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Diagnosis of Treacher-Collins Syndrome: The role of the multidisciplinary team in patient management and family genetic counseling

Authors: B. Tuyishimire[1,2,*,#]; H. Irere[1,2,#]; C. Muhizi[3]; A. Ndatinya[2]; O. R. Karangwa[2]; F. Rutagarama[2]; C. Nsanzabaganwa[1]; L. Mutesa[1,2]

Affiliations: *[1]Centre for Human Genetics, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda; [2]Department of Pediatrics, Rwanda Military Hospital, Kigali, Rwanda; [3]Department of Surgery, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda*
[#]Contributed equally

ABSTRACT

INTRODUCTION: Although Treacher-Collins syndrome has to be considered a differential diagnosis in congenital craniofacial abnormalities, the clinical diagnosis and research related to it still present a gap, especially in African regions. Thus, this work aims at highlighting this syndrome's clinical features for raising medical awareness.
CLINICAL CASE: We reviewed a 1-year-old patient referred to our clinical genetic unit at Rwanda military hospital, Kigali, Rwanda. Physical examinations indicated severe craniofacial abnormalities, including downward-sloping eyes, slight notching of the lower lids, small and underdeveloped eyebrow bones, vision problems, small outer ears, small and underdeveloped cheekbones, and jaw. Within the limits of the techniques used in our laboratory, the cytogenetic analysis revealed a normal karyotype, 46, XY.
CONCLUSION: The patient was diagnosed with Treacher-Collins syndrome based on clinical manifestations of craniofacial features. Nevertheless, laboratory tests performed were limited to karyotyping and should not detect any gene defect. Long-term follow-up of the patient and his family was recommended. Further molecular analyses should be performed to identify causing genetic mutation mainly in the TCOF1, POLR1C, or POLR1D genes.

Keywords: Dystosis, Maxillofacial Defect, Treacle, Mutation, Genetic Counseling, Treacher-Collins Syndrome

INTRODUCTION

Treacher Collins syndrome is an autosomal dominant disorder affecting the development of craniofacial regions whose features include hearing loss and cleft palate [1,2]. Being known as mandibulofacial dysostosis, this syndrome has a wide range of abnormal clinical manifestations,

***Corresponding author:** Benjamin Tuyishimire, email: benjamin.tuyishimire1994@gmail.com, Centre for Human Genetics, College of Medicine and Health Sciences, University of Rwanda, Kigali, Rwanda; Department of Pediatrics, Rwanda Military Hospital, Kigali, Rwanda; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: no funding was sought; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable; **Originality:** All authors: this manuscript is original has not been published elsewhere; **Review:** This manuscript was peer-reviewed by three reviewers in a double-blind review process.

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such as disproportionate bilateral structures within the first and second branchial arches and the nasal placode [3]. Mutation in the TCOF1 gene was found to be the most commonly responsible for Treacher Collins syndrome [4]. This gene encodes treacle, a phosphoprotein that is active during early embryonic development in structures that become bones and other tissues in the face [5,6].

Phenotypic signs of this syndrome have been examined, and results revealed a high prevalence of variable ear defects. Among those ear defects, abnormalities of the external ears affect 77% of patients, while around 36% of the patients were found to be affected by atresia of external auditory canals [7]. This syndrome also affects the structures of the middle ear. Radiographic investigations of the patients indicate malformation of the auditory ossicles with the fusion between the malleus and incus structures, as well as incomplete stapes and oval window, and even total non-appearance of the middle ear and epitympanic space [8]. This high prevalence of aforementioned ear abnormalities accounts for more than half of the patients' hearing loss [3].

Other features of this syndrome are lateral downward slanting of the palpebral fissures seen in around 90% of patients, Hypoplasia of the facial bones, most of the time affecting the mandible, and zygomatic complex are also frequently seen in this syndrome [3]. The zygomatic arch may be absent in severe cases, and a cleft palate may occur. These features are usually bilaterally symmetrical. In most TCS patients, a spectrum of affected features is observed. The limb anomalies are post-axial, most commonly with the absence or incomplete development of the fifth digital ray of all four limbs [9].

