Abstract

Background:

A congenital forearm pseudarthrosis is a rare condition and is strongly associated to neurofibromatosis type 1. Several surgical techniques are described in literature, but the most optimal treatment strategy remains unclear. This systematic review aims to develop a treatment algorithm that may aid in clinical decision making.

Methods: The PROSPERO registration number for this study was CRD42018099602 and adheres to the PRISMA guidelines for systematic reviews. Embase, MEDLINE, Cochrane Central, Web of Science and Google Scholar databases were searched for published studies reporting on congenital forearm pseudarthrosis not related to other underlying pathology like bacterial infection or fibrous dysplasia. Results were not restricted by date or study type, only English literature was allowed. Studies were assessed for quality using the critical appraisal checklist for case reports from the Joanna Briggs Institute. Patient characteristics, underlying disease, type of surgery, union rate and functional outcome were extracted from included studies.

Results: Of 829 studies identified, 47 were included in this review (17 case series and 30 case reports, total of 84 cases). A one-bone-forearm (OBF) procedure showed highest union rates (92%), however it results in loss of forearm rotation. Free vascularized fibula grafting (FVFG) showed high union rates (87%) and was related to good functional outcome of elbow flexion and forearm rotations. Other procedures showed disappointing outcomes.

Conclusions: Congenital forearm pseudarthrosis is best treated with a FVFG, a OBF procedure should be used as a salvage procedure. Evidence extracted from the case reports was sufficient to generate a treatment algorithm to be used in clinical pediatric practice.

Level of Evidence: Therapeutic Level IV.

Introduction

Congenital forearm pseudarthrosis is a rare condition. Cheng et al reported an incidence of congenital forearm pseudarthrosis of 2 cases in a general population of 1 million people over a 10 year period[1]. There seems to be no racial or demographic predisposition for this condition[1]. From 1920 to 1940, Tillier, Ducroquet, Barber and Moore were among the first to report on the frequency of neurofibromas and café-au-lait spots (CAL) in association with congenital pseudarthrosis[2]. These symptoms are distinctive features for neurofibromatosis type 1 (NF1) (i.e. von Recklinghausen's disease)[3]. From the 1960s the possible relation between NF1 and congenital pseudarthrosis was further established[4], and CAL have been reported to be present in 69% of the pseudarthrosis cases[5].

Historically, patients with a congenital dysplasia or pseudarthrosis usually present with a progressive deformity of the arm from birth. Or they present after a (minor) trauma, that may already have been unsuccessfully treated with cast immobilization or open reduction and internal fixation (ORIF). Plain radiographs show an osseous lesion that can be described using several classification systems[6, 7]. Crawford et al described different subtypes of congenital pseudarthrosis and distinct characteristics like failure of tubularization, cystic enlargement, and frank pseudarthrosis with "sucked candy" narrowing of the end of the involved bone[8]. Progressive bowing of the forearm may develop with loss of wrist and elbow function, loss of grip strength and (sub)luxation of the radiocapitellar joint.

Treatment for this condition is challenging, especially since it develops in a growing child. Primary requirements for treatment are: successful pseudarthrosis union, stabilization of the forearm joints (the distal radioulnar joint (DRUJ), ulnocarpal joint, and radiocapitellar joint), and continued skeletal growth[9, 10]. Multiple surgical strategies for congenital pseudarthrosis of the forearm have been described in literature. There are reports on open reduction and internal fixation (ORIF), either with or without autogenous bone grafting, external fixation, free vascularized bone grafting (FVFG), and radioulnar fusion into a one-bone-forearm (OBF). Due to its rarity, only a few case reports and case series describe this condition. No large cohort studies or randomized trials are available.

In 2013, Stevenson et al reported a consensus report on treatment of a NF1 related tibial pseudarthrosis[11], but guidelines for treatment of congenital forearm pseudarthrosis are

lacking. Therefore, the aim of this systematic review was to define a treatment protocol for patients with a NF1 or idiopathic related congenital forearm pseudarthrosis (either radius, ulna, or both bone), not related to other known pathology (e.g. fibrous dysplasia). Through a systematic search, we aim to discuss which treatment strategies are best, based on union rates and functional outcome. Furthermore, we propose a guideline that may aid the clinician during initial patient assessment, pre-operative work-up, and selection of surgical strategy. Furthermore, we will address postoperative follow-up and management of complications.

