ERF-related craniosynostosis in a six-year-old child

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Introduction

Craniosynostosis is the premature fusion of one or more cranial vault sutures restricting the normal growth of the skull, brain and face. Whilst 70-75% of the patients have isolated craniosynostosis, 25-30% present with syndromic cranioisynostosis[1]. The human *Ets2 Repressor Factor* (*ERF)* gene is mapped to chromosome 19q13.2 consisting of 4 exons[2,3]. The *ERF* protein is an Ets domain protein belonging to the Ets family of genes[2]. *ERF* being a transcriptional regulator gene, appears to be involved in cellular proliferation[4]. Mutation in *ERF* gene has recently been described to cause a syndromic craniosynostosis with facial dysmorphism, Chiari 1 malformation, speech and language delay, learning and behavioural difficulties[5]. We describe a 6-year-old child who presented with syndromic craniosynostosis and was subsequently diagnosed to have *ERF*-related craniosynostosis or craniosynostosis-4.

Case report

A six-year-old boy, of Indian origin, born of a non-consanguineous marriage, presented with a history of diminution of vision for 2 months. On examination, facial dysmorphism with proptosis, hypertelorism, depressed nasal bridge, full lips, upturned nose, short columella, pectus excavatum and brachydactyly were present (Figures 1 and 2).

Occipito-frontal circumference (OFC) was 51 cm which was on the 50th centile on the growth chart for the age and sex of the child. Child had global developmental delay and a past history of seizures at two years of age for which he was started on the anticonvulsant levetiracetam. As the child had been seizure free since then, levetiracetam had been tapered and stopped two years back.

Figure 1: ***Facial dysmorphism with proptosis, hypertelorism, depressed nasal bridge, full lips, upturned nose and short columella***
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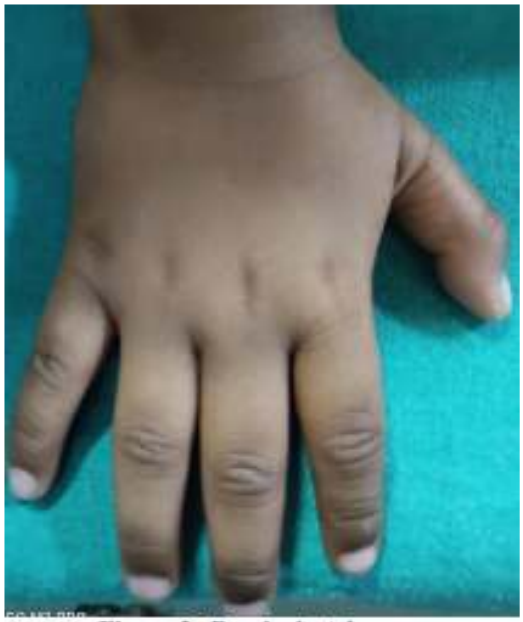

Figure 2: ***Brachydactyly***

Magnetic Resonance Imaging (MRI) of the brain revealed a cerebellar tonsillar descent of 14mm below the level of foramen magnum, suggestive of Arnold Chiari 1 malformation with bilateral distended optic nerve sheaths (Figure 3).

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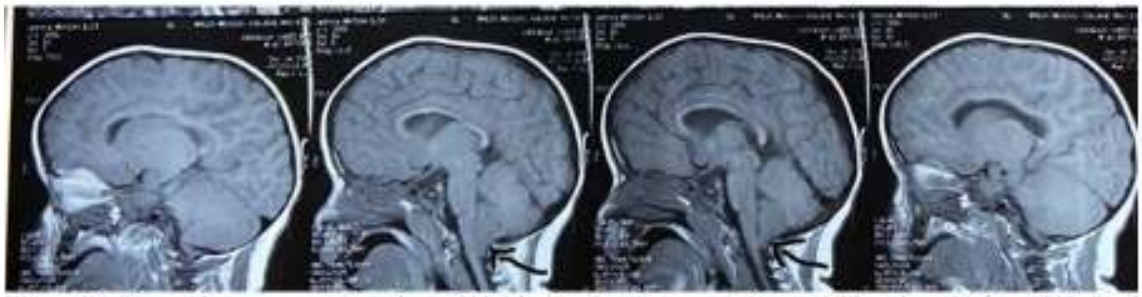

Figure 3: ***Magnetic resonance imaging of the brain showing cerebellar tonsillar descent (Arnold Chiari malformation) indicated by arrow***

X-ray skull showed features of raised intracranial tension with copper beaten appearance and craniosynostosis (Figures 4 and 5).

