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Case Report

Bosma Arhinia Microphthalmia Syndrome: A Rare Case

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Abstract

Purpose: Bosma Arhinia Microphthalmia Syndrome (BAMS) is a very complex and rare malformation, and only few cases are described in the literature and there is no standardized surgical protocol. This article describes a typical BAMS patient and presents the treatment plan of this patient underlining the key role of protocol in obtaining satisfactory results.

Methods: We observed a Moroccan male infant, 7-year-old presented a typical appearance of BAMS, clinically observed and genetically confirmed. He was treated by a 3-step surgical protocol. During the first phase, a Le Fort II maxillary osteotomy with a bicortical approach under submental intubation was done. The effect of this osteotomy was maintained and potentiated by the Delaire Face Mask. In a second step, the patient benefited from a parietal bone graft. In 3rd step, the patient underwent an internal and external nasal reconstruction.

Results: An acceptable morphology for the newly created external nose was obtained, this reconstruction was viable and esthetically acceptable. No internal nose restenosis, a slight external restenosis of a left nave was observed. This result was stable over 1 years.

Conclusion: On the basis of our experience, a multidisciplinary team is very important to succeed the treatment BAMS. Maxillary osteotomy should be considered part of an this approach with external traction of the maxilla, cortical graft and reconstruction of internal and external nose.

Keywords: *Arhinia; Congenital; Reconstruction*

Background

Congenital nasal absence is an extremely rare malformation [1-5]. The lack of an external nose is generally one part of a complex malformative syndrome characterized by the absence of nasal cavities, microphthalmia or coloboma of olfactory bulbs, high arched palate, coloboma of iris, and microtia [6]. The etiology of arhinia is unknown; genetic correlations are inconsistent; and most cases are sporadic.

The literature includes familial cases. No single gene or chromosome has been identified as being responsible for this malformation [7]. Gordon reported missense mutations in the epigenetic regulator SMCHD1 mapping to the extended ATPase domain of the encoded protein cause BAMS in 14 cases studied. All mutations were *de novo* where parental DNA was available. he establishes SMCHD1 as a key player in nasal development and provide biochemical insight into its enzymatic function that may be exploited for development of therapeutics for facioscapulohumeral muscular dystrophy (FSHD) [8].

The pathophysiology of arhinia is poorly understood, and various theories have been proposed [7]. Reduced growth of the medial and lateral nasal processes, excess growth of the medial nasal processes, defective reabsorption of the epithelial plates and arrested migration of neural crest cells are all possible explanations for these malformations [9,10].

Because arhinia is exceptionally rare and few cases have been treated, no standardized treatment protocol is available [7,11]. Very few of the published cases were treated with a global approach [7].

This article presents the treatment plan of the patient observed with arhinia and genetically confirmed and underlines the key role of maxillary osteotomy in obtaining better results.

Case Report

We describe a Moroccan male infant, 7-year-old presented an isolated arhinia or a syndromic presentation compatible with BAMS (Bosma Arhinia Microphthalmia Syndrome). He was born in Morocco to healthy unrelated parents. There was neither a family background of congenital malformations nor a history of any medications during the pregnancy. The prenatal time was uncomplicated.

The child showed complete absence of the external nose, the nasal cavities, paranasal sinuses, and olfactory apparatus and defects. We observed the presence of a very thinner protuberances in the midface, associated, hypertelorism, microphthalmia, colobomas, nasolacrimal duct abnormalities, maxillary anteroposterior, vertical and transverse hypoplasia (midface hypoplasia), high arched palate (a minor form of Treacher Collins syndrome, Binder syndrome) (Figure 1). This child had difficulty in breathing and inability to feed due to airway obstruction and inability to feed. This infant cannot eat and breathe at the same time without the normal nose function, which results in respiratory distress.

