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ORAL MANIFESTATIONS OF PRIMARY IMMUNODEFICIENCIES DISORDERS IN CHILDREN

Elena-Lia Spoială[1*], Aurica Rugină[1]

1- "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania

Corresponding author:

* Elena-Lia Spoială e-mail: lia_spoiala@yahoo.com

ABSTRACT

Primary immunodeficiency disorders (PIDs) represent an increasing number of syndromes which include over 400 inborn errors of immunity. These syndromes should be suspected in children with recurrent respiratory infections, failure to thrive, poor response to prolonged use of antibiotics, persistent thrush or skin abscesses, or family history of PIDs. Severe gingivitis, aggressive forms or early-onset periodontitis, recurrent and/or persistent oral ulcers, gingivostomatitis or oral candidiasis that do not respond to treatment and various types of dental anomalies are among the most common oral manifestations associated with PIDs. The aim of this paper is to review the literature and identify the oral manifestations in children with PIDs. The association between PIDs and oral manifestations require a multidisciplinary approach for diagnosis and management. Medical professionals should be aware that particular oral features may reveal an underlying defect of immunity or complicate the management of PIDs patients.

Keywords: primary immunodeficiency, oral manifestations, children

INTRODUCTION

Primary immunodeficiency disorders (PIDs) include a large and heterogeneous group of conditions that result from anomalies in development and/or function of immune system (1). More than 400 PIDs have been characterized to date, with new disorders continually being identified thanks to the rapid advances in gene identification technology. The latest International Union of Immunological Societies Primary Immunodeficiencies classification list was published on January 10, 2020, featuring 416 human inborn errors of immunity, categorized in 10 groups. PIDs are classified as disorders of adaptive immunity (T cell, B-cell or combined immunodeficiencies) or of innate immunity such as phagocyte and complement disorders (2).

Children with PIDs are predisposed to a variety of systemic and oral manifestation, including, among others, infections (candidiasis, herpetic gingivostomatitis, atypical dental infections), oral aphthous ulcers, severe periodontal diseases, and dental

anomalies (3). The oral manifestations of PIDs often occur early in the development of disease and sometimes even before any other clinical evidence of the disease (4). A better knowledge of the oral manifestations associated to PIDs may therefore contribute to the improvement of early diagnosis and management of these severe conditions.

MATERIAL AND METHODS

We performed a systematic literature search using MEDLINE and Web of Science Core Collection databases, from the time of their inception to August, 2020, to capture all studies investigating the association of PIDs with oral manifestations in children. We used the following search terms: ("Primary immunodeficiency disorder") AND ("oral manifestations" OR "tooth decay" OR "oral cavity" OR "dental anomalies" OR "oral infections") AND ("children" OR "pediatric" OR "paediatric"). The search was limited to humans and performed with restriction to English and French language articles. The reference lists of all relevant articles were manually searched to further identify any additional eligible studies. Articles that did not address the topics were excluded, and the full text of the remaining high-quality articles was reviewed. The study population of interest consisted of children aged from birth up to 18 years old.

RESULTS

Our electronic literature search found 161 references. After removing 23 duplicates, 138 titles and abstracts were screened. From the latter, 94 were excluded for failing to meet the eligibility criteria. The majority of the excluded records did not include either a reference to primary immunodeficiency disorders and some were not in pediatric population. After screening 44 full text articles, 20 were excluded as: no data in children – 3, conference abstracts – 2, poster presentations – 4, and articles focused on secondary immunodeficiency disorders – 11. An additional 2 studies found through examining the reference lists of original articles selected for full text reading met the inclusion criteria. In total, 26 papers were included in this review (fig. 1).

