Case report

CRANIOFACIAL AND DENTAL MANIFESTATIONS OF CROUZON'S SYNDROME: A Review of Literature and Report of an Illustrative Case

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ABSTRACT

OBJECTIVE: This is a report a case of Crouzon Syndrome in a 5-year-old female and review the literature on the presentation and management of this rare craniofacial anomaly.

CASE REPORT: A 5-year-old girl presented with complaints of head swelling and protrusion of the eyes associated with relative prominence of the lower jaw and decreased growth of the mid face about 9 months after birth. Based on clinical and radiological findings, a diagnosis of Crouzon's syndrome was made

CONCLUSION: There is a need for the development of a craniofacial team at this center and other African center in view of the increasing incidence of this anomaly. The patient in the case report did not receive any intervention in view of resource limitation despite her urgent need for intra- cranial decompression

Keywords: Craniosynostoses, Crouzon syndrome, Literature Review

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INTRODUCTION

Craniosynostoses are a heterogeneous group of syndromes characterized by a premature fusion of sutures occurring either in isolation or alongside presence of other skeletal anomalies[1]; the types are defined by the involved obliterated suture(s) with reported observation in1:25000 births worldwide[2, 3]. Crouzon syndrome, which was originally described by Octave Crouzon, French neurologist (1912) is a notable example of craniostenosis that is characterized by premature obliteration and ossification of two or more sutures, mostly the coronal, sagittal and associated facial anomaly as demonstrated by features of exorbitism, retromaxillism, inframaxillism and parodoxic retrognathia[4, 5]. Crouzon syndrome is a rare genetic disorder albeit the most common craniosynostosis without syndactyl, it accounts for about 4.5% and 4.8% of all craniosynostosis[2, 3].

When Crouzon syndrome is associated with syndactyl, it is known as the Crouzon- Apert syndrome and this together with Crouzon syndrome are the most common craniosynostosis syndromes of over 70 known syndromes of craniostenosis[1]. It is inherited with an autosomal dominant mode of transmission with the first described case involving a mother and her daughter with positive family history

reported in about 44-67% of cases[5, 6]; however spontaneous and sporadic occurrence with new mutations has been reported in up to 25 - 50% of cases of Crouzon syndrome[6]. Fibroblast Growth Factor Receptor-2 (FGFR-2) gene, mapped on chromosome locus 10q25-10q26, has been implicated in both the inherited and sporadic cases[7]. Many of these mutations are observed to occur within the Ig III domain of FGFR 2 and a novel mutation, Tyr 281 Cys substitution at the exon IIIa of FGFR 2[8]. The FGFR-2 mutation in Crouzon syndrome displays variable expressivity and phenotypic heterogeneity, on rare instances FGFR3 gene mutation has also been mentioned[9, 10]. Neither sex nor racial predilection has been reported with Crouzon syndrome in the literature and notable risk factors implicated in its pathogenesis include increased paternal age and children of those parents who may be carriers of the mutated gene[11].

Its phenotypic heterogeneity precludes a plethora of skeletal, craniofacial (including orbital), otorhinolaryngological and other clinical manifestations which have been reported in documented literature in cases of Crouzon syndrome[2, 4, 9]. These include facial abnormalities such as brachycephaly, shallow orbits and maxillary hypoplasia: acoustic meatus atresia, hyperacusis and malformations of the middle ear are the commonly associated hearing problems. Cervical spine fusion anomalies affecting C2 to C5 are the most common vertebral deformities in Crouzon syndrome whilst limb anomalies in Crouzon syndrome are nonspecific[12]. Other clinical features reported in Crouzon syndrome include Acanthosis nigricans, which are hyperpigmented and hyperkeratotic lesions located on the neck and near joint flexures[13], mild mental retardation, developmental delays and characteropathy[14]. Intraoral manifestations include mandibular prognathism, overcrowding of upper teeth V-shaped maxillary dental arch[12, 15]; other common manifestations include narrow or high palate (hypsistaphylia), bifid uvula, cleaved shortened upper lip and malocclusion. Occasional oligodontia, macrodontia, peg-shaped and widely spaced teeth have also been reported[16].

Combination of the relevant clinical signs and appropriate radiological investigations will foster the diagnosis of this syndrome and a molecular diagnosis of FGFR2 gene. An early diagnosis of the syndrome will serve as a guide for craniofacial growth and development[2]. While cases of Crouzon syndrome have been documented in scientific literature, only few cases have been reported in sub-Saharan Africa. This is a report of a case of Crouzon Syndrome in a 5-year-old female and review the literature on the presentation and management of this rare craniofacial anomaly.