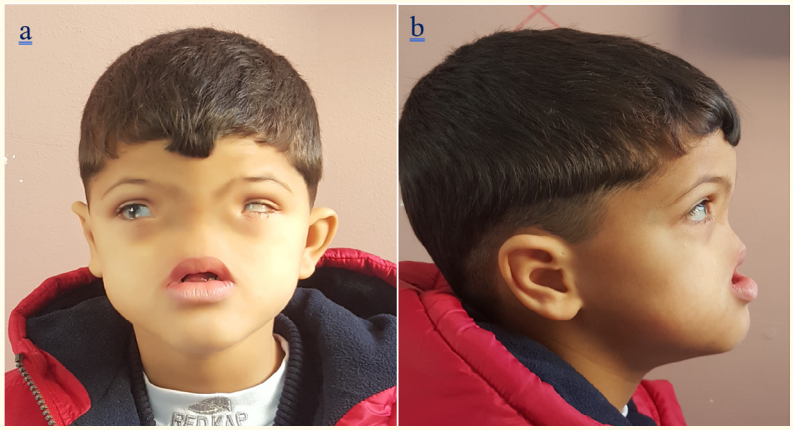

Figure 1: *Frontal preoperative view (a) and right-side preoperative view (b) of patient. Typical appearance of Bosma arhinia microphthalmia syndrome.*

He showed a Class III malocclusions with skeletal relationship and maxillary retrognathism, Angle Class III malocclusion, bilateral crossbite, an asymmetrical anterior open-bite, asymmetrical occlusion, severe crowding (Figure 2).

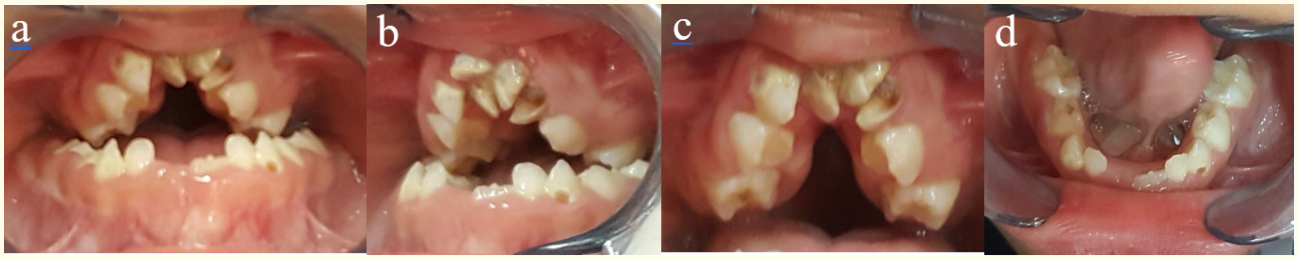

Figure 2: *Occlusal findings in the patient. Occlusal frontal view (a), Right side view (b), maxillary view (b), mandibular view (b) shows a Class III malocclusions with maxillary retrognathism, serious crossbite, open bite, severe crowding, enamel demineralization and delayed tooth eruption in mixed dentition.*

The preoperative x-rays (Figure 3) show a condylar symmetry, the absence of the maxillary sinus, the ethmoid bone and the proper bones of the nose, the proximity of the germs of the incisors of the internal cortex of the frontal and a sever crowding in a mixed dentition (a, b). The lateral cephalometric analysis showed a skeletal Class III, retruded maxilla and hyperdivergent vertical pattern with excessive occlusal plane angle.

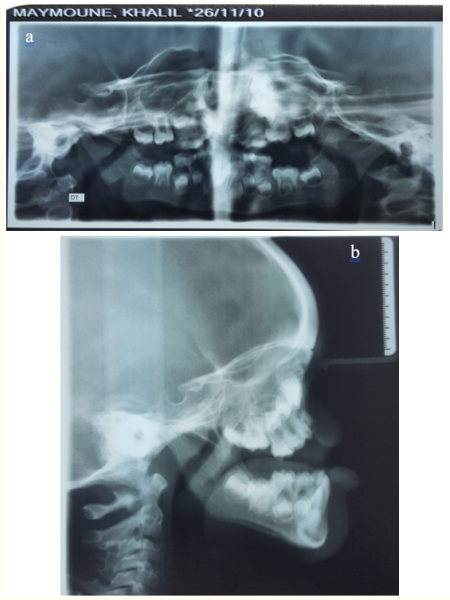

Figure 3: *Preoperative x-rays show an absence of the maxillary sinus, the ethmoid bone and the proper bones of the nose. proximity of the germs of the incisors of the internal cortex of the frontal, a condylar symmetry and a crowed tooth in a mixed dentition (a). The lateral cephalometric analysis showed a skeletal Class III, retruded maxilla and hyperdivergent vertical pattern (b).*

Computed tomography (CT) shows a facial malformation with partial agenesis of the maxilla and ethmoid and confirmed the absence of the internal nasal cavity and paranasal sinuses, Absence of nasal pyramid with integrity of the orbital frames and respect for the mandible (Figure 4).

