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Crouzon Syndrome: A Case Report

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INTRODUCTION

Cranisynostosis defines the premature fusion of the cranial sutures and has an overall prevalence of 1 in 2100–2300 live births.[1,2] Nearly one quarter of craniosynostosis has a genetic etiology.[3,4] There is considerable genetic heterogeneity and frequent phenotypic overlap between different syndromes. Genes encoding three members of the fibroblast growth factor receptor family (FGFR1, FGFR2 and FGFR3) are commonly mutated in individuals with craniosynostosis. Heterozygous mutations in FGFR2, which are frequently recurrent, account for 28% of genetic cases and cause Crouzon, Pfeiffer, Apert, Beare-Stevenson and bent bone dysplasia syndromes.[5]

Crouzon syndrome is a rare genetic disorder with autosomal dominant inheritance. This syndrome was described by Crouzon in 1912 who described a patient with a characteristic group of deformities which were then observed in other individuals. Crouzon syndrome is caused by malformations of the mesenchyme and ectoderm. Mutation of the gene for fibroblast growth factor receptor 2 (FGFR2) is responsible for Crouzon syndrome and this gene has been mapped to the long arm of chromosome 10 and mutations in exon B of FGFR2 gene have been described.[6]

The prevalence of Crouzon syndrome is 1 in 25,000 live births, and it constitutes 4.8% of all craniosynostosis. In 25% of cases, it may also occur sporadically because of a fresh mutation.[7,8] In dr. Soetomo hospital, there were at least 5 cases of Crouzon syndrome every year.

The underlying pathological process is premature synostosis of the coronal, sagittal and occasionally lambdoid sutures beginning in the first year of life and completed by 2-3 years of life. This fusion does not allow the bones to grow normally, affecting the shape of the head, appearance of the face and the relationship of the teeth. The diagnosis is based on clinical findings and radiological examination.[8]

The purpose of this paper is to report case of severe Crouzon syndrome in children, focusing on diagnostic and its management.

CASE REPORT

A, 17 months old male was consulted to Growth and Development Division from Plastic Surgery Department on March 2017, and was diagnosed as severe Crouzon syndrome with chief complained of red eyes and protruded eyes for six months before admission. Eyes increasingly protrude so that he is difficult to wink and close his eyes. The shape of his head also become increasingly protrude upward and different from the shape of a child's head in general. He was consulted because there were lack of normal physiological development (could not stand and walk). He also complained of cough with mucus production a month before admission with no difficulty of breathing. There is no fever, vomiting, and seizure. Since last month, his parents complained decreasing of his vision. He brought to emergency department of Blitar hospital, then referred to dr. Soetomo hospital for further evaluation. He was consulted to Plastic Surgery Department and diagnose with severe Crouzon syndrome.

He was born spontaneously, at term by obstetrician with birth weight of 3500 grams and birth length 50 cm. His mother was healthy during pregnancy. There was no history of consuming alcohol, narcotics and drugs nor radiation exposure during pregnancy. His mother liked to consume herbal (*beras kencur/jamoo*). At birth his father was told if his child needed to had head CT-scan because there was abnormality in his child's head. He had breastfed until 1 month of age and got formula milk until now. He started eating fine porridge at 6 months of age and rough porridge at 12 months of age. He was the third child. The first child was girl, 12 years old, in healthy condition, and already in the six the grade of primary school. The second child was a boy, 5 years old and in healthy condition. There were no family members with similar complaint to the patient or history of congenital anomaly.

Physical examination presented an alert boy, weak, with blood pressure was 90/60mmHg, pulse was 112 beats per minute, respiratory rate was 22 times per minute and the body temperature was 37^0 C, and SpO_2 was 99%. There is no pale, no dyspnea nor cyanotic. His eyes were protruded. His nose, mouth, throat and neck were normal, there was no enlargement of neck lymphnode. Thyroid gland not palpable. The chest was symmetric, there is no retraction observed. The heart and lung were normal. The abdominal examination was normal with abdominal mass not found and no enlargement found of the liver and spleen. The extremities were well perfused and no edema found. There was no abnormalities congenitalia examination. His body weight was 8,6 kg (WAZ = - 2) body length was 82 cm (LAZ = 0), with weight for length is severely wasted. The head circumference 45 cm (HCAZ < -2). We still used the normal WHO growth chart because there were no suitable charts that match with this patient.

