A report of four patients with Moebius syndrome: new oral anomalies and challenges in dental management

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Background
Moebius syndrome (MBS MIM # 157900) is mostly a sporadic disorder characterized by nonprogressive congenital facial and eye abduction paresis. Some patients have associated limb anomalies. Orofacial abnormalities are regularly associated with the syndrome.

Aim
The authors report four unrelated Egyptian patients with MBS presented with variable oral and dental abnormalities. New orodental findings of the syndrome were presented.

Materials and methods
Dental management was offered to the needed patient with suitable modifications to fit the case. The four probands were subjected to full medical history taking and extensive clinical and orodental examinations. Restorative and prosthetic management with special modifications was highly recommended.

Results
Results exhibited commonly detected orodental anomalies. Alveolar ridge asymmetry, microdontia, and premature eruption were new findings of the syndrome. Increasingly, dental management improved speech, mastication, and esthetic of the patient.

Conclusion
The detection of new oral findings could expand the phenotype of the syndrome. The appropriate recognition of the disorder provides accurate management and patient satisfactory parameters. The authors noted a positive correlation between severity of orodental anomalies and limb involvement. The authors recommend further orodental evaluation of more patients with MBS, which may help in understanding its etiopathological aspects in correlation with its phenotypic diversity.

Keywords:
dental management, facial palsy, Moebius syndrome, oral anomalies

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Background

Moebius syndrome (MBS MIM # 157900) is a rare rhombencephalic maldevelopment disorder that affects a group of cranial nerves. Nonprogressive congenital facial nerve palsy and abducens nerve palsy are the primary findings of the syndrome, as well as limb and orofacial anomalies (Verzijl *et al.*, 2003). The syndrome is estimated to be 1/250 000 live births without sex difference (Picciolini *et al.*, 2016).

The etiology of MBS is still unclear, and its pathogenesis is not fully explained. The disruption during rhombencephalon development caused by environmental or genetic insults provides cranial nerve dysfunction (Bavinck and Weaver, 1986). MBS is known to be an erratic condition. Nevertheless, HOXB1, PLXND1, and REV3L gene mutations were reported in MBS, which may imply genotypic/phenotypic diversity (Webb *et al.*, 2012; Tomas-roca *et al.*, 2015). The ocular abduction impairment associated with the disorder differentiates it from congenital facial palsy (Verzijl *et al.*, 2005).

Although the orofacial malformations associated with MBS were previously reported (Rizos *et al.*, 1998), the recording of new oral and dental abnormalities becomes challenging to confirm the syndrome characterization and expand its phenotypic spectrum and orodental management. The dental description of the syndrome may help in the diagnosis especially with nongeneticist practitioners.

We report four unrelated Egyptian patients with MBS presented with variable oral and dental abnormalities. We noted a positive correlation between the severity of limb malformations and the orodental involvement. New orodental findings of the syndrome were noted. We reviewed 51 previously published Moebius cases with oral involvement (Loli, 2017) that did not mention any of our new findings. Dental management

was offered to one patient with suitable modifications to fit the case. The modifications done during dental management could be beneficial to deal with the dental abnormalities during treatment.

Procedure and results

The study included four Egyptian unrelated male patients. Parental consanguinity was positive for one patient. Patients were recruited from the outpatient clinic of the Skeletal Dysplasia and Limb Malformation Clinic. Their age ranged from 5 months to 5 years and 9 months. They were subjected to full medical history taking and extensive clinical and orodental examinations. The patients were included into the study after the approval of their guardians and providing a signed informed consent from the Ethical Committee of the center. Main clinical features of the four patients are shown in Tables 1 and 2.

The orodental findings of the four patients revealed multiple oral and dental abnormalities. Some features were commonly found in the patients. Other features that we report here were not previously published (Tables 1, 2 and Figs. 1, 2). The dental management improved speech, mastication, and esthetics. The patient was extremely satisfied with the work and regained his psychological stability. The assessment was evaluated by the improvement of uttering certain improperly said letters and words. In addition, the parents observed that the child ate in a better way after denture delivery.

