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Pfeiffer Syndrome: A Therapeutic Algorithm Based on a Modified Grading Scale

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Background: Pfeiffer syndrome (PS) is a very rare condition with a wide clinical spectrum. There are only a few studies that address the classification and treatment of PS and take into account the most commonly presented clinical features. Thus, the objectives of this study are to propose an algorithm for PS management based on a modified severity scale and correlate PS severity with tracheostomy placement.
Methods: An observational retrospective study was performed on consecutive patients with PS (n = 12), who underwent surgery between 2008 and 2018. Clinical features and findings of all included patients with PS were classified as types A, B, and C, which guided treatment workflow. The Fisher test was used to correlate the severity of patients with PS with tracheostomy placement.
Results: There were 12 patients, classified as type A (n = 3), type B (n = 6), and type C (n = 3). All patients who received tracheostomies (n = 6) were stratified into the severe category (n = 9; types B and C) ($P < 0.05$). There were 4 minor complications, and 1 major complication according to a modified Clavien–Dindo surgical complication scale.
Conclusion: A treatment algorithm based on the 3 different Pfeiffer types was proposed. Severity of PS statistically correlates to tracheostomy placement. *(Plast Reconstr Surg Glob Open 2020;8:e2788; doi: 10.1097/GOX.0000000000002788; Published online 29 April 2020.)*

INTRODUCTION

Pfeiffer syndrome (PS) is a specific type of craniofacial dysostosis characterized by premature fusion of cranial and facial sutures, accompanied by enlarged thumbs and toes (with or without clinodactylies), and incomplete syndactyly of both hands and feet.[1–3] PS is recognized as the most severe phenotype of syndromic craniosynostosis.[4]

Severe cases of PS may present respiratory, otologic, and neurologic issues, and visual impairment.[5] Cohen[3] has classified PS into 3 types, with type I being classified as mild and types II and III being classified as severe. The presence of a cloverleaf skull is the sole distinction between types II and III.[3] However, these basic classifications do not guide nor facilitate surgical planning and treatment.[5,6] A more recent stratification was proposed by the New York University (NYU) group, which takes into consideration the most common PS symptoms and features.[5]

In our hospital, patients with PS are treated using 1 of 3 different types of surgeries: (1) early cranial vault decompression; (2) posterior cranial vault distraction osteogenesis (PVDO); and (3) fronto-orbital advancement (FOA) using distraction osteogenesis. The literature addressing PS treatment is scarce, and algorithms using PVDO as the first-line treatment for patients with this condition. Thus, the objective of this study is to describe our surgical experience in light of specific clinical characteristics presented by patients with PS and propose an algorithm for the management of PS based on classification of severity. In addition, our goal is to correlate PS syndrome severity with tracheostomy placement.

MATERIALS AND METHODS

A retrospective study was conducted on consecutive patients diagnosed by our multidisciplinary craniofacial team as having PS, who underwent surgery between 2008 and 2018.

Demographic data (sex and age at surgery), surgical data [assessment of neurologic status, need for ventriculoperitoneal (VP) shunt, and surgical technique used], and outcome data (perioperative and long-term

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Table 1. Modified Functional Classification of Pfeiffer Syndrome

Function	Problem	Score
Respiratory	Respiratory crisis or need for emergency airway management	3
	Obstructive sleep apnea but no crisis	2
Ocular	Globe herniation	3
	Corneal exposure	2
	Amblyopia/strabismus	1
Otologic	Hearing impairment	1
Neurologic	**Swiss cheese–type bone/ hydrocephalus**	**3**
	Chiari/syrinx/seizures/brain anomaly/ collaterary emissary veins	2
	Motor/speech delay	1

Current modification from the previous classification by Greig et al[5] is shown in bold.

Table 2. Functional Score

Classification	Score
Type A: mild	0–4
Type B: moderate	5–13
Type C: severe	14–18

complications) were verified via medical records, clinical photographs, radiographic images, and interviews with all included patients and/or their parents. Clinical features and findings of all included patients with PS were classified using a modified NYU scale, which classified patients as types A, B, and C (Tables 1, 2).[5] Patients with severe PS were defined as types B and C.

Patient complications were recorded and stratified based on a modified Clavien–Dindo surgical complication scale.[7] Complications that merely required pharmacologic treatment or intervention without the necessity of hospitalization were recorded as minor. Major complications were substratified into I, II, and III: (I) events requiring initial or subsequent intervention with general anesthesia to address the resulting condition; (II) events with permanent sequelae; and (III) events resulting in fatality.

All subjects were enrolled after patient and/or parental consents were obtained, and the study was performed in accordance with the Helsinki Declaration of 1975, as amended in 1983. Local institutional research ethics board's approval was obtained for this study.

