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CONTENTS

ROBOT SURGERY IN CHILDREN: WHERE WE STAND AND WHERE WE AIM

Boia ES[1,2], Popoiu MC[1,2], Iacob RE[1,2], David VL[1,2]

Abstract

Roboticsis the most advanced technology used in surgery nowadays. The international trend is towards the development of pediatric robotic surgery programs but as per novel technologies, there are still a lot of issues that must be solved. This study focused on the status of robotic surgery in children and over the issues that has to be address in order to make a pediatric robotic program feasible

Key words: robotic pediatric surgery, minimal invasive surgery, children

Introduction

First robotic minimally invasive surgery in children was reported in April 2001 (1). Since than an incising range of surgical procedures were performed in children, pediatric urological procedures being prevalent. Najmaldin et all 2007, Mehan et all, reported first large series. al 2008 (2, 3). Cundy et al. published a comprehensive meta-analysis of the robotic procedures in children in 2013 after a decade of robotic surgery in children (4). Until that date, they found over 130 studies and over 2300 pediatric robotic surgery procedures including genitourinary, gastrointestinal and thoracic procedures (4). Nowadays the international trend is towards the development of pediatric robotic surgery programs but as per novel technologies, there are still a lot of issues that must be solved.

This study focused on the status of robotic surgery in children and over the issues that has to be address in order to make a pediatric robotic program feasible.

The Equipment:

First robotic surgical systems were developed during the Nineties by two independent programs: Intuitive Surgical developing the daVinci System and Computer Motion developing the Zeus System. At the being of the 21st century, the two companies merged. While Zeus program was discontinued in 2003, the da Vinci program was approved for human use by the FDA in 2001 and was until recently the only robotic surgical system available on the market. Even though several models of the DaVinci System were developed since its introduction there are no special models designed for pediatric use. Even the current (XI model) has been a major improvement and has clear benefits over the former SI model (5); there are no specific futures or specially designed instruments for pediatric use (6). The system is composed of surgeon console, a vision cart and a patient cart. There are available 300 and 00 8 mm endoscope and a variety of 8 mm diameter surgical instruments. The major advantages of the robotic equipment over laparoscopy are the better visualization and magnification, tremor filtering and the instruments 7 degrees of motion range (7, 8, 9). Not to forget the improvement over surgeons comfort and fatigue during procedures (10). There drawbacks in pediatric surgery are mainly related to the size of the endoscope and the trocars, procedures in children less than 10 kg being currently very difficult, even impossible to be performed.

Surgical team:

Even though the basic principles of the surgery does apply in robotic surgery as well, the transition from open or laparoscopic surgery towards robotic surgery requires the acquisition of specific knowledge and skills. The surgical team includes a console surgeon, a scrub in assistant, a scrub in nurse and an anesthetist. Intuitive Surgical offer at the being of any robotic surgical program a training pathway for the console surgeon and the scrub in assistant that includes online training and certification, simulator training, clinical observershipp in a medical center with experience in pediatric robotic surgery followed by certification for both surgeons in a designated training center. The first procedures are to be made with the assistance of a proctor and for the following 90 days, the surgical team has to perform at least nine procedures. Learning curve has not yet been clearly defined most of the authors stating that 30 – 40 procedures are required to overpass it (11). It seems to be influenced by factors like proctoring, previous experience with minimal invasive surgery or adequate selection of cases to begin with (11, 12, 13). Strategies to reduce this learning curve are proposed. It has been proved that training in virtual reality increase the surgical skills of the surgeon and reduce the learning curve (14).

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Costs:

The main issue in making feasible a robotic surgery program are the costs. Compared to conventional and laparoscopic surgery there are higher acquisition costs for the equipment, instruments and consumables, high maintenance costs for the equipment and higher cost for anesthesia and for the use of operating room (15, 16, 17). Hospital stay and pain medication related cost were lower for the robotic surgery (15, 16, 17). Altogether the cost/ procedure is significantly higher for robotic procedures versus conventional and laparoscopic surgery and from an economical point of view, robotic surgery "may not make the cut" in pediatric surgery (18). The current debate is over the benefits of the robotic approach justify the higher costs. Unfortunately, this cost/ effectiveness has not been proved only for a few procedures like Pyeloplasty pelvic- ureteric junction obstruction (19, 20). This is mainly due to relatively small cohort of cases treated by the means of robotic surgery in the majority of pediatric medical conditions. However, there are a number of strategies to reduce the cost of robotic surgery in children and focusing on reducing the complication rate, reducing the OR time and the cost of anesthesia, reducing the maintenance cost/ procedure by increasing the number of procedures/ year (21). WE hope that in the nearby future competition on the producer market will increase and which will inevitably lead to lower prices for the consumables..

