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Literature review

Surgical treatment of congenital pseudarthrosis of the forearm: Review and quantitative analysis of individual patient data

Traitement chirurgical de la pseudarthrose congénitale de l'avant-bras : revue de la littérature et méta-analyse

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ABSTRACT

There is little scientific evidence on the best surgical treatment for congenital pseudarthrosis of the forearm due to the rarity of this condition (less than 100 cases described in the literature) and the lack of comparative studies. Our aim was to provide evidence in favor of a certain surgical technique. A comprehensive review of the literature was performed using case series and case reports. The statistical analysis was based on individual patient data to mimic a case-control study. A multiple logistic regression was used to assess the effect of each independent variable (neurofibromatosis status, location of the pseudarthrosis, age at first surgery and type of treatment) on bone union at last follow-up (yes/no). The database searches yielded 1112 articles; 55 articles were selected, reporting on 94 cases. Seventy patients had healed completely at the last follow-up (74%). Neither the age at surgery nor the location of the pseudarthrosis was related to union ($P > 0.7$). The patients' neurofibromatosis type 1 status was weakly related to healing ($P = 0.06$). Vascularized fibula transfer had a higher rate of healing (100%) than did non-vascularized bone graft (70%) (P =$0.002).
Level of evidence: 4 (case-control study of data from case series and case reports).

Mots clés :
Pseudarthrose congénitale de l'avant-bras
Consolidation
Greffe osseuse
Fibula vascularisée
Chirurgie
Neurofibromatose de type 1

RÉSUMÉ

Le niveau de preuve sur le type de traitement chirurgical de la pseudarthrose congénitale de l'avant-bras est très faible en raison de la rareté de cette affection (moins de 100 cas rapportés) et du manque d'études comparatives. Notre objectif était de fournir des preuves en faveur d'une technique chirurgicale et d'explorer les facteurs corrélés avec la consolidation. Nous avons réalisé une revue systématique de la littérature et analysé les données de chaque sujet incluant tous les sujets disponibles à partir des séries et des cas cliniques publiés. Une régression logistique multiple a été utilisée pour évaluer l'effet des variables indépendantes (présence de neurofibromatose, localisation de la pseudarthrose, âge à la chirurgie et type de traitement) sur la consolidation osseuse au recul (oui/non). Des 1112 articles trouvés, 55 ont été sélectionnés, rapportant 94 cas. Soixante-dix patients sur 94 avaient complètement consolidé au dernier recul (74 %). Ni l'âge lors de la chirurgie ni la localisation de la pseudarthrose n'étaient liés à la consolidation ($p > 0,7$) ; le statut NF1 (neurofibromatose type 1) était faiblement lié à la consolidation ($p = 0,06$). Le taux de consolidation était de 100 % pour le transfert vascularisé de fibula, 70 % pour la greffe osseuse non vascularisée ($p = 0,002$). Le transfert vascularisé de fibula a montré le taux de consolidation le plus élevé.
Niveau de preuve. – 4 (étude cas-témoins à partir de données de séries de cas et de rapports de cas).

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1. Introduction

Congenital pseudarthrosis of the forearm (CPF) is a very rare condition (Figs. 1 and 2), with less than 100 cases reported between 1968 and 2018. It is often associated with neurofibromatosis type 1 (NF1) or Von Recklinghausen disease 1. The latter is a genetic disease with frequent skeletal involvement. Pseudarthrosis can affect the ulna, radius, or both. As in the leg, seemingly healthy bones can become secondarily dystrophic after simple trauma and result in so-called congenital pseudarthrosis [1,2]. In the absence of treatment, pseudarthrosis evolves into a progressive deformity of the forearm due to asymmetrical bone lengths [1–3]. The end result is very often a short forearm associated with radial or ulnar deviation of the hand and reduced mobility [1–3].

Conservative treatments, such as casting or physical therapy, have rarely resulted in bone healing. A surgical procedure is often preferred; however, this is a challenging treatment with a significant proportion of failures and/or multiple procedures [1–3]. Various techniques have been described, with the most prevalent being vascularized fibula transfer (VFT) and non-vascularized bone graft with internal fixation. In the literature, there is little consensus and little evidence in favor of a certain type of surgical treatment because the rarity of this condition makes it very difficult to perform comparative studies. Indeed, publications about this subject are rare and often limited to the description of one or more cases.

