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Molecular, Genetic and Clinical Perspectives on Third Molar Impaction: A Comprehensive Review

Mohammed Simal A , A. Sivachandran *, K. T. Magesh , M. Sathya Kumar and R. Aravindhan

Department of Oral and Maxillofacial Pathology, SRM Kattankulathur Dental College and Hospital, Faculty of Medicine and Health Sciences, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, 603 203. Tamil Nadu, India.

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Abstract

Impaction of the third molar is a frequently occurring developmental phenomenon, which is affected by such as anatomic boundaries, craniofacial patterns in growth and biological control. Insufficient retromolar space and deviant mandibular growth have been considered the major causes, but recently, genetic and molecular aspects have gained attention as significant etiological factors. Genetic variations in odontogenesis and bone remodeling-related genes such as MSX1, PAX9, AXIN2 and alteration of signaling pathways (WNT, BMP, FGF and RANK/RANKL/OPG) have been reported to affect eruption timepoint and its success. This review synthesizes current evidence on the clinical, radiologic, genetic, and molecular determinants of third molar impaction. The recent developments of cone beam computed tomography techniques have further enhanced diagnostic accuracy and surgical risk assessment, while the emerging molecular and genetic information offers possibilities for early risk prediction and personalized management. Integration of clinical examination into imaging and biological markers may further enable treatment planning with a view to minimizing complications and optimizing patient outcomes in impacted third molar management.

Keywords: Third Molar Impaction; Tooth Eruption; Genetic Polymorphism; MSX1; PAX9; AXIN2; WNT Signaling; CBCT

1. Introduction

Third molar impaction is a common clinical condition influenced by anatomical limitations, genetic factors, and environmental changes [1]. The reported prevalence of third molar impaction is 20-73% [1]. Eruption normally occurs between the ages of 17 and 21 years. However, this may be disrupted due to variations in jaw growth relative to dental arch space and craniofacial morphology [1,2]. Modern dietary habits, especially softer diets with less masticatory load, result in restricted posterior alveolar development, increasing the chances of insufficient eruptive space [2]. Indeed, investigations into the genetics and molecular biology of dental development show that variations in genes controlling odontogenesis and bone metabolism significantly influence eruption potential [3,4]. Establishing these integrated factors will be instructive for correct prediction and early diagnosis and management of third molar impaction.

2. Clinical and Anatomical Etiopathogenesis

Third molar impaction is due to several interrelated structural, developmental, functional, and evolutionary factors throughout craniofacial growth [1,2]. The most widely accepted theory remains inadequate retromolar space, which limits the tooth's ability to erupt into a functional position [1]. The mechanisms behind space deficiency, however are multifactorial [1,2]. Variations in the remodeling of the mandibular ramus, especially reduced posterior growth rotation, directly limit the available pathway for eruption [2]. Research has demonstrated that mesial angulation of the third

* Corresponding author: A. Sivachandran

molar germ early in its development often dictates an unfavorable eruption trajectory long before a clinically detectable stage [2].

Sex-related craniofacial differences also significantly contribute [5]. Generally, females exhibit smaller mandibular dimensions, narrower retromolar areas, and an earlier cessation of facial growth. This leads to a higher impaction propensity in females [5]. The reduced effect from environmental evolution, as humans transitioned to softer, processed diets, decreased the masticatory load, hence leading to lesser alveolar bone deposition and shorter dental arches [2]. CBCT imaging has expressed evidence demonstrating the crucial role of the gubernacular canal in eruption guidance; its absence or obstruction strongly relates to eruption failure [6]. Other evolutionary theories proffer that the reduction in jaw size occurred without proportional reductions in tooth size in modern humans, creating a phylogenetic predisposition for impaction [2].