Methods

Study protocol and registration

Prior to start of this systematic review, the aim and study protocol was published online using PROSPERO (CRD42018099602, https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=99602).

Search strategy

In this systematic review, we searched five databases (Embase, MEDLINE, the Cochrane library, Web of Science and Google Scholar) in cooperation with a medical information specialist (WMB) to identify relevant studies related to congenital forearm pseudarthrosis. We included all forms of published studies (clinical trial, cohort, cross-sectional, case series, and case reports) that report on congenital forearm pseudarthrosis, without any limit to year of publication. We excluded studies written in any other language than English. The search was executed March 13 2018.

The full electronic search strategy for Embase was: ('pseudarthrosis'/exp OR ('fracture nonunion'/de AND ('congenital disorder'/de OR 'neurofibromatosis'/exp)) OR (pseudarthros* OR pseudoarthros* OR pseud*-arthros* OR ((nonunion* OR non-union*) NEAR/6 (neurofibromat* OR congenit*))):ab,ti) AND ('ulna'/exp OR radius/exp OR 'ulna fracture'/exp OR 'radius fracture'/exp OR 'forearm'/de OR 'forearm injury'/de OR 'forearm fracture'/de OR (ulna OR ulnar OR forearm* OR fore-arm* OR radius):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim NOT ([Conference Abstract]/lim) NOT (adult/exp NOT (juvenile/exp OR pediatrics/exp)). Searches for the other reported databases can be found as supplementary data online.

Two authors (MS, SV) independently reviewed titles and abstracts of the list of studies identified by the search to select those that fulfilled the selection criteria: congenital forearm dysplasia, all treatment modalities were eligible, not tumour related, not infection related, not related to fibrous dysplasia. Disagreement on study eligibility was resolved by consensus, with reference to a third author (DK) if required. After this selection procedure, we retrieved full texts of the selected titles.

Data collection and analysis

As mentioned before, most data on this topic is presented in case reports or case series. These observational studies typically yield very low quality of evidence according to the GRADE guidelines. In order to still asses for quality, we used the checklist for case reports from the Joanna Briggs Institute[12]. Five authors (MS, SV, NK, JB, DK) independently scored all included articles for quality according to this checklist. Disagreement on study quality was resolved by consensus.

Two authors (MS, SV) independently extracted data on the number of patients, age on presentation, family history related to NF1, clinical presentation related to NF1, involved bone of pseudarthrosis (radius, ulna, both bone), underlying disease, histology outcome, cast application and union rate, surgical interventions and union rate, and clinical outcome of elbow and forearm function. Due to the large heterogenity in reporting in elbow and forearm function, this outcome was recorded as either: full range of motion (FROM) as compared to the contralateral side, functional with minor limitations (>⅔ of FROM), major functional limitations (<⅔ of FROM).

The low methodological quality of the original studies limits meaningful statistical comparison. Therefore, all data will be discussed using a descriptive approach.

Source of funding

There was no external funding source for this study, nor any sort of funding that could influence the design or outcome of this study.

Results

After screening of 829 potentially relevant studies, we identified 70 articles which we tried to retrieve in full text. One article could not be retrieved (Tamai et al)[13]. After reading the remaining 69 full text articles, 47 were included for this review (**Figure 1**). None of the included articles discuss long-term follow up (5 year or 10 year follow up data).

Table I shows the demographics of the data synthesis results. From the included 47 studies, 84 cases were included (22 radius, 44 ulna, 18 both bone pseudarthrosis). There was a slight male predominance (males 50%, females 36%, sex unclear 14%). Most patients either presented with a progressive deformity (51%) or post-traumatic (32%). In 74% of all cases, neurofibromatosis was identified as the underlying disease. DNA reporting was lacking however, and there was poor reporting on positive family history (21%) or skin changes (41%). Cast treatment was applied in 45% of all cases, which led to successful union in only one patient.