Two important ingredients of a successful treatment of congenital pseudarthrosis are how early the first intervention is performed [2] and the absence of NF1 [1,3]. The association of CPF with NF1 seems to be a hindrance for obtaining union with a conventional graft, with a 73% failure rate according to Bell [3] and 44% according to Kohler et al. [1]. In the absence of NF1, results appear much better, with a 45% failure rate according to Bell [3] and 0% according to Kohler et al. [1]. While a VFT seems to provide good results, the procedure takes longer and is technically more demanding than a conventional graft because of microsurgical anastomoses [4].

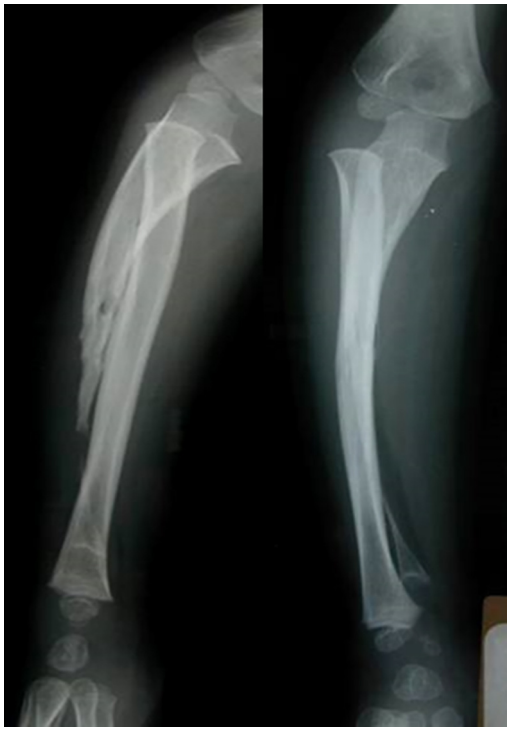

Fig. 1. Example of congenital pseudarthrosis of ulna (personal case) before surgery.

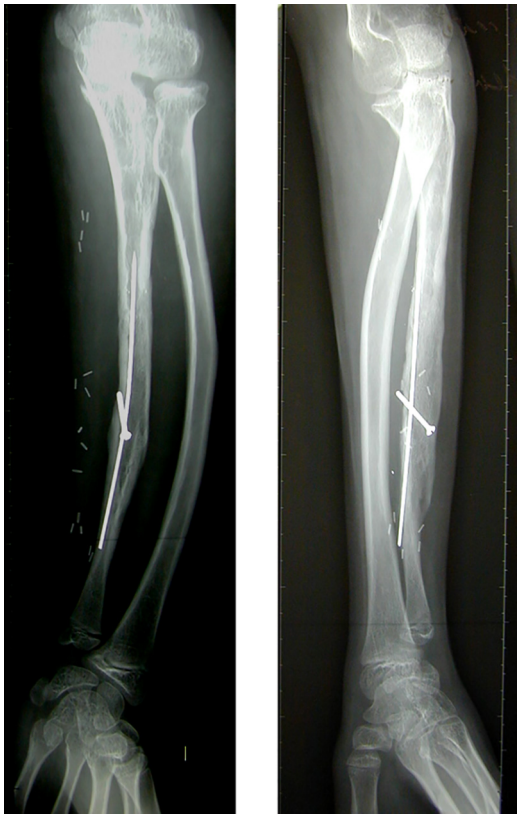

Fig. 2. The same patient after multiple bone grafts.

We conducted a systematic review of the literature with a statistical analysis based on individual patient data to provide evidence in favor of a certain surgical technique and to explore the factors correlated with healing.

2. Methods

We sought to do a "meta-type" analysis of each patient's individual data (characteristics of each case retrieved) in order to collect and analyze the largest possible number of subjects. This review was registered on the PROSPERO website https://www.crd.york.ac.uk/PROSPERO/ as number CRD42018106025. This report was prepared according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5] as suggested by the Enhancing the Quality and Transparency Of health Research (EQUATOR) network (supplementary file). As this is a systematic review, ethics committee approval was not required.

2.1. Eligibility criteria

We included case series and case reports involving patients with CPF written in English, French, Spanish, Italian, or Portuguese. All other types of documents were not retained, i.e. surgical techniques, letters to the editor, or instructional lectures. Articles were further screened for interventions and were included if they clearly reported the type of the treatment and the outcome at last follow-up.