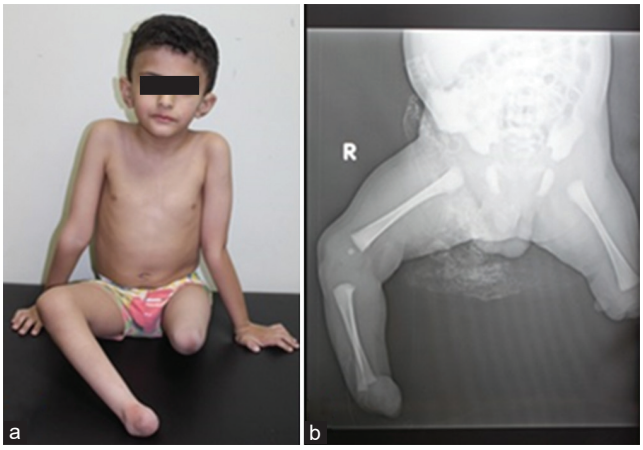
Dental management of case 1

Only one patient aged 5 years and 9 months was subjected to the dental management because his chief complaint was dental pain, whereas the other three were either too young or had no dental problems. Oral hygiene measures were prescribed strictly as on examination. The patient had bad oral hygiene and badly decayed teeth. Follow-up was done to evaluate the case before starting management. Extensive decayed teeth were the sequelae of defective teeth structure and neuromuscular problems which alter the self-cleaning pattern and led to poor oral hygiene. The patient was followed-up 1 month later to assess his oral hygiene condition, and then dental management was started. Lack of neuromuscular coordination and the craniofacial abnormalities associated with our case rendered the dental management challenging. The limited mouth opening, micrognathia, as well as microstomia prohibited the usage of high-speed hand piece. Although the introduction of prosthetic appliance for restoring extracted teeth was a challenge, modifications on our treatment plan was the solution to counteract the complications.

Non-invasive technique by caries excavation was used, and then the cavities of the first three permanent molars were filled with glass ionmer, and chrome steel crowns were afterward used to preserve teeth integrity and to prevent recurrence of decay. The last incompletely erupted left upper first permanent molar could not be managed in the same way. The tooth crown was covered by a protective layer of glass ionmer filling.

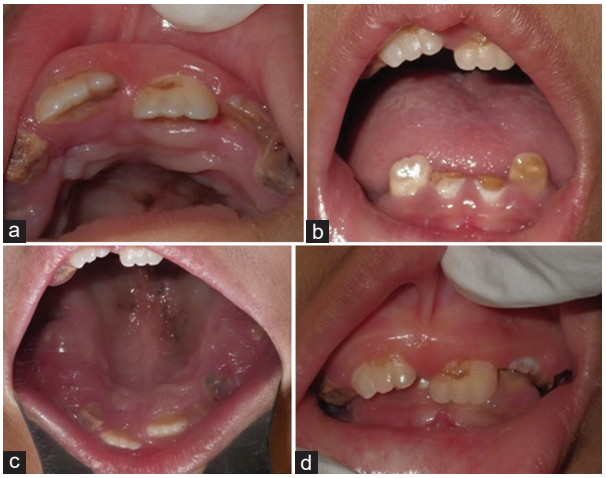
The lower permanent incisors had extensive caries that made the restoration to compensate their morphology problematic. The choice of removing the anterior teeth was refused, so a decision to preserve roots for maintaining ridge height and thickness was made. The

Figure 1



Photograph of a 5-year 9-month male patient (patient 1). (a) Face and trunk asymmetry, camptodactyly of both hands, bilateral absent feet, and absent left leg; (b) radiography of lower limbs showing bilateral apodia and absent left tibia and fibula.

Figure 2



Photographs of patient 1. (a) Upper ridge asymmetry, high-arched palate, thick alveolar ridge, prominent premaxilla, hypoplastic teeth, and badly decayed teeth; (b) tongue asymmetry and median grooved tongue; (c) microdontia of upper left premolar and premature eruption; (d) deep overbite and tooth hypomineralization.

