



## Microsurgical autologous fibula transfer as an optimal method for closure of extensive bone defects in children with neurofibromatosis

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### Abstract

**Introduction** Pseudarthrosis and bone defects are the most common consequence of neurofibromatosis type I in children, a rare hereditary disease. Destruction of bone tissue leads to severe deformities and impaired function of the limbs. Disability in such patients may reach 70 %. Surgical treatment of children with this pathology is long, laborious and multi-stage. Traditional orthopaedic methods for managing bone defects are often ineffective. The development of microsurgical methods enables to perform bone transfer of blood-supplied bone autografts. **Purpose** To prove the effectiveness of using microsurgical autologous transfer of the vascularized fibula for plastic surgery of bone defects in children with neurofibromatosis type I. **Materials and methods** A retrospective monocenter study included 27 pediatric patients who underwent reconstruction of bone defects with a vascularized fibular autograft from 2011 to 2021. The etiology of the bone defect in all patients was neurofibromatosis type I. A fibula graft was used to reconstruct 8 tibiae and 19 forearms. Bone defects averaged 12 cm. Median follow-up was 60 months. **Results** The fibula graft survival rate was 100 %. In 5 cases, nonunion of the proximal part of the fibula and the recipient zone was obtained which required iliac crest grafting. The overall rate of good and excellent results was 74 %. The average time to consolidation was 3 months. **Discussion** According to the literature, the use of autografting of vascularized bone fragments is a rather limited procedure in children with neurofibromatosis type I as it is associated with an increased risk of complications. Due to the restoration of blood flow in the transferred vascularized autograft, it retains its viability and the possibility of bone tissue remodeling. **Conclusion** Microsurgical autologous transfer of a vascularized fragment of the fibula is an effective and at times indispensable method of bone plasty in long bone defects in children with type I neurofibromatosis. Bone defects larger than 5 cm are an indication for free autologous transfer of a vascularized fragment of the fibula. This method, used in combination with traditional orthopedic methods for the treatment of children, allows obtaining good anatomical and functional results.

**Keywords:** microsurgery, free fibula transfer, pseudarthrosis, forearm, bone defect, neurofibromatosis

**For citation:** Golyana S.I., Tikhonenko T.I., Galkina N.S., Grankin D.Yu. Microsurgical autologous fibula transfer as an optimal method for closure of extensive bone defects in children with neurofibromatosis. *Genij Ortopedii*. 2023;29(4):368-375. doi: 10.18019/1028-4427-2023-29-4-368-375

### INTRODUCTION

Neurofibromatosis type I (NF1) or von Recklinghausen's disease is a multisystem autosomal dominant hereditary disease characterized by damage to the skin, central and peripheral nervous system, eyes, and the skeletal system. This type of pathology is the most common hereditary disease from the group of phakomatoses and is characterized by a predisposition to perineurium tumors. The incidence of NF1 is 1:3000-1:4000 of newborns [1]. In about half of the cases, the manifestations of the disease are minimal. Paternal transmission is more common than maternal transmission [2]. In addition to neurofibromas and café-au-lait spots on the skin, skeletal abnormalities develop in 60.0 % of NF1 patients. These include scoliosis, chest deformity, pseudarthrosis, requiring surgical treatment and long-term rehabilitation. Congenital pseudarthrosis of the tibia is diagnosed in 5.0 % of NF1 children, accounting for 80.0 % of all cases of this pathology in the general population. Scoliosis is detected in 60 %, osteoporosis in 50.0 %, chest deformity in 37.6 %, microgenia in

53.0 %, increased head circumference in 25.0 %, dysplasia of the wing of the sphenoid bone in 12.0 %, facial asymmetry in 10.0 % of patients with NF1 [3]. Moreover, changes in the walls of the arteries are diagnosed in these patients which can lead to stenosis or occlusion of the arteries of the circle of Willis and nearby arteries, or to intracranial aneurysm. The NF1 gene is located on the long arm of chromosome 17 (17q11.2) and encodes the synthesis of the cytoplasmic neurofibromin protein, which is expressed in many cell types but predominantly in Schwann cells and neurons. Neurofibromin acts as a tumor growth suppressor by activating Ras-GTPase, which causes suppression of cell signaling through the Ras/mitogen-activated protein kinase pathway. The NF1 gene exhibits a wide range of expression variability and complete penetrance even within the same family. Despite the fact that neurofibromatosis type I is inherited in an autosomal dominant manner, the development of the disease is caused by denovo mutations in 20-50 % of its cases [4-6].