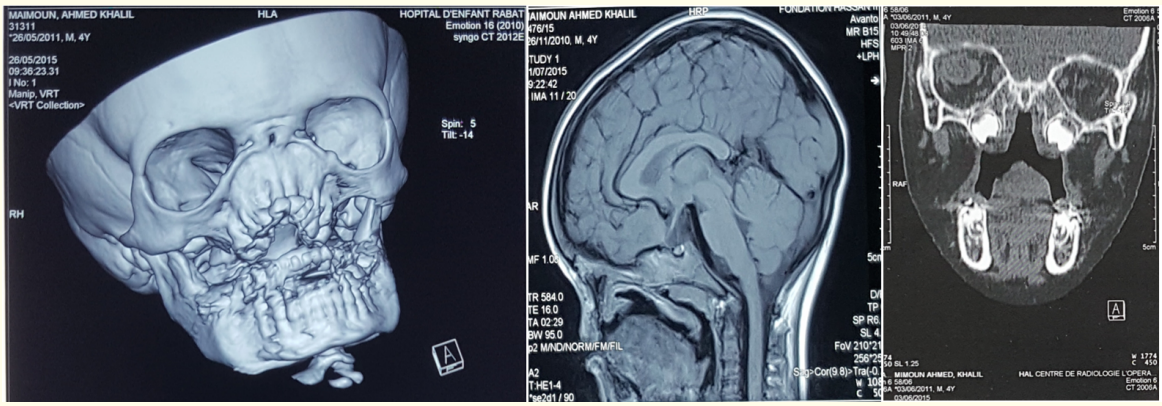

Figure 4: *Preoperative 3D CT scan shows a facial malformation with absence of the pyramid and nasal cavities, palatine bone and ethmoid bone with significant hypoplasia of the maxilla. Ascension of the upper incisors which are visible inter-orbital.*

Genetic analysis and trio or quartet whole-exome sequencing for the case led to the identification of *de novo* heterozygous missense mutations in the *SMCHD1* gene (encoding structural maintenance of chromosomes flexible hinge domain containing 1) (Figure 5), which were confirmed by Sanger sequencing (Figure 6). Given with respect to reference sequence NM_015295.2, the Nucleotide change was c.407A>G; Amino acid change was p.Glu136Gly and Based on PolyPhen-2 score using UniProtKB identifier A6NHR9, the predicted functional effect was 0.999. This mutation was confirmed by Sanger sequencing of SMCHD1**.** Heterozygous missense mutation was identified in this case and the variants were *de novo*, suggesting germline mutations in parental gametes. None of the identified mutations have been reported in the Exome Aggregation Consortium (ExAC), Exome Variant Server (EVS) or dbSNP144 database [8].

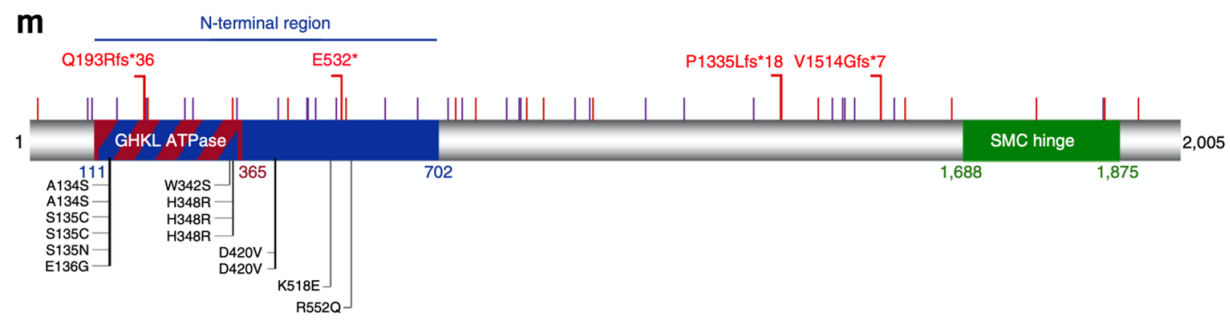

Figure 5: *Genetic analysis of the case shows a mutation of SMCHD1 (encoding structural maintenance of chromosomes flexible hinge domain containing 1). (m) Positions of Bosma arhinia microphthalmia syndrome (BAMS) associated missense variants (black) and heterozygous loss-of-function variants from ExAC (red) in SMCHD1. Short bars represent known missense (purple) and frameshift or nonsense (red) FSHD2-associated variants [8].*