CASE REPORT:

A 5-year-old girl presented with her mother to the Oral and Maxillofacial surgery clinic of Aminu Kano Teaching Hospital Complexes, Kano with the chief complaints of head swelling and protrusion of the eyes associated with relative prominence of the lower jaw and decreased growth of the mid face. Mother noticed swelling of the forehead at about 9 months after birth, which progressed slowly with gradual protrusion of the eyes. There was associated headache with occasional irrational behavior and excessive talk, however no convulsion or loss of consciousness. Mother also noticed gradual narrowing of mid face with relative protrusion of the lower jaw and associated mouth breathing and loud snoring.
The pregnancy, delivery and neonatal history were uneventful and no significant past medical history. There was no positive maternal or paternal family history

Examination revealed obvious craniofacial dysmorphic feature with acanthosis of the neck and lips, however, no abnormality was observed in upper and lower limb. There were enlarged cranial vaults with frontal bossing and a raised hump above the frontal bone; she also had bilateral ocular proptosis, ocular hypertelorism and right divergent strabismus (Fig 1). Dental examination revealed maxillary hypoplasia with

relative mandibular prognathism giving her a concave facial profile and a class III skeletal pattern. The lips were very prominent, incompetent with hyperpigmented perioral halo and no obvious nasal septum deviation. Ears appear low set with no perceptible hearing loss. Intra-oral examination reveals no limitations in mouth opening and no soft tissue abnormality was apparent apart from slight edematous gingivae on both arches. There is high arched palate, upper and lower labial and buccal crowding and retroclination of teeth on both arches with anterior and posterior cross bite. Overjet was also increased. Other soft tissues appeared healthy. All deciduous teeth were present with no carious or mobile tooth (Fig 2).

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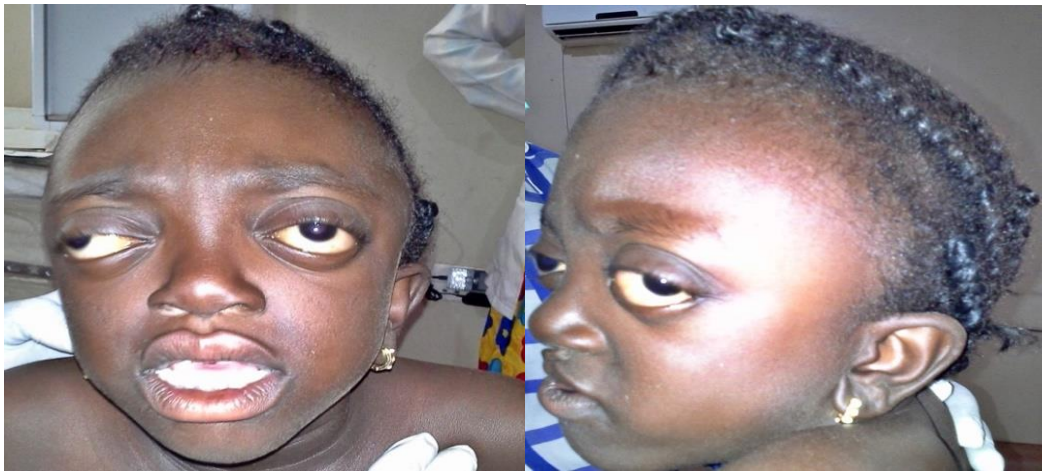

Fig 1. Extra-oral frontal and lateral views: a) showing ocular proptosis, right divergent strabismus, hypertelorism, parrot-beaked nose and maxillary hypoplasia b) elliptical shaped head, maxillary hypoplasia, mandibular prognathism, short cleaved upper lip and low set ears.