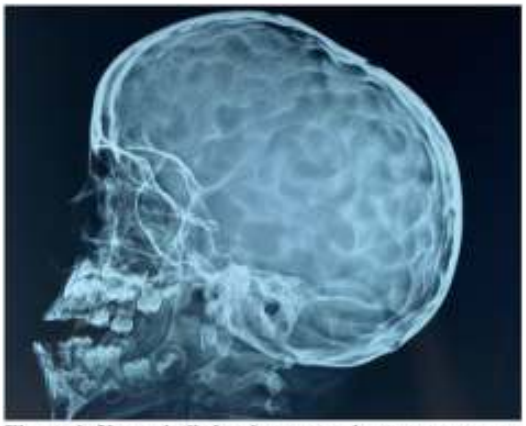

Figure 4: ***X-ray skull showing copper beaten appearance***

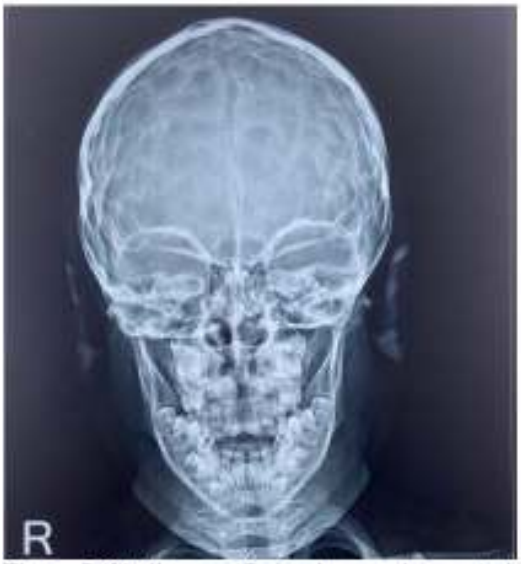

Figure 5: ***Skull x-ray AP showing craniosynostosis***

3D skull reconstruction showed absence of coronal, metopic, lambdoid and sagittal sutures (Figure 6)

Figure 6: 3D skull reconstruction showing multi-sutural craniosynostosis

Figure 7 shows the normal shape of the child's head

Figure 7: Normal shape of child's head
Permission given by parents to publish photograph

Ophthalmologist's opinion was taken and the child was diagnosed to have primary optic atrophy with craniosynostosis. In view of syndromic craniosynostosis, a genetic analysis was sent. Chromosomal microarray analysis showed microdeletion at 19q32.2 involving the *ERF* gene

suggestive of craniosynostosis-4. Child was thereupon referred to a neurosurgeon. However, the parents did not consent for surgery and the child was discharged without any further interventions.

Discussion

Craniosynostosis is a complex genetically heterogeneous condition that occurs in 1 in 2000-2500 newborns[6]. Syndromic craniosynostosis is most commonly caused by mutations in *FGFR1*, *FGFR2, FGFR3, TWIST 1, TCF12 and EFNB1*. Recently in 2013, a new mutation in *ERF* was described by Twigg SR *et al* as a cause of craniosynostosis[5]. Genetic analysis was performed in 411 patients with craniosynostosis and 288 North European controls. A heterozygous loss of function mutation in *ERF* was identified in 11 patients in the craniosynostosis group while there were no such mutations in the control group. The characteristics of 'ERF-related craniosynostosis' observed were sagittal or multiple suture synostosis, Chiari malformation and language delay, craniofacial dysmorphism and raised intracranial pressure. Prevalence of *ERF* mutations in syndromic craniosynostosis is 2% and 0.7% in clinically non-syndromic craniosynostosis[7].

Balasubramaniam M, *et al*[8] reported a recurrent *ERF*:c.266A>Gp.(Tyr 89 Cys) missense variant as the molecular aetiology of Chitayat syndrome. Here he described five patients with similar features including hyperphalangism, brachydactyly, bilateral hallux valgus, pectus excavatum, facial dysmorphism, respiratory distress and bronchomalacia. However, none of the patients had craniosynostosis. In contrast, our child had craniosynostosis with all the above-mentioned features except respiratory distress, bronchomalacia and hyperphalangism. Balasubramaniam M, *et al*[8] observed that patients with c.266A>Gp (Tyr 89 Cys) variant in *ERF* were found to be associated with hyperphalangism phenotype while nearby residues within the ETS domain including p.(Arg 65 Gln) and p.(Arg 86 Cys) were associated with the craniosynostosis phenotype[5]. In addition, 'microdeletions' and not 'deletions' of the *ERF* gene have been reported to cause craniosynostosis[9].