Congenital pseudoarthrosis of the upper and lower extremities is associated with NF1 in most cases, and the bones of the lower leg and forearm most often affected. According to a systematic review by Siebelt et al [7], among 84 patients with extensive defects in the forearm bones, 74 % were diagnosed with NF1. However, this rate may be underestimated as not all patients are adequately tested for NF1 or test results may not have been reported. Identification of the relationship of congenital pseudoarthrosis with NF1 is important for compiling a list of patient examinations, especially if this is the only manifestation [7]. Moreover, according to the reported data, the nonunion rate in congenital pseudoarthrosis associated with NF1 is significantly higher (44-73 %) than the nonunion rate in the pathology not associated with NF1 (0-45 %) [8].

Due to the rarity of congenital pseudoarthrosis of the forearm, there are currently no unified recommendations for the treatment of this pathology. Conservative treatment using plaster immobilization and physiotherapy is performed in a small number of patients and, as a rule, does not lead to complete consolidation of bone fragments [7, 9]. Surgical treatment is indicated for patients with subluxation and dislocation of the radial head, distal radioulnar instability, and progressive deformities of the forearm bones [7, 9].

The clinical picture of congenital pseudarthrosis of the tibia presents an anterolateral curvature of the tibia, accompanied by a narrow medullary canal. It results in a fracture of the tibia and, ultimately, in the development of pseudarthrosis due to a violation of the processes of consolidation between bone fragments [10]. The goal of the management in congenital pseudarthrosis of the tibia is to achieve stable bone union of the fragments, correct the deformity and limb length, and prevent re-fracture.

According to Khan T and Joseph B [11], the rate of primary callus formation in the postoperative period reaches 50-75 %. However, the radiography shows that only 40 to 60 % of normal bone structure is restored.

Lack of consolidation and re-fractures are the main surgical complications of pseudarthrosis treatment in children with neurofibromatosis. After a repeated fracture, the consolidation rate of the pseudarthrosis site is only 35-50 % [11]. Moreover, according to studies, the formation of the callus depends on the age of the child at the time of surgery and the location of pseudarthrosis: the younger the patient and the closer the site of pseudarthrosis to the distal bone part, the easier it is to achieve bone fusion [8].

Surgical approaches adopted by most surgeons include Ilizarov external fixation, intramedullary rod fixation in combination with bone graft, and the use of a vascularized bone autograft [12, 13]. As reported, microsurgical plasty for congenital pseudoarthrosis with an autograft from the fibula in children with this pathology provides fusion in a larger percentage of cases (61-89 %) [14]. Other treatment options include the use of bone morphogenetic proteins (BMP) and bisphosphonates [15].

Due to advance of operating optics, the possibilities for surgeons have expanded significantly; it has become possible to use blood-supplied tissue complex transfer. It led to the development of microsurgical methods in the treatment of children with bone defects and pseudarthrosis [14, 16-21]. The use of these methods has shown its effectiveness in the treatment of children with NF1, although the risk of complications associated with the consolidation of the donor and recipient bones is high. Therefore, the use of microsurgical methods in children with this pathology, according to the literature, is still limited. The literature reports descriptions of case reports [6, 14, 22].

Thus, at present, none of the proposed methods can be considered "ideal". The situation requires further study and improvement of algorithms and treatment tactics.

**Purpose** To show the effectiveness of using microsurgical autologous vascularized fibula transfer for plasty of bone defects in children with neurofibromatosis type I.

