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# CONTENTS

# CONGENITAL DISLOCATION OF THE KNEE - APROPOS OF TWO CASES

**Camelia Vreme[1], Laura Popa[2], Ștefana Carp[2], Eduard Liciu[2], Stefan-Traian Gavriliu[1], Costel Vlad[2]**

**Abstract**

Congenital dislocation of the knee (CDK) is a relatively rare disorder. The deformity may be isolated or part of a syndromic condition. The purpose of this paper is to present the experience with two cases of CDK, one of them being complicated by a simultaneous unilateral hip dislocation.

We present two cases of CDK treated surgically by our team. The first case is an 11 months old girl with bilateral CDK associated with bilateral congenital clubfoot and congenital dislocation of the right hip. The second case is a 6 months old boy having multiple conditions: CDK, atrial septal defect, ventricular septal defect, left ventricular hypertrophy, hypoacusis, postaxial hexadactyly of the right foot.

For CDK, we performed in both cases V-Y quadriceps-plasty, anterior capsule release and spica cast immobilisation with 45 degrees of flexion of the knees for 4 weeks. We performed also surgical procedures for the associated deformities.

The results are very good in both cases. The patients are independent walkers having a normal range of physical activities. The knees are stable; the flexion is about 120 degrees in the first case and at 110 degrees in the second case.

The treatment of CDK is challenging and should be adapted to the particular conditions of the patient: age, state of the soft parts, associated deformities. Establishing the optimum equilibrium between flexion and extension should prevail over the ambition to obtain full flexion of the knee.

**Keywords:** congenital dislocation of the knee, V-Y quadriceps-plasty, surgical treatment

## Introduction

Congenital dislocation of the knee is a rare [1] and debilitating disorder if left untreated. The image of the new-born is striking, the lower limbs being positioned in various degrees of hyper-extension and the tibia displaced in front of the femur in most cases.

The deformity may be unique or part of a syndromic condition [2]. The fundamental pathologic alterations consist of quadriceps tendon shortening, tight suprapatellar bursa, anterior capsule retraction [3,4]. Valgus deformity and posterior capsule excess are secondary to the other pathologic alteration.

Many surgical options are available according to the degree of deformity and age of the patient [5-8]. The variability of the approaches is the indicator that a universal solution is not yet accepted.

The purpose of this paper is to present our experience with two cases of CDK, one of them being complicated by a simultaneous unilateral hip dislocation.

## Materials and Methods

We present two cases of CDK treated surgically by our team.

*Case one*

The first case is an 11 months old girl addressed to our service for a bony protuberance at the posterior aspect of both knees and bilateral clubfoot with major equinus component and mild forefoot adduction (Fig. 1A). During the first eleven months of life the knees and feet were stretched by the parents, under no medical supervision, in order to correct the hyperextension of the knees present at birth. Apparently, the knees were well aligned despite lack of flexion in both knees (Fig. 1B). Clinical examination and X-ray revealed the anterior dislocation of both knees with compensatory flexion deformity of both tibias (Fig. 2A). The right hip was dislocated (Fig. 2B).

The treatment we proposed and performed was bilateral, V-Y quadriceps-plasty, anterior capsule release, Achilles tenotomy, right hip closed reduction, spica cast immobilisation with 90 degrees of flexion and 60 degrees of abduction of the hip and 45 degrees of flexion of the knees for 4 weeks. Duration of surgery was three hours and the blood loss was minimal. The Pavlik harness was worn 6 months after cast removal. Intensive rehabilitation program took place after cast removal.

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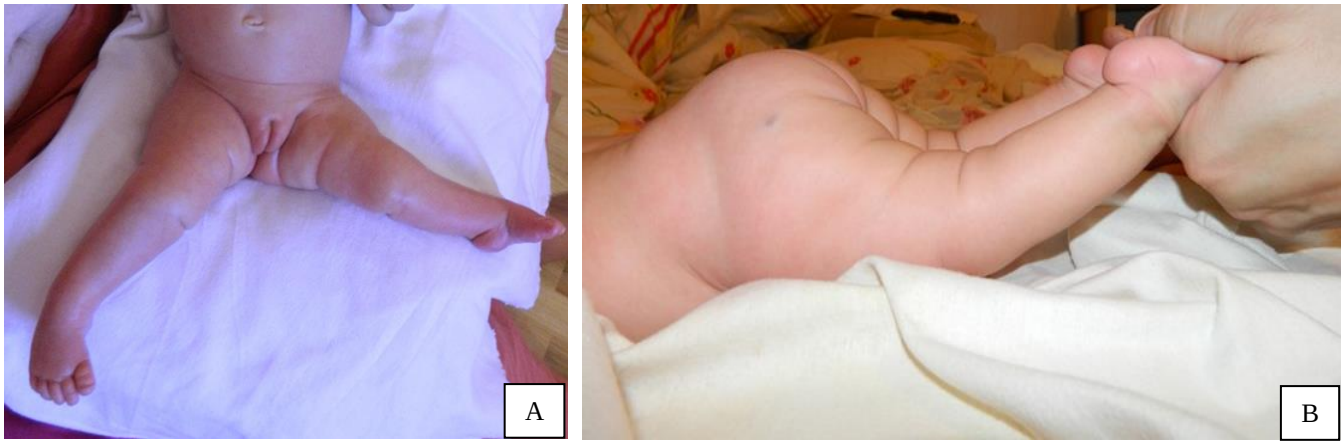


Figure 1: A - Case one, clinical aspect at one month of age. B - Case one, clinical aspect at first presentation in our department.

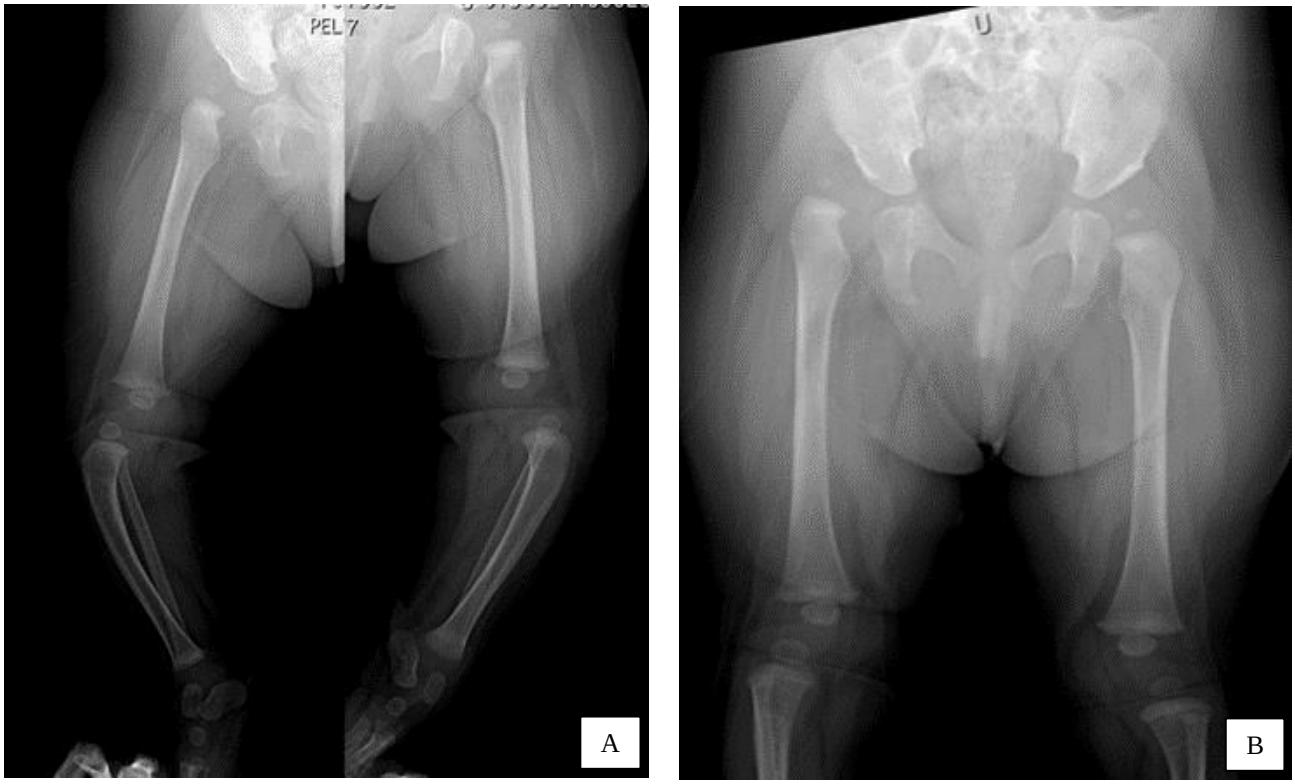


Figure 2. A - Case one, X-ray image of lower limb in lateral view, the bowing of both tibias in sagital plane compensate the knee dislocation. B - Case one, X-ray exam of the right dislocated hip.

*Case two*

The second case is a 6 months old boy having multiple conditions: bilateral CDK, atrial septal defect, ventricular septal defect, left ventricular hypertrophy, hypoacusis, postaxial hexadactyly of the right foot (Fig. 3A, Fig 3B). We proposed and performed the V-Y quadriceps-plasty (Fig. 4A, Fig. 4B), anterior capsule release and resection of the sixth toe followed by spica cast immobilisation for 4 weeks). After this period, the cast was changed with anterior plaster splint for another 4 weeks (Fig. 5A, Fig 5B. The intensive rehabilitation program was started after cast removal.

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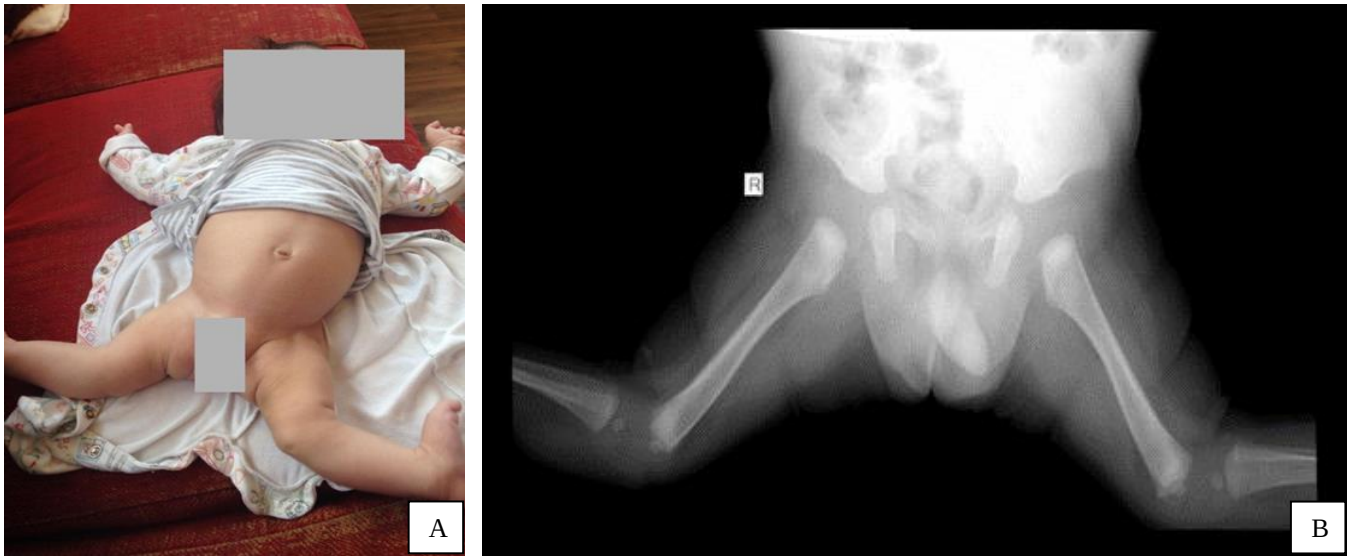


Figure 3. A - Case two, clinical picture at 6 month of age. B - Case two, lateral view on X-ray image of dislocated knees.

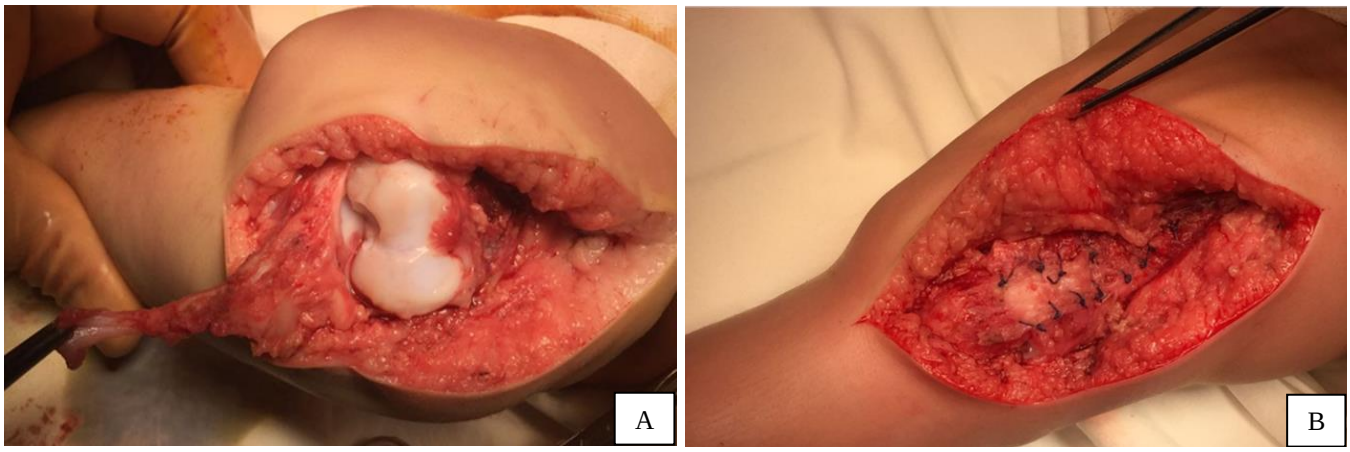


Figure 4. A - Case two, intraoperative image of the knee after full dissection, before the quadriceps stiching. B - Case two, intraoperative aspect after the V-Y stiching of the quadriceps tendon.

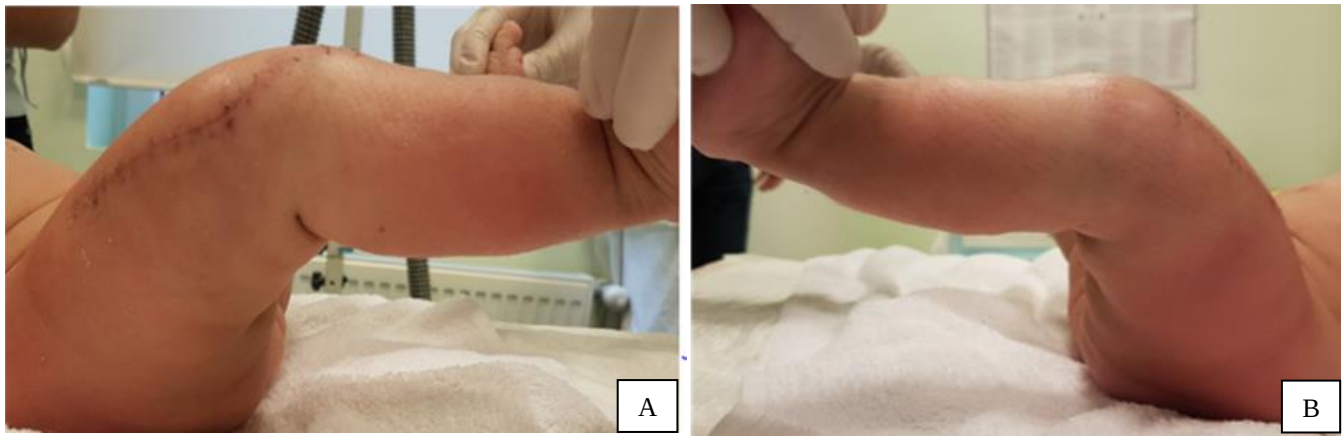


Figure 5. A - Case two, right knee immediately after cast removal. B - Case two, left knee immediately after cast removal.

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**Results**

*Case one*

The evolution was very good. The hip remained stable and the acetabular dysplasia improved slowly. The need for a pelvic osteotomy is not completely ruled out but the MRI exam performed at 4 years of age revealed an excellent potential of ossification of the acetabular rim (Fig. 6A, Fig. 6B).

The knee flexion is at 120 degrees, the knees are stable (Fig. 7A, Fig. 7B). Mild adductus of forefeet still persist. The patient is an independent walker having a normal range of physical activities.

The tibial incurvation regressed spontaneously; during the 5 years postoperatively both tibias achieved almost normal anatomical axis.

*Case two*

At one year of age the boy became independent walker with good range of motion. He is still improving the knees flexion. At last follow up the knees flexion was about 110 degrees (Fig. 8A, Fig. 8B).

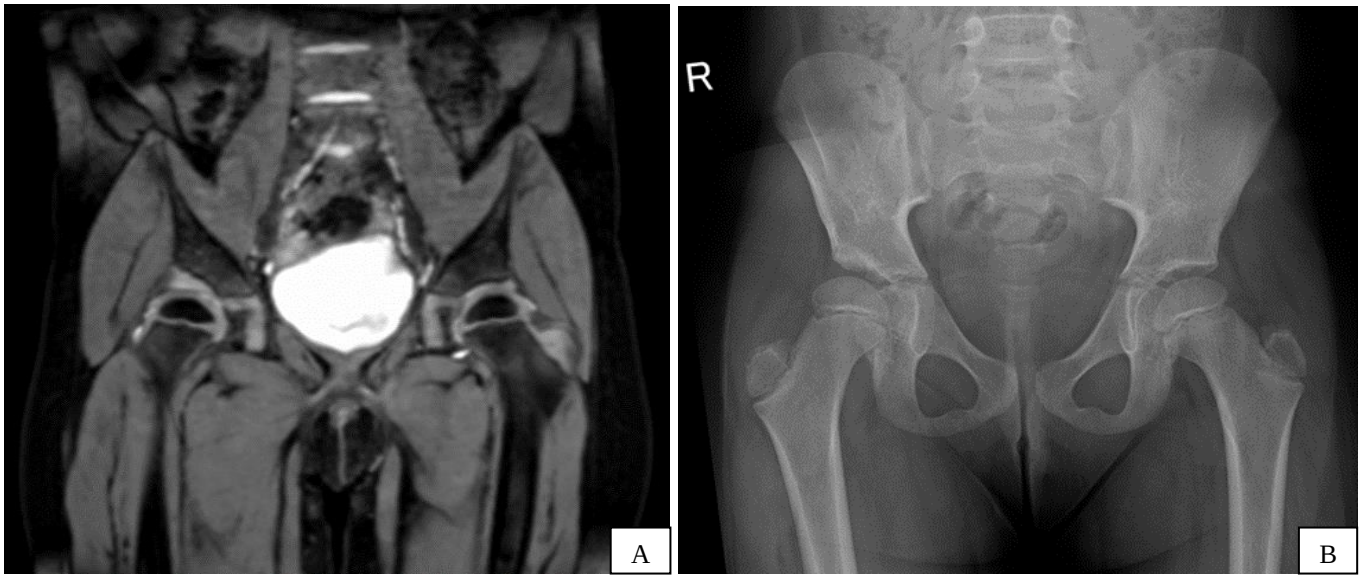


Figure 6. A - Case one, MRI aspect of the hips, at the age of 4 years, the right hip is displastic but the cartilaginous part of the acetabulum covers perfectly the femoral head. B - Case one, X-ray image of the pelvis on A-P view, at the age of 6 years, the right hip is slightly dysplastic but the Wiberg angle is positive, a surgical procedure to improve the right hip coverage may be required in the future.


Figure 7. A,B - Case one, clinical aspect of the knees at 7 years of age.

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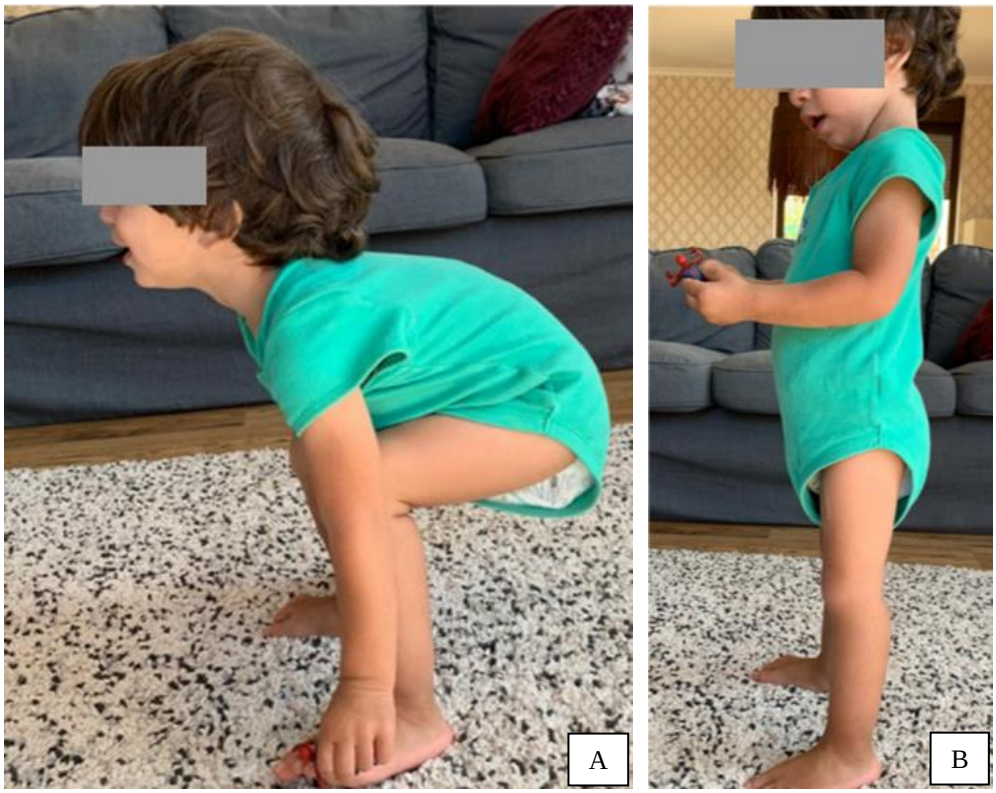


Figure 8. A,B - Case two at 2 years of follow-up.

**Discussion**

Ideally, the diagnostic of congenital dislocation of the knee should be made during the intrauterine life [9] for at least two reasons: to be prepared to apply promptly orthopaedic treatment in mild cases or to prepare the parents for a surgery with good but not perfect results at the end of treatment.

When diagnosed early and the dislocation is reducible [10] the CDK may be managed with serial casting and in some cases with soft parts release. Spontaneous reduction was described [11]. When dislocation is irreducible, the open extensive surgery is mandatory.

Different opinions exist regarding the best approach to restore the knee flexion. Special concerns exist when a simultaneous hip dislocation need to be treated [7]. Johnston et al. propose a simultaneous acute femoral shortening in order to lower the tension generated in the retracted soft tissues secondary to the reduction of both dislocations.

Quadriceps lengthening is proposed by some authors, in Z - shape or V-Y fashion [12]. One concern of this soft tissue release is the weakening of the quadriceps tendon and secondary need for surgery. Söyüncü et al. [12] described a reinforcement procedure of quadriceps tendon with Achilles tendon allograft in cases of quadriceps lengthening failure. The main issue with the lengthening procedure is a massive fibrosis which encounters the quadriceps tendon. Creating good enough flaps in order to provide a strong connection between the quadriceps muscle and patella may be technically difficult. Having access to a tissue bank may be reassuring for the surgeon.

A logical approach to the technical difficulties in these cases is the femoral acute shortening proposed by Johnston et al. [7]. In the comprehensive approach proposed by Johnston we emphasise the need to address both dislocations in the same time; on the other hand, the anterior cruciate ligament reconstruction is advised in order to correct the instability of the knee. In some cases, an osteotomy of the tibia to correct flexion deformity may be required.

In the first case we presented the simultaneous dislocation of the hip who was treated orthopedically, maybe the general laxity of the patient helped to obtain and maintain the hip reduction free of complications. Also, the presence of clubfoot deformity made the rehabilitation treatment more difficult. A good result is characterized by a stable knee and at least 90 degrees of flexion. One of the recommendations concerning the postoperative immobilisation of the knee is to keep flexion below 60 degrees, otherwise the extension recovery will be incomplete or extremely difficult. Having to improve the knee flexion is the preferable attitude.

The hip dysplasia present in the first case may be the subject of future surgery. We postponed a procedure to address the hip dysplasia (Fig. 6A) based on MRI exam revealing a cartilaginous part of the acetabular rim which would provide a good acetabular coverage after full ossification,

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Spontaneous reestablishment of anatomical axis of both tibias was observed and this was presumed preoperatively. Maybe the elasticity of the joints allowed us to obtain a good hip reduction without complications or open surgery.

The second case had a good result, with 110 degrees of flexion. The boy is walking independently. The knees are stable.

**Conclusions**

CDK is a rare and challenging condition to treat, especially when other dislocations are associated. The treatment should be tailored to the particular conditions of the patient: age, state of the soft tissues, associated deformities. Attention to be paid to the temptation to obtain full flexion with the price of never regaining full extension.

**References**


1. Shastri NJ, Winners O. Picture of the month. Congenital Dislocation of the Knee. Arch Pediatr Adolesc Med. 2008;162(8):787. Epub 2008/08/06. doi: 10.1001/archpedi.162.8.787. PubMed PMID: 18678813.
2. Bhatia RK, Pyman J, Gargan MF, Witherow PJ. Cases of congenital dislocation of the knee (CDK) not associated with clubfoot, arthrogryposis multiplex congenita, and Larsen's syndrome can be treated conservatively. J Pediatr Orthop. 1998;18(2):273-4. Epub 1998/04/08. doi: 10.1097/00004694-199803000-00030. PubMed PMID: 9531418.
3. Ooishi T, Sugioka Y, Matsumoto S, Fujii T. Congenital dislocation of the knee. Its pathologic features and treatment. Clin Orthop Relat Res. 1993(287):187-92. Epub 1993/02/01. PubMed PMID: 8448939.
4. Uhthoff HK, Ogata S. Early intrauterine presence of congenital dislocation of the knee. J Pediatr Orthop. 1994;14(2):254-7. Epub 1994/03/01. doi: 10.1097/01241398-199403000-00023. PubMed PMID: 8188844.
5. B KA, Singh KA, Shah H. Surgical management of the congenital dislocation of the knee and hip in children presented after six months of age. Int Orthop. 2020;44(12):2635-44. Epub 2020/08/11. doi: 10.1007/s00264-020-04759-8. PubMed PMID: 32772317; PMCID: PMC7679307.
6. Klein C, Bulaid Y, Deroussen F, Plancq MC, Printemps C, Gouron R. Congenital dislocation of the knee in a three-year-old-child with Larsen syndrome: Treatment with a hexapod-type external fixator. Knee. 2018;25(5):966-71. Epub 2018/08/17. doi: 10.1016/j.knee.2018.07.006. PubMed PMID: 30111500.
7. Johnston CE, 2nd. Simultaneous open reduction of ipsilateral congenital dislocation of the hip and knee assisted by femoral diaphyseal shortening. J Pediatr Orthop. 2011;31(7):732-40. Epub 2011/09/20. doi: 10.1097/BPO.0b013e31822f1b24. PubMed PMID: 21926869.
8. Tercier S, Shah H, Joseph B. Quadricepsplasty for congenital dislocation of the knee and congenital quadriceps contracture. J Child Orthop. 2012;6(5):397-410. Epub 2013/10/02. doi: 10.1007/s11832-012-0437-8. PubMed PMID: 24082955; PMCID: PMC3468735.
9. Elchalal U, Ben Itzhak I, Ben-Meir G, Zalel Y. Antenatal diagnosis of congenital dislocation of the knee: a case report. Am J Perinatol. 1993;10(3):194-6. Epub 1993/05/01. doi: 10.1055/s-2007-994717. PubMed PMID: 8517894.
10. Abdelaziz TH, Samir S. Congenital dislocation of the knee: a protocol for management based on degree of knee flexion. J Child Orthop. 2011;5(2):143-9. Epub 2012/04/03. doi: 10.1007/s11832-011-0333-7. PubMed PMID: 22468158; PMCID: PMC3058203.
11. Haga N, Nakamura S, Sakaguchi R, Yanagisako Y, Taniguchi K, Iwaya T. Congenital dislocation of the knee reduced spontaneously or with minimal treatment. J Pediatr Orthop. 1997;17(1):59-62. Epub 1997/01/01. PubMed PMID: 8989703.
12. Söyüncü Y, Mihçi E, Ozcanli H, Ozenci M, Akyildiz F, Aydin AT. Reconstruction of quadriceps tendon with Achilles tendon allograft in older children with congenital dislocation of the knee. Knee Surg Sports Traumatol Arthrosc. 2006;14(11):1171-5. Epub 2006/06/08. doi: 10.1007/s00167-006-0083-0. PubMed PMID: 16758235.



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# THE ABDOMINAL PAIN SYNDROME – A STARTING POINT IN DIAGNOSING KIDNEY AND URINARY TRACT DISORDERS IN CHILDREN

**Ionela Tămășan[1,2], Sonia Tănăsescu[1,2], Liviu Pop[1,2]**

**Abstract**

The acute abdominal pain in children most often represents the reason why they require specialised medical attendance; this pain may be caused by a series of surgical or non-surgical disorders.

The most frequent causes are the ones related to a gastrointestinal disease (mostly gastroenteritis). Nevertheless, one should not neglect the surgical causes, as acute appendicitis remains a condition that must be ruled out in any patient complaining of abdominal pain.

Some of the frequent causes for abdominal pain in children are represented by the urinary tract diseases. Whether we are talking about congenital causes (i.e. birth defects), or about acquired conditions (urinary tract infections, urinary calculi), this type of diseases must be considered when investigating an abdominal pain syndrome.

The study was carried out at the 2nd Pediatrics Clinic within the "Pius Branzeu" County Hospital from Timisoara, on a 2-year interval (2018 and 2019) and it is a retrospective study.

The purpose of this paper is to identify the kidney and urinary tract diseases, starting from the acute abdominal pain syndrome as the main symptom. It should be pointed out that our main purpose was to identify the relation between the congenital anomalies in the kidney and the urinary tract infections.

Between January 2018 and December 2019, a number of 3,126 children were admitted to the 2nd Pediatrics Clinic. Out of these, we have selected only those cases where the abdominal pain could be linked to a kidney or urinary tract disease. Thus, we identified 146 patients where the acute abdominal pain was suggestive of a possible disorder in the urinary tract. Out of the 146 patients, 82 (56.16%) were diagnosed with urinary tract infections. After complex investigations were performed on these patients, we identified urinary tract anomalies in 32 of the cases.

Starting from symptoms which could normally indicate a gastrointestinal disorder (hence the acute abdominal pain), we managed to diagnose a significant number of patients with kidney and urinary tract disorders.

**Keywords:** acute abdominal pain, urinary tract infection, child

**Introduction**

Along the way, pain was given numerous definitions that attempted at including as much as possible the complex facets of this symptom. Thus, in 1979, the International Association for the Study of Pain (IASP) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1].

Diagnosing the acute abdominal pain in children is not always easy. The clinical signs of the abdominal pain vary according to the patient's age, pain location and associated symptoms [2,3]. Most often, abdominal pain is self-limiting, benign and relatively easy to diagnose (e.g. viral enteritis, gastroenteritis, constipation, etc.) [4]. The real "cornerstone" for the clinician is to identify the cases of atypical and potentially lethal illnesses, which need an attentive assessment and immediate treatment (especially in surgical cases, like appendicitis, volvulus, peritonitis, etc.) [5].

Acute abdominal pain is frequently indicated by the patients coming to the emergency rooms (i.e. 5-10% out of the total number of cases) [6,7].

Some of the most frequent causes for abdominal pain in children are represented by the urinary tract diseases [8]. Whether we are talking about congenital causes (i.e. birth defects), or about acquired conditions (urinary tract infections, urinary calculi), this type of diseases must be considered when investigating an abdominal pain syndrome.

**Materials and methods**

The study was carried out at the 2nd Pediatrics Clinic within the "Pius Branzeu" County Hospital from Timisoara, on a 2-year interval (2018 and 2019) and it is a retrospective study.

The purpose of this paper is to identify the kidney and urinary tract diseases starting from the acute abdominal pain syndrome as the main symptom. It should be pointed out that our main purpose was to identify the relation between the congenital anomalies in the kidney and the urinary tract infections.

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**Results**

Out of the 3,126 children admitted to the 2nd Pediatrics Clinic between January 2018 and December 2019, a number of 807 (25.81%) had acute abdominal pain as a symptom.

Out of these, we have selected only those cases where the abdominal pain could be linked to a kidney or urinary tract disease. Thus, we identified 146 patients where the acute abdominal pain was suggestive of a possible disorder in the urinary tract.

We have drawn up distribution curves, based on the age, gender and kidney conditions identified in the subjects.

The gender distribution of the patients from the group included in the study shows a prevalence of males (56%), while females account for the rest of 44% - this confirms the information from the literature.

Starting from the abdominal pain, correlated with other clinical data (fever, altered general health state, trouble urinating), but also with biological data (presence of an inflammatory syndrome, urinalysis showing changes suggestive for a urinary tract infection, positive urine culture), we could diagnose a urinary tract infection (UTI) in 82 (56.16%) out of the 146 patients.

Based on the analysis of clinical data, correlated with the inflammatory syndrome, *the location of the urinary tract infection* has shown that 47 (56%) patients had lower urinary tract infection, while 35 patients (44%) were diagnosed with upper urinary tract infections.

We have not identified significant differences with regard to age distribution in subjects or the location of the urinary tract infections (upper or lower).

An increased occurrence of lower urinary tract infection (UTI), i.e. cystitis, could be seen in the 6 to 18-year old age group (60%), while the cases of upper UTI (pyelonephritis) were rather evenly distributed in the subjects above 1 month of age. (Fig. 1).

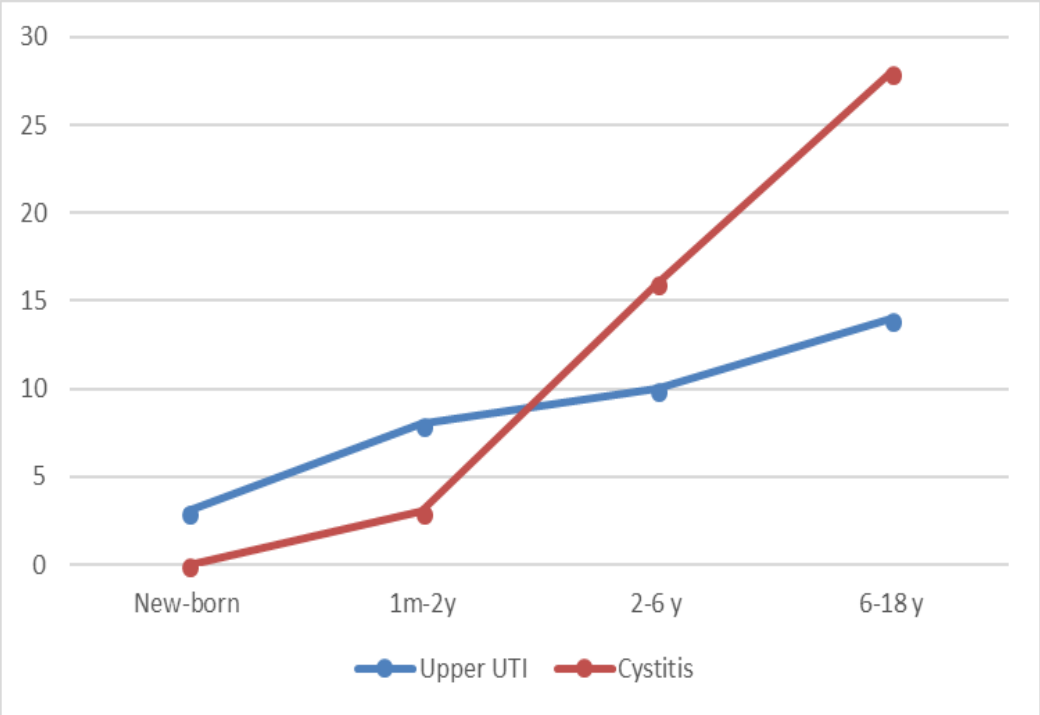


Fig. 1 Distribution of cases according to age and UTI location.

A total number of 195 urine cultures were made for the 146 subjects included in the study. We have included here only the urine cultures performed in order to confirm the diagnosis, and not those urine cultures performed during the regular monitoring, according to protocol, in the patients diagnosed and treated with antibiotics.

Out of the total number of processed urine cultures, 82 (42.05%) tested positive for infection.

The most frequent micro-organisms isolated in the urine cultures of these patients were E. coli - 54 cases (67%) [9], followed by Klebsiella - 19 cases (23%), Proteus - 6 cases (7%), and other micro-organisms for the rest of the 3 cases.

*As a first conclusion, from the total number of patients included in the study (i.e. 82), E. coli is the most frequent bacteria causing UTI ($p < 0.001$), posing a risk 1.8 times higher than other microorganisms (RR = 1.75).*

Based on the results from the urine cultures, we can see an increase in the resistance of the E.coli strains to the antibiotics most frequently used to treat children [10].

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Antibiotic resistance can be seen most often in the case of cephalosporin and aminoglycoside.

Also, we have seen a significant increase in the incidence of Klebsiella strains producing extended-spectrum beta-lactamases (ESBL) [11].

The age distribution in the pediatric patients with infections where *Klebsiella* BLSE strains were identified has shown that most of the cases were recorded in the 0-24 months age group (75% of the cases), then in the children 2 to 5 years old and 6 to 11 years old, however comparably fewer as the child's age increased.

Out of the 146 patients included in the study, 32 presented congenital anomalies in the kidneys and in the urinary tract system.

After complex assessments were performed on these patients, the following congenital anomalies were found: renal agenesis - 1 case; renal hypoplasia - 2 cases; renal ectopia - 2 cases; horseshoe kidney - 2 cases; cystic diseases - 2 cases; ureteropelvic duplex formation - 5 cases; megaureter - 1 case; hydronephrosis - 10 cases; posterior urethral valve (PUV) disorder - 1 case; abnormality involving the bladder or urethra - 6 cases.

In our study, the male:female ratio related to the congenital anomalies in the kidneys and in the urinary tract system shows a larger prevalence in males [12]. Thus, out of the 32 diagnosed cases, 21 were boys (65.62%) and 9 were girls (34.37%).