Selecting the patients:

Virtually all the procedures that could previously be done laparoscopically can be performed by means of robotic surgery. However, two main factors has to be considered when selecting the cases for robotic surgery:

1. Technical limitations of the equipment. The distance between the ports has to be at least 8 cm in order to avoid collision of the robotic arms. In addition, there has to be sufficient working space for the instruments inside the peritoneal or thoracic cavity considering that the current instruments available have 8 mm in diameter and the intra-abdominal section is slightly longer. This means that with current technology robotic surgery can be safely performed in children above 10 Kg and with a pubo-xyphoid distance of minimum 16 cm (3, 22). We hope that current technology will be upgraded soon and these issues can be overpass.
2. The pathological condition and the ability of the surgical team to perform the required surgical procedure. The international trend in pediatric robotic surgery was to perform surgical procedures with the robot only in complicate, very difficult cases mainly due to the high cost/ procedure. The common cases like cholecystectomy, fundoplication were left for cheaper conventional laparoscopic surgery (3). Unfortunately, this approach has a major drawback: there are simply insufficient cases for the surgical team to get sufficient experience. In addition, the potential of complication is higher for difficult cases. So probably, a safe approach at the beginning would be to perform also some easy cases as well as difficult procedures in order to get the sufficient experience and to consolidate the team (3).

Ultimately, the goal shall be patient's best interest and safety. The debate over advantages of the robotic surgery over laparoscopy or open surgery is still in progress mainly because of the lack of large series and meticulous comparative studies. For instance, there is evidence that robotic pyeloplasty is superior to laparoscopy or open surgery (18, 19, 20, 23, 24).

Anesthesia:

Robotic surgery requires general anesthesia with tracheal intubation (25). Special consideration to a large number of physiological modifications related to CO2 insufflation into the abdominal/ thoracic cavity, cardio-respiratory dynamics due to diaphragm elevation, increase duration of the procedure and the patient's position on the operating table should be consider (26). A systematic preanesthetic exam should be meticulous conducted over the renal, cardiac, respiratory and neurologic systems. Contraindication are related to cardiac malformations or impaired function (EF < 60%), Respiratory disease, hypertension, coagulopathy (25). Anesthetic technique usually involves intravenously induction and then carried out inhalatory (25). Adequate analgesia and muscle-relaxant must be provided. Nitrous Oxyde must be avoided due to gaseous distension effect over the intestine (26). Special attention should be considered over the position of patient and access to the airway, catheters and other monitoring devices during surgery. Due to the large space required by the patient cart and arms, there is limited access around the patient (25). In addition, changes in body temperature must be watched given the possibility of malignant hyperthermia reported in minimal invasive surgery (27). Monitoring of the following parameters is required: ECG, non-invasive blood pressure, pulse oximetry, capnography, inspiratory peak airway pressure, inspiratory oxygen, diuresis (25).

Operating room setup and patient positioning:

All three components of the da Vinci robot are large pieces of equipment with patient cart being almost 2 m tall and 900 kg in weight. The OR must accommodate also the anesthetic equipment, the table for instruments and there shall be enough space for the medical personnel to work around the patient. So first of all OR must be cleared from the unnecessary equipment and the OR table shall be carefully positioned before surgery. In addition, when the setup is done, other team should keep in mind that the robotic arms must have adequate clearance in regard not only to the patient but also to the OR table and in relation to the other robotic arms (28). Patient positioning on the table is directly related to the surgical procedure and usually extreme positions are used in order to obtain the maximum exposure to the surgical site: Trendelenburg or reverse Trendelenburg up to 200, lateral position (6). Trocar placement is usually done before putting the patient in the definitive position. As per XI model, the trocars are place in a quasi-straight line. After placement of the trocar, the

patient is rotated in the desired position and the patient cart is docked. No further movement of the patient/ table is allowed afterward (6).

Surgical procedure:

As stated above, virtually all procedures could be perform by the means of robotic surgery and no clear contraindication exists except for the general contraindications of minimal invasive surgery. The debate over some procedures have greater benefits for the patients when done robotically over laparoscopy is still in course. There is clear evidence that in certain procedures, especially in pediatric urology, the robotic approach is better (23). For other procedures the benefits of the robotic approach is not yet demonstrated, but what can be stated is that the results are at least as good as with laparoscopy (29). There is a wide range of surgical procedures that have be done with the help of the surgical robot in children (Table 1).

There is also the perspective of non-scheduled robotic procedures in children (31). Procedures like Meckel diverticulum excision, intestinal occlusion even esophageal atresia or duodenal atresia could be performed in selected case in less than 24h after admission (31). This possibility would significantly expand the use of the robotic in pediatric surgery.