Of all 84 cases, one patient was without complaints and no further treatment was initiated[5]. In nine patients, the surgical procedure was not specified and no records regarding union was described[14-22]. **Table II** describes the pooled results of all reported surgical attempts in the remaining 74 patients. One-hundred-and-eight procedures could be categorized into: osteosynthesis procedures[23-28], osteosynthesis procedure combined with non-vascular bone grafting[2, 5, 14, 16, 23, 29-38], use of external fixation[39-41], use of a FVFG transfer[1, 5, 9, 10, 41-52], radioulnar fusion into a OBF[1, 5, 14, 20, 36, 53-55], and use of a FVFG transfer for creation of a OBF[47, 56].

Reports on final clinical function was poor amongst the included studies. In 31 (42%) patients no comments regarding elbow function were made, forearm rotation was not reported in 34 (46%) patients. Clinical outcome was best reported in the FVFG group. After FVFG, in 24 out of 30 patients showed either a full range of motion or sustained only a minor limitation related to elbow flexion (80%) (**Table III**). Forearm rotations in 18 out of 30 FVFG patients showed either a full range of motion or was restricted to a minor extent (60%). For OBF patients, 11 patients (92%) showed a full range of motion in regards to elbow flexion or sustained only a minor limitation (**Table III**). Limited information about forearm rotations were mentioned in the included studies that present OBF patients. However, since rotations are

lost after this procedure, authors are likely not to report on rotations. For both FVGF and OBF, the most frequent described complication was forearm shortening (n = 12) and was mostly managed by a within graft lengthening procedure.

Discussion

This systematic review covers the literature reported on congenital forearm pseudarthrosis, which is a rare condition associated with NF1. In this discussion, we propose a guideline for management of this rare entity (**Figure 2**). The major limitation for this systematic review is that included studies were predominantly case reports and case series and reduces the level of evidence. But due to its rarity no large cohort studies are likely to be published, and data from case reports and case series are the only source to pursue therapeutic improvement for these patients. However, the quality of reported data was poor. All but one of the included articles were published before publication of guidelines for surgical case reports (SCARE guidelines)[57], and publication of guidelines for preferred reporting of case series in surgery (PROCESS guidelines)[58]. This might explain why most reports were of arguable quality. With data extraction from these published papers, we do feel that we were able to generate a valid treatment algorithm that could be of interest for clinicians confronted with this pathology.

Clinical presentation and work-up

Patients initially often present with a deformity (51%) or after a (mild) trauma (32%) with a persisting fracture (**Table I**). Many pseudarthrosis patients that initially presented after trauma are likely to have undergone previous treatment, like casting (45%) or even open reduction and internal fixation. Successful union rates of both treatments are low (cast 3%; ORIF 23%). Every surgeon confronted with persisting non-union of a forearm fracture after initial cast or surgical management (**Figure 2**), should be aware of possible underlying (NF1) pathology given the fact that congenital forearm pseudarthrosis is mostly NF1 related (74%).

It is important to discriminate the pseudarthrosis lesion from other tumorous lesions. For example, a patient with a fibrous dysplasia has a much better prognosis and a different treatment approach is necessary[15, 59]. Data from this systematic review shows that five cases

(6%) were considered idiopathic and in 17 cases (20%) the underlying pathology remained unclear. We believe that a large portion of these cases is also NF1 related, but proper diagnostic studies were either not performed or not reported on. Mostly histology is mentioned as diagnostic tool for NF1. This was reported for 26% of the cases and from these 22 patients only 6 (27%) proved underlying NF1 pathology. These low numbers are in line with other reports investigating neurofibromatosis in histology specimens[15, 60]. In our opinion, a surgical biopsy for diagnosis through histology is therefore not justified. The included studies did not mention other diagnostic tools like DNA studies, which can be beneficial to further establish the correct diagnosis[61]. It should be noted however, that 5-10% of patients with NF are not detected by DNA testing[62]. But a thorough diagnostic approach including clinical and ophthalmologic investigation combined with DNA testing will further establish a relation with NF1 and congenital forearm pseudarthrosis. We advocate additional referral to an ophthalmologist and pediatrician for further diagnosis of underlying NF1.