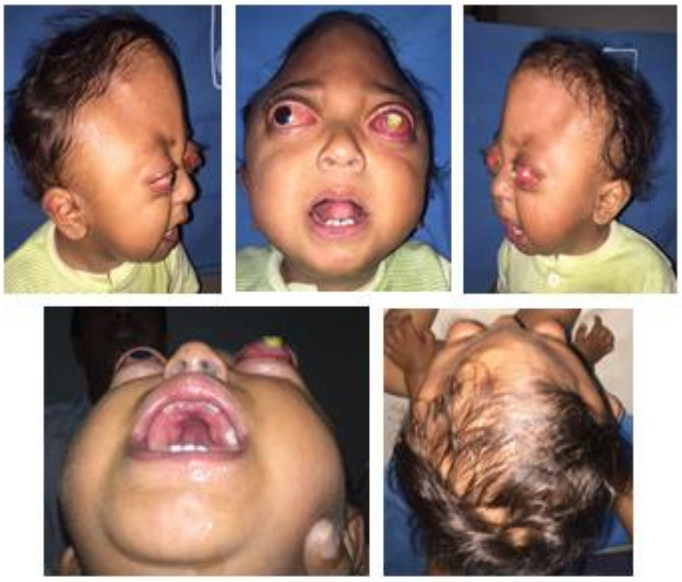


Figure 1. Boy, 17 months old, with head abnormality, red eyes and protruded eyes

Denver Developmental Screening test there were delayed in 4 aspect, gross motor function; lift head, held head 45°, cannot lift head 90°, cannot sit with head steady, fine motor function; cannot follow finger to midline nor past line, language; turns to voice but cannot said mama nor papa in specific and make 3 words, and personal social cannot smile spontaneously.

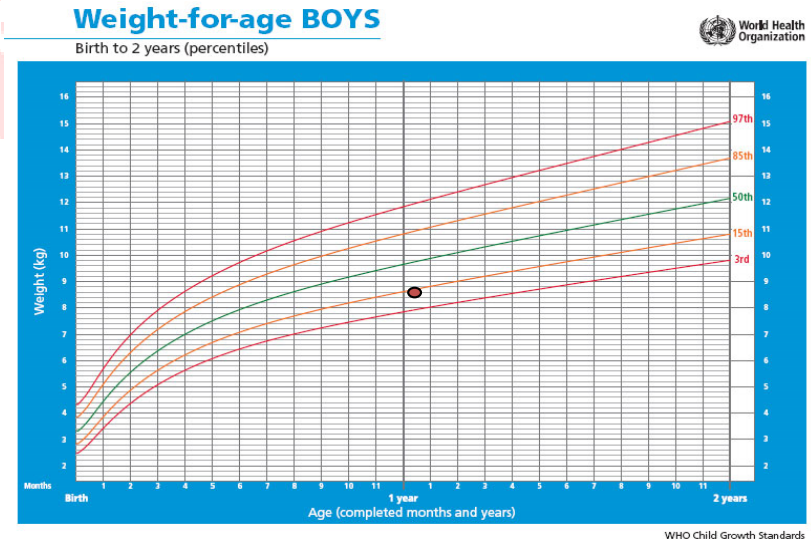


Figure 2. Boy A, Weight for age (WAZ < -3)

