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RESEARCH ARTICLE

CASE REPORT: SQUAMOUS SUTURE SYNOSTOSIS IN RAINE SYNDROME; CASE REPORT AND LITERATURE REVIEW

Hani Ali Shash[1], Sawsan Fahad Almarzouq[1], Abdulrahman Abdulaziz Alghamdi[1] and Hayam Ali Shash[2]

1. Department of Surgery, Plastic Surgery, College of Medicine, Imam Abdulrahman Bin Faisal University.
2. College of Medicine, AlFaisal University, Riyadh, Saudi Arabia.

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Abstract

The purpose of this case study review is to evaluate Squamous Suture synostosis in Raine syndrome. Raine syndrome is characterized by dysmorphic features including exophthalmos, microcephaly, gum hypertrophy, low-set ears, midface hypoplasia, and osteosclerosis. RS is closely associated with squamous suture synostosis, one of the lateral minor skull sutures separating the parietal and squamous temporal bones. The study examined a three-year-old Saudi male born to healthy parents and a known case of Raine syndrome, craniosynostosis, degenerative myopia, and cataract. The Computed tomography (CT) scan results showed that the patient had metopic craniosynostosis with squamosal suture craniosynostosis and high intracranial pressure (ICP). The findings show that the association between Squamous Suture synostosis and Raine syndrome is seen in osteoporosis-related to deficiency of carbonic anhydrase II. However, in Raine syndrome disorder, the calcifications are seen after one year of age in many cases. Thus, it can be noted that Raine syndrome is inherited as an autosomal recessive in *FAM20C* mutation and is most identified among children.

Introduction:-

Raine syndrome, also known as lethal osteosclerotic bone dysplasia, is characterized by dysmorphic features that include exophthalmos, microcephaly, gum hypertrophy, low-set ears, midface hypoplasia, and osteosclerosis. Other features not limited to facial dysmorphism include intracerebral calcifications. It is a sporadic syndrome as there have been only ten cases in eight families reported, with the majority from the Middle East.[1] Familial consanguinity was frequently reported among the cases since it is inherited in an autosomal recessive fashion. [2] Mutations in the FAM20C gene have been shown to play a role in causing osteosclerotic bone dysplasia. Raine syndrome is diagnosed clinically or radiologically by detecting calcifications using ultrasound, x-ray, or CT. Antenatal diagnosis is feasible by ultrasound or molecular testing. [3]

Literature Review:-

A pathological study done by Whyte et al. (2017) showed that RS is a rare autosomal recessive disease that has an estimated prevalence of less than 1% in a population of 1,000,000 people. [4] The most classical phenotype of the RS is microcephaly, hypo-plastic nose, low-set ears, exophthalmos, and gum hypertrophy, leading to severe midface hypoplasia choanal atresia. RS's radiological findings include generalized osteosclerosis and calcification of the

Corresponding Author:- Hani Ali Shash
Address:- Department of Surgery, Plastic Surgery, College of Medicine, Imam Abdulrahman Bin Faisal University.

brain. Perhaps many children suffering from RS are likely to die in their early stages after birth because of the respiratory infection caused by pulmonary hypoplasia and choanal atresia/stenosis. There has been an assumption that RS was lethal and ideal during the neonatal period, while some authors argue that mild phenotypes are closely associated with high chances of survival upon early treatment. [5] It implies that RS is prevalent in children mainly below the age of 10 years. The clinical features of non-lethal forms are highly heterogeneous, and hence early intervention helps prevent death among the children.

The affected children exhibit limb abnormalities, dental and gum alterations, hypophosphatemia rickets, craniofacial, gum alterations, and neurological diseases such as seizures and delays in growth and development. Among the children, the genetic occurrence of RS is due to mutation in the FAM20C gene, which codes for the Golgi-related protein called FAM20C. [6] This is a secreted element mostly embedded on teeth and bones and is responsible for the phosphorylation of peptides that impedes bio-mineralization.