## MATERIALS AND METHODS

Twenty-seven children with pseudarthrosis and bone defects of the upper and lower extremities due to neurofibromatosis type I were admitted at the department for reconstructive microsurgery and hand surgery of the Turner Center for Children's Traumatology and Orthopaedics of the RF Ministry of Health from 2012 to 2021. Type I neurofibromatosis was diagnosed based on criteria adopted by the international community for the study of this pathology, such as the presence of 6 or more café-au-lait spots larger than 5 mm in the prepubertal period or 15 mm in the postpubertal period; the presence of 2 or more neurofibromas, as

well as defects (pseudarthrosis) of long bones. The diagnosis is established if 2 or more of these criteria are present in a patient. All children underwent clinical and instrumental examinations upon admission, as a result of which the diagnosis of neurofibromatosis type I was made in all patients included in this study. The diagnosis was confirmed genetically in 5 patients. The gender distribution was 20 boys and 7 girls. The mean age of the patients was 7 years 8 months (range from 4 years 2 months to 14 years 5 months). Bone defect was localized in forearm bones in 19 patients and in the lower limb in 8 patients.

Criteria for inclusion in the study:

- neurofibromatosis type 1 and pseudarthrosis and defects in the long bones of the forearm and lower leg;
- Neurofibromatosis type 1 in children who underwent plasty of bone defects and pseudarthrosis with the method of microsurgical transfer of blood-supplied bone autografts.

Exclusion criteria:

- Neurofibromatosis type 1 in children who were treated not with microsurgical but with traditional methods of bone grafting.

Statistical analysis was carried out on the basis of parametric and non-parametric criteria. The analysis of quantitative scales for the normality of distribution was carried out according to the Kolmogorov-Smirnov D-test and the Shapiro-Wilk W-test. Statistical analysis was carried out using the IBM SPSS Statistics software package (version 25.0).

Upon admission, the patients underwent a complex of clinical and instrumental studies, including clinical examination, laboratory tests necessary to assess preoperative risks. At admission to the clinic, all children underwent radiography of the affected and intact limb to determine the size and location of the defect, as well as computed tomography with 3D reconstruction to assess the true length of the pseudoarthrosis, the length and width of the medullary canal, as well as visualization of spatial relationships in the joints resulting from pseudarthrosis. Magnetic resonance imaging with a vascular regimen and Dopplerography of the donor and recipient zones were performed in 9 patients (33 %). These studies enabled to carry out preoperative

planning of microsurgical bone defect reconstruction and consider the anatomical features of blood supply to the donor and recipient zones, which excluded the development of vascular complications and lysis of the transferred bone segment in the future.

Based on anamnestic and clinical data, it was determined that 63 % of children had a family history of this pathology. All patients had clinical manifestations of neurofibromatosis type I such as café-au-lait spots and pseudoarthrosis of long bones (Table 1).

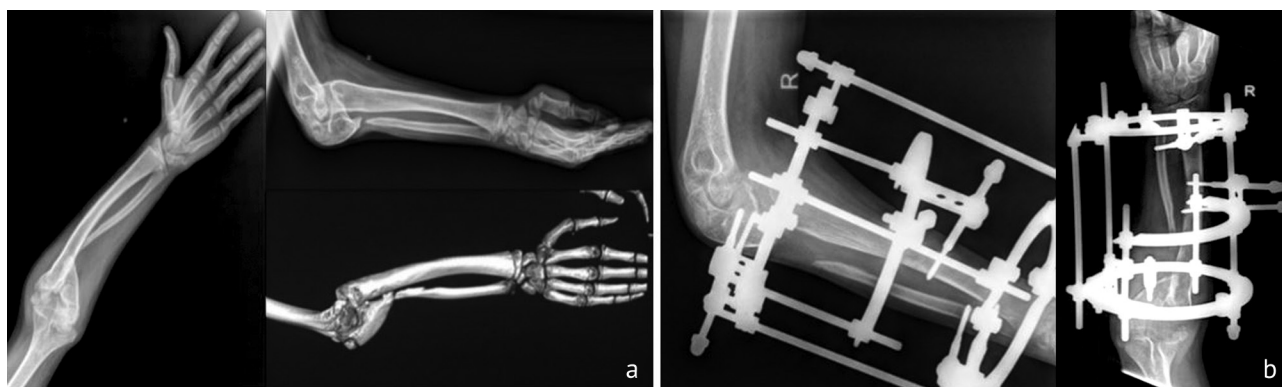
Most children had a history of limb injuries that resulted in pseudarthrosis that accounted for 78 %. Therefore, 89 % of them presented with evident limb deformities, and deformity of the tibia was observed in all the patients with tibial pseudarthrosis at admission. Previous interventions for the disease had been already performed in 93 % (24 cases); thereby 56 % of children had more than three operations per person. It should be noted that the Ilizarov fixator was mounted in 22 patients as a preparation stage to microsurgical intervention for primary deformity correction, bone fragment alignment and formation of the diastasis between the fragments in order to further correct the segment length (Fig. 1).