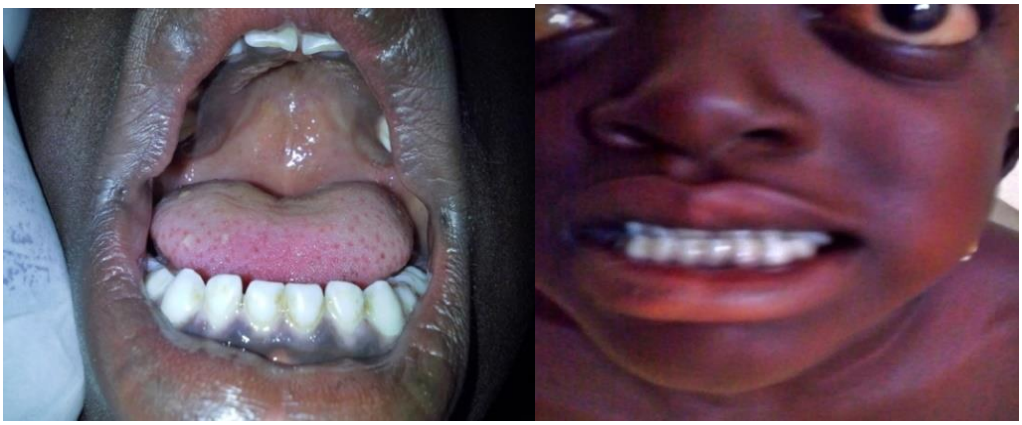

Fig 2. Intra- oral views. a) high narrow palate with reclined mandibular teeth with crowding and screw driver shaped upper anterior incisors b) reverse anterior bite

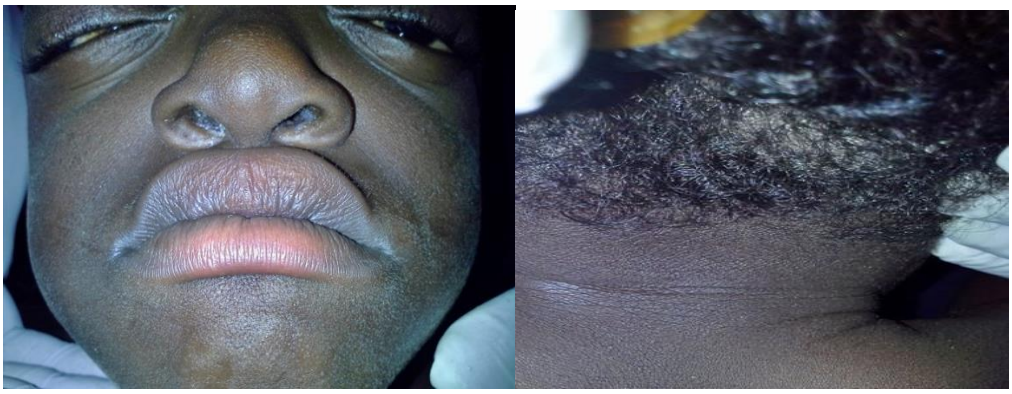

Fig 3. a) Broad nasal bridge and beaked nose, perioral hyperpigmentation b) Thickened hyperpigmented skin on the neck

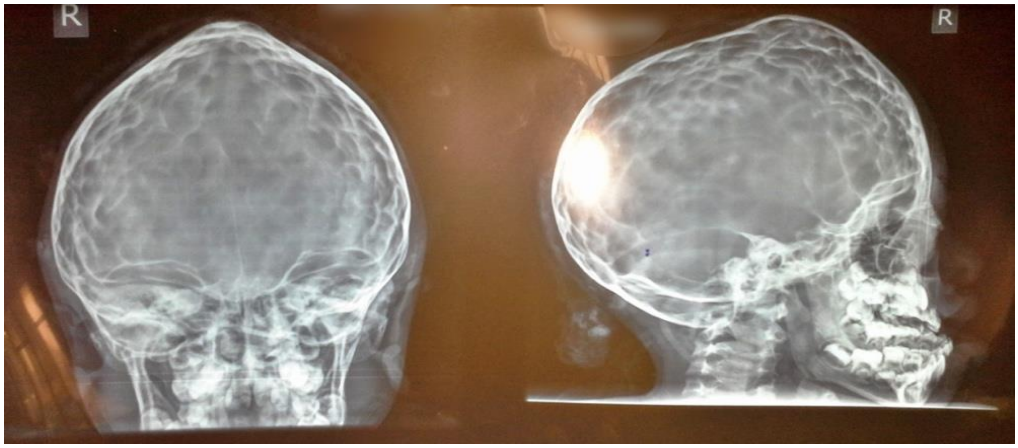

Fig 4. Craniograms showing tower appearance of the skull and mandibular prognathism, small paranasal sinuses and shallow orbits and the copper beaten appearance