2.2. Search strategy

We searched the EMBASE, MEDLINE/PubMed, Science Direct, Scopus, and Web of Knowledge electronic databases from 1968 until April 30, 2018 with following keywords.

Table 1
Individual patient data.

First author	Number of cases	Location	NF 1	Treatment	Bone union
Ali & Hooper [7]	2	U	Yes	Bone graft	No
		U	No	Conservative (radius osteotomy)	No
Allende & Masquijo [8]	1	R+U	Yes	One bone forearm, bone graft[a]	Yes
Allieu et al. [9]	2	R+U	Yes	Fixation, then vascularized fibula	Yes
		U	Yes	Vascularized fibula	Yes
Allieu et al. [10]	1	R+U	No	Graft × 2, then vascularized fibula[a]	Yes
Atar et al. [11]	1	R	No	Ilizarov	Yes
Bae et al. [12]	4	U	Yes	Vascularized fibula	Yes
		U	Yes	Vascularized fibula	Yes
		U	Yes	Vascularized fibula	Yes
		U	No	Bone graft, then vascularized fibula	Yes
Bauer et al. [13]	4	U	Yes	Vascularized fibula + 2 bone grafts	Yes
		U	Yes	Vascularized fibula	Yes
		U	Yes	Vascularized fibula	Yes
		U	No	Vascularized fibula	Yes
Baldwin & Weiner [14]	1	U	No	Osteotomy (other)	No
Bayne [15]	4	U	Yes	Bone graft	Yes
		R	Yes	Fixation (other)[a]	No
		R+U	Yes	Bone graft	No
		R+U	No	Conservative	No
Bell [3]	6	U	No	Conservative	No
		U	Yes	Osteotomy and one bone forearm	Yes
		U	No	Bone graft × 2	Yes
		R+U	Yes	Vascularized fibula	Yes
		R	No	Graft × 5 then vascularized fibula	Yes
		U	Yes	Bone graft × 2	No
Beris et al. [16]	1	R	Yes	Distraction then vascularized fibula	Yes
Brown et al. [17]	1	R	Yes	Bone graft	No
Charles et al. [18]	2	R+U	?	Vascularized fibula	Yes
		u	Yes	Conservative	No
Cheng et al. [19]	2	U	No	Bone graft	Yes
		U	No	Vascularized fibula	Yes
Cleveland et al. [20]	5	R	No	Bone graft	Yes
		R	Yes	Bone graft	Yes
		R	Yes	Bone graft × 6	No
		R	Yes	Conservative	No
		R	No	Bone graft	Yes
Cobb [21]	1	R+U	Yes	Bone graft	No
Craigen & Clarke [22]	2	U	Yes	Conservative	No
		U	Yes	Conservative	No
Ding et al. [23]	1	R	Yes	Bone graft, then vascularized fibula	Yes
Durga Nagaraju et al. [24]	1	R	Yes	Bone graft	Yes
El Hage et al. [25]	2	U	Yes	Vascularized fibula	Yes
		U	Yes	Vascularized fibula	Yes
Fabry et al. [26]	1	U	Yes	Ilizarov [other]	Yes
Greenberg & Schwartz [27]	1	R	No	CONSERVATIVE	Yes
Gregg et al. [28]	1	R	Yes	Osteotomy [other]	No
Hadlow [29]	1	R+U	No	Bone graft[a]	Yes
Herring & Roach [30]	1	R+U	No	Bone graft	Yes
Kaempffe & Gillespie [2]	1	R	Yes	Bone graft	Yes
Kaneyama & Ogawa [31]	1	R	Yes	Bone graft	Yes
Kohler et al. [1]	1	U	Yes	Bone graft	Yes
Lee et al. [32]	1	u	?	Vascularized fibula	Yes
Lloyd-R [33]	1	U	Yes	Bone graft	Yes
Maffulli & Fixsen [34]	4	U	Yes	Bone graft, 1 bone forearm[a]	Yes
		U	Yes	Bone graft	Yes
		U	Yes	Bone graft	Yes
		U	Yes	Conservative	No
Manske [35]	1	R	Yes	Bone graft	Yes
Masihuz-Zaman [36]	1	R	Yes	Bone graft × 4	No
Masterson et al. [37]	1	U	Yes	Vascularized fibula	Yes
Mathoulin et al. [38]	6	R+U	No	Vascularized fibula	Yes
		U	Yes	Vascularized fibula	Yes
		R	Yes	Vascularized fibula	Yes
		R+U	Yes	Vascularized fibula[a]	Yes
		R+U	Yes	Vascularized fibula	Yes
		R+U	Yes	Vascularized fibula[a]	Yes
Mollan & Baird [39]	1	R	Yes	Bone graft × 6	No
Moore [40]	1	U	Yes	Bone graft	Yes
Mukhopadhaya et al. [41]	1	R	Yes	Bone graft	Yes
Ostrowski et al. [42]	2	U	Yes	Bone graft[a]	Yes
		U	Yes	Bone graft[a]	Yes
Rajaratnam et al. [43]	1	U	Yes	Bone graft	No
Ramelli et al. [44]	2	R+U	Yes	Vascularized fibula	Yes
		R+U	Yes	External fixator	Yes
Richin et al. [45]	1	R+U	Yes	Conservative	No