All children, depending on the location of the defect and the level of pseudarthrosis, were divided into 5 groups. The first group included patients who had only a defect of the radius, the second had an isolated defect of the ulna, the third group - a defect of both the radius and ulna. The fourth group consisted of children with isolated defects of the tibia, the fifth included children with defects of both bones of the lower leg (Fig. 2).

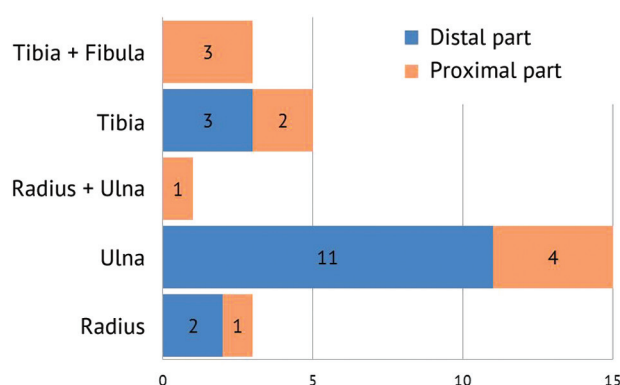
Table 1

Main features of treated patients

Characteristics	Number	
	abs.	%
Family history of NF1	17	63
Clinical manifestations of café-au-lait spots	27	100
Pseudarthrosis of long bones	27	100
Two or more neurofibromas	12	45
History of trauma/fractures	21	78
Limb deformity at time of admission, total number	24	89
♦ Upper limbs	16	84
♦ Lower limbs	8	100
Conseervative treatment (prior to admission)	3	11
Surgical treatment (prior to admission), total number	24	93
♦ once	1	4
♦ twice	8	31
♦ three and more times (not including a preparation stage for microsurgery)	15	56
♦ as a preparation stage for microsurgery (placement of the Ilizarov fixator)	22	81



**Fig. 1** Patient K. Radiographs of the right forearm before (a) and after the 1st stage of surgical treatment (placement of the Ilizarov fixator) (b)



**Fig. 2** Location and level of bone defects and pseudarthrosis

Based on the data obtained, it was found that pseudarthrosis in 71 % of children admitted to the department for microsurgical intervention was located in the upper limb, mainly in the ulna.

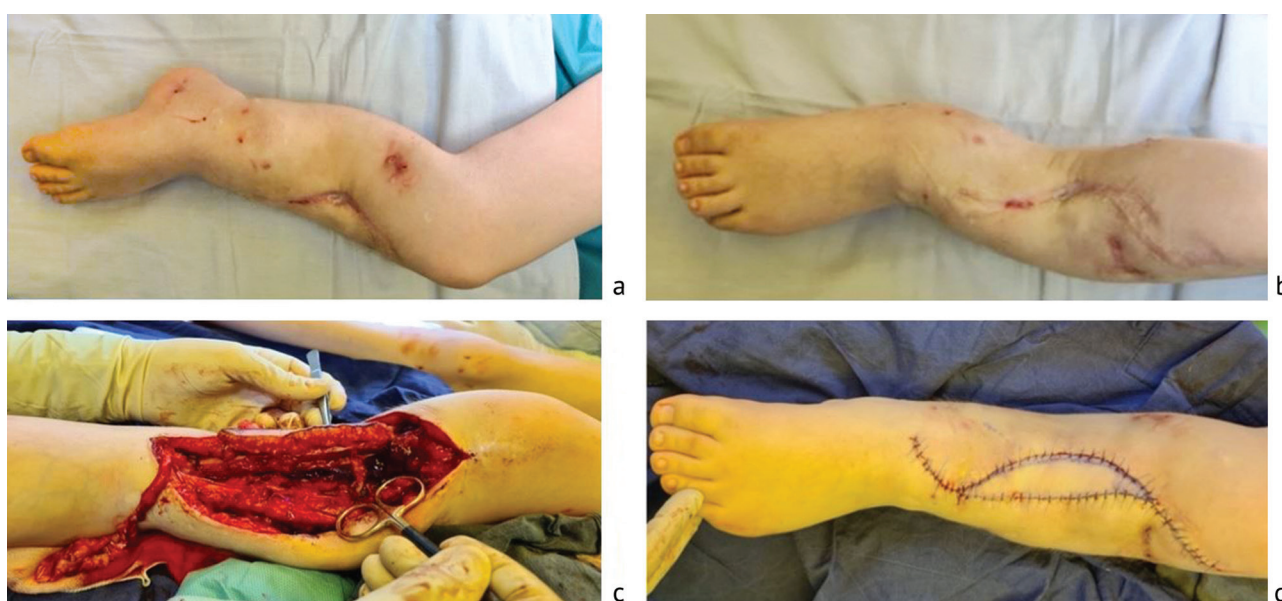
Lower limb pseudarthrosis in three patients was found in both bones of the lower leg (37 %), in 5 patients only