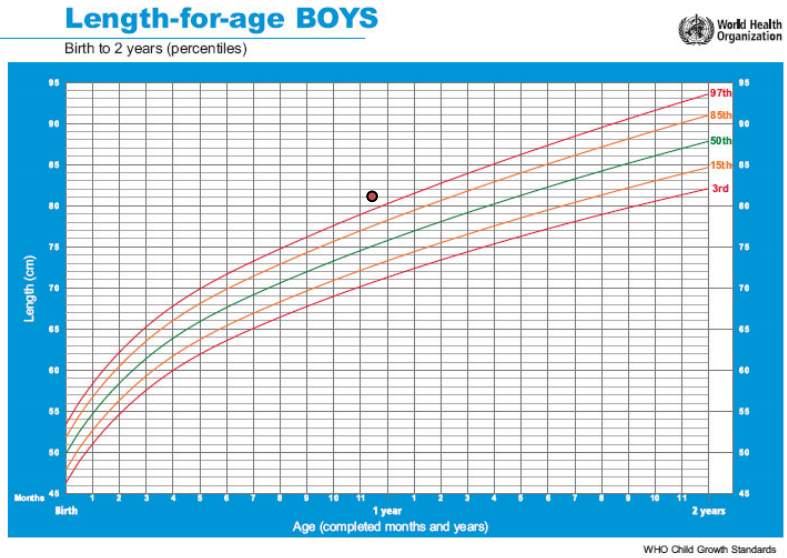


Figure 3. Boy A, Length for age (LAZ = 0)

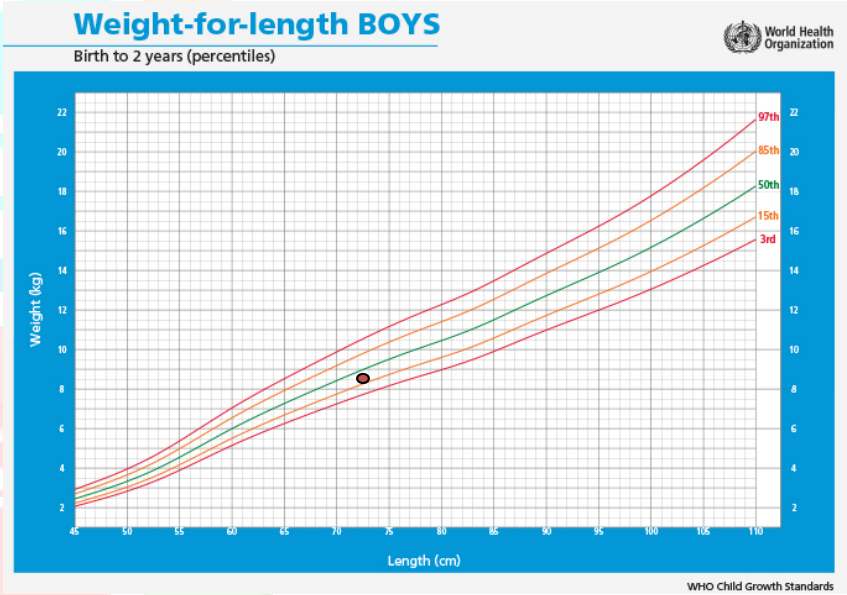


Figure 3. Boy A, Weight for Length (WAZ <-3, severely Wasted)