The different etiological bases of Treacher Collins syndrome have been highlighted and grouped into the disease's molecular, genetic, and cellular basis. The molecular basis and genetic basis explanations of this syndrome suggest abnormal arrays of neural crest cell migration, abnormal mechanisms of cell death, abnormal cell differentiation or an abnormality of the extracellular matrix [10].

On the other hand, the cellular basis theory of this syndrome suggests the abnormal cellular process affecting neural crest cell formation, proliferation, migration, and/or differentiation. While neural crest cells are a migratory cell population resulting from the neuroepithelium during early embryogenesis giving rise to almost all of the cartilage, bone, and connective tissue of the head and face, most craniofacial anomalies, including those linked with Treacher Collins syndrome, are thought to develop from errors in any mechanisms during embryogenesis [7,10].

CLINICAL CASE

We received a 1-year-old female patient in the genetic unit at Rwanda Military Hospital. On physical examination, the patient presented severe dysmorphic craniofacial abnormalities, including downward sloping eyes, slight notching of the lower lids, small and underdeveloped eyebrow bones, vision problems, small outer ears, hearing problems, small and underdeveloped or cheekbones, jaw and lower face, underdeveloped maxilla and mandible, wide mouth, tongue retraction, voice and swallowing problems, airway, breathing and sleep problems (Figure 1). The karyotype was normal (Figure 2).

The patient was given holistic medical care with a multidisciplinary approach and involved intervention from several healthcare professionals. After the geneticist reviewed the patient, another urgent concern was related to breathing problems that were thought to be caused by micrognathia and tongue obstruction of the hypopharynx. The patient was referred to an ENT specialist for early review and management to maintain an adequate airway. The patient was also planned for a long-term follow-up to evaluate the growth and management of any issue resulting from abnormal facial structures. This is because it takes at least 5 years for the complete growth of some facial organs, including mandibles and eye sockets. Therefore, some surgical procedures such as orbital reconstruction and mandibular distraction or maxillo-mandibular osteotomies are expected to be performed at/or around the age of 5 years for our patient. While hearing loss and speech impairment come as the effect of multiple defects in facial organs, which substantially impact a patient's learning ability, self-esteem, and social interaction. It is obligatory to test the patient's hearing tested at an early age and start speech therapy to ensure that speech-related problems are addressed. At around 6 years old, the external and inner ear reconstruction will be performed.

The management and care were not only limited to the patient but also the parents through genetic