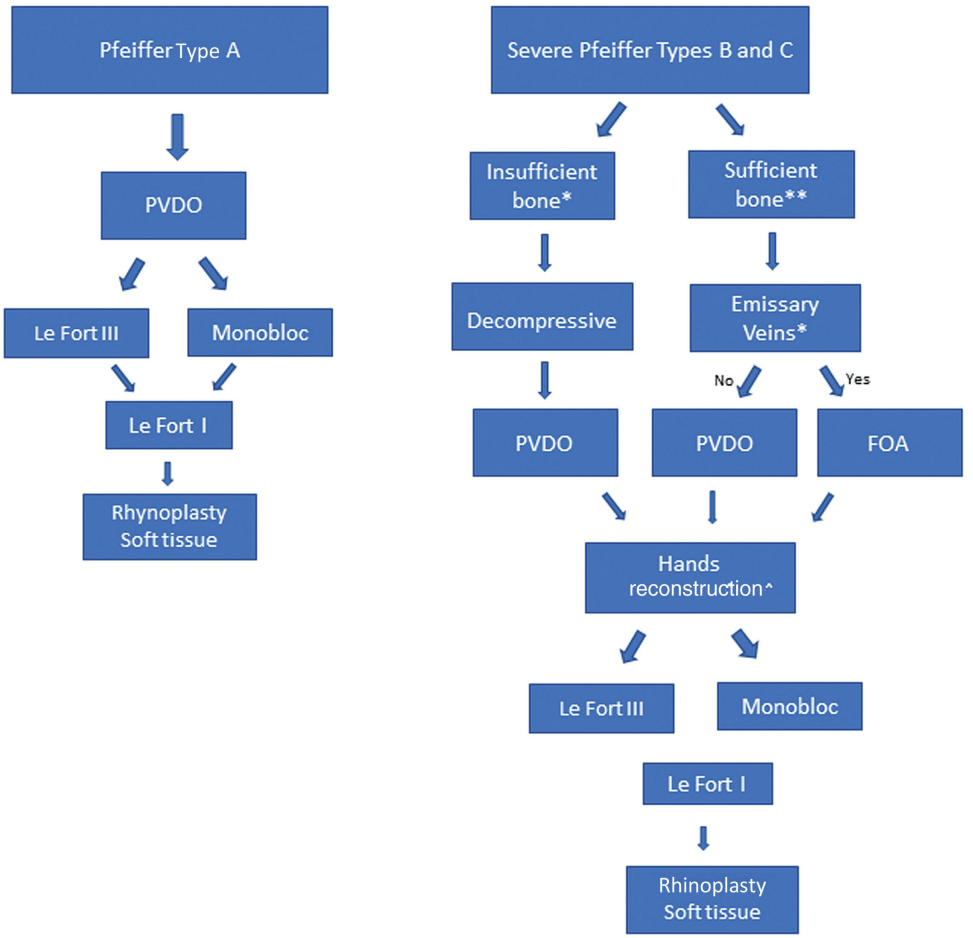

Fig. 1. Pfeiffer syndrome treatment algorithm. *Swiss cheese type of bone formation. **At region of craniotomy site. Occipital veins does not rule out PVDO. ^If needed; VP shunt if hydrocephalus (pre- or postoperative).

Table 3. Characteristics of the Patients with Pfeiffer Syndrome

			Respiratory		Ocular				Neurologic				
Patients	Age (mo)	Sex	Tracheostomy	OSA	Strabismus	Cornea Exposure	Globe Herniation	Hearing Impairment	Hydrocephaly	Swiss cheese–type Bone	Chiari CMEs	Motor/ Speech Delay	Pfeiffer Classification
1	12	M	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Type B
2	216	M	No	Yes	No	No	No	No	No	No	No	Yes	Type A
3	33	M	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Type B
4	14	M	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Type B
5	240	M	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	Type B
6	192	F	No	Yes	No	No	No	Yes	No	No	No	Yes	Type A
7	156	M	No	Yes	Yes	No	No	Yes	No	No	No	Yes	Type A
8	2	M	No	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Type B
9	2	M	No	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Type C
10	2	M	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Type C
11	2	F	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Type B
12	5	M	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Type C

CME, collateral emissary vein; F, female; M, male; OSA, obstructive sleep apnea.

Table 4. Patients Characteristics and Complications

Patients	DS (n = 7)	PVDO (n = 2)	FOA (n = 2)	LF III (n = 1)	Monobloc (n = 3)
Age (y)	2.5	2	6	10	26
Sex					
M	6	2	2	1	1
F	1				
Complications					
Minor	1	1		1	1
Major					
Type 1			1		
Type 2					
Type 3					

Complications stratified according to a modified Clavien–Dindo surgical complication scale.
DS, decompressive surgery; F, female; LF, Le Fort III; M, male.

Surgical Protocol

All patients with PS were initially assessed for respiratory, otologic, and neurologic issues, presence of corneal ulcer, and upper and lower limb syndactylies, and subsequently stratified into A, B, or C types.

Bilateral protective tarsorrhaphy was performed if any sign of corneal ulcer or eyeball luxation was present. The presence of cartilaginous and bony fusion of the auditory canal, including malformations of the ossicles and middle ear, was assessed.