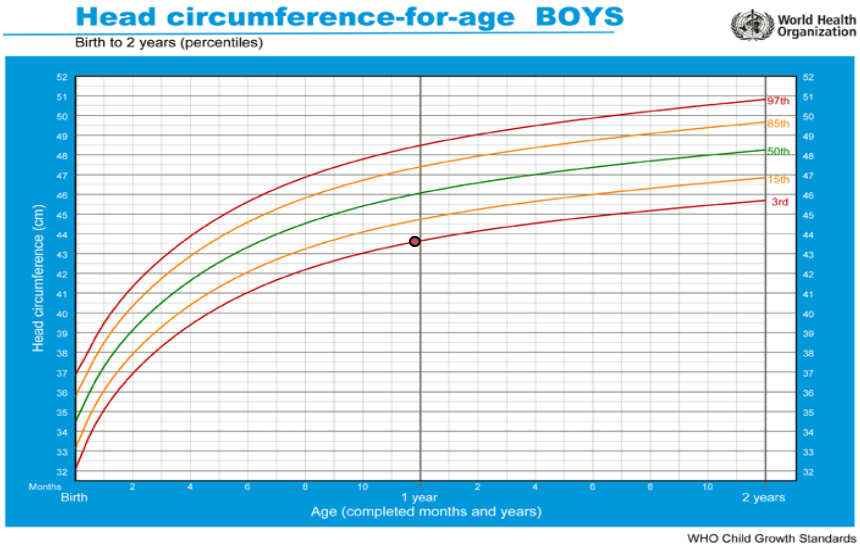
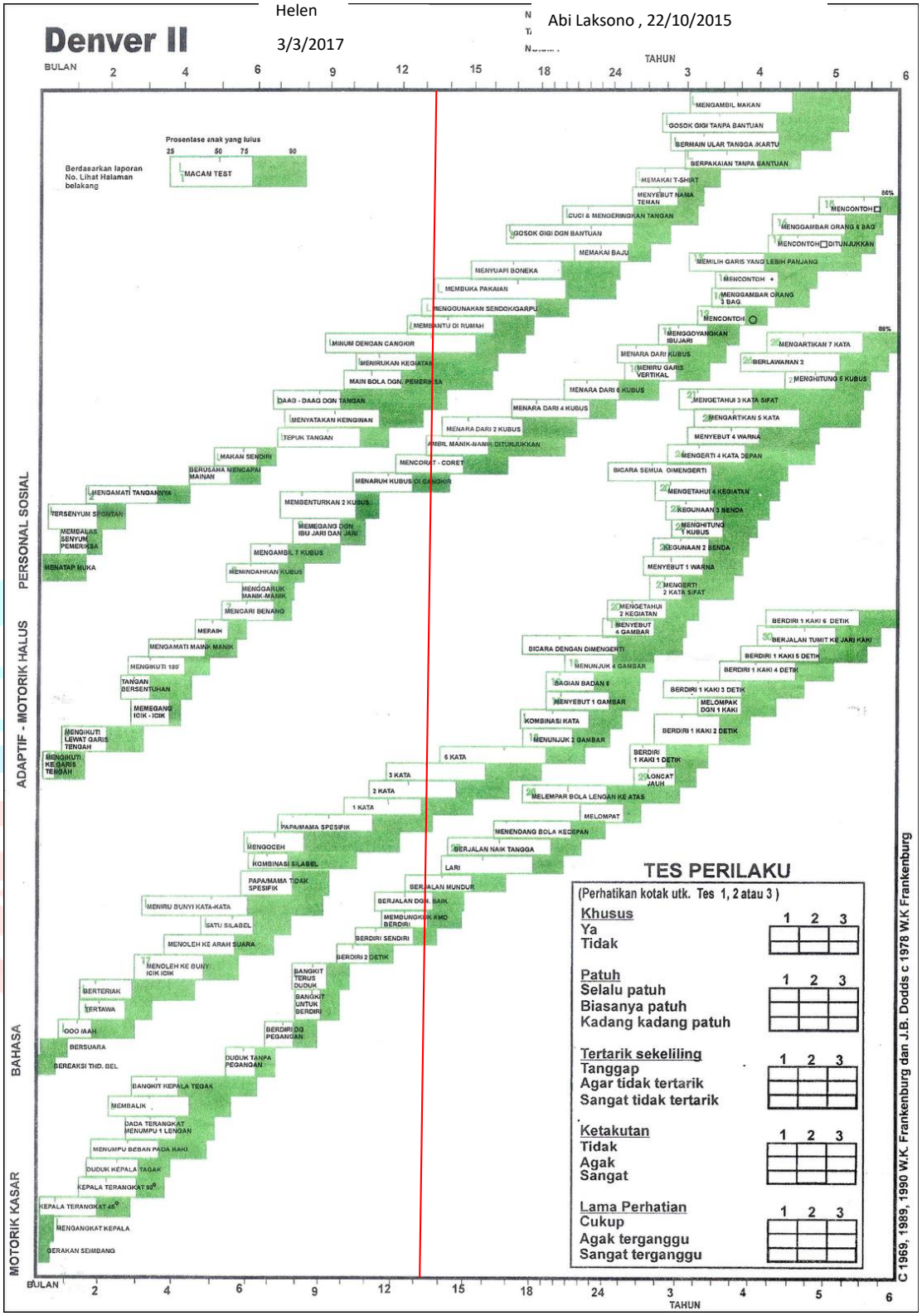


