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Combined bone plasty interventions for rehabilitation of patients with congenital pseudarthrosis of the tibia

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The problem of treating patients diagnosed with congenital pseudarthrosis is due to severe and unpredictable course of this disease, difficulties in choosing surgical techniques, and frequent relapses of the process. **Purpose** Compare the results of treatment of patients with congenital pseudoarthrosis of the tibia (CPT) using non-free Ilizarov bone plasty and a combination of grafting according to Masquelet technique with Ilizarov bone transport. **Materials and methods** The outcomes of 13 patients with CPT aged 1.5 to 35 years who had been treated since 2009 were analyzed. The main group (n = 6) included patients treated using a combination of the Ilizarov and Masquelet methods. In the control group (n = 7), patients were treated only with Ilizarov transosseous osteosynthesis. Histological examination of the periosteum and tissues of the resected pseudarthrosis area was performed. In the index group, fragments of a biomembrane formed around a cement spacer temporarily bridged the diastasis after resection of pseudarthrosis were studied by light and electron scanning microscopy. **Results and discussion** Patients of the analyzed groups had a comparable duration of treatment. In the main group, bone fusion was observed in 83 % of cases, while no relapse was detected in the long-term follow-up. The obtained treatment result was achieved due to good vascularization of the biological membrane formed on the spacer surface, which provides trophic effect at the stages of defect management in the area of resected pseudarthrosis. The presence of poorly differentiated osteogenic cells in it promoted active osteogenesis. In patients of the control group, fusion was achieved in all cases, but relapses in the long-term occurred in 71 % of cases. **Conclusion** The basis of the methodological principles in treating patients with CPT is the use of additional options for osteoplastic interventions and materials in the pseudarthrosis zone. Fixation of a segment without stimulation of bone regeneration does not bring the desired effect. The complex use of non-free Ilizarov bone grafting according to Ilizarov and Masquelet technology achieves bone fusion of the congenital pseudoarthrosis and disease-free course of the conditions.
Keywords: pseudoarthrosis, Ilizarov, Masquelet, biomembrane

INTRODUCTION

The incidence of congenital pseudarthrosis of the lower leg bones is relatively low, one case per 140.000-190.000 newborns [1, 2]. The interest of orthopedists to this condition is due to the severe and unpredictable course of the disease, difficulties of surgical treatment, and frequent relapses of the process. Transosseous osteosynthesis offers a wide variety of surgical technologies, but they do not guarantee a positive outcome of rehabilitation [3, 4, 5, 6]. Bone callus in the zone of pseudarthrosis remains at risk of recurrence of a pathological fracture in the long term. It is partly associated with segment deformities, shortening, contractures of adjacent joints, and pathological deformities of the feet.

The lack of a unified view on the etiopathogenesis of the disease complicates the problem. An association was established between neurofibromatosis type 1 (NF1) and congenital pseudarthrosis of the tibia (CPT). However, the mechanisms of CPT in NF1 have been unexplored yet [7]. In the opinion of many authors, the main cause of the disease is associated with gene mutations [8, 9, 10, 11]. The result of mutation in NF1 is a decrease in the activity of neurofibromin and preservation of active forms of RAS. It affects the natural osteoblastic differentiation [9, 11, 12]. The excess of RAS contributes to the activity of osteoclast precursors and osteoclasts themselves, which explains the incidence of repeated fractures in patients with this pathology [10, 13]. However, genetic abnormalities are not typical for all cases of pseudarthrosis and do not provide a full explanation of the pathogenesis of the development of this congenital disease [11, 14, 15]. It is generally accepted that an intraosseous neurofibroma provokes pathological fractures of the lower leg bones resulting in pseudoarthrosis in the area of its localization.

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However, studies using morphological methods did not confirm this theory [1, 10, 14, 15, 16].

Current literature indicates that a pathological change in tissues in the pseudarthrosis zone is associated with osteolytic activity of a structurally altered periosteum [17, 18, 19, 20, 21].

The essence of a number of technologies (in particular, according to Masquelet technique) is a radical solution using a total excision of the changed periosteum and formation of an inductive membrane. The inductive membrane according to the Masquelet technique creates the conditions for the synthesis of bone growth factors, including bone morphogenetic proteins. Despite the undeniable successes in reconstructive surgery in the treatment of patients with congenital pseudarthrosis of the lower leg bones, orthopedists report high risks of relapse. Dissatisfaction with the results of surgical treatment and, first of all, with the recurrent nature of the process, prompted us to search for new technological solutions based on a combination of surgical techniques and approaches.

