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Case Report

A girl with synostotic plagiocephaly: unfolding as rare case

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ABSTRACT

Dysmorphic head shape can be a presenting complaint of craniosynostosis which needs to be investigated in detail for any genetic or syndromic associations. Many genetic mutations have been associated with craniosynostosis but ERF gene mutation has been found to be very rare. Here, we have discussed about an 8 years old girl who presented with dysmorphic head shape. She had crouzoid features like exorbitism, malar hypoplasia with copper beaten skull appearance and pansynostosis on CT Head but genetic evaluation revealed ERF gene mutation suggestive of craniosynostosis 4. She had short stature which was the unique association with it. Thus, high index of suspicion should be kept for craniosynostosis 4 when phenotypic features are suggestive of crouzon syndrome as crouzon syndrome can phenotypically mimic craniosynostosis with ERF gene mutation and genetic analysis should be done to look for alternate cause of craniosynostosis; especially to look for ERF gene mutation.

Keywords: Craniosynostosis, Copper-beaten skull appearance, ERF gene

INTRODUCTION

Abnormal head shape is often associated with an underlying cause due to aberrant premature fusion of skull sutures called craniosynostosis which has an incidence of three to five per 10000 live births.[1] Craniosynostosis can be classified as primary or secondary; syndromic and non-syndromic; and according to the sutures involved.[2] Approximately 20% of cases have an underlying genetic cause and 50% of these have de-novo gene mutation of which ERF gene is the rare one.[2] Here we report a rare case of craniosynostosis in pediatric age group with an underlying ERF gene mutation with its important clinical aspects.

CASE REPORT

An eight-year-old female child born to non-consanguineous marriage came with a chief complaint of disproportionate increase in head size involving the upper-middle part of the skull for the past two years which was gradual in onset, progressive in nature. It was not associated with headache, nausea, vomiting, altered sensorium, abnormal body movements, nystagmus, ataxia, blurred vision, drooling of saliva, difficulty in swallowing or limitation of any routine activity. There was no history of any chronic illness, hospitalization, or intake of any prolonged medication in the past. There was no history of similar complaints or any genetic disorder in any of three generations of the family. Our index case had only one elder sibling and is healthy. Antenatal history of mother was uneventful with no significant history of any maternal complications including drug or radiation exposure.

It was a term, normal vaginal delivery and baby cried immediately at birth. Developmental history of this child was normal for her age as she was good in academics and

communication with her peers. She was immunized for her age as per National immunization schedule (NIS) and the last vaccine received was at five years of age with no optional vaccines coverage. On examination, her vitals were normal for her age. Head to toe examination revealed abnormal head shape with protruberance of upper-middle part of head; malar hypoplasia and exorbitism (Figure 1).

Figure 1: Phenotypic features showing dysmorphic head shape, exorbitism and malar hypoplasia.

In anthropometry, weight and height for age were less than third centile and mid parental height was between third to 50th centile as per Indian Academy of Pediatrics charts. Head circumference was within normal range. BMI was between 25th to 50th centile. So, this girl was wasted and stunted. Her upper segment to lower segment ratio was 0.9. On evaluating further, her height age corresponded to five years whereas; her bone age was around eight and a half years which was equal to her chronological age. On systemic examination, her higher mental functions, cranial nerve examination, sensory system, neuromuscular system were normal. Rests of systemic examinations including respiratory, cardiovascular, gastrointestinal and genitourinary system were also normal. Therefore, with an impression of abnormal head shape, proptosis, dysmorphic facies and short stature; working diagnosis of syndromic craniosynostosis (most likely Crouzon syndrome) was kept and multi-disciplinary approach was followed for further management including hearing and speech assessment, ophthalmic evaluation and neurosurgery consultation. Her routine investigations including Complete Blood Count (CBC), Peripheral Blood Film (PBF), serum electrolytes, liver function tests (LFTs) with alkaline phosphatase, Renal Function Tests (RFTs), fasting blood sugar sent were normal. Other first tier investigations for short stature like Erythrocyte Sedimentation Rate (ESR), inorganic phosphorous, chest X-ray, Thyroid Function Tests (TFTs), urine and stool routine microscopy were also normal. CT scan of head showed copper beaten skull appearance with fusion of all sutures and elongation of the calvaria ventrodorsally suggestive of craniosynostosis (Figure 2). Whole Genome Sequencing (WGS) was done to evaluate any genetic cause. To our surprise, results showed ERF gene mutation with an autosomal dominant inheritance, likely pathological variant. Variant nomenclature was identified as c.145C>T (pGIn49Ter) and genomic nomenclature was chr19:g.42754595G>A thus, classifying it as craniosynostosis 4. This girl is currently doing well and is under routine follow up. Her family has been advised genetic counseling for the same.

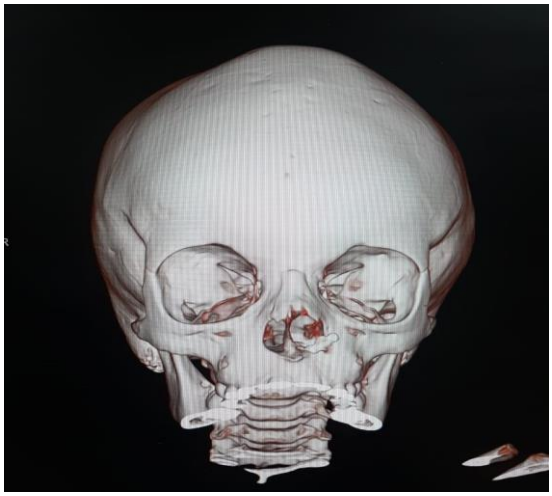

Figure 2: CT head showing gyral impressions on the inner table of the skull seen throughout the skull vault giving copper beaten skull appearance and Closure of the coronal, metopic, sagittal, lambdoid sutures with elongation of the calvaria ventrodorsally suggestive of craniosynostosis.

DISCUSSION

Often, syndromic craniosynostoses are reported to have been associated with gene mutations like FGFR1, FGFR2, FGFR3, TWIST1, and EFNB1. FGFR2 and FGFR3 gene mutations are typical seen in Crouzon syndrome which phenotypically resemble craniosynostosis with ERF gene mutation but differ at genetic level.[3] ERF gene mutation has been found even rare with prevalence of two percent and 0.7% with syndromic and non-syndromic craniosynostosis respectively.[4] Phenotypic characteristics reported with ERF mutation are sagittal or multiple suture synostosis; dysmorphic facies including hypertelorism; exorbitism; depressed nasal bridge and retrognathia.[5] Other associated features are Chiari-1 malformation, raised intracranial pressure in few, behavioural abnormalities and learning disabilities.[6] Our index case has crouzoid phenotype appearance but differ in other features. Short stature was the new finding seen in our case which has never been reported before in cases of craniosynostosis. CT head was consistent with findings of pansynostosis whereas WGS came out with unique finding of craniosynostosis 4 with ERF gene mutation.

CONCLUSION

Crouzon syndrome and craniosynostosis with ERF gene mutation are close phenotypic differentials of each other but differ at molecular level. Hence, every suspected case of craniosynostosis should undergo genetic testing in order to discover existing and new genetic mutations associated with it with an aim to make better understanding of this topic. Simultaneously, we should aim at diagnosing it as early as possible so as to provide early management, improving the survival rate and providing better quality of life.

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