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CASE REPORT

MISDIAGNOSIS OF TRACHER-COLLINS SYNDROME INITIALLY ATTRIBUTED TO DRUG TERATOGENICITY: A MOROCCAN CASE REPORT

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ABSTRACT

Background

Treacher Collins syndrome (TCS) is a rare congenital disorder of craniofacial development characterized by numerous developmental anomalies that are restricted to the head and neck. Most TCS cases are inherited in an autosomal dominant manner. The diagnosis of TCS relies on clinical and radiographic findings. The four genes involved in TCS are *TCOF1*, *POLR1D, POLR1C,* and *POLR1B*.

Case presentation

In this report, we present the case of a 7-year-old Moroccan boy who exhibited distinctive dysmorphic features, including coloboma and zygomatic bone hypoplasia. Upon genetic analysis, a mutation in the *TCOF1* gene was identified, conclusively confirming the presence of Treacher Collins Syndrome. It is worthy that the correct etiological diagnosis was significantly delayed due to the initial misperception that the observed malformation syndrome was a result of drug teratogenicity.

Conclusions

This case highlights the importance of seeking pharmacovigilance advice if any adverse event occurs following medication use. Furthermore, requesting a genetic consultation to establish a confirmed etiological diagnosis for any malformation syndrome can significantly reduce the protracted social and psychological suffering that patients and their families may endure.

Keywords: Genetic consultation, Pharmacovigilance, *TCOF1* gene, Teratogenicity, Treacher Collins syndrome

INTRODUCTION

Treacher Collins syndrome (TCS, OMIM # 154500), also known as mandibulofacial dysostosis and Franceschetti-Zwahlen-Klein syndrome, is a rare congenital disorder of craniofacial morphogenesis with an estimated prevalence of 1/50000 births [1]. Most TCS cases are inherited in an autosomal dominant manner. Typical cases of TCS are characterized by four major clinical manifestations**,** hypoplasia of the zygomatic bones and mandible, external ear abnormalities, lower eyelid abnormalities, and family history consistent with autosomal dominant inheritance. The four genes involved in TCS are *TCOF1*, *POLR1B, POLR1C,* and *POLR1D*.

In this report, we present the case of a 7-year-old Moroccan boy exhibiting characteristic traits of TCS. Unfortunately, an initial misdiagnosis, which erroneously attributed the child's condition to the mother's medication, led to profound psychological and social challenges for the family. Subsequent molecular genetic testing definitively confirmed the presence of TCS.

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CASE PRESENTATION

The patient is a 7-year-old male, first child of Moroccan consanguineous parents (first-degree), aged of 29-year-old for the mother and 37-year-old for the father. Pregnancy and delivery were normal, and the child was born at term with normal physical measurements. The mother had no history of abdominal trauma or radiographic examination, but she had been taking an antidepressant treatment based on trimipramine Surmontil® during the first two months of pregnancy. The child had normal psychomotor development and has been schooled with good follow-up.

Upon general examination at 7 years, the patient's body weight was 23 Kg (50th percentile), head circumference 45 cm (50th percentile), and height 123 cm (70th percentile). He was dysmorphic with coloboma of the lower eyelids, downslanting palpebral fissures, missing eyelashes, and bilateral symmetrical hypoplasia of the zygomatic bones (Fig. 1). The rest of his physical examination was normal; in particular, he has no ear abnormalities. Ophthalmological examination revealed a corneal ulcer with palpebral coloboma, otorhinolaryngol-scopic and dental examinations were normal.

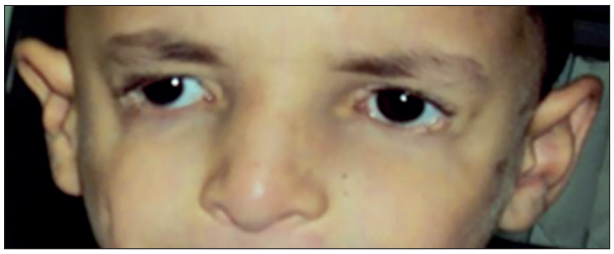

Figure 1. Patient photograph showing dysmorphic facies.

From the very first months of their child's life, the parents keenly observed facial dysmorphia. Upon seeking medical advice, the consulting pediatrician attributed this dysmorphia to the antidepressant treatment that the mother had undergone during her pregnancy. At that time, neither a genetic consultation nor a pharmacovigilance assessment was sought.

The attribution of the child's condition to the mother's medication has precipitated profoundly distressing psychological and social consequences. This includes a deterioration in the mother's depressive syndrome, characterized by self-blame, self-indignation, and a substantial decline in her self-esteem. Adding to her distress, the child's father has consistently expressed a threat of divorce, associating the mother with misfortune, even extending to their own child.

It was not until the child reached the age of seven that the mother, realizing the existence of a national pharmacovigilance center, made the decision to formally report her child's case. Her primary motivation was to share her personal ordeal and to raise awareness about the potential risks associated with the medication.

Upon receiving the case report, the physician conducted a causality assessment using the French method of imputability study [2]. To establish a comprehensive semiotic score and eliminate potential differential diagnoses, a genetic consultation was deemed necessary. Consequently, a genetic consultation was sought, ultimately leading to the accurate rectification of the etiological diagnosis of dysmorphia. According to the French method for assessing the causality of adverse drug reactions, the pharmacologist assigned a level of doubt regarding the drug's origin, as indicated by an Intrinsec Score of I2. The chronological score was noted as C2, and the semiological score as S1. The extrinsic score, designated as B1, was based on the available data for trimipramine, which although limited, appeared to suggest the absence of a specific malformation risk associated with trimipramine antidepressants [3].