Out of the 32 congenital anomalies, 7 were diagnosed in infants (i.e. the megaureter, 2 cases of ureteropelvic duplex formations, 2 cases of) ureteropelvic junction obstructions, with consecutive hydronephrosis, 2 cases of vesicoureteral reflux). For example, the cases of agenesis/hypoplasia, the cystic kidney disease, the horseshoe kidney were all diagnosed in children above 6 years of age. This should raise some questions, especially if we think of the "extremely technical and computerised" medicine that is available in our century. It is hard to accept that a child can reach 17 or 18 years of age (actually, adult age), without knowing that he/she is missing a kidney, for example.

In every patient, we have assessed the kidney function, by looking at the kidney's capacity to filter the blood and to remove waste products. For this purpose, we have determined the blood urea and creatinine, and later compared the values in their dynamic evolution.

Our study does not include patients with a significant nitrogen retention; however, we had patients who, ever since their congenital anomalies were diagnosed, had a low or "borderline" glomerular filtration rate (GFR).

The results for the serum creatinine were interpreted according to the child's age and based on the reference values. Out of the 32 patients, 28 had normal blood creatinine values, regardless of the time the blood test was performed. One of the patients presented a GFR < 40 ml/min/1.73 $m^2$ SC (also diagnosed with polycystic kidney disease, associated with psychogenic polyuria and mental retardation), while in other 3 cases we have seen blood creatinine above normal values (GFR under 90 ml/min/1.73 $m^2$ SC).

The estimated glomerular filtration rate (eGFR) was calculated using the eGFR calculator, made available by the National Kidney Foundation (an application for Android systems).

Out of the 32 patients diagnosed with congenital anomalies, 19 (59.37%) also presented an urinary tract infection at the moment of diagnosis. In these cases, we have concluded that the acute abdominal pain was caused by the infection and not by the actual congenital anomaly.

Therefore, we can see that the incidence of UTI in children with urinary tract congenital anomalies is statistically larger than in children without such anomalies.

Two of the diagnosed congenital anomalies were most interesting - one, diagnosed in an infant, the other, in a teenager.

***Case 1:***

V.A., female, 3 months of age, admitted to the Clinic with loss of appetite, agitation, low-grade fever, excessive crying.

*The clinical examination upon hospital admission identified the following*: skin lividity, facies with shiners. Optimally fed. No changes in the heart and lungs were identified upon auscultation during the initial visit.

Abdomen sensitive to touch (the child becomes extremely agitated during the examination). External genitals normally developed. Diuresis present. No other changes were identified.

*Biology tests:* Urine culture: > 100,000 Klebsiella spp/ml of urine.

The abdominal ultrasound examination was seen as a natural progression in this case, as it was required both by the symptoms and by the diagnosed urinary tract infection.

The imagery suggest a bilateral grade 2/3 hydronephrosis (more pronounced in the right kidney) – Fig.2.

The clinician suspected an ureteropelvic junction obstruction and/or a vesicoureteral reflux (confirmed by higher-quality imaging).

Starting with June 2019, the patient is monitored by the 2nd Pediatric Clinic - the regular visits have shown a favourable evolution, accompanied by other 2 episodes of pyelonephritis.

***Case 2:***

C.R., male, aged 14 years, without significant history of illnesses, presents at the emergency room with fever, diarrhea and abdominal pain. The abdominal ultrasound examination does not find the left kidney in the renal fossa. He is recommended to repeat the ultrasound examination.

The abdominal ultrasound examination identifies the right kidney in the renal fossa, with normal shape and size, without urinary stasis. The left kidney is not found in the renal fossa; a kidney-like structure may possibly exist behind the bladder.

Urinary system MRI investigation - Fig 3:

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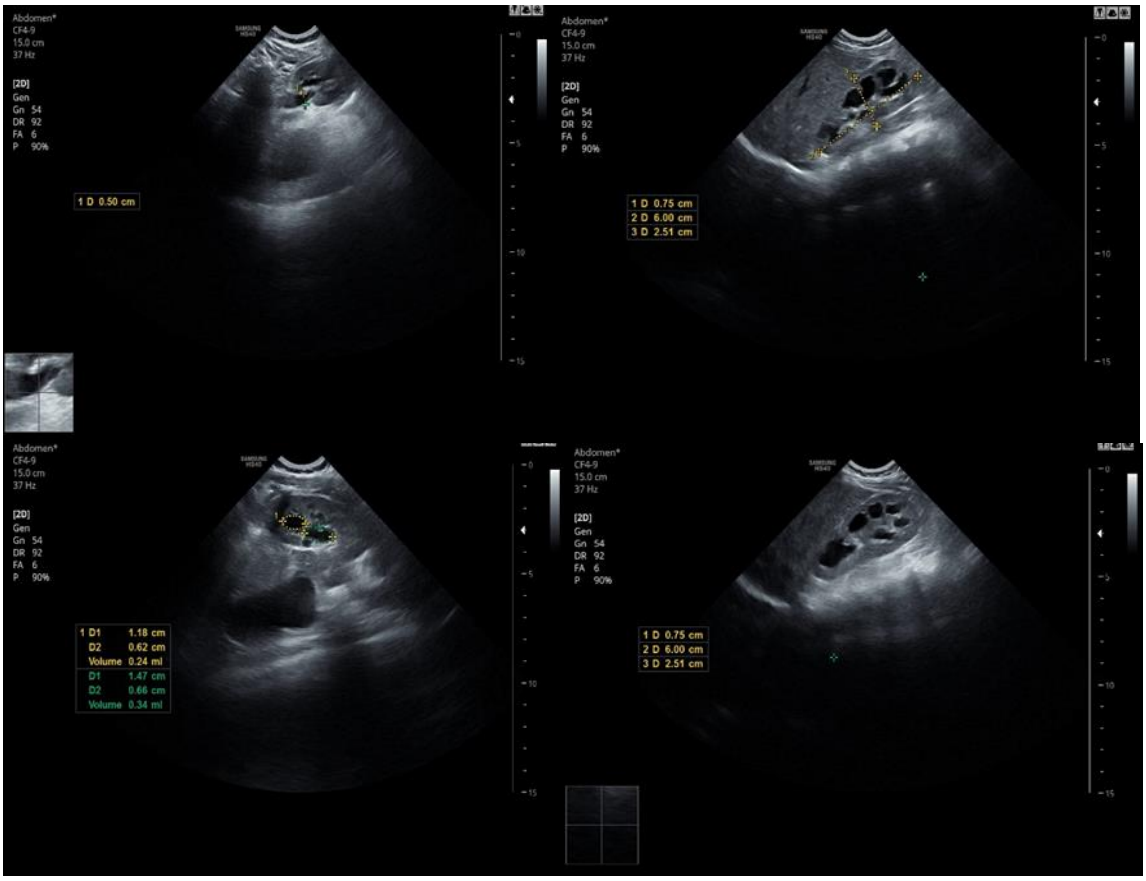


Fig.2 V.A., ultrasound imaging in evolution, with decreased urinary stasis (images from the archive of the Clinic).

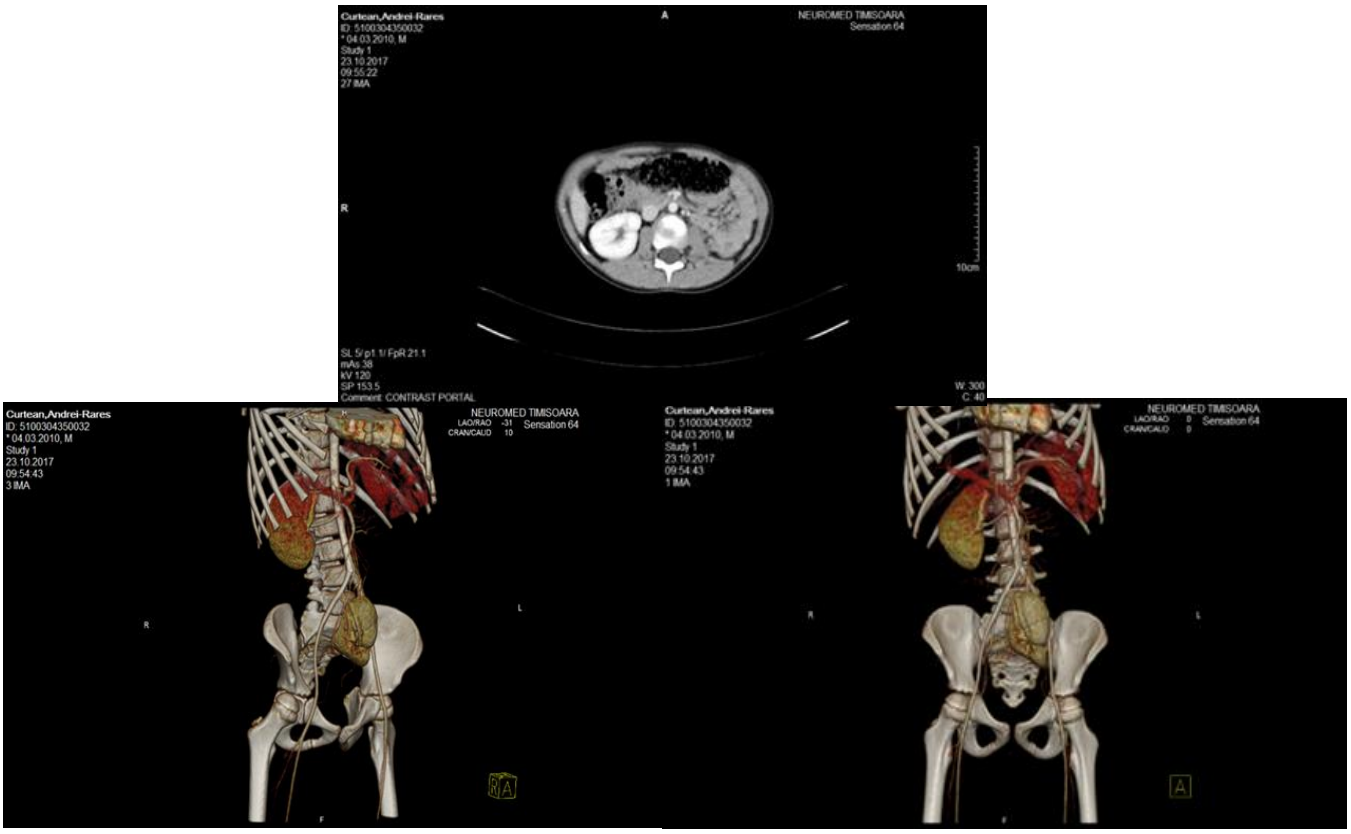


Fig.3 Left ectopic kidney (kidney in the pelvis), diagnosed in a 7-year old child (images from the archive of the 2nd Pediatric Clinic).

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**Conclusion**

All the literature reports confirm that the acute abdominal pain is one of the most common pain indicated by children, and also one of the most frequent causes of their presentation at the pediatric emergency rooms [13].

The UTI in the subjects with urinary tract anomalies are caused my strains of microorganisms with increased antibiotic resistance [14]. Regardless of the patient's age, the abdominal ultrasound is the most common method to investigate the urinary tract. The main disadvantage of the ultrasound examination is that it does not provide information on the renal function.

Starting with 2018 and until the present day, the children with kidney and urinary tract anomalies are attentively monitored and regularly assessed. Electronic patient charts are being put in place, to include the clinical, biological and imaging records of these patients, which will ensure an efficient processing of such information.

In conclusion, this paper shows the importance of a cross-disciplinary approach in diagnosing the child patients. Starting from symptoms which could normally indicate a digestive system disorder (hence the acute abdominal pain), we managed to diagnose a significant number of patients with kidney and urinary tract disorders.

**References**


1. Sharma KK, Agrawal P, Toshiniwal H. Acquired gastric outlet obstruction during infancy and childhood: a report of five unusual cases. J Pediatr Surg 1997;32:928–930.
2. Ormarsson OT, Haugen SE, Juul I. Gastric outlet obstruction caused by heterotopic pancreas. Eur J Peditr Surg 2003;13:410–413.
3. Azarow K, Kim P, Shandling B, et al. A 45-year experience with surgical treatment of peptic ulcer disease in children. J PediatrSurg 1996;31:750–753.
4. Perdereau S, Touzot F, Robin L, et al: Recurrent pyloric stenosis in a 7-year-old child with chronic granulomatous disease. Arch Pediatr 2013;20(12):1337-1339.
5. Shukla RM, Mukhopadhyay M, Tripathy BB, et al. Pyloric and antral strictures following corrosive acid ingestion: A report of four cases. J Indian Assoc Pediatr Surg 2010;15(3):108-109.
6. Sharma KK, Ranka P, Goyal P, et al. Gastric outlet obstruction in children: an overview with report of Jodhpur disease and Sharma's classification. J Pediatr Surg 2008;43(10):1891-1897.
7. Chan KL, Saing H. Balloon catheter dilatation of peptic pyloric stenosis in children. J Pediatr Gastroenterol Nutr 1994;18:465–468.
8. Ratan SK, Dhua AK, Sinha S, et al. Acquired nonspecific cicatrizing inflammation causing pyloric stricture and gastric outlet obstruction in infancy: is it Jodhpur disease? Trop Gastroenterol 2013;34(4):274-277.
9. Hameury F, Mcheik J, Lardy H, et al. Acquired non hypertrophic pyloric stenosis in children. Arch Pediatr 2007;14(4):330-333.



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# ARTHROSCOPIC SURGERY IN CHILDREN AND ADOLESCENT – A DOMAIN TO BE DEVELOPED

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**Abstract**

The application of arthroscopic surgery in children is becoming wider and a more complete understanding of its use is needed.

In this article we present our experience with arthroscopic surgery over the course of 17 months, from April 2019 until October 2020.

We diagnosed and treated minimally invasive 49 patients, with ages between 6 and 18 years old, 22 boys (44.9%) and 27 girls (55.1%). The pathologies varied, the most common being anterior cruciate ligament tears with 49 cases representing 49%, some of which also needed meniscal repair with sutures or by partial meniscectomies. Second most common condition was isolated meniscal tears in 8 patients representing 16.33% of all cases.

But the application of arthroscopic approach is not limited to the treatment of knee instability or related sports injuries. We also want to emphasize the importance of a minimal invasive treatment when it comes to lose bodies in the elbow by presenting a case of an incarcerated medial humeral epicondyle after an elbow dislocation, a case of a symptomatic os trigonum in a 14 years old swimmer or a fractured anterior calcaneal process unresponsive to the conservative treatment, tibial spine fracture in a six years old child.

The benefits of minimally invasive surgery are widely accepted among the orthopaedic surgeons, but it is yet under a lot of reluctance in the paediatric professionals because of the sometimes slow and difficult learning curve.

**Keywords:** arthroscopy, children, anterior cruciate ligament, epicondyle fracture, os trigonum

## Introduction

Since the late 50's when arthroscopy was invented by Watanabe et all [1] the advantages of minimally invasive surgery increasingly has led to the expansion of arthroscopic procedure in adults and later in children. As many other devices, the arthroscopy tools and procedures needed to be adapted to childhood conditions and to the slower learning curves in paediatric field of orthopaedic surgery.

Virtually, all joints may be approached arthroscopically [2-4], ankle, knee, hip, elbow, shoulder, many excisional, reparative or reconstructive gestures being possible via small portals.

Unfortunately, the expansion of arthroscopic techniques in children encounters the same economic and cultural obstacles as any other new technique.

The purpose of this paper is to report our experience with the arthroscopic techniques in children.

## Materials and Methods

Between April 2019 and October 2020, we used arthroscopic techniques in different paediatric conditions. Most of our arthroscopic procedures addressed the adolescent knee to reconstruct anterior cruciate ligament (ACL) or repair the menisci. Besides, some uncommon conditions were approached arthroscopically: anterior calcaneal process pseudarthrosis, removal of os trigonum, tibial eminence fracture in small child, removal of incarcerated medial epicondyle of humerus.

All cases of arthroscopic procedures in our department were identified and the data were collected afterward. The patients' charts were reviewed, the main characteristic of patients is centralised in Table 1: sex, age, type of surgery, achievement of full recovery, complications and follow-up.

## Results

We performed arthroscopic surgery in 49 patients, with ages between 6 and 18 years old, with various pathologies. Of the 49 patients 22 were boys (44.9%) and 27 were girls (55.1%). There were 25 patients (49%) who required ACL repair, of which 3 (12%) also had meniscal sutures and 5 (20%) had partial meniscectomies. Of the 25 patients, 13 (52%) were boys and 12 girls (48%).

Another 8 (16.33%) patients had meniscal tears that required meniscal sutures, and 9 (18.37%) patients were treated by partial meniscectomy. Of these 17 patients, two girls, ages 8 and 13 were diagnosed with discoid meniscus.

The median age of patients who needed knee arthroscopy for ACL tear or meniscal repair was 15 years.

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Table 1: Main characteristics of study group.

| Patient | Sex | Age (years) | Surgery | Joint | Complete recovery achieved | Remarks | Follow up (months) |
|---|---|---|---|---|---|---|---|
| 1 | F | 12 | Meniscectomy | Right Knee | yes | | 20 |
| 2 | F | 16 | Meniscectomy | Right Knee | yes | | 20 |
| 3 | M | 16 | ACL reconstruction + meniscectomy | Left Knee | yes | | 19 |
| 4 | F | 14 | ACL reconstruction | Left Knee | yes | | 18 |
| 5 | M | 17 | ACL reconstruction | Left Knee | yes | | 17 |
| 6 | M | 13 | ACL reconstruction + meniscectomy | Right Knee | yes | | 17 |
| 7 | M | 15 | ACL reconstruction | Right Knee | yes | | 17 |
| 8 | M | 11 | Tibial eminence fixation | Right Knee | yes | | 4 |
| 9 | F | 13 | Meniscectomy | Left Knee | yes | | 16 |
| 10 | M | 17 | ACL reconstruction | Right Knee | no | Graft rupture | 13 |
| 11 | F | 12 | Meniscectomy | Right Knee | yes | | 13 |
| 12 | F | 14 | ACL reconstruction + meniscectomy | Left Knee | yes | | 13 |
| 13 | M | 18 | PCL reconstruction | Right Knee | yes | | 12 |
| 14 | M | 17 | ACL reconstruction + meniscal suture | Left Knee | yes | | 12 |
| 15 | M | 16 | Meniscal suture | Right Knee | yes | | 12 |
| 16 | F | 15 | ACL reconstruction | Left Knee | yes | | 11 |
| 17 | F | 15 | ACL reconstruction | Right Knee | yes | | 11 |
| 18 | M | 11 | Meniscectomy | Right Knee | yes | | 11 |
| 19 | M | 16 | Meniscectomy | Right Knee | yes | | 11 |
| 20 | M | 15 | Meniscectomy | Left Knee | yes | | 11 |
| 21 | M | 16 | ACL reconstruction | Left Knee | yes | | 10 |
| 22 | F | 6 | Tibial eminence fixation | Left Knee | no | Incomplete range of motion | 11 |
| 23 | F | 12 | Meniscal suture | Left Knee | yes | | 10 |
| 24 | F | 12 | Meniscal suture | Left Knee | yes | | 10 |
| 25 | M | 16 | Loose body extraction | Right Knee | yes | | 10 |
| 26 | F | 17 | ACL reconstruction | Right Knee | no | Incomplete range of motion | 10 |
| 27 | F | 16 | ACL reconstruction | Left Knee | yes | | 10 |
| 28 | F | 14 | Meniscal suture | Left Knee | yes | | 10 |
| 29 | M | 17 | ACL reconstruction | Right Knee | yes | | 10 |
| 30 | F | 14 | ACL reconstruction | Left Knee | yes | | 9 |
| 31 | F | 15 | ACL reconstruction + meniscal suture | Left Knee | yes | | 9 |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 32 | F | 8 | Meniscal suture | Right Knee | yes | | 9 |
| 33 | F | 14 | Os trigonum resection | Left Ankle | yes | | 10 |
| 34 | M | 17 | Meniscal suture | Left Knee | yes | | 5 |
| 35 | F | 17 | ACL reconstruction | Right Knee | yes | | 5 |
| 36 | M | 18 | ACL reconstruction + meniscal suture | Left Knee | yes | | 5 |
| 37 | M | 17 | ACL reconstruction + meniscectomy | Left Knee | yes | | 5 |
| 38 | M | 17 | ACL reconstruction | Right Knee | yes | | 5 |
| 39 | F | 14 | Anterior calcaneal process resection | Left Ankle | yes | | 4 |
| 40 | M | 15 | ACL reconstruction | Right Knee | yes | | 3 |
| 41 | F | 14 | Meniscal suture | Left Knee | yes | | 3 |
| 42 | F | 16 | ACL reconstruction | Left Knee | yes | | 3 |
| 43 | F | 16 | ACL reconstruction | Left Knee | yes | | 3 |
| 44 | F | 17 | Meniscal suture | Left Knee | yes | | 2 |
| 45 | M | 17 | ACL reconstruction + meniscectomy | Left Knee | no | | 1 |
| 46 | F | 17 | Meniscectomy | Right Knee | no | | 1 |
| 47 | M | 11 | Loose body extraction | Left Elbow | no | Incomplete range of motion | 1 |
| 48 | F | 14 | Meniscectomy | Right Knee | no | | 1 |
| 49 | F | 13 | ACL reconstruction | Left Knee | no | | 1 |

Other pathologies which needed arthroscopic intervention were: knee arthroscopy for tibial spine fractures (2 patients) and for a posterior cruciate ligament rupture (1 patient), ankle arthroscopy for anterior calcaneal process fracture (1 patient) and for a symptomatic os trigonum (1 patient), elbow arthroscopy for an incarcerated medial humerus epicondyle (1 patient). We also had a case of a 16-year-old boy with multiple intraarticular loose bodies after lateral femoral condyle osteochondritis dissecans.

Time of full recovery varies on the pain threshold of each patient, but it is expected that in 6 to 8 weeks, full range of motion is acquired. In the ACL reconstruction group, we had two patients (8%) who didn't achieve full recovery, a girl because of a failure to maintain the recovery program, and a boy who suffered a graft rupture at 3 months after surgery.

The recovery of full range of motion can be more problematic when it comes to intraarticular fracture, even the ones treated minimally invasive. To this idea we have the example of a tibial spine fracture on a 6 years old girl, currently at 11 months after surgery, and an incarcerated medial epicondyle humerus fracture on a 11 years old boy, at 2 months after surgery, who have yet to achieve full range of motion.

*Anterior cruciate ligament reconstruction*

All surgeries were performed under pneumatic tourniquet assistance, the patient being positioned in decubitus with knee flexed at 90 degrees and hip flexed so the foot and buttock are on the same level (Figure 1.A). The technique we use in our department is based on principle of anatomical single bundle reconstruction of ACL. The autograft source was semitendinosus and gracillis tendons (Figure 1.B). The tunnels were transphyseal in all cases (Figure 1.C,D ). The fixation in the femoral tunnel is made with adjustable loop and the fixation in the tibial tunnel is achieved with interference screw. The placement of tunnels is based on principle of respect of native ligaments footprints. On occasions we preferred to verify the tunnel placement with fluoroscopy according to lateral X-ray criteria of tunnel placement [5].

Suction drainage was placed in all cases and removed at 24-48 hours after surgery. The knee was immobilised in 15 degrees of flexion with an adjustable hinged knee brace. The patient was mobilised early after surgery with contact of the foot with the ground but no load for 3 weeks. The load is started after the 3rd week and progressively completed to the 6th week post-surgery. In all this time the passive and active recovery of the knee flexion is worked. The recovery protocol is started during the hospital stay and continued after discharging.

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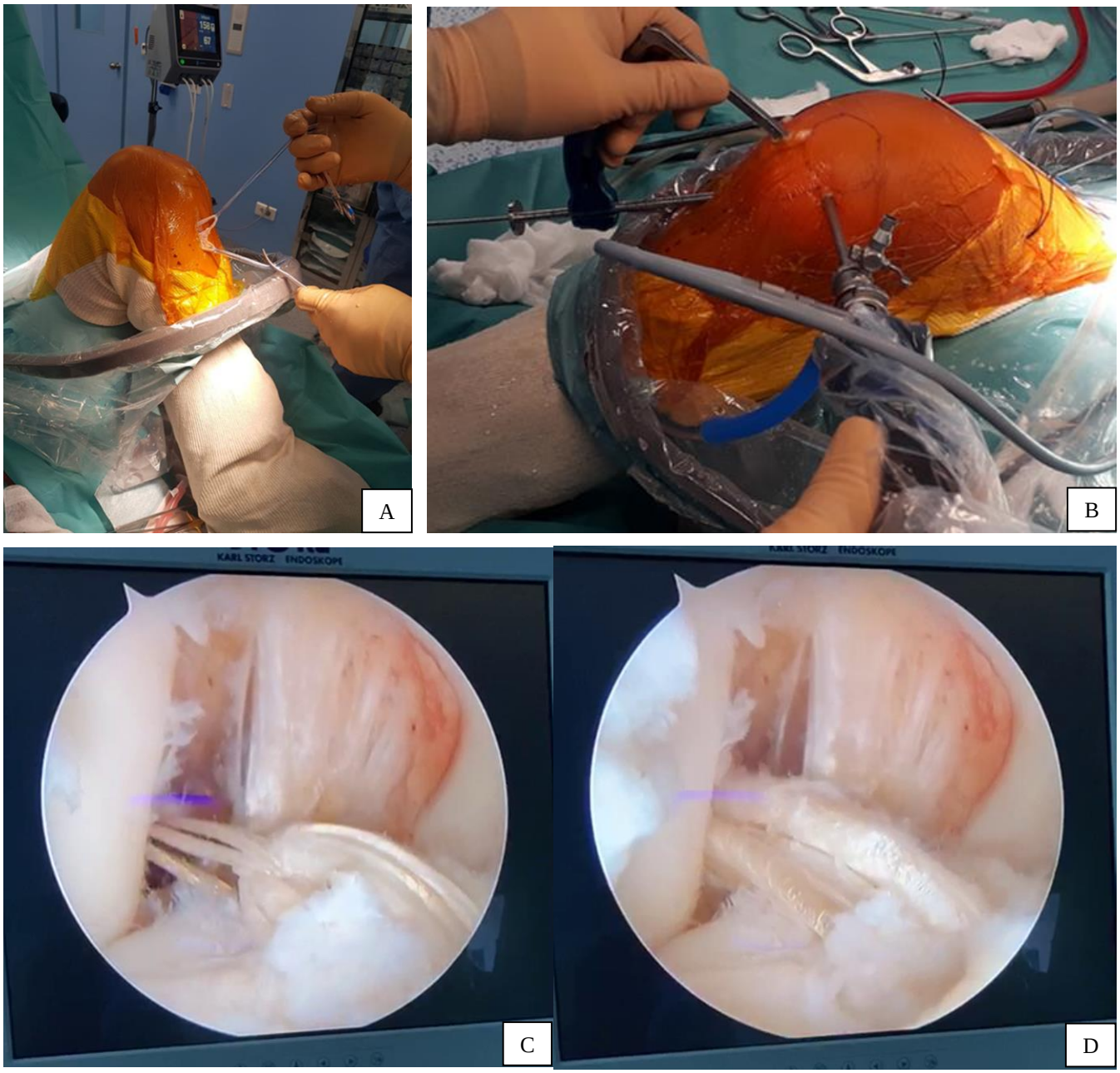


Figure 1. A - Semitendinous and gracillis tendon dissection. B - The tibial tunnel is made transphyseal. C - Intraoperative image of the right femoral notch, the graft is about to enter the joint and travel (upward and laterally) to the lateral femoral condyle, pulled by the adjustable loop. D - Intraoperative image of the right femoral notch, the graft is in place.

In some cases, the recovery treatment was assisted remotely via smart devices providing learning tools for the patient to execute passive flexion-extension of the knee with settings of time and speed that allow calibration according to the individual needs and pain threshold.

In 3 patients the ACL reconstruction was accompanied by the meniscus repair and in 5 patients the ACL reconstruction was accompanied by meniscus partial resection.

Even though complete range of motion was accomplished in one case, unadvised sport activity resulted in a graft complete tear at 3 months after arthroscopic repair. In one case the recovery protocol was not properly followed so at 10 months post-surgery the lack of 5 degrees of full extension is to be recovered.

In one case a discrete snap during knee flexion persisted for 8 months after surgery. The subjective “giving way” or “giving out” sensation of the knee disappeared in all cases.

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*Os trigonum resection*

A 14 year old girl, swimmer, presenting with posterior ankle impingement was operated because of important function impairment during walk and run. X-ray exam (Figure 2.A) and CT (Figure 2.B) exam were performed prior to surgery. The patient was placed in prone position. Two portals adjacent to the Achilles tendon were used. The work chamber was created prior to portals creation by injecting saline solution in the ankle. The os trigonum was identified and harvested with a motorized burr. The flexor hallucis longus was exposed during surgery. The resection was complete and the recovery was fast (Figure 2.C,D). At 48 hours after surgery the patient was able to walk on heals and on tiptoes without any pain. Very discrete hemarthrosis was present.

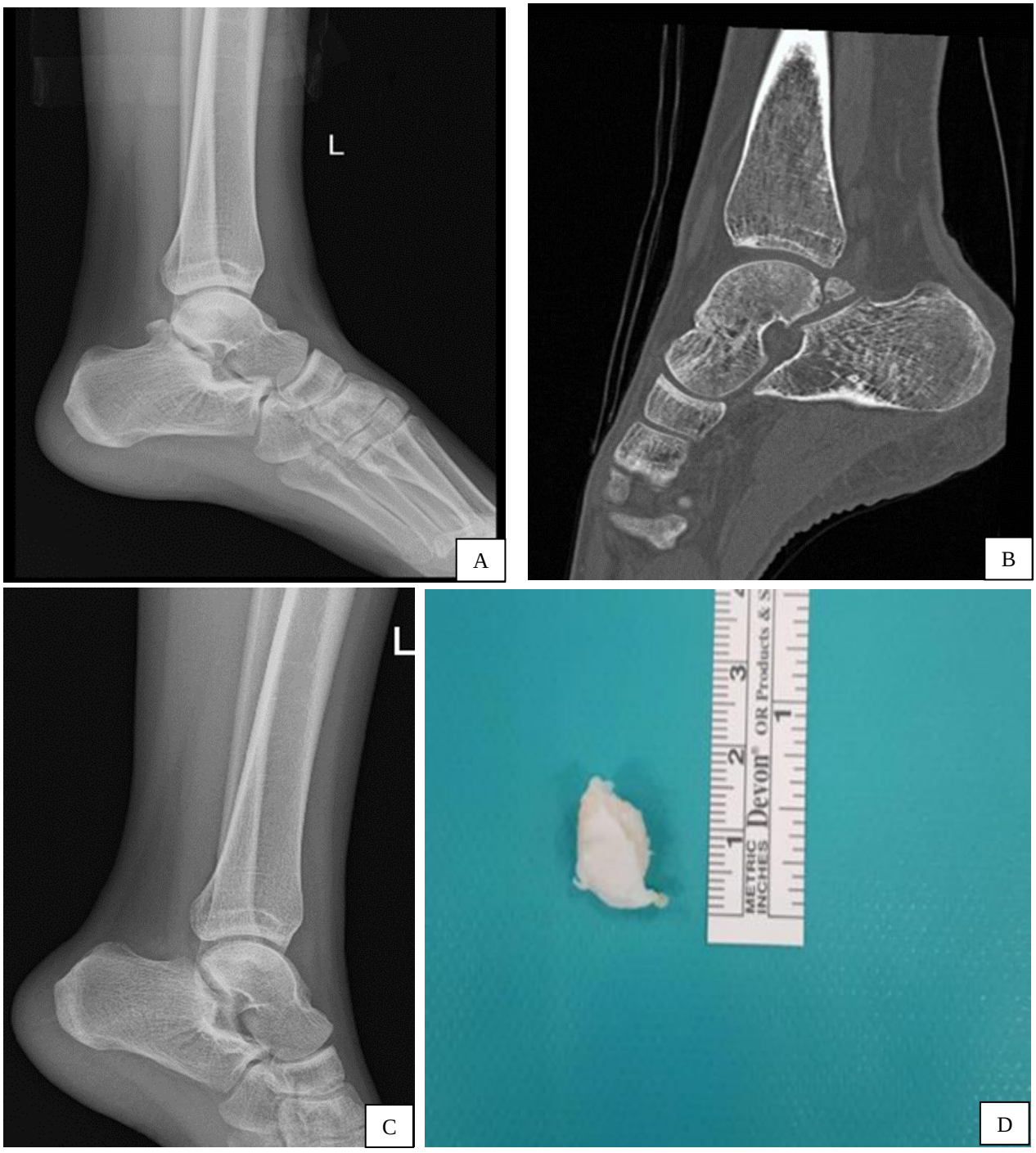


Figure 2. A - Lateral view of the ankle on the X-ray demonstrating the presence of os trigonum. B - Figure 2.b: CT scan examination of os trigonum. C - Postoperative X-ray of the ankle, showing good resection of os trigonum. D - The osteocartilaginous fragment removed from the ankle joint.

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*Anterior calcaneal process pseudarthrosis*

A 14 years old girl presented in our department with chronic pain of the midfoot, without known history of trauma. The pain was provoked by medium walking, 500-1000 meters, since few months. Clinical examination revealed fixed pain corresponding to a point 2 centimetres in front of the sinus tarsi. The subtalar joint mobilisation and the attempt to mobilise the Chopart joint triggered the pain corresponding to anterior calcaneal process. The X-ray (Figure 3. A) and CT (Figure 3. B,C) scan revealed a small bony fragment seeming to be avulsed from the anterior calcaneal process. We described this as an old fracture with no signs of healing. An immobilisation with short leg cast was recommended. After 6 weeks of immobilisation no signs of healing process or symptoms improvement were identified and we recommended the arthroscopic removal of the avulsed fragment. The operation was performed arthroscopically under fluoroscopy (Figure 3. D,E). The avulsed fragment was removed with a burr. The recovery process was started immediately after surgery. Full weight bearing of operated foot was authorized 3 weeks after surgery with no pain. The tolerance to long distance walks returned to normal.

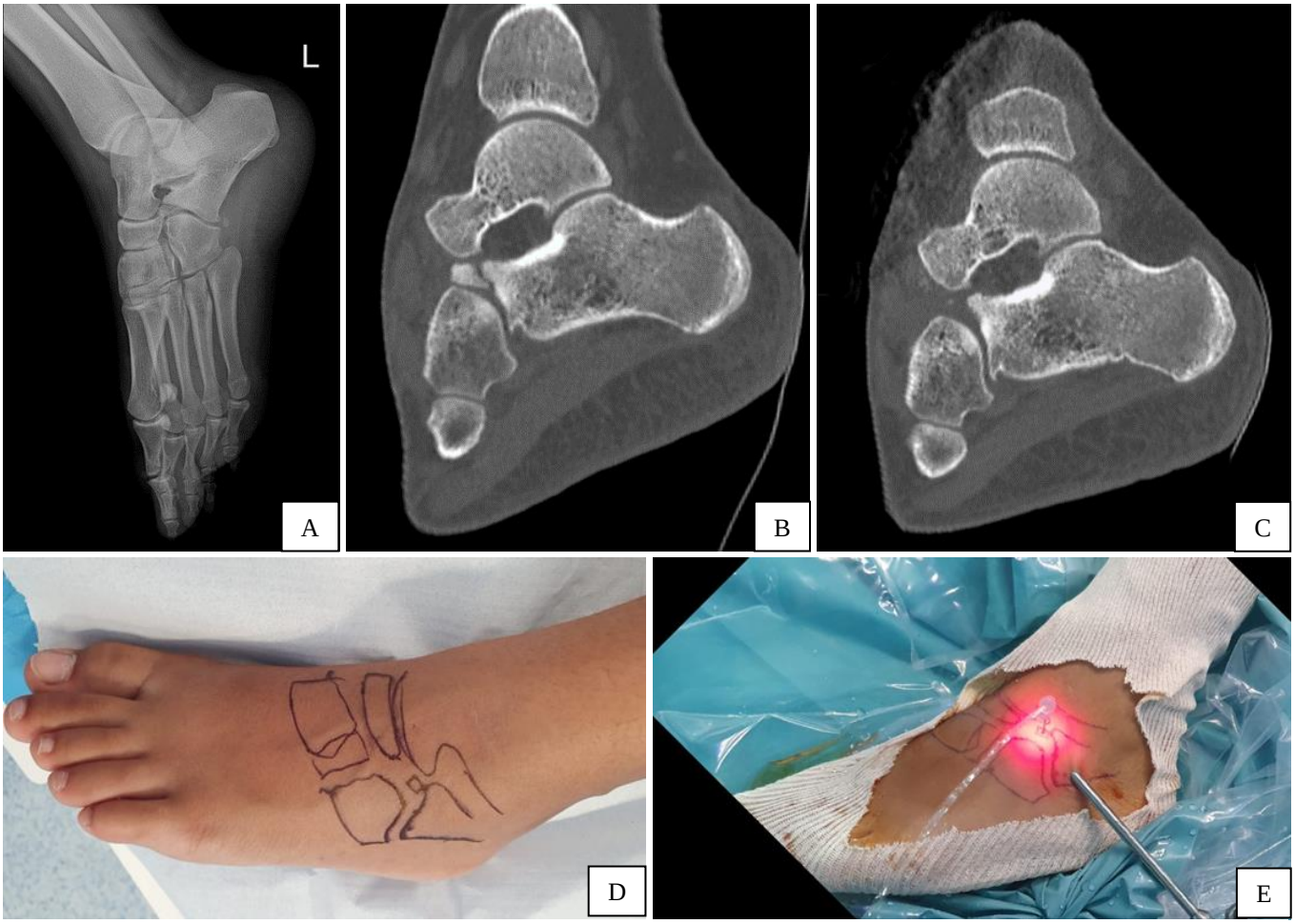


Figure 3. A - Anterior calcanean process is fractured, visible at X-ray exam. B - Preoperative CT scan demonstrating the fracture of anterior calcaneal process. C - Postoperative CT scan examination, the intraarticular fragment was completely removed. D - Intraoperative landmarks identified under fluoroscopy. E - Intraoperative aspect of portal placement to remove the anterior calcaneal process.

*Tibial spine fracture*

A 6 years old girl was referred to our service one week after a fall from toboggan, presenting a type IV Meyers and McKeever tibial spine fracture (Figure 4. A). An arthroscopic assisted transphyseal fixation with nonabsorbable suture and anterior button was performed. Intraoperative exploration revealed the anterior horn of medial meniscus incarcerated. The fixation material was removed 3 months after the surgery. The recovery has begun 3 weeks after surgery and was disrupted due to pandemics rush. The flexion recovered slowly, at 10 months after surgery 20 degrees of flexion is to be recovered. Postoperative CT showed good integration of avulsed bony fragment (Figure 4. B).