Purpose Compare the results of treatment of patients with congenital pseudarthrosis using traditional non-free bone plasty according to Ilizarov and a combination of grafting according to Masquelet with bone transport.

MATERIAL AND METHODS

We analyzed the results of treatment of 13 patients with CPT. The typical CPT location was the lower third of the tibia. In 61.5 % of cases (8 patients), the etiology of the disease was associated with type I neurofibromatosis, in 30.8 % (4 patients) with fibrous dysplasia, and one case was idiopathic. All patients showed CPT type 4 according to the Crawford classification.

Prior to admission to the clinic of RISC for RTO, all patients were treated surgically at other hospitals (1–8 failed outcomes). One patient had bilateral CPT. CPT was located in the upper third of the tibia in two patients. Stiff deformity at the level of CPT was detected in three patients (23.1 %). Twelve patients had pathological mobility of tibial fragments (Table 1).

Shortening of the segment before treatment at the Ilizarov Center averaged 8.1 cm and made 36.3 % of the length of the contralateral limb segment.

Only three patients (23.1 %) had full movement of the ankle joints (Table 2).

There were two groups of patients. The index group included six patients treated using a combination of the Ilizarov and Masquelet methods. The control group consisted of seven patients in whom only Ilizarov transosseous osteosynthesis was used.

Table 1

Distribution of patients by pathological mobility of tibial fragments before treatment

Pathological mobility	Number of patients	%
Less than 5º	5	38.5
Within 5 to 10º	6	46.21
More than 10º	1	7.7
Stiff angulation	1	7.7

Table 2

Anatomical and functional disorders of the affected segment

Type of disorder	Number of patients	%
Weight-bearing disorders	13	100.0
Angular deformity	13	100.0
Anatomical shortening	11	84.6
Disorders of adjacent joint functions	10	76.9
Foot deformities	12	92.3

Patients of the main group underwent resection of the pathological area of the bone and periosteum and a spacer, made of methyl acrylate cement, was introduced in the defect formed. The estimated level of resection was determined in the preoperative period according to the data of radiological methods (radiography and CTG). The final resection was determined intraoperatively by visual estimation of the state of the bone tissue and periosteum. The main criterion for the level and volume of resection was the appearance of bleeding at the ends of the fragments, the so called "bloody dew". The segment was fixed with the Ilizarov apparatus, consisting of 2–4 supports. After 6–8 weeks, the spacer was removed; an osteotomy of the longest fragment or of two opposite ones was performed. On the 5th–7th day, bone fragment transport started in order to bridge the defect. The rate of distraction was individual, judged by the activity of distraction osteogenesis in control radiographs. The rate of distraction ranged from 0.5 to 1 mm per day (0.25 mm × 2–4 steps) throughout the day. Upon contact between the fragments, the apparatus was put into fixation mode but supportive compression at the junction of the fragments was executed. Fixation of the segment with the apparatus until consolidation of bone fragments continued from four to six months.

Patients in the control group underwent the surgery of transosseous osteosynthesis of the lower leg bones with open adaptation of the ends of the fragments in order to increase the bone mass volume in the pseudarthrosis zone. Preference was given to mutual immersion of the ends of the fragments or overlapping the pseudarthrosis zone with the bone fragment. The segment was fixed with the Ilizarov apparatus, assembled of 3–4 supports. Compression at the junction of the fragments was maintained once every 10–14 days until bone union.

Patients of the analyzed groups had a comparable duration of treatment. The average fixation time with the apparatus on was 183.3 days.

RESULTS

In the main group, there were no recurrences at the long-term follow-up period of more than a year. In the control group, fusion was achieved in all cases, which is consistent with the data of our previous studies [4, 5]. In the control group, one episode of disease recurrence occurred in four patients; one patient had two episodes (Table 3).

Table 3

Treatment outcomes

Result	Index group (n = 6)		Control group (n = 7)	
	number of patients	%	number of patients	%
Bone union achieved	5	83	7	100
Recurrence	0	0	5	71

In both groups, the periosteum of the tissues of the resected pseudarthrosis was studied histologically.

In the main group, fragments of a biomembrane formed around a cement spacer, temporarily bridging the defect gap after resection of pseudarthrosis, were investigated. Material was taken intraoperatively. Tissue fragments were fixed in a 10 % solution of neutral formalin, decalcified in a mixture of hydrochloric and formic acid solutions, and dehydrated in ethanol (from 80 to 100°). Then the pieces of tissues were poured into paraffin.

Histological sections 5–7 μm thick were prepared on a sledge microtome (Reichard, Germany), stained with hematoxylin and eosin according to Masson, and immunohistochemical staining was performed using polyclonal antibodies to osteopontin (protocol and reagents of Abcam, England).