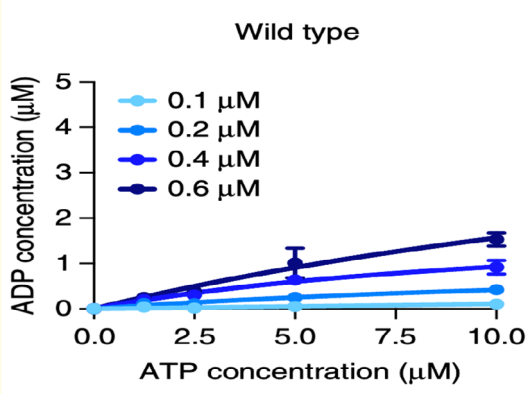

Figure 6: *ATPase assays performed using recombinant protein encompassing amino acids 111–702 of mouse Smchd1. Results are shown for wild-type. Details on the exact amino acids mutated in FSHD2 (Facioscapulohumeral Muscular Dystrophy 2) in the N-terminal region and biochemical assays indicate that BAMS-associated SMCHD1 mutants have increased ATPase activity [8].*

A surgically reconstruction of this case was performed by a multidisciplinary team. The patient underwent a primary surgical intervention in which a Le Fort II maxillary osteotomy with a superior vestibular and bicortical approach under submental intubation. This osteotomy was done to give enough height of maxillary (Figure 7a and 7b). This was extended through the maxilla-zygomatic consoles and toward the medial end of the inferior orbital edge and ran through the infraorbital foramen. A horizontal arm linked the two sides. Then the maxilla was down fractured.

The effect of this osteotomy was maintained and potentiated by the Delaire Face Mask performed in the operating room under general anesthesia (Figure 7b and 7c). The Delaire face mask was applied force at a 25 - 30° angle to the occlusal plane in a downward direction for 3 months. The Delaire Face Mask allowed external distraction and provides additional facial height in a reasonable time period and has sufficient midfacial vertical length to accommodate a nasal reconstruction and suitable aesthetic proportions. This mask was supported by a resin splint screwed into the hard palate. this gutter carries two shaped ratchets on each side which support extra-oral elastic (Figure 8). The magnitude of the force was 500g per side. The duration of the force was 24h/day [12].

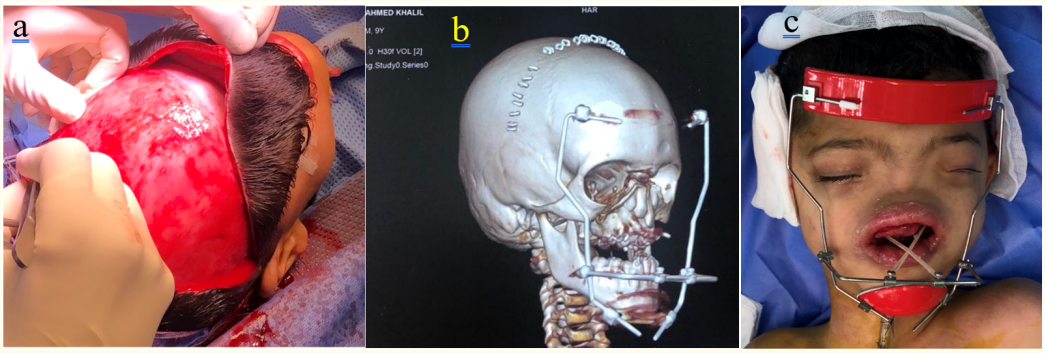

Figure 7: *The patient underwent a primary surgical intervention in which a Le Fort II maxillary osteotomy with a superior vestibular and bicortical approach under submental intubation (a). The effect of this osteotomy was maintained and potentiated by the Delaire Face Mask (b, c) supported by a resin splint screwed into the hard palate.*