Neurologic assessment was performed via computed tomography or magnetic resonance imaging venograms and determined surgical planning and craniofacial technique. The presence of hydrocephalus, supratentorial collateral emissary veins (CEVs), and stenosis of the superior sagittal sinus (SSS) were important factors that influenced decision-making and treatment workup.[8]

The distinction between ventriculomegaly and hydrocephalus is of paramount importance; the latter being defined by progressive enlargement of ventricles over time,[9] which is a life-threatening condition associated with acute and malignant intracranial hypertension (ICH), resulting in increased bone thinning and Swiss cheese type of bone formation.

Patients with PS accompanied by hydrocephalus require a VP shunt. The VP shunt alleviates excessive intracranial pressure, which results in an enhanced ossification pattern, and enables sufficient bone stability for distraction osteogenesis that can be anterior or posterior. Placement of a shunt in patients with PS with ventriculomegaly does not result in an enhanced ossification pattern, increased bone thickness, nor cranial vault homogeneity, as the primary cause of ICH remains untreated. Moreover, placement of the shunt can result in a rapid reduction in cerebrospinal fluid (CSF) from the ventricles and cisterns, which can exacerbate venous hypertension.

Early cranial vault decompression is reserved solely for patients with PS with ICH and significant craniocerebral disproportion, bone indentation, and a Swiss cheese type of bone formation, with or without cloverleaf deformity.

Our procedure of choice is PVDO at 6 months of age, as PVDO effectively treats ICH, and preserves the forehead and pristine tissue for subsequent monobloc advancement or subcranial Le Fort III. As previously stated, we always perform computed tomography or magnetic resonance imaging venograms for our patients with PS to detect the presence of venous hypertension and critical supratentorial CEV. FOA is reserved solely for those patients who have both stenosis of the SSS and evidence of supratentorial CEV drainage dependence because these conditions preclude exposure of the parietal and occipital bones. Eyeball luxation is not a primary indicator for FOA because it can be controlled via early tarsorrhaphy.

Indications for surgery may vary according to our algorithm. Patients may need >1 craniofacial procedure during craniofacial growth.

All patients with PS require annual evaluation to monitor ICH and regular ophthalmologic examinations to monitor papilledema and loss of visual acuity.[10]