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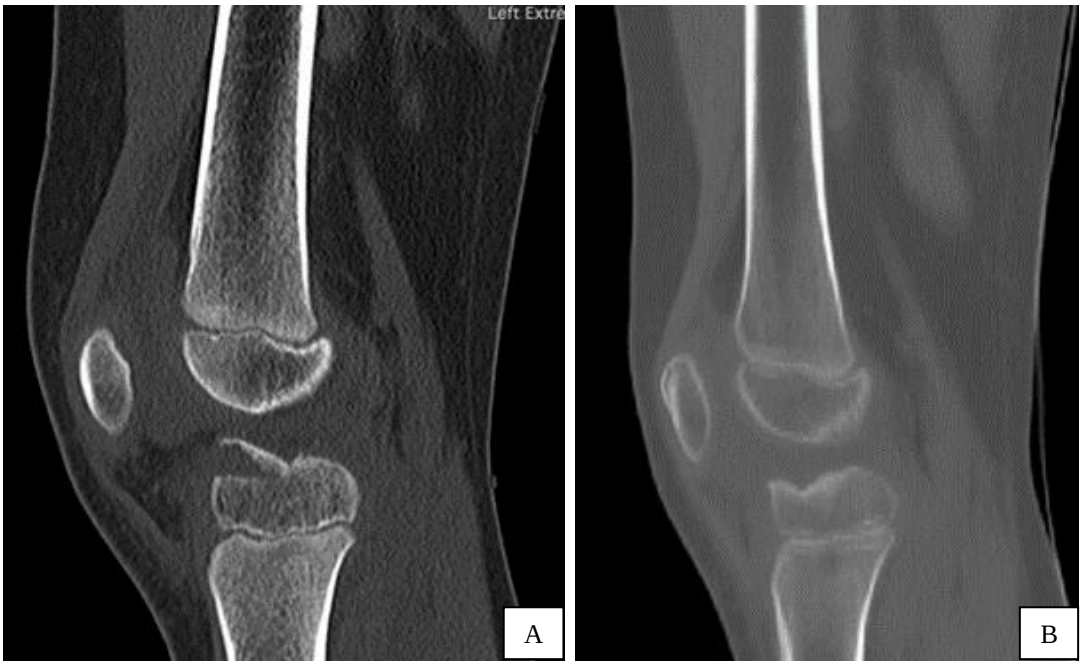


Figure 4. A Preoperative CT scan demonstrating displaced tibial spine fracture in 6 years old girl. B - Postoperative CT scan at 6 months follow-up demonstrating good integration of avulsed fragment.

*Humerus medial epicondyle removal*

An 11 years old boy presented in our department with fixed stiff elbow and a misdiagnosed fracture of medial epicondyle of left humerus, after 4 weeks of immobilisation because an elbow dislocation (Figure 5. A). The CT scan and MRI exam revealed the incarceration of an osteochondral fragment of the medial epicondyle into the humeroulnar joint. The removal of the fragment was performed arthroscopically via posteromedial and posterolateral portals (Figure 5. B). Intraoperatively we discovered a small defect in the olecranon articular surface; a reparation procedure was considered unnecessary (Figure 6. A,B). The stiffness changed rapidly postoperatively from fixed to elastic. The recovery is ongoing, the patient gained 90 degrees of mobility during the first month postoperatively. The elbow is stable and nonpainful.

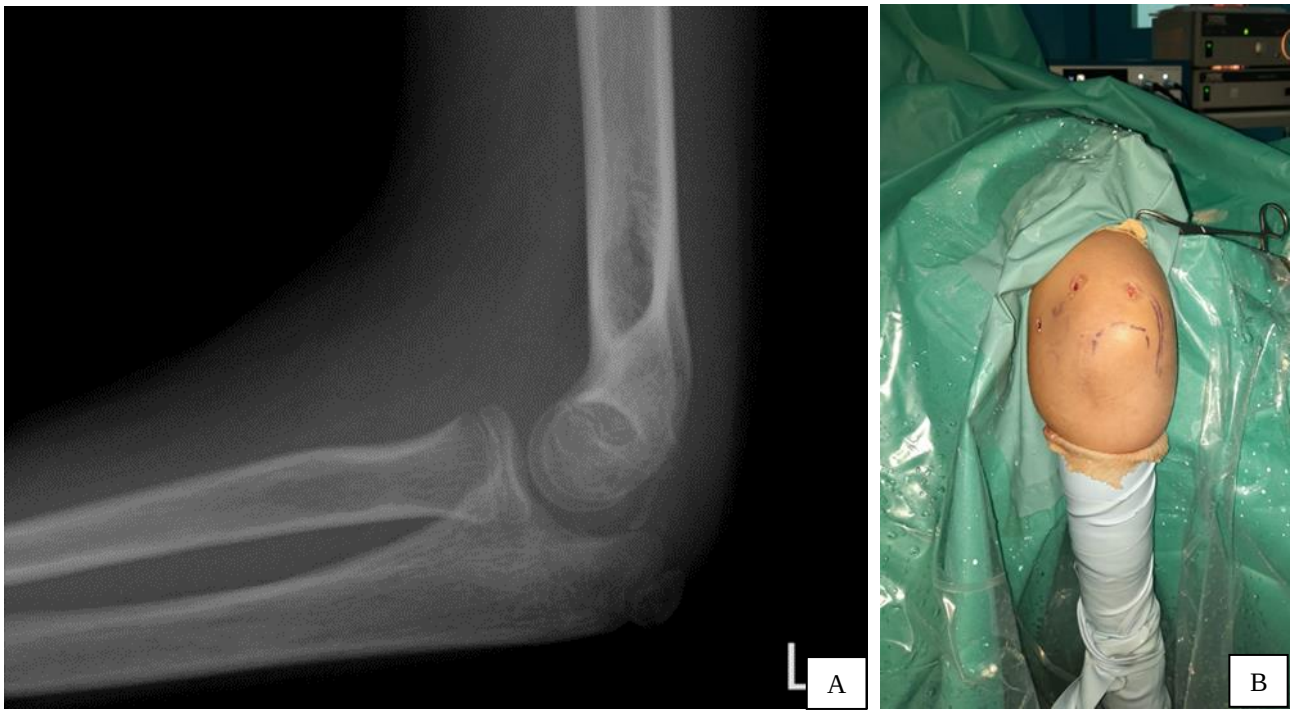


Figure 5. A - Humeroulnar subluxation secondary to incarceration of osteochondral medial epicondyle fragment. B - Portals placement for elbow arthroscopy.

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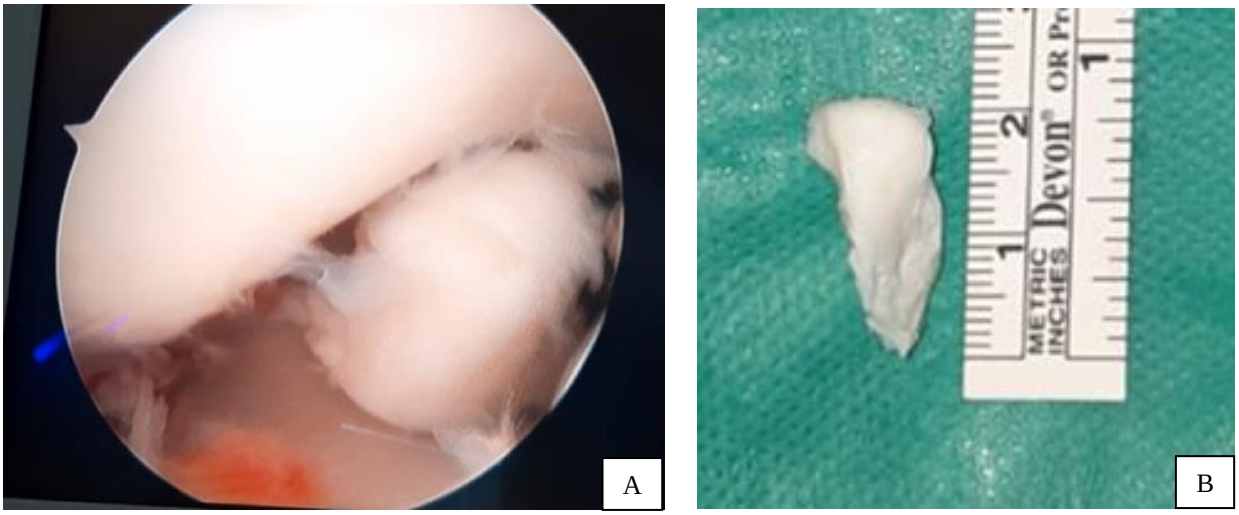


Figure 6. A - Intraoperative aspect demonstrating the large osteochondral fragment trapped between the humeral trochlea and olecranon. B - Osteochondral fragment removed from the elbow joint.

**Discussion**

ACL reconstruction in paediatric population was subject of debate. Few aspects of ACL tears diagnosis and treatment were the subject of international consensus [6].

Concerning the diagnosis there are two remarks to keep in mind. When the clinical exam does not reveal instability of the knee or the MRI exam is negative the probability of having an ACL injury is low; on the other hand, the positive clinical examination or MRI exam cannot rule in an ACL tear in all cases. However, the decision making should not rely on one single test or examination technique.

One of the concerns raised by the ACL reconstruction is the physeal injury during tunnel creation. The international consensus [6] agreed the transphyseal techniques may be used in paediatric patients with the condition of not to place rigid plugs (bone or screws) in the growth plate. The soft tissue occupying the tunnel is protective against the development of bony bridges and growth disturbances.

The moment to return to sport activities is another topic of debate. Two numbers should be emphasized. The duration of rehabilitation procedure should continue at least 9 months after the surgery. Returning to pivot activities should be delayed after $12^{th}$ months post-surgery [6] given high risk of re-rupture during the first 12 months after surgery.

Posterior ankle impingement syndrome is a recently entity approached with arthroscopic tools[7]. The condition is generated by the mechanical conflict in the rear ankle. Removal of os trigonum is reserved for people engaged in athletic activities or if the conservative treatment has failed. Despite the small space to work and the neighbourhood of the posterior tibial bundle the technique is reliable giving good access and even better visualisation than open technique. Yasui [7] described a four staged systematic arthroscopic approach to the posterior ankle. After a systematic inspection of the ankle the fragment is removed with a burr.

The technique we used in the treatment of anterior calcaneal process pain syndrome was inspired by the treatment of calcaneonavicular coalition [8]. However, the mechanism we illustrated in this case may be part of TLAP syndrome[9]. Given the fibrous attachment on the fragment we found during surgery a fracture secondary to fibrous calcaneonavicular coalition is highly probable. Few open or miniopen techniques are described to remove the calcaneonavicular coalition [10]. Arthroscopy is an attractive method given the minimisation of the articular instability of the midfoot joint secondary to surgical approach.

Displaced tibial eminence fracture in children is a rare condition requiring surgical treatment. The choosing of hardware fixation is limited by the presence of growth plate and the poor bone quality immediately below the avulsed fragment. Transphyseal techniques are attractive due to the strength generated by the new nonabsorbable sutures [11]. We used a simplified technique and passed a suture behind the ACL, the loop was closed outside the bone, over a titanium button. The MRI showed an excellent reduction of the fracture. The slow progression of the rehabilitation pushed us to remove the implant three months after the surgery due to some skin discomfort in front of the titanium button. Arthrofibrosis is a known complication of the tibial spine fracture [12]. Early start of rehabilitation program may enhance the development of such complication. The quality of recovery is in direct relation to the quality of fixation, given the limitation of hardware volumes we can use in children, the suture fixation is a better option.

Medial epicondyle fracture in children may be easily misdiagnosed [13]. The incomplete ossification of the distal humerus at different stages of development make the diagnosis even more difficult. Advanced diagnosis tools as CT or MRI may be necessary to have a correct description of the fracture. Incarcerated medial epicondyle fracture needs early surgical treatment in order to avoid articular stiffness [14]. Elbow stiffness secondary to the elbow

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dislocation is an invalidating condition needing surgery [15] to restore the range of motion. Foreign body removal using arthroscopic tools is an attractive alternative allowing early start of rehabilitation. The case we presented in this paper is particular because of small amount of bone tissue in the avulsed fragment and difficulty of visualisation on X-ray exam and even at CT scan.

Patient comfort and duration of full recovery are indicators of quality of life after surgery. The pain is influencing considerably the recovery process, the level of pain is in direct relationship with the soft tissue damage during the surgery. Minimally invasive techniques are expected to generate less pain comparing with open surgery and consequently better quality of life after surgery. This domino effect may explain the amount of work to develop minimally invasive techniques. Given the techniques developed for small patient are based on lessons learned after the development in adult surgery a gap is appearing between the development of such techniques for paediatric patient when comparing with adults.

**References**


1. Accadbled F, N'Dele D: Arthroscopic Treatment of Pediatric Fractures. J Pediatr Orthop 2018, 38 Suppl 1:S29-S32.
2. Alt V, Gasnier J, Sicre G: Injuries of the scapholunate ligament in children. [Miscellaneous Article]: Journal of Pediatric Orthopaedics B September 2004;13(5):326-329.
3. Memisoglu Ka, Muezzinoglu USa, Atmaca Hb, Sarman Hc, Kesemenli CCa: Arthroscopic fixation with intra-articular button for tibial intercondylar eminence fractures in skeletally immature patients. [Miscellaneous Article]: Journal of Pediatric Orthopaedics B January 2016;25(1):31-36.
4. Lee D-HMD, Jeong W-KMD, Lee S-HMDP: Arthroscopic Excision of Osteoid Osteomas of the Hip in Children. [Miscellaneous Article]: Journal of Pediatric Orthopaedics September 2009;29(6):547-551.
5. Parkar AP, Adriaensen ME, Strand T, Inderhaug E, Harlem T, Solheim E: How to read post-operative radiographs and CT scans after single-bundle anterior cruciate ligament reconstruction. Skeletal Radiol 2013, 42(11):1489-1500.
6. International Olympic Committee Pediatric ACLICG, Ardern CL, Ekas G, Grindem H, Moksnes H, Anderson AF, Chotel F, Cohen M, Forssblad M, Ganley TJ et al: 2018 International Olympic Committee Consensus Statement on Prevention, Diagnosis, and Management of Pediatric Anterior Cruciate Ligament Injuries. Orthop J Sports Med 2018, 6(3):2325967118759953.
7. Yasui Y, Hannon CP, Hurley E, Kennedy JG: Posterior ankle impingement syndrome: A systematic four-stage approach. World J Orthop 2016, 7(10):657-663.
8. Knörr J, Accadbled F, Abid A, Darodes P, Torres A, Cahuzac JP, Sales de Gauzy J: Arthroscopic treatment of calcaneonavicular coalition in children. Orthop Traumatol Surg Res 2011, 97(5):565-568.
9. [9] Guignand D, Journeau P, Mainard-Simard L, Popkov D, Haumont T, Lascombes P: Child calcaneonavicular coalitions: MRI diagnostic value in a 19-case series. Orthop Traumatol Surg Res 2011, 97(1):67-72.
10. Kothari A, Masquijo J: Surgical treatment of tarsal coalitions in children and adolescents. EFORT Open Rev 2020, 5(2):80-89.
11. Gamboa JT, Durrant BA, Pathare NP, Shin EC, Chen JL: Arthroscopic Reduction of Tibial Spine Avulsion: Suture Lever Reduction Technique. Arthrosc Tech 2017, 6(1):e121-e126.
12. Gans I, Babatunde OM, Ganley TJ: Hybrid fixation of tibial eminence fractures in skeletally immature patients. Arthrosc Tech 2013, 2(3):e237-242.
13. Fernandez FF, Vatlach S, Wirth T, Eberhardt O: Medial humeral condyle fracture in childhood: a rare but often overlooked injury. Eur J Trauma Emerg Surg 2019, 45(4):757-761.
14. Dodds SD, Flanagin BA, Bohl DD, DeLuca PA, Smith BG: Incarcerated medial epicondyle fracture following pediatric elbow dislocation: 11 cases. J Hand Surg Am 2014, 39(9):1739-1745.
15. Strauss NL, Lattanza L: Open surgical treatment of posttraumatic elbow contractures in children. Tech Hand Up Extrem Surg 2010, 14(2):108-113.



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# RADIOFREQUENCY ABLATION OF OSTEOID OSTEOMA IN CHILDREN, SHORT TERM RESULTS

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**Abstract**

The purpose of this paper is to evaluate the postoperative results in paediatric patients with osteoid osteoma. We present a retrospective study including 16 patients under 18 years old treated surgically in our institution between April 2019 and September 2020. Patient demographic data, clinical aspects and imaging studies used to establish the diagnosis, lesion location, the size of the nidus, surgical data, hospitalization periods, complications and particular conditions were noted.

Sixteen patients with mean age of 11.19 years (between 5 and 17 years) were treated using surgical excision (open or minimal invasive) or radiofrequency ablation (RFA). All patients presented with night pain highly responsive to nonsteroidal anti-inflammatory drugs. Imaging studies before surgery included radiographs, CT scans and/or MRI, technetium-99 bone scans. Interval between symptoms onset and surgery varied from 3 to 18 months (mean 8.18 months). Eight patients were treated using radiofrequency ablation under fluoroscopy, 5 cases were treated using minimal invasive surgery (resection-biopsy with trocar) and 3 cases were treated by open surgical excision. We have obtained histopathologic diagnosis in all cases. One patient had a superficial wound infection and two patients presented recurrent pain. In 13 patients the pain disappeared during the first 48 hours after surgery. Mean follow-up time was 10.12 months.

RFA is the treatment of choice in paediatric cases of osteoid osteoma. Vicinity of important anatomical structure are contraindications for RFA. Using ablation probes with cooled tips may result in more predictable outcomes. The tendency to use less and less invasive procedures in the surgical fields seems to lead to development of non-invasive procedure.

**Keywords:** osteoid osteoma, children, radiofrequency ablation, cooled tip

## Introduction

Osteoid osteomas are benign, painful, solitary lesions of bone. Described by Jaffe in 1953 [1] is still subject of research for new treatments. Osteoid osteoma consists of a central round nidus of 1.5-2 cm surrounded by an area of dense reactive bone. The central nidus is composed by variable amounts of osteoid, osteoblasts and fibrovascular stroma. The cortical bone adjacent to osteoid osteoma may be pink due to increased local vascularity. The lesion is a round or oval reddish tumour less than 2 cm, most frequently around 1 cm. The nidus may be very dense if the calcification process is intense or may be soft or granular if calcification is little. Osteoid osteoma presents small spicules of immature trabeculae lined by osteoblast and osteoclasts. The pain associated to osteoid osteoma is generated by nonmyelinated axons present in the nidus.

The typical presentation is of localized, nocturnal, or quasi continuous pain, related to the nidus location, alleviated by salicylates or other NSAIDs intake. The pain may be cause of misdiagnosis, for example a femoral neck osteoid osteoma may generate pain to the knee and vice-versa, imagistic exam being misoriented by consequence. According to the affected limb, a limp may be present or another functional impairment. Muscular atrophy is always present in variable extent. Local swelling is uncommon. In cases of vertebral osteoid osteoma, a muscle contracture may develop. On conventional X-ray the nidus may be visible, on occasion central calcification may be present. In unusual locations, when reactive sclerosis is not visible bone scintigraphy may be necessary to reveal the location. CT scan and MRI are useful tools for diagnosing this entity.

The treatment of osteoid osteoma evolved over time. There is always place for conservative treatment due to fear of surgery or difficult approach [2, 3]. Surgical treatment and open or percutaneous resection of the lesion are available options [4]. Modern techniques, such radiofrequency ablation, are widely used today to treat osteoid osteoma [5, 6]. Other emerging techniques are developing such cryoablation [7] or magnetic resonance focused ultrasound [8].

The purpose of this paper is to present the short-term results obtained in our department with the treatment of osteoid osteoma in children and to report the early results with radiofrequency ablation (RFA) in children with osteoid osteoma.

## Materials and Methods

From April 2019 to September 2020 sixteen patients with osteoid osteomas were treated by our team (Table 1).

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Table 1: The case series of 16 patients with osteoid osteoma operated in our department.

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| CASE | SEX | AGE (years) | LOCATION | PROCEDURE | TIME FROM ONSET OF PAIN TO SURGERY (months) | FOLLOW-UP (months) |
|---|---|---|---|---|---|---|
| 1 | M | 5 | FEMUR | RFA | 12 | 3 |
| 2 | M | 6 | FEMUR | RFA | 7 | 11 |
| 3 | M | 10 | TIBIA | RFA | 12 | 12 |
| 4 | M | 10 | TIBIA | RFA | 3 | 9 |
| 5 | M | 11 | FEMUR | RFA | 6 | 4 |
| 6 | F | 13 | FEMUR | RFA | 18 | 19 |
| 7 | F | 14 | TIBIA | RFA | 6 | 11 |
| 8 | M | 18 | TIBIA | RFA | 6 | 12 |
| 9 | M | 4 | TIBIA | SURGERY | 12 | 10 |
| 10 | M | 6 | TIBIA | SURGERY | 5 | 4 |
| 11 | F | 9 | FEMUR | SURGERY | 4 | 9 |
| 12 | M | 10 | TIBIA | SURGERY | 6 | 15 |
| 13 | M | 14 | FEMUR | SURGERY | 3 | 5 |
| 14 | M | 16 | TALUS | SURGERY | 14 | 15 |
| 15 | M | 16 | PUBIC RAMUS | SURGERY | 5 | 6 |
| 16 | M | 17 | FEMUR | SURGERY | 12 | 17 |

There were 3 girls and 13 boys in the study group. The age ranged from 4 to 18 years with an average of 11 years. The time between the onset of symptoms and the moment of treatment was between 3 months and 18 months with an average of 8 months. Two main types of treatment were used: surgical removal of the lesion in 8 cases and RFA in 8 cases. The age range in the surgery group was between 4 and 17 years with an average of 11.5 years respectively between 5 and 18 years with an average value of 11 years in the RFA group. Plain X-ray were obtained in all patients. CT scan, MRI exam (Figure 1A) or both exams were performed in all patients. The decision making was based on clinical presentation and imaging investigations. When the imagistic investigations were not conclusive the resection biopsy alone was preferred instead of RFA.

Informed consent was obtained from all patients, the limits and risks for every procedure were explained. All patients were treated in the operating room according to surgical protocols preparative.

The first step before any treatment was the fluoroscopic identification of the lesion. We observed that at least for long bones the nidus is better visualised under fluoroscopy compared with plain X-ray. All the procedures were meticulously prepared by studying the CT scan and/or MRI imaging to facilitate the heuristic learning to identify the nidus position. The lesion was approached through the opposite cortex by creating a 5 mm oblique tunnel with a power drill without touching the nidus. A 2 mm K wire was placed in the nidus (Figure 1B, 1C) in order to create the space for the RFA probe (Figure 1D). The position of the K-wire tip was always verified on multiple views. Afterward, according to the proposed method, the nidus was coagulated with RFA or surgically removed.

In the resection biopsy cases, the K wire was used to guide the 5 mm trocars to harvest the maximum amount of bone tissue. Small changes of the direction of the trocar allowed us to harvest more bone fragments. All fragments were conditioned to be sent to the pathology department.

We preferred to generate three cycles of RFA for each lesion. The 5 mm tunnel allowed the probe to be placed in three different direction around the nidus. According the nidus dimensions we used the appropriate probe to ensure the generation of the heat in a sufficiently large volume of tissue. The RFA device allows the customisation of final temperature at the probe tip, the time of heat generation, the velocity of temperature increment. When radio ablation was used, the RFA device was set to provide 4 minutes of 70 degrees heat at the tip of the probe (Figure 1E). In cases of RFA we also collected small samples of bone with 3 mm trocars from the reactive bone region in order to confirm the benign nature of the lesion.

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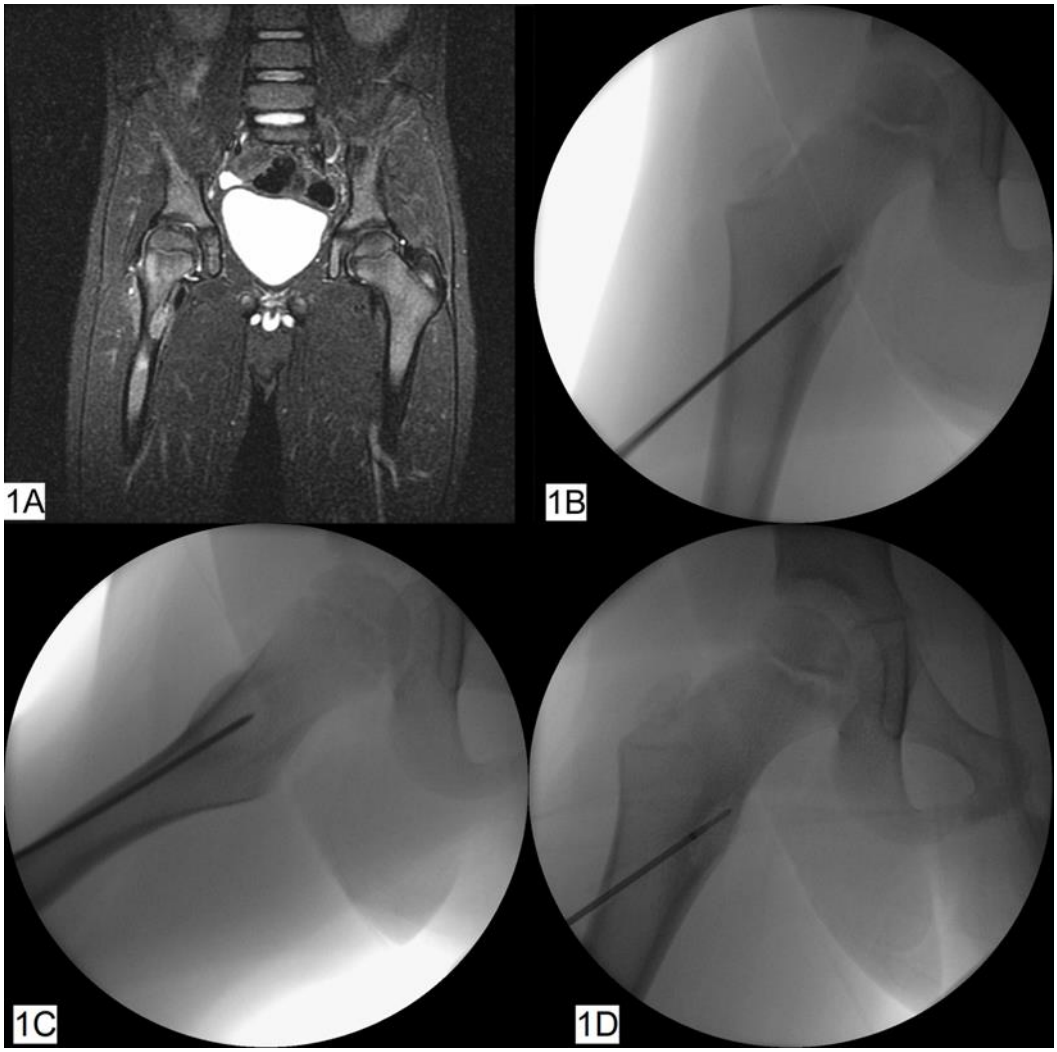


Figure 1. A - Case no.1, MRI aspect of the right sub trochanteric osteoid osteoma. B - K wire placement under fluoroscopic control, anteroposterior view. C - K wire placement under fluoroscopic control, lateral view. D - The fluoroscopic image of RFA probe in the nidus.

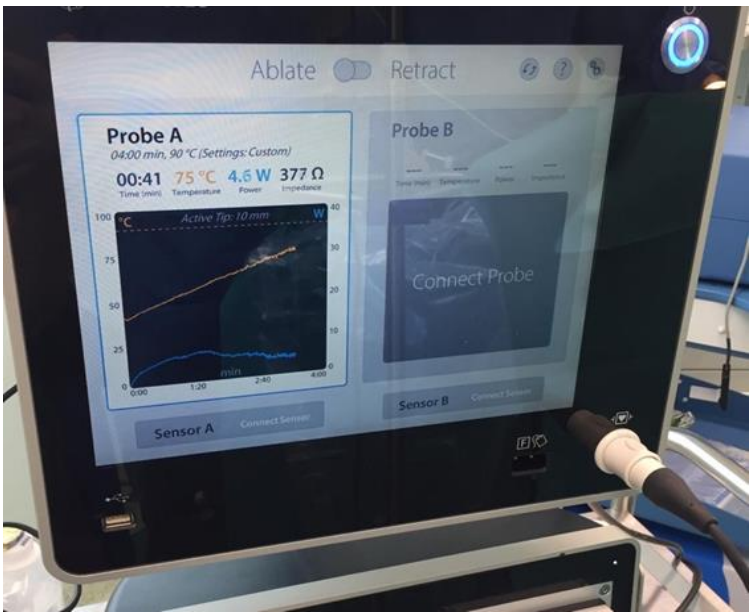


Figure 1E. The RFA device showing the temperature curve control (yellow line).

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**Results**

In all cases the diagnosis was confirmed by the pathologist. All patients received analgesic drugs during the first 24-48 hours post-surgery. Before discharge, the analgesic medication was cut for at least 24 hours, in order to certify that the nocturnal pain has ceased. The follow-up period ranged from 3 months to 19 months with an average of 10 months. The pain recurred in two cases, both in the surgery group.

In the RFA group the location was the femur in four cases and the tibia in four cases. In one case of the RFA group, case 6, the radio ablation was performed after failure of minimally invasive surgical resection. All eight cases in RFA group presented very satisfactory results the pain disappearing immediately after surgery. No complications related to surgery were observed. The patients were mobilised the next day after the surgery. All patients were able to accurately differentiate the pain related to the skin after the surgical procedure from the pain generated by the osteoid osteoma before the surgery. There was no need for NSAIDs intake after discharge, in any patient.

In the surgery group the pain disappeared in all cases but recurred in two cases, cases 13 and 16. The decision to take larger samples of bone was based on unusual presentation on CT-scan or MRI exam. A larger reaction around the supposed nidus or an irregular morphology of the nidus caused a more precautious approach. In the case no. 14 (Figure 2), because of the superficial situation of nidus, we preferred to perform an open curettage of the lesion. In the case no. 15, the vicinity of the femoral vessels (Figure 3A, 3B, 3C) was considered a contraindication for RFA. On the other hand, the superficial situation of the nidus allowed the open surgery and good quality resection.

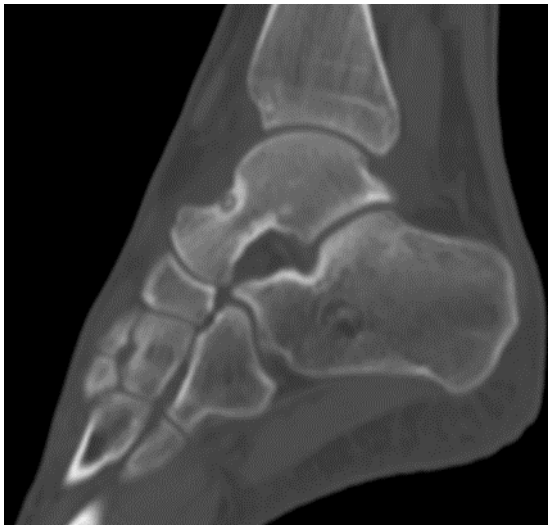

Figure 2. Superficial situation of the osteoid osteoma on the talar neck (case no. 14).

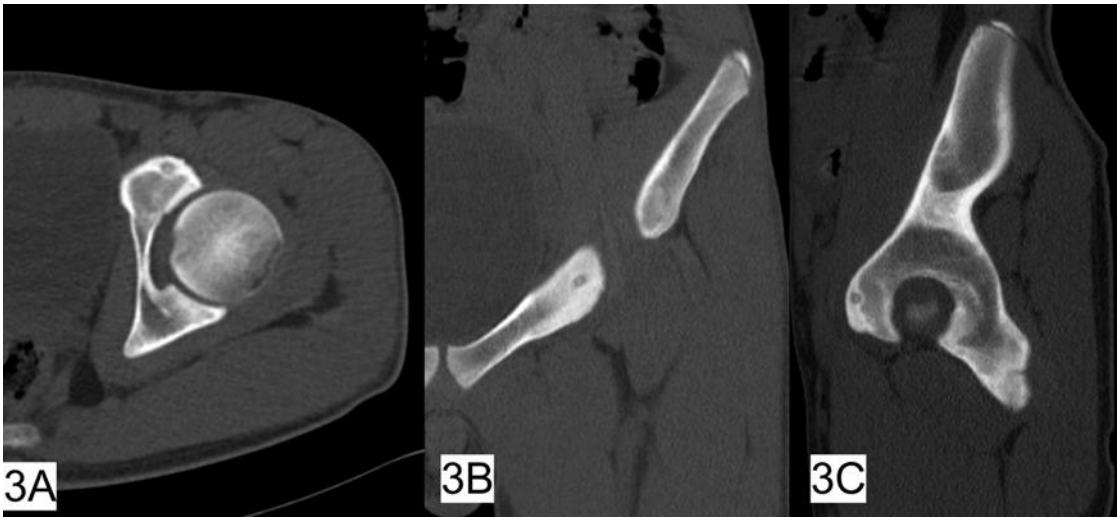


Figure 3. A - Case no. 15, osteoid osteoma of the pubic ramus, CT scan transversal section. B - Case no. 15, osteoid osteoma of the pubic ramus, CT scan frontal section. C - Case no. 15, osteoid osteoma of the pubic ramus, CT scan sagittal section.

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Case no. 16 presented the recurrence of pain 14 months after the surgery. Further investigations are needed. We suppose an incomplete removal of the nidus explain the recurrence of pain.

Case no. 13 was not labelled as having osteoid osteoma at first presentation. He presented in our department after three months of persistent pain in the proximal thigh and progressive stiffness of the hip. Given the extent of the lesions around the proximal femur and the intraarticular collection visible on MRI exam the most probable diagnosis was considered the chronic osteomyelitis with intraarticular extent or septic arthritis with subperiosteal fusion and chronic evolution (Figure 4A). An open diagnostic biopsy was proposed. During the surgery, the fish meat aspect of the soft tissues was very evocative for a neoplasia; by consequence, the hip joint was not inspected, and the procedure was limited to the bone and soft tissue biopsy. Later on, the histology exam diagnosed the osteoid osteoma. New MRI exam (figure 4B, 4C) and CT scan (Figure 4D) added some imaging arguments in favour of osteoid osteoma. The worsening of hip stiffness has led to the second surgery, the hip joint was decompressed, and articular samples were collected. The pain disappeared and the hip stiffness improved. The case is still under investigations.

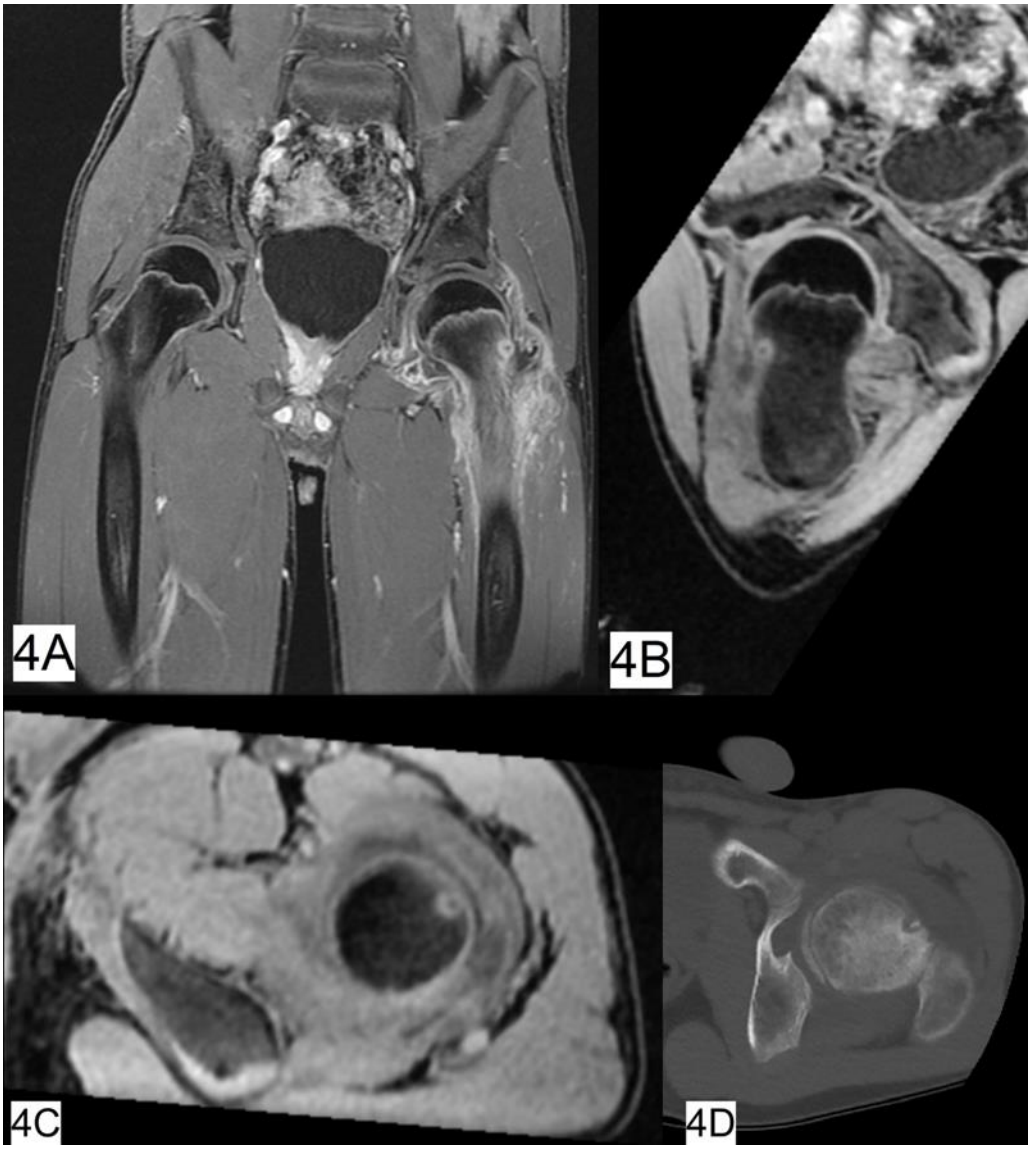


Figure 4. A- Case no. 13, MRI image showing infiltration of the soft tissues and proximal left femoral metaphysis with massive intraarticular effusion. B - Case no.13, MRI transversal section within femoral neck. C - Case no.13, MRI sagittal section within femoral neck. D - Case no.13, CT transversal section within femoral neck revealing the nidus in the anterior cortex of the left femoral neck.