Microscopic light-optical study of histological preparations was performed using an AxioScope. A1 stereo microscope and an AxioCam ICc 5 digital camera, complete with Zen blue software (Carl Zeiss MicroImaging GmbH, Germany).

The architectonics of the fibrous skeleton of the biomembrane was studied using a JSM-840 scanning electron microscope (Japan).

Methods of descriptive statistics were used. Data processing was performed using Microsoft Excel.

The study complies with all the requirements of the 2013 Helsinki Declaration Revision

Results of histological study

Histological research methods in patients with type I neurofibromatosis revealed bone tissue sections with osteoporotic and/or dystrophic changes in the resected fragment from the pseudoarthrosis zone. There were cystic cavities, rarefaction of bone structures, and a significant number of empty osteocytic lacunae as well as avascular zones were detected. Foci of necrosis were frequent.

Cavities filled with loose fibrous connective tissue with single microvessels, most often of venous type, with dilated neglected lumen were found in bone tissue. Osteoclasts were attached on the inner surface of the cavities. Also, areas of fibrous cartilage and fibrous connective tissue with signs of fibrosis, calcification sites were visualized.

Signs of fibrosis were revealed in the thickened periosteum. The lumens of most of the microvessels were obliterated, and nerve trunks were destructively altered. Walls of some arteries were thickened.

Presence of cystic cavities was a characteristic change in the bone tissue of a compact plate bordering the pseudarthrosis site in patients with fibrous dysplasia. In the bone tissue itself, there were unevenly distributed fields with an increased density of osteocytes and areas with a low cell density or cell-free fields that border areas of fibrous tissue with rare bone trabecules of a reticulofibrotic structure included in it. Extensive foci of sclerosis in the compact plate were found, alternating with areas with poorly expressed osteogenesis, mainly at the ends of fragments. In the area of the pseudarthrosis, sections of fibrous cartilaginous tissue were seen.

Thus, according to our findings, one of the reasons of dystrophic changes in bone tissue, which led to CPT in patients with neurofibromatosis, was locally associated with impaired neurotrophic function. It is evidenced by pathological destructive changes in blood vessels and nerves. In patients with fibrotic dysplasia, osteogenesis disorders were associated with disturbance of osteogenic differentiation of cells, shifted towards desmogenesis.

However, the histological study of the connective tissue membrane that formed around the cement spacer in patients of the main group showed that, regardless of the pathology, it had the same structure at the time of extraction of the spacer.

At the macro level, the soft tissue membrane was represented by an elastic connective tissue or a whitish film with microvessels and areas of brown blotches.

At the micro level, the connective tissue membrane had a three-layer structure. The first layer, which is closest to the spacer, consisted of low-differentiated connective tissue cells with osteogenic potency lining it, located in the structure of fibrous connective tissue extended along the long axis of the spacer (Fig. 1a). The belonging of the cells, lining the spacer, to osteogenic differentiation was confirmed by staining of the pericellular matrix and the cells themselves in shades of red using the Masson technique (Fig. 1b), as well as by the expression of osteopontin by most of these cells during the immunohistochemical reaction (Fig. 1c).

The second layer was represented by loose fibrous connective tissue with a large number of capillary loops (Fig. 2a), in which pronounced hyperemia of the vessels was observed, accompanied by local erythrocyte diapedesis in some cases.

Small and medium vessels of the arterial type mainly had a structure close to normal (Fig. 2b).

The third (outer) layer consisted of a less vascularized connective tissue with pronounced tortuosity of collagen fibers (Fig. 2c). Small neural trunks, mainly of normal structure, were revealed in it. However, in patients with neurofibromatosis, some nerve branches showed signs of destruction (Fig. 2d).