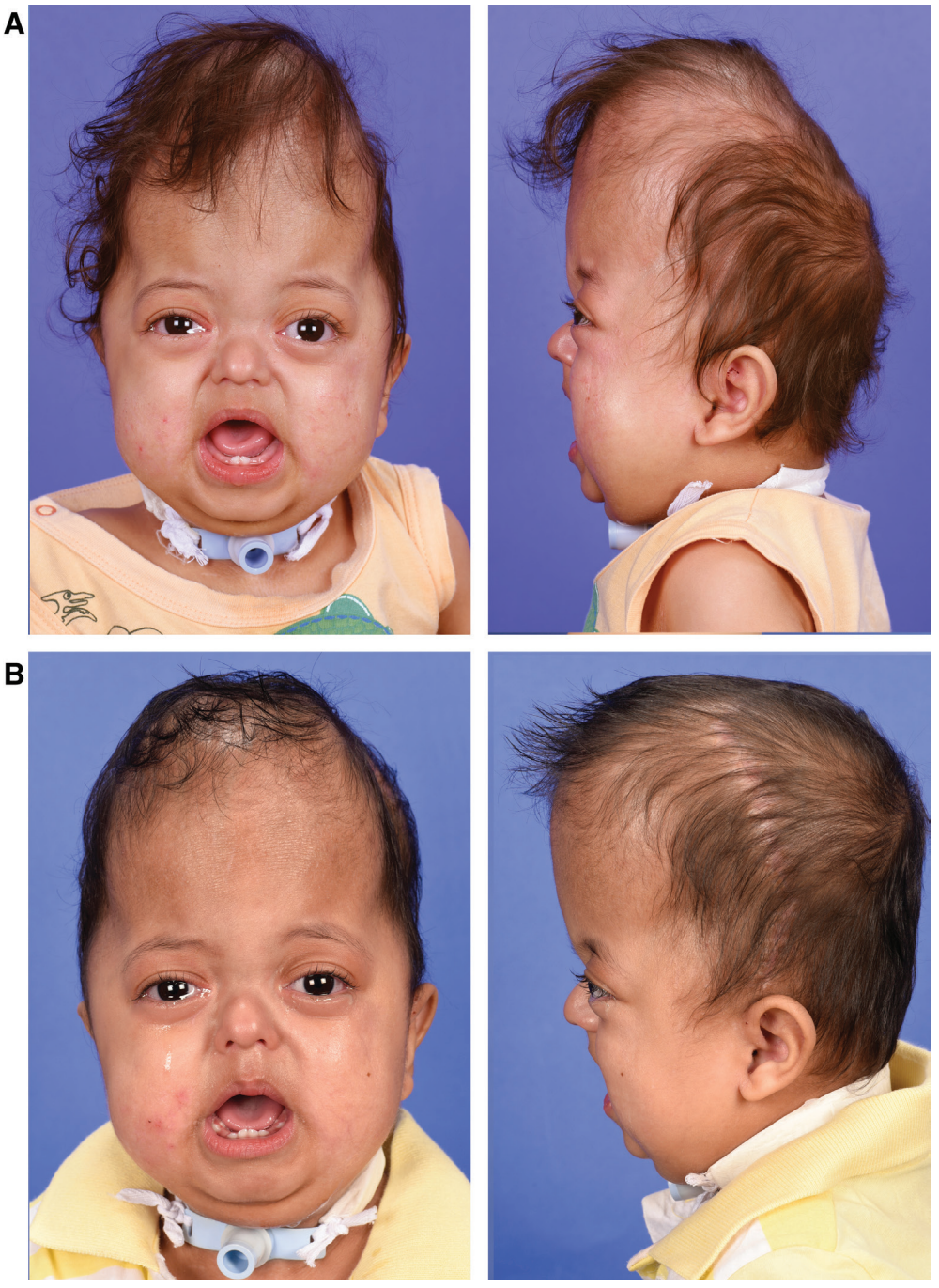

Fig. 2. A, Preoperative photographs (above) of a patient with severe Pfeiffer syndrome who subsequently underwent placement of a VP shunt due to hydrocephalus, followed by decompressive surgery at 2 years of age (patient 8 of Table 3). B, Postoperative photographs (below) of the same patient after removal of Swiss cheese type of bone formation from the mid and posterior cranial vault regions.

When a patient with PS reaches 7 years of age, our hospital performs a comprehensive assessment, which includes fundoscopy, an ophthalmologic examination for visual acuity, a sleep apnea screen, a nasal endoscopy, and a dental evaluation. We also provide both orthodontic and psychological treatments. Midface advancement is preferably performed at 9 years of age but can be performed earlier to remove an existing tracheostomy, which will result in significant breathing improvement. Monobloc advancement or subcranial Le Fort III is performed with distraction osteogenesis, depending on the projection of the forehead, presence of intracranial pressure, and the patient's overall condition.

Subsequent procedures to treat residual digit deviation, midface and nose deformities, and soft-tissue refinements are performed as needed, similar to our Apert syndrome treatment protocol[11–13] (Fig. 1).