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**Discussion**

Rosenthal [9] is credited to be the first to use the radiofrequency to ablate the osteoid osteoma. The principle of the method consists of creating a heating process in a controlled volume of tissue in order to destroy the proteins in the tissue. The denaturation of the proteins will have two consequences: the bone forming process will stop and the nervous fibbers in the tumour tissues will be destroyed so the pain stimuli will not pass. The problem of the heating process control was addressed by new technical development. The water-cooled probes used for RFA seems to produce more predictable and lasting effects on tissue denaturation [10]. Zacharias et al., in an experiment on mice, proved that the amount of energy generated in tissue is higher for the cooled-tip probe [10]. Another physical process to consider is the velocity of temperature increase. A too rapid increase in the temperature will necrotise the protein rapidly, on a small radius around the probe; a slow increase of the temperature will allow a more uniform denaturation of the protein on larger radius.

In a study on 263 patients the efficacy of RFA was evaluated to 91% for procedures performed as initial treatment and 60% for recurrent lesions by Rosenthal et al [11]. Long term results were not influencing by age, sex, location of the lesion. Few authors evaluated the success rate of RFA in children with comparable results [12-14]. The safety of the procedure was proved by the low rate of complications. When comparing to the resection-biopsies there are few advantages to emphasise. Removing a bone fragment may alter the mechanical strength of bone becoming susceptible to fracture. RFA does not alter the mechanical strength of the affected bone. The recurrence of the symptoms is caused by the incomplete removal of the lesion. The advantage of RFA consist in the possibility of treating a larger volume of tissue without removing it, we performed a few cycles of radio ablation around the nidus to prevent recurrence.

Our case series is not statistically significant to emit some conclusions concerning the efficacy of the RFA in the treatment of osteoid osteoma in children, but it allowed us to learn some lessons. First of all, the use of RFA is reassuring for the surgeon. There is no fear about the consequences of missing the lesion as in open surgery when visual identification of the nidus is almost impossible. Even in case of failure to identify and coagulate the nidus there is always the possibility to return to operating room without the consequences of an excisional procedure. Another lesson consists in heuristic learning to identify the bone anatomy. Some papers report the results with 3D navigation to identify the nidus which is safer [15]; a thoroughly study of 3D reconstruction on CT or multiplanar reconstructions on MRI will train the surgeon to have good mono-planar landmarks on fluoroscopy in the operating room. An empirical observation consists of that the nidus is easier to identify on fluoroscopic images than on plain X-ray.

All cases in our series which raised concerns about the positive diagnosis of osteoid osteoma were confirmed at histologic exam. The cautions may never be enough, but the probable diagnosis based on non-invasive imagistic technique is a grey-zone subject to local regulations among experts, in order to avoid unexpected misdiagnosis. In case of doubt, having a histologic confirmation, is advisable.

Intraarticular or juxtaarticular location of the osteoid osteoma is a subject of concern given the extent of local reaction of soft tissues. Intraarticular locations of osteoid osteoma are less common, representing 12% of all lesions, and the hip is the most frequently affected joint [16-18]. Intraarticular osteoid osteoma may produce a wide spectrum of manifestations as soft tissue swelling, joint tenderness, effusion, and synovitis, simulating inflammatory arthritis or degenerative arthropathy [19-21]. Growth disturbances or scoliotic deformity were reported in skeletally immature patients, and intraarticular lesions can create a chronic inflammatory cascade leading to osteoarthrosis [22, 23]. Alternative initial diagnosis and delays in diagnosis are common due to the rarity of the location about the hip of the osteoid osteoma and to the unclear clinical and imaging findings [24]. Erroneous diagnosis was found in 22 of 31 patients by Goldberg and Jacobs, with synovitis and Legg-Calvé-Perthes disease being most common [25]. Delays in diagnosis can lead to prolongation of symptoms and can produce skeletal deformity, scoliosis, and if located intraarticular, joint degeneration [22, 23, 26, 27].

**Conclusions**

RFA is the treatment of choice in paediatric cases of osteoid osteoma. Vicinity of important anatomical structure are contraindications for RFA. Using probes with cooled tips may result in more predictable outcomes. The tendency to use less and less invasive procedures in the surgical fields seems to lead to development of non-invasive procedure.

**Conflicts of interest**

The authors declare that they have no conflict of interests.

**References**


1. Jaffe HL. Osteoid-osteoma. Proc R Soc Med. 1953;46(12):1007-12. Epub 1953/12/01. PubMed PMID: 13120827; PMCID: PMC1918782.
2. Yokouchi M, Nagano S, Shimada H, Nakamura S, Setoguchi T, Kawamura I, Ishidou Y, Komiya S. Early complete remission of osteoid osteoma with conservative medical management. Pediatr Rep. 2014;6(1):5311. Epub 2014/04/09. doi: 10.4081/pr.2014.5311. PubMed PMID: 24711915; PMCID: PMC3977163.
3. Jayakumar P, Harish S, Nnadi C, Noordeen H, Saifuddin A. Symptomatic resolution of spinal osteoid osteoma with conservative management: imaging correlation. Skeletal Radiol. 2007;36 Suppl 1:S72-6. Epub 2006/09/13. doi: 10.1007/s00256-006-0198-x. PubMed PMID: 16967288.

4. Baunin C, Puget C, Assoun J, Railhac JJ, Cahuzac JP, Clement JL, Sales de Gauzy J. Percutaneous resection of osteoid osteoma under CT guidance in eight children. Pediatr Radiol. 1994;24(3):185-8. Epub 1994/01/01. doi: 10.1007/bf02012187. PubMed PMID: 7936795.
5. Ghanem I, Collet LM, Kharrat K, Samaha E, Deramon H, Mertl P, Dagher F. Percutaneous radiofrequency coagulation of osteoid osteoma in children and adolescents. J Pediatr Orthop B. 2003;12(4):244-52. Epub 2003/06/25. doi: 10.1097/01.bpb.0000049571.52224.81. PubMed PMID: 12821840.
6. Göksel F, Aycan A, Ermutlu C, Gölge UH, Sarısözen B. COMPARISON OF RADIOFREQUENCY ABLATION AND CURETTAGE IN OSTEOID OSTEOMA IN CHILDREN. Acta Ortop Bras. 2019;27(2):100-3. Epub 2019/04/17. doi: 10.1590/1413-785220192702158113. PubMed PMID: 30988655; PMCID: PMC6442716.
7. Wu B, Xiao YY, Zhang X, Zhao L, Carrino JA. CT-guided percutaneous cryoablation of osteoid osteoma in children: an initial study. Skeletal Radiol. 2011;40(10):1303-10. Epub 2011/02/12. doi: 10.1007/s00256-011-1119-1. PubMed PMID: 21311882.
8. Arrigoni F, Napoli A, Bazzocchi A, Zugaro L, Scipione R, Bruno F, Palumbo P, Anzidei M, Mercatelli D, Gravina GL, Zoccali C, Ghanouni P, Barile A, Catalano C, Masciocchi C. Magnetic-resonance-guided focused ultrasound treatment of non-spinal osteoid osteoma in children: multicentre experience. Pediatr Radiol. 2019;49(9):1209-16. Epub 2019/05/28. doi: 10.1007/s00247-019-04426-0. PubMed PMID: 31129699.
9. Rosenthal DI, Alexander A, Rosenberg AE, Springfield D. Ablation of osteoid osteomas with a percutaneously placed electrode: a new procedure. Radiology. 1992;183(1):29-33. Epub 1992/04/01. doi: 10.1148/radiology.183.1.1549690. PubMed PMID: 1549690.
10. Zachariah C, Mayeux J, Alas G, Adesina S, Mistretta OC, Ward PJ, Chen A, English AW, Washington AV. Physiological and functional responses of water-cooled versus traditional radiofrequency ablation of peripheral nerves in rats. Reg Anesth Pain Med. 2020;45(10):792-8. Epub 2020/08/14. doi: 10.1136/rapm-2020-101361. PubMed PMID: 32784232; PMCID: PMC7513268.
11. Rosenthal DI, Hornicek FJ, Torriani M, Gebhardt MC, Mankin HJ. Osteoid osteoma: percutaneous treatment with radiofrequency energy. Radiology. 2003;229(1):171-5. Epub 2003/08/29. doi: 10.1148/radiol.2291021053. PubMed PMID: 12944597.
12. Albisinni U, Chiatante M, Rinaldi R. Efficacy of percutaneous radiofrequency ablation of osteoid osteoma in children. Pediatr Radiol. 2008;38(12):1356. Epub 2008/09/18. doi: 10.1007/s00247-008-0986-7. PubMed PMID: 18797860.
13. Donkol RH, Al-Nammi A, Moghazi K. Efficacy of percutaneous radiofrequency ablation of osteoid osteoma in children. Pediatr Radiol. 2008;38(2):180-5. Epub 2007/11/28. doi: 10.1007/s00247-007-0690-z. PubMed PMID: 18040677.
14. Hage AN, Chick JFB, Gemmete JJ, Grove JJ, Srinivasa RN. Percutaneous Radiofrequency Ablation for the Treatment of Osteoid Osteoma in Children and Adults: A Comparative Analysis in 92 Patients. Cardiovasc Intervent Radiol. 2018;41(9):1384-90. Epub 2018/04/14. doi: 10.1007/s00270-018-1947-7. PubMed PMID: 29651579.
15. Rajasekaran S, Karthik K, Chandra VR, Rajkumar N, Dheenadhayalan J. Role of intraoperative 3D C-arm-based navigation in percutaneous excision of osteoid osteoma of long bones in children. J Pediatr Orthop B. 2010;19(2):195-200. Epub 2009/12/03. doi: 10.1097/BPB.0b013e328333997a. PubMed PMID: 19952798.
16. Gaeta M, Minutoli F, Pandolfo I, Vinci S, D'Andrea L, Blandino A. Magnetic resonance imaging findings of osteoid osteoma of the proximal femur. Eur Radiol. 2004;14(9):1582-9. Epub 2004/03/12. doi: 10.1007/s00330-004-2293-5. PubMed PMID: 15014975.
17. Freiberger RH, Loitman BS, Helpern M, Thompson TC. Osteoid osteoma; a report on 80 cases. Am J Roentgenol Radium Ther Nucl Med. 1959;82(2):194-205. Epub 1959/08/01. PubMed PMID: 13670322.
18. Cohen MD, Harrington TM, Ginsburg WW. Osteoid osteoma: 95 cases and a review of the literature. Semin Arthritis Rheum. 1983;12(3):265-81. Epub 1983/02/01. doi: 10.1016/0049-0172(83)90010-0. PubMed PMID: 6603021.
19. Franceschi F, Marinozzi A, Papalia R, Longo UG, Gualdi G, Denaro E. Intra- and juxta-articular osteoid osteoma: a diagnostic challenge : misdiagnosis and successful treatment: a report of four cases. Arch Orthop Trauma Surg. 2006;126(10):660-7. Epub 2006/08/24. doi: 10.1007/s00402-006-0203-9. PubMed PMID: 16927097.
20. Corbett JM, Wilde AH, McCormack LJ, Evarts CM. Intra-articular osteoid osteoma; a diagnostic problem. Clin Orthop Relat Res. 1974(98):225-30. Epub 1974/01/01. doi: 10.1097/00003086-197401000-00026. PubMed PMID: 4817234.

21. Allen SD, Saifuddin A. Imaging of intra-articular osteoid osteoma. Clin Radiol. 2003;58(11):845-52. Epub 2003/10/29. doi: 10.1016/s0009-9260(03)00213-7. PubMed PMID: 14581007.
22. Sherman MS. Osteoid osteoma; review of the literature and report of 30 cases. J Bone Joint Surg Am. 1947;29(4):918-30. Epub 1947/10/01. PubMed PMID: 20270357.
23. Norman A, Abdelwahab IF, Buyon J, Matzkin E. Osteoid osteoma of the hip stimulating an early onset of osteoarthritis. Radiology. 1986;158(2):417-20. Epub 1986/02/01. doi: 10.1148/radiology.158.2.3941866. PubMed PMID: 3941866.
24. May CJ, Bixby SD, Anderson ME, Kim YJ, Yen YM, Millis MB, Heyworth BE. Osteoid Osteoma About the Hip in Children and Adolescents. J Bone Joint Surg Am. 2019;101(6):486-93. Epub 2019/03/21. doi: 10.2106/JBJS.18.00888. PubMed PMID: 30893229.
25. Goldberg VM, Jacobs B. Osteoid osteoma of the hip in children. Clin Orthop Relat Res. 1975(106):41-7. Epub 1975/01/01. doi: 10.1097/00003086-197501000-00006. PubMed PMID: 1126090.
26. Sherman MS. Osteoid osteoma associated with changes in adjacent joint; report of two cases. J Bone Joint Surg Am. 1947;29(2):483-90. Epub 1947/04/01. PubMed PMID: 20240209.
27. Foeldvari I, Schmitz MC. Rapid development of severe osteoarthritis associated with osteoid osteoma in a young girl. Clin Rheumatol. 1998;17(6):534-7. Epub 1999/01/16. doi: 10.1007/bf01451295. PubMed PMID: 9890687.

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# PROGNOSTIC BIOMARKERS AND FACTORS IN POSTERIOR URETHRAL VALVES

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**Abstract**

Posterior urethral valves (PUV) are among the most common causes of obstructive nephropathies in the pediatric population. Despite early urinary drainage and endoscopic valve ablation, the evolution of this pathology is frequently oriented towards chronic kidney disease (CKD). Progressive renal failure is initiated by the intrauterine urethral obstruction, which in turn leads to the aggravation of the bladder dysfunction, even after the relief of the obstruction. These children need proper monitorization and management, based on their risk factors, in order to prevent or to delay the evolution to end stage renal disease. Early prognostic markers for renal failure are searched. So far, nadir creatinine and creatinine velocity proved useful in risk stratification. Other factors, biologic, imagistic and urodynamic, were found, but they still need to prove their degree of correlation on long term with renal function.

**Keywords:** posterior urethral valves, chronic kidney disease, bladder dysfunction, children

## Introduction

Posterior urethral valves (PUV) are the most common cause of bladder outlet obstruction in male patients, with an incidence in the general population ranging between 1:7000-1:8000 [1]. The obstruction is represented by a fine membrane that arises from the verumontanum and extends towards the posterior urethra, producing an obstacle in the outflow of urine, with consequences both on the bladder function and on the upper urinary tract [2].

The severity of the disease varies from patients with mild symptomatology and late diagnosis to cases with severe neonatal respiratory distress syndrome with potential impact on survival, in the context of oligohydramnios.

Postpartum urinary drainage by placing a urethral catheter or by vesicostomy, and the endoscopic ablation of the valves have reduced the neonatal death to less than 3 per cent. Although the treatment addresses the immediate uropathy, the progression to kidney failure continues. By the age of 10, 34 per cent of the patients have chronic kidney disease (CKD), 10 per cent of them having end stage kidney disease (ESKD). By the time they are 20 years old, 51 per cent of the patients with PUV will develop CKD, 38 per cent of them having ESKD [2]. Considering this high risk of renal failure, the clinicians are interested in finding new biological, imagistic and urodynamic markers, that can be helpful in the early prediction of the patient's evolution. Some of these markers and risk factors are synthetized in Table 1.

**Table 1. Prognostic factors for CKD evolution in patients with PUV**

| | |
|---|---|
| **Antenatal factors** | -progressive oligohydramnios/ anhydramnios<br>-poor renal cortex echogenity<br>-poor bladder refilling |
| **Biologic markers** | -serum creatinine<br>-nadir creatinine<br>-creatinine velocity<br>-urinary cytokines TGF-1, TNF-α, IL-6<br>-microalbuminuria<br>-plasmatic renin |
| **Imagistic measurements** | -SWRD index (cystography)<br>-estimated renal parenchyma<br>-the cortico-medullar index<br>-the renal echogenity |
| **Urodynamic studies** | -the bladder contractility index |

Adapted from Wein, A. J., Kavoussi, L. R., & Campbell, M. F. (2012). *Campbell-Walsh urology (10th ed.).* Philadelphia: Elsevier Saunders, pp. 3252-3271.

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Antenatal diagnosis and prognostic factors

As for many other complex congenital conditions, the antenatal suspicion of posterior urethral valves is of paramount importance in planning the birth and placing the newborn in a tertiary center. Therefore, it is essential to identify the key elements of diagnosis and prognosis. On one side, the presence of bilateral hydronephrosis with or without the keyhole sign in a male fetus should always raise the suspicion of posterior urethral valves. One the other side, different indicators can be suggestive for this pathology, including an enlarged fetal bladder (>7mm) in the first trimester and poor bladder cycling [2,3,4].

Besides the diagnostic criteria, several elements in the prenatal evaluation have a prognostic role, allowing the clinician to make predictions regarding the short- and long-term outcome. Progressive oligohydramnios and anhydramnios are associated with a high risk of severe lung dysplasia and death. Furthermore, a poor echogenity of the renal cortex and a poor bladder filling during the ultrasonography are signs of poor prognosis and are associated with renal failure in newborns [5]. According to Sarhan et al 2017, the birth weight does not influence the prognosis regarding kidney function in patients with PUV. However, newborns with low birth weight have a higher risk for vesicostomy, longer hospitalization, vesicoureteral reflux and higher nadir creatinine [6, 7].

Regarding the antenatal evaluation of patients with PUV, an important mention has to be made with regard to the *in utero* therapeutic options. Fetoscopy, decompression of the bladder by vesicoamniotic shunting or fetal cystoscopy with valve ablation are among the considered options. Nevertheless, the randomized controlled PLUTO trial and Nassr meta-analysis in 2017 showed no long-term benefits on renal function [8, 9].

Sequelae of PUV

The bladder outlet obstruction during the fetal development creates a series of consequences, that affect the patients with PUV, despite proper and early treatment of the valves. The bladder dysfunction is progressive, from a hypertrophied bladder with good voiding in the compensated phase, to a decompensated bladder, without adequate emptying [2, 3].

Two major events take place during the compensated phase. First of all, the bladder hypertrophy corelates with high voiding pressures, which further lead to the remodeling of the bladder wall. Secondly, the co-existing renal dysplasia causes polyuria, which in turn increases the urinary volume that needs to be stored by the bladder. The dilatation of the bladder represents the beginning of the decompensated phase and places the upper tract at risk for higher dilatation [2].

Ureteral dilatation is correlated with the vesicoureteral reflux, which is seen in 70 per cent of patients with PUV, but it can also be determined by the increased bladder pressure and by the polyuria from the renal dysplasia. The chronic ureteral dilatation leads to ureteral wall thickening, loss of peristalsis, urine stasis and increased pressure in the renal pelvis [3]. The increased pelvic pressure produces alterations in the morphology and function of the kidneys, leading to irreversible dysplastic changes and poorly concentrated urine.

Biologic markers

As part of the paraclinical evaluation for patients with PUV, serum creatinine level was initially considered an important prognosis marker. However, it has failed to prove its accuracy over time, and, during the last two decades, it has been replaced with nadir creatinine. This represents the lowest creatinine level during the first year after diagnosis and shows a strong correlation with long term risk of CKD and ESKD. Coleman et al. divided the patient into risk groups, based on the value of nadir creatinine. A low risk is represented by values of nadir creatinine lower than 35 µmol/L or 40mg/dL and the high-risk group includes the patients with nadir creatinine higher than 75 µmol/L(0.85mg/dl). Another parameter, introduced more recently, is creatinine velocity, defined as the change in the level of creatinine after the urinary drainage. An increase more than 3µmol/L/day is associated with a higher risk of progression of the disease towards CKD. Coleman also affirms that the association of the creatinine velocity >3mmol/L/day in patients from the high-risk group – based on nadir creatinine level – will lead to CKD in 100 per cent of the cases. In the same time, the patients from the low risk group, with nadir creatinine <35 µmol/L and creatinine velocity <3 µmol/L/day are at very low risk of CKD [10, 11].

The urinary cytokines TGF-1, TNF-α, IL-6 and microalbuminuria are mentioned in a lot of studies, but their predictive value for long term renal function still needs to be proven. Mandelia describes a raise in the postoperative values of these biomarkers, compared to the preoperative values, in patients with risk of long-term renal damage, a decrease of the postoperative values being associated with a good outcome [12]. Three other studies analyse the prognostic value of the urinary inflammatory cytokines in obstructive nephropathies, showing that increased values may be correlated to progressive renal insufficiency [13, 14, 15]. In one study, Vieira suggested that the inflammatory molecules have a high level in fetuses with PUV at 22 weeks of gestation, showing an important role of inflammation right after the valve formation [15]. The plasmatic renin activity is proposed as an early prognostic factor by Bajpai, but further investigations are needed in order to clarify the mechanisms involved [16].

Imagistic factors

In 2016, Odeh presented the results of a study involving ultrasonographic kidney measurements at patient's admission and the correlation with the clinical outcome. The conclusion of his study is that estimated renal parenchyma, the cortico-medullar index and the renal echogenity may represent prediction factors for the long-term outcome [17].

Another imagistic index was suggested by Niyogi, who proposed the acronym SWRD (shape, wall, reflux, diverticula), representing the cystographic measurements of

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the patients with PUV. According to him, a high SWRD index describes a bladder dysfunction with low compliance and high pressure. The study also presents the correlation between a high index and the need for an invasive method of urinary drainage – vesicostomy, urinary derivation [18].

Urodynamic studies

Urodynamics is an essential part of the evaluation of children with PUV, allowing an estimation of the bladder contractility. The progression of bladder dysfunction represents an independent factor that worsens the prognostic. Several theories try to explain the mechanism underlying bladder hypocontractility and myogenic failure, including the hyperactivity of the detrusor muscle, the bladder neck hypertrophy, the co-existent vesicoureteral reflux and the anticholinergic medication. The morphologic changes are represented by the increasing extracellular matrix in the bladder wall, as well as changing the ratio between collagen type III and I [19, 20].

In a recent study, Ansari analyzed urodynamic parameters and their correlation with chronic kidney disease, showing a strong association between the bladder contractility index, calculated with the formula BCI= PdetQmax+5Qmax, and the long-term progression towards chronic kidney disease stage III [20].

Urological management of bladder dysfunction

Knowing the type of bladder dysfunction in patients with PUV plays a vital role in order to establish a proper management and to reduce the progression to end stage kidney disease, but also to maintain a bladder function that is suitable for a renal transplantation.

The pharmacological treatment plays an important role in the treatment of bladder dysfunction. Anticholinergic medication (oxybutynin, solifenacin) are useful for low- capacity bladder, with high pressure, and for hypercontractile bladder. The high-pressure bladder can also be managed medically, with tricyclic antidepressants (imipramine). Alpha blockers (terazosin, tamsulosin) are used for bladder neck hypertrophy with outlet obstruction or bladder neck obstruction and myogenic failure. Incomplete bladder emptying with clinical sequelae despite medication can be managed by clean intermittent catheterization.

Regarding renal transplantation, poor graft survival was initially reported in patients with PUV, probably because of a persistent bladder dysfunction. Before the renal transplant, the bladder should store and empty at low pressures [3]. An augmentation cystoplasty is recommended before transplant, in the case of a poorly managed bladder dysfunction. In their recent study, Saad et al. idetified no difference in long term graft outcome in patients with or without lower urinary tract disorders, in the presence of a good bladder emptying [21].

**Conclusion**

Posterior urethral valves represent a complex malformation, that involves the whole urinary tract. Unfortunately, the treatment of the urethral obstruction does not bring definitive cure for the patients. Except the nadir creatinine and creatinine velocity, the biologic markers still need to prove their predictive value for CKD. Imagistic measurements, such as ultrasonographic kidney measurements, cystographic SWRD index, as well as the bladder contractility index determined by urodynamic studies, constitute a key element of diagnostic. Altogether, these factors play an essential role in creating an estimation of risk for children with PUV. This stratification, correlated with a proper management of bladder dysfunction, allow the maintenance of good bladder function and the prevention or delay of the evolution towards renal failure.

**Conflict of interest:** NO CONFLICT

**References**

1. Bilgutay, A.N., Roth, D.R., Gonzales, E.T.Jr., Janzen, N., Zhang, W., Koh, C.J., et al. Posterior urethral valves: Risk factors for progression to renal failure. Journal of Pediatric Urology. 2016;12(3):179.e1-7.
2. Wein, A.J., Kavoussi, L. R., & Campbell, M. F. (2012). Campbell-Walsh urology (10th ed.). Philadelphia: Elsevier Saunders, pp. 565-567.
3. Deshpande, A.V. Current strategies to predict and manage sequelae of posterior urethral valves in children. Pediatric Nephrology. 2018 Oct;33(10):1651-1661.
4. Chevalier, R.L. Prognostic factors and biomarkers of congenital obstructive nephropathy. Pediatric Nephrology. 2016;31(9):1411-20.
5. Harper, L., Waubant, A., Vignes, J., Amat, S., Dobremez, E., et al. Can quantity of amniotic fluid reliably predict postnatal renal function in boys with posterior urethral valves: a decision curve analysis. Prenatal Diagnosis. 2017;37(9):931-4.
6. Sarhan, O.M. Posterior urethral valves: Impact of low birth weight and preterm delivery on the final renal outcome. Arab Journal of Urology. 2017;15(2):159-65.
7. DeFoor, W.R.Jr. Challenges in Predicting Renal Outcomes in Boys with Posterior Urethral Valves. The Journal of Urology. 2016;196(3):639-40.
8. Nassr, A.A,, Shazly, S.A.M., Abdelmagied, A.M., Araujo, E.Jr., Tonni, G., et al. Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: an updated systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017 Jun;49(6):696-703

https://doi.org/10.37224/JP.2020.9192.05

9. Morris, R.K., Malin, G.L., Quinlan-Jones, E., Middleton, L.J., Hemming, K., et al.. Percutaneous vesicoamniotic shunting versus conservative management for fetal lower urinary tract obstruction (PLUTO): a randomised trial. Lancet. 2013 Nov 2;382(9903):1496-506.
10. Coleman, R., King, T., Nicoara, C.D., Bader, M., McCarthy, L., et al. Nadir creatinine in posterior urethral valves: How high is low enough? Journal of Pediatric Urology. 2015;11(6):356.e1-5.
11. Coleman, R., King, T., Nicoara, C.D., Bader, M., McCarthy, L., et al. Combined creatinine velocity and nadir creatinine: A reliable predictor of renal outcome in neonatally diagnosed posterior urethral valves. Journal of Pediatric Urology. 2015;11(4):214.e1-3.
12. Mandelia, A., Bajpai, M., Agarwala, S., Gupta, A.K., Kumar, R., et al. The role of urinary TGF-$\beta_1$, TNF-$\alpha$, IL-6 and microalbuminuria for monitoring therapy in posterior urethral valves. Pediatric Nephrology. 2013 Oct;28(10):1991-2001.
13. MacRae Dell, K., Hoffman, B.B., Leonard, M.B., Ziyadeh, F.N., Schulman, S.L. Increased urinary transforming growth factor-beta(1) excretion in children with posterior urethral valves. Urology. 2000 Aug 1;56(2):311-4.
14. Trnka, P., Ivanova, L., Hiatt, M.J., Matsel,l D.G. Urinary biomarkers in obstructive nephropathy. Clin J Am Soc Nephrol. 2012 Oct;7(10):1567-75.
15. Vieira, É.L.M., Pessoa Rocha, N., Macedo Bastos, F., da Silveira, K.D., Pereira, A.K., et al. Posterior urethral valve in fetuses: evidence for the role of inflammatory molecules. Pediatr Nephrol. 2017 Aug;32(8):1391-1400.
16. Bhadoo, D., Bajpai, M., Panda, S.S.. Posterior urethral valve: Prognostic factors and renal outcome. J Indian Assoc Pediatr Surg. 2014;19(3):133-7.
17. Odeh, R., Noone, D., Bowlin, P.R., Braga, L.H., Lorenzo, A.J. Predicting Risk of Chronic Kidney Disease in Infants and Young Children at Diagnosis of Posterior Urethral Valves: Initial Ultrasound Kidney Characteristics and Validation of Parenchymal Area as Forecasters of Renal Reserve. The Journal of Urology. 2016;196(3):862-8.
18. Niyogi, A., Lumpkins, K., Robb, A., McCarthy, L. Cystometrogram appearance in PUV is reliably quantified by the shape,wall, reflux and diverticuli (SWRD) score, and presages the need for intervention. Journal of Pediatric Urology. 2017;13(3):265.e1-.e6.
19. Concodora, C.W., Reddy, P.P., Vander Brink, B.A. The Role of Video Urodynamics in the Management of the Valve Bladder. Current Urology Reports. 2017;18(3):24.
20. Ansari, M.S., Nunia, S.K., Bansal, A., Singh, P., Sekhon, V., et al. Bladder contractility index in posterior urethral valve: A new marker for early prediction of progression to renal failure. J Pediatr Urol. 2018 Apr;14(2):162.e1-162.e5.
21. Saad, I.R., Habib, E., El Sheemy, M.S., Abdel-Hakim, M., Sheba, M., et al. Outcomes of living donor renal transplantation in children with lower urinary tract dysfunction: a comparative retrospective study. BJU Int. 2016 Aug;118(2):320-6.



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# REPETITIVE OVARIAN TORSION AS WARNING SIGN OF SEROUS AND MUCINOUS CYSTADENOMA IN CHILDREN - REPORT OF TWO CASES

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**Abstract**

Cystadenomas are surface epithelial-stromal tumors. Although they are the most common type of ovarian tumor, seen mostly from late adolescent age, yet, they remain difficult to accurately diagnose clinically due to their diverse presentations similar to other diseases like functional cyst and appendicitis. We report the cases of two pediatric patients. The first one aged seventeen years and six months old with serous cystadenoma and the second patient aged seventeen years and three months old with mucinous cystadenoma, presenting with abdominal pain in the level of the right iliac fossa and abdominal pain in the inferior part of the abdomen respectively aiming to reveal some warning signs and particularities in diagnosis and management of female pediatric patients with ovarian cystadenomas. Conclusion: Recurrent ovarian torsion or recurrent cyst formation is a warning sign of mucinous cystadenoma and serous cystadenoma tumor requiring further investigations and treatment.

**Keywords:** serous cystadenoma, mucinous cystadenoma, ovarian torsion, recurrent cyst, pediatric patients

## Introduction

Ovarian tumors are neoplasm found in the ovary and rarely seen in children, with 2.6 per 100,000 children yearly [1]. Cystadenoma ovarian tumors are usually benign in children but malignant in 10-20% of pediatric patients [2,3]. These patients usually present with pelvic and abdominal pain in diverse forms, vomiting, bloating, loss of appetite, vaginal bleeding, increased abdominal volume, constipation, or sometimes fever [4], which are similar to patients with appendicitis or a functional cyst; hence it can be quite challenging to diagnose accurately, especially if not large in size or a benign tumor but with radiological, laparoscopic and histopathology investigations, a specific diagnosis can be made to a large extent. We present the cases of two girls with mucinous cystadenoma and serous cystadenoma treated by surgical tumoral excision.

## Case 1

A 17 years and six months old girl presented at our hospital with complaints of abdominal pain in the right iliac fossa and nausea. She had no previous significant medical history and she had a regular menstrual cycle. On physical examination, she weighed 52kg and had a height of 160cm, afebrile, abdominal pain in the right iliac fossa on superficial and deep palpation, without any palpable mass. The number of leukocytes was 8,81 x10^3/ul and C-reactive protein 2.71mg/l, urinalysis, and tumor markers were normal. Abdominal ultrasound showed a cyst of 5.27/5.1cm on the right ovary, but after admission, the pain disappeared, and we placed the patient on paracetamol. Three days later, she was discharged with the diagnosis of a right ovarian cyst. The patient returned after five months complaining of pain at the inferior abdominal level, nonresponsive to antalgic medication, number of leukocytes was 6,37x10^3/ul, C-reactive protein was 0,15mg/l, and other laboratory results were normal. Abdominal ultrasound showed the presence of a gigantic abdominal pelvic tumor with dimensions of 15.73/8.04cm, uniloculated, originating from the left ovary (Figure 1). The thoracic x-ray was normal. We performed exploratory laparoscopy and cystectomy and placed the patient on antalgic and anti-inflammatory drugs. The histopathological result from the biopsy showed benign serous cystadenoma, irregular cystic fragment, containing clear liquid with whitish - caffein color and elastic consistency, unilocular. The cystic wall lined with simple cylindric ciliated epithelium similar to the fallopian tube epithelium (Figure 2). With a favourable evolution, the patient was discharged after three days.

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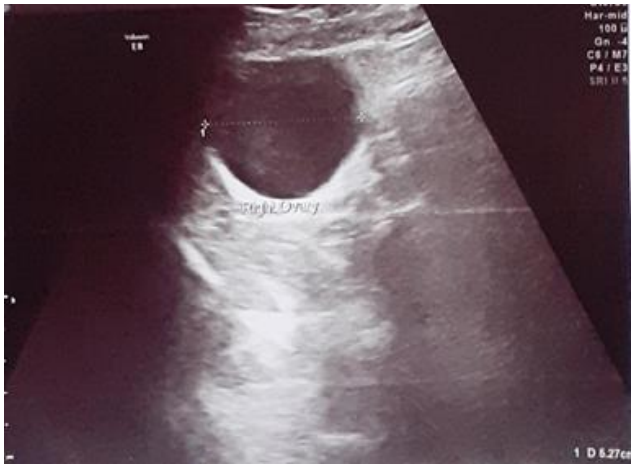

Figure 1. Ultrasound of the right ovary.

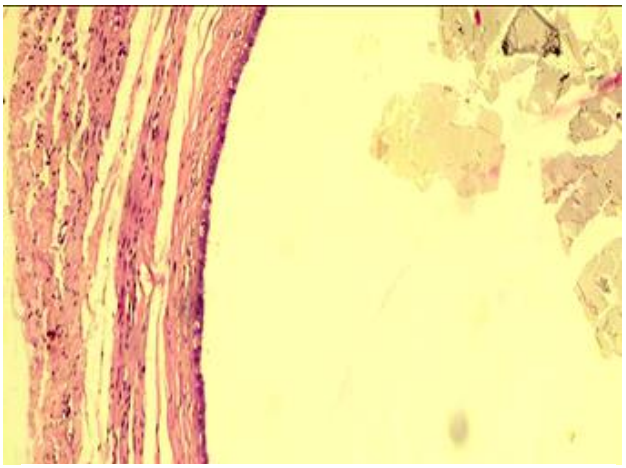

Fig 2. Histopatological aspect of the cystadenoma. Hematoxylin-Eosin stains 20X.

**Case 2**

A 16 year-old girl presents with colic abdominal pain at the inferior abdominal level that debuted four days ago. Se had loss of appetite and recurrent vomiting episodes. She was unresponsive to antalgic and antiemetic treatment. The patient had a medical history of repetitive biliary colic and irregular menstruation. On physical examination, she weighs 72kg and has height of 165cm with a BMI of 26,47; obese and with dental caries. The number of leucocytes was 8,0 x 10^3/ul and C-reactive protein was 0,45 mg/l, with normal urinalysis. At superficial and deep palpation the patient accused abdominal pain in the left flank and at the peri-umbilical level. Abdominal ultrasound showed transonic ovary of 5/3.5cm, no vascularization present, hence we diagnose the patient of torsion of the left ovary in remission. After two days of treatment, with a favourable condition, she was discharged. Seven months later the patient returned to our hospital, weighing 68kg, complaining of abdominal pain in the right iliac fossa. Laboratory analysis showed that the number of leucocytes was 6.67 x 10^3/ul and C-reactive protein 0,19mg/l.

Urinalysis indicated urinary tract infection. The abdominal ultrasound revealed a second torsion of the left ovary, 14/12,5cm, and cyst of the fallopian tube 9/7,5cm. Exploratory laparoscopy showed 360°C torsions of left ovary (Figure 3). Detorsion of the ovary and excision of the ovarian cyst was performed and the resected mass was sent for histopathological examination. The result revealed mucinous cystadenoma of the ovary. The cystic wall is lined by an epithelium mucinous columnar, unilocular nuclei at the basal pole, fibrous stroma, ovarian parenchyma attached to a primordial, cystic follicle, and papillary projections (Figure 4). The patient was placed on antalgic and anti-inflammatory treatment. She spent a day in the intensive care unit. Two days later, the patient had a favourable evolution and was discharged.

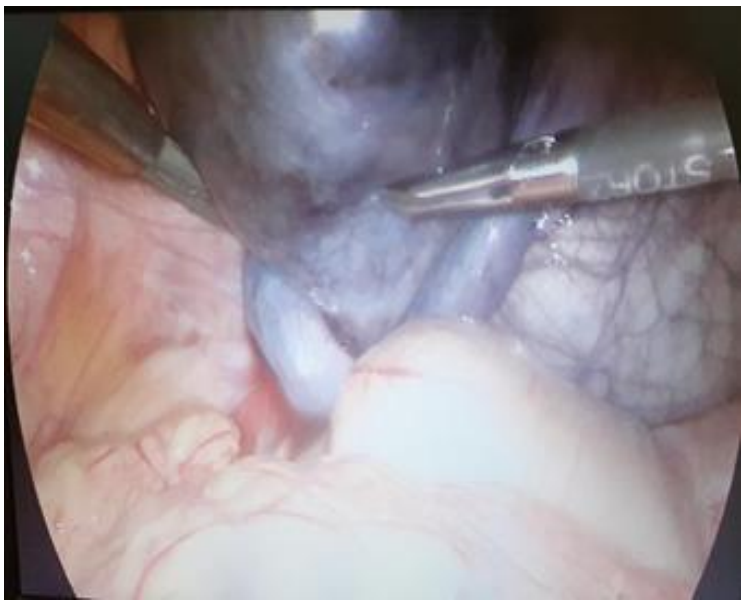

Figure 3. Intra operative image of the torsioned ovary.

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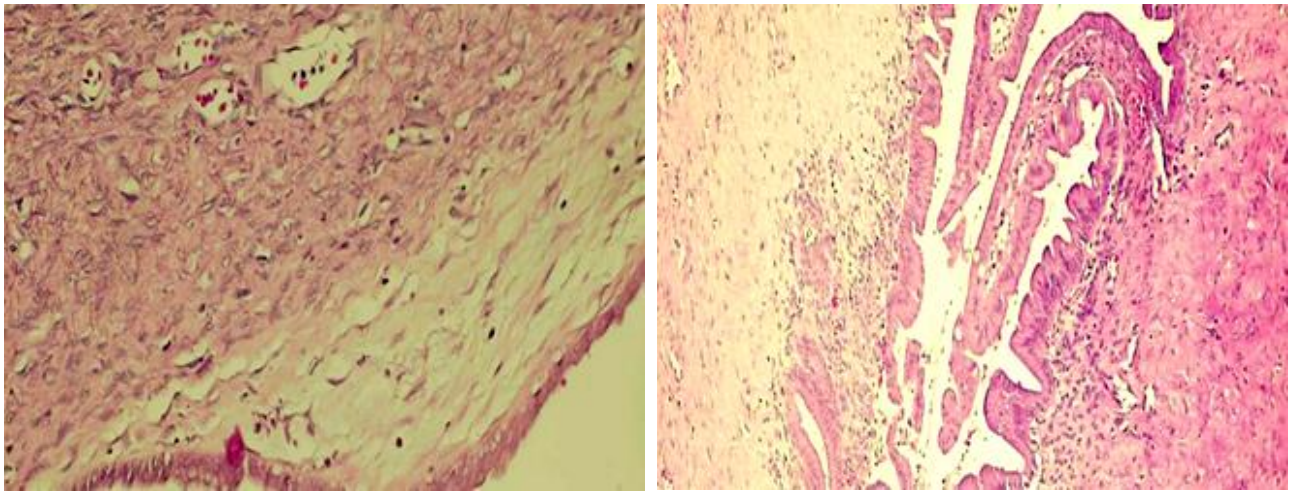

Figure 4. Mucinous cystadenoma of the ovary, endocervical subtype. Hematoxylin-Eosin stain 20X.