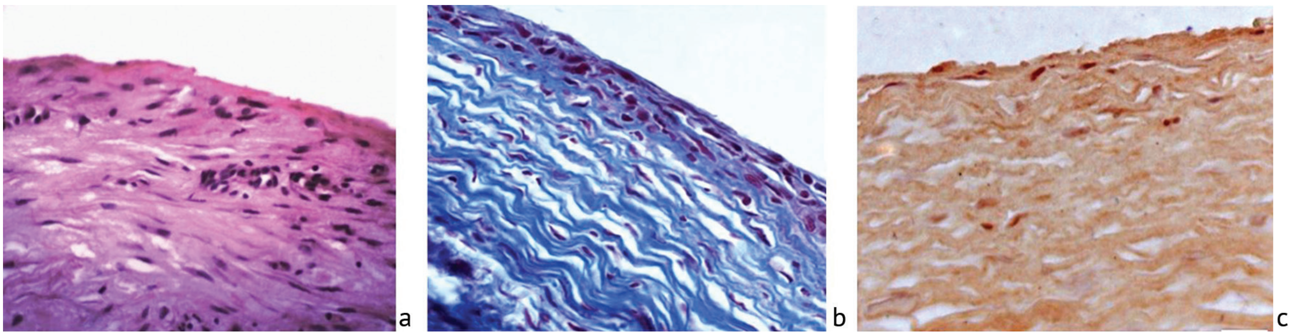

Fig. 1 The inner layer of the biomembrane formed on the surface of the cement spacer: ***a*** staining with hematoxylin and eosin; ***b*** according to Masson; c expression of osteopontin (immunohistochemical staining). Magnification – 600 ×

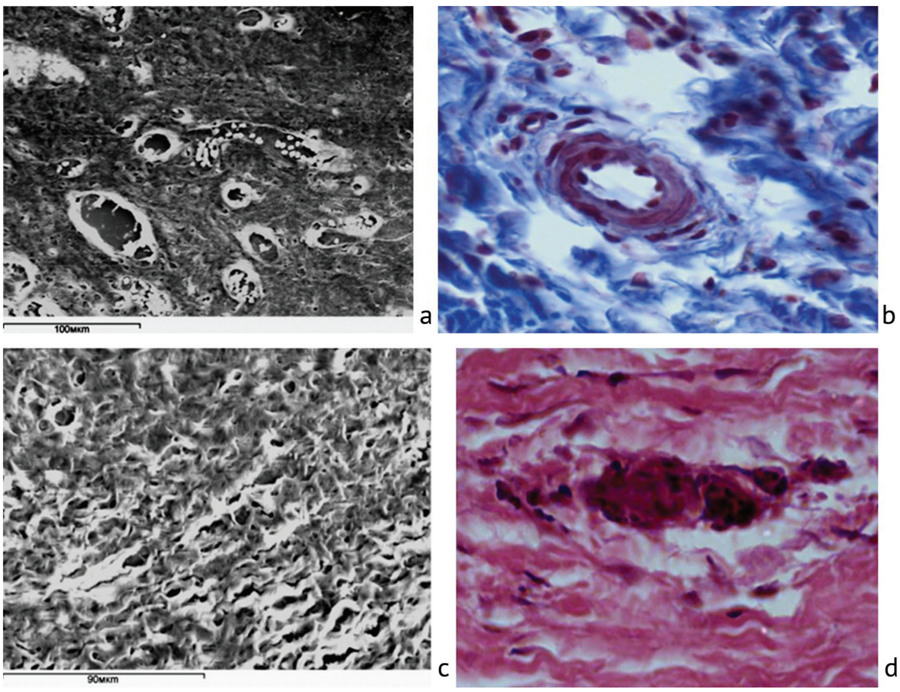

Fig. 2 Structural features of the middle and outer layers of the biomembrane: ***a*** vascularized layer of the connective tissue membrane featuring an increased density of microvessels; ***b*** artery of a typical structure in the middle layer of the biomembrane; ***c*** outer layer of the connective tissue membrane with sinuous collagen fibers; ***d*** destructively modified nerve stem in the outer layer of the biomembrane; ***a***, ***c*** scanning electron microscopy, magnification: ***a*** – 200; ***c*** – 550 ×; ***b*** Masson staining, magnification – 600 ×; ***d*** staining with hematoxylin and eosin, magnification – 600 ×

Thus, good vascularization of the biological membrane formed on the spacer surface provided a trophic effect at the stages of defect management in the area of resected pseudarthrosis, while presence of poorly differentiated osteogenic cells in it promoted active osteogenesis. A newly formed connective tissue membrane was formed, similar in structure and function to the normal periosteum instead of the resected deformed periosteum.

It should be noted that single nerve trunks in the newly formed periosteum or biological connective tissue membrane underwent destructive changes again in patients with neurofibromatosis, which could have a negative impact on the achieved treatment result in the long term.

DISCUSSION

The technologies described in this paper are based on the principles of non-free bone plasty according to Ilizarov, as well as on the combination of transosseous osteosynthesis and Masquelet technology. A number of technological solutions currently has no domestic and foreign analogues and has not published yet.

In our opinion, the basic concept for restoring segment integrity is to increase bone mass in the problemati area and is based on the idea of MacFarland surgery, proposed in 1951. Later, surgeons used various osteoplastic materials, mainly allo- and autografts, including vascularized ones, duplicated fragments or performed bone grafting with local tissues [3, 4, 5, 8, 22, 23, 24, 25]. To fix the affected segment, orthopedists used external fixation and internal one, mainly intramedullary fixators, or combined osteosynthesis techniques [4, 5, 23, 24, 25, 26, 27, 28].