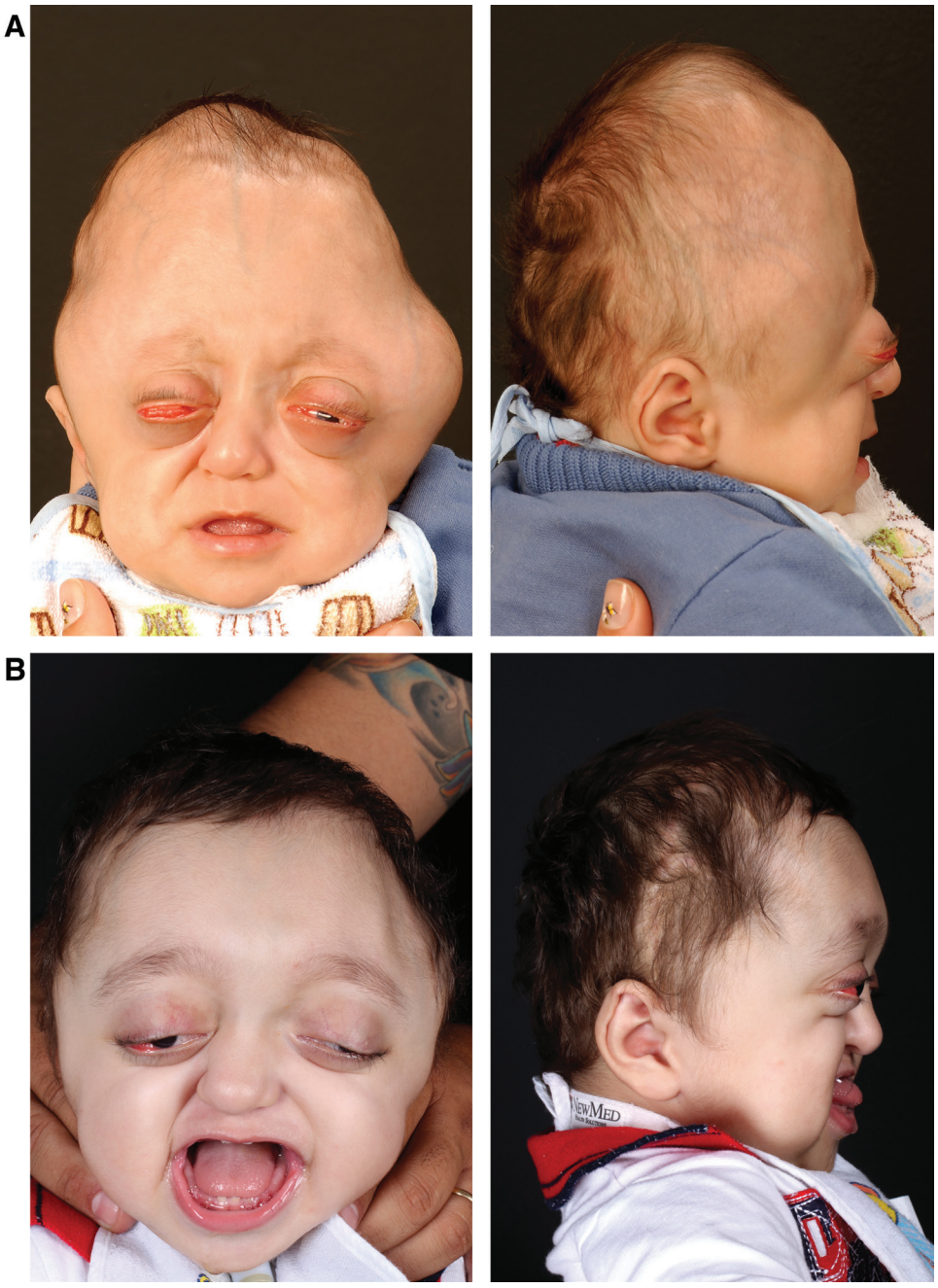

Fig. 3. A, Photographs of 5-month-old patient with PS after VP shunt placement, and after bilateral tarsorrhaphy due to eyeball luxation (above), which was more pronounced on the right side, causing a corneal ulcer (patient 11 of Table 3). B, Postoperative photographs of the same patient (below) after FOA advancement with distraction osteogenesis and partial release of the tarsorrhaphy, which was performed to preserve visual acuity. The corneal ulcer was completely resolved.

Justification for Modification of Pfeiffer Severity Scale

One of the most important features in the neurologic domain of the Pfeiffer severity scale is the presence of Swiss cheese type of bone formation caused by ICH. When this condition is present, PVDO cannot be performed, and decompressive surgeries may be necessary at an early age. In the presence of hydrocephalus, a VP shunt is necessary to alleviate intracranial pressure. Placement of a VP shunt results in improved bone quality, thickness, and distribution. Swiss cheese type of bone formation, characterized by bone thinning, precludes performing a PVDO and, therefore, receives the highest score in the modified neurologic domain of our proposed severity scale.

Statistical Analysis

For the descriptive analysis, the mean was used for metric variables, and percentages were given for categorical variables. The Fisher test was used to correlate the severity

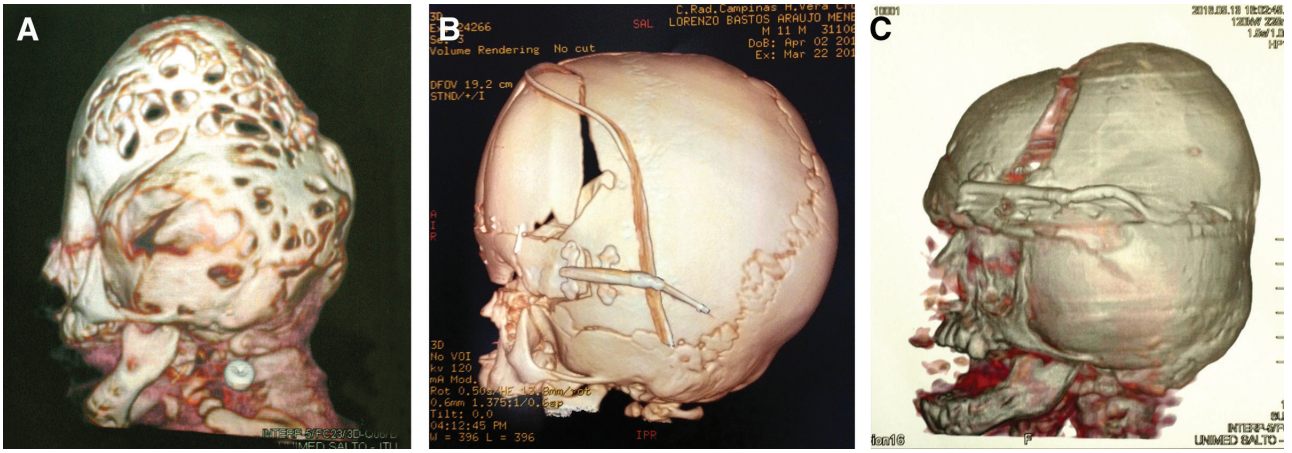

Fig. 4. A, Preoperative CT scan of the same patient shown in Figure 3 above. B, Postoperative CT scan after VP shunt placement before distractor activation after FOA. C, Postoperative CT scan at conclusion of consolidation period showing 20 mm advancement. CT indicates computerized tomography.