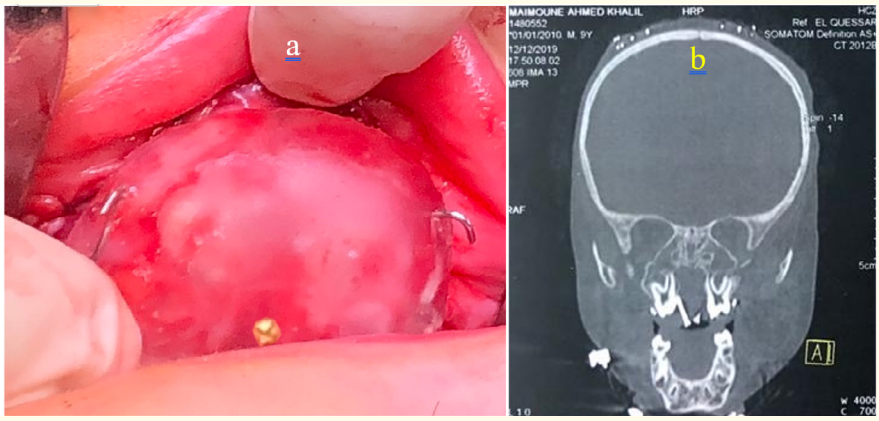

Figure 8: *The Delaire Face Mask was supported by a resin splint screwed into the hard palate (a). This splint was performed in the operating room under general anesthesia. The radiological control shows the absence of contact between the screw and the tooth roots (b).*

In a second step, the young patient benefited from a parietal bone graft to fill the distracted zone. The patient continues to wear the Delaire Face Mask (Figure 9). In 3rd step, the patient underwent a nasal reconstruction (Figure 10). A wide median nasal cavity was created with a round bur, reaching posteriorly to the upper portion of the rhinopharynx and then extend it along the maxillary bone. A paramedian forehead flap was raised using a plastic template (patron) and rotated over the graft and sutured with the lining flaps to cover the grafts entirely. To clear the nostril openings two caouatchoutic probes were put and sutured inside the new nose to leave the respiratory tract clear. Finally, the forehead flap was rotated over the graft and sutured with the lining flaps to cover the grafts entirely and the donor site was primarily closed. Two nasal splints were placed in the newly created nares and held in place for 6 months [7].

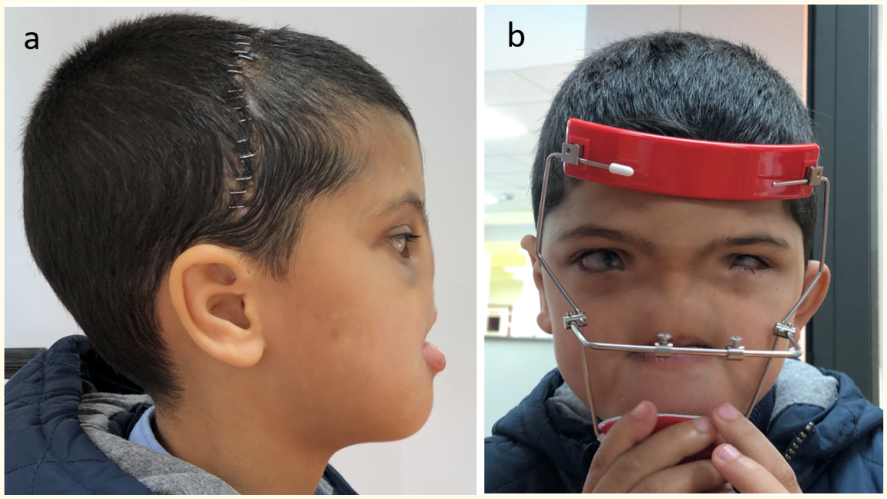

Figure 9: *In a second step, the young patient benefited from a parietal bone graft to fill the distracted zone (a). The patient continues to wear the Delaire Face Mask (b).*