Table 1 (*Continued*)

First author	Number of cases	Location	NF 1	Treatment	Bone union
Sellers et al. [46]	1	R+U	No	Vascularized fibula	Yes
Shertzer et al. [47]	2	U	Yes	Bone graft	Yes
		U	Yes	Bone graft	Yes
Sprague & Brown [48]	1	R	Yes	Conservative	No
Suzuki et al. [49]	3	U	?	Vascularized fibula, Ilizarov	Yes
		U	?	Vascularized fibula	Yes
		U	?	Vascularized fibula	Yes
Talab [50]	1	R	No	Bone graft	Yes
Tosun et al. [51]	1	R	?	Osteotomy, 1 bone forearm,	Yes
Valente et al. [52]	1	R	Yes	Bone graft	Yes
Vandergugten et al. [53]	1	R+U	Yes	Ilizarov, then bone graft	Yes
Williamson et al. [54]	1	R	Yes	Bone graft then vascularized fibula	Yes
Witoonchart et al. [55]	3	U	No	Vascularized fibula	Yes
		R	Yes	Vascularized fibula	Yes
		U	Yes	Vascularized fibula	Yes
Wolfe et al. [56]	1	R	?	Ulnar resection	No
Yoshimura et al. [57]	1	R	?	Vascularized fibula	Yes
Younge & Arford [58]	1	U	No	Internal fixation (other)	No
Total	94		64 yes		70 yes
			22 no		24 no

NF1: neurofibromatosis type 1; R: radius; U: ulna.
[a] Indicates one-bone forearm.

"congenital" + "pseudarthrosis" + "forearm" / "ulna" / "radius". To be comprehensive, bibliographies of relevant reviews and selected studies were examined. We repeated our search on February 28, 2019 to ensure we had not missed any recent publications. Study selection was performed in two stages by paired reviewers (first and second authors), screening articles independently and in duplicate. Titles and abstracts were screened in the first stage, followed by full text screening of potentially eligible citations.

2.3. Data collection process

The same-paired reviewers extracted the data independently and in duplicate using electronic data extraction forms. Disagreements were resolved by consensus or through discussion with a third investigator (last author). The selection of the articles is summarized in the PRISMA diagram (Table 1).

2.4. Variates

The main endpoint was bone healing (yes/no) at last X-rays. The secondary endpoint was bone healing after the first procedure (yes/no).

The independent variables were the NF1 status (yes/no), location of pseudarthrosis (ulna, radius, or both), age at first surgery, sex, and type of surgical technique, which we grouped into five categories: "vascularized fibula transfer", "bone graft", "conservative" (non-surgical or surgical not related to pseudarthrosis, e.g. ulnar resection), "external fixation" and "other surgical treatment"; the latter include all other surgeries without bone graft or external fixation (osteotomies, internal fixation, etc.). Demographic data and histology were also collected, when available.

2.5. Analysis

We sought to determine whether one treatment was more effective than another, and to assess whether the NF1 status, pseudarthrosis location and demographic data influenced bone healing. The statistical analysis was performed with XLSTAT software through Fisher's exact tests or Student's *t*-test initially. A multivariate regression analysis was performed with NF1 status, treatment type and age at first surgery as independent variables and healing (yes/no) as the response variable. The results of the multiple regression models are presented with odds ratio (OR), 95% confidence interval (95%CI) [6] and p-value.