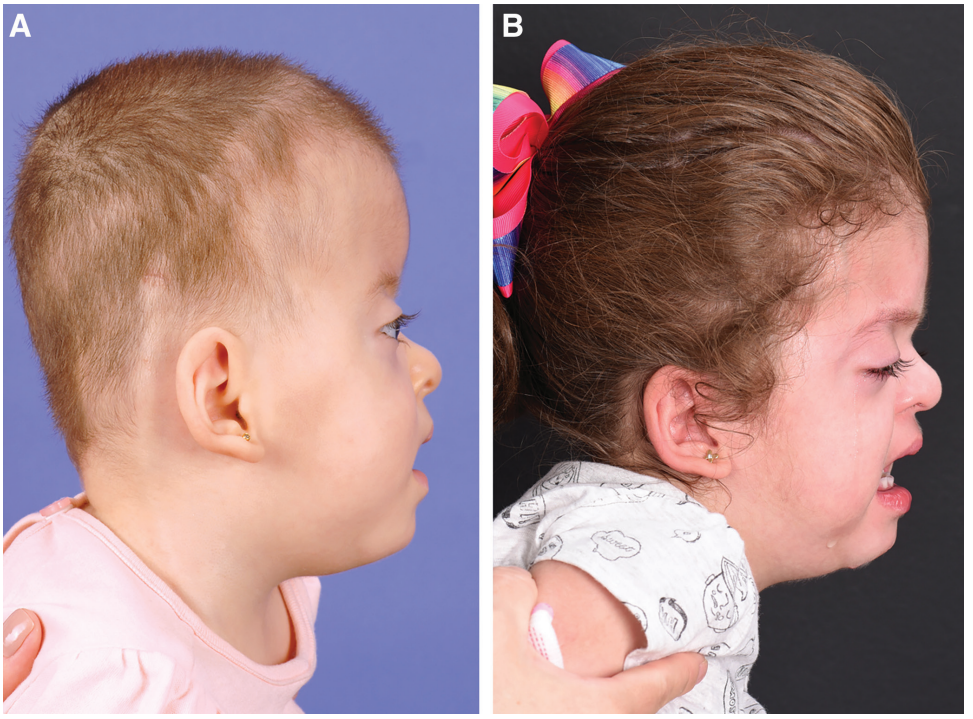

Fig. 5. A, Preoperative photograph of a severe 9-month-old patient with Pfeiffer syndrome after VP shunt placement before posterior vault distraction osteogenesis. B, Postoperative photograph following posterior cranial vault distraction osteogenesis.

of PS with tracheostomy placement. All analyses were performed using IBM SPSS Version 20.0 (IBM Corp., Armonk, NY). Values of $P \leq 0.05$ were deemed to be statistically significant.

RESULTS

The present study included 12 patients with PS (10 male and 2 female patients). There were 3 type A (mild) patients with PS, 6 type B patients with PS, and 3 type C patients with PS. Out of a total of 9 patients with severe PS in our group (types B and C), 6 of those patients presented compromised airways and received tracheostomies ($P < 0.05$) (Table 3).

There were 4 minor complications and 1 type I major complication. One patient with severe PS had a CSF leakage following a Le Fort III advancement, which was resolved by placement of an external lumbar shunt for 7 days (Table 4 and Figs. 2–7).

DISCUSSION

Because PS is a rare syndrome among patients with craniofacial dysostosis, comprehensive treatment requires an

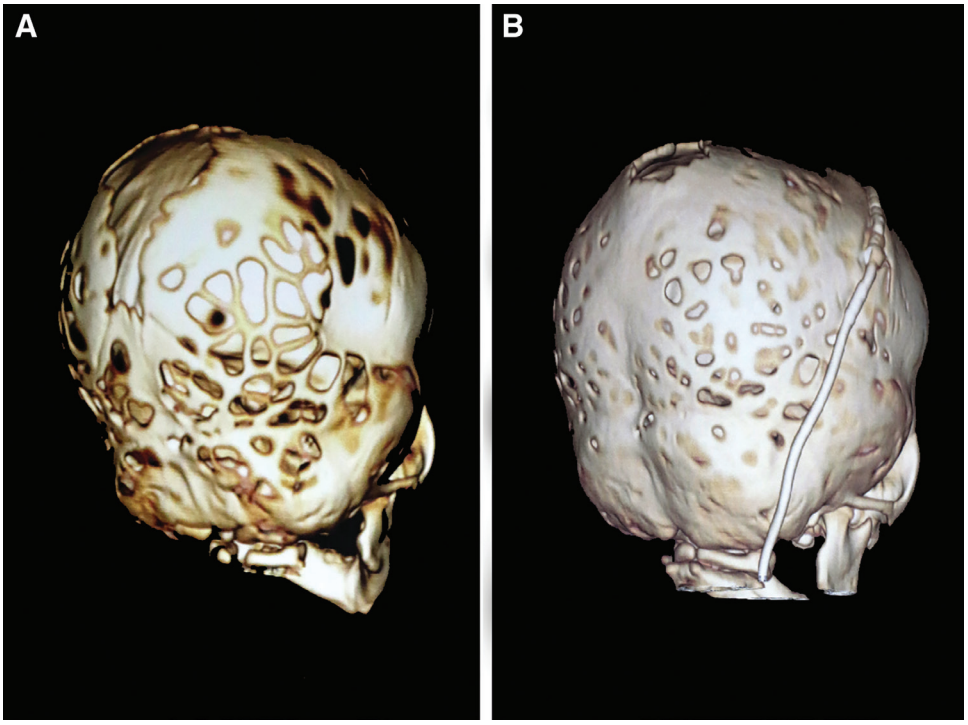

Fig. 6. A, Preoperative CT scan of the same patient shown in Figure 5 above. B, Postoperative CT scan after VP shunt placement before PVDO. CT indicates computerized tomography.

experienced multidisciplinary craniofacial team.[14–16] Even a busy craniofacial center might not have an opportunity to treat a large series of patients with PS.[6] Thus, it is important to collect data detailing treatment of PS.