Table 1 Main genetic and clinical manifestations of the four patients

Findings	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Male	Male	Male
Age	5 years and 9 months	5 months	1 year and 4 months	5 years and 4 months
Parental consanguinity	-	+	-	-
Maternal age at pregnancy (years)	34	39	33	30
Paternal age at pregnancy (years)	39	45	52	38
Pregnancy history	Exposed to progesterone and Duvadilan (vasodilator drug)	-	Fever attacks	Exposed to progesterone
Skull	-	-	Microcephaly	-
Face				
Dysmorphic facies	-	+	+	+
Asymmetry	+	-	+	+
Expressionless	-	-	+	+
Facial weakness	+	-	+	+
Eyes				
Duane anomaly	-	+	+	+
Ptosis of eyelids	-	-	+	-
Antimongoloid slanting of eyelids	+	+	-	+
Epicanthic Folds	-	+	+	+
Long eye lashes	-	-	+	+
Small palpebral fissure	-	-	+	+
Ears				
Dysplastic ears	-	+	-	-
Low set	-	+	-	-
Rotated	-	+	-	-
Prominent ears	-	-	+	+
Generalized muscle and tendon weakness	+	+	+	+
Laryngeal anomalies	+	-	-	-
Trunk				
Asymmetry	+	+	+	+
Hypoplastic pectoralis	-	-	-	+
Narrow pelvis	+	-	-	-
Short chest	-	+	+	-
Feeding problems in infancy	+	-	-	-
Hands				
Absent fingers	-	+	-	+
Fusiform fingers	-	-	+	+
Hypoplastic nails	-	-	+	+
Camptodactyly	+	-	+	+
Simian crease	-	-	+	-
Short lower limbs	+	+	+	+
Foot				
Absent	+	-	-	-
Brachydactyly	-	-	-	+
Bilateral talipes	-	+	+	+
Clinodactyly	-	-	+ (5th toe)	+ (5th toe)
Cranial nerve palsies	+	+	+	+
Hypoplastic skin of the affected side	-	+	+	+
Intellectual disability/developmental delay	+	+	+	+
Karyotyping	N	N	N	N

N, normal.

destructed anterior teeth were subjected to root canal treatment using short files. The cavities were then filled with amalgam plugs and the crowns were reduced forming dome shaped teeth (Fig. 3). In addition, all badly decayed deciduous teeth were abscessed, and their extraction was mandatory. Overdenture was planned to cover the anterior teeth and the edentulous ridge till the eruption of permanent teeth.

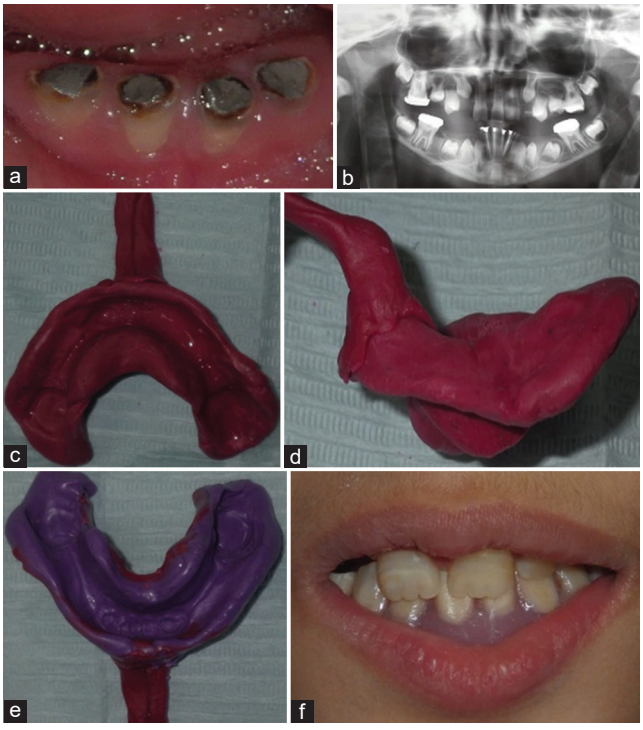
The ultimate problem encountered in the prosthetic management was primary impression. The available tray sizes were not suitable in our condition. A preprimary impression made with impression compound which was softened and inserted into the patient's mouth, and then the impression was shaped intraorally to properly replicate oral structures. A shellac primary tray was created to fit patient's mouth size (Fig. 3).