In a literature review done by Ferreira, Leal & Oliveira (2021) on the risk factors associated with Raine Syndrome, the research showed that positive family history is one of the significant risk factors since children can inherit TRS from their parents. [7]

This implies that children whose close relatives had suffered RS carry a high risk of RS. It is prudent to note that having a high-risk factor does not translate to infection. However, a risk factor significantly influences the chances of getting the condition compared to the individual without a risk factor.

Notably, a genetic mutation in the FAM20C gene is considered to have a causative role in RS, where the condition is transmitted in an autosomal recessive way. For instance, if both parents have an autosomal recessive condition, there are high chances, almost 100%, that the mutated genes will be passed to the children. [8] However, if one mutant gene is inherited, the child is likely to be a carrier but will not show any symptoms of RS. On the other hand, children born from both parents have a 25% chance of being homozygous RS dominant, 50% of being a carrier, and 25% of being affected with RS. The following image shows a skull infected with RS.

RS is closely associated with squamous suture synostosis, one of the lateral minor skull sutures separating the parietal and squamous temporal bones. Although there is good documentation of phenotypic appearances and the sequence of synostosis of the major cranial vault sutures, there has been a little report about synostosis of the squamosal suture. A retrospective review by Eley et al. (2016) about diagnostic imaging of 422 children with RS from 2008-2013. [9] Out of the total sample size, 38%, which represents 9%, had squamosal suture synostosis. The incidence of the squamosal suture increased with a decrease in ages, meaning that children below five years are more prone to squamosal suture in RS.

The study also found that squamosal suture synostosis mainly occurs with coronal and sagittal synostosis, not related to calvarias deformity. Due to the increased prevalence of squamosal suture synostosis in RS, the diagnosis is based on the clinical presentation and calcification demonstrated by ultrasound, X-rays, and CT scans. [10] The radiological findings of RS include general osteosclerosis of bones and the base of the skull, which comprise cortical hyperostosis and formation of periosteal new bones. The following image shows an obtuse mandibular angle of a deformed skull.

Genetic testing and prenatal diagnosis may help understand the risk of Squamous Suture synostosis in Raine syndrome during pregnancy. [11] The significance of the squamous suture in the RS is that it enhances the vertical height of the cranium during the skeletal maturation period. It runs from the top of the head to the child's soft spot, near the front of the head. Perhaps, if the suture closes early, the child's head will likely grow narrow and more prolonged than an ordinary child.

The antenatal diagnosis of RS is challenging, but there are two sonographic findings cerebral hyper-echogenicity and facial signs, highly suggestive of RS when present on antenatal ultrasound. [3] The cerebral hyper-echogenicity reflects the brain calcification, which can be found predominantly around the lateral ventricular and in the basal ganglia. Furthermore, microcephaly, underdeveloped mid-face, and marked proptosis are the characteristic facial features on antenatal ultrasound. Other characteristics confirmed to be observed prenatally among patients with RS are polyhydramnios, microcephaly, short limbs, intrauterine growth retardation, unilateral hydronephrosis, cataract, and small thorax. However, the absence of facial features and cerebral hyper-echogenicity does not rule out RS. [1]

The diagnosis of RS is based on facial appearance and radiological findings. Furthermore, computed tomography (CT) imaging of the head and face is essential for detecting the skull's narrow or atretic choanae and osteosclerosis. Also, genetic testing of FAM20C should be undertaken. [1]

Clinical presentation:
A 3 years-old Saudi male was born to healthy parents, full-term at 37 weeks via normal vaginal delivery with an APGAR score of 9 and 10 at 1 and 5 minutes, respectively. The boy's birth weight was 3KG. The child has dysmorphic features of abnormal skull shape, exophthalmos, hypertelorism, wide anterior fontanelle, cleft palate, micrognathia, and retrognathia. The family was then referred for genetic consultation for the facial dysmorphy and the possibility of Raine syndrome. The boy was also diagnosed with degenerative myopia and cataract. On examination patient was a fully conscious, communicative, playful, and had appropriate response to his age with frontal bossing and bilateral proptosis. Whole-exome sequencing and microarray were unremarkable, and no specific genetic disorder was reached in this case.