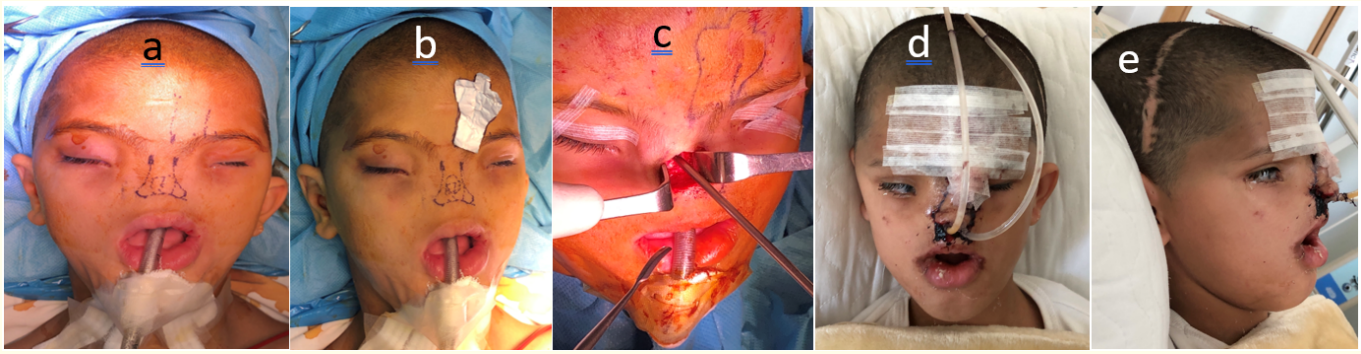

Figure 10: *In 3rd step, the patient underwent a nasal reconstruction (a, b). A wide median nasal cavity was created reaching posteriorly to the upper portion of the rhinopharynx and then extend it along the maxillary bone (c). A paramedian forehead flap was raised using a plastic template and rotated over the graft and sutured with the lining flaps to cover the grafts entirely (c, d). Two caouatchoutic probes were put and sutured inside the new nose to leave the respiratory tract clear (d, e).*

At this time, the transverse expansion was achieved by a tri-helix manually shaped so that it is perfectly adapted to this very narrow shape of the palate. This device was performed in the operating room to provide simultaneously molar rotation control, shaping the palate and transverse expansion (Figure 11). To continue the expansion of this this narrow transverse dimension, the tri-helix has been replaced by a Hyrax expander chosen from the trade and fixed by two screws at the level of the palate. The hyrax is used at the same time as an anchoring means for the traction of the impacted incisors using elastomeric chains (Figure 12 and 13).

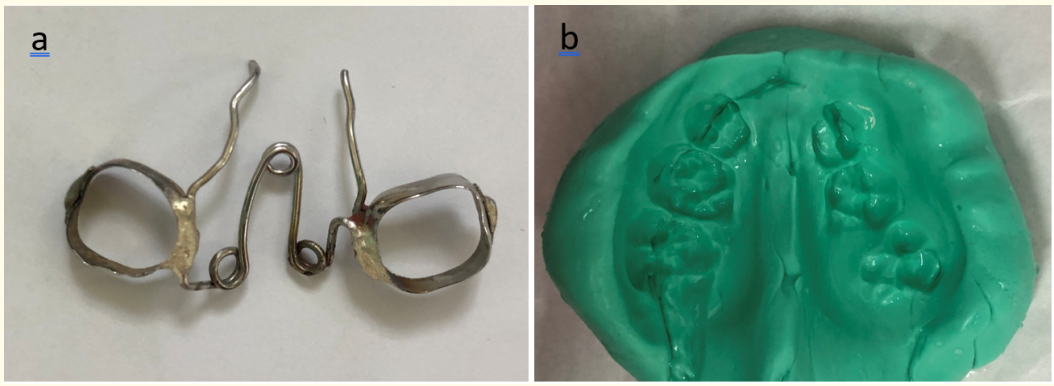

Figure 11: *At this time, the transverse expansion was achieved by a tri-helix (a) manually shaped so that it is perfectly adapted to this very narrow shape of the palate (b). This device was performed in the operating room to provide simultaneously molar derotation, shaping the palate and transverse expansion.*

