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A Case Report Of Cleft Lip and Palate: Review Articles on its Associated Genetic Factors.

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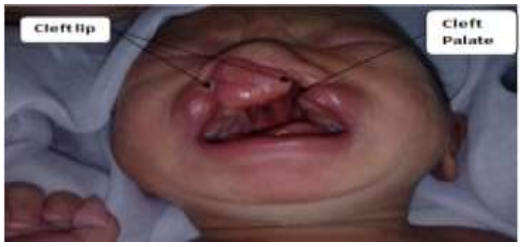
Abstract
Introduction. *Cleft lip and palate are among the most frequent craniofacial anomalies of the human species. The etiology of isolated and non syndromic cleft lip and palate is complex and multifactorial, often results from the interaction between genetic and environmental factors. As of now, many genes are reported by different authors for their involvement in clefting. These are Irf6, Msx1, Pvrl1, Tbx22, Fgfr1, Tgfa, Tgfb3, Rare, Nat2.*
Case report*: A female baby was born to 32 year old primigravida in the labour room of RIMS, Imphal. On examination the baby had a bilateral cleft lip and left sided cleft palate. Clefting is complete on the left side affecting whole of the upper lip and palate whereas it is partial on the right side.*
Conclusion: *With the use of modern sophisticated tools further research is required so as to pin point the exact cause of clefting of lip and palate and its associated genetic factors for prevention of the baby from this distressing congenital anomaly.*

I. Introduction

Cleft lip and palate are among the most frequent craniofacial anomalies of the human species. It is estimated that cleft lip and palate affects 1 in 700 live births with large geographical and racial variation. [1] In India it occurs in every 1 in 1000 live birth.[2] It has a great negative social impact on the patient and his/her family.[3] Cleft lip and palate results in complications affecting feeding, speech, hearing and psychological development. Patients will undergo multiple rounds of surgical repair starting in the first year of life and may continue until 18 or 20 years old. Frequently, extensive dental and orthodontic treatment, speech and hearing therapy may be required as well as referral for psychotherapy and genetic counselling.[4] The etiology of isolated and non syndromic cleft lip and palate is complex and multifactorial, often results from the interaction between genetic and environmental factors.[5] Maternal exposure to environmental factors during the embryonic developmental period may increased the likely hood of an embryo to develop anomalies that include cleft lip and palate.[6] There is an evidence that genes contributes to the etiology of syndromic and non syndromic clefts, perhaps by variable penetrance or action of different modifiers.[7] It has been reported that cleft lip and palate occurs more frequently in males, while the sex bias is reversed for cleft palate, which is more common in females.[8]

II. A Case Report

A female baby was born to 32 year old primigravida in the labour room of RIMS, Imphal. On examination the baby had a bilateral cleft lip and left sided cleft palate. Clefting is complete on the left side affecting whole of the upper lip and palate whereas it is partial on the right side. Immediately baby was shifted to neonatal intensive care unit. After 2 days, baby was referred to the department of Plastic surgery for further management. Family history does not reveal any hereditary disorders.



III. Review Articles

Fogh- Anderson P,[9] first defined genetic involvement of cleft lip and palate. As of now, many genes are reported by different authors for their involvement in clefting. These are IRF6, MSX1, PVRL1, TBX22, FGFR1, TGFA, TGFb3, RARE, NAT2. [10, 11]

In autosomal dominant Van der woude syndrome mutation of IRF6 gene is related to the cleft lip and palate.[12]The MSX gene proteins have a known role in epithelial-mesenchymal interactions during craniofacial development.[13] MSX1 first came to prominence as a candidate for cleft lip or palate following the generation of a gene knockout with cleft palate and oligodontia.[14] A candidate gene-based association study reported significant linkage disequilibrium between both cleft lip and palate with polymorphisms in MSX1.[15] In a patient with non syndromic clift lip and palate of different ethnic groups, it was observed that up to 25 of the patients had mutation in the gene MSX1.[16] MSX1 gene mutation caused dental agenesis and various combination of cleft lip and palate in a Dutch family.[8]

Autosomal recessive cleft lip and palate with ectodermal dysplasia is generally rare but occurs with a much higher frequency on Margarita Island (north of Venezuela). Positional cloning mapped the locus to 11q23 and mutations were identified in the cell adhesion molecule PVRL1 (Nectin-1), which is expressed in the developing face and palate.[17] On Margarita Island, it is generally caused by homozygosity of the nonsense mutation W185X, while heterozygosity is high in the unaffected population. It has been speculated that, since Nectin-1 is the principle cell surface receptor for α-herpes viruses, the high frequency of heterozygotes might have resulted from relative resistance to infection by viruses such as HSV1 and HSV2.[18] The same mutation is also present on the Venezuelan mainland, where heterozygosity was found to be a significant risk factor for non-syndromic cleft.[19]

X-linked Mendelian inherited form of cleft palate (CPX), has been extensively studied as a rare but strongly genetic influence for nonsyndromic cleft palate.[20] Positional cloning identified the CPX locus as the gene encoding T-BOX 22 (TBX22).[21] In addition to TBX22, several other T-box genes have been implicated in human syndromes, emphasizing their importance in development. For example, insuficiency of TBX3 or TBX5 causes ulnar–mammary and Holt–Oram syndromes respectively;[22] TBX1 is deleted in DiGeorge syndrome;[23] and TBX19 is mutated in isolated ACTH deficiency.[24]

In addition to families with clear X-linked inheritance, mutations were also found in smaller families where ankyloglossia is a diagnostic feature.[21] TBX22 expression correlates precisely with the phenotype seen in CPX patients, both in the vertical palatal shelves and the base of the tongue corresponding to the frenulum.[25] EEC syndrome is an autosomal dominant disorder of ectrodactyly, ectodermal dysplasia and cleft lip and palate. EEC syndrome was mapped to 3q27 and heterozygous mutations were identified in the p63 gene.[26] One unusual phenomenon with p63 is that mutation to different parts of the gene can influence the cleft phenotype. Missense mutation of the conserved DNA binding domain region gives cleft lip and palate while C-terminal mutations give cleft or cleft palate. Mutation at the N-terminal end outside of the conserved domains gives rise to cleft lip or no clefting at all. Only a small number of non-syndromic cleft lip/palate patients have been screened for mutations to date and no mutations have been found.[27]

Mutation of FGFR1 result in autosomal recessive Kallmann syndrome and cleft lip/ palate is a part of this syndrome.[28] TTF-2 mutations cause thyroid abnormalities and cleft palate,[29] while FOXC2mutations lead to distichiasis, lymphoedema and cleft palate.[30]

IV. Conclusion

With the use of modern sophisticated tools further research is required so as to pin point the exact cause of clefting of lip and palate and its associated genetic factors for prevention of the baby from this distressing congenital anomaly.

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