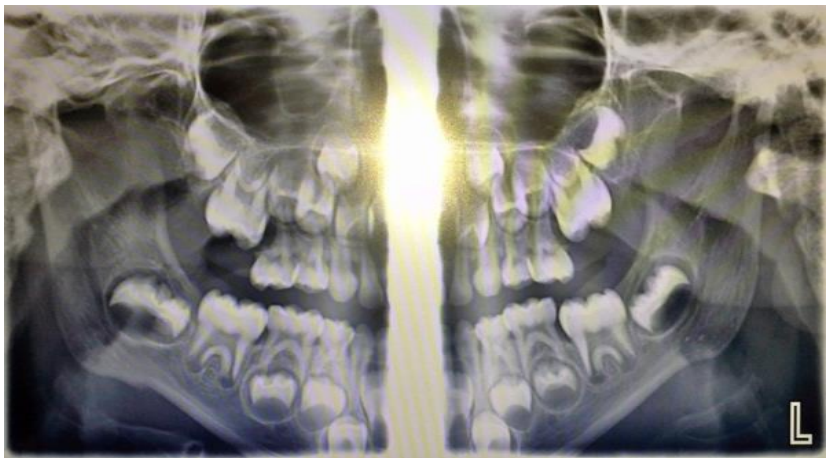

Fig 5. Orthopantomogram of the jaws

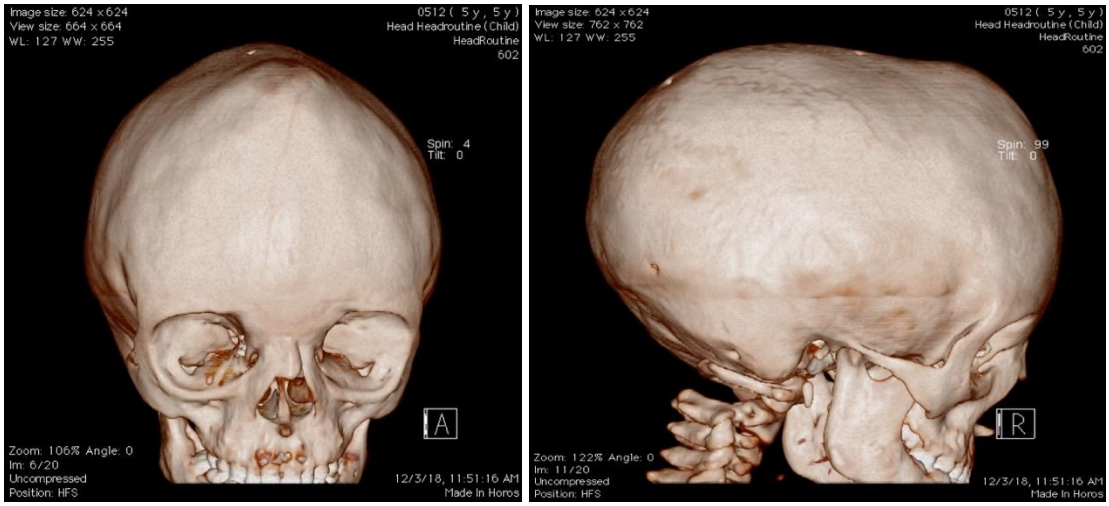

Fig 6. 3D Skull showing fusion of coronal and sagittal suture

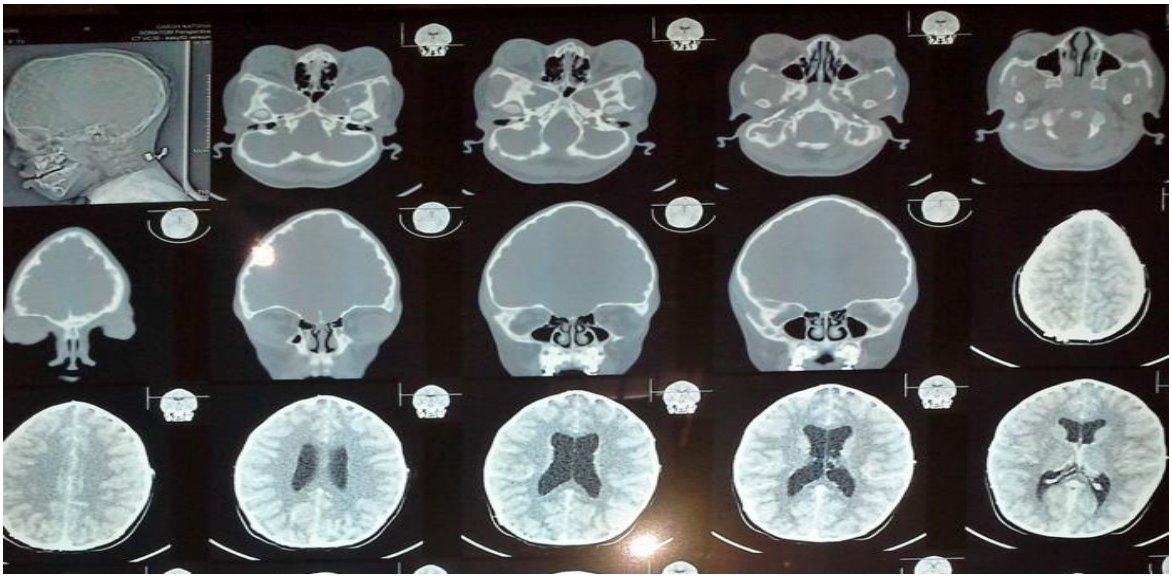

Fig 7. CT Scan showing the shallow orbits and proptosis and brachycephalic cranium.

General findings include cutaneous hyperpigmentation observed on the neck which extended to the upper back of the patient (Fig 3). There were no limb or trunk anomalies. Patient also displayed a strong personality with interest in all examinations and write-ups with verbose appraisal of all our actions. Craniograms (posterior anterior and lateral views) [Fig 4], orthopantomogram (Fig 5) and craniofacial computed tomographic scan (with 3D reconstruction) were requested [Fig 6]. Craniograms and craniofacial CT scan revealed fusion of the coronal and sagittal sutures, convoluted markings suggestive of copper beaten appearance, multiple indentations and prominence of the lateral ventricle (Fig 7). The radiological features were consistent with findings in Crouzon's craniostenosis. Therefore, based on clinical and radiological findings, a diagnosis of Crouzon's syndrome was made.

DISCUSSION

After Crouzon described a case in a mother and her child, several authors have also described

cases with positive family history involving siblings[7, 16], parents and child[5, 17, 18] and close relatives[3, 5]. Sporadic isolated cases have also been widely reported in documented studies with negative family history[19, 20] with a report stating almost 25%- 50% of patient cases arising due to new mutations[1, 7]. This proportion could have however been overestimated as most of the documented studies neither queried nor carried out molecular studies on "unaffected" parents nor close relatives as Crouzon syndrome can be inherited from related family units that are carriers of the mutated gene: nevertheless, new mutations have been extensively documented[1]. There is however no positive family history in our case and no isolated risk factor except the increased paternal age of the father at the time of her conception (45yrs). Glasser et