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REVIEW ARTICLE

Congenital pseudarthrosis of the tibia[☆]

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KEYWORDS

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Summary Congenital pseudarthrosis of the tibia (CPT) is an uncommon disease with various clinical presentations ranging from simple anterolateral tibial angulation to complete non-union with extensive bone defects. Classifications of radiographic findings include atrophic or hypertrophic pseudarthrosis as well as cystic or dystrophic lesions. Although the relationship between CPT and type 1 neurofibromatosis is well known, the exact pathogenesis still remains unclear. The fibrous soft tissue found in the pseudarthrosis and the abnormal periosteum are certainly a key to the pathology, possibly due to decreased osteogenic capacities and impaired local vascularization. Treatment of CPT is still challenging in pediatric orthopedics because of bone union difficulties, persistent angulation, joint stiffness and sometimes severe limb length discrepancy sequelae. Numerous treatments based on biological and/or mechanical concepts, surgical or not, have been reported with variable success rates. Vascularized fibular grafts and the Ilizarov technique have greatly transformed the prognosis of CPT. Despite these steps forward, repeated surgical procedures are often necessary to obtain bone union and the risk of amputation is never entirely eliminated. The effectiveness of new treatments (bone morphogenetic protein, bone marrow stromal cell grafts, pulsed electromagnetic fields, induced membrane technique...) still requires to be confirmed. Combining these new techniques with existing treatments may improve the final prognosis of CPT, which nevertheless remains poor.

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Introduction

Of all the diseases in children, congenital pseudarthrosis of the tibia (CPT) is probably one of the most difficult to treat. Even today, failure to obtain bone union is frequent and the functional prognosis is mediocre because of residual defor-

mities, joint stiffness and remaining length inequalities. The aim of surgical treatment is to achieve bone union of the pseudarthrosis while restoring alignment in the leg to prevent the risk of recurrent fracture and to preserve function and bone growth in the leg.

CPT is a rare disease in children, with an estimated frequency of 1/150,000 births. It can be defined as a disorder of the diaphysis which is revealed by either pseudarthrosis at birth or by a pathological fracture presenting in bone with modifications such as bowing, narrowing of the medullary canal or a cyst. Although its relationship with type 1

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neurofibromatosis (NF1) or von Recklinghausen's disease was confirmed in 1950 [1], the physiopathology of CPT has still not been clearly defined. This disease has many presentations, both clinical and radiographic.

Numerous mechanical and/or biological based approaches have been described in the literature to treat this disease with success rates that vary. The prognosis of CPT has changed considerably in the last few decades thanks to vascularized fibular transfers and the Ilizarov technique. Despite these advances, several operations are often necessary to obtain union of the pseudarthrosis, and the risk of amputation is never entirely eliminated.

Discovery and clinical diagnosis

Bowing may be discovered during a clinical examination at birth or in the first weeks in life which presents as bowing of the tibia convex anterolaterally or a discontinuity between the two bones of the tibial segment [2]. Severe neonatal forms or primary pseudarthrosis, in which signs are present at birth, can be distinguished from secondary pseudarthrosis, which is revealed by a pathological fracture when the child begins walking [3]. The clinical presentation varies considerably, from simple bowing to various extensive bone deformities causing more or less severe bowing in one or two bones of the leg, and which may result in a pathological fracture and pseudarthrosis (Fig. 1). Severity of shortening in the leg also varies.

Normally CPT is unilateral, located at the junction of the middle and distal thirds of the tibial segment with no predominance for sex or side. The fibula is also affected in more than half the cases. A complete clinical examination, in particular neurological and dermatological, associated with an investigation of the family history must be performed in the presence of limb anomalies in a newborn or an infant [2] to differentiate a diagnosis of isolated CPT from one

of the bone anomalies associated with NF1. The latter is a multisystemic neurocutaneous disease with an autosomal dominant pattern and an estimated frequency of 1/4000 births. The diagnosis of NF1 is clinical, based on a series of criteria defined at the 1987 consensus conference [4]. These bone abnormalities correspond to primary dystrophic bone lesions, or are secondary to damage to the soft tissues, which affect bone growth. While the incidence of bowing and CPT is less than 4% in NF1 [5,6], half of the patients (40–80%) presenting with CPT are NF1 carriers [5,7].

Imaging

Standard X-rays show heterogeneous lesions from simple convex anterolateral bowing to true tibial discontinuity, with an image of resorption of the two ends of the fracture responsible for significant loss of bone substance.

Cystic forms are also found, in which bowing appears at between 6 weeks and 1 year. The cortices are continuous and condensed and thickened in the concave part of the curvature. The medullary canal is narrow and an image of a cyst can be seen at the apex of the curvature. The deformity gradually worsens until the cortex finally breaks, causing a transverse fracture [8]. In dysplastic forms, the bowing is visible at birth and sometimes pseudarthrosis may already be present. The tibia is narrow with an hourglass appearance and the medullary cavity is partially or completely obstructed. The fibula is frequently affected in these types. When pseudarthrosis has developed, the ends of the bone may be thin, atrophic or on the other hand, wide and hypertrophic. These radiological features define a certain number of criteria which are the basis of the different classifications of CPT.