3. Results

The database searches yielded 1112 articles; after deleting duplicates, we retained 545 articles; after manually adding references, there were 559 articles. Five hundred and two abstracts did not meet the inclusion criteria, so 57 titles were selected for full reading. After a thorough reading, 3 others were excluded. In total, our study included 54 articles, reporting on 94 cases (Fig. 3 and Table 1) [1–3,7–58]. Out of 94 patients, 70 had completely healed at last follow-up (74%). The individual patients' data are summarized in Tables 1 and 2.

3.1. Univariate results

The type of treatment was related to healing (P = E-8 = 10^{-8}), with 0% for conservative treatment, 70% for bone graft, 100% for VFT, 100% for external fixation and 0% for other surgical procedures (Table 3). When synostosis was excluded, the healing was higher for VFT than for bone graft (P = 0.0004, OR = infinite). The patients' NF1 status was weakly related to healing (Table 4, P = 0.26). There were 7 patients with insufficient data. The location of the lesion was not significantly associated with healing (Table 5, P = 0.81). There were no missing data.

Mean age at surgery was similar between patients with healed bones and those without (5.7 years vs 6.2, P = 0.7) and between patients operated on with conventional graft and VFT (6.2 years vs 6.11, P = 0.9); 18 patients had missing or imprecise data. Mean follow-up was similar between patients operated on with conventional graft and VFT (4.4 years vs 4.8, P = 0.7); 30 patients had missing or imprecise data. Male sex was weakly related to healing (33 boys and 23 girls healed, 6 boys and 10 girls did not, P = 0.22); 21 patients had missing data.

3.2. Subgroup analysis based on NF1 status

Out of 64 patients with NF1, 46 healed: 15 with bone graft, 3 with external fixation, 21 with VFT, 7 with synostosis. The other 18 did not heal: 9 after bone graft, 1 after synostosis (without