Computed tomography (CT) scan was taken (Figure.1), showing metopic craniosynostosis with squamosal suture craniosynostosis and high intracranial pressure (ICP). The patient was then admitted and underwent cranial reconstruction and orbital bar advancement. Post-operation, the boy was doing well, tolerating diet, and fully conscious with no complications.

Discussion:-

The RS is a common disorder mainly in children and is characterized by craniofacial anomalies, generalized osteosclerosis, and intracranial calcification. The leading cause of RS is a biallelic mutation in the FAM20C gene, located on chromosome 7. The prevalence of RS is one in a million individuals with Arab ancestry, accounting for most cases. [7,8]

According to previous cases, RS is fatal within the first few weeks of life because of pulmonary hypoplasia and choanal atresia/stenosis. However, several cases have been found in which the patient survived into adolescence or adulthood, implying a non-lethal type of RS, and highlighting that lethality is not essential for diagnosis. [5,6,8] Moreover, there is no explicit distinction between the lethal and non-lethal forms of RS in terms of genetic and phenotypical expression. [12]

The most common findings in newborns with RS are depressed nasal bridge, micrognathia, underdeveloped midface hypoplasia, wide fontanelles, microcephaly, tented upper lip, low-set ears, prominent exophthalmos, choanal atresia, hyperplastic gum, cleft soft palate. [1]Furthermore, facial anomalies and osteosclerosis are the most striking features. [5] Moreover, skeletal dysplasia has a more significant impact on craniofacial growth than it does on the spine and limbs.

Various studies have shown that most of the reported cases of RS die at infantile age. There have been few cases of non-lethal RS since it is not a common disorder. It is prudent to note that one RS significant feature is facial anomalies and osteosclerosis. [13] The case presented in this study exhibited abnormal head/ skull deformity, bilateral proptosis with frontal bossing was noted, and a previous surgical scar of the mandible with no facial asymmetry nor gross motor deficits. The developmental delay was also observed in a case study, a rare phenomenon observed among patients suffering from RS.

Another crucial clinical indication in RS is skeletal defection. Mutations in FAM20C can lead to the loss of mental functioning, which in turn results in hypophosphatemia. Although RS is synonymously considered lethal osteosclerotic, several reported cases and studies have shown that the non-lethal clinical phenotype is closely related to the *FAM20C* mutation. [12,4] In mild RS cases, patients with Squamous Suture synostosis are likely to survive beyond their infancy. In this case, RS reflects a marked variability in different exhibitions, including non-diffuse, non-diffuse, and mild bone osteosclerosis. It can also be noted that the appearance of the face and radiological findings prompt the RS clinical diagnosis.

Based on the case, the patient reported some neurodevelopmental delay which was identified during diagnosis. The findings showed seizures while hearing impairment was also recorded. On the other hand, there was a variable degree of hypophosphatemia rickets detected in the patient. Generally, this study found that there was a significant heterogeneity based on the patient follow-up. Some Orthopedic and neurological issues were recorded during the

diagnosis and patient's follow-up. The findings show that children affected with Raine syndrome are likely to showcase intracranial calcifications, which are identified in a parietal and occipital periventricular white matter but do not occur in the brain stem.

The primary association between Squamous Suture synostosis and Raine syndrome is osteoporosis-related to deficiency of carbonic anhydrase II. However, in Raine syndrome disorder, the calcifications are seen after one year of age in most cases. [7,11] Thus, it can be noted that Raine syndrome is inherited as an autosomal recessive in *FAM20C* mutation and is most identified among children.

Conclusion:-

This study has shown that the clinical course of patients suffering from Raine syndrome varies from case to case and shows the possibility of survival beyond childhood. Bilateral proptosis with frontal bossing were the most neurological manifestations identified by the patient. The study also noted that RS is associated with squamous suture synostosis, separating the parietal and squamous temporal bones. Based on the findings, this study suggests close monitoring of the patients diagnosed with RS. Neurological evaluation should be done to detect any delay in neurodevelopment. In addition, a complete and regular calcium and phosphate homeostasis assessment among the children to monitor the developmental phase of children. The study recommends further studies comprising many patients to demonstrate the relationship and correlation between the genetic aspect of RS and squamous suture synostosis.

Disclosure

The author reports no conflicts of interest in this work.

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