The recent development of magnetic resonance imaging (MRI) will provide more detailed analysis of both bone and especially soft tissue lesions, in particular the periosteum



Figure 1 Clinical (A) and radiographic (B) heterogeneity of congenital pseudarthrosis of the tibia (CPT) with anterolateral bowing of the leg and atrophic pseudarthrosis of the lower third of the leg (C).



Figure 2 Pseudarthrosis of the distal quarter of the fibula with a cystic appearance (A) MRI features (B, C) with an isosignal on T1-weighted sequences of the area of pseudarthrosis and the thickened periosteum.

around the pseudarthrosis [9] (Fig. 2). New bone perfusion sequences can show bone vascularization defects, help define the limits of resection and increase understanding of the physiopathological mechanisms of this disease.

Classification

Numerous classifications have been described, which is a sign of the heterogeneity of this disease and the difficulty of including the etiology, natural history and treatment in one classification [10]. Among these we can mention:

- the Crawford classification [7], which is the most frequently used today (Fig. 3). This classification has the advantage of being descriptive and identifying the different stages as CPT progresses:
 - type I: anterior bowing with an increase in cortical density and a narrow medulla;
 - type II: anterior bowing with narrow, sclerotic medulla,
 - type III: anterior bowing associated with a cyst or signs of a prefracture,
 - type IV: anterior bowing and a clear fracture with pseudarthrosis often associating the tibia and fibula;
- the Boyd classification [11] with 6 types, which has prognostic value:
 - type I: anterior bowing associated with other congenital malformations,
 - type II: anterior bowing with an hourglass appearance to the tibia. A fracture usually occurs before the age of 2. The ends of the bone are thin, rounded and sclerotic with obliteration of the intramedullary canal. This type is more often associated with NF1 and there is a poor prognosis with frequent recurrence during bone growth,
 - type III: pseudarthrosis developing from an intraosseous cyst, usually at the middle and distal third junction. Anterior bowing can precede or follow the development of the fracture. This type has a high rate of union and recurrence is rare,
 - type IV: sclerotic bone with no pathological bowing. The medullary canal is partially or completely obliterated. A fatigue fracture may occur and progress to pseudarthrosis. The prognosis is good if treatment begins before the fatigue fracture occurs,
 - type V: dyplasic appearance to the fibula. Pseudarthrosis can be located on either of the two bones of the tibial segment. The prognosis is good if the lesion is located only on the fibula, extension to the tibia has a prognosis similar to type II,
 - type VI: associated with an intraosseous fibroma or a schwannoma. The prognosis depends on the aggressivity of the intraosseous lesion.
- Apoil 2 stage classification [3] (Fig. 4):
 - type I: atrophic pseudarthrosis with thin bone ends. The ends of the bone are said to look like "barley sugar", which results in a more or less significant long-term loss of bone substance, or overlap. The inferior fragment is often small and aplasic, ending in an atrophic epiphysis. There is no medullary canal. The fibula has an identical lesion,
 - type II: tight, extensive hypertrophic pseudarthrosis. The bone ends are dense, wide and the medullary canal has disappeared, the cortex thickens on the concave side. The fibula is often bowed and abnormally shaped.

The limitation of all these classifications is disease progression and the possible passage from one stage to another in the classification in the same patient as he grows making it difficult to analyse the series in the literature.

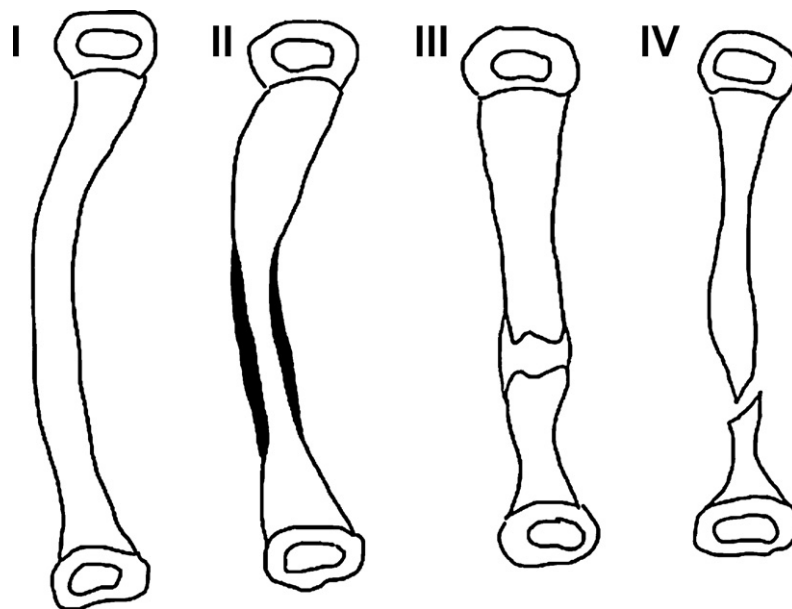


Figure 3 4 stage Crawford classification.