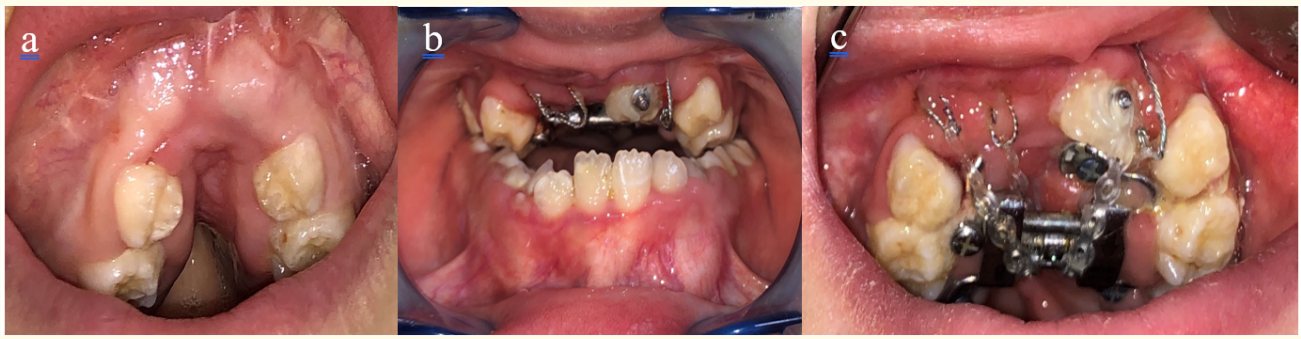

Figure 12: *To continue the expansion of this this narrow transverse dimension (a), the tri-helix has been replaced by a Hyrax expander chosen from the trade and fixed by two screws at the level of the palate (b, c). The hyrax is used at the same time as an anchoring means for the traction of the impacted incisors using elastomeric chains (c).*

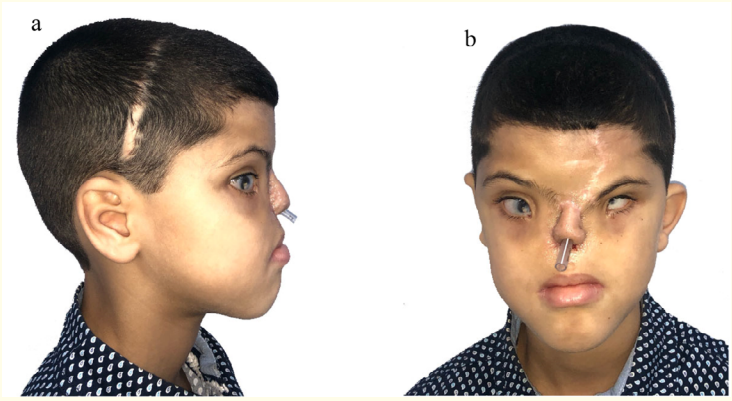

Figure 13: *Frontal postoperative view (a) and right-side postoperative view. The new nose shows good esthetic and functional results 1years after surgically reconstruction.*

Discussion

Because arhinia is exceptionally rare, the pathogenesis of this disease has not been fully understood. It is postulated that lack of development of the nose results from medial failure and lateral nasal process growth, but it is also possible that overgrowth and premature fusion of the nasal medial process result in the formation of the atretic plate [6,13].

Several genes involved in nose and facial development have been shown to be causes of arhinia. However, no consistent gene mutations have been discovered [6]; therefore, genetic testing and whole-exome sequencing for the case led to the identification of *de novo* heterozygous missense mutations in the *SMCHD1* gene (encoding structural maintenance of chromosomes flexible hinge domain containing 1), which were confirmed by Sanger sequencing. Heterozygous missense mutation was identified in this case and the variants were *de*

novo, suggesting germline mutations in parental gametes. None of the identified mutations have been reported in the Exome Aggregation Consortium (ExAC), Exome Variant Server (EVS) or dbSNP144 database [8].

The chromosomal analysis in patients with arhinia showed normal results, excepting 3 cases that had abnormal karyotypes [6]: mos46,XX/47,XX,+9; 1046,XY,inv(9); 1146,XX,t(3;12) (q13.2;p11.2) [14]. In addition to the karyotype, the all reported cases are normal. Factors of deformity gene and the mother are still unknown. Some publications reported a familial aspect of arrhinia [15-17].

The reconstruction of arhinia is very complex and it should be performed only by a multidisciplinary team that includes oto-laryngology, plastic surgeons, and prosthodontists. The arhinia reconstruction progress mainly consists of 2 parts: reconstruction of the nasal cavity and reconstruction of the external nose [6]. There are 2 goals in the treatment of arhinia. The first one is to manage any peripartum complications [6]. The literature includes some reports of neonatal respiratory distress accompanying this disease [18-20]. Remarkably, our patient did not show any signs of respiratory distress except some difficulty in breathing and eating.