Our data show that the majority (67%) of type B and C patients with PS required tracheostomies, and presented ICH, accompanied by a Swiss cheese type of bone formation in the entire posterior region, which represents a strong clinical correlation between these 3 variables. A total of 8% of these patients presented otologic problems. VP shunt placement was required in 33% of these patients, thereafter improving the ossification pattern in those patients with PS with hydrocephalus. Placing a VP shunt in these particular patients was challenging because of the unique combination of venous and CSF hypertension. Bleeding may occur during VP shunt placement due to the abrupt change in transmural pressure within the particularly fragile ventricular veins. When CSF pressure is rapidly reduced, intraluminal venous high pressure, however, remains unchanged. To prevent excessive bleeding, our protocol includes the use of programmable valves, initially set at high pressure (150 mm/Hg), which are then gradually reduced to lower pressure (120 mm/Hg).

Early cranial vault expansion is the first-line procedure used to treat patients with PS who have ICH accompanied by a Swiss cheese type of bone formation, as removal of the thin bone and its indentations alleviates ICH, and enables osteogenesis with improved bone quality. It is important to remove the midline posterior bone to avoid kinking of the sagittal sinus and preserve venous brain outflow.[17] In patients operated on at an early age, ossification occurs at a rapid rate, enabling us to perform a PVDO as a second operation. In the most severe cases, a second cranial vault expansion may be necessary before a PVDO can be performed.

Hydrocephalus also may occur after early cranial vault expansion, especially with those patients who experience severe multisuture fusion. Some of these patients may present normal or even small ventricles due to the magnitude of bony indentations and excess compression within the cranial vault. In these patients, the pressure caused by multisuture fusion and stenosis of the SSS is so high that the CEV cannot regress. Even after successful cranial vault decompression, venous hypertension may sometimes prevent sufficient CSF absorption, resulting in hydrocephalus which then requires placement of a VP shunt.

Although there is no consensus regarding the primary cause of hydrocephalus in patients with PS, venous hypertension, Chiari I malformation, and crowded posterior fossa are suspect, with venous hypertension being viewed as the main contributing factor. Both posterior fossa decompression and endoscopic third ventriculostomy have been used without success as potential treatments for hydrocephalus, with placement of a VP shunt being the procedure of choice.

PVDO has significantly changed the current treatment algorithms for PS because it results in a higher intracranial volume than the classic FOA formerly used to treat these patients.[18] However, PVDO is not indicated if there is bone thinning that jeopardizes distraction stability and footplate fixation or supratentorial CEV that may be responsible for brain venous outflow.