Anatomical pathology

Histological studies show that there is a marked cuff of fibrous tissue in the area of pseudarthrosis, also called the fibrous hamartoma [12], in continuity with abnormal periosteal thickening [13]. Most of the cells of this hamartoma have been identified as fibroblasts [14]. A certain quantity of fibrocartilage and hyalin cartilage [15] is also associated with the fibrous tissue as well as several areas of endochondral ossification. Resorption lacuna with giant osteoclasts are present at the pseudarthrosis-bone junction [16]. This osteolytic component seems to be more marked in young children and decreases with growth, then disappears at skeletal maturity [11]. All of these phenomena are a sign of a bone remodeling defect [12] which is responsible for

the sclerotic, hourglass appearance of the bone adjacent to the pseudarthrosis as well as the atrophy of the bone ends [16]. Localized growth of this fibrous tissue, associated with excess bone resorption participates in the development of cystic intracortical lesions, deformity and sclerosis in mixed types of CPT [16]. The composition of the pseudarthrotic tissue seems to be identical whether or not it is associated with NF1 [16].

Physiopathology

The etiology of CPT is still a subject of debate. Numerous mechanical, vascular or genetic theories have been proposed in the literature. None of them provide an entirely

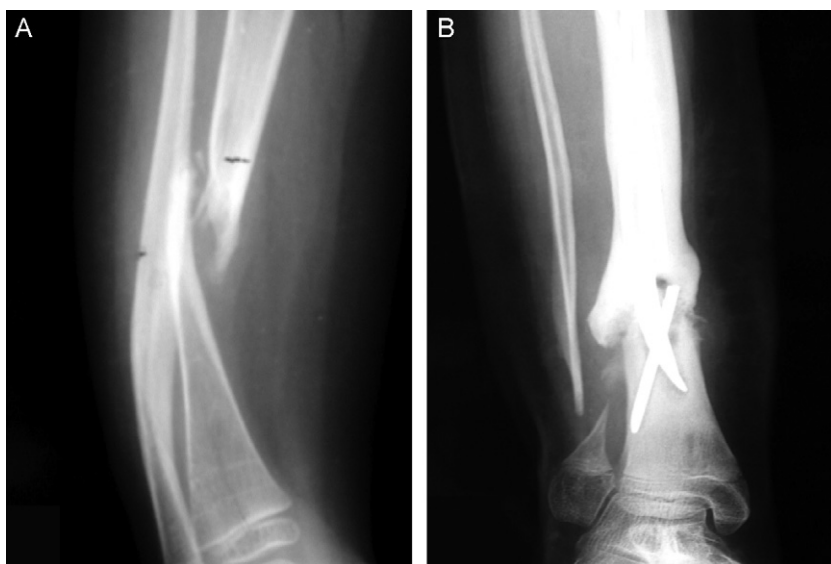


Figure 4 Atrophic (A) and hypertrophic (B) CPT (JP Damsin collection).

satisfying explanation for the pathogenesis of CPT or its location, probably because of the heterogeneity of the disease and its inconsistent association with NF1.

The key role of the fibrous hamartoma and of the pathological periosteum has been extensively described in the etiology of CPT. They are said to prevent union by a mechanical effect of interposition and be responsible for defective vascularisation in the bone. The periosteum could create a fibrous band causing an increase in local pressure around the bone resulting in reduced vascularization as well as bone atrophy [14]. The vascularization defect could also be secondary to thickening of the vessel walls in the area of pseudarthrosis [13].

The association of NF1 in 40 to 80% [5] of the cases of CPT suggests a genetic cause. *NF1* codes for a ubiquitous protein, neurofibromin, whose functions include the negative regulation of Ras, a protein involved in cell differentiation and proliferation [5]. In its normal state, neurofibromin possesses a role of tumor suppressor, by converting Ras-GTP into an inactive form of Ras-GDP. The mutation of *NF1* results in a loss of neurofibromin activity resulting in the maintenance of the active form of Ras [5]. In certain cases of CPT associated with NF1, a double activation of the *NF1* gene was found in pseudarthrotic tissue [17]. This genetic anomaly was not found in all cases and cannot explain alone the pathogenesis of CPT [15,18]. The loss of function of neurofibromin can result in a Ras-MAPK pathway anomaly resulting in defective osteoblastic differentiation. Overexpression of the Ras pathway can also result in an increase in osteoclast activity and their precursors, explaining bone resorption in CPT [12] and the high rate of recurrent fractures.

In case of NF1, the absence of nerve cells in the pseudarthrotic tissue suggests that the bone abnormalities in NF1 correspond to primary bone dysplasia [15,19]. The physiopathology of CPT could therefore be identical, whether or not it is associated with NF1, especially since there is no histological difference in the composition of the fibrous hamartoma. The physiopathology of CPT probably involves the various different hypotheses, with signal anomalies causing increased osteoclast activity associated with an osteoblastic differentiation anomaly resulting in a bone-remodeling defect, which is also favored by the decrease in local vascularization.

Prognostic factors

The general factors are:

- the association with NF1 was long considered to be a negative predictive factor for bone union in CPT [20]. Today, results in the literature do not support this notion with comparable rates of union in these groups [10];
- age is certainly an important factor with a better prognosis when the disease is not markedly progressive and the fracture occurs later.