**Discussion**

Cystadenomas are epithelial tumors representing about 60% of the ovarian tumors. They can be serous, mucinous, clear cell or endometrioid. Also, they can be benign, borderline, or malignant tumors and can also be cystic, solid, or mixed form [2]. Both patients had abdominal pain in the right iliac fossa, left flank and at peri-umbilical level, loss of appetite, and vomiting (which can be a sign of appendicitis), but neither of them had fever nor an increase in number of leukocytes [4]. Unlike functional cyst, which is unharmful and can self-resolve, cystadenoma has the potential to transform into malignancy as reported in the literature, especially if it is borderline [5-7]. Hence differentiating them is crucial and a method to achieve this accurately and easily is needed. Ovarian torsion is usually found in females of reproductive age, especially in the presence of a mass >5cm, which can be a cyst or benign tumor and in rare cases a malignant tumor [8]. The incidence rate of ovarian torsion is estimated to be 4.9: 100000 persons and requires immediate surgical intervention to detorsion the ovary. It rarely re-occurs as a tumor diagnosis, and one of such few cases reported was in a ten years old premenarchal girl [9]. Cyst re-occurrence has been attributed to incomplete excision or infection [10-11], but we see that it can also suggest a tumor's presence. Overweight was another observation noticed in both patients, which is recognized as a contributing risk factor of tumors. Histopathological examination remains the efficient diagnostic method used. Surgical treatment is the standard management for mucinous a serous cystadenoma tumor ranging from cystectomy to gonadectomy. Depending on if it is a malignant cystadenoma, or large tumor, or if the ovary is invaded, then it is difficult to preserve the gonads, but ovary-sparing surgery is the choicest option when possible.

**Conclusion**

Irregular menstruation, loss of appetite, a normal laboratory result in an afebrile patient can be used to rule out appendicitis. However, a patient presenting with recurrent ovarian torsion or recurrent cyst formation is a warning sign of mucinous and serous cystadenoma requiring further investigations and the appropriate treatment.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**References**


1. Péroux E, Franchi-Abella S, Sainte-Croix D, et al. Ovarian tumors in children and adolescents: a series of 41 cases. Diagnostic and Interventional Imaging. 2015 Mar 1;96(3):273-82.
2. Limaiem F, Mlika M. Treasure Island, FL: StatPearls Publishing; 2020. Ovarian Cystadenoma
3. Elizabeth Kehr, Thing RindaSoong, Michelle S. Hirsch. Chapter 28 - Metastatic Tumors Involving the Ovary. In 2018 Christopher P. Crum, Marisa R. Nucci, Brooke E. Howitt, Scott R. Granter, Mana M. Parast, Theonia K. Boyd (Eds). Third Edition. Diagnostic Gynecologic and Obstetric Pathology. Elsevier, 2018, Pages 1050-1069. ISBN 9780323447324.
4. Bankhead CR, Kehoe ST, Austoker J. Symptoms associated with diagnosis of ovarian cancer: a systematic review. BJOG.2005;112:857-865.
5. Zheng J, Benedict WF, Xu HJ, et al. Genetic disparity between morphologically benign cysts contiguous to ovarian carcinomas and solitary cystadenomas. J Natl Cancer Inst. 1995;87:1146-1153.
6. Fischerova D, Zikan M, Dundr P, Cibula D. Diagnosis, treatment, and follow-up of borderline ovarian tumors. The oncologist. 2012 Dec;17(12):1515.
7. Puls LE, Powell DE, DePriest PD, Gallion HH, Hunter JE, Kryscio RJ, van Nagell Jr JR. Transition from benign to malignant epithelium in mucinous and serous

ovarian cystadenocarcinoma. Gynecologic oncology. 1992 Oct 1;47(1):53-7.
8. Huang C, Hong MK, Ding DC. A review of ovary torsion. Tzu-chi Medical Journal. 2017 Jul;29(3):143.
9. Yee Lin Lee, Xinyi Chin, Aravind Venkatesh Sreedharan et al (2019). Recurrent Ovarian Torsion in a Premenarchal Girl. Int. J. Surg. Case Rep. 2019 1-3. 10.31487/j.
10. Li J, Qian M, Huang X, Zhao L, Yang X, Xiao J. Repeated recurrent epidermoid cyst with atypical hyperplasia: A case report and literature review. Medicine. 2017 Dec;96(49).
11. Rutherford SA, Leach PA, King AT. Early recurrence of an intracranial epidermoid cyst due to low-grade infection: case report. Skull Base. 2006 May;16(2):109.

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# MALIGNANT JUVENILE AND ADULT OVARIAN GRANULOSA CELL TUMORS IN PEDIATRIC PATIENTS - REPORT OF TWO CASES

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**Abstract**

Juvenile ovarian granulosa cell tumor is a sex chord stromal tumor derived from granulosa cells. It rarely occurs in children. Although it is usually classified as a benign tumor in children due to its good prognosis after surgical intervention, it is a malignant tumor and can be deadly, especially if recurrence occurs. We report two rare cases. The first one is a five-year-old girl with a malignant juvenile ovarian granulosa cell tumor stage 3 FIGO, presenting with abdominal pain in the inferior part of the abdomen and very early pubertal development. On physical examination, she was at stage two puberty. The second case is a 12 years old girl presenting with two periods monthly. An 8.3/5.4cm mass was found at the pelvic region on ultrasound examination. Exploratory laparoscopy with histological examination led to the diagnosis of stage 2A FIGO, combined juvenile and adult ovarian granulosa cell tumor. Conclusion: Precocious puberty accompanying abdominal pain or more than a period in a month is a pointer to juvenile and adult ovarian granulosa cell tumor requiring immediate investigations and patient management. Early diagnosis with the assistance of inhibin test and a FISH test of p53(17p13) aids better management of patients with Juvenile ovarian granulosa cell tumor, preventing tumor recurrence for a favorable outcome. Juvenile and adult ovarian granulosa cell tumors in pediatric female patients can present in different forms but gearing towards menstruation abnormalities.

**Keywords:** precocious puberty, juvenile ovarian granulosa cell tumor, adult granulosa cell tumor, irregular menstrual cycle, gene P53

## Introduction

The incidence of malignant tumors in prepubertal girls is 0.102 per 100.000 girls [1]. Granulosa cell tumor is a malignant sex cord-stromal ovarian tumor classified into adult-type or juvenile-type, which is usually at stage 1 in 90% of cases [2]. Pediatric patients account for 4-5% of ovarian granulosa cell tumors, which are responsible for 10% of very early puberty in prepubertal girls [2,3]. The factors that contribute to poor prognosis in these patients include: high tumor stage, high tumor marker level, large tumor, late diagnosis, presence of cancer-related genetic abnormalities, and recurrence that mainly occurs after puberty [4]. We present a rare case of a 12 years old girl with both juvenile and adult ovarian granulosa cell tumor staged 2A and a second case of a malignant juvenile ovarian granulosa cell tumor stage 3 in a five years old girl presenting with abdominal pain and very early pubertal development, although normal puberty starts in girls between 8-9 years old [5]. Both patients were diagnosed and managed with surgical intervention and chemotherapy.

## Case 1

A 5 years old girl presented at our hospital with complaints of abdominal pain for two months and loss of appetite. She had no significant medical or family history, except repeated urinary infection from infancy and dental caries. She was not on any medication. She was the first child to a 22 years old mother, while the father was 30 years old. She weighed 3300g at birth with APGAR score of 9, delivered at nine months, naturally and in cranial presentation. The patient was breastfed for one week before started on artificial milk and diversification, taking all vaccine required and vitamin D. On physical examination, she weighed 20kg and had a height of 117cm, afebrile, with precocious puberty signs: thelarche with eminent breast areola-Tanner 2 and some fine hair strands in the pubic region -Tanner 2. The abdomen was slightly distended in volume and painful at superficial palpation in the left iliac region, with a mass detected at deep palpation.

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She had normal female external genital organs and confirmed as a virgin. Her thyroid function tests were normal. ↓LH-0,1ui/l, ↑ estradiol-58pg/ml, ↑prolactin-22ng/ml, LDH-358u/l, ↑Inhibin B was 34pg/ml. The patient had a urinary tract infection. Ultrasound examination showed a mass in the abdominopelvic region with both cystic and solid components with mild ascites. Karyotype test by the GTG 450 bands showed 46XX karyotype. The cytogenetic analysis with FISH test techniques using metasystem genetic probes detected a deleted p53 (del17p13) gene.

Exploratory laparoscopy revealed a 13.2/7.1cm mass on the left ovary (Figure 1). We performed adnexectomy, excision of the tumor formation and biopsy. The histopathology result showed a juvenile ovarian granulosa cell tumor (Figure 2). The tumor invaded the fallopian tube and the retroperitoneal lymph node - stage 3 FIGO. The ovary was transformed into a tumor, grey smooth and discrete mass surface with multiple zones of ruptured capsules. Multiloculated, inhomogenous section with solid yellowish-white areas mixed and a cystic zone containing serocitrine liquid were also found. Medium-sized cytoplasm was full of eosinophils in the nucleus with moderately atypical mitotic activities in areas over two camps to large sizes with macrofollicular structures of various sizes and forms. Endothelium material of eosinophilia secretion, lined with cellular layers, stroma with fibrothecoma, and some necrotic areas were identified. The tumor section examined appears to compress the ovarian capsule but not exceeding it. Immunochemical examination revealed ER+ 50%, Ki 67+25% and PGR+ 55%. We placed her on chemotherapy: four cycles of PEI, three cycles of paclitaxel +carboplatin and two BEP cycles. At revaluation, after six months of treatment, she had a favorable outcome. Her abdomen was without pain or mass on superficial and deep palpation. Ultrasound showed no secondary intrabdominal parenchymatous lesion, no sign of recurrence of the tumor, the right ovary was normal and the level of Inhibin B was 8.1ng/l. The bleeding also stopped.

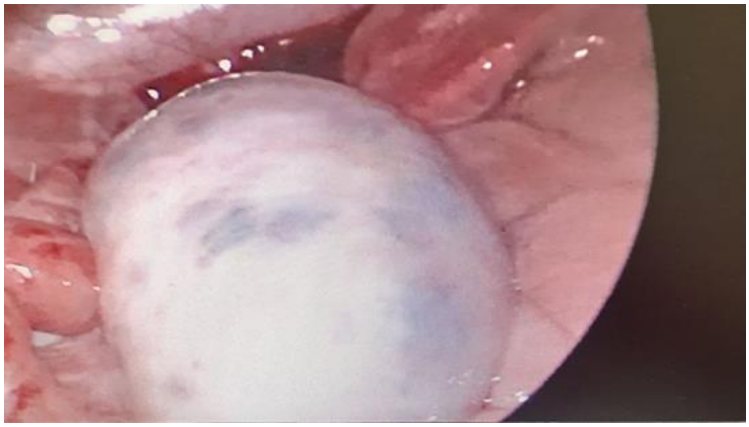

Figure 1. Intraoperative image of the ovary with Granulosa cell tumor.

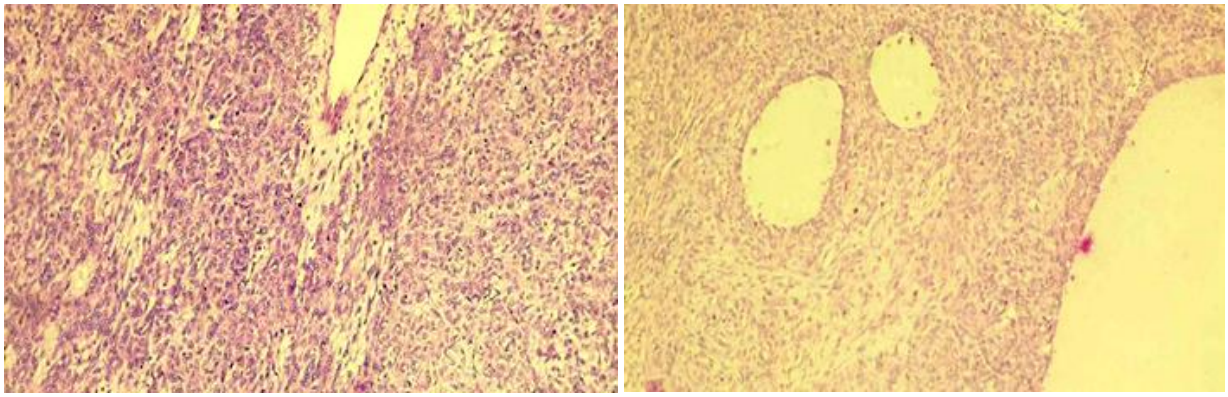

Figure 2. Histopathology of Granulosa cell tumor Hematoxylin-Eosin stains 20X.

**Case 2**

A 12 years old girl without any significant family or personal medical history, one year after menarche, presented at our hospital with complaints of irregular menstrual cycles, having two periods in a month. She was placed on vitex agnus-castus and progesterone, but symptoms persisted after five months. On physical examination, she weighed 45kg and had a height of 165cm. No abdominal pain or mass at superficial and deep palpation of the abdomen were found. She had normal

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female external genital organs, normal thyroid function test, ↑prolactine:30 ng/ml, ↑ estradiol:120pg/ml, ↑LDH:624u/l. The ultrasound examination revealed a tumoral formation, with cystic and solid components, 8,3/5.4cm in dimension at the right ovary (Figure 3). We performed exploratory laparoscopy and right salpingo-oophorectomy and mounted an abdominal drainage tube, which was removed three days after the operation. We placed her on anti-biotherapy, antalgic and anti-inflammatory therapy. The histopathological examination results revealed ovarian granulosa cell tumors with predominant juvenile and some adult components. They were also present in the fallopian tube and vascular invasion – stage 2A FIGO. Round hyperchromatic nucleus, rare aspects of coffee bean chromatin with eosinophilic cytoplasm and luteinized aspect were present. Solid nodes associated with the presence of some microfollicular focal like call-Exner bodies with unregulated lumen secreting eosinophilia and some papillary structures from the fibrous conjunctive arc and bistratified periphery cylindrical cell were present. There was an area of vascular invasion in the examined fragment, some section of the fallopian tube showed small groups of tumoral cells, 8/10HPF mitosis, and a fragment of lymphatic ganglion and nodes with stasis without tumoral infiltration. Immunochemical examination showed positive K16, inhibin, and calretinin tumor cells (Figure 4).

With favorable evolution, good general state, afebrile, the patient was placed on BEP chemotherapy and discharged. We re-evaluated her after 4 BEP cures, and the treatment was well tolerated with secondary emetic syndrome and slight normochromic normocytic anemia; 10g/dl, with the normal menstrual cycle. Ultrasound examination showed left ovary, uterus, liver, kidney, spleen and urinary bladder without modifications.

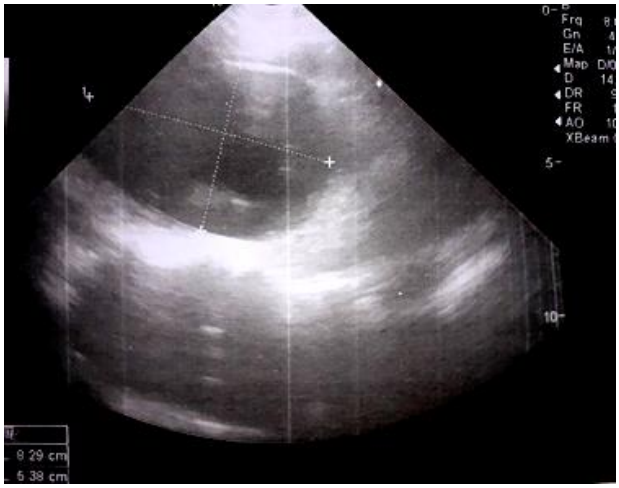

Figure 3. Ultrasound of the right ovary.

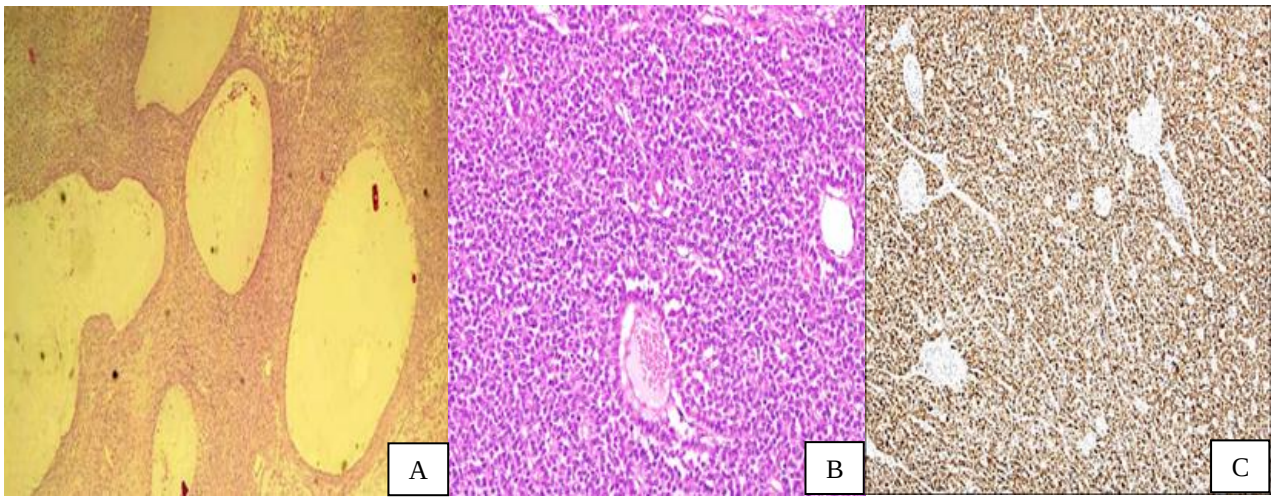


Figure 4. The histopathological result shows Granulosa cell tumor Hematoxylin-Eosin stain 20X A. Ovarian granulosa cell tumor with Juvenile components B. Ovarian granulosa cell tumor with adult components C. Immunohistochemical result showed positive calretinin tumor cell inhibin and KI67.

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**Discussion**

In patients with granulosa cell tumors, the tumor usually secrets estrogen hormone because the action of cytochrome P450 aromatase is not controlled [4], hence estrogen levels are elevated. The presented cases show that when this pathology appears in prepubertal girls, it can cause very early puberty, while when it appears in pubertal girls, it can cause multiple periods in a month. According to literature precocious puberty is when secondary sexual characteristics are present in a girl before eight years and can be a pointer to the presence of a tumor, such as juvenile ovarian granulosa cell tumor [5]. Mutations of AKT1 and FOXL2 genes have been identified in juvenile and adult granulosa ovarian cell tumors. In a study, Follicular Stimulating Hormones in an eight-year-old girl were responsible of causing juvenile ovarian granulosa cell tumor [6,7]. Call-Exner bodies, coffee-bean, groove nucleus, or microfollicular pattern are present in adult OGCT, but macrofollicular space and round nuclei are present in the Juvenile type. The juvenile type grows aggressively in comparison to the adult one [8,9]. A report shows that ovarian granulosa cell tumor can combine with other tumors like cystadenomas [10]. Mitosis greater than 4/10HPF or a high level of Inhibin B, a tumor marker useful for detecting OGCT, have both proved to be related to the recurrence of ovarian granulosa cell tumor, which results in poor prognosis [11,12]. The inhibin value of the first patient was higher than the average level of 26.5pg/ml in girls at pubertal stage 1 (average age 9), and estradiol level was higher than 40.5, which is the average level for girls at pubertal stage 2 with an average age of 11,4 years old [13]. The 2nd patient returned after four cycles of BEP with a better outcome and had a lower inhibin level, unlike the 1st patient who was on four cycles of PEI, three cycles of paclitaxel +carboplatin, and two cycles of BEP for more than six months, which can be attributed to the high tumor stage and deletion of Tp53 gene. Tp53 gene protein is a tumor suppressor which, if altered, leads to poor prognosis, especially if at stage II-IV or with large tumor sizes like 10-15cm, hence further adjuvant chemotherapy after surgical intervention is given to improve the patient's outcome and prevent recurrence [14, 15]. Malignancy aggression, the affected organs, or tumor size determines the treatment options like tumor excision, adnexectomy, gonadectomy, or hysterectomy, with the efforts to save the gonads and the goal to save the patient's life. Our patients show that juvenile ovarian granulosa cell tumors in females can be present in different forms but gearing towards abnormalities in menstruation according to the given age.

**Conclusion**

A patient presenting with precocious puberty accompanying abdominal pain is a pointer of juvenile ovarian granulosa cell tumor requiring further investigations and immediate intervention. Early diagnosis with the assistance of inhibin B and a FISH test of Tp53 helps in deciding the best choice of management of patients with juvenile ovarian granulosa cell tumor preventing recurrence for a better outcome. Juvenile ovarian granulosa cell tumor in pediatric female patients can present in different forms, but gearing towards abnormalities in menstruation.

**Conflicts of interest**

All authors have no conflicts of interest to declare.

**References**


1. Ali SW, Ali NN, Ashraf MS, et al. Juvenile granulosa cell tumor in a nine year old. Journal of Pediatric Surgery Case Reports. 2020 Apr 1;55:101397.
2. Rusterholz KR, MacDonald W. An unusual case of juvenile granulosa cell tumor of the ovary. Radiology case reports. 2009 Jan 1;4(1):178.
3. Nikumbh DB, Suryawanshi KH, Chitale AM, et al. Ovarian juvenile granulosa cell tumour in childhood: uncommon gynecological malignancy. Journal of clinical and diagnostic research: JCDR. 2014 Oct;8(10):FL01.
4. Kottarathil VD, Antony MA, Nair IR, Pavithran K. Recent advances in granulosa cell tumor ovary: a review. Indian journal of surgical oncology. 2013 Mar 1;4(1):37-47.
5. Lacourt P, Soto J, Rumié H, et al. Granulosa cell ovarian tumor: precocious puberty in infant less than 1 year of age. Case report. Rev Chil Pediatr. 2017 Dec 1;88(6):792-7.
6. Auguste A, Bessière L, Todeschini AL, Caburet S, Sarnacki S, Prat J, D'angelo E, De La Grange P, Ariste O, Lemoine F, Legois B. Molecular analyses of juvenile granulosa cell tumors bearing AKT1 mutations provide insights into tumor biology and therapeutic leads. Human molecular genetics. 2015 Dec 1;24(23):6687-98.
7. Calcaterra V, Nakib G, Pelizzo G, Rundo B, Rispoli GA, Boghen S, Bonetti F, Del Monte B, Gertosio C, Larizza D. Central precocious puberty and granulosa cell ovarian tumor in an 8-year old female. Pediatric reports. 2013 Jul 29;5(3).
8. Raghavan D, Ahluwalia MS, Blanke CD, Brown J, Kim ES, Reaman GH, Sekeres MA, editors. Textbook of uncommon cancer. John Wiley & Sons; 2017 May 8.
9. Calaminus G, Wessalowski R, Harms D, Göbel U. Juvenile granulosa cell tumors of the ovary in children and adolescents: results from 33 patients registered in a prospective cooperative study. Gynecol Oncol. 1997;65:447–52
10. McKenna M, Kenny B, Dorman G, McCluggage WG. Combined adult granulosa cell tumor and mucinous cystadenoma of the ovary: granulosa cell tumor with


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heterologous mucinous elements. International journal of gynecological pathology. 2005 Jul 1;24(3):224-7.
11. Fletcher CD. Diagnostic Histopathology of Tumors: 2-Volume Set with CD-ROMs. 4Edition.Elsevier Health Sciences; 2007 Mar 29.
12. Cooke I, O'Brien M, Charnock FM, Groome N, Ganesan TS. Inhibin as a marker for ovarian cancer. British journal of cancer. 1995 May;71(5):1046-50.
13. Sehested A, Juul A, Andersson AM, Petersen JH, Jensen TK, Müller J, Skakkebaek NE. Serum inhibin A and inhibin B in healthy prepubertal, pubertal, and adolescent girls and adult women: relation to age, stage of puberty, menstrual cycle, follicle-stimulating hormone, luteinizing hormone, and estradiol levels. The Journal of Clinical Endocrinology & Metabolism. 2000 Apr 1;85(4):1634-40.
14. Ala-Fossi SL, Mäenpää J, Aine R, Koivisto P, Koivisto AM, Punnonen R. Prognostic significance of p53 expression in ovarian granulosa cell tumors. Gynecologic oncology. 1997 Sep 1;66(3):475-9.
15. Khosla D, Dimri K, Pandey AK, Mahajan R, Trehan R. Ovarian granulosa cell tumor: clinical features, treatment, outcome, and prognostic factors. North American journal of medical sciences. 2014 Mar;6(3):133.

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# PROX1 IMMUNOHISTOCHEMICAL ANALYSIS OF PEDIATRIC VASCULAR ANOMALIES, A POSIBLE PROGNOSTIC AND THERAPEUTIC FACTOR OF HEMANGIOMAS?

**Rodica Heredea[1,2], Simona Cerbu[3], Emil Radu Iacob[4], Teodora Hoinoiu[5], Maria-Corina Stănciulescu[4]**

**Abstract**

Infantile and congenital hemangiomas still a challenge for both the pediatric surgeon and the pediatrician. The treatment of hemangiomas must be individualized according to: the type of lesion, location, size, depth, stage of growth and evolution of the lesion. To date, none of the available therapies is considered standard therapy. Currently, personalized therapy is not widely applied in Romania, not being included in the usual therapy protocols in any of the types of hemangioma. This is a starting point for the identification of new specific therapeutic targets that preserve normal endothelial cells and determine the regression of hemangioma, especially recurrent ones and those with an increased proliferation rate. Another controversial and unexplained aspect, consequently unexploited from a therapeutic point of view is represented by the expression and role of lymphatic markers in infantile and congenital hemangiomas.

**Keywords:** vascular anomalies, PROX-1, hemangiomas, arteriovenous malformations, PDGF B

## Introduction

It is well known that childhood hemangioma is the best known childhood tumor (5-10% incidence), consisting of endothelial cell proliferation and pericytes [1]. Despite the benign morphopathological character, infantile hemangiomas can have a "malignant" behavior, especially if they appear in organs located at the level of the cranial box or those in the thoracic box. The evolution of hemangiomas is unpredictable, most regress spontaneously, only about 10% are destructive, disfiguring and endanger the patient's life; the factors that determine the progression, regression and heterogeneity of the response to conventional therapy are not known in totality [2]. All this is due to the lack of a customized molecular profile for each type of hemangioma [3].

Infantile hemangioma can be routinely diagnosed by clinical means and rarely require therapy, but rare vascular tumors are frequently difficult to diagnose, for the diagnosis and treatment of these lesions is important multidisciplinary approach, thorough clinical examination, appropriate imaging and histopathological diagnosis [4]. Thus, the ISSVA classification was developed in 2014 [5] which was revised in 2018, it is based on the relationship between clinical, radiological, histological and molecular aspects of vascular anomalies [6].

Recently, the histopathological classification of hemangiomas has been revised, but recurrences following discontinuation of adjuvant or combination drug therapy could not be explained.

The expression of lymphatic markers is inconsistent and there is currently no clear classification and therapeutic orientation based on their existence. It seems that the expression of lymphatic markers is variable, depending on the topography of hemangiomas, but also on the evolutionary stage [7,8,9].

Platelet-derived growth factor (PDGF) is little studied in infantile vascular malformations. The same is true for Prox1 or CLIC1. PDGF is reported to be expressed in hemangiomas in only 22 of articles in PubMed while Prox1 is associated with hemangiomas with spindle type morphology [10]. Prox1 (prospero homeobox 1 protein) is an endothelial transcription factor considered a regulator of lymphatic endothelial differentiation, it is expressed in the nuclei of the developing and adult lymphatic endothelial cells [11,12,13,14,15]. Prox1 is also expressed in other epithelial tissues, more frequently liver and pancreas, especially during development [16,17,18].

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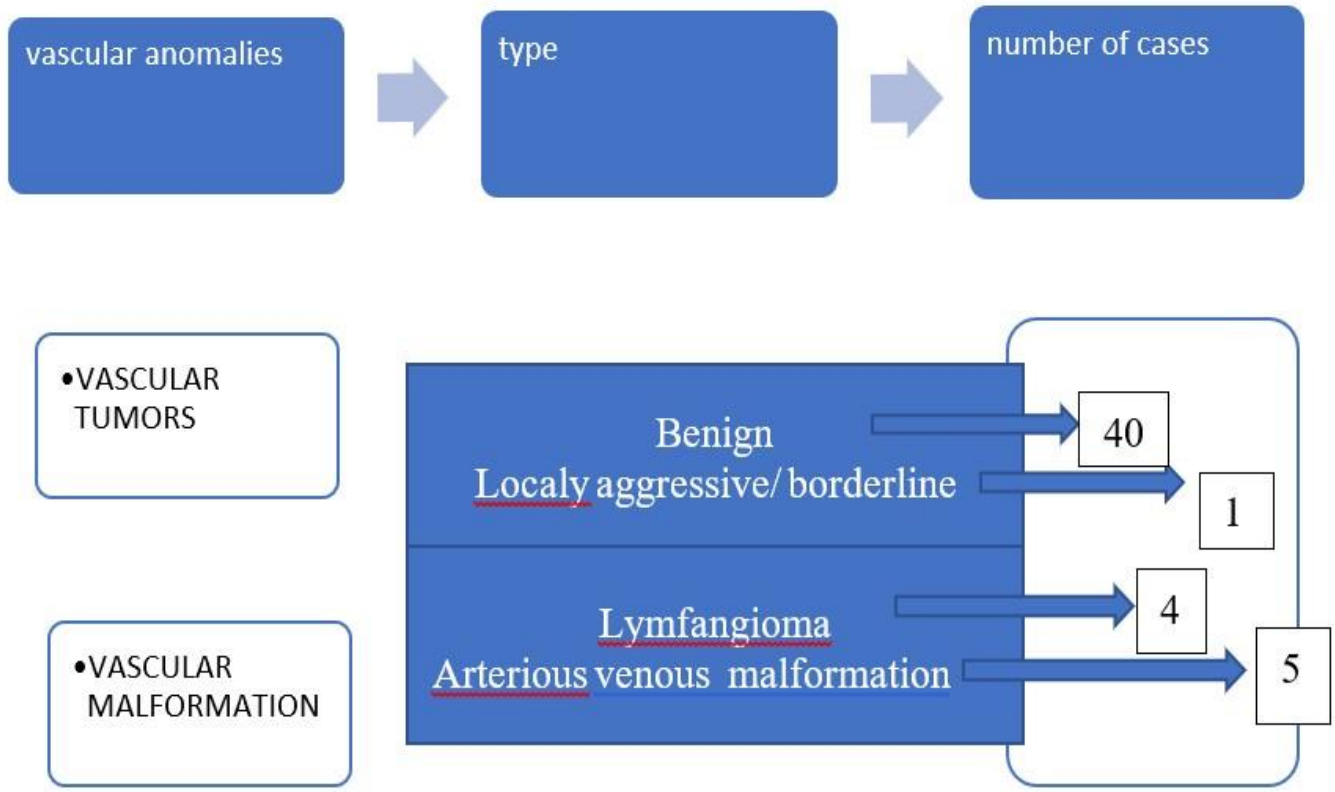
**Materials and methods**

*Patiens selection*

We performed a retrospective study of 50 specimens of vascular anomalies obtained by surgical excision in the Pediatric Surgery Department of Emergency Clinical Hospital for Children "Louis Țurcanu" Timișoara.

The studied cases are divided, according to the ISSVA 2018 classification, into vascular tumors- 41 cases and simple vascular malformations - 9 cases (table 1). Vascular tumors are infantile and congenital hemangiomas (33 cases), glomangiomas (2 cases), pyogenic granulomas (5 cases) and one of Kaposiform hemangioendothelioma.

Table 1. – Classificasion of vascular anomalies from the study.




*Methods*

The tissue fragments taken were within the size limits standard, having less than 1cm.

Sampling was followed by fixation of the fragments. This step was performed in 10% buffered formalin for 48 hours. This was followed by the removal of excess fixative by washing with running water for two hours. Following the removal of excess fixative, the parts were embedded in paraffin.

The sectioning was performed with the microtome. The 3µ sections thus obtained were spread on silane slides and then spread hot, in medium aqueous. The drying process followed, performed at a temperature of 37˚C. The slides were thus exposed for 20-30 minutes.

Deparaffining was performed over a period of 30 minutes in a benzene bath at 57 ˚C. Two baths of benzene followed, lasting 10 minutes each, at room temperature. For rehydration, the dewaxed sections were passed for 10 minutes in individual alcohol baths, concentrations of 100%, 96%, 80%, 70%. For another 10 minutes, each alcohol bath is followed by a bath with distilled water. At the end of all these stages, the sections are ready for coloring.

The cases selected for the immunohistochemical technique were stained by simple reactions using the following primary antibodies Prox1 and PDGF B.

**Results**

Of the 50 cases studied are divided, according to the ISSVA 2018 classification, into vascular tumors (41 cases) and simple vascular malformations (9 cases), from the figure below it can be seen that most cases are represented by vascular tumors (figure 1).

Most cases of infantile and congenital hemangioma were identified in females (25 cases), this distribution correlates with data from the literature [19]. Lymphangioma and muscular hemangioma were found in the female population, and pyogenic granuloma in boys. The figure 2 shows the sex distribution of hemangiomas and arterio-venous malformations.

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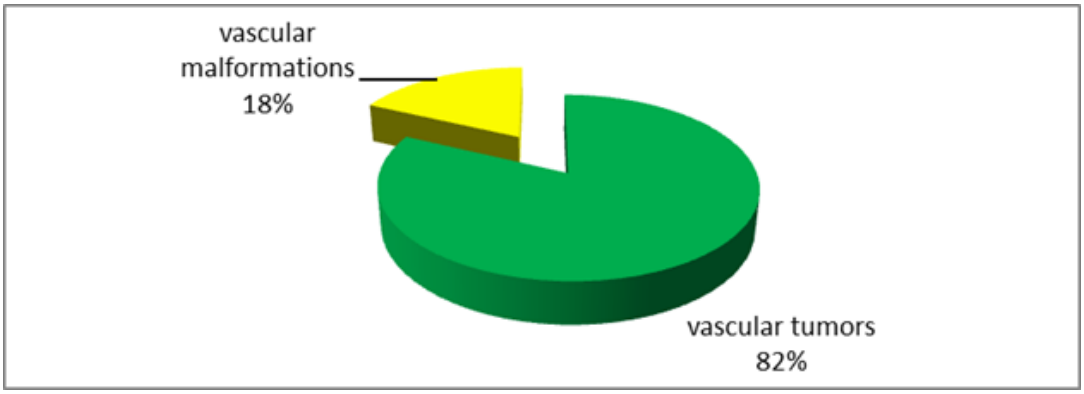


Figure 1 - The vascular anomalies studied and their incidence.

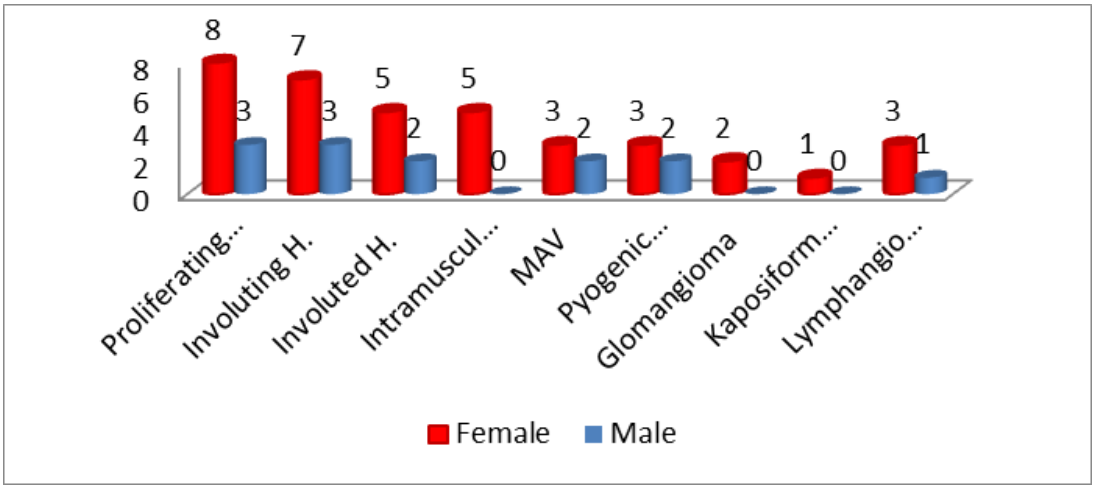


Figure 2 - Vascular anomalies, sex distribution.

The cases of infantile and congenital hemangiomas included in the study were classified according to the predominance of solid areas of endothelial cells and the density of vascular structures with lumens evident in: proliferating, involuting and involuted hemangioma

Hemangiomas in the proliferating and involuting phase were diagnosed in children aged between 2 months and two years, most of them were highlighted in the first year of life. Changes corresponding to an involuted phase of hemangioma appear from the first year of life and were found until the age of 12 years. The youngest patient who was diagnosed with intramuscular hemangioma was 4 years old and the oldest 17 years old. Arterio-venous malformation has been identified in children older than 2 years.

In the hemangioma the lobes are composed of capillary-type vascular structures, packed, some with a well-visible lumen or endothelial cells arranged in the form of beaches / islands. In the proliferative phase (fig. 3a), solid masses and capillaries packed with inconstantly evident lumens predominate. Hemangioma in the involuting phase (fig. 3b) has thicker septa, the lobules contain more vascular structures and less solids, they are directly proportional to the type of involution. The vascular structures are lined with swollen endothelial cells, some of which have a hobnail appearance. In the hemangioma involuted in the lobules richer fibrous and adipose tissue is identified, the vessels have a larger caliber, a wall of variable thickness and isolated in the lumen, thrombi can be identified in different evolutionary stages. On Giemsa staining, a higher number of mast cells was identified in proliferative and involuting hemangiomas and fewer in involuted hemangiomas.