After a possible relation with NF1 is established, the physical examination is most important for further treatment of the congenital pseudarthrosis. Casting should not be attempted to achieve union, but should only be considered to reduce further bowing and prevent (sub)luxation of the radiocapitellar joint and functional loss[19, 52]. Patients with a proximal deformity or pseudarthrosis are less likely to suffer from progressive bowing and therefore good candidates for non-operative cast treatment[17]. Preliminary abnormalities (e.g. dysplasia) with normal function and strength of elbow, forearm and wrist, could initially be treated non-operatively using serial casting (**Figure 2**)[20, 43]. During this non-operative management, patients have to be monitored regularly with serial physical examination and repeated plain radiographs.

Indication for surgery

Progressive deformities in congenital forearm pseudarthrosis often lead to impaired wrist and elbow function. It is stated that the ulna makes the elbow and the radius makes the wrist[63]. Pseudarthrosis of the radius is likely to induce DRUJ instability, and pseudarthrosis of the ulna is associated with instability of the radiocapitellar joint. For the latter, it is thought that tethering of the ulna and normal growth of the radius, leading to increased pressure on the

lower humeral epiphysis may cause impaired development of the capitellum and trochlea, making the radiohumeral joint unstable[23]. In all untreated ulnar pseudarthrosis, radial head dislocation is likely to occur[1]. The vast majority of cases with untreated congenital ulnar pseudarthrosis above one year of age are associated with lateral dislocation of the radial head and degeneration of the radiocapitellar joint[5]. Furthermore, chronic radial head dislocation leads to increasing valgus deformity of the elbow and may induce subsequent ulnar or radial nerve disturbance[64, 65]. Presence of joint instability and loss of function are clear indications for operative management.

In the reviewed literature, there is no clear consensus whether patients without complaints should be operated on. From NF1 related tibia pseudarthrosis, it is known that age is a factor that influences union outcomes[7]. Older reports state that surgery should be postponed until skeletal maturity[32, 33]. However, these authors used bone grafting and osteosynthesis as treatment modality. This has poor union rates (35%). FVFG shows more successful union rates (87%), in articles concerning FVFG surgery at younger age is advocated. For example, Allieu et al reports that surgical treatment should be performed as early as possible to minimize epiphyseal involvement and abnormal growth[56]. More recently, Bauer et al proposes to utilize surgery before 3 years of age in order to avoid further progression of pseudarthrosis and deformity[43] (**Figure 2**). In line of these reports, we suggest that non-operatively treated patients should be closely monitored. Serial casting can be continued in rare cases that patients remain clinically well (no loss of function, no radial head (sub)luxation, no DRUJ instability), are without radiologic progression of pseudarthrosis and progression of the deformity is limited. Follow-up should be intensified after three years of age, since loss of function and bowing can be more progressive and surgery should be considered more easily.

Surgical management

Historically, it is difficult to acquire union of the pseudarthrosis and various treatment methods have been described. Union rates of cast immobilization, osteosynthesis, cortico-cancellous autologous bone grafting in congenital pseudarthrosis patients have shown to be rather disappointing and should be disregarded as treatment option (**Table II**). Only in rare

cases with very mild deformities, a resection can be considered if the forearm shortening does not exceed 3cm[29, 40] (**Figure 2**). Other techniques, like free vascularized fibular graft (FVFG) and radioulnar fusion into a one-bone-forearm (OBF) show improved fusion rates (respectively 87% and 92%).

Since FVFG has good union rates (**Table II**) and good clinical outcome (**Table III**) this procedure is central for treatment of congenital forearm pseudarthrosis (**Figure 2**). There are several reports that provide an excellent detailed description of the operative technique[10, 43]. Some authors report use of an angiography of both donor site and graft site, in order to check the vascular status[10, 42, 50, 52]. However, Bauer et al reported not to routinely perform this evaluation, but stated that when the surgeon has concerns about the vascularity or the child has undergone prior surgery in the area that makes the blood supply questionable, angiography can be performed[43]. Patients with insufficient vascular supply should be treated with a OBF (**Figure 2**). Graft fixation in FVFG can be achieved with using several techniques (**Table I**). In our opinion, K wire fixation is the best alternative which allows for fixation without damaging vascular supply[51]. Furthermore, a valgus deformity at the ankle due to proximal migration of the lateral malleolus is a common complication. Allieu et al advocate fusion of the distal fibula to the distal tibia[42], in order to prevent valgus deformity after harvesting the distal fibula for FVFG[10].