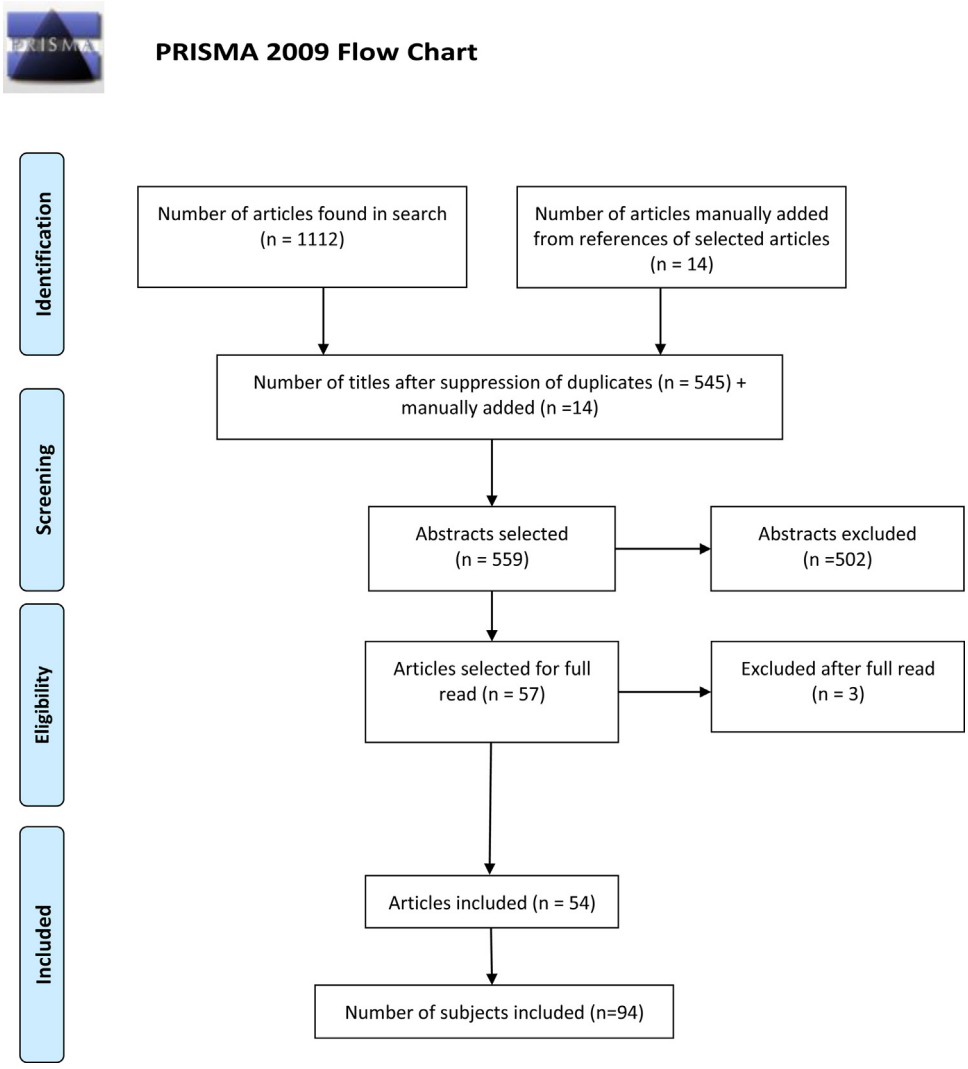

Fig. 3. PRISMA flow chart.

graft), 1 with osteotomy, and 7 with conservative treatment. In the NF1 subgroup, the healing rate was higher after VFT than after bone grafting (21/21 vs 15/24, $P = 0.004$).

Out of 22 patients without NF1, 17 healed: 6 after bone graft, 7 after VFT, 2 after synostosis, 1 with conservative treatment, 1 with Ilizarov. The other 5 did not heal: 3 after conservative treatment, 2 after internal fixation. The healing rate at last follow-up was 100% for both bone graft and VFT. However, 3 patients required VFT after failure of bone grafting.

Out of 8 patients with unknown NF1 status, 7 healed (6 after VFT, one after synostosis) and one did not heal after simple ulnar resection.

3.3. Multivariate analysis

We built a multivariate model mimicking a case-control study (Table 6). The multivariate regression achieved a coefficient of determination (R^2) of 0.623 [6]; it found a tendency for a negative influence of NF1 ($P = 0.06$); the type of treatment was significant ($P < 0.001$), with OR = 20.8 for bone graft and OR = 511 for VFT versus conservative treatment. The proportion of patients whose bone healed with VFT was higher than that of patients whose bone healed with bone graft: OR = 25.7, 95% CI = [1.42; 466], $P = 0.002$ (Tables 3 and 6).

3.4. Secondary outcomes

The proportion of patients whose bone healed after the first procedure was higher for VFT than for bone graft (32/35 vs 15/30, OR = 10.2, 95% CI: 2.4; 63.6, $P = 0.001$).

3.5. Histology

Histology was available for 16 patients, showing evidence of neurofibromatosis in 4 cases, fibrous or fibrocartilaginous pseudarthrosis in 8 patients, and uncertain diagnosis in 2 (Table 2).

4. Discussion

Surgical treatments for CPF mainly consists of bone grafts and VFT. The latter technique was first described for this indication in 1981 by Allieu et al. [8] and it has been increasingly used since, to the point where it is now the most common. The most recently published case reports only used this technique [23]. Publications about external fixation (e.g. Ilizarov technique) stopped in 2001 [9]; one-bone forearm was frequent before 1990 and is currently still reported in national journals [8,52], but rarely in the international literature.

Our statistical analysis strongly suggest that 1) the type of treatment influences healing, and 2) VFT provides more reliable

Table 2
Individual patient demographic data.