Our data on the pathogenesis of tissues in the CPT region in patients with type I neurofibromatosis and with a diagnosis of fibrotic dysplasia are consistent with modern histological and pathomorphological studies, indicating significant anatomical and functional tissue disorders in the pseudarthrosis area [11, 18, 19; 20, 22, 23, 29].

Based on the results of the study, we believe that compromised neurotrophic functions are the main reason for the development of dystrophic changes in the bone tissue, which led to CPT in patients with neurofibromatosis at the local level. In patients with fibrous dysplasia, the disturbance of osteogenetic processes associated with defective osteogenic differentiation of cells is shifted towards desmogenesis.

Findings confirming our conclusions were reported in other studies [30, 31, 32].

Previous information about the absence of significant structural changes in soft tissues in patients with fibrous dysplasia and patients with type I neurofibromatosis (J. Briner, 1973; M. Blauth et al., 1984) is debatable, because our study found more pronounced pathological changes in the periosteum blood vessels and nerves in patients with neurofibromatosis [33, 34]. This is also due to the difference in the causes of the CPT development at the genetic level. H.V. Leskelä et al. noted similar differences in the pathogenesis of bone tissue in the pseudoarthrosis area in patients with type 1 neurofibromatosis as compared to patients with other congenital orthopedic pathologies [10].

Good vascularization of the biological membrane on the surface of the spacer revealed by us explains the persistent positive results of CPT treatment in patients of the main group according to the combined technology proposed. The mechanism consists in providing the newly formed vascularized connective tissue biomembrane with neurotrophic function in the area of resected pseudarthrosis at all stages of defect management, and the presence of poorly differentiated osteogenic cells in it contributes to active osteogenesis in this area.

Other researchers that used the Masquelet technique for bone defects caused by infection and resection of the tumor, as well as some experimental studies, reported that the biomembrane has a rich capillary network and secrets the growth factors VEGF and TGF-beta 1, as well as the osteoinductive factor (BMP -2) [35, 36, 37, 38, 39, 40], which is consistent with the results of this study, confirming the trophic and osteogenic function of the biomembrane.

Thus, instead of the resected pathologically changed periosteum by the time the temporary cement spacer is removed, a connective tissue membrane is formed on its surface, similar in structure and function to it, a kind of neo-periosteum. A.C. Masquelet, L. Obert (2010) described the cement-facing biomembrane surface as a synovium-like epithelium, and the outer layer as a connective tissue layer consisting of fibroblasts, myofibroblasts, and collagen. The authors showed that membrane extracts stimulate proliferation and differentiation of bone marrow cells by the osteoblastic way [41]. In our study, the cells of the inner layer of the biomembrane lining the spacer structurally corresponded to poorly differentiated connective tissue cells with signs of osteogenic differentiation, as evidenced by the expression of osteopontin.

However, this process requires further accumulation of material and its analysis.

It should be noted that part of the nerve trunks in the newly formed biological connective tissue membrane underwent destructive changes again in patients with neurofibromatosis,, which, possibly, in the long-term follow-up period, can negatively affect tissue trophism and, as a result, the achieved treatment result, increasing the risk of relapse diseases.

CONCLUSION

The optimal approach to rehabilitation of CPT patients is to achieve full fusion of bone fragments through formation of a sufficient bone mass volume that minimizes the risk of relapse, eliminating deformities of fragments and lower leg in general, as well as foot malposition. The use of additional options for osteoplastic interventions and materials in the area of pseudarthrosis should form the basis of methodological principles. A purely mechanical approach to CPT which provides only fixation without stimulating bone regeneration does not bring the desired effect due to the pathological nature of the bone in the pseudarthrosis area. The monotechnological approach does not ensure a disease-free course in the long-term. The complex use of non-free bone grafting according to Ilizarov and Masquelet technology provides full bone fusion of the congenital pseudoarthrosis and disease-free course.

