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Long-term results of facial animation surgery in patients with Moebius syndrome

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ABSTRACT

Gracilis neuromuscular transplant is considered the gold standard for facial animation in Moebius syndrome patients. However, long-term evaluation of the results has not been critically examined in the international literature. Thus, it remains unknown how the transplanted flap changes with facial growth, and whether contraction (smiling) is maintained.

Pediatric patients with Moebius syndrome who underwent facial animation surgery with at least 5 years of follow-up were retrospectively examined. Photographs taken at the 1-year and most recent follow-up visits were analyzed and compared using Emotrics software. Analyses focused on the rest position, and on gentle and maximum smiles.

Eighteen patients were enrolled. Seven patients had bilateral and 11 unilateral Moebius syndrome; therefore, 25 gracilis transplants were analyzed. The latest follow-ups ranged from 5 to 13.2 years (mean 7.6 years).

The three principal facial expressions that were examined did not differ significantly between 1 year and a mean of 7.6 years after surgery, but tended to improve in most patients. Commissure excursion and smile angle for the maximum smile did improve significantly ($p = 0.002$ and 0.029, respectively).

The series examined in this study supports the limited literature regarding the long-term stability of gracilis transplantation to animate the faces of Moebius syndrome children.

1. Introduction

Moebius syndrome is a very rare congenital disorder that affects approximately 1/100 000 newborns in the USA and Europe. The etiology of Moebius syndrome remains unknown; both vascular and genetic hypotheses have been proposed (Abramson et al., 1998). The principal diagnostic feature is palsy of cranial nerves VI and VII, which triggers unilateral or bilateral facial paralysis and eye strabismus. Other malformations are often encountered, including: club foot; cleft palate; micrognathia; involvement of other cranial nerves (principally V, IX, X, XI, and XII); Poland and Charge syndromes; muscular dystrophia; and other rare diseases (Picciolini et al., 2016). Thus, management is often difficult and a multidisciplinary approach is essential (Guijarro-Martínez and Hernández-Alfaro, 2012). However, facial palsy is the feature most frequently addressed, because of its associations with severe functional, cosmetic, and social impairments. For patients with Moebius syndrome, it is impossible to communicate emotions (for example, by smiling) (Terzis and Noah, 2002).

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Over the past 20 years, facial animation surgery featuring a gracilis neuromuscular transplant has become the gold standard procedure. This procedure was first described by Harii (Harii et al., 1976) and popularized by Zuker (Zucker and Manktelow, 1999). The free flap can be reinnervated by running a motor nerve from the masseter in patients with bilateral palsy (Manktelow et al., 2006; Bianchi et al., 2010a), or by delivering a branch of the contralateral facial nerve (via sural cross-grafting) in patients with unilateral palsy (Ueda et al., 1998). Smile surgery is typically performed at the age of 5 or 6 years (i.e. before schooling commences) to optimize psychological development. The technique is reliable, safe, and successful, with a very low rate of complications (Bianchi et al., 2009). Many clinicians (Bianchi et al., 2013a; Hohman and Hadlock, 2014) have described their surgical experiences and the short-term results (Roy et al., 2019a), both in patients with Moebius syndrome (Bianchi et al., 2010b) and in patients with many other forms of facial palsy (Hontanilla and Marre, 2015). However, long-term evaluations have been only occasionally reported in aging patients. Greene et al. analyzed a cohort of 40 pediatric patients and 13 of these had a follow-up of 5 years or longer (Greene et al., 2018). However, their series included only one case of Moebius syndrome. Thus, it remains unknown how the transplanted flap changes with facial growth, and whether contraction (smiling) is maintained in this specific group of patients. To the best of our knowledge, only one paper focusing on the long-term outcomes of patients with Moebius syndrome has been published (Domantovsky et al., 2018); that report included 'only' 12 patients. Our study aimed to build on this valuable contribution, because the syndrome is exceedingly rare.