al[21] hypothesized that older men could have either accumulated mutations or they were more susceptible to germ line mutations. A global incidence of 1 in 25000 live births has been reported in documented literature[11, 20], with prevalence varying between 1:50.000 and 1:1.000 children depending on methods of diagnosis and the study population[1].

Crouzon's syndrome is inherited in autosomal dominant transmission with high penetrance and variable phenotypic expressivity[1]. The implicated molecular pathway in this craniostenosis is mutagenesis associated with the fibroblast growth factor receptor 2 (FGFR2) gene, which is mapped to chromosome locus 10q25-q26[22]. Approximately 50% of the cases diagnosed with Crouzon's syndrome present with FGFR2 mutation with a myriad of the mutations located at the Ig III domain of FGFR 2[2]. Novel mutations including , Tyr 281 Cys substitution at the exon IIIa of FGFR 2 were also observed[8] .

In general, close to 25- 30 mutations have been identified in the FGFR2 gene[11, 23], mutations in FGFR3 have also been observed in rare instances[19, 22]. The fibroblast growth factor receptors (FGFRs), are members of the tyrosine kinase (TK) receptors and are transmembrane receptors activated by ligand binding of fibroblast growth factors (FGFs)[23]. They possess an extracellular ligand-binding region, with three (I, II, and III) immunoglobulin-like (Ig) domains, a transmembrane domain, and two intracellular TK subdomains[24]. Virtually all detected mutations are located on the Ig-III domain of the FGFR2 in patients with Crouzon syndrome [25, 26]. The resultant effect of this mutations is incongruous inactivation of the FGFRs with downstream effects of increased osteoblast differentiation and maturation, which may culminate in premature sutural fusion as observed in Crouzon syndrome[27]. Molecular analyses of the FGFR genes (1,2 and 3) thus provide useful information and serve as confirmatory diagnosis (including pre-natal diagnosis) of Crouzon's syndrome[9]. Recent studies have also identified mutations in FGFR1, MSX2, TWIST1, EFnB1, NELL1, GLI3 and TCF12 genes in the pathogenesis of Crouzon syndrome[9, 28].