***Ethical statement**: all research-based procedures involving patients were performed in accordance with the requirements of the 2013 Helsinki Declaration Revision. Formal informed consent is not required for this type of study.*

***Conflict of interest**: not declared.*

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REFERENCES

1. Andersen K.S. Congenital pseudarthrosis of the leg. Late results. *J. Bone Joint Surg. Am.*, 1976, vol. 58, no. 5, pp. 657-662.
2. Kim H.W., Weinstein S.L. Intramedullary fixation and bone grafting for congenital pseudarthrosis of the tibia. *Clin. Orthop. Relat. Res.*, 2002, no. 405, pp. 250-257. DOI: 10.1097/00003086-200212000-00032.
3. Borzunov D.Y., Dyachkova G.V., Kutikov S.A. Reabilitatsiia bolnykh s vrozhdennymi lozhnymi sustavami kostei goleni metodom chreskostnogo osteosinteza po Ilizarovu [Rehabilitation of patients with congenital pseudoarthroses of leg bones by the transosseous osteosynthesis method according to Ilizarov]. *Genij Ortopedii*, 2012, no. 3, pp. 118-121. (in Russian)
4. Kutikov S.A., Lettreuch A.R., Saighi-Bouaouina A., Borzunov D.Y., Dyachkova G.V. Vrozhdennyi lozhnyi sustav goleni. Problemy, vozmozhnye variant resheniia [Pseudoarthrosis of the leg. Problems, possible solutions]. *Genij Ortopedii*, 2014, no. 3, pp. 24-30. (in Russian)
5. Borzunov D.Y., Chevardin A.Y., Mitrofanov A.I. Management of congenital pseudarthrosis of the tibia with the Ilizarov method in a paediatric population: influence of aetiological factors. *Int. Orthop.*, 2016, vol. 40, no. 2, pp. 331-339. DOI: 10.1007/s00264-015-3029-7.
6. Gubin A., Borzunov D., Malkova T. Ilizarov method for bone lengthening and defect management. Review of contemporary literature. *Bull. Hosp. Jt. Dis.*, 2016, vol. 74, no. 2, pp. 145-154.