Identification

Records identified through database searches
(n = 161: MEDLINE 41 Web of Science Core collection 99)

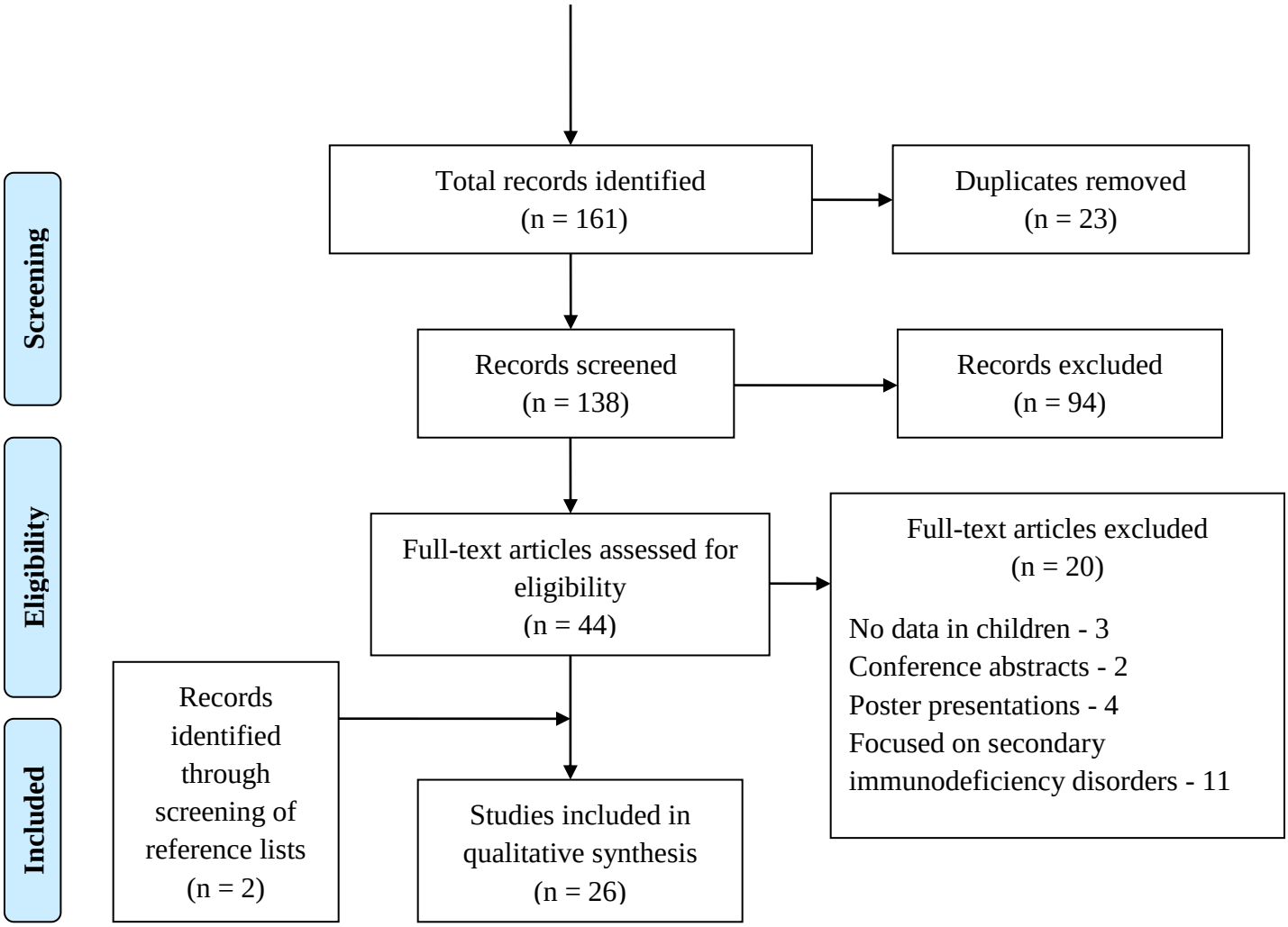


Figure 1. The PRISMA flow diagram for selection of studies for the review (NOTE: "Records" include a mixture of full journal articles of original research, published abstracts, protocols, invited commentaries, and reviews)

The most common oral manifestations associated with primary immunodeficiency disorders are illustrated in Table I.