The age of presentation of Crouzon syndrome's is variable with reports of age ranging from 5 months to 42 years[5, 12, 17]. In all cases however, deformation of the bony face was visible at or after birth while other craniofacial anomalies and systemic factors become accentuated with time; *ditto* in our case. The mother indicted that though there was marked facial deformation with time, the facial bony distortions were visible at birth. Due to the aesthetic impact of the craniofacial features, most patients present within the first decade of life with 5-7years being the most common age of presentation[2, 3, 18, 19], as observed with this 5-year-old patient in our case. Stankovic-Babic et al[3] surmised in their study that sex and race neither contribute nor have any role in the etiology nor serve as a predisposing factor in Crouzon syndrome. Some authors however noted a male predilection in Crouzon syndrome[7, 23, 29]. Despite the accepted nil racial predilection of Crouzon syndrome, only few case reports have been reported in Sub Saharan African[15, 30, 31] with no case series and literature review.

In general, craniostenosis syndromes involving the sagittal and metopic type sutures have a male predilection while craniostenosis involving the coronal exhibit a predisposition for the female gender[1]. Most documented studies affirm an equal sex predilection in Crouzon syndrome[3, 11, 19, 20]. The patient in our case study is a female child. The social and psychological impact of this craniosynostosis on the parents and the developing child was extensively reported by the Swedish study of Stavropoulos[23] . The author itemized dissatisfaction with facial appearance, fewer same-sex close friends, social withdrawal, and dislike by peers as personal challenges faced by the patients. This was coupled with negative adolescence experiences amidst a barrage of traumatically offensive remarks, unpleasant stares, stunned reactions, and outright avoidance. Pruzinsky[32] et al also highlighted low cognitive development and negative emotional attachment between the child and parents; people born with craniofacial disfigurement have also been reported to experience discrimination in employment or social settings. Our patient, even at 5 years, spoke brazenly about offensive remarks at school and in social gatherings where she has been tagged with sobriquet such as "big eyes'' and "googly eyes". The mother also complained of the financial burden of "multiple hospital visits and numerous costly investigations" and also discussed her fears about the patient's quality of life afterwards. The father was not available at any of the hospital visits.

Since Crouzon described the triad of cranial deformities, facial anomalies and exophthalmia in 1912, a plethora of clinical features of Crouzon syndrome have been extensively documented in scientific literature in case reports[11, 17-19], case series and comprehensive reviews[1, 9]. Ahmed et al[5] highlights the commonly observed features and attributes in this syndrome; these features preclude craniofacial and dento-alveolar features (including ophthalmological features), Otorhinolaryngologic manifestations, functional impairment and general features. The functional impairment depends on the severity of the features and the extent of the craniofacial anomalies. The craniofacial anomalies observed in our patient included brachycephaly (and a prominent hump) with a large and high forehead (tower appearance) combined with a flattened occiput and frontal bossing. Mid-facial hypoplasia due to maxillary hypoplasia and slightly retropositioned zygomatico-maxillary complex gave her a concave facial profile. Maxillary hypoplasia in Crouzon syndrome results from the dislocation of the lower orbital floor, anterior cranial fossa and the shortening of the orbital floor[33].

Ocular anomalies observed were shallow orbits, bilateral exophthalmos (ocular proptosis) and orbital hypertelorism. She had right divergent strabismus and downward slanting palpebral features. The exophthalmos could lead to exposure keratoconjunctivitis and a unexplained loss of visual acuity from optic nerve atrophy[9]. However, there was no loss of visual acuity at time of presentation. Otorhinolaryngologic features include very prominent beak like nose (psittichornia), which is more accentuated due to the midface hypoplasia; no nasal septum deviation observed and she presented with low set ears. There was however no hearing loss.