The local factors are:

- the site of pseudarthrosis: a lower location, in the inferior metaphysis, makes it difficult to control the distal

fragment. The necessity of including the ankle and hind foot in fixation may result in articular sequelae.

- the type of pseudarthrosis is an important parameter: severe deformities with bone atrophy, extensive sclerotic lesions with a small diameter bone and significant shortening have a poor prognosis [21]. Associated fibular involvement seems to worsen the prognosis [22].
- lower limb length discrepancies: can be caused by bone from not applying weight and stimulating growth or be linked to the angulation and overlap of bone ends [8].

Response to treatment

The surgical history and remaining bone capital are important prognostic factors, in particular the number of surgical interventions and the persistence of marked angulation favoring recurrent fractures. The resorption rate of the graft may also have a poor prognosis.

Methods of treatment

Treatment of CPT is surgical, as the natural progression of CPT is towards worsening, deformity and shortening [2]. Wearing a protective brace before the child has begun walking delays the moment of the fracture in case of bowing or limits the deformity in case of confirmed pseudarthrosis.

The aims of surgical treatment are not only limited to union of CPT. It must also restore satisfactory alignment of the leg to prevent the risk of recurrent fracture and limit leg length discrepancies while preserving articular function. Finally, clinical and radiological union of the area of pseudarthrosis is only a criteria for real cure when correction is maintained after growth is complete [3].

The three surgical techniques, which are traditionally described as achieving the best rates of union are intramedullary nailing associated with a bone graft, vascularized fibular transfer and the Ilizarov technique. We will first present these three techniques before describing new emerging surgical and/or biological techniques.

Intramedullary nailing associated with a bone graft

First described in 1956 by Charnley [23], the principle is based on resection of areas of pseudarthrosis associated with stable intramedullary fixation and transfer of a large graft that may or may not be supported by the fibula (Fig. 5). Intramedullary fixation results in alignment, correction of the deformity and guides bone lengthening during growth. Different types of fixation are used depending on the surgical teams. The use of a telescopic nail or pins helps protect the reconstructed area during growth and avoids having to change the internal fixation. In case of distal pseudarthrosis or small bone fragments, stable fixation is obtained by talocalcaneal and tibiotalar joint bridging with material inserted by transplental approach. Associated intramedullary fixation of the fibula reinforces the stability if fixation is located in area of the pseudarthrosis or stabilizes an osteotomy for shortening.

The rate of union with this technique varies greatly in the literature from 28% [24] to more than 80% [25] probably in



Figure 5 AP view X-ray of Crawford stage IV congenital pseudarthrosis of the tibia (CPT) (A). Union after an intertibiobfibular graft associated with intramedullary fixation with a telescopic nail AP (B) and profile (C) views. (JP Padovani collection).

relation to the technique, the fixation used and an associated fibular procedure. All recent publications report a rate of union of more than 80% [26,27].

The negative points of intramedullary nailing with a bone graft are the frequent need to bridge the ankle and the hind-foot resulting in pain and stiffness. Release of the ankle after union of the pseudarthrosis only slightly increases range of motion in the ankle [25]. Pes cavus and/or valgus ankle can develop during growth. This technique also results in residual leg length discrepancies in more than half the cases [26].

Vascularized bone transfers

Since it was described in 1978 by Judet and Gilbert [28] in the treatment of CPT, free fibular transfer has been extensively used for this indication. The principle is based on wide resection of the dystrophic tibia, which is replaced by healthy vascularized bone. Hypertrophy of the bone transfer is then observed in response to mechanical stimulation. Classically, the vascularized bone was transferred from the contralateral fibula. The use of the homolateral fibula has also been described [29]. To avoid the gradual valgus deformity of the ankle in young children, temporary or definitive distal metaphyseal tibiofibular fusion can be performed.

There are numerous types of graft fixation and a stable system is essential for union. If possible the fibula is forcefully inserted into the tibial diaphysis for primary stability. Screwing or pinning can be associated at each end for reinforcement. An external unilateral or circular fixator can also be associated to increase stability of the system [30], so that walking can be begun again and to reduce the risk of early recurrence (Fig. 6).

The results of multicenter studies [21,31,32] show that the rate of primary union of vascularized transfers is more

than 70% [32] with a success rate that increases with the patient's age.

The negative points of vascularized fibular transfer are the frequent necessity of a 2nd graft at the bone-fibular junction to obtain union of the pseudarthrosis. A second operation is necessary in more than 30% of cases. The risk of recurrent fracture is high, usually at the bone-fibular junction or in the body of the fibular graft before hypertrophy [33]. This technique is also the source of residual angulation, occurring in more than half the cases in particular valgus and recurvatum deformities, which do not resolve during growth. Valgus ankle deformities on the side of the harvested fibula in growing children may cause chronic pain to develop later on [34].

Ilizarov technique

Ilizarov was the first to use his fixation technique in CPT [35]. The external circular fixation makes it possible to use many combinations, which can be adapted to the type of pseudarthrosis [36]. Small bone fragments can be stabilized with this technique, a residual deformity can gradually be restored, and length discrepancies in the affected limb can be treated during the same surgical procedure. The external fixation can be extended to the foot depending on the anatomical form of pseudarthrosis.