During the parental evaluation, it was observed that the father exhibited discreet coloboma and mild hypoplasia of the zygomatic bones.

Treacher Collins syndrome was considered a potential diagnosis due to the presence of characteristic dysmorphic features and a family history consistent with autosomal dominant inheritance. Prior to conducting genetic studies, informed consent was obtained from the proband's parents.

The genetic testing conducted involved a multigene panel, including genes *TCOF1, POLR1B, POLR1C*, and *POLR1D*. The results revealed a heterozygous frameshift mutation NM_001371623.1(*TCOF1*): c.4372_4376del (p.Lys1458fs) in exon 24 of the *TCOF1* gene for the proband.

However, the father declined to participate in the genetic study, as he was unwilling to accept that he could be the carrier of the disease.

DISCUSSION

Treacher Collins syndrome is named after the English surgeon Edward Treacher Collins, who initially described the syndrome's traits in 1900. It is a rare congenital disorder of craniofacial development with an estimated prevalence of 1/50000 births [1]. Most TCS is inherited in an autosomal dominant manner; a small portion (~4%) is inherited in an autosomal recessive manner [4]. TCS is characterized by major clinical manifestations including hypoplasia of the zygomatic bones and mandible resulting in midface hypoplasia, micrognathia and retrognathia; lower eyelid abnormalities including coloboma and partially or totally absent lashes; external ear abnormalities comprising absent

or malformed ears; and a family history consistent with autosomal dominant inheritance. Minor clinical features related to TCS are atresia or stenosis of the external auditory canals; conductive hearing loss; ophthalmologic defects; airway abnormalities comprising tracheostoma and choanal stenosis or atresia; cleft palate; preauricular hair displacement; and delayed motor or speech development. Da Silva Dalben et al. found dental anomalies in 60% of TCS patients, with one to eight anomalies per individual [5]. These anomalies consist in tooth agenesis, enamel deformities and malposition of the maxillary first molars. In some cases, dental anomalies in combination with mandible hypoplasia result in a malocclusion, thus possibly leading to problems with food intake and the ability to close the mouth [5]. Our patient has none of these dental anomalies. Less commonly, TCS has been associated with heart defects, malformed or absent thumbs and cryptorchidism [6].

To date, four genes have been identified in TCS whose diagnosis is established by detection of a heterozygous (autosomal dominant) pathogenic variant in *TCOF1*, *POLR1D* or *POLR1B* [7,8], or biallelic (autosomal recessive) pathogenic variants in *POLR1C* or *POLR1D* [7,9].

TCOF1, located on the 5q32-q33.1 region, is the major gene involved with heterozygous mutation in up to 93% of individuals with TCS [4].

TCOF1 encodes a nucleolar phosphoprotein called treacle, thought to play a central role in various cellular processes such as ribosome biogenesis, rRNA transcription, and potentially neural crest cell migration. Pathogenic variants in the *TCOF1* gene lead to haploinsufficiency of treacle, disrupting its normal functions. This would affect nuclear localization signals and triggers apoptosis of cephalic neural crest cells during embryogenesis, thereby contributing to the symptoms observed in Treacher Collins Syndrome [10,11,12]. The specific variant identified in our patient, c.4372_4376del, results in a premature stop codon, producing a truncated protein. Already described in the literature, this variant is classified as pathogenic according to American College of Medical Genetics and Genomics (ACMG) guidelines. In individuals with TCS, hundreds of pathogenic variants within *TCOF1* have been documented [13], and while some have been observed more than once, our patient's variant is noteworthy for its recurrence in 16% of cases [4]. The genes *POLR1D, POLR1C*, and *POLR1B*, located at 13q12.2, 6p21.1, and 2q14.1, respectively, exhibit limited mutations, being associated with a small subset of TCS patients.

These three genes are also expressed in neural crest cells, impacting ribogenesis and potentially disrupting cell division. *POLR1D* and *POLR1C* encode subunits that are integral to both the RNA polymerase I and RNA polymerase III complexes, critical for the synthesis of ribosomal RNA precursors and small RNA, and *POLR1B* encodes the RNA polymerase I subunit B [7,8].

Roughly 40% of individuals with autosomal dominant TCS have an affected parent [4], and this is the case of our patient, whose father exhibits a mild expression of TCS. The risk to the siblings is 50%, the specific malformations or their severity cannot be predicted because significant inter- and intrafamilial clinical variability is common in TCS.

Treatment should be customized to meet the unique requirements of each person, ideally carried out by a comprehensive craniofacial management team. Such a team typically includes a medical geneticist, plastic surgeon, head and neck surgeon, otolaryngologist, oral surgeon, orthodontist, audiologist, speech pathologist, and psychologist, ensuring a holistic approach to care.

CONCLUSION

In conclusion, it is crucial to emphasize two key points that hold immense significance for healthcare professionals in general, and pediatricians, in particular. Firstly, a profound awareness of the social and psychological implications of any malformation syndrome in children is paramount. It is essential to recognize that seeking a genetic consultation to establish a confirmed etiological diagnosis can significantly alleviate the prolonged social and psychological distress that patients and their families may endure. This step can lead to more targeted and effective interventions, ultimately improving the quality of life for affected individuals. Secondly, healthcare practitioners must act swiftly in seeking pharmacovigilance guidance whenever adverse events emerge after medication administration. This proactive approach is essential to ensure a precise assessment of causality. It also safeguards against prematurely attributing blame to the medication, as establishing drug causation should be a diagnosis of exclusion, requiring a thorough and meticulous process of elimination.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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