Gastro-intestinal	Cholecystectomy	Ileocecectomy
	Fundoplication	Right colectomy
	Heller myotomy	Sigmoid colectomy
	Pyloroplasty	Total proctocolectomy with pull-through
	Adrenalectomy	Kasai portoenterostomy
	Neuroblastoma	Choledochal cyst
	Splenectomy	Duodenal anomalies
	Splenic cyst	Duodenal atresia
	Small bowel resection	Duodenal web
	Crohn's	Annular pancreas
	Enteric duplication	Ladd's procedure
	Meckel's diverticulum	Jejunal or ileal atresia
	Partial colon	Gastrotomy with foreign body retrieval
	Left colectomy	Congenital diaphragmatic hernia (Morgagni)
Genital	Ovarian cystectomy	Ovarian teratoma
Reno-urainary	Pyeloplasty	Mitrofanoff procedure
	Nephrectomy	Bladder neck reconstruction
	Hemi nephrectomy	Urethral diverticula
	Ureteral reimplantation	Urachal remnant
	Bladder diverticulectomy	Utricle
	Bladder augmentation	
Chest	Pulmonary resections	Tumors
	CCAM	Ganglioneuroma
	Pulmonary sequestration	Neuroblastoma
	Thymectomy	Ganglioneuroblastoma
	Cystic hygroma	Germ cell tumor
	Mediastinal masses	Teratoma
	Congenital anomalies	Esophageal atresia with tracheoesophageal fistula
	Bronchogenic cyst	Congenital diaphragmatic hernia (Bochdalek)
	Esophageal duplication	Eventration of the diaphragm

Table 1. Surgical procedures performed with the robot in children (3, 4, 28, 29, 30)

Discussions and conclusions:

Besides being the „trendy" new thing in pediatric surgery, the surgical robot is a step forward in the field of minimal invasive surgery. Almost all pediatric surgical operations have been performed successfully with the robot and most of the studies found that robotic surgery enables better vision, superior dissection and suturing skills, better dexterity and access to places hard to reach for the conventional surgery. Unfortunately, current robotic systems are not without drawbacks for pediatric surgery, with instrument size and high cost being the most cited ones. Market competition would probably drive medical companies into further development of this technology. For instance, the development and use of single port robotic surgery may overcome the limitation of port placement in small children (32). Several international centers are currently involved in the development and implementation of this technology in children. There are also a number of other robotic platforms under evaluation by the European Medicines Agency and FDA: flexible robotic arms ore dedicated robotic systems for ENT, brain or spine surgery, miniature in vivo robots (33). Undoubtedly the answer for Thomas P. Cundy's question "Adopt now, await or dismiss?" is: adopt (34). The future of surgery is in technology and robotic technology is promising new spectacular dawns.

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EMERGENCY ATTITUDE IN A CASE OF ANAPHYLACTIC SHOCK AT GRINTUSS ADMINISTATION IN A 4 MONTH OLD BABY

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Abstract

It was wanted to bring into the forefront a rare case encountered in a 4-month-old, potentially fatal at grintuss syrop administration. Anaphylactic shock is an immediate, brutal, dramatic, hypersensitivity reaction with hemodynamic collapse and respiratory failure after the entry into the body of any substance, especially protein that causes the release of chemical mediators. Recognizing anaphylactic shock and initiating emergency treatment can save the patient's life.

Key words: anaphylactic shock, sugar, grintuss

Introduction

Anaphylaxis is a generalized immunological reaction that suddenly occurs when the body is exposed to various foreign substances being a type 1 hypersensitivity reaction with degranulation of mast cells and basophils mediated by IgE, in response to triggering by various agents. The rapidity with which clinical signs are installed and severity is closely related to the type of allergen and its amount. Anaphylactic shock is therefore a severe anaphylaxis with cardio-circulatory and respiratory collapse.

Grintuss is indicated for the treatment of cough, both dry and productive. It has the warning "Do not use in case of hypersensitivity or individual allergy to one or more components of the product". Grintuss adult syrup is formulated with plant molecular complexes such as resins, polysaccharides with a molecular weight> 20,000 dalton ≥ 20% and flavonoids from grindelia *, patalaginum * and helichrysum * (Poliresin®). It also contains: sugar cane sugar *; the water; essential oils of: eucalyptus, star anise, lemon; natural lemon flavor; gum arabic; xanthan gum. All functional substances are ingredients from organic farming.