2. Material and methods

Patients with Moebius syndrome who underwent facial animation surgery in the Division of Maxillo-Facial Surgery, University Hospital of Parma, Italy, were included in this retrospective study; the work was approved by our local ethics committee. The inclusion criteria were: monolateral or bilateral Moebius syndrome, defined as unilateral or bilateral palsy of the VI and VII cranial nerves; age at surgery <14 years; facial animation via gracilis neuromuscular transplantation and reinnervation by means of either the ipsilateral masseteric nerve or contralateral facial nerve (delivered via sural-cross grafting); at least 5 years of follow-up data; and written informed consent by the patient or guardian, as appropriate. Photographs taken at the 1-year and most recent follow-up visits were analyzed and compared using Emotrics software (Guarin et al., 2018); analyses focused on the rest position, as well as the gentle and maximum smiles (Fig. 1). The software created facial landmarks that could be checked and corrected by an operator. The software accepted the corrections, compared the two photographs, and reported changes in landmark positions. The landmarks analyzed were brow height, marginal reflex distance, commissure excursion (CE), smile angle (SA), and dental show. The vertical midline was defined as the perpendicular line through the midpoint of the horizontal interpupillary distance. Because we sought to assess smiling, we considered two measurements: CE (the distance from the midline of the vertical/lower lip vermilion junction to the oral commissure) and SA (the angle between the horizontal plane at the vertical midline/lower lip vermilion junction and the oral commissure). All statistical analyses were performed using IBM-SPSS v. 25 (IBM Corp.). Quantitative variables were described by measures of central tendency, dispersion, and shape. The data included the arithmetic means, medians, standard deviations, standard errors of the mean, skewness, kurtosis, minima, and maxima. The statistical significance of differences between repeated quantitative measures was explored using Student's *t*-test for paired observations. Differences with $p < 0.05$ were considered to be statistically significant.

3. Results

Eighteen patients (nine of each sex) met the inclusion criteria (Table 1). Age at surgery ranged from 6 to 13 years (mean 8.8 years). Seven patients had bilateral Moebius syndrome and 11 had unilateral Moebius syndrome. All patients who had bilateral Moebius syndrome underwent gracilis neuromuscular transplantation reinnervated using the ipsilateral masseteric nerve (two separate

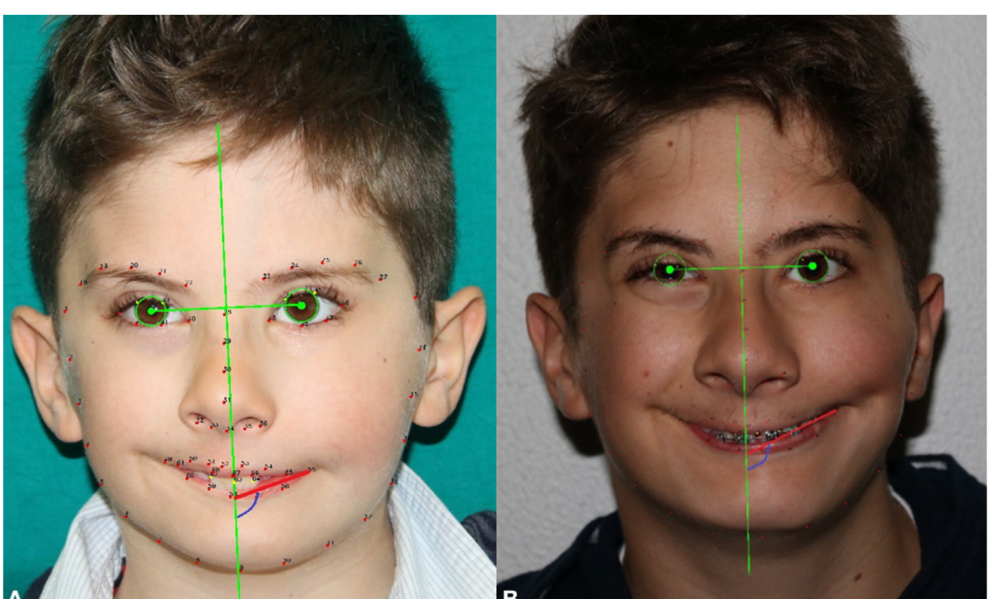

Fig. 1. Early (a) and late (b) follow-up comparison using Emotrics software for maximum smile. Commissure excursion (red line) is the distance from the vertical midline/lower lip vermilion junction point to the oral commissure. Smile angle (blue line) is the angle between the horizontal plane at the vertical midline/lower lip vermilion junction point and the oral commissure.

Table 1
Study population.

