patient was born at term with normal weight and length. His psychomotor development was referred in the norm up to seven–eight months of age, then patient presented a delay of psychomotor and language development. Dietary history reveals highly selective eating since the second year, based exclusively on ham and white meat homogenized, with refusal of fruits and vegetables. Since about one year the mother reports difficulty in eating, and several episodes of gingivitis with antivirals and topical antifungals with partial benefit. When patient came to our department he was in fair general conditions, his weight was 17 kg (25–50th) and his height was 105 cm (25–50th). The physical examination was difficult because of the patient's developmental delay, however it revealed pale and dry skin, corkscrew hair and signs of follicular hyperkeratosis in the lower and upper limbs. Child refused to walk, with legs fixed in flexion at hips and knees ("Frog leg-position"). Both legs were diffusely tender to palpation. The child was uncooperative for oral examination but erythematous, hemorrhagic, and swollen gums in maxillary anterior region were noted (Figure 1). The rest of physical examination was normal. Blood examinations revealed low iron and vitamin D level, while complete blood count, serum chemistries, liver and kidney, function panel, coagulation panel (prothrombin time, activated partial thromboplastin time, and international normalized ratio) and inflammatory parameters (C-reactive protein and erythrocyte sedimentation rate) were normal. Hips, knees and ankle ultrasound did not reveal joints effusion or signs of tenosynovitis. X-ray of the lower limbs (Figure 2) did not reveal fractures, but generalized osteopenia and typical features of malnutrition, including a ground glass appearance, Pelkan spur, which represents a healing metaphyseal pathologic fracture, and a Wimberger ring sign, which denotes a thin sclerotic cortex surrounding a lucent epiphysis. Periosteal reaction due to subperiosteal hemorrhage with a dense provisional calcification immediately adjacent to the physis (Frankel line), and an adjacent lucent band more diaphyseal in location (Trummerfeld line) were noted. In consideration

of the result of blood examinations and of the lower limbs X-ray, we hypothesized a state of nutritional deficiency. Furthermore, peculiar elements of both personal history and clinical examination, such as selective dietary habits, follicular hyperkeratosis, corkscrew hair, relapsing gingivitis and joint pain in the absence of signs of local inflammation led to the diagnostic hypothesis of vitamin C deficiency. This clinical suspicion was confirmed by the finding of low levels serum vitamin C $< 2.4 \mu\text{mol/L}$ (normal value 26.1–84.6). Supplementary treatment with oral vitamin C (300 mg daily) and D (800 UI daily) was started. Patient clinical condition improved with recovery of walking and an oral clinical healing of the gingival enlargement (Figure 3). One month after discharge, the boy had normal vitamins' levels: $35.6 \mu\text{mol/l}$ (normal value 26.1–84.6).



Figure 1. First oral clinical presentation (T0).



Figure 2. Lower limb X-ray showing typical features such as radio-dense band (Frenkel line), marginal spur formation.



Figure 3. Oral tissues healing presentation after four weeks of Vitamin C administration (Tf).

3. Materials and Methods

A systematic review of the literature was performed through PubMed, ISI Web of science, and Cochrane Library. “Scurvy”, “vitamin C deficiency”, “Moeller’s disease”, “Cheadle’s disease”, “scorbutus”, “Barlow’s disease”, “hypoascorbemia”, “lack of vitamin C”, “scorbutic”, “child”, “children”, “pediatric”, “toddler”, “infant”, “infancy” and “childhood” were employed as Medical Subject Headings (MeSH) terms (Table 1). Search operations have been completed in December 2020. The PICOS criteria and PRISMA checklist have been fulfilled in the review execution [18,19]. Male and female children (age ≤ 16 y), with confirmed diagnosis of scurvy, characterized by any kind of clinical manifestation related to vitamin C deficiency was set as population of interest (intervention); “no intervention” was comparison. Comparative studies, cross-sectional studies, retrospective studies, prospective studies, survey studies, case series and case reports were included. We aimed to identify the clinical manifestations and diagnostic methods of scurvy. The inclusion criteria of the selected studies were: presence of any clinical manifestation in humans, pediatric age, edited in English language, published since 1990. Review articles and studies without full text available were excluded. Three reviewers, once the initial results were collected, analyzed the titles and abstracts; then duplicates were excluded, and all those articles that did not match the inclusion criteria were ruled out. The full texts of the remaining articles were read in depth by two reviewers to better assess the content of the studies: demographic data, clinical manifestations, diagnostic path, therapeutic approach and all the extracted data have been organized in Table S1. The Risk of Bias in Non-randomized Studies of Interventions (ROBINS I) assessment tool was employed to evaluate quality of non-randomized studies [20]. This tool analyzes seven bias domains and each one refers the Risk of Bias (RoB) in five grades: low (LR), moderate (MR), serious (SR), critical (CR) and no information. The overall evaluation is based on the combination of these seven domains [21] (Table S2). A study based on a non-randomized design rarely presents a low level of RoB. The review was submitted and registered on PROSPERO [22] (registration code: CRD42021225174).