Table 2 The orodental anomalies detected in the four examined patients (new findings are in Italic)

Oral structure	Orodental anomalies	P 1	P 2	P 3	P 4	Total
Mouth	Asymmetry		+		+	2
	Microstomia				+	1
	Deviation				+	1
	Limited mouth opening				+	1
Lip Alveolar ridge	Thin	+			+	2
	Incompetent			+		1
	Fusion between lip and alveolar ridge		+			*1*
	Asymmetry		+		+	*2*
	Thick	+		+	+	*3*
Palate	High-arched palate	+	+		+	3
	Asymmetry soft palate shape		+			1
	V-shaped palate	+			+	2
	Long uvula	+	+	+	+	*4*
	Prominent premaxilla			+	+	2
Mandibular retromicrognathia		+	+			2
Tongue	Asymmetry	+			+	2
	Microglossia/hypoplasia		+	+		2
	Median grooved tongue	+	+		+	3
Occlusion	Deep overbite	+			+	2
	Wide overjet	+				1
Teeth	*Microdontia*	+				*1*
	Enamel hypocalcification	+			+	2
	Enamel hypoplasia	+			+	2
	Premature eruption[a]	+			+	*2*
	Caries	+			+	2

[a]In patient 1, the fully erupted teeth are upper and lower incisors, the lower incisors with root completion, and eruption of upper left first premolar. In patient 4, the eruption of upper and lower incisors was noted.

Figure 3



Photographs of prosthetic and restorative management of patient 1. (a) Amalgam plugs of four lower anterior teeth for coronal seal after root canal treatment, (b) panoramic view showing root canal treatment of the four lower anterior teeth, glass ionomer copping of the four first permanent molars, (c) shellac tray top view, (d) shellac tray side view for primary impression, (e) rubber base impression material to provide an accurate fitting special tray, and (f) lower denture after being delivered.

Another primary impression was taken using impression silicone rubber base impression material to provide an accurate special tray (Fig. 3). The resulted special tray was shortened distobuccally to allow tray insertion, and a primary impression was made. Another special tray was fabricated to make the final impression. The rest of prosthodontic procedures were completed with the conventional manner. The final denture flanges were trimmed distobuccally from both sides to allow ease of insertion and removal by the patient. After denture checking, a permanent soft liner was applied to the fitting surface to produce intimate contact between the fitting surface and the ridge to enhance stability and retention.

Discussion

MBS is defined as 'congenital, non-progressive facial weakness with limited abduction of one or both eyes' (Miller, 2007). There is a theory which supports that MBS could be a mesodermal dysplasia encompassing muscles originated from branchial arches. Moreover, cranial nerves VI, VII, and XII originate from the rhombencephalon or hindbrain. The developmental malformation of the hindbrain can lead to cranial nerve paresis (Pitner *et al.*, 1965; Wang, 2005).

The hypoglossal cranial nerve innervates the tongue muscles. Impaired innervation could arise from either

tongue hypoplasia, fasciculation, or deviation. The more the damage to the nerve, the more the tongue deformity (Wendy, 1994). Tongue hemiatrophy/asymmetry was previously reported (Pedraza *et al.*, 2000). Tongue asymmetry and tongue hypoplasia herein were due to hypoglossal nerve affection. The alteration in fusion of the two lingual swellings during embryological state generates median grooved tongue. The unequal bilateral tongue size produces the same median groove. It is normally presented among population. However, it was described in association with MBS (Verzijl *et al.*, 2003). Hence, median grooved tongue was found in three of our patients.

Facial nerve impairment ends by facial palsy, mouth deviation to the affected side, as well as mouth asymmetry (Srinivas *et al.*, 2016). Microstomia is considered a feature of MBS. The small-sized mouth leads to limited mouth opening (Rizos *et al.*, 1998; Scarpelli *et al.*, 2008). Our patients exhibited microstomia, restricted mouth opening, mouth asymmetry, and deviation. The lips are dramatically influenced by the dilemma of impaired facial nerve leading to thin and incompetent lips (Scarpelli *et al.*, 2008; Picciolini *et al.*, 2016; Ghosh *et al.*, 2017). Both lip anomalies were described in this study. Fusion between lips and alveolar ridges was a new finding in one of our patients; it could be owing to muscle weakness.