First author	Number of cases	Sex	Age at first surgery (or diagnosis in case of conservative treatment)	Follow-up	Histology
Ali & Hooper [7]	2	M	5 years	20 years	Fibrous
		F	Young adult	9 months	No
Allende & Masquijo [8]	1	F	8 years	4 years	No
Allieu et al. [9]	2	?	5 years	17 years	Fibrous or neurofibroma?
		?	4 years	3 months	?
Allieu et al. [10]	1	M	17 years	13 years	No
Atar et al. [11]	1	?	6 years		No
Bae et al. [12]	4	2 M+2 F	3 years	7 years	No
			5 years	3 years	
			16 years	4 years	
			15 years	7 years	
Bauer et al. [13]	4	4 M	9 years	>2 years	
			3 years		
			12 years		No
			7 years		
Baldwin & Weiner [14]	1	?			
Bayne [15]	4	?			
		?			
		?			
		?			
Bell [3]	6	F	6 years	7 years	No
		M	2 years	3 years	No
		M	10 years	6 months	No
		M	3 years	6 months	No
		M	5 years	6 years	No
		F	9 years	4 years	No
Beris et al. [16]	1	M	9 years	10 years	No
Brown et al. [17]	1	?			
Charles et al. [18]	2	F	4 years		No
		F	12 years	7 years	No
Cheng et al. [19]	2	M	4 years	6	No
		F	1 years	8 months	No
Cleveland et al. [20]	5	M	1 years?	7 years	Fibrous
		F	9 years	16 months	Neurofibromatosis
		F	9 years	2 years?	Neurofibromatosis
		F	1 years?		Neurofibromatosis
		M	5 years		Fibrous
Cobb [21]	1	?			
Craigen & Clarke [22]	2	F	1 years	2 years	No
		F	9 years	20 years?	No
Ding et al. [23]	1	M	7 years	18 months	No
Durga Nagaraju et al. [24]	1	M	7 years	2 years	No
El Hage et al. [25]	2	F	18 months	4 years	No
		F	10 years	3 years?	Fibrous
Fabry et al. [26]	1	M	9 years	4 months	No
Greenberg & Schwartz [27]	1	M	Birth	3 months	No
Gregg et al. [28]	1	M	7 years	16 months	Fibrous
Hadlow [29]	1	M	2 years	7 years	Fetal mesenchyme (fibrous)
Herring & Roach [30]	1	M	3 years		
Kaempffe & Gillespie [2]	1	F	9 years		
Kaneyama & Ogawa [31]	1	M	11 years	4 years	
Kohler et al. [1]	1	F	5 years	10 years	Fibrous
Lee et al. [32]	1	M	7 years	1 years	Fibrous and cartilaginous
Lloyd-R [33]	1	?			
Maffulli & Fixsen [34]	4	F	3 years	1 years	
		F	9 years	1 years	
		M	6 years	1 years	
		F	10 years	1 years	
Manske [35]	1	?			
Masihuz-Zaman [36]	1	F	3 years		
Masterson et al. [37]	1	F	5 years	9 months	Fibrous?
Mathoulin et al. [38]	6	M	1 years	11 years	
		M	3 years	12 years	
		F	13 years	18 months	
		F	11 years	2 years	
		M	7 years	6 years	
		M	9 years	2 years	
Mollan & Baird [39]	1	M	2 years		
Moore [40]	1	?			
Mukhopadhaya et al. [41]	1	F	9 years	17months	
Ostrowski et al. [42]	2	?			
		?			
Rajaratnam et al. [43]	1	M	6 years	1 years?	Fibrous
Ramelli et al. [44]	2	F	3 years	1 years?	
		?	10 years	1 years?	

Table 2 (*Continued*)

First author	Number of cases	Sex	Age at first surgery (or diagnosis in case of conservative treatment)	Follow-up	Histology
Richin et al. [45]	1	M	Birth	5 years	
Sellers et al. [46]	1	?			
Shertzer et al. [47]	2	?			
		?			
Sprague & Brown [48]	1	M			
Suzuki et al. [49]	3	M	3 years	7 years	
		F	2 years	8 years	
		M	18 months	5 years	
Talab [50]	1	F			
Tosun et al. [51]	1	M	7 years		
Valente et al. [52]	1	M		2 years	
Vandergugten et al. [53]	1	F	8 years	6 months	
Williamson et al. [54]	1	F	6 years	3 years	Neurofibromatosis
Witoonchart et al. [55]	3	M	2 years	4 years	
		F	3 years	3 years	
		F	5 years	3 years	
Wolfe et al. [56]	1	F	20 years	12 years	
Yoshimura et al. [57]	1	?	2 years	5 years	
Younge & Arford [58]	1	?			

M: male; F: female.

Table 3
Contingency table for type of treatment/healing.

		Treatment					
		VFT	Graft	Ilizarov	Other	Conservative	Total
Healing	Yes	37	26	4	2	1	70
	No	0	9	0	4	11	24
	Total	37	35	4	6	12	94

Fisher's Exact test on healing (yes/no) vs type of treatment; $P = 4 \times e{-}11$. VFT: vascularized fibula transfer.

Table 4
Contingency table for neurofibromatosis type 1/healing.