the tibia was affected. At the same time, pseudarthrosis in on the upper and lower limbs was located in the distal part in 59 % of cases.

The extent of the bone defect depended on the location of the pathological process. Thus, it was more than 80 % in 13 patients and in the rest of the children it did not exceed 1/3 of the bone length. The true size of the defect ranged from 5 to 15 cm (12 cm on average).

The indication for microsurgical reconstruction of the defect was the length of the defect more than 5 cm, failure of the previous stage of treatment (CDA, bone grafting with non-vascularized auto- or allografts, etc.).

Due to the extent of the defect, all children underwent microsurgical reconstructive surgery using a blood-supplied fibula autograft on a vascular pedicle. In 5 patients, due to the presence of gross cicatricial changes in the soft tissues following multiple surgical interventions, the graft sampling included a fibular flap to replace the soft tissue defect (Fig. 3).



**Fig. 3** Patient M. Clinical manifestations at admission (a, b); transfer of the fibular flap and bone (c); view after surgical treatment (d)



The surgical intervention was started from the recipient zone. If needed, partial or complete dismantling of the Ilizarov apparatus was carried out. Next, an arch-like incision was made in the projection of pseudarthrosis (bone defect). During the revision of the wound on the forearm, multiple fusiform thickening from the side of the ulnar nerve (in the form of a pigtail) was revealed in 27 % of cases. Then, the proximal and distal bone fragments, as well as the connective tissue bands between them, were isolated from the soft tissues, the pathologically altered ends of the distal and proximal fragments were resected, and the total length of the defect was measured. Next, the fibula autograft with feeding vessels (peroneal artery

with accompanying veins) was mobilized according to the standard method. To assess the adequacy of blood circulation, the so-called "buoy flap" was included in the autograft. In cases with the excision of scar tissues in the recipient area, there was a soft tissue defect and the autograft was formed with a fibular flap. The graft was fixed using an axial pin of various diameters. If necessary, osteosynthesis was additionally performed using remounting of the CDA.

Early postoperative complications were noted in 2 patients and consisted of bleeding from the branches of the vascular pedicle of the autograft, which was eliminated during surgery. There were no late postoperative complications.

## RESULTS

The mean time for fragment consolidation was 12 weeks  $\pm$  4 weeks. The maximum follow-up was 10 years, the minimum – 6 months. The results of treatment depending on the location of the defect are shown in Figure 4.