Oral manifestations in our patient included short cleaved upper lip, hypoplastic maxilla with relative mandibular prognathism, a high arched palate (hypsitaphylia), anterior and posterior crossbite, retroclined lower teeth with lower labial crowding, periorbital hyperpigmentation with prominent darkening of the upper lips and hyperpigmentation of the palate were observed. An Angle Class III malocclusion is observed due to the maxillary hypoplasia. Other mentioned dental anomalies include malformed teeth, delayed dental eruption and impactions, dental agenesis and ectopic dental eruptions[4,32]. The mother also complained of chronic mouth breathing, this has been attributed to the reduction in the nasopharyngeal and oropharyngeal space which may be worsened by stenosis of the posterior nasal choanae[23]. Our

patient had a fair oral hygiene which contrasts the report of Mustafa et al[34] where a higher plaque and gingival inflammation was found in patients with Crouzon's syndrome.

Kanarpathy et al[12] emphasized on the role of a dentist in the diagnosis of Crouzon's craniostenosis as dentists might be the first point of call for a considerable number of the patients. They further suggested the dentist's role in counselling the patient and/ or parents as well as coordinating a multi-disciplinary team for corrective measures. This is the scenario in our patient who first presented at the pediatric unit of the hospital and referrals were sent to specialties (ENT, ophthalmology and neurosurgery) for assessment, being a multidisciplinary form of presentation.

Acanthosis Nigricans (AN), characteropathy, developmental delays and hydrocephalus are other common general findings in Crouzon's patient[9]. Acanthosis nigricans is the most commonly reported cutaneous finding in Crouzon's syndrome with incidence of 5%[19] and a subset of Crouzon syndrome patients that present mainly with are termed the "Crouzon syndrome with acanthosis nigricans(CSAN)"[6]. AN characteristically presents with hyperpigmentation on locations such as the neck, axillae perioral, periorbital regions, the chest and around the umbilicus in the absence of endocrine abnormalities[35]. The patient in our case study presented with hyperpigmentation of perioral, neck and back region. CSAN has been reported to arise as a missense mutation in the (FGFR3 gene) on chromosome 4p16.3[35] and a female predilection was observed. Our patient displayed no signs of mental retardation, she however displayed a strong personality disorder (characteropathy) throughout all her visits to the clinic.

In tandem with its clinical features, CS also presents with characteristic radiological features which have been widely reported in documented literature. Stankovic-Babic et al[3] and Pournima et al[19] highlighted various radiological findings observed in CS. These deformities can be observed on routine x-ray views as well as in orthopantomograms and CT scans. The craniograms (posterior anterior and lateral views of the skull) for the patient in our case study revealed characteristic tower appearance of the skull and scaphocephaly, raised intracranial pressure (as shown by thinning of vault), small orbits and relative mandibular prognathism. CT scan revealed fusion of the coronal and sagittal sutures, the characteristic "copper beaten appearance", convolutions in the inner calvarium of the skull, shallow orbits, multiple indentations on the inner table of the skull (with preserved outer table), prominence of the lateral ventricles; the cerebral hemispheres, cerebellum, basal ganglia and stem were all adequately preserved. Molecular testing (detailing mutational analysis in FGFR2) is a more accurate and reliable diagnostic tool than radiography and imaging modalities[36]. However, in resource limited settings such as ours where genetic studies are not available; clinico-radiological findings are the foremost diagnostic tools. Other modalities for diagnosis include magnetic resonance imaging and pre-natal diagnosis[19].

Differential diagnosis of Crouzon's syndrome includes syndromes such as Apert, Pfeiffer, Carpenter and Sayre-Chotzen. Apert syndrome comprises craniosynostosis, midfacial hypoplasia and symmetric syndactyly of the hands and feet, minimally involving the digits 2, 3, and 4 (acrocephalosyndactyly). It shares almost similar general craniofacial and dental features with Crouzon's except the syndactyly which forms the major basis for exclusion. Limb anomalies (including syndactyly) differentiates Crouzon from these other syndromes, it is however expedient to note mutations in FGFR2 gene have also been reported in the syndromes of Apert, Pfeiffer, Carpenter indicating the utmost importance of the FGFR2 gene in craniogenesis[2]

Management of CS patient is based on the severity of functional and appearance- related

needs[37]. Early diagnosis and comprehensive assessment by competent multidisciplinary craniofacial team is necessary for optimization of care to avoid severe functional impairment[38, 39]. This sub-specialty team includes maxillofacial surgery, neurosurgery and plastic surgery[37, 38] Other ancillary components of this team include the orthodontist and paediatric dentist[9, 40]. Counselling of parents and patients is also very paramount as they usually would have been burdened by the social and psychological impact of the craniostenosis. While the non – surgical approach[41] has been documented in literature, further review showed that the management protocol adopted is characterized by a severity index as determined by Partington et al[42]. The outcome of management is usually assessed using the Atkinson protocol[43] although this has not been useful in the prediction of future preoperative aesthetic needs.