Case report

Follow-up of the clinical evolution after the diagnosis and the rapid establishment of the treatment of a 4-month-old patient discharged for 10 hours from the pediatric department where he was admitted for a 7-day period diagnosed with: Bronchiolitis; IRA light; Iron deficiency anemia. The patient comes from a low-income family with 5 illiterate children and parents, with a history of several admissions in the pediatric ward, predominantly respiratory diseases, in which he is without a doctor. The mother decided to administer the grintuss syrup because it was used in older children without complying with the medical indication at discharge. The grintuss syrup was for use in children over 12 years and in adults, the mother gave it only 1 ml affirmatively, and at 15 minutes there was a maculo-papular eruption, dysphonia and psycho-motor agitation; mother asks for the ambulance service that affirmatively confirms the possibility of consultation only in 10-15 minutes so the mother decides to come to our emergency service with the taxi service.

At the entrance to the emergency department, the patient is unconscious with respiratory arrest, generalized rash, cold, cyantic extremities, F.C-158 / min, TA- 40/25 mmHg, Glasgow-10. Ventilation on mask and balloon is decided. Immediate adrenaline 0.1% -0.15-150 μg ml of 1/1000 dilution is administered together with 25 mg hydrocortisone hemisuccinate. A venous line is obtained by which 0.3 ml arnetine 50 mg/2 ml and another 25 mg hydrocortisone hemisuccinate are administered, 0.9% physiological PEV is mounted.

The patient resumes spontaneous breathing and so nebulization can begin with dexamethasone, the plaques begin to resume, in dynamic clogging with dysphonic component. The vital constants stabilize F.C-144b / min, FR-24 / min SaO2- 99%, TA-80/45 mmHg when deciding on admission for follow-up and specific treatment.

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Discussion

In recent years, significant advances in diagnosis and Through its α1 adrenergic effects adrenaline improved laryngeal spasm and circulatory collapse, and through β2 adrenergic action induced bronchodilatation and reduced release of histamine and other mediators (1,2). It is known that there is a short period of opportunity, as only a dose by injecting im was effective (2,3). The lack of prompt administration of adrenaline increases the risk of biphasic anaphylactic reactions and even death (4).

The mother mistakenly administered cough syrup because she has administered the product for adults and children over 12 years of age. It is hard to see which ingredient the trigger factor in the anaphylactic shock was. Even if the syrup is given to children under the age of 12, we can not demonstrate when the anaphylaxis reaction occurred because the concentration of the substances is different from the adult recommended syrup.

It may also be suspected to increase immune reactivity due to the administration of antibiotics in association, ampicillin with gentamicin for 7 days for respiratory infectious pathology from recent history, discontinued treatment for only 24 hours. Confirmation of anaphylaxis could be made by determining the serum level of tryptase within 30-60 minutes of the onset of the reaction, when we should have values above 11.4 μg / L, values that are maintained 4-6 hours with decreasing in their 24h.

Determination of allergen-specific IgE may be useful in the future assessment of the patient, taking into account his age, with the possibility of defining the specificity of sensitization to certain substances but also of confirming the hypersensitivity to food. As a classic "challenge" test, the basophil degranulation test is the only in vitro tool for studying a large number of adverse reactions to food additives and medications (5, 6,7).

Children are described with 5 anaphylactic shock variants: typical, hemodynamic, with asphyxia, cerebral and abdominal variants. Reactions and allergic diseases in children up to one year are predominantly of food origin and occur in 40-60% of children (8,9). Unlike adults, children with systemic reactions limited to the skin have fewer chances of severe, respiratory or vascular manifestations (10,11).

The principles of treatment of anaphylactic shock in children are the same as in mature patients, respecting the doses of drug remedies in kg / body weight / 24 hours (12).

Conclusions

Intramuscular administration of adrenaline, airway management, vascular bed filling should be promptly established, depending on the life of the patient.

Allergic reactions occur in different body sectors: cutaneous, cardiovascular, respiratory, gastrointestinal, separately or in combination. Anaphylactic shock presents all clinical signs and hypotension.

Patients who have had anaphylaxis will be monitored for at least 24 hours.

The appearance of anaphylactic shock on the administration of a product with ingredients from organic farming is very rare, especially as it is a 4-month-old baby.

Even if we have the warning: "Do not use in case of hypersensitivity or individual allergy to one or more components of the product" the product is not free from the risk of producing an anaphylactic reaction.

The 3 flavonoid extracts from grindelia, patlagina, and helichrysum are known and used in antiquity in medicine for various therapeutic effects as opposed to eucalyptus oil which, even in relatively small amounts, can cause fatal overdoses as warned by the National Institutes of Health, and infants and young children should not ingest or inject eucalyptus oil. An allergic reaction to the anise in the composition of the cough syrup that falls under the category of coding allergens and food additives may also be incriminated.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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MULTICYSTIC RENAL DYSPLASIA IN CHILDREN. CLINICAL-PARACLINICAL SPECIFICS. CLINICAL PRESENTATION FEATURES

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Abstract

The aim of the study is to investigate the clinical-paraclinical features, especially imagistic, morphopathological, in the diagnosis of multichistic renal dysplasia in children, especially in asymptomatic forms and therapeutic approaches to this subject.