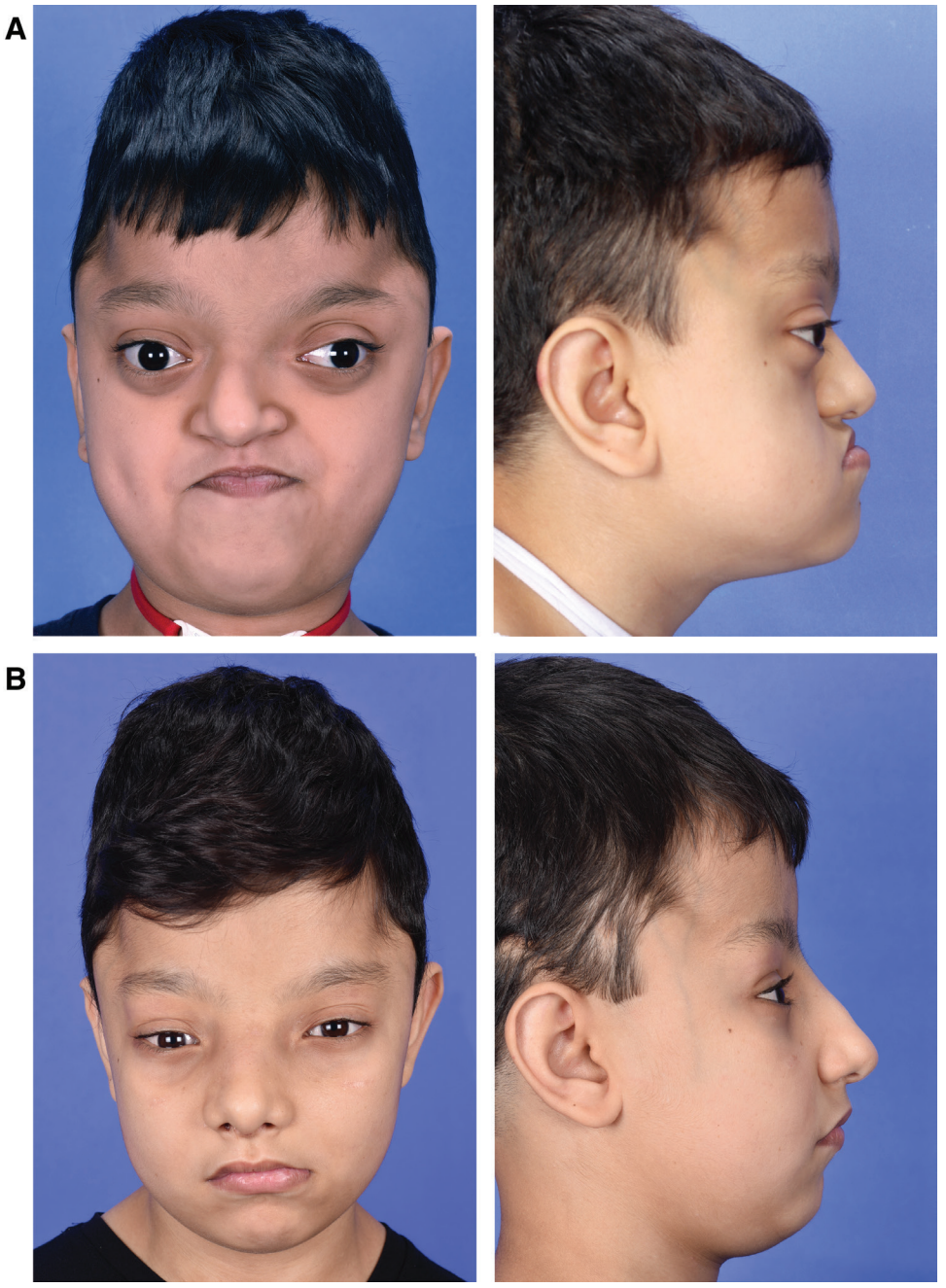

Fig. 7. A, Preoperative photographs of a 10-year-old patient with severe PS with tracheostomy (above; patient 3 of Table 3). B, Two-year postoperative photographs of the same patient following a Le Fort III advancement and tracheostomy removal (below).

PVDO is the first-line procedure used to treat type A patients with PS, as those patients have a posterior region with sufficient bone quality to enable fixation of the distractor footplates. This operation is usually performed at 6 months of age.

FOA with distraction osteogenesis is solely reserved for patients with supratentorial CEV. Distraction osteogenesis of the fronto-orbital region enables us to gain an average anterior length of 20 mm, with a lower relapse rate which follows immediate advancement as previously described for midface advancement.[19] Because patients with PS always present significant supraorbital bar retrusion, these patients usually benefit from major anterior advancement, which is difficult to achieve with immediate advancement using bone grafts. Our hospital no longer performs traditional FOA to treat patients with PS and instead uses distraction osteogenesis. For those patients with PS who have accompanying incomplete syndactylies, hand reconstruction is performed in stages that are similar to our algorithm for Apert hand reconstruction.

The complication rate for patients with PS significantly varies in the literature, and morbidity can reach

85%.[3,20,21] Some of these patients also present other systemic health issues, such as cardiologic diseases and gastroenterologic problems, which can contribute to the fatal course.[22]

Dural tearing may occur in patients with severe PS (types B and C). High intracranial pressure, bone thinning, and indentation may also contribute to tearing of the dura mater during bone harvesting and removal. It is important to harvest a periosteal flap that is sufficiently large so that it can be sutured to the dura mater. A CSF leakage was observed in one patient during Le Fort III advancement but was fully resolved by placement of an external lumbar shunt for 7 days.[23] Although various craniofacial surgical teams are not in agreement regarding the benefits of preoperative tracheostomy placement for the most severe Pfeiffer patients, we believe that tracheostomy placement for those patients can prevent serious postoperative complications such as pulmonary arrest and even death.

In the majority of these patients, the severity of the midface retrusion is responsible for compromised breathing. Although we do not advocate early midface advancement, performing an early tracheostomy is a life-saving procedure, which we do not view as a surgical failure. Staging early decompressive surgery results in reduced operating times, a lower complication rate, and paves the way for a subsequent PVDO. For reasons of patient safety, we are hesitant to perform procedures that involve the posterior region, if supratentorial CEVs are present. It is nevertheless possible to perform a PVDO in the presence of supratentorial CEV, after confirmation that these specific veins are not directly responsible for venous brain outflow.

Our study is limited by the small sample size and represents the combined experience of one craniofacial plastic surgeon (C.E.R.-A.) and a neurosurgeon (E.G.), who worked in tandem for almost a decade. That being said, our study represents an attempt to create a specific algorithm for PS management and treatment based on a validated severity scale, which may ultimately guide craniofacial surgeons in addressing the various phenotypes among patients with PS.

CONCLUSIONS

An algorithm was proposed to guide therapeutic planning and surgical approach. Severity of PS statistically correlates with tracheostomy placement.

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