The Ilizarov method involves direct compression of the area of pseudarthrosis with or without resection. Depending on the amount of loss of bone substance, the area of bone is compressed or diaphyseal transfer is performed (Fig. 7). In the latter case, epiphyseal distraction [36] or proximal metaphyseal corticotomy is performed at a distance from the dystrophic area. A bone graft in the form of a simple graft or an

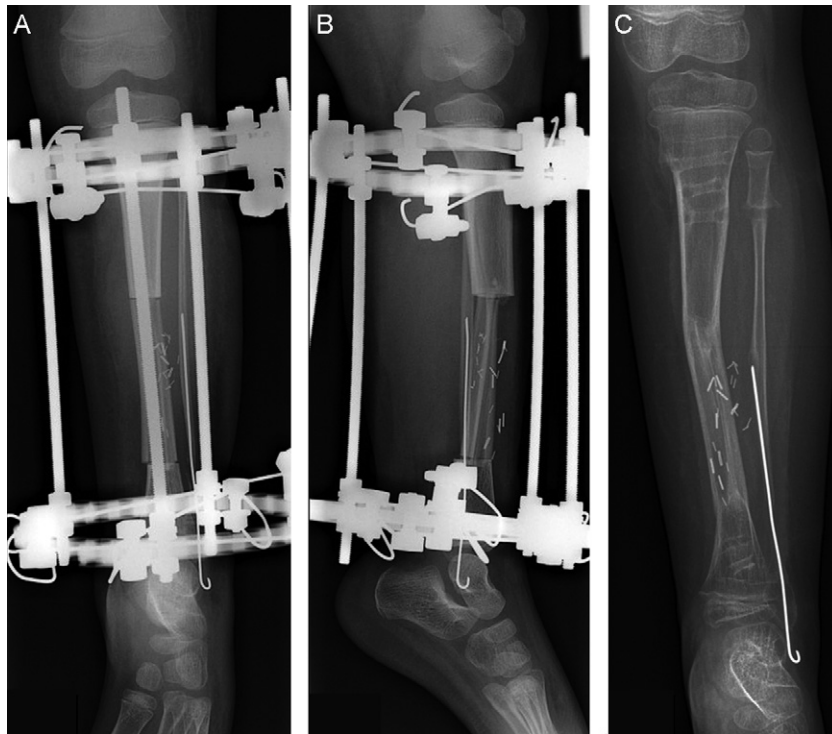


Figure 6 Double barrelled vascularized fibular transfer using the contralateral fibula associated with circular external Ilizarov fixation and an intramedullary pin for the fibula AP(A) and profile(B) views. Appearance after union and ablation of external fixation (C). (A. Hamel Collection).

intertibiofibular graft may be performed during the same procedure or in a second step to reinforce union [37].

The rate of union varies from between 50 and 90% [38]. The study performed by the European Paediatric

Orthopaedic Society (EPOS) [24] in 108 patients treated by the Ilizarov method shows that the best results were obtained with resection of the areas of pseudarthrosis with compression of the affected area and metaphyseal lengthening with a system that included the foot.

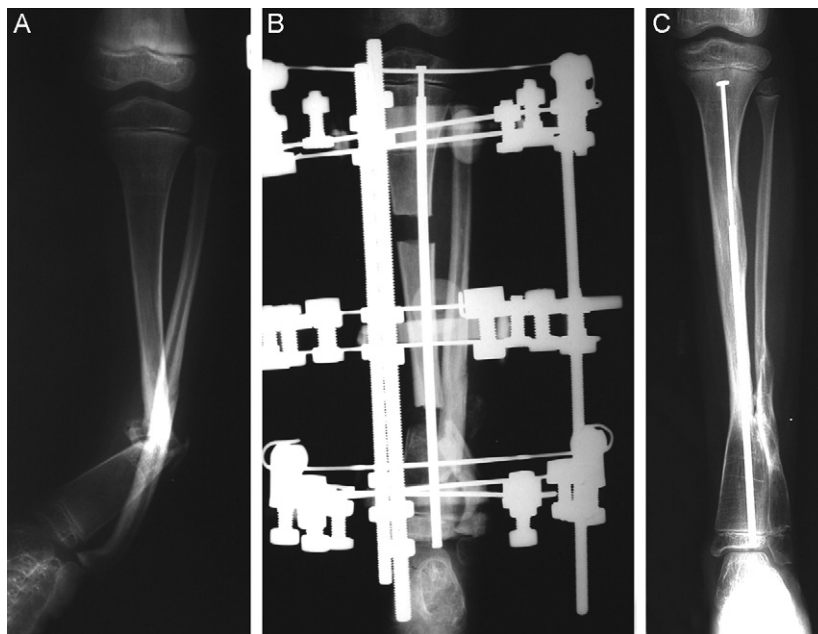


Figure 7 AP view X-ray of Crawford stage IV Congenital pseudarthrosis of the tibia (CPT) (A). Ilizarov technique with intramedullary fixation, bone transfer and compression of the area of pseudarthrosis (B). Appearance after union and ablation of the external fixation (C). (JP Damsin Collection).