Figure 3. Boy A, Head circumference for age (HCAZ < -2)



Laboratory examination revealed normal complete blood count (Hb 11.3 g/dl, WBC 9.400/cmm, Hct 36.1g/dl, and platelet 337.000/cmm, normal electrolyte serum (sodium 139 meq/l, potassium 4.9 meq/l, chloride 100 meq/l and calcium 8.9 meq/l). Liver function test was normal (AST 36 U/l,ALT 31 U/l) with albumin level 4.5 mg/dl. Renal function test was normal (BUN 5 mg/dl, creatinine 0.4 mg/dl). From hemostasis with normal (APTT 35.3 second, PPT 10 second).

From Radiologic examination, thorax roentgen revealed normal heart with CTR 48% and without any pulmonary abnormality (Figure 4.)

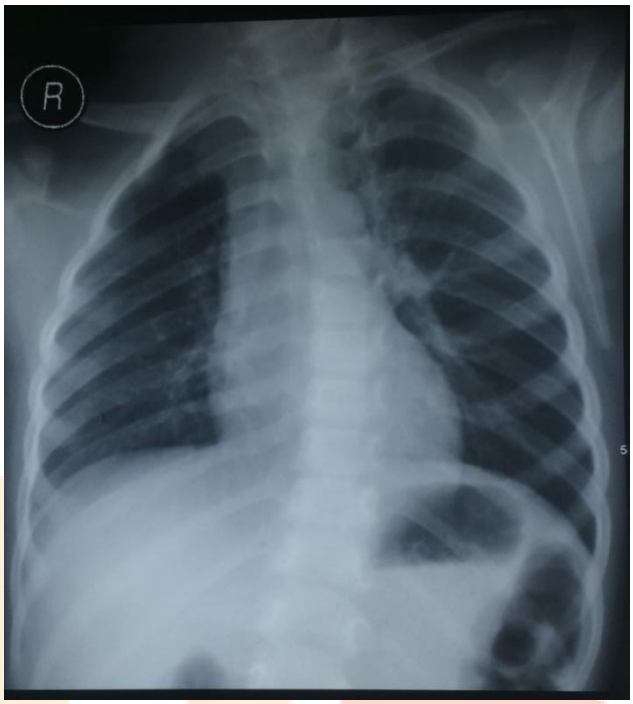
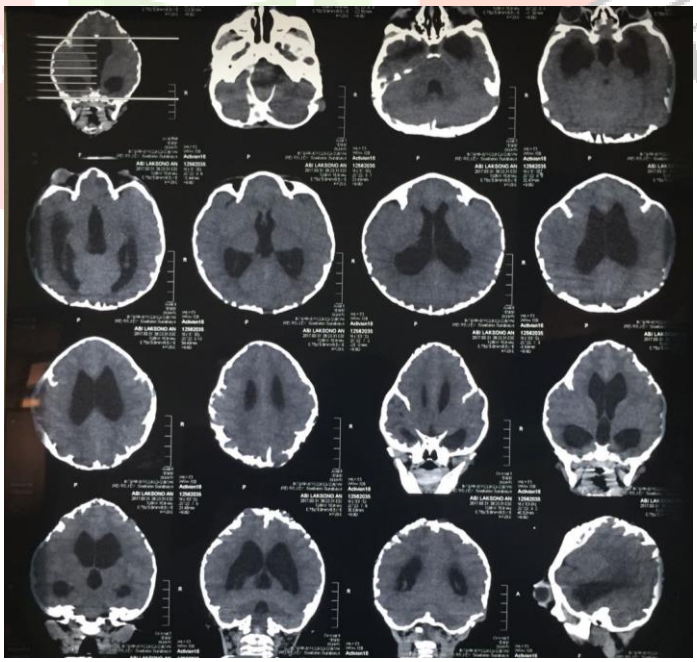


Figure 4. Thorax Roentgen, Male 17 month , March 2017

From CT-scan examination revealed craniosynostosis, bilateral exophthalmos and communicating hydrocephalus (Figure 5.).