The second point to be managed in arhinia is the definitive correction of the malformation with functional and esthetic aims. An integrated approach should address all the issues of the disease, and we believe that the treatment objectives are to create 1) a wide nasal cavity and 2) an external nose. Finally, the ideal treatment should have the lowest possible morbidity and a low relapse rate [6] but clearly, our patient needed maxillary expansion and impacted tooth placement. The treatment solutions described in the literature are based on single case experiences, given the exclusive character of arhinia is an exceptionally rare condition. For these reasons, many aspects of the treatment are controversial.

The most difficulty in the approach is the creation and maintenance of a nasal cavity. Because of the completely subverted local anatomy due to the reduced vertical dimensions of the palatal vault and ethmoid, the procedure is technically difficult to realize and quite risky. Moreover, there is a definite risk of entering the cranium while trying to create a sufficiently wide nasal cavity because the maxilla and palate are in close proximity to the cranial base [6]. In addition, because restenosis of the new cavity with time, there is a definite relapse rate reported in the literature, Finally, some techniques require dental extractions to create space for the new cavity [11,21]. Our patient showed a slight external restenosis of a nave on the left side because of the loss of caouatchoutic drink, which requires a reoperation to put it back.

According to the literature, we believe according to what has been reported by Brusati-Colletti that maxillary osteotomy followed by a down-fracture is ideal from this perspective because it allows the safer creation of a wide new nasal cavity while simultaneously eliminating the need for dental extractions [7]. And the distraction is necessary to obtain a good vertical increase of the maxilla in accordance with Feledy., *et al* [22]. However, Brusati-Colletti thinks that it is not necessary to rely on distraction to obtain a good vertical increase of the maxilla. They believe that a wide single cavity is safer with respect to relapse than 2 smaller cavities. As a last weapon against relapse, it is of prime importance to line the entire cavity with epithelium [7].

In accordance with Brusati-Colletti [7], maxillary osteotomy allows one to address the maxillary vertical hypoplasia, which can normalize the labial-dental proportions and dental appearance simultaneously. But in our case, this is not sufficient because, there is a severe narrowness of the transverse dimension to the maxilla which contaminates the teeth in retention. for this in our opinion it is essential to act on the transverse direction in parallel with the different therapeutic means to control the eruption of the impacted teeth.

The last treatment objective is the creation of an external nose. This is attained with a combination of standard techniques, including a forehead flap and bicortical graft. An acceptable morphology for the newly created external nose was obtained. this result was stable over 1 years.

One last controversy pertains to the optimal timing of treatment. We agree with the general statement reported by Brusati and Colletti [7], that the best time to perform this procedure is just as the children reach school age. Our patient was operated on at the age of 7 years. Earlier surgical construction would lead to a nose that is too small for the patient's face by the end of his or her growth. Inversely, postponing the surgical correction further would burden the patient with an excessive psychological load [7,23].

Conclusion

A Moroccan male infant, 7-year-old presented the typical signs an arhinia like a complete absence of the external nose, internal nasal cavity and paranasal sinuses and nasal pyramid, a partial agenesis of the maxilla and ethmoid. Genetic analysis for the case led to the identification of *de novo* heterozygous missense mutations in the *SMCHD1* gene, which were confirmed by Sanger sequencing. Cephalometrically, he showed a Class III malocclusions with skeletal relationship and maxillary retrognathism, Angle Class III malocclusion, bilateral crossbite, an asymmetrical anterior open-bite, asymmetrical occlusion, severe crowding.

A complex surgically reconstruction of this case was performed by a multidisciplinary team starting with a Le Fort II maxillary osteotomy with a bicortical approach under submental intubation. The effect of this osteotomy was maintained and potentiated by the Delaire Face Mask. In a second step, the patient benefited from a parietal bone graft. In 3rd step, the patient underwent an internal and external nasal reconstruction to reduce negative effects on patient psychology and physiology. At this time, the transverse expansion was achieved by a by a series of orthodontic appliances performed simultaneously to control the transverse dimension and to allow eruption of impacted teeth and/or teeth that are difficult to erupt.

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