7. Leskelä H.V., Kuorilehto T., Risteli J., Koivunen J., Nissinen M., Peltonen S., Kinnunen P., Messiaen L., Lehenkari P., Peltonen J. Congenital pseudarthrosis of neurofibromatosis type 1: Impaired osteoblast differentiation and function and altered NF1 gene expression. *Bone*, 2009, vol. 44, no. 2, pp. 243-250. DOI: 10.1016/j.bone.2008.10.050.
8. Paley D., Catagni M., Argnani F., Prevot J., Bell D., Armstrong P. Treatment of congenital pseudoarthrosis of the tibia using the Ilizarov technique. *Clin. Orthop. Relat. Res*., 1992, no. 280, pp. 81-93.
9. Johnston C.E. 2nd. Congenital pseudarthrosis of the tibia: results of technical variations in the Charnley-Williams procedure. *J. Bone Joint Surg. Am*., 2002, vol. 84, no. 10, pp. 1799-1810.
10. Crawford A.H., Schorry E.K. Neurofibromatosis update. *J. Pediatr. Orthop*., 2006, vol. 26, no. 3, pp. 413-423. DOI: 10.1097/01.bpo.0000217719.10728.39.
11. Sakamoto A., Yoshida T., Yamamoto H., Oda Y., Tsuneyoshi M., Iwamoto Y. Congenital pseudarthrosis of the tibia: analysis of the histology and the NF1 gene. *J. Orthop. Sci*., 2007, vol. 12, no. 4, pp. 361-365. DOI: 10.1007/s00776-007-1142-1.
12. Mustafin R.N., Khusnutdinova E.K. Rol epigeneticheskikh faktorov v patogeneze neirofibromatoza 1-go tipa [Role of epigenetic factors in Type 1 neurofibromatosis pathogenesis]. *Uspekhi Molekuliarnoi Onkologii*, 2017, vol. 4, no. 3, pp. 37-49. (in Russian) DOI: 10.17650/2313-805X-2017-4-3-35-49.
13. Heervä E., Alanne M.H., Peltonen S., Kuorilehto T., Hentunen T., Väänänen K., Peltonen J. Osteoclasts in neurofibromatosis type 1 display enhanced resorption capacity, aberrant morphology, and resistance to serum deprivation. *Bone*, 2010, vol. 47, no. 3, pp. 583-590. DOI: 10.1016/j.bone.2010.06.001.
14. Kuorilehto T., Kinnunen P., Nissinen M., Alanne M., Leskelä H.V., Lehenkari P., Peltonen J. Vasculopathy in two cases of NF1-related congenital pseudarthrosis. *Pathol. Res. Pract.*, 2006, vol. 202, no. 9, pp. 687-690. DOI: 10.1016/j.prp.2006.03.006.
15. Pannier S. Congenital pseudarthrosis of the tibia. Orthop. Traumatol. Surg. Res., 2011, vol. 97, no. 7, pp. 750-761. DOI: 10.1016/j.otsr.2011.09.001.
16. Cui G., Lei W., Li J., Hu Y., Ma P., Huang Y., Zhao L., Lu R., Yang L. Histopathology of congenital pseudarthrosis of tibia. *Zhonghua Yi Xue Za Zhi*, 2002, vol. 82, no. 7, pp. 487-491.
17. Hermanns-Sachweh B., Senderek J., Alfer J., Klosterhalfen B., Büttner R., Füzesi L., Weber M. Vascular changes in the periosteum of congenital pseudarthrosis of the tibia. *Pathol. Res. Pract*., 2005, vol. 201, no. 4, pp. 305-312. DOI: 10.1016/j.prp.2004.09.013.
18. Li Shu-Qiang, Wang P., Yu Ya-Qin, Zhang Xin, Li Dong-Song. Expressions of VEGF and TGF-β in periosteum in patients with congenital pseudarthrosis of tibia. *Journal of Jilin University* (Medicine Edition), 2007, no. 2, pp. 327-329.
19. Li Shu-Qiang, Yang F., Zhang X., Wang P. Influence of matrix metalloproteinase on osteogenesis in the tibial periosteum of congenital pseudarthrosis. *Journal of Clinical Rehabilitative Tissue Engineering Research*, 2008, vol. 12, no. 2, pp. 213-216.
20. Thabet A.M., Paley D., Kocaoglu M., Eralp L., Herzenberg J.E., Ergin O.N. Periosteal grafting for congenital pseudarthrosis of the tibia: a preliminary report. *Clin. Orthop. Relat. Res*., 2008, vol. 466, no. 12, pp. 2981-2994. DOI:10.1007/s11999-008-0556-1.
21. Trigui M., De Billy B., Metaizeau J.P., Clavert J.M. Treatment of congenital pseudarthrosis of the fibula by periosteal flap. *J. Pediatr. Orthop. B*, 2010, vol. 19, no. 6, pp. 473-478. DOI: 10.1097/BPB.0b013e32833cb749.
22. Andrianov V.L., Pozdeev A.P. *Vrozhdennye poroki razvitiia goleni* [Congenital malformations of the leg]. In: Shaposhnikov Iu.G., editor. Travmatologiia I Ortopediia. Guide for physicians. In 3 Vol. Moscow, Meditsina, 1997, vol.3: Ortopediia, pp. 290-306. (in Russian)
23. Pozdeev A.P., Zakharian E.A. Osobennosti techeniia vrozhdennykh lozhnykh sustavov kostei goleni u detei distroficheskogo i displasticheskogo geneza [Particular characteristics of the course of congenital pseudoarthroses of the leg bones in children of dystrophic and dysplastic genesis]. *Ortopediia, Travmatologiia I Vosstanovitelnaia Khirurgiia Detskogo Vozrasta*, 2014, vol. 2, no. 1, pp.78-84. (in Russian) DOI: 10.17816/PTORS2178-84.
24. Bumbasirević M., Brdar R., Djukić V., Milićević M., Tomić S., Bumbasirević V., Lesić A. Congenital pseudoarthrosis of the tibia treated with the free microvascular fibula. *Acta Chir. Iugosl*., 2005, vol. 52, no. 2, pp. 121-123.
25. Paley D. *Congenital Pseudarthrosis of the Tibia: Combined Pharmacologic and Surgical Treatment Using Biphosphonate Intravenous Infusion and Bone Morphogenic Protein with Periosteal and Cancellous Autogenous Bone Grafting, Tibio-Fibular Cross Union, Intramedullary Rodding and External Fixation*. In: Zorzi A., editor. Bone Grafting. In-Tech, 2012, Ch. 6.
26. Molina A.R., Ali E., Van Rensburg L., Malata C.M. Successful reconstruction of a gunshot segmental defect of the radius with a free vascularised fibular osteocutaneous flap. *J. Plast. Reconstr. Aesthet. Surg*., 2010, vol. 63, no. 12, pp. 2181-2184. DOI: 10.1016/j.bjps.2010.03.022.
27. Senchenko E.V., Ryzhikov D.V., Gubina E.V., Semenov A.L., Revkovich A.S., Andreev A.V., Mezentsev E.M. Kombinirovannyi osteosintez v lechenii vrozhdennykh lozhnykh sustavov goleni u patsientov s fibroznoi displaziei [Combined osteosynthesis in the treatment of congenital pseudoarthroses of the leg in patients with fibrous dysplasia]. *Mezhdunarodnyi Zhurnal Prikladnykh I Fundamentalnykh Issledovanii*, 2015, no. 11-5, pp. 672-675. (in Russian)
28. Tishkov N.V., Rudakov A.N., Puseva M.E. Klinicheskoe primenenie chreskostnogo apparata Orto-SUV pri lechenii lozhnykh sustavov nizhnikh konechnostei [Clinical use of Ortho-SUV transosseous device in the treatment of lower limb pseudoarthroses]. *Biulleten VSNTs SO RAMN*, 2016, vol. 1, no. 4(110), pp. 78-84. (in Russian)
29. Vilks A., Ozols D.Z., Boka V., Murovska M., Mamaia B. Rezultaty khirurgicheskoi korrektsii vrozhdennogo psevdoartroza bolshebertsovoi kosti v zavisimosti ot aktivatsii virusnoi infektsii HHV-6/HHV-7 u rebenka s neirofibromatozom 1-go tipa [Results of surgical correction of congenital tibial pseudoarthrosis depending on HHV-6/HHV-7 viral infection activation in a child with Type 1 neurofibromatosis]. *Anesteziologiia i Reanimatologiia*, 2014, no. 1, pp.61-63. (in Russian)
30. Feldman D.S., Jordan C., Fonseca L. Orthopaedic manifestations of neurofibromatosis type 1. *J. Am. Acad. Orthop. Surg*., 2010, vol. 18, no. 6, pp. 346-357.
31. Shnaider N.A.., Shapovalova E.A. Neirofibromatoz 1-go tipa (bolezn Reklingkhauzena) [Type 1 neurofibromatosis (Recklinghausen disease)]. *Voprosy Prakticheskoi Pediatrii*, 2011, vol. 6, no. 1, pp. 83-88. (in Russian)