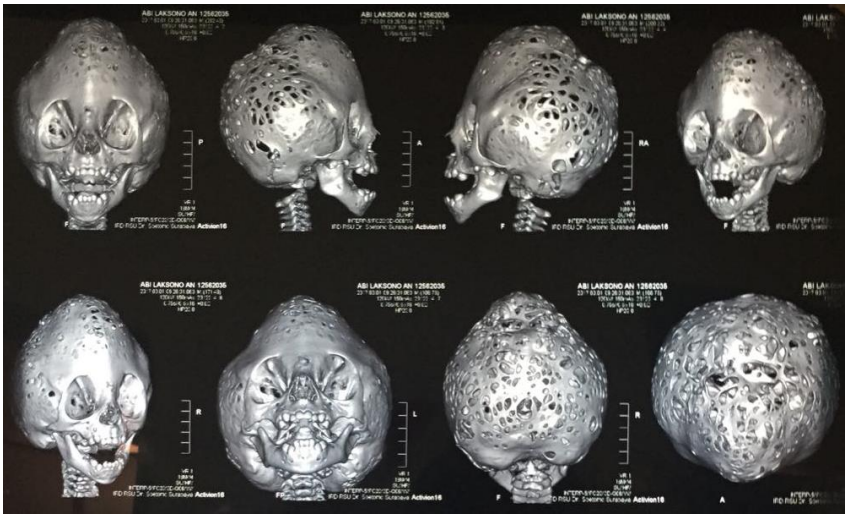


Figure 5. Head CT-scan, March 2017

Based on history taking, physical examination, radiology examination (head CT scan) the diagnosis of this patient is Crouzon syndrome and susp eight days of admission the child was performed craniotomy and frontoorbital advancement.

seven days after operation the child was discharged and scheduled to control to plastic surgery, department growth and development division of pediatric.

DISCUSSION

A, 17 months old male was consulted to Growth and Development Division from Plastic Surgery Department with delayed in physiological development. From Denver Developmental Screening test there were delayed in 4 aspect, gross motor function; lift head, held head 45°, cannot lift head 90°, cannot sit with head steady, fine motor function; cannot follow finger to midline nor past line, language; turns to voice but cannot said mama nor papa in specific and make 3 words, and personal social cannot smile spontaneously. From physical examination his fore head was protruding with cone or triangle shaped, and proptosis of the eyes indicate cranio facial dysostosis.

Craniofacial abnormalities are usually present at birth and may progress with time. These cranial malformations are not very common, but it compromises not only the function but also the mental wellbeing of the person. Crouzon syndrome, is one of the autosomal dominant disorder that characterized by craniosynostosis it caused by a mutation in the Fibroblast Growth Factor Receptor 2 gene (FGFR2).[9] Other characteristic are shallow orbits, ocular proptosis, midface hypoplasia, and a curved, beaklike nose.[10] It accounts for approximately 4,8% of all cases of craniosynostosis making it the most common syndrome within the craniosynostosis group.[5,6]

In child A, from CT-scan examination revealed there was craniosynostosis. There were calvaria deformities characterized premature closure of sagittal, coronal, frontal, and left right lamboid sutures and clebbatschaedel feature.

Craniosynostosis describes partial or complete premature fusion of cranial sutures. Ocular hypertelorism, proptosis, breaking of the nose and midface hypoplasia are the common facial features of the craniosynostoosis.[10-12] The syndromic craniosynostosis is the hereditary form of craniosynostosis, which is associated with extracranial phenotypes such as limb, cardiac, central nervous system and tracheal malformations. Syndromic craniosynostosis comprises 15-30% of the total and specific single gene mutations or chromosome abnormalities could be identified in at least 20% of all cases. The prevalence of craniosynostosis is estimated to be 1 in 2100 to 2500 live births. The sagittal suture is the most commonly affected (40-55%). followed by the coronal (20-25%) and lamboid (<5%) sutures.[11-12]

In this patient molecular genetic analysis in the FGFR2 receptor gene had not been performed yet. Although advances in molecular genetic has led to a better understanding of the molecular pathology, the clinical impact is still limited to prenatal diagnosis. The karyotyping examination had not been performed yet.