Table 1. The entire list used in the search and the combinations used in the research phase.

Search Topic								
#1	and #10	OR	#2	and #10	OR	#3	and #10	OR
	and #11			and #11			and #11	
	and #12			and #12			and #12	
	and #13			and #13			and #13	
	and #14			and #14			and #14	
	and #15			and #15			and #15	
#4	and #16	OR	#5	and #16	OR	#6	and #16	OR
	and #10			and #10			and #10	
	and #11			and #11			and #11	
	and #12			and #12			and #12	
	and #13			and #13			and #13	
	and #14			and #14			and #14	
#7	and #15	OR	#8	and #15	OR	#9	and #15	OR
	and #16			and #16			and #16	
	and #10			and #10			and #10	
	and #11			and #11			and #11	
	and #12			and #12			and #12	
	and #13			and #13			and #13	
#8	and #14	OR	#9	and #14	OR	#10	and #14	OR
	and #15			and #15			and #15	
	and #16			and #16			and #16	
	and #10			and #10			and #10	

1. Scurvy; 2. Vitamin C deficiency; 3. Moeller's disease; 4. Cheadle's disease; 5. Scorbutus; 6. Barlow's disease; 7. Hypoascorbemia; 8. Lack of vitamin C; 9. Scorbutic; 10. Child; 11. Children; 12. Childhood; 13. Infant; 14. Infancy; 15. Toddler; 16. Pediatric.

4. Results

Systematic Review of the Literature

The initial search yielded 719 results; 171 articles were excluded as they were duplicates. Another 373 articles were excluded following the reading of titles and abstracts. Reading the full text of the 175 remaining articles, 68 were excluded because they did not meet our inclusion criteria. At the end of the selection, 107 articles were included in this systematic review (Figure 4). Details on the 107 selected items and their main contents such as number of cases, clinical information, diagnostic path, and therapeutic protocol are summarized in Supplementary Table S1. Through the evaluation of the 107 analyzed studies, 88 are classified as overall moderate RoB (MR), and 19 as serious overall RoB (SR). Definitely, in the analysis of 107 non-randomized studies, no article appears to have a critical RoB in the individual domain or in the analysis of the overall domain and, therefore, all the studies confirm evidence (Supplementary Table S2). A total number of 134 patients were described within the 107 selected studies, with a minimum age of 6 months old and a maximum age of 16 years (mean 6.06 ± 3.81). Only 31 out of the 134 patients (23.1%) were female, and 103 (76.9%) were male. A total of 69 (51.5%) patients were affected by neurodevelopmental disorders, and 41 (31.3%) suffered of autistic spectrum disorder. On the clinical examination, 66 out of 134 (49.3%) patients showed cutaneous manifestations of scurvy, 92 of 134 (68.7%) patients showed musculoskeletal manifestation and 112 out of 134 (83.6%) patients showed oral manifestation. Among these 112 patients with oral manifestations, 1 of 112 (0.89%) was affected by oral ulcers, 1 of 112 (0.89%) had a chronic glossitis and 110 of 112 (98.21%) had gingival involvement, such as gingival bleeding,