The negative points of the Ilizarov method are the high rate of recurrent fractures, linked to persistent axial deformities and pin infections. A second intervention is necessary in nearly half the cases to correct a residual angular deformity, to treat a recurrent fracture or an infection. A valgus ankle deformity was found in 25% of the cases because of persistent fibular pseudarthrosis or a distal tibial epiphyseal growth defect. Associating internal fixation with pins or telescopic nails with the external fixation has been proposed because of the high rate of recurrent fracture and axial deformities [37,39].

Osteoinductive proteins or « bone morphogenetic proteins »

The role of bone morphogenetic proteins (BMPs) in fracture union has been extensively studied in the literature [40]. By analogy with post-traumatic pseudarthrosis in adults, certain authors used BMPs in the treatment of CPT. At present, the use in children is limited because of the lack of information about the long-term risks in immature skeletons [41], in particular the possibility of deleterious results on growth and a potential tumor-inductive effect. Nevertheless, there is ongoing clinical research on the use of BMP's in the specific case of pediatric diseases, in particular CPT [42]. Two recombinant human osteogenic proteins (RhBMP) have been described for this indication in children, RhBMP-7 (OP-1® or Osigraft®) [43–47] and RhBMP-2 (Inductos®) [41]. The different surgical techniques used, the types of pseudarthrosis, the association of allo- or autografts and the few number of cases, makes it difficult to analyze results. The choice of BMP must also be evaluated. Physiologically, BMP-2 acts earlier on the proliferation and differentiation of mesenchymous cells into chondroblasts while BMP-7 acts on osteoblast differentiation.

A French national PHRC study on the evaluation of rhBMP-2 in association with classic surgical treatment was

performed in 2007. A prospective randomized multicenter study was performed (EPOPEE study), to define the efficacy of Inductos® as adjuvant treatment in CPT.

Induced membrane and spongy autologous graft

This technique was developed by A.C. Masquelet for the treatment of infected pseudarthroses of the leg [48] and diaphyseal bone defects in the limbs [49]. The principle is based on inducing a pseudosynovial membrane by inserting a cement spacer in the first stage of surgery, which fills the defect to be reconstructed associated with stable internal fixation. Reconstruction is possible in the second stage by a spongy autologous graft after the cement spacer has been removed. The pseudosynovial membrane creates a true biological chamber. High concentrations of endothelial and osteoinductive cell growth factors including BMP-2 were identified in the cells of the membrane [50]. Besides this biological role, the induced membrane and the cement spacer saves space for diaphyseal reconstruction.

Its application in the treatment of CPT includes complete resection of diseased bone and fibrous tissue, stable intramedullary fixation and a cement spacer [51] (Fig. 8). The replacement of the fibrous hamartoma and of the diseased periosteum by a vascularized membrane producing vascular and osteoinductive cell growth factors associated with stable fixation makes it possible to respond to most of the existing hypotheses on the physiopathology of CPT.

Periosteal grafts

Paley [52] recently described a technique using a free periosteal graft harvested from the iliac wing, based on the source of osteoprogenitor cells contained in the periosteum. This technique involves complete resection of the diseased periosteum around the area of pseudarthrosis, which is replaced with a periosteal graft which covers the resected

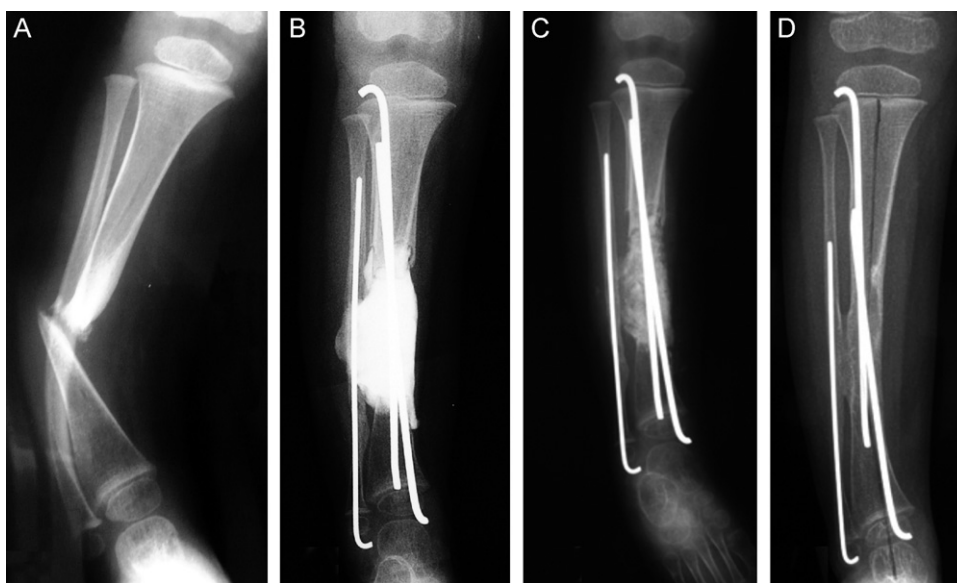


Figure 8 AP view X-ray of Crawford stage IV CPT (A). Placement of a cement spacer pressing on the fibula (B). Ablation of the cement spacer and autologous graft (C). Appearance after union (D).

area after placement of a bone graft and intramedullary tibular and fibular internal fixation associated with an external Ilizarov fixator [53].

