LETTER TO THE EDITOR

Undiagnosed and rare diseases: current challenges, perspectives and contribution of oral cavity examination

To the Editor:

In a recent article, Haendel et al. suggested that one of the main challenges of precision medicine is to categorize patients on the basis of similarities of specific characteristics and phenotypes.[1] However, there is no standardized pattern to collect information on and describe those features. Indeed, the phenotypic information about individual patients is often insufficiently detailed or inaccessible, hampering detection and classification of similarities into clinically useful groups. This situation tends to be worse with regard to uncommon diseases, for which available information is sparse.[1] Because of the complexity of undiagnosed and rare diseases, we can ask ourselves, what would be the role of the dentist with regard to these conditions?

Each rare disease, taken separately, affects a limited number of people. However, considering that there are up to 8000 types of rare diseases worldwide, when grouped under a single category, their epidemiologic impact may become quite significant. It is estimated that in Brazil, there are 13 to 15 million people with a rare disease in Brazil.[2] Rare diseases are characterized by numerous signs and symptoms that vary not only among different diseases but also among patients with these diseases (http://portalms.saude.gov.br/atencao-especializada-e-hospitalar/especialidades/doencas-raras). About 80% of such diseases are caused by genetic factors and the rest by environmental, infectious, immunological, and other factors.[1] Thus, undiagnosed and rare diseases are a global challenge that must be overcome. Global networks, funds, and new technology development are necessary to meet this goal.[3]

All international programs involve multiprofessional and interdisciplinary interactions among several specialties, such as pediatrics, neurology, cardiology, nephrology, hematology, surgery, rheumatology, endocrinology, ophthalmology, otology, orthopedics, clinical genetics, laboratory medicine, bioinformatics, physiotherapy, speech therapy, nutrition, and psychology.[2,3] However, teams composed of specialists from these fields usually do not include a dentist; however, the inclusion of pediatric dentistry, oral medicine, and oral pathology is essential to better understand and diagnose rare diseases.

The participation of the dentist in the era of the genome can make a significant contribution to the interdisciplinary approach to the management of various conditions. In this context, is highlighted research on the hereditary components of dental caries; the genetic basis of third molar agenesis, periodontal diseases, and dentofacial development in general; the genetic−environmental interaction in the development of oral clefts, for which a deletion in the amelogenin gene has been identified as a causative factor in X-linked amelogenesis imperfecta; mutation of *CFTR,* the cystic fibrosis−causing gene, which also causes enamel defects; an association between the interleukin-1β genotype and periodontal disease; and the discovery of the role of *PAX9* in tooth organ development and palatogenesis, among others.[4]

One of the oral features that may be important in the diagnosis of rare diseases is the presence of dental anomalies, which frequently occur in a number of genetic disorders and are a major sign in these disorders.[5] During clinical examination of patients with undiagnosed and rare diseases, the presence of hypodontia, oligodontia, anodontia, solitary median maxillary central incisor, mesiodens, supernumerary teeth, enamel pearls, supernumerary cusps, natal tooth, Leung cusps, microdontia, and macrodontia, among other conditions, should be investigated. Some rare diseases, such as ectodermal dysplasia; renal enamel syndrome; Waardenburg syndrome, type 1; Axenfeld-Rieger syndrome, type 1; Bloom syndrome; Kabuki syndrome; Sotos syndrome 1; and Jalili syndrome, present with dental anomalies.[5-8]

According to a recent Editorial in *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, both academic joint endeavors and dissemination of widespread information constitute the basis for scientific progress. Such collaborations do not always result in coauthorship, but they do improve the quality and direction of scientific research, nonetheless. This is of paramount importance in the case of studies on rare diseases, given that the limited number of clinical cases poses a challenge to a single researcher, or even an institution, because such an effort would require a large number of researchers to achieve the critical number required.[9]

In summary, the inclusion and participation of dentists in such collaborations would improve in a significant way the diagnosis and treatment of patients with undiagnosed and rare diseases.

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