The study refers to a group of 33 children with multiple urinary tract dysplasia (MUD) complicated with urinary tract infection 2009-2017. The authors present their own experience on the clinical-morphological diagnosis and treatment during the given period. It emphasizes the need for a differential diagnosis for choosing the optimal therapeutic solution. Multidisciplinary renal dysplasia in the child is a congenital kidney malformation due to embryonic disturbances, diagnosis being determined by the ultrasound examination during the intrauterine development of the fetus in the antenatal screening programs.

Key words: multicystic kidney, clinical-morphological examination, children

Introduction

Multicystic renal dysplasia (MRD) is a rare congenital abnormality, occurring in 1.1% of all renal and urinary abnormalities [1]. According to some studies, the incidence of MRD varies between 1: 3500, 1: 4000 live newborns [2]. Bilateral multicystic affection has a frequency of 1: 3600 newborns. In 55% cases the left kidney is affected, and in 45% - the right kidney [3]. The antenatal screening data compared to the neonatal one reveals MRD as a vicious disease of the reno-ureteral system encountered in fetuses, may be present both unilaterally and bilaterally and the latter is frequently incompatible with life. By gender, MRD is considered to be a higher predominance in male 2:1, a more frequent impairment of the left-sided ureteral complex [4].

Due to the mandatory use of ultrasound screening methods during the perinatal period, including the urinary system, perinatal ultrasound diagnosis has led to the detection of malformations at much earlier periods. On ecography MRD is described as a kidney malady without renal parenchyma, presenting multiple cystic formations of different size and number, filled with liquid that do not communicate with each other, forming a cystic pseudotumor with irregular shape. In the unilateral form, MRD is attested as a renal-ureteral dysplastic complex with an attenuated ureter, whereas the contralateral complex, attesting a well-functioning reno-ureteral system. Some studies reveal the MRD ureter, more commonly, as a hypoplasic ureter, atrestic or even totally absent, sometimes associated with vesicoureteral reflux, or the vesicoureteral reflux may also be present in the contralateral kidney, features encountered in 15-30% of patients [1,2]. According to the morphopathological studies, the cystic structures are cuboid epithelium-cladded, containing transparent liquid, but sometimes also reddish or brown. The cyst walls contain fibrous tissue, sometimes with hygienic sectors with calcinated islets. Embryologically, an abnormality occurs during the fusion of the ureteral burr and distal countersunk tubes. In some cases, the ureter may remain obstructed for much of its length [5]. The spectrum of other urinary tract abnormalities reported in association with the multicystic dysplasia kidney includes obstruction of the pituitary junction in up to 15% of patients and, less frequently, obstruction of the ureteral bladder junction, ureter and ureteral ectopia [2]. The ideal diagnostic approach for asymptomatic ureteral bladder reflux in patients with multicystic dysplasic kidney remains controversial.

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Fig.1. MRD: a) 1 - bilayer kidneys in conglomerates of thin-walled cysts; 2 - rudimentary pelvis with segmental ureter partially hypoplastic in the form of fibrous cord with well differentiated distal segment. *Anatomical postoperative sample*; b) 1 - kidney with multicystic conglomerate appearance with medium and giant volume cysts with microcysts in the wall area; 2 - hypoplastic ureter in the form of fibrous cord. *Anatomical postoperative sample*

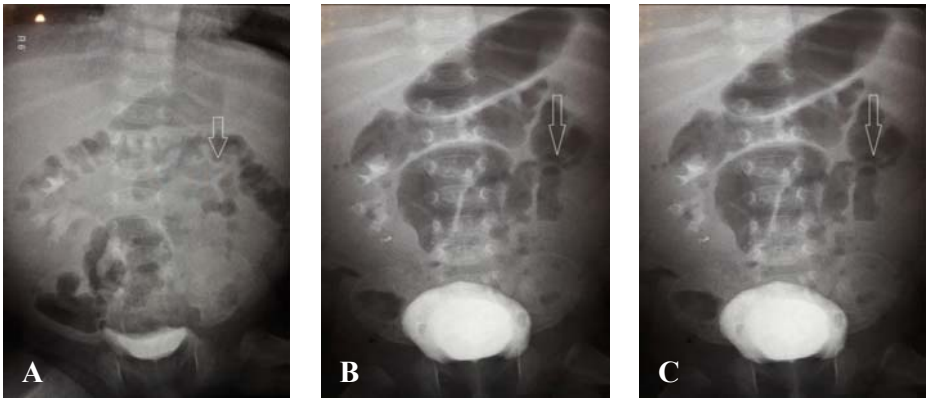

Fig. 2. Intravenous urography. A - after a 6-min exhibition: urographic uterine kidney on the left, preserved kidney function on the right; B- after a 40-minute exhibition. Urographic uterine kidney on the left, preserved kidney function on the right; C - after a 1.5 hour exposure, urographic left kidney, maintained kidney function on the right