Intramuscular hemangioma (fig. 3c) present striated muscle fibers dissected by a proliferation of vascular structures with variable lumen, most with cavernous appearance, focal with interanastomotic appearance, similar to arterial-venous malformation. The wall is thin, lined with cubic endothelial cells, swollen, without atypia. Some vascular structures show thrombi at various stages of evolution, isolated with aspects of intravascular papillary endothelial hyperplasia [20]. The stroma presents with an inflammatory lymph-plasma cell infiltrate, foamy histiomacrophages, giant multinucleated cells, hemosiderin deposits and isolated dystrophic calcifications.

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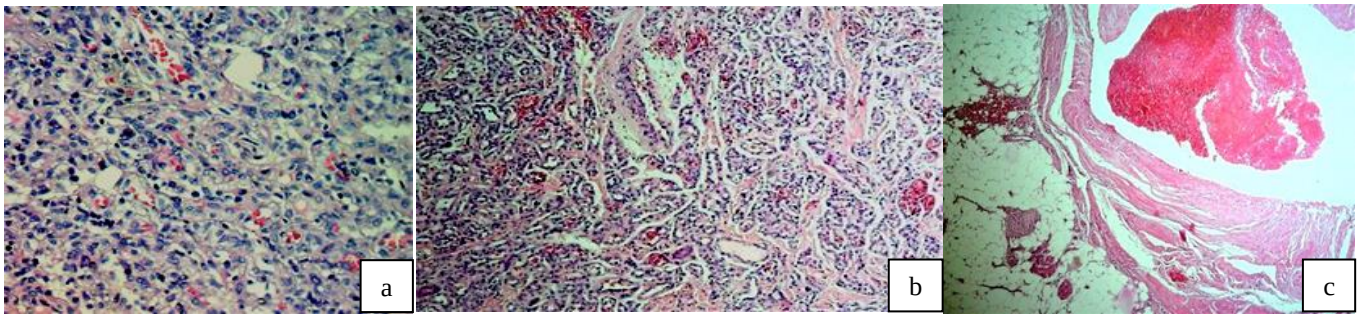
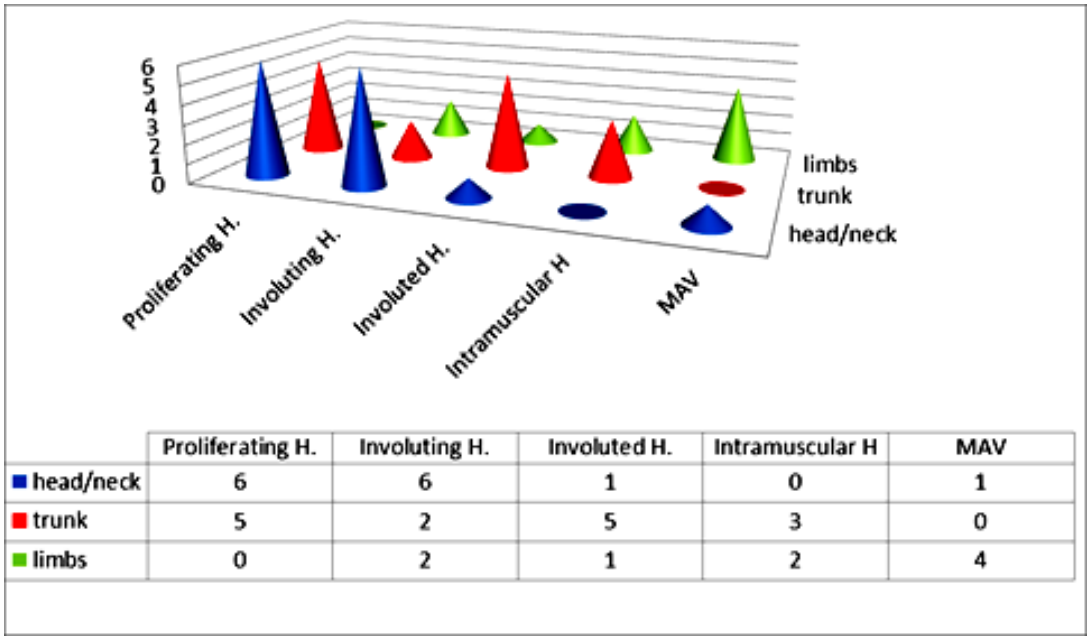



Figure 3 - a) proliferating hemangioma, b) involuting hemangioma, c) intramuscular hemangioma.

The figure 4 shows the correlation of the lesions with the anatomical location. It can be seen that vascular tumors are most commonly located in the trunk and region of the head or neck, while arterio-venous malformations are common in the limbs. Proliferative hemangioma was identified in the trunk, head and neck, and was not found in the limbs.

Depending on the histopathological characters and the intensity of PROX1 expression, infantile hemangiomas were divided into four categories: proliferative, involuting early, involuting tardive and involuted (table 2).




| | Proliferating H. | Involuting H. | Involuted H. | Intramuscular H | MAV |
|---|---|---|---|---|---|
| head/neck | 6 | 6 | 1 | 0 | 1 |
| trunk | 5 | 2 | 5 | 3 | 0 |
| limbs | 0 | 2 | 1 | 2 | 4 |

Figure 4 - Anatomical distribution of hemangiomas and arterio-venous malformations.

Table 2 - Vascular anomalies and PROX1 reaction intensity.

| LESION | PROX1 |
|---|---|
| Intramuscular hemangioma | 3 |
| Infantile hemangioma proliferative phase | 0 |
| Infantile hemangioma involuting phase-early | 1 |
| Infantile hemangioma involuting phase-tardive | 2 |
| Infantile hemangioma involuted phase | 3 |
| Kaposiform hemangioenothelioma | 0 |
| Pyogenic granuloma | 2/3 |
| Glomangioma | 0 |
| Lymfangioma | 0/3 |
| Arterio venous malformation | 0/1/3 |

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From the table above, it can be seen that the intensity of the PROX1 reaction is maximum in the involuted hemangioma and the muscular one, and in the proliferative phase hemangioma it is negative. The intensity of the reaction to infantile hemangioma in the involuting phase is variable, it can probably be correlated with the appearance of vascular lumens and with the decrease of the number of endothelial cells arranged in solid masses (figure 5a,b,c).

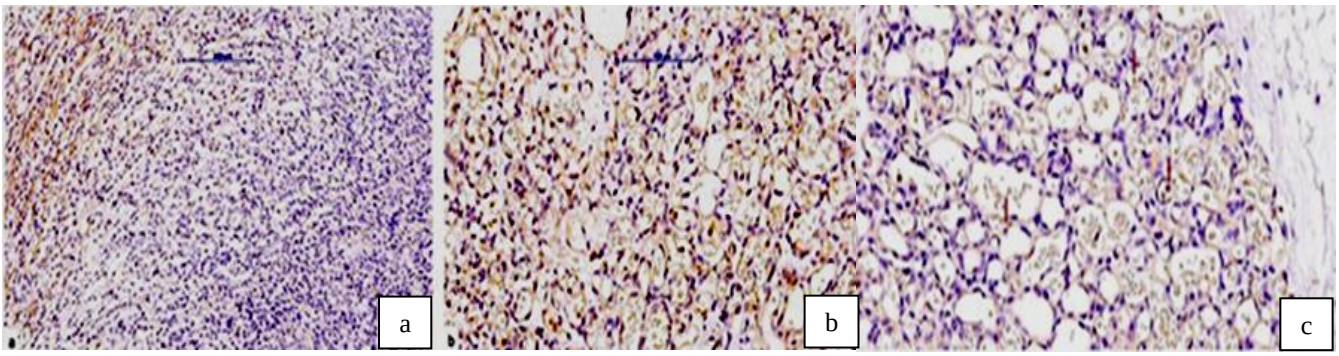


Figure 5 - Prox1 expression in undifferentiated areas (a), differentiated (b). Note the lack of Prox1 in undifferentiated areas and the gradual appearance in differentiating (a, b) and differentiated (c) areas.

PDGF B expression is variable in infantile hemangiomas, so in the proliferative phase most have the intensity of reaction 1 (5 cases) and only one case has the intensity 3, probably a late proliferation phase. The intensity of the reaction is variable as the hemangioma evolves, most of those involuted have a maximum intensity of the reaction. A maximum intensity of the PDGF B reaction is also identified in the case of arterio-venous malformations.

In the cases studied there were two cases of treated hemangiomas. In the one treated with propranolol the intensity of the PROX reaction is 3, it was considered an involuted hemangioma. The second case is a proliferative hemangioma treated with propranolol (without results, it grew and ulcerated), which was surgically excised, cauterized and then relapsed, the PROX1 reaction is negative.

Intramuscular hemangiomas were all diagnosed in female patients, in the upper or lower limbs and, as a particular aspect, all cases showed a +3 reaction to Prox1.

Involutive hemangiomas were analyzed using the same criteria as for proliferative hemangiomas.

The global analysis of involutive hemangiomas demonstrated a statistically significant correlation between PDGF-BB and PROX1 expression (Table 3 and Figure 6).

**Correlation Matrix**

Correlation Matrix

| | | PDGF-BB | PROX1 |
|---|---|---|---|
| PDGF-BB | Pearson's r | — | 0.738 ** |
| | p-value | — | 0.001 |
| | 95% CI Upper | — | 0.903 |
| | 95% CI Lower | — | 0.382 |
| | Spearman's rho | — | 0.753 *** |
| | p-value | — | <.001 |
| | Kendall's Tau B | — | 0.696 ** |
| | p-value | — | 0.004 |
| PROX1 | Pearson's r | 0.738 ** | — |
| | p-value | 0.001 | — |
| | 95% CI Upper | 0.903 | — |
| | 95% CI Lower | 0.382 | — |
| | Spearman's rho | 0.753 *** | — |
| | p-value | <.001 | — |
| | Kendall's Tau B | 0.696 ** | — |
| | p-value | 0.004 | — |

*Note.* * p < .05, ** p < .01, *** p < .001

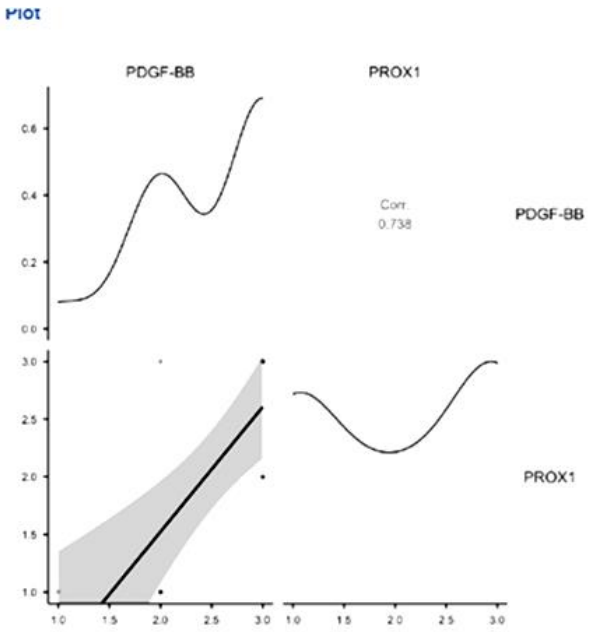


Table 3 / Figure 6 - Correlation between PROX1 and PDGF-BB in involutive hemangiomas.

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**Discussions**

The highest number of cases of proliferating and involuting hemangiomas were excised from the head and neck region, and the involuted hemangioma is located predominantly on the trunk. Arterio-venous malformations were most frequently excised from the limbs, having the same location as the data in the literature [21].

In the studied cases, the hemangioma is frequently located in the dermis with extension in the subcutaneous cellular tissue and consists of lobules separated by fibrous septa containing vascular structures of larger caliber, in variable numbers [22].

In this study we immunohistochemically examinated the expression of Prox1 protein, who is known to be expressed in lymphangiomas and lymphatic endothelium [11,13,14,15], but Prox 1 is involved in development of heart, liver, and pancreas. [16,18,23]. In our study intensity of the PROX1 reaction is maximum in the involuted hemangioma and the muscular one, and in the proliferative phase hemangioma it is negative.

Intramuscular hemangiomas were all diagnosed in the upper or lower limbs and, as a particular aspect, all cases showed a +3 reaction to Prox1.

It remains to be determined whether Prox1 contributes to clinico-pathologic and evolution distinction of hemangioma vs. vascular malformation [24].

Further studies are needed to determine whether there is a correlation of Prox1 with other lymphatic / endothelial markers or with clinio-pathological aspects [25].

**Conclusions**

In our study, the benign lesions were the majority, and among them most were infantile and congenital hemangiomas.

Proliferative infantile hemangioma has been located on the trunk, head and neck.

Vascular tumors are most commonly located on the head,neck, trunk region, while vascular malformations are frequently found in the limbs.

Arteriovenous malformations were most commonly located on the limbs, having the same location as the data in the literature.

The intensity of the PROX1 reaction is maximum in the involved hemangioma and the muscular one. In the proliferative phase of hemangioma it is negative.

The intensity of the reaction to involute phase of hemangioma is variable, it can probably be correlated with the appearance of vascular lumens and with the decrease the number of endothelial cells arranged in solid masses.

Our study demonstrates the need to establish multidisciplinary teams that will aim to standardize methods of diagnosis and treatment of vascular anomalies.

**References**


1. Mulliken JB, Enjolras O: Congenital hemangiomas and infantile hemangioma: Missing links. J Am Acad Dermatol 50:875-882, 2004
2. Della Rosa N, Bertozzi N, Adani R. Vascular malformation and their unpredictable evolution: A true challenge for physicians. Acta Biomed. 2020 Aug 25;91(3):e2020067. doi: 10.23750/abm.v91i3.8298. PMID: 32921762; PMCID: PMC7716989.
3. Ricci KW. Advances in the Medical Management of Vascular Anomalies. Semin Intervent Radiol 2017; 34: 239-249
4. Wildgruber M, Sadick M, Müller-Wille R, Wohlgemuth WA. Vascular tumors in infants and adolescents. Insights Imaging. 2019 Mar 13;10(1):30. doi: 10.1186/s13244-019-0718-6. PMID: 30868300; PMCID: PMC6419671.
5. Wassef M, Blei F, Adams D. et al. Vascular Anomalies Classification: Recommendations From the International Society for the Study of Vascular Anomalies. Pediatrics 2015; 136: e203-e214
6. Sadick M, Müller-Wille R, Wildgruber M, Wohlgemuth WA. Vascular Anomalies (Part I): Classification and Diagnostics of Vascular Anomalies. Rofo. 2018 Sep;190(9):825-835. English. doi: 10.1055/a-0620-8925. Epub 2018 Jun 6. PMID: 29874693.
7. Nonogaki S, Campos HG, Butugan O, Soares FA, Mangone FR, Torloni H, Brentani MM. Markers of vascular differentiation, proliferation and tissue remodeling in juvenile nasopharyngeal angiofibromas. Exp Ther Med. 2010 Nov;1(6):921-926.
8. Le Huu AR, Jokinen CH, Rubin BP, Mihm MC, Weiss SW, North PE, Dadras SS. Expression of prox1, lymphatic endothelial nuclear transcription factor, in Kaposiform hemangioendothelioma and tufted angioma. Am J Surg Pathol. 2010 Nov;34(11):1563-73.
9. Benoit MM, North PE, McKenna MJ, Mihm MC, Johnson MM, Cunningham MJ. Facial nerve hemangiomas: vascular tumors or malformations? Otolaryngol Head Neck Surg. 2010 Jan;142(1):108-14.
10. Wang L, Gao T, Wang G. Expression of Prox1, D2-40, and WT1 in spindle cell hemangioma. J Cutan Pathol. 2014;41(5):447-450. doi:10.1111/cup.12309.
11. Hirakawa S, Hong YK, Harvey N, Schacht V, Matsuda K, Libermann T, Detmar M. Identification of vascular lineage-specific genes by transcriptional profiling of isolated blood vascular and lymphatic endothelial cells. Am J Pathol. 2003 Feb; 162(2):575-86.
12. Johnson NC, Dillard ME, Baluk P, McDonald DM, Harvey NL, Frase SL, Oliver G. Lymphatic endothelial cell identity is reversible and its maintenance requires Prox1 activity. Genes Dev. 2008 Dec 1;22(23):3282-91. doi: 10.1101/gad.1727208. PMID: 19056883; PMCID: PMC2600759.

13. Wigle JT, Harvey N, Detmar M, Lagutina I, Grosveld G, Gunn MD, Jackson DG, Oliver G. An essential role for Prox1 in the induction of the lymphatic endothelial cell phenotype. EMBO J. 2002 Apr 2;21(7):1505-13. doi: 10.1093/emboj/21.7.1505. PMID: 11927535; PMCID: PMC125938.
14. Wilting J, Papoutsi M, Christ B, Nicolaides KH, von Kaisenberg CS, Borges J, Stark GB, Alitalo K, Tomarev SI, Niemeyer C, Rössler J. The transcription factor Prox1 is a marker for lymphatic endothelial cells in normal and diseased human tissues. FASEB J. 2002 Aug;16(10):1271-3. doi: 10.1096/fj.01-1010fje. Epub 2002 Jun 7. PMID: 12060670.
15. Hong YK, Detmar M. Prox1, master regulator of the lymphatic vasculature phenotype. Cell Tissue Res. 2003 Oct;314(1):85-92. doi: 10.1007/s00441-003-0747-8. Epub 2003 Jul 22. PMID: 12883994.
16. Dudas J, Elmaouhoub A, Masuroglu T, et al. Prospero-related homeobox 1 (Prox1) is a stable hepatocyte marker during liver development, injury and regeneration, and is absent from "oval cells" Histochem Cell Biol. 2006;126:549–562.
17. Dudas J, Papoutsi M, Hecht M, et al. The homeobox transcription factor Prox1 is highly conserved in embryonic hepatoblasts and in adult and transformed hepatocytes, but is absent from bile duct epithelium. Anat Embryol (Berl) 2004;208:359–366.
18. Burke Z, Oliver G. Prox1 is an early specific marker for the developing liver and pancreas in the mammalian foregut endoderm. Mech Dev. 2002;118:147–155.
19. Niu HL, Zhou SY, Lin QQ, Yi P, Wang FH, Gao Q, Chen ZR, Xia JQ, Zheng HC, Zeng RX. [Clinicopathologic study of pediatric vascular anomalies: a report of 117 cases]. Zhonghua Bing Li Xue Za Zhi. 2016 Apr 8;45(4):252-7. Chinese. doi: 10.3760/cma.j.issn.0529-5807.2016.04.008. PMID: 27033389.
20. Simona Cerbu, Florin Bîrsăşteanu, Elena Rodica Heredea, Daniela Iacob, Emil Radu Iacob, Maria Corina Stănciulescu, Eugen Sorin Boia. Acute limb ischemia in neonates: etiology and morphological findings – short literature review. Rom J Morphol Embryol 2018, 59(4):1041–1044, ISSN (print) 1220–0522.
21. Kawaguchi A, Kunimoto K, Inaba Y, Mikita N, Kaminaka C, Kanazawa N, Yamamoto Y, Kakimoto N, Suenaga T, Takeuchi T, Suzuki H, Baba N, Jinnin M. Distribution analysis of infantile hemangioma or capillary malformation on the head and face in Japanese patients. J Dermatol. 2019 Oct;46(10):849-852. doi: 10.1111/1346-8138.15051. Epub 2019 Aug 16. PMID: 31418467.
22. Simona Cerbu, Teodora Smaranda Arghirescu, Maria Corina Stănciulescu, Cristian-Eugen Timofte, Elisa Mussuto, Elena Rodica Heredea, Ioana Delia Horhat, Emil Radu Iacob, Florin Bîrsăşteanu, Eugen Sorin Boia. Role of imagistic techniques in diagnosing soft-tissue vascular anomalies in pediatric population – a 5-year experience. Rom J Morphol Embryol 2019, 60(2):495-500, ISSN 1220–0522.
23. Riseboro CA, Searles RG, Melville AA, et al. Prox1 maintains muscle structure and growth in the developing heart. Development. 2009;136:495–505
24. Marler JJ, Mulliken JB. Vascular anomalies – classification, diagnosis, and natural history. Review Facial Plast Surg Clin North Am. 2001;9:495–504.
25. Miettinen M, Wang ZF. Prox1 transcription factor as a marker for vascular tumors-evaluation of 314 vascular endothelial and 1086 nonvascular tumors. Am J Surg Pathol. 2012 Mar;36(3):351-9. doi: 10.1097/PAS.0b013e318236c312. PMID: 22067331; PMCID: PMC3288441.

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# CLINICAL AND BIOLOGICAL EVOLUTION OF THE NEWBORN WITH THROMBOCYTOPENIA IN THE NEONATAL INTENSIVE CARE UNIT

**Andrei Munteanu[1,2], Aniko Manea[1,2], Cristian Jinca[2,3], Marioara Boia[1,2]**

**Abstract**

*Introduction:* Thrombocytopenia is one of the most common haematological disorders detected in the newborn period, especially in neonates admitted to intensive care units and usually indicates an underlying pathological process. *Objectives:* To determine the etiology, the time of onset, the clinical characteristics and the evolution of newborns with thrombocytopenia. *Material and method:* 97 newborns with platelet counts (<150,000 / µl) were selected from those admitted to the Neonatology section of the Timisoara Children's Emergency Hospital "Louis Turcanu" for a period of 3 years. The determination of the initial values of platelets was performed at the hospitalization and then daily monitoring or even twice daily in the case of newborns with severe thrombocytopenia. *Results:* Grade IV thrombocytopenia (<25000 / µl) was present in 13.4% of cases, grade III (25000-50,000 / µL) in 16.5% of cases, grade II (50,000-75,000 / µL) in 9 , 3% of cases and grade I (75,000-150000 / µL) in 60.8% of cases. Most of the newborns (55.7%) were premature and the major causes of thrombocytopenia were sepsis, in 69.1% of cases and hypoxic suffering in 66% of cases. Mortality was 12.6% (n = 14). *Conclusion:* Thrombocytopenia occurring in newborns admitted to the neonatal intensive care unit is not a negative prognostic factor but rather a marker of severity of the underlying pathology.

*Abbreviations:* HIE, hypoxic ischemic encephalopathy; SGA, small for gestational age; AGA, appropriate for gestational age;

**Keywords:** thrombocytopenia, newborns, infections, hypoxia

## Introduction

Studies of fetal blood obtained by cordocentesis show that the mean fetal platelet count reaches 150 x $10^9$/µL by the end of the first trimester of pregnancy and increases above 150 × $10^9$ / µL by end of the second trimester. Several population studies also show that >98% of term neonates born to mothers with normal platelet counts have platelets above 150 × $10^9$ / µL at birth. Therefore thrombocytopenia in a neonate of any viable gestational age can be defined as a platelet count of <150 × $10^9$ / µL The incidence is 1-5% of newborns and 22-35% of newborns admitted to neonatal intensive care units[1,2,3,4].

The risk of severe thrombocytopenia is higher in preterm infants. In newborns with extremely low birth weight (<1,000 grams), the incidence of thrombocytopenia is greater than 70% and the incidence of severe thrombocytopenia (<50,000 / µL) is 40%[5]. The period of onset of thrombocytopenia can be: early (within 72 hours after birth) and late (after 72 hours of life).

Causes of early thrombocytopenia are placental insufficiency, perinatal asphyxia, autoimmune or alloimmune. Hypoxia-ischemia (HI) is a contributing factor to neonatal morbidity and mortality, often leading to chronic neurological disorders and disabilities, such as mental retar-dation, motor and behavioral developmental issues, cerebral palsy, seizure, and epilepsy. Newborns with mild HIE (grade I) have a favorable evolution. Approximately 80% of the patients with grade II encephalopathy recover; however, the mortality rate is 3 and 20-45% have neurological sequelae. Patients with severe HIE (grade III) have a mortality rate of 50% and survivors present severe neurological consequences [6].The incidence of HIE ranges from 1 to 8 per 1,000 live births in developed countries and is as high as 26 per 1,000 live births in underdeveloped countries [7].

Manifestations of HIE involve heart rhythm disorders, basic acid balance disorders (pH<7.0 or basic deficiency ≥12 mmol/l), low Apgar index, amniotic fluid impregnated with meconium or the need for respiratory support in the first few minutes of postnatal life [8].

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The redistribution of cerebral blood flow induced by asphyxia is the main post asphyxiation change. Brain injury results from hypoxia and ischemia. As a result of asphyxia, cardiac output is compensated by redistribution, thus increasing cerebral blood flow. If hypoxia persists, this self regulatory mechanism is no longer effective, resulting in decreased heart rate, with systemic hypotension and decreased cerebral flow leading to brain damage. At the cellular level, oxygen depletion blocks oxidative phosphorylation resulting in an anaerobic metabolism, which is energy inefficient, resulting in: i) Rapid depletion of phosphate reserves, including adenosine triphosphate, ii) accumulation of lactic acid and iii) inability to maintain cellular functions.

Severe maternal autoimmune thrombocytopenic disease, before or during pregnancy, was associated with an increased risk of severe fetal thrombocytopenia [9].

Late onset of thrombocytopenia is most commonly caused by infections / septicemia and necrotizing enterocolitis. Sometimes the causes of thrombocytopenia are prenatal viral infections (Cytomegalovirus, Toxoplasmosis, Rubella, HIV), perinatal bacterial infections (Group B streptococcus, Escherichia coli and Haemophilus Influenzae), or aneuploidy (especially trisomy 18, 13 and 21) [1,10].

Thrombocytopenia is usually seen with Gram positive septicemia as compared to Gram negative septicemia and low platelet is usually seen even before the pathogens are cultured from the blood. Therefore, thrombocytopenia may be considered as an important and early tool in diagnosis of septicemia in neonates [11].

Also among the factors that cause thrombocytopenia were incriminated in the literature also H2 antagonists - a case of severe thrombocytopenia induced by Ranitidine [4] and also by Vancomycin [12] has been described.

Previous detailed studies have attempted to define the mechanisms by which these conditions cause thrombocytopenia, but, until recently, the mechanism underlying many neonatal thrombocytopenias remained unknown [13].

The rather complex process of platelet production and release can be schematically represented as being made up of four main stages:

1) the production of thrombopoietic cytokines, mostly thrombopoietin, which is produced in the liver and is the main regulator of platelet production in humans [14]. Platelets are involved in hemostasis, influence the coagulation cascade and are the main source of many biologically active substances [15].

2) proliferation of megakaryocyte progenitors;

3) maturation of megakaryocytes in large polypoid cells capable of producing platelets;

4) release of platelets into circulation. Megakaryocytes in newborns are smaller and less mature than adult megakaryocytes, and smaller megakaryocytes are known to produce fewer platelets than larger and more mature megakaryocytes. This developmental feature may limit the ability of newborns to increase platelet production in response to platelet consumption. In addition, preterm infants appear to have relatively low levels of thrombopoietin during thrombocytopenia, which may limit their ability to rapidly regulate platelet production during increased platelet consumption [16]. Thrombopoietin is elevated during hypoxia. The number of platelets is negatively correlated with thrombopoietin levels on days 1, 3 and 7 of life in hypoxic infants [17].

Current evidence suggests that most platelet destruction in the newborn is immunologically mediated. It is shown that 15% to 20% of all neonatal thrombocytopenia present at birth results from transplacental passage of allo and / or autoantibodies [10]. Alloimmunization is the most common cause of severe thrombocytopenia [18].

Prematures babys born from the mother with preeclampsia who develops early bacterial sepsis and the baby with intrauterine growth restriction who develops necrotizing enterocolitis can both become thrombocytopenic (after pre-eclampsia or intrauterine growth restriction), combined with thrombocyte intake (during sepsis or necrotizing enterocolitis) [13].

It was found a strong correlation between delivery by cesarean section and thrombocytopenia. Disseminated intravascular coagulation occurs during sepsis and is found in 10% - 15% of thrombocytopenia cases admitted in neonatal intensive care [19].

In some studies it was concluded that birth weight and head circumference in infants with thrombocytopenia were significantly lower than in infants without thrombocytopenia. There was also a smaller number of hematopoietic progenitor cells in the blood from the umbilical cord of the SGA compared to the AGA [20].

**Material and method:**

This is a retrospective, cross-sectional cohort study carried out in the Neonatology Section of the Emergency Hospital for Children "Louis Turcanu" Timisoara. The study was conducted for a period of 3 years, from 01.01.2016 to 31.12.2018. The study included 97 newborns with a birth weight between 450 grams and 4900 grams.

Inclusion criteria:

1) Newborn suffering from birth asphyxia and subsequently developing hypoxic ischaemic encephalopathy or newborns with neonatal infection.

2) Newborn who fulfill the case definition criteria

3) Birth weight 450 grams and 4900 grams

4) Neonates surviving more than 24 hrs.

Exclusion Criteria:

1) incomplete data about the patient, information unavailable in the computer system of the hospital unit

2) major congenital anomalies, birth trauma

3) newborn borns to mothers having major diseases like malaria, severe anaemia, pre eclamsia/eclamsia, thyroid disorder, idiopathic purpura, placental disorder like vascular thrombosis, abruptio placenta

4) H/o maternal intake of any drugs causing bone marrow suppression/ thrombocytopenia

5) Newborn with congenital leukaemia, those having exchange transfusion.

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The demographic, gestational and perinatal data for the newborns included in the study were reviewed, including the presence of antenatal risk factors for both thrombocytopenia and sepsis of any kind (especially when associated with maternal diabetes, maternal use of steroid, maternal fetal infections, chorioamniotitis etc.).

All thrombocytopenic newborns were identified by computerized search of medical records in the online medical unit database.

Hemotological investigation. Hematological investigations were performed with a Sysmex XS800i analyzer using imped-ance spectroscopy, flow cytometry, Hydro Dynamic Focusing (DC Detection method) and the reagents were provided by Sysmex Corp. (Kobe, Japan). The cell blood count (CBC) was collected from peripheral venous blood, 1 ml of blood, and the sample was taken in a test tube with EDTA (sodium calcium edetate). The unit of measurement for thrombocytopenia was µl.

Data analyzes were performed using the statistical package (SPSS), version 23.0. Comparisons between group means were analyzed using the ANOVA test. Pearson's chi-squared test was used for each separate variable. If Pearson's chi-squared test could not be used the Fisher test was used. A p value of less than 0.05 was considered to be significant.

**Results and discussion:**

Thrombocytopenia is a common problem in the newborn period and is a significant cause of morbidity and mortality in children with different pathologies, both for term and premature births. Newborns are particularly vulnerable to infections due to a deficient immune defense.

Neonatal thrombocytopenia is usually mild to moderate; with spontaneous resolution and without requiring any specific therapy. The major risk of severe thrombocytopenia is intracranial hemorrhage leading to death or neurological disability [21,22], but no direct relationship between the severity of thrombocytopenia and the severity of intracranial hemorrhage has been observed [22]. The frequency of intracranial hemorrhage was estimated in 1% -3% of cases [23]. The relationship between platelet count and hemorrhage was unclear.

The frequency of bacterial infections in intensive care units was 10% - 32.3%, with an average occurrence of thrombocytopenia around the 17th day. Another study reports that thrombocytopenia was observed in 38% of all sepsis episodes. This was however not significantly different in infections by gram-negative and fungal versus gram-positive organisms [24,25].

The frequency of neonatal hypoxia reported in the literature was 23.9% term hypoxic neonates and 33.3% at preterm hypoxic neonates [26]. Reduced platelet count is a frequent finding in HIE. During the early period (0-2) days it is related to severity of HIE [found only in HIE Gr III], but in the later period (3-14 days) it may be found in all categories [27].

Studies report that the most common etiological diagnosis in all the admitted cases was sepsis (67%) followed by prematurity (52%) and perinatal asphyxia (21%). More than one diagnosis was present in the cases admitted with thrombocytopenia. Disseminated intravascular coagulation, necrotizing enterocolitis, and meconium aspiration syndrome were also some of the important causes identified [28].

During the 3 years in which the study was performed, 1247 newborns were hospitalized in the Neonatology Department of the "Louis Turcanu" Children's Emergency Hospital in Timisoara, of which 97 (7.7%) were included in the study with the diagnosis of neonatal thrombocytopenia. Of these, 57 (58.8%) were male and 40 (41.2%) were female. As a medium of origin, 55.7% came from urban areas and 44.3% from rural areas. Of these, 54 (55.7%) were premature and 43 (44.3%) full-term newborns. The average gestational age was 35.51 weeks and an average weight of 2401.55 grams at birth.

The mean onset of thrombocytopenia was 8.76 days.

Regarding the duration of thrombocytopenia, we have an average of 4.97 days (figure 1).

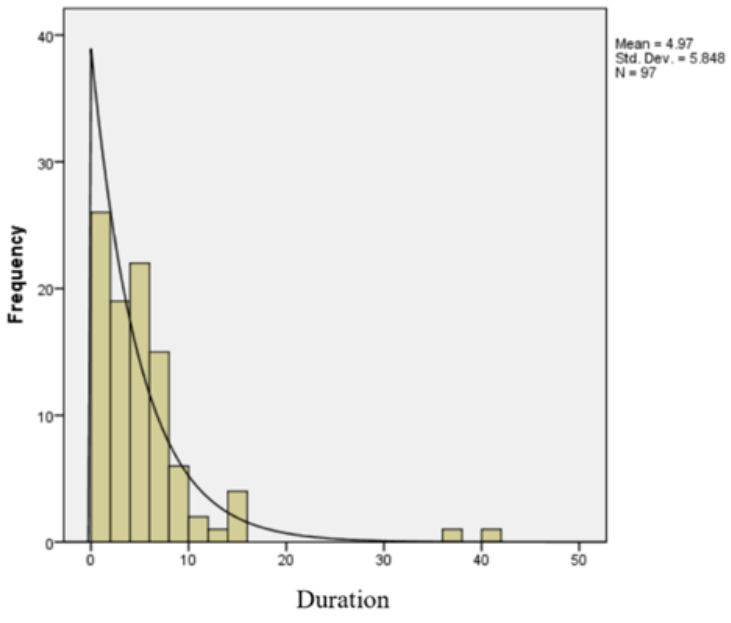


Fig.1 Mean duration of thrombocytopenia.

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Patients were divided into two study groups, namely, a group with a duration of thrombocytopenia less than 3 days and a group with an evolution over 3 days. Thus, 46.4% (n = 45) had an evolution duration of less than 3 days with subsequent remission and 53.6% (n = 52) had an evolution duration of thrombocytopenia over 3 days. It can be deduced that in our study group the vast majority of patients developed mild thrombocytopenia compared to the other study groups where moderate and severe thrombocytopenia predominated both in the first 72 hours and at more than 72 hours (table 1).

The mean value of platelets was 93.510 / µl. Depending on the value of platelets, patients were classified in severity, so 59 newborns (60.8%) were classified in the first grade of severity (75000 – 150000 /µL), 9 newborns (9.3%) in grade II (50000 – 75000 /µL), 16 newborns (16.5%) in grade III (25000 – 50000 /µL) and 13 newborns (13.4%) in grade IV (<25000 /µL) (figure 2).

Table 1. Duration of thrombocytopenia.

| Study on neonatal thrombocytopenia in NICUs | **<72 hours** | | **>72 hours** | |
|---|---|---|---|---|
| | **Moderate** | **Severe** | **Moderate** | **Severe** |
| Castle et al[24] | 66.11% | 47.01% | 39.24% | 52.23% |
| Rajeev mehta[24] | 13% | 20% | 36.2% | 51% |
| Patil et al[24] | 73.11% | 44.68% | 26.88% | 55.31% |
| **Our study** | **12.9%** | **11.2%** | **22,8%** | **14.2%** |

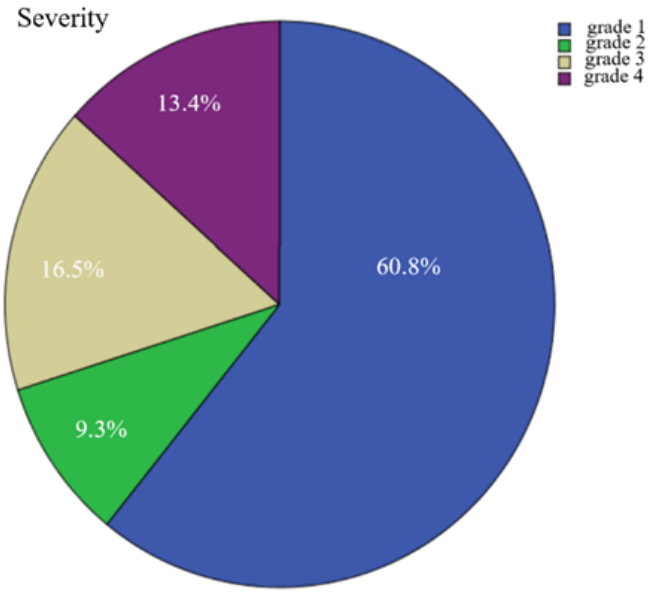


Fig.2 Severity of thrombocytopenia.

Knowing that thrombocytopenia occurs more frequently in the first 3 days in patients with hypoxia and after 3 days in patients with infections or ulceronecrotic enterocolitis, it was observed that the onset of thrombocytopenia in the first 3 days of life was found in 62 newborns (63.9 %), and after 3 days of life in 35 newborns (36.1%).

Hypoxia was found in 66% of thrombocytopenic patients, of whom 51.5% were premature newborns, predominantly male (57.5%) (Table 2).

Infections were detected in 69.1% of newborns, and hemorrhagic pathology or hemorrhagic syndromes were observed in 37.1% of newborns (table 3).

Tabel 2. Prevalence of hypoxemia.

| Studies on neonatal thrombocytopenia in NICUs | Prevalence of hypoxemia |
|---|---|
| Nadkarniet al[21] | 23.9% term hypoxic neonates<br>33.3% preterm hypoxic neonates |
| **Our study** | **48.5% term hypoxic neonates**<br>**51.5% preterm hypoxic neonates** |

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Tabel 3. Prevalence of infections.

| Studies on neonatal thrombocytopenia in NICUs | Prevalence of infections |
|---|---|
| Castle et al[24] | 10% |
| Hale Oren et al[24] | 5.4% |
| Patil et al[24] | 28.17% |
| **Our study** | **69.1%** |

37.1% (n = 36) of male patients and 23.7% (n = 23) of female patients were classified in the first grade of severity of thrombocytopenia.

Regarding the severity of thrombocytopenia, we can say that 41.2% (n = 40) of the patients in grade I had a limited evolution in less than 3 days, and 19.5% (n = 19) of those in grade I had an evolution more than 3 days of thrombocytopenia, while the evolution of all patients in grade IV severity (13.4%) was over 3 days (figure 3).