32. Liubchenko L.N., Filippova M.G. Neirofibromatoz: geneticheskaia geterogennost i differentsialnaia diagnostika [Neurofibromatosis: genetic heterogeneity and differential diagnosis]. *Sarkomy Kostei, Miagkikh Tkanei i Opukholi Kozhi*, 2011, no. 4, pp. 29-36. (in Russian)
33. Briner J., Yunis E. Ultrastructure of congenital pseudarthrosis of the tibia. *Arch. Pathol.*, 1973, vol. 95, no. 2, pp. 97-99.
34. Blauth M., Harms D., Schmidt D., Blauth W. Light- and electron-microscopic studies in congenital pseudarthrosis. *Arch. Orthop. Trauma Surg.*, 1984, vol. 103, no. 4, pp. 269-277. DOI: 10.1007/BF00387333.
35. Pelissier P., Masquelet A.C., Bareille R., Pelissier S.M., Amedee J. Induced membranes secrete growth factors including vascular and osteoinductive factors and could stimulate bone regeneration. *J. Orthop. Res.*, 2004, vol. 22, no. 1, pp. 73-79.
36. Gupta G., Ahmad S., Zahid Mohd, Khan A.H., Sherwani M.K., Khan A.Q. Management of traumatic tibial diaphyseal bone defect by "induced-membrane technique". *Indian J. Orthop.*, 2016, vol. 50, no. 3, pp. 290-296. DOI: 10.4103/0019-5413.181780.
37. Pelissier P., Martin D., Baudet J., Lepreux S., Masquelet A.C. Behaviour of cancellous bone graft placed in induced membranes. *Br. J. Plast. Surg.*, 2002, vol. 55, no. 7, pp. 596-598.
38. Spinella-Jaegle S., Roman-Roman S., Faucheu C., Dunn F.W., Kawai S., Galléa S., Stiot V., Blanchet A.M., Courtois B., Baron R., Rawadi G. Opposite effects of bone morphogenetic protein-2 and transforming growth factor-beta 1 on osteoblast differentiation. *Bone*, 2001, vol. 29, no. 4, pp. 323-330.
39. Wang X., Luo F., Huang K., Xie Z. Induced membrane technique for the treatment of bone defects due to post-traumatic osteomyelitis. *Bone Joint Res.*, 2016, vol. 5, no. 3, pp. 101-105. DOI: 10.1302/2046-3758.53.2000487.
40. Christou C. , Oliver R.A., Yu Y., Walsh W.R. The Masquelet technique for membrane induction and the healing of ovine critical sized segmental defects. *PLoS One*, 2014, vol. 9, no. 12, pp. e114122. DOI: 10.1371/journal.pone.0114122.
41. Masquelet A.C., Obert L. Induced membrane technique for bone defects in the hand and wrist. *Chir Main.*, 2010, vol. 29, no. Suppl. 1, pp. S221-S224. DOI: 10.1016/j.main.2010.10.007.

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