Outcome		NF1 (neurofibromatosis type 1)			Total
		NF1+	NF1−	Unknown	
Healing	Yes	46	18	8	72
	No	18	5	0	23
	Total	64	23	8	95

Fisher's Exact test on healing (yes/no) vs NF1 (yes/no); $P = 0.25$.

Table 5
Contingency table for location of the pseudarthrosis/healing.

Outcome		Location			Total
		Ulna	Radius	Both	
Healing	Yes	31	17	13	61
	No	10	8	4	22
	Total	41	25	17	83

Fisher's Exact test on healing (yes/no) vs location; $P = 0.80$.

bone union than does conventional bone graft. Moreover, the proportion of patients whose bone healed after the first procedure was higher for VFT, which supports the current trend in the literature. Indeed, if we consider each patient's treatment history, VFT did not result in any failures at last follow-up. In our opinion, wide bone resection and stable fixation are the keys to successful healing after either vascularized or simple bone graft.

The other surgical techniques (Ilizarov, resection, etc.) were not analyzed in detail because there were very few available cases. However, the four cases treated with external fixation healed; conversely, the only cases of failure after surgical treatment in the subgroup without NF1 were after internal fixation without bone graft. Synostosis was excluded from the univariate analysis because it results in a one-bone forearm with fixed pronation–supination. Therefore, we consider this technique as a salvage procedure in case of revision surgery or when it is impossible to perform a more conservative (but more complex) surgery, e.g. VFT or Ilizarov.

There is a trend in the literature for congenital pseudarthrosis of the tibia—a very similar condition—towards using the induced membrane technique, also known as Masquelet's procedure, a two-step reconstruction that uses a cement spacer to induce a reactive membrane [4]. The latter is filled with autologous bone in a second surgical procedure. This technique has also been used successfully for CPF treatment in scientific conferences, although it has not been published (personal communications from C. Romana and A. Fassier).

The results of our multivariate analysis suggest a weakly significant NF1 association with CPF bone union, thus putting the previous literature into perspective [1,3]. However, the subgroup analysis suggests that a simple bone graft can achieve healing in cases not related to NF1.

The analysis of the impact of age and sex was incomplete since there were some missing data; however, our results suggest that

Table 6
Multivariate regression analysis.

Variable	Coefficient	Standard error	*P*-value	Coefficient 95% confidence interval	
Constant	0.953	0.065	< 0.0001	0.822	1.085
NF1 (No vs Yes)	0.194	0.102	0.064	−0.012	0.399
Treatment : bone graft vs vascularized fibula	−0.295	0.090	0.002	−0.476	−0.113
Sex	0.000	0.000			

$R^2 = 0.62$; Hosmer-Lemeshow; *P*-value = 0.92. NF1: neurofibromatosis type 1.

early age was not related to healing (P = 0.7) and male sex was weakly related to healing (P = 0.2).

Our study has numerous shortcomings: the analysis is based solely on studies with low levels of evidence with very small sample sizes, almost all being case-reports; therefore, multiple surgeons and hospitals were involved in the treatment, and the techniques were not exactly the same; e.g. we grouped under the category "graft" all the treatments combining an autologous bone graft with various types of fixation. Moreover, we did not analyze the patients' functional status or quality of life because there was no standardized outcomes in the articles. Furthermore, there is probably a publication bias since failures are more rarely published than successes. In addition, it was impossible to preserve the clustering of subjects within centers due to the very low number of subjects in each article.

However, in the case of such a rare condition, comparative studies are not reported, and a randomized clinical trial is not possible; therefore, a quantitative analysis mimicking a case-control study seemed to be the only way to gather a larger sample size and to answer essential questions about the management of these patients. Moreover, statistical analyses based on individual patient data with binary outcomes are currently considered the gold standard for meta-analyses and are becoming increasingly common [59]. The use of multiple logistic regressions is common and useful in this framework [59], as it is in ordinary case-control studies [60].

We did not call our study a meta-analysis because it is mostly used for analyses of randomized studies. However, it could be used *strictly speaking* for this study because we performed an analysis of combined data from multiple articles.

5. Conclusion

VFT is effective for treating CPF, providing a high rate of healing and a limited risk of revision surgery. A conventional bone graft is an acceptable option as the first procedure in absence of NF1. The Ilizarov technique seems effective but there are few cases reported. The radioulnar synostosis procedure results in a high healing rate but limits forearm function.

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Disclosure of interest

The authors declare that they have no competing interest.

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