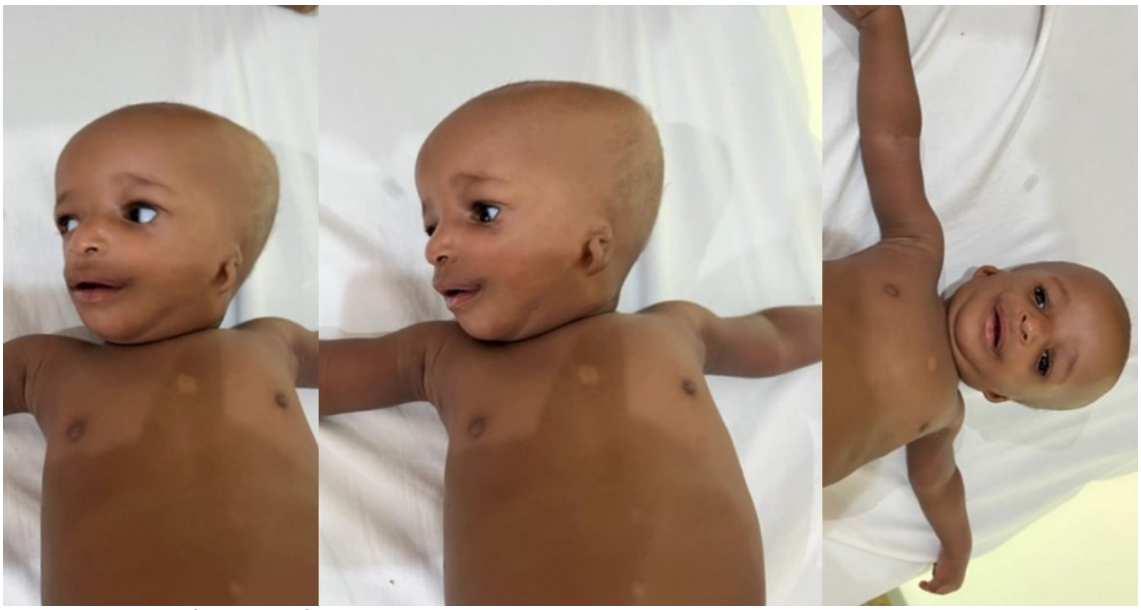

Figure 1: Clinical features of Treacher Collins syndrome

counselling. A deep unstructured, and exploratory interview with the parents revealed some symptoms of psychological disturbance. Parents felt confused and experienced the symptoms of grief. This grief comes because of losing the normal child they were expecting to have. Parents also were worried and extremely concerned about future births, with repetitive thoughts of having offspring with the same syndrome for the next pregnancies. Psychosomatic symptoms and hyperarousal were also reported. Problems reported were not only limited to individual psychological disturbance; family dysfunction was also reported.

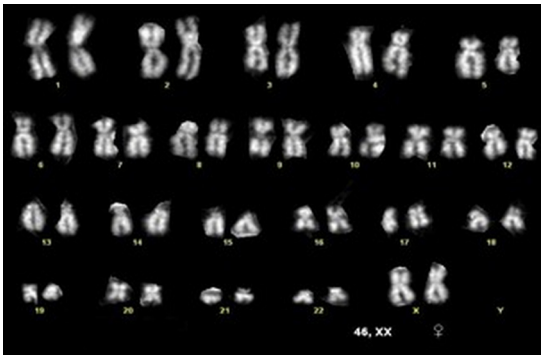

Figure 2: Normal male (46, XY) karyotype result of the patient

One of the parents reported the change in communication patterns in the family and repetitive accusations by the partner to be the source of the syndrome in the child. This attribution led to the resignation of parental responsibility. Genetic counselling aims to provide general information about genetic diseases, specifically Treacher Collins syndrome. We provided the genetic basis of Treacher Collins syndrome, its prognosis, and available management options. Counselling was also aimed at managing the psychological suffering of the parents. While this cannot be achieved in a short number of sessions, we set a long-term family follow-up for the counselling to be effective.

DISCUSSION

We aimed at describing our patient's clinical features of Treacher Collins syndrome. Through physical examinations, we found signs identified in different studies. Those include a wide range of mandibular and facial abnormalities, of which abnormal auricle development is further linked with atresia of the external auditory canal and deformed ear ossicles, leading to congenital hearing loss. Pointing down of palpebral fissures indicating antimongoloid-shaped eyes [11]. Other found coloboma lower lids with deficient or absent eyelashes similar to what was found in our patient [12]. Micrognatia resulting from hypoplasia of the facial structures, mostly the mandibular and zygomatic bones, are also similar features in our patient. However, the signs and symptoms may vary among patients, while some may present

intellectual disability, renal deformation, and limb defects [7].

Different studies have highlighted the pathogenesis of Treacher Collins syndrome, and findings revealed deletions of TCOF1 and mutations of POLR1D genes. Deleted areas on the TCOF1 gene are (exons 9–13), (c.381_382delAG), and (c.4131_4135delAAAAG and c.2394_2395delAG), while identified mutation on POLR1D gene is (c.91C> T) [13]. Contrary to other researchers who were able to identify responsible genes through genomic sequencing, our case report only involved karyotype analysis which revealed a normal chromosomal formula of 46,XY. However, this analysis was inconclusive and should not rule out any genetic defect in our patient.

As a limitation, the laboratory tests performed in our laboratory were not too advanced to detect genomic defects linked with observed clinical features of Treacher Collins syndrome observed in our patient. Further molecular testes have been recommended for better diagnostic management.

CONCLUSION

The patient was clinically diagnosed with Treacher Collins syndrome. The patient was scheduled for a long-term follow-up to achieve outstanding treatment outcomes. This follow-up will require a team of craniofacial surgeons, orthodontists, ophthalmologists, otolaryngologists and speech pathologists, geneticists, occupation therapists, and psychologists. While family misunderstandings and dysfunctions may hinder the desired outcome, family genetic counselling is a paramount.

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