The etiology of malformation is still controversial. Autosomal dominant as well as genetic inheritance seems possible. FGFRs play a central role in the growth and differentiation of mesenchymal and neuroectodermal cells by binding to FGF and initiation of signal transduction. FGFRs regulate cranial suture fusion on a macroscopic level.[13] Animal suggest that defective FGF signal transduction due to mutations on FGFRs leads to growth arrest of the cranium and the midface. Mutations in FGFRs have been linked to various clinical craniosynostosis syndromes including Apert, Pfeiffer, Crouzon, Antley-Bixler, Muenke, Beare-Stevenson, and Jackson-Weiss syndromes.[14] These *FGFR*-related craniosynostosis syndromes are autosomal-dominantly inherited, and share several craniofacial features including premature closure of multiple cranial sutures. On the other hand, a wide phenotypic range has been shown even in patients with identical *FGFR2* mutations. Therefore, differential diagnosis is usually based on presence or absence of distinct limb and dermatological features.[1,9]

Table 1. Common genetic syndromes associated with craniosynostosis

Genetic syndrome	Gene	Chromosome	Inheritance	Involved sutures	Hand/foot anomalies
Apert syndrome	*FGFR2*	10q26	Autosomal-dominant	Multiple	Syndactyly of hands and feets
Pfeiffer syndrome	*FGFR2* *FGFR1*	10q26 8p11.2–11.1	Autosomal-dominant	Multiple	Broad and medially deviated thumbs and big toes, brachydactyly
Crouzon syndrome	*FGFR2* *FGFR3*	10q26 4p16.3	Autosomal-dominant	Multiple	Normal hands and feet, normal intelligence
Antley-Bixler syndrome	*FGFR2* *POR*	10q26	*FGFR2*; autosomal-dominant *POR*; autosomal-recessive	Multiple	Radio-humeral or radio-ulnar synostosis, congenital adrenal hyperplasia (*POR*)
Saethre-Chotzen syndrome	*TWIST1*	7p21	Autosomal-dominant	Coronal	Ptosis, syndactyly, hearing loss
Muenke syndrome	*FGFR3* (p.Pro250Arg)	4p16.3	Autosomal-dominant	Coronal	Normal hands and feet
Craniofrontonasal syndrome	*EFNB1*	Xq12	X-linked dominant	Coronal	Bifid nasal tip, cleft lip and/or palate, syndactyly, grooved nails

Source : Ko JM. Genetic syndrome associated with craniosynostosis. J Korean Neurosurg soc 2016;59:187-91

There were some disorders with craniosynostosis can be similar to those of Crouzon syndrome, especially those with the FGFR mutations. We do some comparisons that useful for a differential diagnosis.

Table 2.Comparisson of Clinical Findings in related syndromes

Syndrome	Clinical Findings
Antley – Bixler	- Trapezoidocephaly - Joint stiffness - Midface hypoplasia - Frontal bossing - Short “pear- shaped” nose - Protruding eyes
Apert	- Acrocephaly - Syndactyly, Brachydactyly - High-broad forehead - Hypertelorism - Flattened nose with low bridge - Mental retardation
Crouzon	- Scapocephaly, Trigonocephaly - Proptosis, Exophtalmus, Strabismus - Hypertelorism - “Parrot-Beaked” Nose - Underdevelopment of Jaw - Mental retardation
Pfeifer	- Acrobrachycephaly - Syndactily - Big thumbs and toes - Deformities head, jaws, teeth - Protruding eyes

In this patient from physical appearance there was calvarial deformities, facial anomalies, and exophthalmos without digital deformity leads to Crouzon syndrome.