	Sex	Age at surgery (years)	Moebius syndrome (monolateral/bilateral)	Donor nerve	Latest follow-up (years)
ID1	F	7	Monolateral (R)	Cross graft	9
ID2	M	7	Monolateral (L)	Masseteric nerve	6
ID3	F	7	Monolateral (R)	Cross graft	5
ID4	F	13	Monolateral (L)	Masseteric nerve	13
ID5	M	12	Bilateral	Masseteric nerve	14
ID6	M	12	Monolateral (L)	Cross graft	9
ID7	M	12	Bilateral	Masseteric nerve	5
ID8	F	7	Bilateral	Masseteric nerve	5
ID9	F	6	Bilateral	Masseteric nerve	14
ID10	M	7	Bilateral	Masseteric nerve	5
ID11	F	7	Bilateral	Masseteric nerve	8
ID12	F	9	Monolateral (L)	Cross graft	9
ID13	M	9	Monolateral (R)	Cross graft	6
ID14	M	10	Bilateral	Masseteric nerve	5
ID15	M	6	Monolateral (L)	Cross graft	5
ID16	F	8	Monolateral (R)	Cross graft	6
ID17	F	7	Monolateral (L)	Masseteric nerve	7
ID18	M	13	Monolateral (L)	Cross graft	6

procedures — one for each side of the face). All were evaluated 1 year after the second surgery. Of the 11 patients who had unilateral Moebius syndrome, three received gracilis neuromuscular transplants reinnervated by the ipsilateral masseteric nerve (one-step surgery). The remaining eight patients underwent two-step surgery: first, sural cross-grafting brought a branch of the healthy facial nerve to a sural graft placed in the upper oral vestibulum; at 9–12 months after the first surgery, gracilis neuromuscular transplantation was performed using the first graft as the source of gracilis reinnervation.

Thus, 25 gracilis grafts were analyzed; 17 were reinnervated by the ipsilateral masseteric nerve and eight by the contralateral facial nerve via sural cross-grafting.

Table 2
Smile angle (degrees) and commissure excursion (mm) measurements by Emotrics software. Mass: masseteric nerve. Cross: cross graft.