swelling and hypertrophy. The diagnosis was based on clinical hypothesis for 132 of the 134 patients (99.3%); serological dosage was obtained in 103 out of 134 patients (76.9%), histological examination was performed in 27 patients (20.1%); an ex juvantibus diagnostic approach was carried out in 17 cases (12.7%). The mean vitamin C serum level was 0.105 ± 0.118 mg/dl ranging from 0.000 to 0.700 mg/dl. Therapy was described in 78/134 patients. Only one patient of the 78 (1.28%) did not undergo vitamin C administration, but was only prescribed dietary recommendations. The remaining 77 patients (98.72%) underwent vitamin C therapy with a mean dosage of 384.81 ± 272.74 mg ranging from 50 to 1500 mg daily.

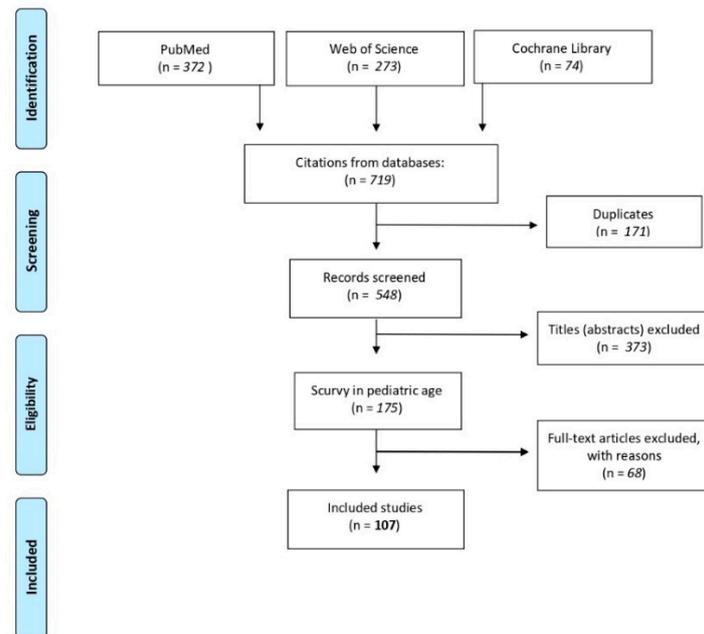


Figure 4. PRISMA flowchart.

5. Discussion

Main findings encountered in our case report, in fact, meet with the manifestations most commonly reported in the literature. Hahn et al. described the data obtained from 77 patients but did not mention any oral manifestation [12]. A recent literature review by Kothari et al. yielded 77 cases and gingival swelling, pain and bleeding were noted in all but three of the cases in which intraoral findings were described [23]. A review by Ratanachuek et al. reported 86% of pediatric scurvy cases were initially misdiagnosed; a correct diagnostic approach should be based on the recognition of clinical manifestations [24]. Oral soft tissue involvement was the most striking sign that we observed in our patient, and it was also described in 92 out of the 107 selected studies (83.7% of examined patients). This important observation is the reason why clinicians that treat children and pediatric dentists should consider atypical gingival swelling or other gingival manifestations as one of the early signs of scurvy [25]. Scurvy is rare, but it still occurs among children with autism and developmental disorders, so this condition should be kept in mind in a clinical constellation of gingival involvement, lower extremity pain, limp, non-blanching rash, fatigue, anemia, in particular in children with an history of selective diet [26]. Having a comprehensive dietary history as part of the data gathering is fundamental to the early recognition of nutritional deficiency diseases in order to avoid invasive procedures and/or their severe complications [27].

6. Conclusions

The heterogeneity and time delay of diagnostic path encountered in the analyzed studies reveal a gap in our knowledge: a more focused clinical approach and a more

detailed investigation on diet habits, neurodevelopmental disorders and on dermatological or orthopedic status should make up for this knowledge gap, in order to put dentists among the first actors against scurvy suspicions. This will lead to:

1. early detection and reduction in a misdiagnosis of scurvy
2. early intervention of vitamin C deficiency
3. subsequent prevention of the morbidities of this extremely distressing condition in pediatric patients.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/app11188323/s1>. Table S1 Data extraction from included items. Table S2 Risk of Bias assessment.

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