Surgical treatment consists of 2 phases, according to the McCarthy treatment protocol[44], most authors[37, 39-44] recommend early correction , that is ,within the first year and the goals of treatment during the first phase include; correction of the cranial deformity and reduction of intracranial pressure and optic nerve damage: the second phase consists of mid-facial advancement which takes place at an older age. The use of Distraction Osteogenesis prevents the complications associated with osteotomies such as, reduced operating time, surgical relapse, need for bone grafting and massive fluid shifts resulting from blood loss[45].

McCarthy et al[46] highlighted the protocol of care using these 2 phases and divided this protocol into 6 treatment periods ranging from phase 1 (3-6 months) to stage 6 (17 years onwards) with various surgical procedures including but not restricted to Cranial vault decompression, fronto-orbital advancement, midfacial bipartitioning, strip craniectomy, and distraction osteogenesis[46]. The McCarthy surgical protocol, however is not sacrosanct as several authors[40 45]have performed surgical procedures based on the functional, aesthetic and psychological needs of each patient, irrespective of time.

The Orthodontic care is interspersed within the surgical phase and it is administered in 2 phases[9, 40] ;1) Orthodontic treatment during childhood and 2) Orthodontic treatment during adolescence. Management of ectopic eruptions, crowding, delayed eruptions and posterior crossbites are the problems of the first phase. These problems are managed with exodontia, the use of lingual arches and /or fixed appliances, segmental Le forte osteotomies when the palatal suture is also fused. Phase 2 procedures are key in preparing the patient for craniomaxillofacial skeletal mobilization through Orthognathic surgery and these include all procedures that decompensates for the dentition in the presence of skeletal mal-relationship. The Paedodontists subsequently ensures good oral hygiene and elimination of periodontal disease. Fluoride supplementation pits and fissure sealants and restorative treatment are treatment protocols that benefit such patient.

The complications of surgical management include; mortality cerebrospinal fluid leak. intraoperative bleeding, wound infection, post-operative visual loss distraction device failure and relapse among others[47].

CONCLUSION

There is a need for the development of a craniofacial team at this center and other African center in view of the increasing incidence of this anomaly. The patient in the case report did not receive any intervention in view of resource limitation despite her urgent need for intra-cranial decompression. Resource limitation should not be a mitigating factor as expertise may be acquired cheap from regions of Africa where craniofacial surgery may still be at a rudimentary level. Absence of genetic counselling and exhaustive rehabilitation services also prevent complete management of patients with craniosynostosis.

REFERENCES

1. Regezi JA, James JS, Richard CKD. Abnormalities of Teeth: Dentinogenesis Imperfecta. Oral pathology: Clinical Pathologic Correlations 2017 (16)382.
2. Shields E, Bixler D, El-Kafrawy A. A proposed classification for heritable human dentin defects with a description of a new entity. Arch Oral Biol. 1973; 18:543-553. http://dx.doi.org/10.1016/0003-9969(73)90075-7
3. Kim JW, Simmer JP. Hereditary dentin defects. J Dent Res. 2007; 86(5):392–399.
4. Barron MJ, McDonnell ST, MacKie I, Dixon MJ. Hereditary dentine disorders: dentinogenesis imperfecta and dentine dysplasia. Orhanet J Rare Dis. 2008; 3 (31) https://doi.org/10.1186/1750-1172-3-31
5. Sapir S, Shapira J: Dentinogenesis imperfecta: an early treatment strategy. Pediatr Dent. 2001, 23: 232-237.
6. Subramaniam P, Mathew S, Sugnani SN. Dentinogenesis imperfecta: A case report. J Indian Soc Pedod Prev Dent. 2008; 26: 85-87.
7. McDonald Avery. Dentistry for the child and adolescent. 8th ed, St Louis: CV Mosby Co; 2004.
8. Wei SH. Paediatric dentistry: Oral patient care. 1st ed. Philadelphia: Le and Febiger; 1988.
9. Shafer WG, Hine MK, Levy BM, Tomich CE. A textbook of oral pathology. Philadelphia. WB Saunders Co; 1993 p. 58-61.
10. Bhandari S, Pannu K. Dentinogenesis imperfecta: A review and case report of a family over four generations. Indian J Dent Res. 2008; 19: 357-361.