Table I. Oral manifestations in PIDs

Category	Immunodeficiency type	Oral manifestations
Immunodeficiencies affecting cellular and humoral immunity	Severe combined immune deficiency (SCID)	candidiasis, viral infections, ulcerative stomatitis (5)
	MHC (class I and class II) deficiency (Bare Lymphocyte Syndrome)	oral herpetic infection (6)
Combined immunodeficiencies with associated or syndromic features	Wiskott-Aldrich syndrome	gingival ulceration/bleeding, palatal petechiae (7)
	Ataxia-telangiectasia	herpetic gingivostomatitis, candidiasis (8)
	DiGeorge anomaly	malformations in dental anatomy, hypomineralization, missing teeth, altered dental eruption patterns, and caries (9)
	HyperIgE syndromes	ligneous gingivitis/periodontitis, retained primary teeth, arched palate, recurrent fungal infection (10)
	Schimke Syndrome	microdontia, hypodontia, short and thin tooth roots, malformed primary and/or permanent molars (11)
Predominantly antibody deficiencies	X-linked agammaglobulinemia	ulcerations, candidiasis, and gingivitis, recurrent aphthae (12)
	Common variable immune deficiency with no gene defect specified (CVID)	aphthae, herpetic ulcerations, lichenoid-like lesions, odontogenic infections, necrotizing periodontitis (13)
	CD40L/CD40 Deficiencies (Hyper-IgM Syndrome)	increased susceptibility to infection and recurrent mucosal ulcerations (14)
	Selective IgA deficiency	aphthous-like ulcerations, candidiasis, recurrent herpes labialis (15)
	Transient Hypogammaglobulinemia of Infancy (THI)	oral candidiasis (16)

Table I. Oral manifestations in PIDs (continued from previous page)

Diseases of immune dysregulation	Chediak-Higashi Syndrome	recurrent ulcers, candidiasis, and early-onset aggressive periodontitis (17)
	Autoimmune PolyEndocrinopathy with Candidiasis and Ectodermal Dystrophy	chronic candidiasis, enamel hypoplasia (18)
	SAMHD1 Deficiency	oral ulcerations (19)
Congenital defects of phagocyte number or function	Severe Congenital Neutropenia	oral ulcerations, abscesses, oropharyngeal candidiasis, desquamative gingivitis, and severe periodontitis (20)
	Cyclic Neutropenia	periodic aphthous stomatitis, severe periodontal disease (21)
	Glycogen Storage Disease Type 1b	oral ulcers, giant cell granulomatous epulis, hypomineralized enamel (22)
	Leukocyte Adhesion Deficiency Type 1	recurrent infections without pus formation, periodontitis (23)
	Chronic Granulomatous Disease	oral ulcerations, gingivitis, and periodontitis (24)
Defects in intrinsic and innate immunity	Chronic Mucocutaneous Candidiasis	oropharyngeal candidiasis (25)
Autoinflammatory disorders	Familial Mediterranean Fever	moderate to severe periodontitis (26)
	Hyper IgD Syndrome	oral ulcerations (27)
Complement deficiencies	C3 Deficiency	infections with encapsulated microbes (28)
Phenocopies of inborn errors of immunity	Chronic Mucocutaneous Candidiasis	fungal infections (29)

The conditions have been grouped according to the latest International Union of Immunological Societies Primary Immunodeficiencies classification list which was published on January 10, 2020.

DISCUSSION

According to International Union of Immunological Societies Primary Immunodeficiencies, up to date, there are 416 human inborn errors of immunity and the number is continuously rising as more and more advances in genetic technology are made. PIDs are categorized in 10 groups: Immunodeficiencies affecting cellular and humoral immunity, Combined immunodeficiencies with associated or syndromic features, Predominantly antibody deficiencies, Diseases of immune dysregulation, Congenital defects of phagocyte number or function, Defects in intrinsic and innate immunity, Complement deficiencies, Autoinflammatory disorders, and Phenocopies of inborn errors of immunity. The phenotypic spectrum of PIDs is very large and includes several orofacial features (2).