Also a OBF removes the restraining effect of the pseudarthrosis. After this procedure, the humeroulnar and radiocapitellar joints remain functional and proper elbow and hand function is anticipated[20]. The major difference between OBF and FVFG, is that FVFG does not impair forearm rotation and a OBF does not[23]. In this review, we found good clinical outcome in 58% of FVFG treated patients. For OBF patients, there were 3 patients (25%) for who only minor functional limitations were mentioned. However, exact reports in degrees of motion were lacking, and is likely they need compensatory movements because of restricted forearm rotation. Therefore, the OBF should be considered to be a salvage procedure, for cases that are not considered for a FVFG. For patients with involvement of the ulna and radius, a combination of both procedures can be considered, in which an FVFG is used to create a OBF (**Table 2**)[47, 56].

For both procedures, several aspects are important for good outcome. First, the abnormal surrounding soft tissues in congenital forearm pseudarthrosis are known to have an important role in the establishment and maintenance of the condition[24]. Therefore, wide surgical resection is of utmost importance[41, 66]. Especially a FVFG allows for proper wide resection and bridging of the remaining defect, without increasing risk for non-union[51]. However, a surgeon should always estimate whether there is sufficient length of the vascularized graft to bridge the bony defect after wide resection. If there are concerns of this sort, an OBF might be warranted. Amongst NF1 patients, bone involvement may vary widely and a preoperative MRI might help to estimate to what extent the surgical resection should be performed. However, only a few papers mention use of MRI of bone scintigraphy in their workup. Second, in case of radiohumeral instability an open wedge osteotomy in the ulna in order to restore ulna length can be considered[64, 67] with or without annular ligament reconstruction[58, 60], should be considered to properly reduce the radial head and prevent future degeneration of the radiocapitellar joint[5]. However, specific timing when a radiohumeral stabilization procedure should be performed is not mentioned in the papers included for this systematic review and should be further reported on.

Follow up

During follow up, serial radiographs should show proper union. If not, one may attempt to perform a resection of the pseudarthrosis in combination with (plate)osteosynthesis and autogenic bone graft[9, 43]. If this attempt fails, or the transplanted fibular graft fails, literature describes conversion to a OBF procedure as the best procedure with a predictable good functional outcome. However, this decision should be made after careful evaluation why the first FVFG failed and whether other surgical options remain. All patient after a transplanted fibular graft should be monitored regularly. A frequently seen complication is shortening of the transplanted graft[43, 47, 51, 52]. This may be dealt with through a lengthening procedure within the transplanted (fibular) graft[49].

Conclusion

Most important in management of congenital pseudoarthrosis is to make proper distinction with other underlying pathology than NF1. Operative management is warranted in case of loss of function and joint instability. In case of moderate deformity, a FVFG is the most promising technique with an OBF as reliable alternative.

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Figure and Table legends

Figure 1: Flow diagram for inclusion and exclusion of articles for this systematic review.

Figure 2: Flowchart for treatment of congenital pseudarthrosis of the forearm. The gray boxes represent a clinical decision which is still debated, these points are more extensively addressed in the discussion.

Table 1: Demographic characteristics of all included cases with a congenital forearm pseudoarthrosis

Table 2: Pooled results for all surgical procedures related to pseudarthrosis union. This table shows pooled results of all reported surgical attempts (n = 108) in the remaining 74 patients. [1]: free vascularized fibula graft, [2]: one-bone-forearm.

Table 3: Pooled results for functional outcome related to all surgical procedures. Due to the large heterogeneity in reporting of elbow and forearm function, this outcome was recorded as either: full range of motion (FROM), functional with minor limitations (>⅔ of FROM), major functional limitations (<⅔ of FROM). [1]: full range of motion, [2]: free vascularized fibula graft, [3]: one-bone-forearm.