Electrostimulation

Its use in CPT was developed in the 1980's for linear pseudarthroses or with bone defects of less than 5 mm, then it was nearly completely abandoned. The rate of union was approximately 70% [54]. Treatment by pulsed electromagnetic fields is now being developed in the treatment of pseudarthroses and delayed union of fractures in adults with good results. Its efficacy must be evaluated in the treatment of CPT.

Autologous and bone marrow grafts

The capacity for osteogenic differentiation of mesenchymal stem cells has been used in adults to treat femoral head necrosis and pseudarthrosis, in particular of the tibia [55]. Several cases of bone marrow grafting have been reported in the treatment of CPT associated with traditional treatment [56]. The capacity of bone marrow cells to differentiate into osteoblastic cell lines could be enough to justify its use in the treatment of CPT. [57].

Discussion, therapeutic indications

The superiority of one treatment over another remains difficult to determine. The many different clinical presentations of CPT, the lack of differentiation between NF1 and non NF1 patients, the effect of prior treatment, the necessity of having a follow-up that is long enough and until skeletal maturity, the age at surgery and the few number of cases in each series make comparison of treatments and evaluation of results difficult. The most recent series show comparable rates of union for the 3 main techniques.

In the multicenter study performed by the EPOS in 2000 in 340 patients [24], the Ilizarov technique was shown to be the best surgical technique because of stable fixation with circular rings and preservation of alignment and length by the lengthening created by bone segment transport. A multicenter series performed in Japan in 2005 in 73 cases [21], found that the best results were obtained with the Ilizarov technique and vascularized fibular transfers. The poor results obtained with intramedullary nailing in these series were related to a greater variability in surgical technique, fixation with the ankle and systematic use or not of a graft. This surgical technique is probably more accessible than the two others and success certainly depends upon the surgeon's experience.

Although the best treatment for CPT remains controversial, there is a consensus on a certain number of points in the literature. Whatever the technique used, realignment of the tibial segment and stable internal fixation are essential for union. Intramedullary fixation is the best technique to maintain alignment during growth and prevent the risk of recurrent fracture. The association of an intramedullary nail with the Ilizarov technique is now being developed [58]. Although the risk of infection is increased, this approach

increases stability, preserves long-term alignment and/or guides lengthening. The rate of recurrent fracture is reduced in more than 50% of cases [52] in particular during ablation of the external fixator. Intramedullary fixation is more difficult with vascularized fibular transfer because of the risk of injury to the vascularized transplant. Axial deformities, which are a source of recurrent fracture, cannot be prevented with external fixation.

The role of fibular surgery has probably been underestimated in the literature. Indeed, persistent fibular pseudarthrosis favors valgus ankle and can explain the high rate of recurrent fractures some time after primary union [26]. For many authors, treatment of the fibula is systematic in case of pseudarthrosis. Fibular union associated or not with internal fixation by intramedullary nailing reinforces stability by distributing loads and protects, in particular, from rotational trauma [26,36]. If continuity is preserved or if the fibula is the site of hypoplasia or bowing, the choice of treatment is more debatable. Some authors do not intervene [59], others perform fusion by intertibiofibular graft after tibial union [25]. Finally for certain [27], osteotomy to shorten the fibula is necessary for realignment. This mainly serves to prevent distraction of the area of tibial pseudarthrosis by favoring the contact of the two bone ends and their union.

If stable fixation is essential for union, what role does resection of the fibrous hamartoma and of the associated diseased periosteum play? At present these elements seem to be the key elements in the physiopathology of this disease. Although this resection is indispensable for numerous authors [21,24] it increases instability, in particular of the distal fragment. Resection can be "cancerologic" by removing sclerotic bone, interpositioned tissue and the diseased periosteum or be limited to the fibrous hamartoma and the sclerotic bone. It is difficult to define the effect of the extent of resection on results, because this variable is not clearly described in the literature. At present the extent of resection is determined by the surgeon during surgery by macroscopic evaluation of the bone and the reappearance of a permeable intramedullary canal. MRI could play an important role in the preoperative evaluation of the fibrous hamartoma, the periosteum and bone lesions to improve identification of the extent of bone and soft tissue lesions to be excised.

Indications for surgery should take into account the child's family situation, his/her age, the type and location of pseudarthrosis as well as the surgical history. EPOS [24] recommends surgical management in children after the age of 3 because of the difficulty of stabilizing small bone fragments in younger children. These mechanical difficulties are also supported by the biological notions found in the studies by Boyd [11] who showed that osteolytic activity in the area of pseudarthrosis was more important in the young child. The best results were obtained with the Ilizarov technique in children over 4 to 5 years old in most series [60], or between 6 and 9 years old for EPOS [24]. The best results were obtained with vascularized transfers in children between 3.5 and 7.5 years old [31]. Certain authors who recommend intramedullary nailing with bone grafts suggest early surgery in children under the age of 3 and obtain better fusion rates and especially less affect on growth [10,61]. For others [20,27], age does not affect the chances of union.