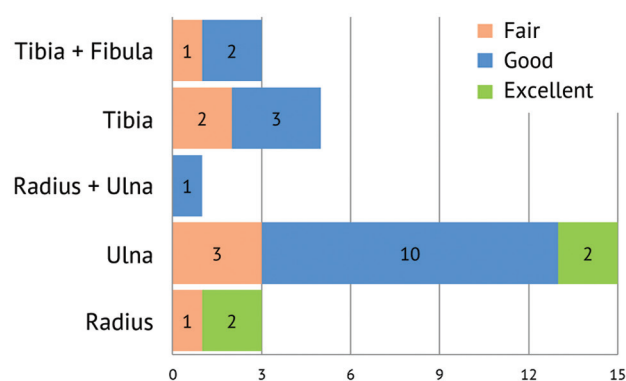


Fig. 4 Treatment results of patients with NF1

The evaluation of the outcomes was carried out according to the scale developed at our department on the basis of examination of patients and radiography of the affected limb 1 year after surgical treatment. This scale included excellent, good, fair and poor results.

An excellent result was a position when the patient showed complete consolidation of the fragments after surgical treatment, and later the child no longer needed surgical treatment in this area. The proportion of such children was 15 %. Complete consolidation of fragments

of the recipient and donor bone after surgical treatment was considered a good result; however, secondary deformities or shortening of the limb persisted, which subsequently required repeated surgical interventions. In our case, the proportion of such children was 59 %. In 6 patients who underwent microsurgical reconstruction of the tibia, graft hypertrophy was noted after 3 years: the final diameter of the reconstructed tibia almost corresponded to that of a healthy limb, which was one and a half times greater than the initial diameter of the fibula before transfer. Fracture of the graft occurred in 2 patients with reconstruction of the tibia more than a year after microsurgical reconstruction; most likely due to failure to follow the recommendations of the attending surgeon and full axial load without additional support.

Fair results were found in 7 patients with a proximal pseudarthrosis. The lack of consolidation between the autograft and the fragment of the recipient bone required a second surgical intervention, bone grafting with a cancellous-cortical bone graft from the iliac crest. This situation was regarded as a fair result, although the goal of restoring the bone was achieved. According to literature sources, failure of consolidations happens in up to 25-30 % if pseudarthrosis is located in the proximal bone part [7, 9]. In our study, satisfactory results were 26 %. At the same time, there were no cases of lysis of the transferred blood-supplied bone autograft, which would mean a poor result of treatment.

## DISCUSSION

According to the literature, one of the methods of bone grafting for defects or pseudoarthrosis in both children and adult patients is microsurgical autografting of vascularized bone fragments [9, 13, 18-20, 23-28]. However, in children with neurofibromatosis type I, the use of this treatment method is rather limited, and is

associated with an increased risk of complications. The reports are descriptions of clinical cases [14, 27, 29], and only a few studies provide an analysis of a more numerous series on the surgical treatment of congenital pseudarthrosis, including those that developed due to neurofibromatosis [16, 17, 23, 30].

Most authors start performing microsurgical transfer of blood-supplied bone autografts at the age of 5-7 years [17, 26, 31, 32]. Bone resorption and the development of pseudarthrosis of the forearm and lower leg bones usually occur by this age, which was the indication for the start of surgical treatment. Some authors report successful results of bone autograft technique at an earlier age (3-4 years). El-Gammal reported the treatment outcomes of 21 children and showed that the restoration of the integrity of the bone segment is more effective if microsurgical interventions are performed at the age of 3-4 years. In our study, the youngest age of a child who underwent microsurgical autografting of a blood-supplied bone segment was 4 years, and the average age of children was 7 years 8 months. The older age of the others was due to the use of multiple and unsuccessful traditional methods of surgical treatment prior to the microsurgical stage.

An alternative technique used in patients with the lower leg pseudarthrosis due to neurofibromatosis is non-free bone Ilizarov grafting (bone transport). The authors report a high rate of fusion, an acceptable period of hardware fixation, and good long-term results [35-37]. However, a pronounced scars in the tibial area (due to numerous previous surgical interventions), as well as the size of the post-resection defect (more than 2/3 of the diaphysis) did not allow us to use this technique.

A number of authors report on ankle joint instability in the donor area after the harvesting of a bone autograft [16, 18, 19]. This complication occurs in the long-term of more than 1 year after surgery and is associated with a violation of the stability of the ankle joint due to a short (less than 6 cm) distal fragment. Taking this fact into account, the fibula autograft was cut in such a way that the length of the remaining distal fragment of the fibula was at least 7 cm.