Patient	Donor Nerve	Rest				Mild smile				Maximum smile			
		Smile angle		Commissure excursion		Smile angle		Commissure excursion		Smile angle		Commissure excursion	
		Early	Late	Early	Late	Early	Late	Early	Late	Early	Late	Early	Late
Id1	Cross	118.03	117.4	28.87	32.72	118.49	122.21	27.36	33.59	118.68	121.91	33.82	42.48
Id3	Cross	107.02	116.63	21.21	25.86	105.93	119.94	22.39	30.52	123.21	125.16	31.87	30.56
Id6	Cross	103.59	103.18	30.61	25.16	108.59	103.53	30.5	29.3	106.97	105.13	31.73	30.71
Id12	Cross	108.82	112.65	26.47	33.58	108.8	107.54	34.48	35.24	114.94	129.59	32.45	44.32
Id13	Cross	113.88	111.04	25.54	26.48	114.61	117.98	28.82	29.53	113.8	124.86	28.97	35.94
Id15	Cross	100.27	101.84	30.59	32.4	102.54	109.87	31	39.09	105.61	109.61	34.96	37.1
Id16	Cross	120.1	120.51	26.85	27.49	121.01	126.14	37.14	32.12	122.94	124.57	40	35.61
Id18	Cross	113.13	118.73	24.15	26.51	114.33	114.17	24.86	33.44	114.06	121.37	36.5	35.05
Id2	Mass	111.05	107.17	25.79	30.72	114.27	110.77	30.68	35.37	106.72	114.89	31.09	40.17
Id4	Mass	117.63	112.8	22.55	17.8	119.36	114.31	41.5	28.61	125.61	117.69	30.64	33.3
Id5	Mass	114.93	101.19	23.36	21.48	110.75	99.85	27.64	19.8	111.1	107.65	27.24	27.14
Id5	Mass	109.87	102.95	32.76	28.6	120.12	103.56	38.57	28.87	114.74	113.36	30.75	43.16
Id7	Mass	109.71	107.08	22.79	23.13	110.6	106.79	21.97	28.68	108.17	113.37	20.82	29.79
Id7	Mass	107.59	103.64	27.23	31.94	116.93	106.92	33.93	30.8	114.34	110.33	37.1	36.6
Id8	Mass	105.39	109.1	23.49	21.66	110.51	112.55	21.76	23.46	107.3	109.78	25.07	27.39
Id8	Mass	105.67	110.38	20.64	26.31	110.79	117.31	24.72	24.59	113.16	119.87	27.54	26.92
Id9	Mass	117.12	108.11	27.22	26.64	120.17	117.17	29.14	30.29	120.93	115.86	32.1	34.33
Id9	Mass	121.87	106.74	23.78	14.23	120.37	114.78	22.7	28.91	119.87	115.59	31.28	34.05
Id10	Mass	114.63	113.04	19.92	23.87	112.21	112.21	25.76	25.97	112.85	119.42	27.66	39.83
Id10	Mass	109.81	110.59	24.86	31.28	117.46	113.9	33.84	33.2	117.88	120.39	31.34	38.7
Id11	Mass	113.65	117.47	22.01	21.33	118.27	115.99	26.8	23.62	116.36	120.48	29.75	23.7
Id11	Mass	110.56	109.56	24.38	28.97	111.34	111.12	28.36	31.84	110.68	114.71	30.86	32.45
Id14	Mass	118.94	123.63	27.59	29.89	117.63	123.84	31.79	39.66	121.59	122.89	34.2	42.64
Id14	Mass	120.15	120.85	27.53	36.5	120.16	123.62	32.01	40.82	122.94	120.78	37.84	43.37
Id17	Mass	113.71	110.26	23.9	32.01	105.26	115.87	31.41	29.58	107.46	115.28	30.32	31.08
Mean (SD)	Cross	110.60 (6.90)	112.75 (7.00)	26.79 (3.23)	28.78 (3.49)	111.79 (6.36)	115.17 (7.78)	29.57 (4.83)	32.85 (3.28)	115.03 (6.54)	120.28 (8.43)	33.79 (3.39)	36.47 (4.92)
Mean (SD)	Mass	113.08 (4.90)	110.27 (5.99)	23.34 (6.14)	26.26 (5.82)	115.07 (4.65)	112.97 (6.30)	29.56 (5.55)	29.65 (3.28)	114.81 (5.92)	116.02 (4.31)	30.33 (4.08)	34.39 (6.23)
Mean (SD)	All cases	112.28 (5.63)	111.6 (6.31)	25.36 (3.24)	27.05 (5.28)	114.02 (5.36)	113.68 (6.73)	29.57 (5.23)	30.68 (5.09)	114.88 (5.99)	117.38 (6.10)	31.43 (4.14)	35.06 (5.83)
Early vs late *p*-value	All cases	0.303		0.075		0.806		0.359		0.029		0.002	

Photographs were taken at the 1-year follow-up and the most recent follow-up (5–13.2 years after the last surgery; mean 7.6 years) (Table 2). In the rest position, the average 1-year and most recent CE measurements were 25.36 ± 3.24 mm and 27.04 ± 5.28 mm; these did not differ significantly. The SA measurements were 112.28 ± 5.63° and 111.06 ± 6.31°; these also did not differ significantly. For the gentle smile, the CE measurements were 29.56 ± 5.23 mm and 30.68 ± 5.09 mm, while the SA measurements were 114.02 ± 5.35° and 113.68 ± 6.73°; neither of these measurements exhibited a significant difference. For the maximum smile, the CE measurements were 31.43 ± 4.14 mm and 35.06 ± 5.83 mm ($p = 0.002$), while the SA measurements were 114.88 ± 5.99° and 117.38 ± 6.10° ($p = 0.029$).

4. Discussion

Management of patients with Moebius syndrome is often complex because multiple issues must be addressed simultaneously; thus, an interdisciplinary approach is essential (Magnifico et al., 2018; Bianchi et al., 2013b). The head-and-neck reconstructive surgeon focuses on facial animation because facial palsy is stigmatizing. Surgery is typically performed at 5–6 years of age, when nutritional, speech, eye, and foot issues have been adequately addressed (Zuker, 2015). Families are often concerned about the lifetime outcomes of facial animation (Bianchi et al., 2017). Indeed, it is essential to determine whether the initial remarkable results will persist (Bianchi et al., 2016; Butler et al., 2019). Reinnervation is particularly successful, typically becoming evident within 3–5 months if the masseteric nerve is used and within 5–7 months after cross-grafting (Ferrari et al., 2017). The numbers of truly functioning muscle fibers then rapidly decrease, thereby reducing the excessive cheek bulk caused by gracilis grafting. With this aim in mind, one of the major technical challenges is determination of the ideal amount of gracilis that will eventually provide a satisfactory outcome in the absence of an obviously bulky cheek. Some authors have tried to assess this parameter in adults and found variation in the ideal amount in relation to the motor innervation source (Braig et al., 2017). In our experience with children, we have found that one-third of the gracilis should be transplanted, with removal of cheek bulk and muscle thinning rarely required, in contrast with adult patients, in whom it is frequently required. This is presumably related to muscle thickness, rather than muscle width determined by gracilis split. However, we do not know whether a small amount of muscle guarantees lifelong success, especially in growing ages, when head-and-neck structures increase in dimensions, and facial proportions change markedly.