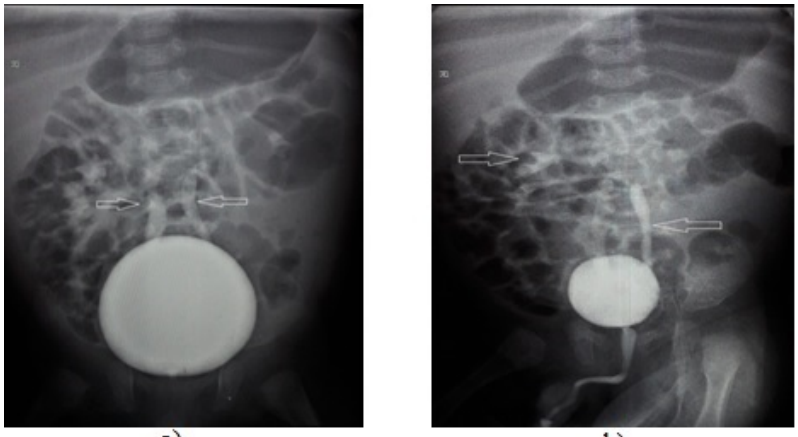

Fig. 3. Micturition cystourethrography. Bilateral vesico-ureteral reflux, III degree: a) passive; b) active

Considering the high incidence of ureteral bladder reflux in both the multicystic dysplastic kidney and the contralateral kidney, and the potential risk of infection-induced scarring and renal lesion in solitary cells, it is important to perform micturition cysturethregraphy during neonatal evaluation [6]. Simultaneously with the features mentioned in the literature, a much rarer form of MRD is described, such as hydrophonerotic, characterized by the presence of peripheral cysts, that communicate with a larger, centrally located cyst and do not open on the very dilated

The aim of the study is to investigate the clinical-paraclinical features, especially imagistic, morphopathological, in the diagnosis of multichistic renal dysplasia in children, especially in asymptomatic forms and therapeutic approaches to this subject.

Material and methods

This study included a sample of 33 children (13 girls and 20 boys) aged 7 days - 5 years with MRD diagnosis, including complicated urinary tract infection, who were treated at the Academician Natalia Gheorghiu National Center for Scientific and Practical Pediatric Surgery, Clinic of Pediatric Urology and Neonatal Surgery during 2009-2017, on the basis of biological samples collected according to the contemporary research principles, approved by the Research Ethics Committee of Nicolae Testemitanu SUMPh (favorable opinion of 13.05.2015, no.55).

Clinical-paraclinical investigations included anamnestic laboratory, imaging examinations: ultrasound, intravenous urography, retrograde cistouretrography, renal dynamic scintigraphy, computered tomography (CT) . Speaking about methods of examining and investigating the renal ureteral malformation, for all patients the initial method of urinary ultrasound and renal dynamic scintigraphy was used. Intravenous Urography (IVU) with contrast substance Verografin 3-4 ml / kg bodyweight in the newborn baby and 2-3 ml / kg body weight in the 3-5 year old child, as well as Retrograde Cistouretrography (R-CUG) were widely used. There have been taken into account the statements in the literature that MRD treatment begins with investigations that make the diagnosis, this claim wishing to emphasize the importance of early diagnosis, a determinant of therapeutic effectiveness. All children with definite diagnosis of MRD have undergone surgical treatment with postoperative monitoring. The anatomical-surgical parts were carefully examined post-operatively microscopically, using organometry and macrometry. After histological processing, photon microscopy was applied using conventional Hematology - Hemoglobin - Eosin (H & E) histological methods and selectively van Gieson (VG) in the estimation of conjunctival tissues features.

Results and discussions

The analysis of the obtained results, especially of the anamnestic and clinical data in the patients included in the study, revealed that in 23 (60.6%) of MRD cases, these lacking any specific clinical manifestations, the pathology being detected in the ultrasound examination routine or occasionally in the newborn. In 30.4% (10) of cases, pelvis. MRD etiopathogenesis is still under discussion; in the literature, it is more often explained as an embryo-fetopathy, but also the family syndrome as the hereditary aspects. Another side that contributed to the initiation of a study was the fact that the MRD etiopathogenesis, as well as its actual incidence, possible complications, or malignant degeneration, are not fully understood to date. Also the therapeutic approach to the malformation is still under discussion [7,8].