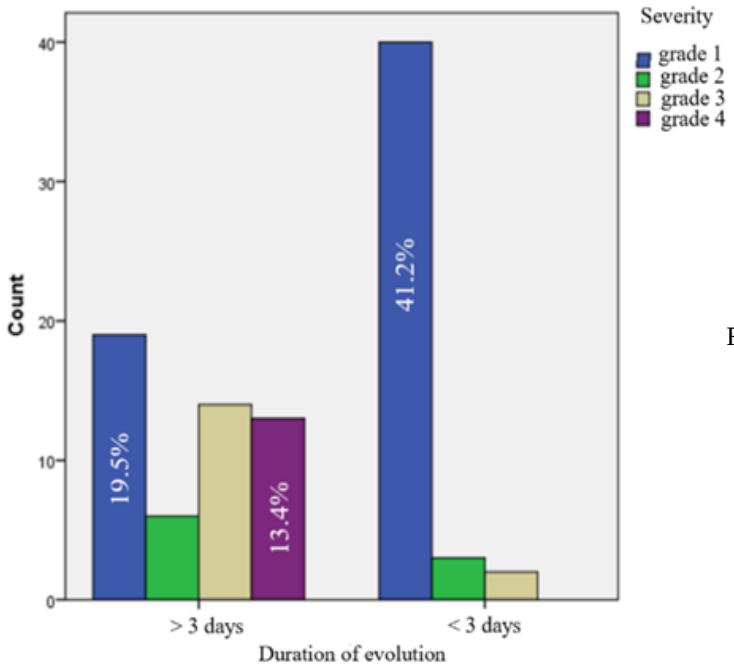


Fig.3 Severity depending on the duration of evolution.

Knowing that 53.6% (n = 52) of patients with thrombocytopenia had a duration of evolution over 3 days, 30.9% (n = 30) were male and 22.6% (n = 22) female. In both the group with evolution less than 3 days and in the group with evolution over 3 days, male patients were predominant.

Prematurity was found in 55.7% (n = 54) of cases, predominating male - 51.8% compared to 48.1% females. We observe that in case of the study group with evolution over 3 days of thrombocytopenia, 34% (n = 33) were born prematurely, while in the case of the group with evolution under 3 days, 24.7% (n = 24) were newborn at term. Knowing that in the first 3 days thrombocytopenia is more common due to hypoxia, we can say that in newborns at term thrombocytopenia the date of hypoxia was more common in the first 3 days (figure 4). Regarding the severity of thrombocytopenia, the vast majority of premature infants 48.4% (n = 31) were classified in the first grade of severity (figure 5).

Hypoxia was found in 66% (n = 64) of thrombocytopenic patients, 54.6% (n = 35) were male and 45.4% (n = 29) female. Analyzing the incidence of hypoxia depending on the duration of thrombocytopenia, we observe that in patients with less than 3 days of evolution, 45.3% (n = 29) were hypoxic, while in the case of the group with more than 3 days of thrombocytopenia, 54.6% (n = 35) were hypoxic (figure 6). The vast majority of 40.2% hypoxic patients (n = 39) were classified in the first grade of severity (figure 7).

In figure 8 are supported the previously reported, that 68.7% (n = 44) of premature babies were hypoxic.

As values with statistical significance ($p < 0.05$), it was observed that in the case of female newborns, thrombocytopenia started on average at 4.43 days; while in male newborns at 11.8 days (table 4).

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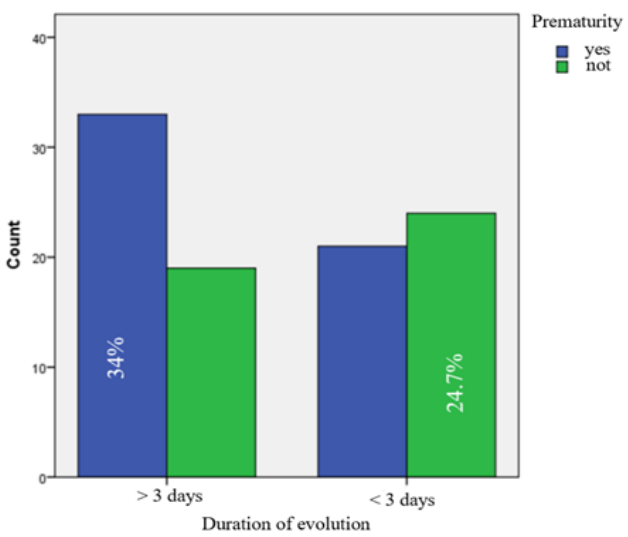


Fig.4 Duration of evolution in premature newborns.

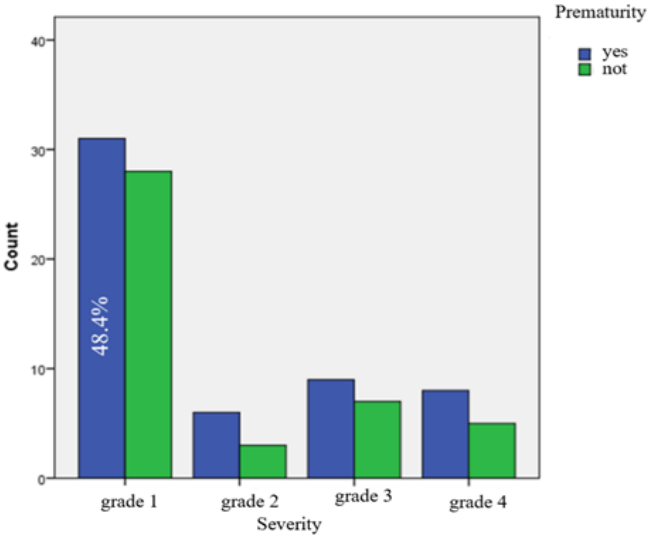


Fig.5 Severity of thrombocytopenia in premature infants.

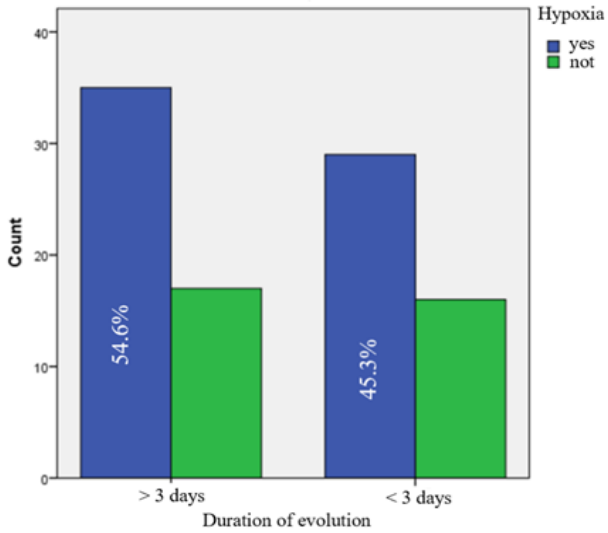


Fig.6 Duration of thrombocytopenia in hypoxic newborns.

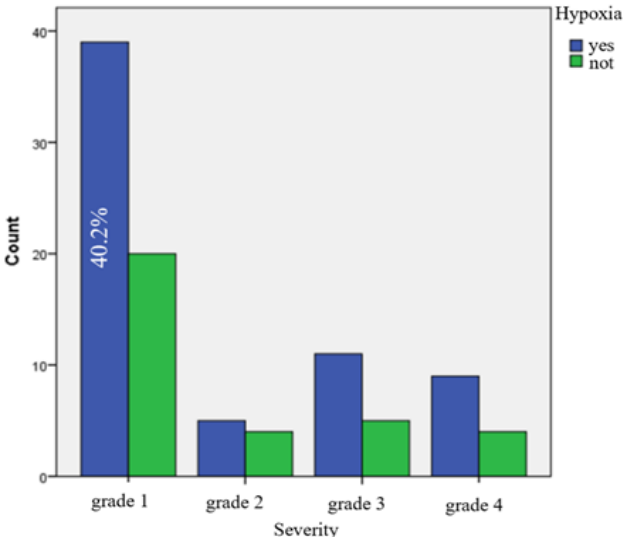


Fig.7 Severity of thrombocytopenia in hypoxic newborns.

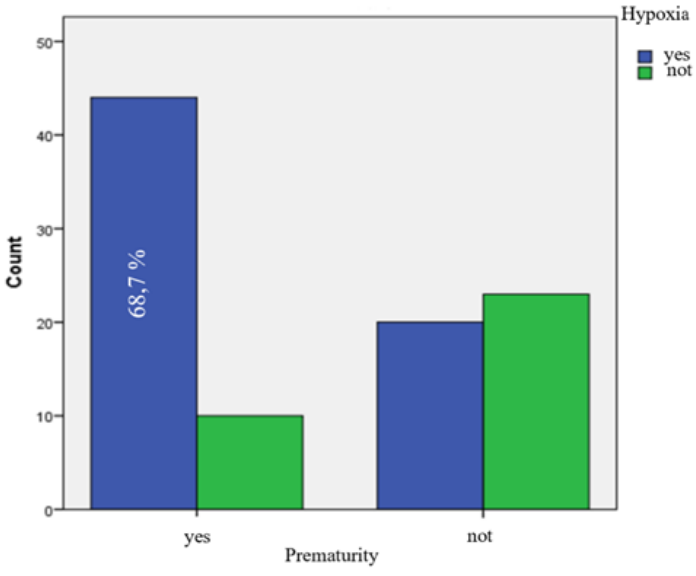


Fig.8 Prematurity in hypoxic newborns.

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Table 4. The onset of thrombocytopenia by gender.

| Gender | | Gestation | Weight | Onset (p<0,05), | Duration | Platelet count/ x10$^9$/µl |
|---|---|---|---|---|---|---|
| **F** | N | 40 | 40 | 40 | 40 | 40 |
| | Mean | 35.90 | 2280.25 | 4.43 | 4.60 | 93.85 |
| | Std. Deviation | 3.774 | 750.782 | 6.193 | 5.697 | 43.857 |
| | Std. Error of Mean | .597 | 118.709 | .979 | .901 | 6.934 |
| **M** | N | 57 | 57 | 57 | 57 | 57 |
| | Mean | 35.23 | 2486.67 | 11.81 | 5.23 | 93.26 |
| | Std. Deviation | 4.448 | 934.135 | 19.251 | 5.988 | 44.033 |
| | Std. Error of Mean | .589 | 123.729 | 2.550 | .793 | 5.832 |

In grade I thrombocytopenic patients (n = 59), the mean weight was 2404.41 grams, the onset of thrombocytopenia was on average on day 8.37, the mean duration of thrombocytopenia was 3 days and the mean platelet count was 117,000 /µL. Grade II thrombocytopenic patients (n = 9) had an average weight of 2308.89 grams, the onset of the pathology was on day 17.44, the mean duration of thrombocytopenia was 4.78 days and the mean platelet count was 102,670/µL. Grade III newborns (n = 16) had an average weight of 2285 grams, the pathology began on average day 7.19, an average duration of thrombocytopenia of 8.38 days and an average value of platelets of 60,690/µL. Grade IV (n = 13) had an average weight of 2596.15 grams, the onset was on day 6.46, an average duration of 9.8 days and an average platelet count of 17,770/µL.

Values with statistical significance (p <0.05) were observed when comparing duration with severity, where it is observed that the lower is the severity, the lower is the duration of thrombocytopenia, so it can be seen that the first grade of severity corresponds to a duration of 3 days of evolution, compared to grade IV where a duration of 9.85 days is observed (table 5).

Table 5. The severity of thrombocytopenia depending on the duration.

| Severity | | Gestation | Weight | Onset | Duration (p<0.05) | Platelet count/ x10$^9$/µl |
|---|---|---|---|---|---|---|
| **grade 1** | N | 59 | 59 | 59 | 59 | 59 |
| | Mean | 35.29 | 2404.41 | 8.37 | 3.00 | 117.69 |
| | Std. Deviation | 4.263 | 911.836 | 15.113 | 2.512 | 23.496 |
| | Std. Error of Mean | .555 | 118.711 | 1.968 | .327 | 3.059 |
| **grade 2** | N | 9 | 9 | 9 | 9 | 9 |
| | Mean | 36.11 | 2308.89 | 17.44 | 4.78 | 102.67 |
| | Std. Deviation | 4.755 | 920.346 | 28.880 | 2.906 | 27.281 |
| | Std. Error of Mean | 1.585 | 306.782 | 9.627 | .969 | 9.094 |
| **grade 3** | N | 16 | 16 | 16 | 16 | 16 |
| | Mean | 35.50 | 2285.00 | 7.19 | 8.38 | 60.69 |
| | Std. Deviation | 4.099 | 774.700 | 11.940 | 9.150 | 31.455 |
| | Std. Error of Mean | 1.025 | 193.675 | 2.985 | 2.287 | 7.864 |
| **grade 4** | N | 13 | 13 | 13 | 13 | 13 |
| | Mean | 36.08 | 2596.15 | 6.46 | 9.85 | 17.77 |
| | Std. Deviation | 3.840 | 767.078 | 7.501 | 8.513 | 17.589 |
| | Std. Error of Mean | 1.065 | 212.749 | 2.080 | 2.361 | 4.878 |

Depending on the duration of thrombocytopenia, patients were divided into two groups; lasting less than 3 days and lasting more than 3 days.

Thus with the statistically significant value (p <0.05) it was observed that in the case of patients in whom thrombocytopenia lasted up to 3 days (n = 45) the average onset was on day 12.36; the mean duration of thrombocytopenia was 1.6 days and the average platelet count was 115,640/µL. In neonates in whom thrombocytopenia lasted more than 3 days (n = 52), it was observed that on average the onset was in day 5.65, the mean duration of thrombocytopenia was 7.88 days and the mean value of platelet count was 74,350/µL (table 6).

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Table 6. Duration of thrombocytopenia.

| Duration | | Gestation | Weight | Onset (p<0.05) | Duration (p<0.05) | Platelet count/ x10$^9$/µl (p<0.05) |
|---|---|---|---|---|---|---|
| **>3 days** | N | 52 | 52 | 52 | 52 | 52 |
| | Mean | 35.65 | 2335.77 | 5.65 | 7.88 | 74.35 |
| | Std. Deviation | 4.134 | 810.213 | 8.232 | 6.720 | 45.251 |
| | Std. Error of Mean | .573 | 112.356 | 1.142 | .932 | 6.275 |
| **<3 days** | N | 45 | 45 | 45 | 45 | 45 |
| | Mean | 35.33 | 2477.56 | 12.36 | 1.60 | 115.64 |
| | Std. Deviation | 4.264 | 927.940 | 20.775 | .780 | 29.399 |
| | Std. Error of Mean | .636 | 138.329 | 3.097 | .116 | 4.382 |

In the case of hypoxic patients (n = 64) compared to those who did not suffer from hypoxia, with statistically significant value (p <0.05), it was observed that the average birth weight was 2197.66 grams, the average gestational age was 34.42 weeks and onset of thrombocytopenia on day 5.33. In the case of newborns without hypoxic distress, it was observed that the average birth weight was 2796.97 grams, the average gestational age was 37.6 weeks and the onset of thrombocytopenia on day 15.42 (Table 7).

Table 7. Evaluation of hypoxic newborns.

| Hypoxia | | Gestation (p<0.05) | Weight (p<0.05) | Onset (p<0.05) | Duration | Platelet count/ x10$^9$/µl |
|---|---|---|---|---|---|---|
| **yes** | N | 64 | 64 | 64 | 64 | 64 |
| | Mean | 34.42 | 2197.66 | 5.33 | 5.09 | 91.89 |
| | Std. Deviation | 4.305 | 897.327 | 12.947 | 5.628 | 44.687 |
| | Std. Error of Mean | .538 | 112.166 | 1.618 | .703 | 5.586 |
| **not** | N | 33 | 33 | 33 | 33 | 33 |
| | Mean | 37.61 | 2796.97 | 15.42 | 4.73 | 96.64 |
| | Std. Deviation | 2.989 | 644.765 | 18.329 | 6.336 | 42.319 |
| | Std. Error of Mean | .520 | 112.239 | 3.191 | 1.103 | 7.367 |

It was also observed that in the case of hypoxic patients the mean duration of thrombocytopenia was 5.09 days with a mean platelet count of 91,890/µL, and in neonates without hypoxic distress, the mean duration of thrombocytopenia was 4.7 days with a mean platelet count of 96,640/µL.

In patients with infection (n = 67), the mean time to onset of thrombocytopenia was 10.99 days, while in patients without infection (n = 30) the mean time to onset of thrombocytopenia was 3.80 days, with a mean duration smilara and an average platelet value approximately equal (Table 8).

Table 8. Evaluation of thrombocytopenic infections in newborns.

| Infections | | Gestation | Weight | Onset | Duration | Platelet count/ x10$^9$/µl |
|---|---|---|---|---|---|---|
| **yes** | N | 67 | 67 | 67 | 67 | 67 |
| | Mean | 35.55 | 2433.13 | 10.99 | 4.75 | 90.85 |
| | Std. Deviation | 4.415 | 914.965 | 17.990 | 5.417 | 44.618 |
| | Std. Error of Mean | .539 | 111.781 | 2.198 | .662 | 5.451 |
| **not** | N | 30 | 30 | 30 | 30 | 30 |
| | Mean | 35.40 | 2331.00 | 3.80 | 5.47 | 99.43 |
| | Std. Deviation | 3.654 | 751.598 | 6.155 | 6.786 | 41.807 |
| | Std. Error of Mean | .667 | 137.222 | 1.124 | 1.239 | 7.633 |

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**Conclusion**

The most common cause of early-onset thrombocytopenia is fetal hypoxia; most often it is self-limited and rarely severe.

After 72 hours, the most common cause of thrombocytopenia among newborns admitted to the intensive care unit is infectious pathology.

In our study, the hypoxic infants with whom thrombocytopenia was associated were predominant in males.

In the case of hypoxic patients, thrombocytopenia started earlier, had a longer duration and a higher grade of severity compared to newborns without hypoxic suffering.

It was observed that the more severe are the form of thrombocytopenia, the longer is the regeneration period. As the severity of thrombocytopenia was lower, the duration of thrombocytopenia was shorter and appeared later. The onset of thrombocytopenia among the patients in study was 8.7 days and with an average duration of 4.97 days.

Thrombocytopenia occurring in neonates admitted to the neonatal intensive care unit is not a negative prognostic factor but rather a marker of severity of the underlying pathology.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

AIM and MB conceived and designed the study; AIM and AMM collected the data. AMM and CMJ analyzed the data; AIM and CMJ edited the figures and AIM, AMM and CMJ drafted the manuscript. MB revised the manuscript critically for important intellectual content. All authors contributed to the data interpretation and approved the submitted version.

**Ethics approval and consent to participate**

Approval of the local ethics committee (Ethics Committee for Scientific Research of the Emergency Hospital for Children 'Louis Turcanu) was obtained prior to starting the study. Parental or caregiver consent was obtained where applicable. This publication and the database does not contain personal data, does not compromise anonymity or confidentiality or breach local data protection laws.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**References**

1. Roberts I, Stanworth S, Murray NA. Thrombocytopenia in the Neonate. Blood Rev. 2008;22(4):173–86.
2. Jerónimo M, Azenha C, Mesquita J, Pereira DF. A rare manifestation of neonatal alloimmune thrombocytopaenia. BMJ Case Rep. 2014;10–3.
3. von Lindern JS, van den Bruele T, Lopriore E, Walther FJ. Thrombocytopenia in neonates and the risk of intraventricular hemorrhage: A retrospective cohort study. BMC Pediatr [Internet]. 2011;11(1):16. Available from: http://www.biomedcentral.com/1471-2431/11/16
4. Hoste L, George I. Ranitidine-induced Thrombocytopenia in a Neonate – A Case Report and Review of Literature. J Pediatr Pharmacol Ther. 2019;24(1):66–71.
5. Yurdakök M. Immune thrombocytopenia in the newborn. J Pediatr Neonatal Individ Med. 2017;6(1):1–10.
6. Chaparro-Huerta V, Flores-Soto ME, Merin Sigala ME, Barrera de León JC, Lemus-Varela M de L, Torres-Mendoza BM de G, et al. Proinflammatory Cytokines, Enolase and S-100 as Early Biochemical Indicators of Hypoxic-Ischemic Encephalopathy Following Perinatal Asphyxia in Newborns. Pediatr Neonatol. 2017;58(1):70–6.
7. Douglas-Escobar M, Weiss MD. Hypoxic-Ischemic Encephalopathy A Review for the Clinician. JAMA Pediatr. 2015;169(4):397–403.
8. Allen KA, Brandon DH. Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments. Newborn Infant Nurs Rev [Internet]. 2011;11(3):125–33. Available from: http://dx.doi.org/10.1053/j.nainr.2011.07.004
9. Valat AS, Caulier MT, Devos P, Rugeri L, Wibaut B, Vaast P, et al. Relationships between severe neonatal thrombocytopenia and maternal characteristics in pregnancies associated with autoimmune thrombocytopenia. Br J Haematol. 1998;103(2):397–401.
10. Roberts IAG, Murray NA. Neonatal thrombocytopenia: New insights into pathogenesis and implications for clinical management. Curr Opin Pediatr. 2001;13(1):16–21.
11. Arif SH, Ahmad I, Ali SM, Khan HM. Thrombocytopenia and bacterial sepsis in neonates. Indian J Hematol Blood Transfus. 2012;28(3):147–51.

12. Kalra K, Mittal HG, Maria A. Vancomycin-induced thrombocytopenia in a newborn. Drug Metab Pers Ther. 2016;31(4):235–7.
13. Roberts I, Murray NA. Neonatal thrombocytopenia: Causes and management. Arch Dis Child Fetal Neonatal Ed. 2003;88(5):359–64.
14. 14. Kaushansky K. The molecular mechanisms that control thrombopoiesis. J Clin Invest. 2005;115(12):3339–47.
15. Brucknerová I, Ujházy E, Dubovický M, Mach M. Early assessment of the severity of asphyxia in term newborns using parameters of blood count. Interdiscip Toxicol. 2008;1(3–4):211–3.
16. Sola-Visner M, Saxonhouse MA, Brown RE. Neonatal thrombocytopenia: What we do and don't know. Early Hum Dev. 2008;84(8):499–506.
17. Bauman ME, Cheung PY, Massicotte MP. Hemostasis and platelet dysfunction in asphyxiated neonates. J Pediatr [Internet]. 2011;158(2 SUPPL.):e35–9. Available from: http://dx.doi.org/10.1016/j.jpeds.2010.11.011
18. Bertrand G, Leguen A, Delugin L, Renac V. Severe neonatal thrombocytopenia due to fetomaternal anti-A alloimmunization: A case report. Pediatr Neonatol [Internet]. 2018;59(4):421–2. Available from: https://doi.org/10.1016/j.pedneo.2017.11.007
19. Beiner ME, Simchen MJ, Sivan E, Chetrit A, Kuint J, Schiff E. Risk factors for neonatal thrombocytopenia in preterm infants. Am J Perinatol. 2003;20(1):49–54.
20. Kadhum RJ, Muhsen HJ, Hussein AA. Original paper The Effect of Birth Asphyxia on the Coagulation Status in Neonates. 2017;10(2).
21. Fontão-Wendel R, Wendel S, Odone V, Carneiro JD, Silva L, Isfer E. A case report of neonatal alloimmune thrombocytopenic purpura: The importance of correct diagnosis for future pregnancies. Sao Paulo Med J. 2005;123(4):198–200.
22. Stanworth SJ, Clarke P, Watts T, Ballard S, Choo L, Morris T, et al. Prospective, observational study of outcomes in neonates with severe thrombocytopenia. Pediatrics. 2009;124(5).
23. Sunumu O, Report C. Neonatal Autoimmune Thrombocytopenia Due To Maternal Immune Thrombocytopenic Purpura: Report of Three Cases. Türkiye Çocuk Hast Derg. 2012;6(4):249–52.
24. Gonzalez BE, Mercado CK, Johnson L, Brodsky NL, Bhandari V. Early markers of late-onset sepsis in premature neonates: Clinical, hematological and cytokine profile. J Perinat Med. 2003;31(1):60–8.
25. Patil S, Mangshetty R, Patil B. Outcome of Neonates With Thrombocytopenia. J Evol Med Dent Sci. 2014;3(17):4533–8.
26. Nadkarni J, Patne S, Kispotta R. Hypoxia as a predisposing factor for the development of early onset neonatal thrombocytopenia. J Clin Neonatol. 2012;1(3):131.
27. Bala D, Som S, Das S. A Study of Platelet Count as a Marker of Severity of Hypoxic Ischemic Encephalopathy. IOSR J Dent Med Sci [Internet]. 2015;14(5):2279–861. Available from: www.iosrjournals.org
28. Kumar Ray R, Panda S, Patnaik R, Sarangi G. A Study of Neonatal Thrombocytopenia in a Tertiary Care Hospital: A Prospective Study. J Neonatol. 2018;32(1):6–11.

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# INITIAL SERUM CREATININE AND NADIR CREATININE – PROGNOSTIC MARKERS FOR RENAL OUTCOME IN PATIENTS WITH PUV

**Teodora Luchița[1], Nicolae Sebastian Ionescu[1,2]**

**Abstract**

*Objective*: This study aims to analyze the correlation between the initial creatinine and the nadir creatinine values and the risk of chronic kidney disease in patients with posterior urethral valves. *Materials and methods*: The medical records of all patients with PUV treated in the surgery department of The Emergency Children's Hospital "Marie Curie" between January 2007 – January 2020 were analyzed. The age at presentation, serum creatinine, nadir creatinine, and glomerular filtration rate were noted. The patients were divided in three groups based on the marker values. *Results*: 77 patients were studied. The high-risk group (13%) was represented by patients with initial creatinine and nadir creatinine >0.85 mg/dL, with 100% progression to CKD. The low-risk group (33%) showed a very low development of renal insufficiency for values of <0.4 mg/dL.

**Keywords:** posterior urethral valves, initial serum creatinine, nadir creatinine, chronic kidney disease

## Introduction

Posterior urethral valves are the most common cause of lower urinary tract obstruction in children, with a broad spectrum of consequences on the bladder and kidneys. Despite the early treatment realized by valve ablation or urinary deviation, 25-40% of the patients develop chronic kidney disease [1,2].

The study aims to analyze some prognostic factors associated with the worsening of renal function. The initial serum creatinine and the nadir creatinine are cheap and easy to obtain in any medical center. Knowing the risk of the patient to develop CKD can be very helpful in planning proper management for the patient and early parental counseling.

## Material and methods

The study included registered and followed-up patients from the Emergency Children's Hospital "Marie Curie" Bucharest, between January 2007 and January 2019. The prognostic factors that were studied were: abnormal antenatal ultrasound, oligohydramnios, age at initial urinary drainage, initial serum creatinine value, nadir creatinine, and current renal function. The nadir creatinine value is defined as the lowest serum creatinine in the first 12 months after bladder drainage [1,3-5]. The value was recorded in mg/dL. The chronic kidney disease stage was determined by calculating the eGFR using the Schwartz formula. Chronic renal insufficiency was defined by stage-2 or higher CKD according to the Kidney Disease Outcomes Quality Initiative guidelines (eGFR <90 ml/min) [6]. SPSS Statistics for Windows version 17.0 was used for statistical analysis. In order to establish the correlation between the creatinine value and the renal kidney disease, the Mann-Whitney U test and the Shapiro-Wilk test were used.

## Results and Discussions

A number of 81 patients were identified, with available progress data in 77 patients. The mean age at diagnosis was 28.61 months (10 days – 156 months), IQR (1,39). The median follow-up was 7.5 years. The mean age at the CKD was 52.01 months, IQR 17.5 (10.75-56.25).

Recorded initial creatinine ranged between 0.18 and 2.2 mg/dL, while the nadir creatinine ranged between 0.2 and 1.2 mg/dL. The patients were divided into three groups, depending on the initial creatinine and nadir creatinine values. In the first group (creatinine <0.4mg/dL), no CKD during follow-up was seen. On the other hand, in the group of patients with initial creatinine higher than 0.85%, 8 out of 10 patients developed CKD during the follow-up. In the middle group (creatinine between 0.45 and 0.85 mg/dL) the ratio of patients with and without CKD was almost equal (Table 1). However, as the values of initial creatinine are lower and closer to 0.4 mg/dL, the change of CKD is lower (Figure 1 and Figure 2).

The analysis of the nadir creatinine showed that only 3 out of 40 patients (7.5%) developed chronic kidney disease during follow-up (Figure 3 and Figure 4). Therefore, a value lower than 0.4 mg/dL might be considered a prognostic factor for a good renal outcome. In the high-risk group, with nadir creatinine values >0.85 mg/dL, all the patients developed CKD. The data is available in table 2.

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Table 1. Comparison of the initial creatinine values depending on CKD

| ***Creatinine <0.4*** | **Valid cases** | **Mean ± SD** | **Median (IQR)** | **Rank.avg** | **p*** |
|---|---|---|---|---|---|
| **Without CKD** (p=0.207**) | 26 | 0.297 ± 0.064 | 0.305 (0.237-0.35) | - | - |
| **With CKD** (p= -**) | 0 | - | - | - | |
| ***0.4 < Creatinine < 0.85*** | **Valid cases** | **Mean ± SD** | **Median (IQR)** | **Rank.avg** | **p*** |
| **Without CKD (p<0.001**)** | 21 | 0.469 ± 0.087 | 0.45 (0.405-0.49) | 13.62 | **<0.001** |
| **With CKD (p=0.023**)** | 19 | 0.63 ± 0.135 | 0.56 (0.52-0.78) | 28.11 | |
| ***Creatinine > 0.85*** | **Valid cases** | **Mean ± SD** | **Median (IQR)** | **Rank.avg** | **p*** |
| **Without CKD (p=-**)** | 2 | 1.46 ± 0.756 | 1.465 | 5.5 | 1.000 |
| **With CKD (p=0.001**)** | 8 | 1.125 ± 0.373 | 0.985 (0.94-1.15) | 5.5 | |

*Mann-Whitney U Test, **Shapiro-Wilk Test

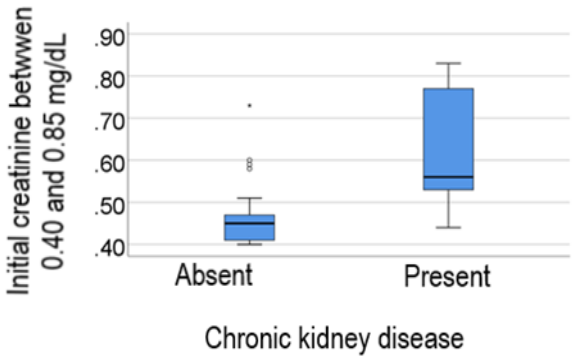


Figure 1. Comparison of the initial creatinine value between 0.45 and 0.85 mg/dL in patients, divided in categories, by the CKD outcome.

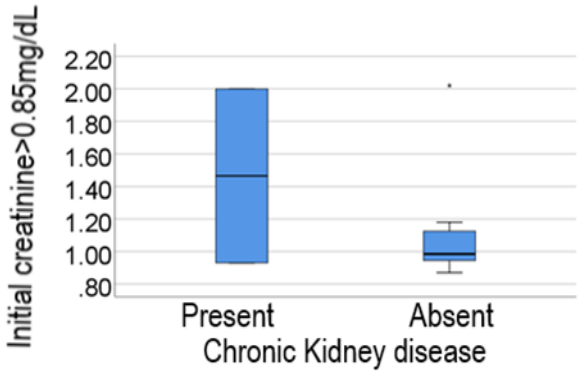


Figure 2. Comparison of the initial creatinine values >0.85 mg/dL depending on CKD development.

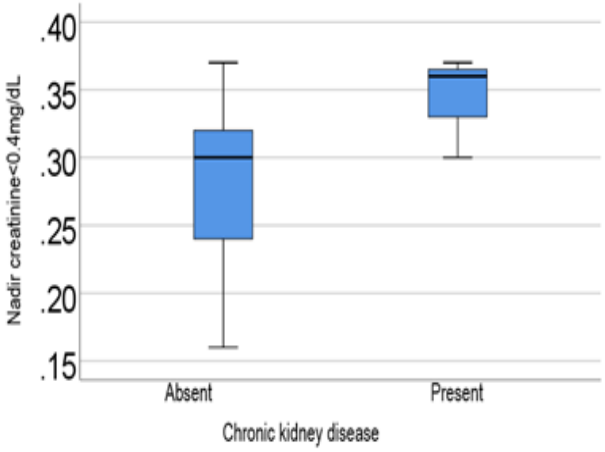


Figure 3. Comparison of the nadir creatinine values <0.4 mg/dL depending on CKD development.

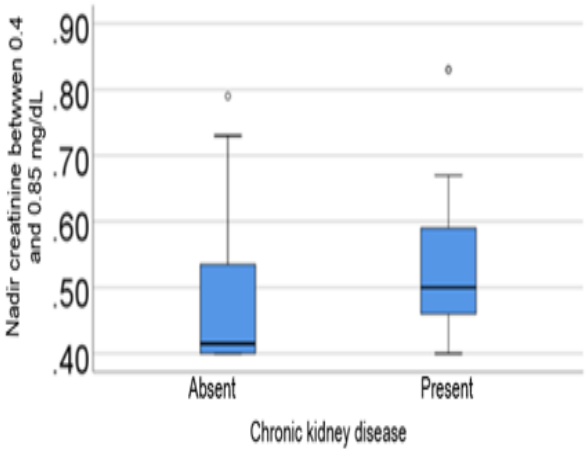


Figure 4. Comparison of the nadir creatinine values (between 0.4 and 0.85 mg/dL) depending on CKD development.

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Table 2. Comparison of the nadir creatinine values depending on CKD.

| **Nadir creatinine<0.4** | **Valid cases** | **Mean ± SD** | **Median (IQR)** | **Rank.avg** | **p*** |
|---|---|---|---|---|---|
| **Without CKD (p=0.008**)** | 37 | 0.284 ± 0.056 | 0.3 (0.235-0.32) | 19.53 | 0.064 |
| **With CKD (**p=0.253**) | 3 | 0.343 ± 0.037 | 0.36 | 32.5 | |
| **Nadir creatinine between 0.4 and 0.85 mg/dL** | **Valid cases** | **Mean ± SD** | **Median (IQR)** | **Rank.avg** | **p*** |
| **Without CKD (p=0.001**)** | 12 | 0.491 ± 0.136 | 0.415 (0.4-0.552) | 12.21 | 0.140 |
| **With CKD (p=0.011**)** | 17 | 0.54 ± 0.131 | 0.5 (0.455-0.595) | 16.97 | |
| **Nadir creatinine >0.85 mg/dL** | **Valid cases** | **Mean ± SD** | **Median (IQR)** | **Rank.avg** | **p*** |
| **Without CKD (**p=-**)** | 0 | - | - | - | - |
| **With CKD (**p=0.263**) | 7 | 1.021 ± 0.093 | 1 (0.97-1.08) | - | |

*Mann-Whitney U Test, **Shapiro-Wilk Test

**Conclusions**

Initial serum creatinine and nadir creatinine are cheap and easy to obtain in any hospital. These markers were widely studied in literature as reliable markers for renal outcome in patients with PUV. Initial creatinine <0.4mg/dL was associated with no progression to renal insufficiency. The nadir creatinine value <0.4mg/dL was associated with CKD only in 7,5% of patients. Both markers higher than 0.85% were correlated with 100% progression to renal insufficiency.

They can guide the clinicians in establishing proper follow-up protocols and early parental guidance. However, other factors can lead to a poor renal outcome. Multiple urinary infections, untreated bladder-valve syndrome, co-existence of ureteral dilatation (due to vesicoureteral reflux or to ureterovesical junction stenosis) are factors that can contribute individually to chronic kidney disease development.

**Conflict of interests**: no conflict

**References**

1. W. DeFoor, C. Clark, E. Jackson, P. Reddy, E. Minevich, C. Sheldon, "Risk factors for end stage renal disease in children with posterior urethral valves". J Urol 2008;180(4 Suppl.):1705e8. Discussion 1708.
2. P. Yohannes, M. Hannah, "Current trends in the management of posterior urethral valves in the pediatric population". Urology 2002;60(6):947-53.
3. M.S. Ansari, A. Gulia, A. Srivastava, R. Kapoor, "Risk factors for progression to end-stage renal disease in children with posterior urethral valves". J Pediatr Urol 2010;6(3):261-4.
4. R. Coleman, T. King, C.D. Nicoara, M. Bader, L. McCarthy, H. Chandran, "Nadir creatinine in posterior urethral valves: How high is low enough? Journal of pediatric urology. 2015;11(6):356.1-5.
5. R. Coleman, T. King, C.D. Nicoara, M. Bader, L. McCarthy, H. Chandran, "Combined creatinine velocity and nadir creatinine: A reliable predictor of renal outcome in neonatally diagnosed posterior urethral valves". Journal of pediatric urology. 2015;11(4):214.1-3.
6. H.F. Parkhouse, C.R. Woodhouse, "Long-term status of patients with posterior urethral valves". Urol Clin North Am 1990;17(2):373-8.

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# AN INNOVATIVE APPROACH TO TREAT EARLY CHILDHOOD CARIES (ECC) USING SILVER DIAMINE FLOURIDE – A CASE REPORT

**Mălina Popa[1,2], Nicoleta Nikolajevic-Stoican[1], Simina Boia[3], Eugen Radu Boia[4], Magda Mihaela Luca[1,2]**

**Abstract**

Dental decay affects 4-86% of preschoolers (temporary dentition), and regarding mixed and permanent dentition, the percentage of affected children is between 27-86%. Caries lesions of the temporary teeth is the main dental problem that the preschooler encounters, a problem that affects to some extent the permanent dentition, with repercussions on the development of the stomatognathic system. The use of silver diamine fluoride (SDF), in dental treatment of Early Chilhood Caries (ECC) has been drawing increasing attention cause to its antimicrobial effect on the species Streptococcus Mutans, Actinomyces Naeslundii and Lactobacillus Acidophilus, which are the pathogens most commonly associated with both the onset and the progression of caries, being usually discovered on the surface and in the depth of the lesion. A case report of a 4 years-old female patient suffering of SECC is presented with the application of SDF and glass-ionomer cement restauration showing advantages as carious lesions arrest, improved esthetic appearance avoiding early teeth loss.

**Keywords:** SDF, ECC, SECC, conservative dentistry

## Introduction

In the century of speed, in which dentistry has become less and less invasive and pain control is becoming more effective, our younger patients are still struggling with the fear of dentist and the dental instruments. The desire to alleviate these apprehensions and to eliminate from the treatment the most feared factors for children, namely the rotating instrument, while maintaining a quality therapeutic act, required the replacement of conventional methods of treating carious lesions with less frightening procedures for the pacients.