Asymmetry of upper alveolar ridge was presented in two patients. This finding was not reported before. The presence of facial nerve dysfunction weakens the facial musculature which may hinder the growth of alveolar bone correctly (Pandey *et al.*, 2011). Increasingly, thick alveolar ridge was found in three patients as a new description. The abnormal facial growth pattern has a direct effect on the thickness of alveolar ridge, besides improper alignment of the bite (Garib *et al.*, 2010).

Dentoskeletal malformations are commonly associated with MBS. Nose breathing is a normal process which preserves normal lateral maxillary growth and proper palatal height. Lip incompetence followed by mouth breathing affects seriously palatal dimensions and provides V-shaped and high-arched palate (Indiantri *et al.*, 2017). Both V-shaped palate and high-arched palate were detected in our patients, in accordance with many researchers (Verzijl *et al.*, 2003; Ghosh *et al.*, 2017; Bell *et al.*, 2018; Loli, 2017). Asymmetry of soft palate was also present herein. This asymmetry occurred as a consequence of improper innervation of palatal nerve supply (Jacob *et al.*, 2014). The four patients showed long uvula which could be a new finding for syndrome characterization. Thin uvula was newly found in two of our patients. We point out that our patient 1 with the most severe limb involvement had the most marked orodental anomalies, thus emphasizing their developmental correlation. This observation needs to be confirmed by report of additional cases.

The altered craniofacial development in MBS may create jaw relation discrepancies. Mandibular micrognathia was the predominating skeletal abnormality in the disorder, whereas maxillary micrognathia was not common (Ha and Messieha, 2003; Scarpelli *et al.*, 2008; Bell *et al.*, 2018). Our reported two cases showed retromicrognathia. Shawky (2015), reported microretrognathia as ours. On the contrary, prominent premaxilla was found in two of our patients, a finding that was previously reported in the syndrome (Guijarro-martínez and Hernández-alfaro, 2012; Pedersen *et al.*, 2017).

Malocclusion occurs consequently to the aforementioned dentoskeletal discrepancies represented by either deep overbite, wide overjet, or open bite (Magnifico *et al.*, 2017; Pedersen *et al.*, 2017). Our examined patients exhibited malocclusion.

Improper mastication results from weak muscles, arch discrepancy, and malocclusion. The masticatory malfunction with swallowing difficulty impairs the lubrication effect of saliva and disrupt the food intake process, which may lead to caries (Furuta and Yamashita, 2013). MBS is one of the syndromes where badly decayed teeth exist vigorously. In association, defective teeth structure promotes caries initiation (Scarpelli *et al.*, 2008; Guijarro-martínez and Hernández-alfaro, 2012; Pedersen *et al.*, 2017). Teeth hypoplasia, hypocalcification, and caries were features in our study. Microdontia and premature eruption were two newly found teeth anomalies in our cases. The indistinct pathophysiology of the syndrome still cannot elucidate the origin of teeth complications.

The systemized coordination between trigeminal and facial nerves preserves the neuromuscular control keeping the oral cavity as an entity in a good harmony. Facial palsy and muscle weakness disrupts the synchronization of neuromotor system (Vanswearingen, 2008). Denture wearers with facial paresis lose stability and retention of the appliance owing to neuromuscular impairment (Luthra *et al.*, 2015). The shift to overdenture was the solution in our case to overcome this complication. Soft liner was used to reduce ridge damage.

The restricted mouth opening, microstomia, and loss of neuromuscular control are considered an obstacle, which hinders an accurate management. To give the

patient the optimum satisfaction, the modifications added to dental management were of high attention. The offered dental approach and modifications were a new strategy acknowledged to treat Moebius cases, and follow-ups revealed its success and great patient satisfaction.

Conclusion

The proper diagnosis of the syndrome is based on variable clinical features. The detection of new oral findings could be added to expand its phenotype spectrum. The appropriate recognition of the disorder provides accurate management and patient satisfactory parameters. The exposure to variable cases of MBS is ultimately important to understand its etiopathological aspects in correlation with phenotypic diversity. Correlation between severity of limb and orodental involvement needs future attention. Patients with MBS should be examined very early and advised to maintain good oral hygiene measures and preventive procedures to reduce decay as early as possible.

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Conflicts of interest

There are no conflicts of interest.

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