3. Radiologic and Surgical Perspectives

Radiographic examination is important not only for the determination of impaction but also for assessing surgical risks [7]. Though panoramic imaging is the most widely used, CBCT offers better three-dimensional visualization regarding root morphology and mandibular canal proximity and bone quality [8]. Darkened roots, canal deviation, and cortical interruption are some predictive radiographic indicators associated with a higher risk of injury to the inferior alveolar nerve [9]. Loss of cortical integrity around the mandibular canal significantly increases the risk of postoperative paranesthesia [10]. CBCT-based classification helps assess extraction difficulty and appropriate flap designs [1].

4. Genetic Perspectives

Genetic studies confirm that third molar impaction is a polygenic condition controlled by odontogenesis and craniofacial development genes [3]. Variants of MSX1, such as rs12532 and rs8670, influence dental lamina formation and eruptive force [6]. Mutations involving PAX9, such as rs4904210 and rs2073247, affect tooth morphogenesis and root development, which leads to eruption failure [4]. AXIN2 polymorphisms, such as rs2240308, modify the activity of the WNT pathway, thus bone remodeling and eruption timing [6]. Other genes, including MSX2, with its polymorphism rs4868444, and ARNT2, with its polymorphism rs140220410, have been linked to altered craniofacial morphology and higher impaction risk in families with craniofacial anomalies [11]. Associations between ABO blood groups and eruption patterns further confirm that genetic influence plays a role in eruption variability [12].

5. Molecular Pathways and Biomarkers

The WNT, BMP, FGF, and RANK/RANKL/OPG pathways all interact in a coordinated manner to regulate tooth eruption [13]. Interruptions of these pathways disrupt the recruitment of osteoclasts and remodeling of the alveolar bone, leading to failures in eruption [13]. WNT pathway constituents like AXIN2 and WNT9B itself modulate osteoblast differentiation and follicular signaling critical in bone resorption above the tooth crown [3]. FGF2 controls aspects of proliferation and extracellular matrix turnover within the dental follicle. Dysregulation of these factors contributes to delayed eruption [14]. Long non-coding RNAs such as MEG3 and NORAD are also known to regulate osteogenic gene expression, and altered expression levels have been identified in impacted dental follicles [14]. Epigenetic modifications that include alterations in DNA methylation and changes in histone modifications also make significant contributions to individual variation in eruption timing [3].

6. Clinical Implications

Integration of genetic, molecular, and radiographic assessment forms a basis for personalized strategies of management [3]. Early identification of the individuals with high genetic susceptibility allows for pro-active orthodontic or surgical interference [3]. CBCT evaluation in combination with the genotyping enhances the predictive value regarding the possibility of inferior alveolar nerve injury and post-surgical complications [7]. Genetic markers may inform orthodontic extraction timing and patient counselling, particularly in those with familial impaction patterns [11].

7. Future Directions

Future research will involve GWAS and transcriptomic studies to identify more genes responsible for impaction [3]. Integration of molecular diagnosis into AI will further improve risk prediction and treatment planning [13]. Longitudinal studies integrating the genetic, molecular, and radiologic information would be required to develop predictive algorithms [7]. Further studies on epigenetic and environmental interactions will increase the understanding

regarding bone remodeling and eruption failure [14]. A multidisciplinary approach will further improve personalized management of third molar impaction [1,15].

8. Conclusion

Anatomical restriction, craniofacial growth pattern, genetic predisposition, and molecular regulation of bone remodeling and tooth eruption all interplay in the causation of third molar impaction. Although impaction has classically been mechanically explained by insufficient space, evidence suggests that polymorphisms in important developmental genes and changes in molecular signaling pathways have a greater effect on eruption outcome and susceptibility to impaction. Advanced radiologic evaluation in combination with genetic and molecular analysis allows for a paradigm shift in treatment strategy toward one that can be more patient-specific and predictive. Future research focused on genomic profiling, epigenetics mechanisms, and artificial intelligence-based diagnostics could be expected to continue to improve the precision, safety, and efficacy of planning for third molar

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed

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