Dental decay affects 4-86% of preschoolers (temporary dentition), and regarding mixed and permanent dentition, the percentage of affected children is between 27-86%. [1]. Caries lesions of the temporary teeth is the main dental problem that the preschooler encounters, a problem that affects to some extent the permanent dentition, with repercussions on the development of the stomatognathic system. In this context we note Early Childhood Caries (ECC) but especially Severe Early Childhood Caries (SECC), both types being caused by demineralization of dental structures due to bacterial biofilm [2]. The terms ECC and SECC have been defined by the National Institute of Dental and Craniofacial Research (NIDCR) [3] as:

- It is considered to be ECC when there is one or more carious lesions, with or without the presence of cavities, missing teeth due to caries complications or restorations on the buccal surface of temporary teeth in children up to 6 years of age, or younger. Any rough carious surface present on the teeth in children under 3 years of age is an indicator of SECC;
- SECC refers to children aged 1 to 5 years who have one or more acute or rampant carious lesions, missing teeth due to caries complications or restaorations on the buccal surface.

Silver diamine fluoride (SDF) is a substance based on silver and fluoride that influences the development of carious lesions. The mechanism of action is based on the bactericidal properties of silver that disrupt the cariogenic bacteria and stop the demineralization and degradation of collagen, the process not being fully clarified. Silver-based preparations have a long history in dentistry due to their antimicrobial properties, and its association with fluoride has led to the hypothesis that the solution has the ability to stop the development of carious lesions and also prevent the appearance of new lesions. SDF can also be used in the treatment of dental hypersensitivity [4].

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SDF is a colourless liquid with a pH value around 10, that has an antimicrobial effect on the species Streptococcus Mutans, Actinomyces Naeslundii and Lactobacillus Acidophilus, which are the pathogens most commonly associated with both the onset and the progression of caries, being usually discovered on the surface and in the depth of the lesion. In this sense, fluoride and silver ions contained in the SDF solution have an inhibitory effect in the formation of cariogenic biofilms, binding to enzymes that influence carbohydrate metabolism and sugar absorption, but also through the three antimicrobial effects of silver: destruction of the bacterial cell wall, inhibition of enzymatic processes and replication of bacterial DNA. The most frequently used SDF concentration was 38% but there are studies that mention concentrations of 30% or 12%, the best results being obtained with SDF solutions in the highest concentration. SDF 38% contains 44,800 ppm fluoride, being the highest concentration allowed for dental use, building chemical reactions with hydroxyapatite and forms the insoluble fluoroapatite and some silver metal nanoparticles that are attached to hydroxyapatite crystals, with an inhibitory role on the development of cariogenic bacteria, which is supposed to result in the ability of SDF to stop caries without the need to remove the affected structure, placing the application technique in the class of non-invasive methods of caries assessment [5].

**Case report**

We present the case of an uncooperative 4 years-old female child with Severe Early Childhood Caries. After obtaining informed written consent from the parents, photos of the case were taken. Intra-oral examination revealed the presence of multiple carious lesions on teeth 51, 52, 61, 62, 74-disto-occlusal lesion, 84-disto-occlusal lesion (Fig. 1). After brushing the teeth, the teeth were isolated with cotton rolls and saliva ejector to ensure a dry working environment, to prevent dilution of the SDF, commercial product Advantage Arrest with a 38% solution, and to facilitate deep penetration at an optimal concentration. During the 60 seconds in which the SDF solution infiltrates the carious lesion, the patient's attention was distracted with various age-specific jokes and questions to avoid the situation when the child gets bored and becomes agitated or wants to explore the lesion with the tongue, thus compromising the success of treatment.

After the time of action of the material, the carious lesion acquires a black color, being an indicator for the effectiveness of the antimicrobial agent and is given by the silver oxide that binds to the denatured collagen from caries, demineralized tissues or soft tissues (Fig. 2).

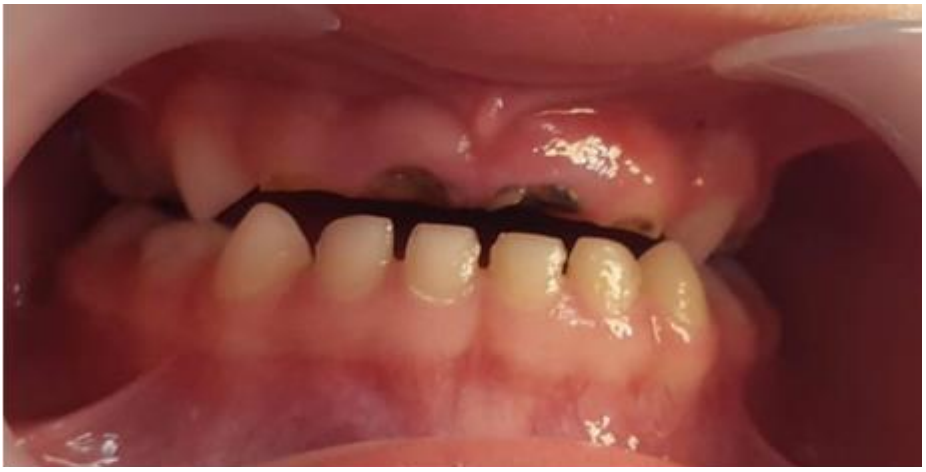

Fig.1. Intra-oral examination reveals the presence of Sever Early Childhood Caries.

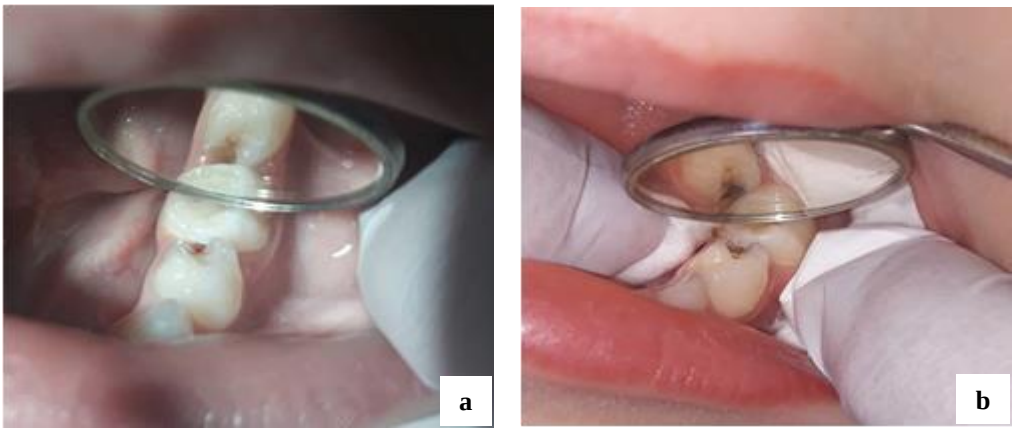


Fig.2 a,b. Initial and final appearance of the disto-occlusal carious lesion on tooth 74.

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Black staining occurs after the SDF solution has acted and is an indicator that the lesion has been arrested. Glass-ionomer cement was applied on the arrested caries to improve the esthetic result and to have a space maintainer effect, considering the proximal placement of the carious lesions (Fig.3).

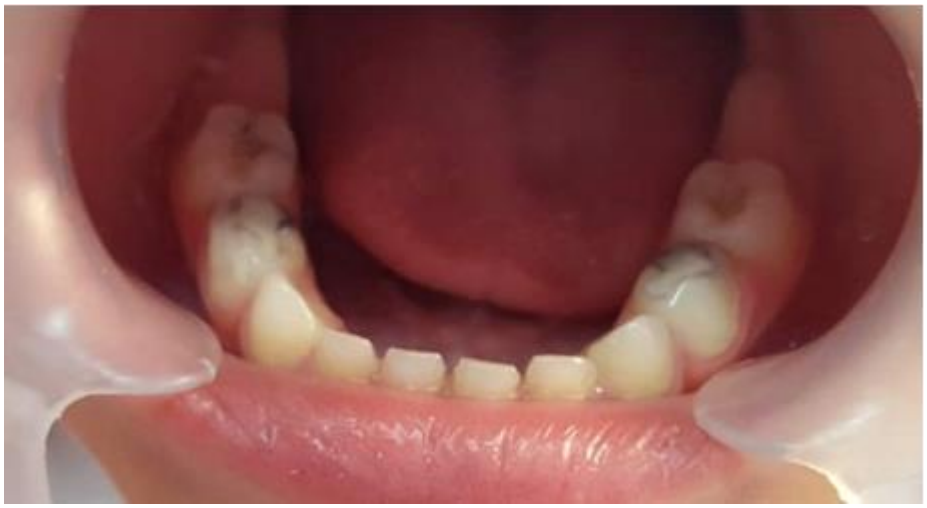

Fig. 3. Final aspect of the arrested and restaurated carious lesions on the mandibular first primary molars.

**Discussion**

Arresting carious lesions using SDF solution has a number of advantages given both the simplicity and velocity of clinical procedures, important features that must be taken into account when discussing paediatric patients. A number of features of interest to the medical staff, represented by the elimination of rotary instruments that in the conventional method of treatment can cause pain and anxiety are replaced by a simple application of the SDF liquid. Achieving a complete treatment (treating the carious lesion and applying a final restauration) in such a short time, is a benefit in paedodontic practice because it eliminates all the inconveniences caused by classical treatments with chronophagous stages, rotary handpieces or even with handtools where auxiliary chelators are used in the chemo-mechanical method [6].

Another advantage is the elimination of difficulties of understanding the commands needed to give to the paediatric patient in the situation of a classic treatment of longer duration, but also the elimination of the stages of preparation, etching, photopolymerization of adhesive systems and photopolymerization of the restauration in layers, all of which require special effort from the patient, and the isolation must be optimal. In comparison, the SDF application is easier, its needed only to isolate the tissues to avoid staining and a soaked in solution micro-brush [7].

SDF treatment eliminates any risk of cross-infection, the 0.1 ml doses being disposable, with no possibility of reconnecting the cap and reusing, and also the other utensils required for the application protocol are disposable (applicators, bibs, saliva ejectors, cotton rolls, single-dose glass-ionomer and even disposable consultation kits) [8].

According to the clinical records from the literature, in cases where the application of SDF is not followed by glass-ionomer coverage, applications will be continued twice a year until the affected tooth is exfoliated [8].

Another discussion that arises is about the side effects associated with the use of SDF, because the reviews in the literature do not reveal data on long-term use of the solution, blackening of the affected dental areas, currently representing the certain known adverse effect [9].

**Conclusion**

The short working time, the comfort of the patient, the simplicity of the technique of use and the complete elimination of the rotary instrumentation, are the clear advantages for which the SDF solution has gained its position among the favorite materials of paediatric dentists. It has shown to be an effective agent in preventing new caries and arresting existing dentine caries.

Compared to other techniques applicable to carious lesions on temporary teeth, arresting lesions with SDF is by far the most advantageous from a financial point of view, the investment being minimal, requiring only the purchase of the product, other special materials not being necessary.
Following the application of the SDF solution to arrest carious lesions, the demonstration of the technique and obtaining valid results was a success, and the next step towards evolution will be to improve the aesthetic effect more than is currently done with glass-ionomer cement restauration.

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**References**


1. Wyne AH. Caries Prevalence, Severity, and Pattern in Preschool Children. The Journal of Contemporary Dental Practice. 2008.
2. American Academy of Pediatric Dentistry, Definition of Early Childhood Caries, 2008
3. Dye, Bruce & Hsu, Kuei-Ling & Afful, Joseph. (2015). Prevalence and Measurement of Dental Caries in Young Children. Pediatric dentistry. 37. 200-16.
4. Mei ML, Ito L, Cao Y et al. An ex vivo study of arrested primary teeth caries with silver diamine fluoride therapy. J Dent 2014 42: 395–402
5. Irene Shuping Zaho, Sherry S.G, Noriko H, Michael Francis B, Duangporn Duangthip, May Ley Mey, Edward Chin-Man Lo, Chun-Hung Chu, Mechanism of Silver Diamine Fluoride of arresting caries: a literature review, International Dental Journal, 2018.
6. Chu, C. H., and E. C. M. Lo. "Promoting caries arrest in children with silver diamine fluoride: a review." Oral health & preventive dentistry 6.4 (2008).
7. Mei, May L., E. C. Lo, and Chun-Hung Chu. "Clinical use of silver diamine fluoride in dental treatment." Compend Contin Educ Dent 37.2 (2016): 93-98.
8. Horst, Jeremy A., et al. "UCSF protocol for caries arrest using silver diamine fluoride: rationale, indications, and consent." Journal of the California Dental Association 44.1 (2016): 16.
9. Rosenblatt, A., T. C. M. Stamford, and Richard Niederman. "Silver diamine fluoride: a caries “silver-fluoride bullet”." Journal of dental research 88.2 (2009): 116-125.



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# SPACE CONTROL IN MIXED DENTITION - SPACE MAINTAINERS

**Magda-Mihaela Luca[1,2], Ștefania Dinu[1,2], Nicoleta Nikolajevic-Stoican[2], Simina Boia[3], Eugen-Radu Boia[4], Bianca Dragoș[5], Mălina Popa[1,2]**

**Abstract**

Maintaining the child's oral cavity in optimal health by preserving the morpho-functional integrity of primary teeth, given the influence they have on the growth and development of the stomatognathic system is the duty and responsibility of the pedodontist. In addition to prevention, increased attention should be granted to the space control in case of early loss of primary teeth in the support area, recommending the use of space maintainers until the eruption of permanent successors, to intercept the appearance of future anomalies.

**Keywords:** premature loss, space maintainers, interception

**Introduction**

Early loss of primary molars affects millions of patients worldwide with a significant negative impact on somatic growth and development of the stomatognathic system, social function and quality of life. Primary dentition plays an essential role in the healthy growth of the child influencing the development of the orofacial system functions. Exfoliation of primary teeth is a physiological process and is closely related to the development of successive permanent teeth. When this process is interrupted by the premature loss of primary molars due to complications of carious lesions, malocclusions occur resulting in disruption of the integrity of the dental arch that negatively affects the eruption process and proper alignment of permanent teeth [1]. The lack of space through the premature loss of teeth, especially of the primary molars, causes shifting of adjacent teeth into the extraction gap resulting abnormal axial inclination, dental crowding, ectopias, supraalveolodontia of antagonist teeth, mesialized eruption of the first permanent molar. Whenever early loss of primary teeth affects the anterior area there are physiognomic disorders with the appearance of bad oral habits of interposing the tongue or objects [2].

The main factors that lead to the premature loss of primary teeth are trauma and carious lesions complicated with endodontic pathology which often due to the increased permeability of the pulp chamber floor by the presence of furcation canals is usually the cause of furcation lesions, which requires early extraction of these teeth [3].

The best way to avoid these problems is to preserve the primary teeth on the arch until they are exfoliated. There are data in the literature that claim that the primary tooth is the best space maintainer [4]. However, there are currently many children with such problems. Therefore, to prevent these undesired effects, it is mandatory to use space maintainers until the eruption of the permanent successors [5].

The stainless-steel band and loop space maintainers are commonly used in pediatric dentistry, as they are well-tolerated by children and the realisation technique is very easy [6].

With the rapid progress of 3D scanning, printing and milling technology in the medical field that has grown in recent times, studies have been performed in which the application of this technology in pediatric dentistry has been attempted in order to obtain aesthetic space maintainers or with better clinical adaptation [7].

**Materials and Methods**

Space maintainers are medical devices whose main role is to prevent the loss of space needed for the eruption of permanent teeth, by preventing the mesialization of first permanent molars [8]. These devices can be classified according to several criteria, according to the mode of aggregation they can be fixed, removable and mobile according to their function they can be active or passive.

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Most often these devices are made of metal alloys and acrylate, but but in order to improve the aesthetic appearance has also tried the use of physiognomic materials such as resin-reinforced fiberglass, thermoplastic resins, zirconia, polyetheretherketone [9-11]. Usually these devices are made in the dental laboratory by the classic melting-casting technique or using an orthodontic band with a soldered wire by a welding machine with an electric arch. It can also be designed by laser sintering, thermoforming and milling. The choice of the type of space maintainer is the responsability of the pedodontist depending on the clinical situation, which requires to establish an individualized treatment plan.

Types of space maintainers used in the Pedodontics clinic - University of Medicine and Pharmacy Victor BabeșTimișoara [12]:

*Case 1* - A 9-year-old patient with early loss of 6.3, 6.4, 6.5, 7.5, 8.4 following evolutionary decays associated with pulpal complications presented for treatment accusing dental pain. Associated with dental therapy, a first phase was chosen for the application of a passive Band and loop space maintainer made by welding a loop on an orthodontic band cemented with CIS on 3.6 (figure 1).

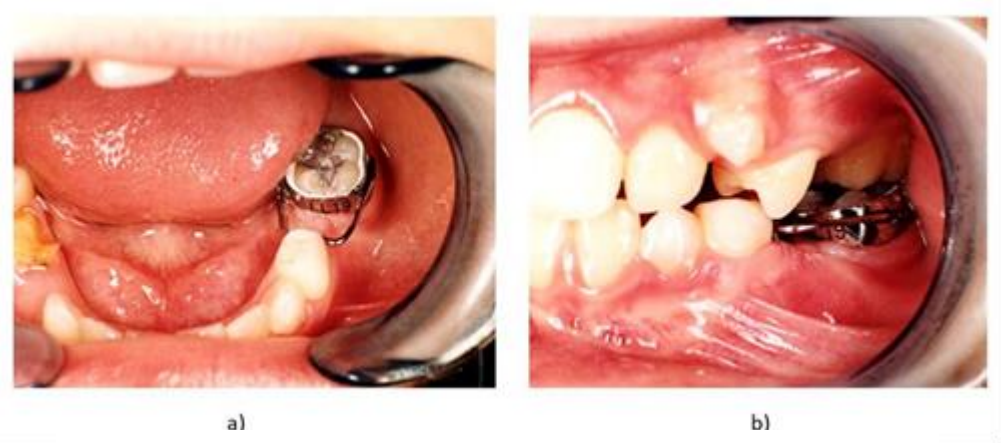


Fig. 1. a) the clinical aspect of the space maintainer; b) the device in occlusion.

*Case 2* - 8-year-old patient with early loss of primary molars 6.4, 6.5, following pulpal diseases presented for treatment. Following the analysis of the complementary exams and the exploratory milling, it was found that both 6.4 and 6.5 are no longer restorable. After performing the extractions, it was decided to apply a passive band and loop type space maintainer with long arms welded on an orthodontic band (figure 2).

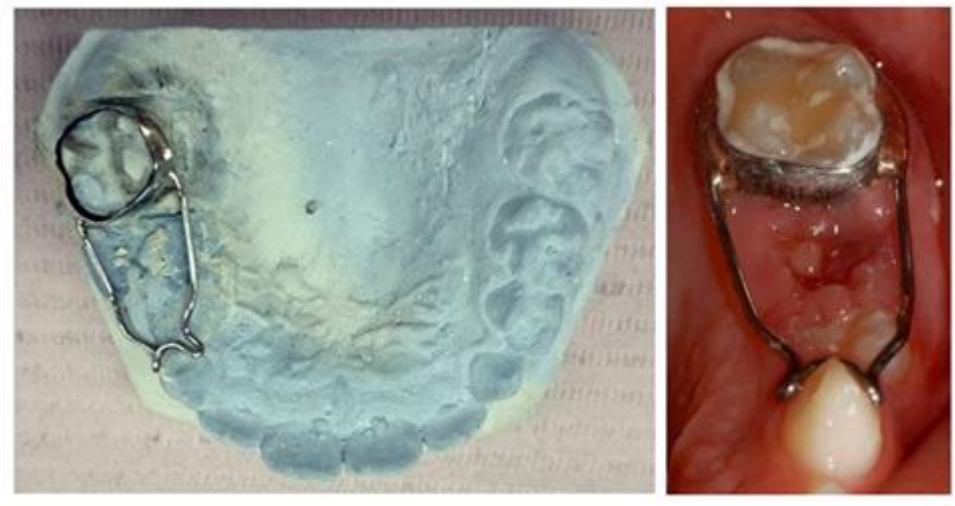

Fig. 2 Band and loop space maintainer – working cast and clinical appearance.

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*Case 3* - 8-year-old patient, following the clinical examination, the presence of a 7.4 radicular rest and multiple carious processes was found. Given the need to apply a space maintainer, it was decided to restore 7.5 with CIS and apply a pedodontic crown. Thus, for the manufacturing of the space maintainer, the orthodontic band was replaced with a pedodontic crown on which a loop was welded (figure 3).

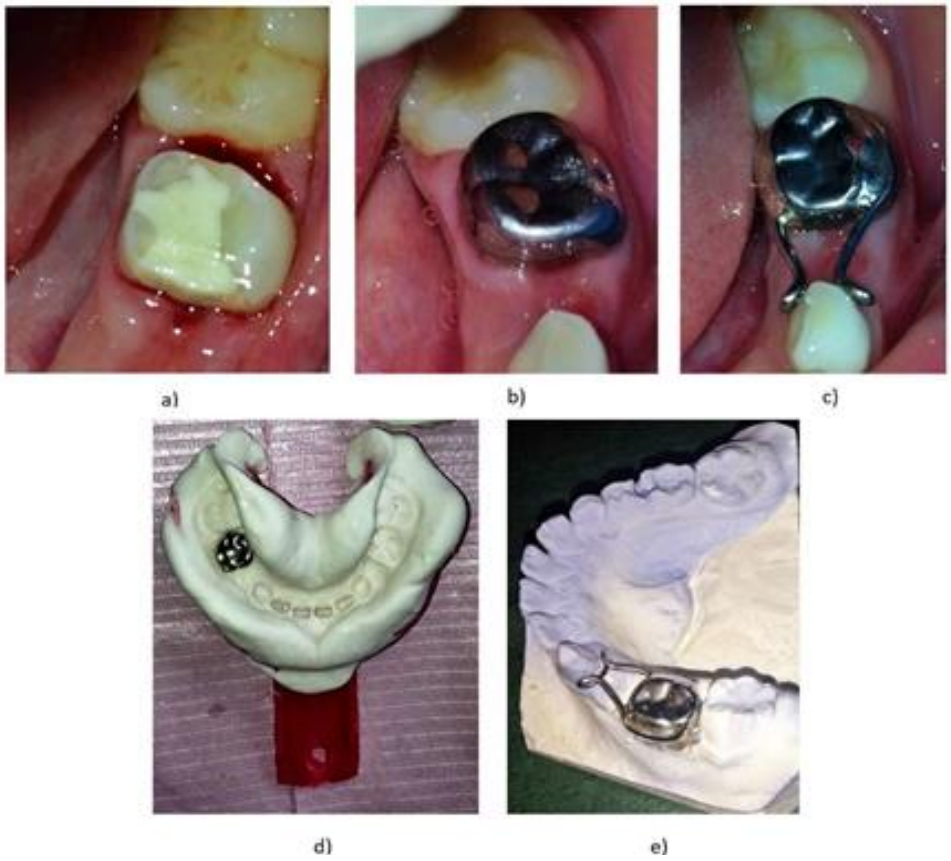


Fig. 3. Crown and loop - a) the aspect of the preparation of the primary tooth for the application of the steel pedodontic crown, b) the intraoral aspect of the pedodontic crown, c) the intraoral clinical aspect of the space maintainer, d) the alginate impression for making the space maintainer, e) the aspect on the working cast of the space maintainer.

*Case 4* - Patient with mixed dentition, with early bilateral loss of primary molars at the upper arch 5.4, 5.5, 6.4, 6.5 following multiple dental lesions, the patient having an increased cariogenic index. It was chosen for the application of a Nance device (figure 4), it is provided with an acrylic button that fits intimately in the anterior area of the hard palate and a metal component that is welded on orthodontic bands applied to the first permanent upper molars. This device prevents mesial migration of the first permanent molars.

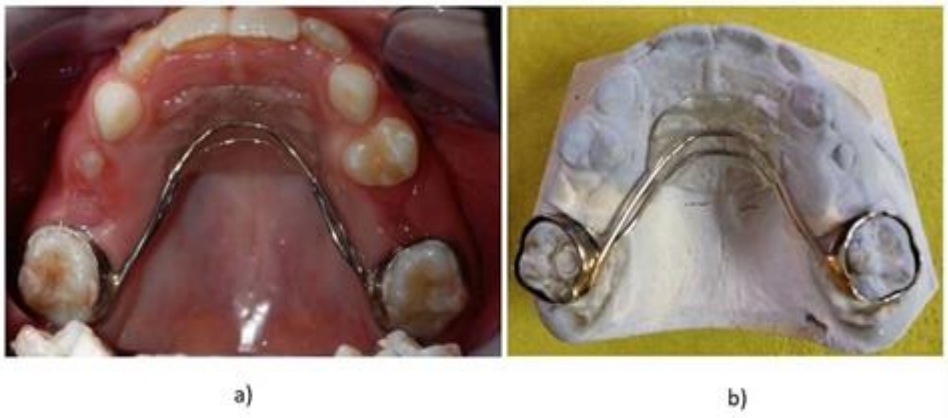


Fig. 4. Nance device: a) intraoral aspect; b) the aspect of the working cast.

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*Case 5* - Patient with mixed dentition, aged 8 years, following the clinical examination, it was found that the lower primary molars could not be restored, the patient requiring multiple extractions. After performing the dental extractions (7.4, 7.5, 8.4, 8.5) in order to keep the space necessary for the eruption of the permanent successors, it was decided to apply a fixed lingual arch (figure 5).

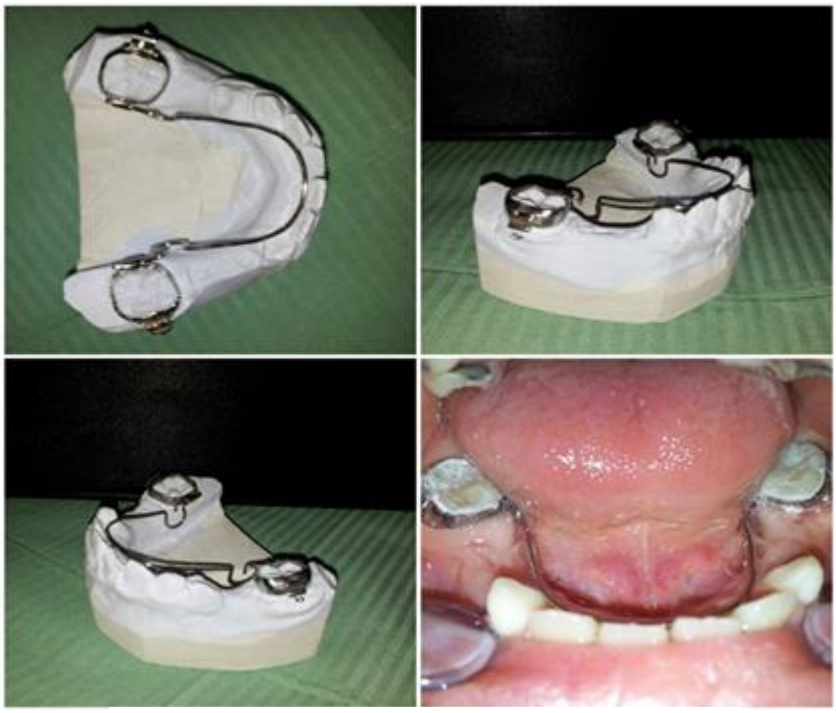

Fig. 5. Lingual arch - intraoral and working cast aspect.

*Case 6* - Patient with major space loss and dental crowding presented to the clinic for treatment. To correct the compression in the molar region, a removable transpalatal bar (figure 6) was applied, the patient subsequently requiring an orthodontic treatment for the creation of space and dental alignment with the establishment of neutral occlusal ratios.

Fig. 6. TPA – removable device.

*Case 7* - A 7-year-old patient with early loss of primary molars in the lower arch against the background of carious disease, the patient with a history of bottle caries, presented to the Pedodontic Clinic accusing eruption disorders. A lingual removable space maintainer was applied to the patient, type – lingual appliance (figure 7).

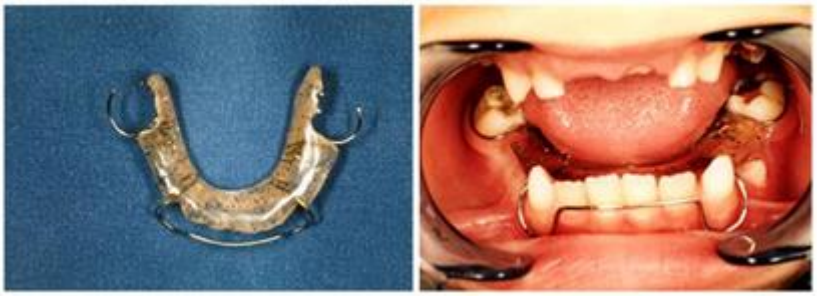

Fig.7. Lingual appliance provided with acrylate space maintainer.

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*Case 8* - 8 years-old-pacient, following the clinical examination, it was found the absence from the arch of 7.5, 7.4, 8.4 following dental extractions performed in the past. Due to the incomplete eruption of the lower incisor group in order not to interfere with the dental eruption process, it was decided to apply a lingual space maintainer (figure 8).

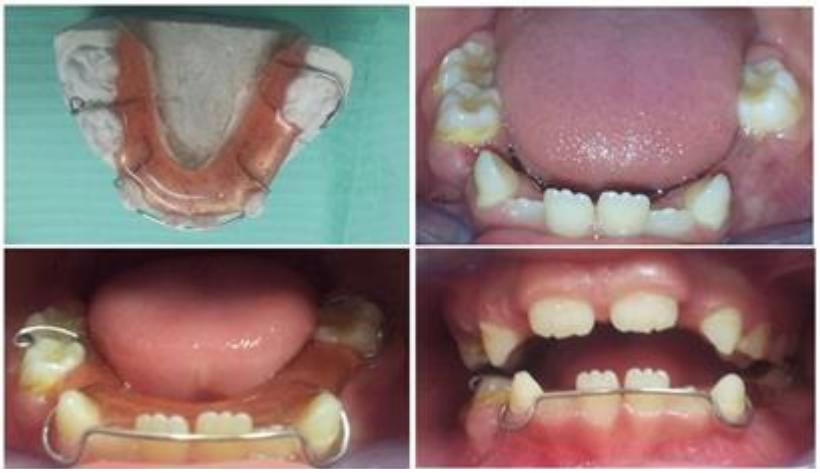

Fig. 8. Lingual appliance provided with anchoring elements, vestibular arch and acrylate space maintainer.

*Case 9* – 4 year-old patient, with early loss of upper central incisors 5.1, 6.1, following a trauma was rehabilitated by applying a palatal appliance provided with acrylic teeth, artificial gums and hooks in the lateral area for anchoring (figure 9). This therapeutic solution was chosen to restore both the aesthetic function and to improve the phonation.

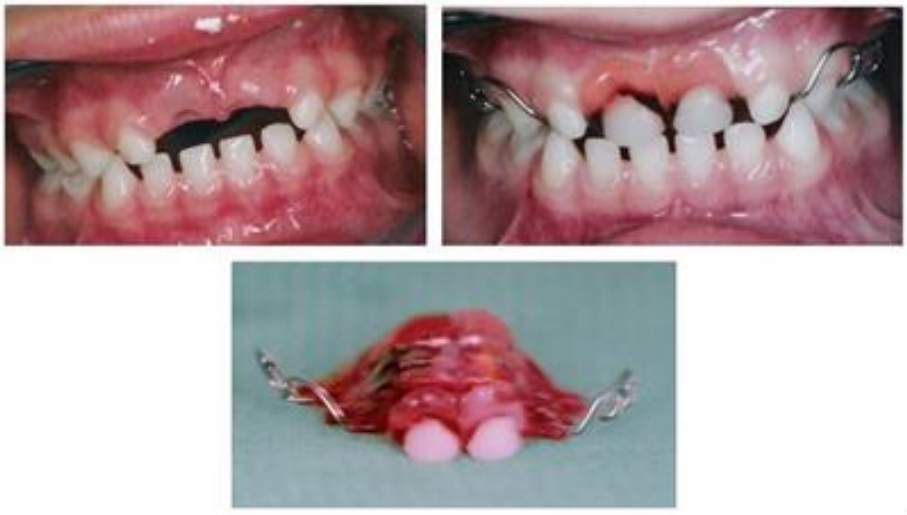

Fig. 9. Palatal appliance provided with dental elements to restore the aesthetic function of the child.

**Results**

Following periodic inspections, it has been observed that treatment with these devices ensures effective control of the space. These devices have an optimal dimensional stability and do not interfere with the eruption of permanent teeth but also have certain shortcomings such as the possibility of decementation of the orthodontic band or clogging of the loop under the action of masticatory forces.

In some cases where the Nance device has been applied, has been observed in the case of unilateral decementation and clogging of a band in the gingival groove an increase in pressure at the level of the acrylic button, which can cause damage to the palatal mucosa. Also, if there is an increased retention of bacterial plaque between the acrylic button and the mucosa, a local inflammation may occur which requires temporary decementation of the device until the remission of inflammatory phenomena.

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Fixed space maintainers need to be decementated every six months to apply fluorinated gels to the permanent primary molars to achieve caries prophylaxis.

Space maintainers with acrylate can generate an unpleasant odor due to the porosity of the material, if rigorous hygiene of both the oral cavity and these devices is not achieved.

**Discussion**

Arikan V et al., 2015, observed that both fixed and removable space maintainers are associated with the presence of a high number of microorganisms in the oral cavity, especially in patients with high bacterial plaque index. Candida has been found frequently in patients with removable space maintainers, while Enterococcus faecalis has been isolated from fixed devices [13].

Various space maintainers such as band and loop, crown and loop and lingual bar are regularly used in space management. Certain disadvantages, such as corrosion and fracture of the device have contributed to the development of more aesthetic and metal-free space maintainers, examples that include composite resin-reinforced fiberglass and the ceramic space maintainer made by CAD-CAM technique [14].

Bishara SE et al. and Agaoglu G et al., highlighted the fact that metal orthodontic devices, used in the oral cavity, corrode in the oral environment releasing both nickel and chromium [15,16]. Patients with allergic terrain should be monitored more often because there are studies with patients who have developed metal allergies in the form of gingivitis, burning sensation, gingival hyperplasia, numbness on the tongue edges caused mainly by nickel [17,18].

**Conclusions**

Regarding the interceptive therapy with space maintainers, the doctor must establish an individualized work protocol with alternatives of treatment because we are in mixed dentition where the exfoliation process of the primary teeth is active and an unforeseen situation can occur at any time. The space maintainers have an increased efficiency in the interception of the installation of dental anomalies with crowding, without interfering with the physiological processes of growth and development, respectively with the eruption of the permanent successors, being well tolerated by children.

**References**


1. Pawar BA. Maintenance of space by innovative three-dimensional-printed band and loop space maintainer. J Indian Soc Pedod Prev Dent 2019;37:205-8.
2. Watt E, Ahmad A, Adamji R, Katsimbali A, Ashley P, and Noar J. Space maintainers in the primary and mixed dentition – a clinical guide. British Dental Journal. 2018; 225(4): 293-8.
3. Demars-Fremault C, Pilipili Muhima C. [Furcation lesions in deciduous teeth] Actual Odontostomatol (Paris). 1991 Mar;45(173) 9-23. PMID: 1853749.
4. Setia V, Pandit IK, Srivastava N, Gugnani N, Sekhon HK. Space maintainers in dentistry: Past to present. J Clin Diagn Res 2013;7:2402-5
5. Holan G, Needleman HL. Premature loss of primary anterior teeth due to trauma--potential short- and long-term sequelae. Dent Traumatol. 2014 Apr;30(2):100-6. doi: 10.1111/edt.12081. Epub 2013 Oct 20. PMID: 24138100.
6. Vinothini V, Sanguida A, Selvabalaji A, Prathima GS, Kavitha M. Functional Band and Loop Space Maintainers in Children. Case Rep Dent. 2019;2019:4312049. Published 2019 Apr 24. doi:10.1155/2019/4312049
7. Sharma S, Goel S. 3D printing and its future in medical world. J Med Res Innov 2019;3:e000141
8. Singh, Pheiroijam Herojit & Naorem, Herojit & Chaoba, Thokchom & Debbarma, Nirmal. (2020). Modern concepts of space maintainers and space regainers: a review article.
9. Soni,H.K.,(2017).Application of CAD -CAM for Fabrication of Metal-Free Band and Loop Space Maintainer, 11(2), ZD14-ZD16. https://www.doi.org/10.7860/JCDR/2017/23459/9246
10. Guo, H., Wang, Y., Zhao, Y. et al. Computer-aided design of polyetheretherketone for application to removable pediatric space maintainers. BMC Oral Health 20, 201 (2020). https://doi.org/10.1186/s12903-020-01184-6
11. Ierardo G, Luzzi V, Lesti M, Vozza I, Brugnoletti O, Polimeni A, Bossù M. Peek polymer in orthodontics: A pilot study on children. J Clin Exp Dent. 2017 Oct 1;9(10):e1271-e1275. doi: 10.4317/jced.54010. PMID: 29167720; PMCID: PMC5694159.
12. Space Management in Primary and Mixed Dentition, Timișoara 2019, ISBN 978-606-786-144-0.
13. Arikan V, Kizilci E, Ozalp N, Ozcelik B. Effects of Fixed and Removable Space Maintainers on Plaque Accumulation, Periodontal Health, Candidal and Enterococcus Faecalis Carriage. Med Princ Pract. 2015;24(4):311-7. doi: 10.1159/000430787. Epub 2015 Jun 4. PMID: 26044443; PMCID: PMC5588238.
14. Tuloglu N, Bayrak S, Tunc ES. Different clinical applications of bondable reinforcement ribbond in pediatric dentistry. Eur J Dent 2009;3:329-34
15. Bishara SE, Barrett RD, Selim MI. Biodegradation of orthodontic appliances. Part II. Changes in the blood level of nickel. Am J Orthod Dentofacial Orthop. 1993;103(2):115–19.

16. Ağaoğlu G, Arun T, Izgi B, Yarat A. Nickel and chromium levels in the saliva and serum of patients with fixed orthodontic appliances. Angle Orthod. 2001;71(5):375–79.
17. Kulkarni P, Agrawal S, Bansal A, Jain A, Tiwari U, Anand A. Assessment of nickel release from various dental appliances used routinely in paediatric dentistry. Indian J Dent. 2016;7:81–85.
18. Noble J, Ahing SI, Karaiskos NE, Wiltshire WA. Nickel allergy and orthodontics, a review and report of two cases. Br Dent J. 2008;204(6):297–300.

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## MANUSCRIPT REQUIREMENTS

The manuscript must be in English, typed single space, one column on A4 paper, with margins: top – 3 cm, bottom – 2, 26 cm, left – 1, 5 cm, right – 1,7cm. A 10-point font Times New Roman is required.

The article should be organized in the following format: Title, Names of all authors (first name initial, surname), Names of institutions in which work was done (use the Arabic numerals, superscript), Abstract, Keywords, Text (Introduction, Purpose, Materials and Methods, Results, Discussions and/or Conclusions), References, and first author's correspondence address.