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patients experienced undiagnosed episodes of repeated urinary incontinence of acute pyelonephritis, with persistent chills in 3 children (9.1%), cloudy urine in 2 children (6.06%), vague abdominal pain with digestive manifestations in 5 children (15.1%). Clinical manifestations correlated with the presence of urinary tract infection (positive uroculture) constituted the decisive element in determining the indication of complete urinary tract investigation.

In 9.1% (3) of cases, the diagnosis of upper urinary tract abnormality associated with acute pyelonephritis was uncertain, the use of micturition cystureterography made the MRD diagnosis, leaving a combined MRD, in 3% (1) of cases the presence of vezico-ureteral reflux of Mixed I-II degrees in vicious multichistic kidney, with a frequency of 3.03% (1) of cases, bilateral vezico-ureteral reflux, mixed I-II degrees, and with a frequency of 1 (3.03%) of the cases, the presence of mixed bilateral vesico-ureteral reflux, III degree, being confirmed.

Retrograde filling cistoureterography, standard or late cluster, revealed passive reflux, and micturition cystoureterography allowed to establish retrograde urine passage to the kidneys (active reflux) and the intravesical obstruction. These explorations have been an integral part of initial imaging investigations in the establishment and differentiation of urinary tract infection. The presence of a parenchymal fixation defect has facilitated the diagnosis of pyelonephritis, but it also does not allow a distinction to be made between acute and chronic.

Intravascular urography in all patients under study revealed a lack of MRD kidney function, manifested by urographic "mutant" kidney, with retained function of the contralateral kidney. In 2 (6.1%) of patients intravenous urography had a number of radiological signs suggestive of kidney disease, such as segmental dilation of the ureter, ureter visible throughout its tract. Dynamic renal scintigraphy indicated the lack of dysplastic kidney function in MRD.

Laboratory studies indicated ESR, hyperleukocytosis, ferrites anemia, blood ionogram and moderately modified acid-base balance. The uroculture performed on all the children admitted in the study group identified germs responsible for urinary tract infection. The frequency of germs involved in urinary infections in patients with positive urocultures at admission was noted by E. coli in 3 children (9.09%), followed by Staphylococcus aureus in 2 children (6.06%).

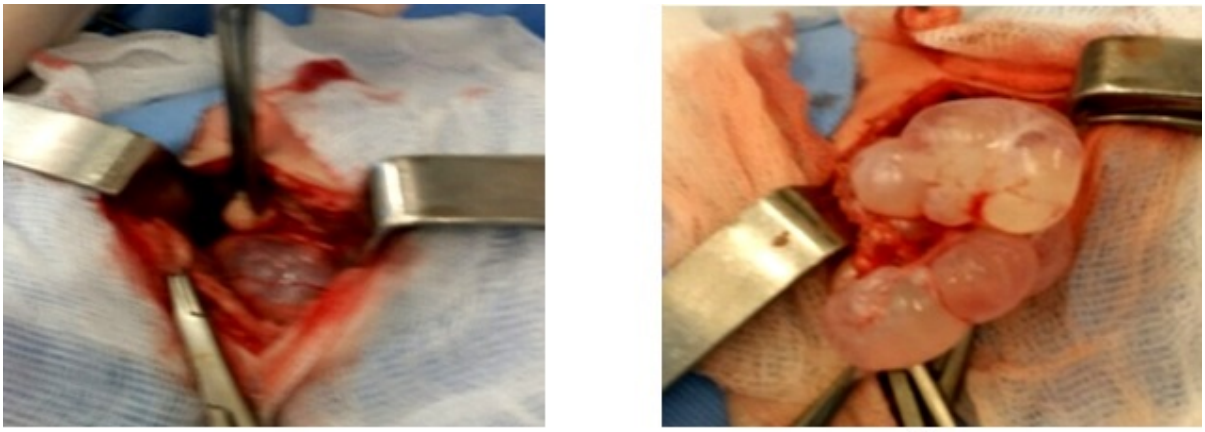

Fig.4. a). Dysplasic multicystic kidney in surgical wound: a) Macroscopic intraoperative aspect; b) Intraoperative aspect.