Elevated intracranial pressure (ICP) is the most serious functional problem associated with premature suture fusion and may occur in 42% of untreated children in whom more than one suture is affected [14]. The clinical signs and symptoms related to elevated ICP may have a slow onset and be difficult to recognize in the pediatric population. [15]

In this patient from eyes examination revealed proptosis, conjungtiva hyperemia, cloudy cornea, and ulceration in left eye. From funduscopy examination revealed papil edema. Visual examination 6/360 for right eye and left eye difficult to evaluate.

Untreated craniosynostosis with elevated ICP causes papilledema and eventual optic nerve atrophy, which results in partial or complete blindness. If the orbits are shallow (exorbitism) and the eyes are proptotic (exophthalmus), which occurs in the craniofacial dysostosis syndromes, the cornea may be exposed and abrasions or ulcerations may occur. An eyeball that extends outside of a shallow orbit is also at risk for trauma. If the orbits are extremely shallow, herniation of the globe may occur, which necessitates emergency reduction followed by tarsorrhaphies or urgent orbital decompression.[17]

From head CT scan revealed hydrocephalus. Hydrocephalus affects as many as 10% of patients with a craniofacial dysostosis syndrome.[18] Hydrocephalus may be secondary to a generalized cranial base stenosis with constriction of all the cranial base foramina that impact a patient's cerebral venous drainage and cerebrospinal fluid flow dynamics. The key of craniosynostosis management is a multi-staged surgery, from birth to maturity stage, and with multi-disciplinary team. The initial treatment for any craniofacial dysostosis is syndrome generally requires bilateral coronal suture release with decompression and simultaneous anterior cranial vault and upper orbital osteotomies with reshaping and advancement. Operation procedure preference is when a child is 9 to 11 months of age unless clear signs of increased ICP are identified earlier in life. The goals at this stage are to provide increased intracranial space in the anterior cranial vault for the brain, increase the orbital volume, which allows the eyes to be positioned more normally for better protection from exposure, and improve the morphology of the forehead and upper orbits. Guideline qualification for pediatric surgery recommended a multidisciplinary perioperative care for those with syndromic craniosynostosis. The team consist of plastic surgeon, neurosurgeon, pediatrician, pediatric anesthesiologist, and Growth and Development Division of Pediatric.[18,19] There were some protocols that used for management planning for craniosynostosis. One of them that has been used widely was the protocol from Australian Craniofacial Unit.

Table 3. Treatment Protocol for Craniosynostosis

Age Stage	Management
Birth – 3 months	Total assessment
3-6 months	Planning Meeting Surgery : • Fronto-orbital advancement (FOA) • Bone graft • Lambdoid craniectomy
1 year	Total Review Craniofacial clinic Hand surgery for syndactily
1 – 10 years	Yearly reviews + Craniofacial clinics 3 yearly Dentistry (6 monthly checks) + Orthodontic treatment Surgery : • Facial/fronto-facial advancement • Bone grafts
Teenage years	Complete workup Dentistry (6 monthly checks) + Orthodontic treatment Orthognatic surgery
Maturity	Touch-up surgery

Source : Australian Craniofacial Unit Protocols. 2001

SUMMARY

A case of Crouzon Syndrome in a 17 months old male has been reported. The patient was consulted to Growthand Development outpatient clinic because there was lack of normal physiological development. His CT scan findings revealed craniosynostosis and bilateral exophthalmos. He also had some clinical features abnormality such asshalloworbits, midfacehypoplasia, and a curved, beakliken osethatistypicalto Crouzon syndrome. Altough this syndrome commonly caused by mutation of the chromosomes, themolecular genetic analysis and karyotyping hadn't performedyet in this patient.

Operation procedure preferenceis when a child is 9 to 11 months of ageunless clear sign so fincreased ICP are identifiedearlier in life. The goals at this stage are to provide increased intracranial space in the anterior cranial vault for the brain, increase the orbital volume, which allows the eyes to be positioned more normally for better protection frome exposure, and improve themorphology of the fore head and upperorbits.

This first surgery of this patient was performed when he was 17 month old, but there was no significant result for visual improvement. Growth and developmental aspects of this patient has not evaluated further more because after surgery he never came back to outpatient clinic.

COMPETING INTEREST STATEMENT

The authors declare no conflict of interest.

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