Glass GE, *et al*[10] presented the data from 16 unrelated probands and an additional 20 family members with *ERF*-related craniosynostosis It was observed that this type of craniosynostosis presented later than other syndromic craniosynostosis with a median age at presentation of 42 months. Majority of patients demonstrated multi-sutural synostosis, predominantly involving the sagittal and lambdoid sutures. However only subtle change in head shape was noticed which was attributed to the delayed development of craniosynostosis. Our child too had a delayed presentation involving multiple sutural synostosis leading to raised intracranial pressure with no abnormalities in head shape observed (Figure 7).

ERF-related craniosynostosis is often confused with Crouzon syndrome. The differentiating feature is the presence of a mild mid-facial hypoplasia with *ERF*-related craniosynostosis and typical behavioural and developmental abnormalities like attention deficit hyperactive disorder in Crouzon syndrome.

In conclusion, *ERF*-related craniosynostosis is a new and emerging cause of syndromic craniosynostosis. Any child presenting with multi-sutural craniosynostosis in infancy or early childhood should be evaluated for *ERF* gene mutation.

References

1. Körberg I., Nowinski D, Bondeson ML, Melin M, Kölby L, Stattin EL. A progressive and complex clinical course in two family members with *ERF*-related craniosynostosis: a case report. *BMC Medical Genetics* 2020; 21: Article No. 90.
https://doi.org/10.1186/s12881-02001015-z
PMid: 32370745 PMCid: PMC7201657

2. Sgouras DN, Athanasiou MA, Beal GJ Jr, Fisher RJ, Blair DG, Mavrothalassitis GJ. ERF: an ETS domain protein with strong transcriptional repressor activity can suppress ETS-associated tumorigenesis and is regulated by phosphorylation during cell cycle and mitogenic stimulation. *EMBO Journal* 1995; **14**: 4781–93.
https://doi.org/10.1002/j.14602075.1995.tb00160.x

3. Petrovic N, Bhagwat SV, Ratzan WJ, Ostrowski MC, Shapiro LH. CD13/APN transcription is induced by RAS/MAPK-mediated phosphorylation of ETS-2 in activated endothelial cells. *Journal of Biological Chemistry* 2003; **278**: 49358–68.
https://doi.org/10.1074/jbc.M308071200
PMid: 14507917

4. Liu D, Pavlopoulos E, Modi W, Moschonas N, Mavrothalassitis G. ERF: genomic organization, chromosomal localization and promoter analysis of the human and mouse genes. *Oncogene* 1997; **14**: 1445–51.

https://doi.org/10.1038/sj.onc.1200965
PMid: 9136988

5. Twigg SR, Vorgia E, McGowan SJ, Peraki I, Fenwick A, Sharma VP, *et al.* Reduced dosage of ERF causes complex craniosynostosis in humans and mice and links ERK1/2 signaling to regulation of osteogenesis. *Nature Genetics* 2013; **45**: 308–13.
https://doi.org/10.1038/ng.2539
PMid: 23354439 PMCid: PMC3683605

6. Lattanzi W, Barba M, Di Pietro L, Boyadjiev SA. Genetic advances in craniosynostosis. *American Journal of Medical Genetics Part A* 2017; **173**(5): 1406–29.
https://doi.org/10.1002/ajmg.a.38159
PMid: 28160402 PMCid: PMC5397362

7. Wilkie AOM, Johnson D, Wall SA. Clinical genetics of craniosynostosis. *Current Opinion in Pediatrics* 2017; **29**(6): 622–8.
https://doi.org/10.1097/MOP.0000000000000542
PMid: 28914635 PMCid: PMC5681249

8. Balasubramanian M, Lord H, Levesque S, Guturu H, Thuriot F, Sillon G, *et al.* Chitayat syndrome: hyperphalangism, characteristic facies, hallux valgus and bronchomalacia results from a recurrent c.266A>G p.(Tyr89Cys) variant in the *ERF* gene. *Journal of Medical Genetics* 2017; **54**(3):157-165.
https://doi.org/10.1136/jmedgenet-2016-104143
PMid: 27738187

9. Yuan H, Meng Z, Liu L, Deng X, Hu X, Liang L. A de novo 1.6Mb microdeletion at 19q13.2 in a boy with Diamond-Blackfan anaemia, global developmental delay and multiple congenital anomalies. *Molecular Cytogenetics* 2016; **9**: 58.
https://doi.org/10.1186/s13039-016-0268-2
PMid: 27486481 PMCid: PMC4970238

10. Glass GE, O'Hara J, Canham, N, Cilliers D, Dunaway D, Fenwick AL, *et al*. ERF-related craniosynostosis: The phenotypic and developmental profile of a new craniosynostosis syndrome. *American Journal of Medical Genetics Part A* 2019; **179**(4): 615–27.
https://doi.org/10.1002/ajmg.a.61073
PMid: 30758909 PMCid: PMC6491982