To assess this issue, we compared the three principal facial expressions (rest, gentle smile, and maximum smile) at 1 year and a mean of 7.6 years after surgery: these did not differ significantly, but tended to improve in most patients. Moreover, the CE and SA measurements for maximum smile did improve significantly ($p = 0.002$ and 0.029, respectively), presumably because patients learned how best to use their new muscles and responded well to speech therapy. These findings support the long-term data

Fig. 2. Preoperative (a, b), early (c, d), and 7 years late follow-up (e, f) comparison of a 14-year-old patient treated for unilateral Moebius syndrome with gracilis muscle reinnervated with cross-graft.

Fig. 3. Preoperative (a, b), early (c, d) and 14 years late follow-up (e, f) comparison of a 21-year-old patient treated for bilateral Moebius syndrome with gracilis muscle reinnervated with masseteric nerve.

reported by clinicians in Toronto, who confirmed the stability of facial animation with gracilis neuromuscular transplant over the years covered by their study (Roy et al., 2019b).

Notably, although the small number of patients prohibited robust stratification, we observed no differences, even when gracilis transplants that were reinnervated by the masseteric and contralateral facial nerves were considered separately (Table 2), meaning that the source of motor innervation did not affect the stability of treatment. Importantly, although the CE was similar between the two groups, the mean maximal CE was slightly higher in cross-grafted patients. This is contrary to the concerns that have been expressed regarding cross-graft reinnervation, with weak contraction often reported (Chuang et al., 2018). In this regard, many attempts have been made to improve contraction, including double innervation procedures (Min Ji et al., 2020). Despite the small number of patients in our study, our results suggest that if cross-grafting is performed carefully, and if a good zygomatic—buccal branch of the healthy facial nerve is selected without fear for impairment of that nerve (indeed, if such impairment were to occur, it could improve final symmetry), the results of the two procedures may be comparable (Figs. 2 and 3).

It is initially counterintuitive that the CE measurements of the two groups are similar, because the powerful contraction provided by the masseteric nerve would suggest stronger excursion in such patients. The real-life outcome could probably be explained as follows: the contraction provided by the masseteric nerve is often excessive; patients and their speech therapists endeavor to modulate such over-excursion and render the smile natural, seeking to avoid the 'joker' appearance that is an important problem in patients treated for bilateral Moebius syndrome. Secondary cross-graft patients activate the gracilis for each smile passively, with spontaneity and synchronism provided by the healthy contralateral facial nerve (Gur et al., 2018). In contrast, masseteric nerve patients activate the muscle only voluntarily, at least during the first few years after surgery, with spontaneity presumably achievable but not yet demonstrated (Chuang et al., 2018), and eventually requiring considerable time and training (Dusseldorp et al., 2019). Furthermore, the contralateral facial nerve provides a rest tone that is markedly stronger than the tone provided by the masseteric nerve. Therefore, the extent of activation of gracilis reinnervated by the masseteric nerve is presumably lower than the extent of activation of gracilis reinnervated by means of cross-grafting, with fewer muscle fibers selected in patients who undergo reinnervation by the masseteric nerve. Together, these observations may explain why the results for the two groups are similar despite the different characteristics of innervation.

5. Conclusion

The major limitation of our study was the small number of patients; this caused difficulty in stratification based on innervation. However, this is inevitable for all studies of patients with Moebius syndrome, which is an exceedingly rare condition. Multicenter international studies may overcome this limitation. Nonetheless, our results support the limited literature regarding the long-term stability of gracilis neuromuscular transplantation to animate the faces of children with Moebius syndrome.

Declaration of Competing Interest

None of the authors has any conflicts of interest in relation to this work, including any financial interest in any of the products, devices, or drugs mentioned in this manuscript.

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