According to the literature, primary consolidation at the bone-graft interface is achieved in 96-98 % of cases, and the average consolidation time ranges from 2 to 10 months [7, 28, 31, 33]. The average period of fragment consolidation in our study was 12 weeks  $\pm$  4 weeks. Some literature sources pointed that the choice of a method for fixing the bone autograft can affect the outcome of treatment. Thus, in cases of intramedullary fixation with a rod or screw, a lower frequency and a longer union time were observed compared with external fixation: 76 % and 9 months versus 100 % and 1.9 months, respectively [26]. However,

in neurofibromatosis type I, the process of consolidation in the proximal part of the recipient bone and the bone fragment of the receiving bed is usually slowed down due to the changes in blood supply in this area due to the underlying disease [7, 9]. At the same time, Kesireddy et al [34] observed that in external fixation, secondary fractures of the restored bone are more frequent compared with the cases of intramedullary fixation: 45 % versus 29 %, respectively. In the El-Gammal study [30], re-fractures occurred in 21 cases (51.3 %), and in almost half of the patients in this group they recurred 2 to 4 times.

All authors who performed bone grafting of tubular bones using a blood-supplied bone fragment claim that these autografts are more effective than other methods of bone grafting, especially for closure of extensive bone defects. Despite the development of bone substitutes, growth factors, endoprotheses and distraction osteosynthesis, the method of bone grafting using a blood-supplied bone autograft remains relevant and often indispensable in the most difficult cases. The key to the success of traditional bone grafting is the blood supply to the recipient bone and surrounding tissues [18, 19, 23]. Without an adequate blood supply, non-vascularized bone grafts are unable to remodel and there is delayed consolidation between them and the recipient bone. To control the blood supply of the bone fragment, in most cases, we included in the graft a skin flap on the perforating cutaneous branches of the peroneal artery, the so-called "buoy". The absence of circulatory disorders in the "buoy" flap allowed us to conclude that, the blood supply to the autograft was adequate in all patients included in our study. Due to the restoration of blood flow in the transferred vascularized autograft, it remains alive, while maintaining the possibility of bone tissue remodeling. In these cases, a callus between the autograft and the recipient bone develops, and consolidation occurs similar to the regular fracture [19, 23, 24, 33]. Moreover, the analysis of our long-term results showed that the transferred bone autograft, due to blood supply and functional load, tends to hypertrophy. And the fragment of the fibula on the vascular pedicle, grafted into the defect of the tibia, developed the same diameter as the recipient tibia. And, although the rate of complications is more than 50 % (nonunion in the bone-graft interface, infection of postoperative wounds, neuropathy), there are no alternatives for pediatric patients with extensive defects, especially if the articular parts of the bone are involved in the pathological process [20].

## CONCLUSION

This study shows the relevance, high efficiency and the need to use the method of microsurgical autologous transfer of the vascularized fibula to close extensive bone defects in children with neurofibromatosis type I.

In the majority of cases, there is a significant reduction in the union time (by 3-4 times) between the transferred autograft and bone fragments in the recipient zone compared to free non-vascularized bone autografts. Despite the improvement in blood supply in the recipient area due to a vascularized bone autograft, there was

delayed consolidation resulting in pseudarthrosis in seven cases of our study (usually in the proximal bone-autograft junction), which required a second surgical intervention. Thus, we can conclude that microsurgical transfer of a vascularized bone autograft is not a panacea, but one of the necessary and effective stages in the complex surgical treatment of affected by neurofibromatosis patients with extensive bone defects. The effectiveness of these surgical interventions is confirmed by a high rate of good and excellent results, 74 %.

**Conflict of interests** The authors declare that there are no clear and potential conflicts of interests related to the publication of this study.

**Funding source** The study was carried out as part of the state assignment "Use of microsurgical autologous grafting of blood-supplied bone segments in children with congenital and acquired pathology of the musculoskeletal system" (state registration number of research, development and technological works 121031700123-3).

**Ethical approval** The study was approved by the institution ethical board. Protocol № 22-4 dated 15.12.2022.

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The article was submitted 20.02.2023; approved after reviewing 14.04.2023; accepted for publication 20.06.2023.

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