Orofacial manifestations associated with PIDs have been rarely evaluated in dedicated clinical studies and most of the conclusions arise from case studies. Periodontal disease, tooth decay and disorders of the oral mucosa are among the most common oral manifestations in PIDs. Humoral immune deficiencies are associated with tooth decay, while severe forms of periodontal disease are common in phagocytic cell deficiencies (30). Structural abnormalities of the teeth can occur in immunodeficiencies associated with apoptosis defects. A rare, but severe complication of immunodeficiencies associated with DNA repair defects is oral squamous cell carcinoma (31).

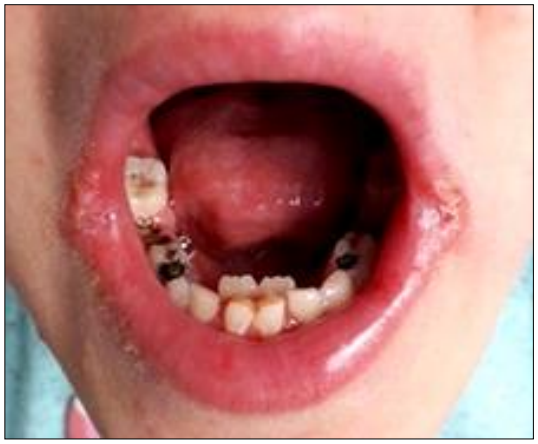
Besides severe systemic manifestations, orofacial manifestations are frequently seen in these patients and often remain underdiagnosed. Patients with impaired innate immunity are predisposed to a variety of oral manifestations including oral infections (candidiasis, herpes gingivostomatitis), aphthous ulcers, and severe periodontal diseases (32). Although less frequently, orofacial developmental abnormalities

can be seen in these patients. Oral lesions can represent the main clinical manifestation of some PIDs or even be inaugural (30). Previous studies showed that oral candidiasis and herpetic infections are frequently seen in patients with T-cell deficiencies, while patients with B-cell deficiencies are most susceptible to bacterial infections. Medical professionals should also take into consideration the influence of the immunosuppressant drugs used in PIDs patients, which can predispose to oral infections and affect the progression of periodontal inflammation (33).

Predisposition to bacterial infections, cytokine dysregulation, tissue inflammatory process, and necrosis explain the early-onset oral lesions and periodontitis in children with PIDs (30). Oral manifestations associated to PIDs are often characterized by early onset with frequent recurrences. Whereas most of the oral manifestations are not specific to a particular immunodeficiency disorder, some of them are specific to a particular disease group. For example, hyperimmunoglobulin E syndrome is associated with a delayed exfoliation of the primary teeth leading to failure of eruption of the permanent dentition (34).

Oral manifestations like retained deciduous teeth, fissured tongue, missing permanent tooth buds, recurrent oral candidiasis, oral mucosal and gingival lesions can be seen in these children. Figure 2 shows an example of oral manifestions in a 9 year old girl with hyperimmunoglobulin E syndrome: persistence of primary mandibular central incisors, multiple tooth decay and angular cheilitis (fig. 2).

Figure 2. Oral manifestations in HyperIg E syndrome



Moreover, a premature loss of the deciduous and permanent teeth strongly suggests a phagocytic defect such as Chediak-Higashi syndrome, Papillon-Lefevre syndrome, or Leukocyte Adhesion Deficiency. Oral health care

practitioners should be aware of these syndromes as they may be the first ones to evaluate these patients (35).

CONCLUSIONS

Although once considered rare, nowadays the prevalence of PIDs is on the rise as more and more scientific breakthroughs facilitate earlier and more accurate diagnosis. The impact of orofacial involvement on the quality of life is underestimated and has only been poorly investigated. Both dentists and pediatricians dealing with patients with different oral lesions should differentiate the manifestations signaling a systemic disease from those appearing without any concomitant serious health problem.

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