It is certain that early surgery avoids hypoplasia of the leg and foot, muscular atrophy and increased risk of leg length discrepancies but this can also pose technical problems in young children. Successful union seems to be influenced more by the type of pseudarthrosis and the choice of surgical technique than by the age at surgery.

At present, there is no gold standard surgical technique to successfully treat all types and presentations of CPT. The choice of technique should be adapted to the type of pseudarthrosis and especially to the extent of the bone defects. In normo- and hypertrophic types, when there is little shortening, good results can be obtained with intramedullary nailing with a bone graft or the Ilizarov technique [60]. The debate usually involves atrophic forms in which resection results in significant loss of bone substance. The vascularized fibula and the Ilizarov method with bone transport play an important role in this indication. Transfer of healthy vascularized bone in the first case, and increasing blood flow by proximal corticotomy and diaphyseal transfer [36] in the second, creates a favorable vascular environment for union while compensating for bone defects. The induced membrane technique is also appropriate for this indication by creating a biological chamber with osteogenic and vascular growth factors while filling large volume bone defects. If bone substance loss is no more than 4 cm, these three techniques can be used depending on the experience of the surgical team. Beyond this or in case of extensive sclerotic forms which make diaphyseal transport impossible, a vascularized graft which would fill bone defects and result in faster union, or the induced membrane technique, can be considered.

The efficacy of treatments that can be called "complementary to traditional surgery", must be determined. The addition of BMPs or bone marrow cells during initial surgery or secondarily could help improve and/or accelerate union in particular at the graft/healthy bone junction. It is clear that these treatments are only complementary and do not replace stable fixation and vascularized or non-vascularized bone grafts. The role of pulsed electromagnetic therapy, which is easy to administer with existing portable devices, must still be determined in the management of CPT.

A protection or a Sarmiento type brace to be worn systematically by the child is recommended by most teams once union is obtained for protection, in particular in case of residual axial deviation or fragile union.

Finally long-term monitoring is necessary until the patient reaches skeletal maturity to evaluate the results of each method in the treatment of CPT. Johnston's postoperative method of evaluation [27] could be used for objective comparison of results of different series. This includes:

- stage 1, clear union with full normal function during full weight-bearing;
- stage 2, incomplete union with useful function but a protective brace is needed; X-rays show a transverse cortical or longitudinal defect and/or frontal or sagittal deformity of more than 15° which may or may not be associated with shortening of more than 3 cm;
- stage 3, with persistent pseudarthrosis or a recurrent fracture.

Sequellae and complications

Valgus ankle is frequent, and found in nearly 45% of cases [62], linked to proximal migration of the lateral malleolus. This causes valgus tibiotarsal instability, increasing stress on the lateral side of the tibial epiphysis and causing asymmetric growth. This deformity can be corrected by epiphysiodesis of the medial malleolus by stapling or percutaneous screws [5], which is simpler than a supramalleolar osteotomy which can progress to pseudarthrosis. Ankle stiffness develops because of the necessity of rigid immobilization during treatment or transplantation and may cause pain or foot deformities, in particular in the arch because of upright positioning of the calcaneus.

Leg length discrepancies are also a frequent problem. They may be due to the disease itself or be iatrogenic. If the discrepancy is less than 5 cm it can be treated by contralateral epiphysiodesis. If there is a significant discrepancy, the Ilizarov technique is indicated. Lengthening can be performed by proximal corticotomy (as long as the bone is normal on X-ray) or by physeal distraction, but there is a risk of sterilizing the growth cartilage. Femoral lengthening has also been described [25] with the inherent problem of knee displacement.

Recurrent fractures are frequent after union. They can occur early as long as the medullary canal has not become permeable again and can be prevented in part by a protective brace. If they occur after primary union they are usually a sign of persistent axial deviation. The initial treatment is orthopedic but non-union is frequent and revision surgery is then necessary.

Finally, it is important to note that a diagnosis of pseudarthrosis often reveals a diagnosis of NF1. These patients must then have regular follow-up to detect other complications which they are at risk of developing.

Conclusion

CPT is still a disease whose physiopathology has not been completely clarified. The key elements of this review are the necessity of stable fixation, which is essential for bone union, and restoration of anatomical alignment. Union of fibular pseudarthrosis and radical resection of the diseased bone and surrounding tissue are certainly important elements. The development of preoperative MRI will help define the diseased areas to be resected.

Congenital tibial pseudarthrosis is a severe disease whose prognosis is uncertain and amputation of the leg can never be completely excluded. There is no surgical technique guaranteeing permanent primary union with a well-aligned leg and no length discrepancies until bone growth is complete. New emerging techniques combine mechanical and biological notions associated with traditional techniques and may become the ideal treatment, but this must to be validated in future studies.

Disclosure of interest

The author declared that they have no conflicts of interest concerning this article.

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