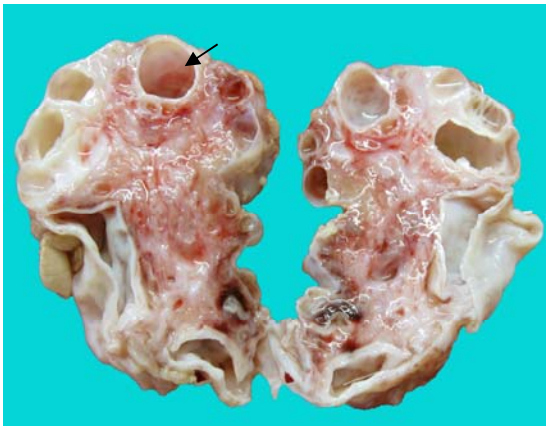

Fig.5. Macroscopic aspect of MRD absence of the pelvic and calcified system. *Anatomical postoperative sample*

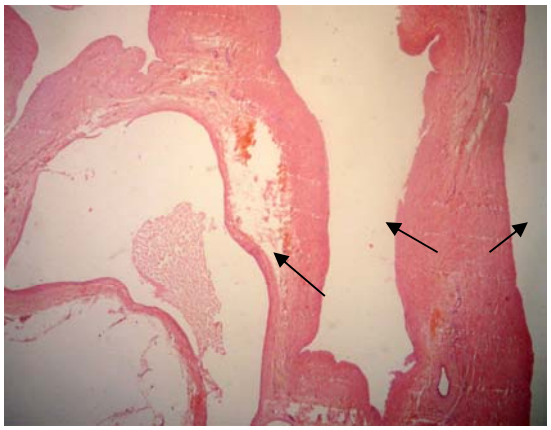

Fig.6. Multiple cysts with fibrous capsule and edema of interferic anefronial connective tissue ×25. H-E staining

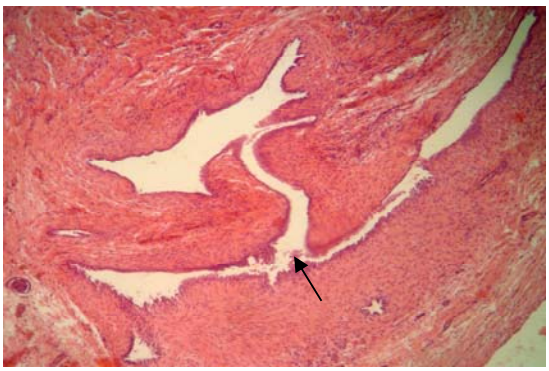

Fig.7. Rudiment of the pelvic and calcified system in the fissure aspect without serous contents × 25. H-E staining

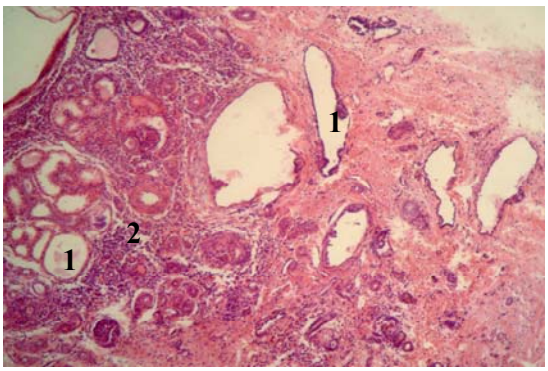

Fig.8. Mezenchimal tissue plates: 1) cystic nephronous islands dilated with cysts of tubular and glomerular origin; 2) Inflammatory polymorphic-cellular infiltration × 25. H-E staining

The results of investigations in the study group demonstrate the notion that there is no rational basis for waiting two, three or more episodes of urinary tract infection before making a decision to investigate a child to exclude or detect a kidney malformation, especially MRD in young children.

Children with mixed vesicoureteral reflux, I-II degrees and mixed III degree, have benefited from a complex conservative medical treatment that aimed to combat urinary infection and to ensure a free urine drainage from upper to lower urinary ways, restoration of bladder function, at the inefficiency of conservative treatment, the last one was followed by surgical treatment.

Surgical treatment by nephrectomy on the dysplastic multicystic kidney was performed with all children with MRD, and in the case of association of vesicoureteral reflux on this kidney, suppressed ureteric ureterectomy ipsilateral to affected kidney was performed.

In our observations, the morphopathology of the reno-ureteral complex in MRD varied in form, volume, the number of cystic formations, yet it was characterized by the cystic aspect with the presence of cystic formations of various dimensions, lined with serous content without communication, cubic epithelial wall. According to the assemblage of the kidney shape in MRD, it was characterized in 6.15% (2) of cases by the giant solitary cyst aspect of 4.2cm and 5.1cm at the base with the presence of a macroscopically multichannel parenchyma with a diameter of 0.2-0.6cm. With a frequency of 21.2% (4) of cases a multichistic bilobulus aspect being attested (fig.1). The most common form was MRD with a number of over 25-30 cysts with dimensions in the range of 0.8 - 2.5 cm with single cysts of 3 cm in diameter. The cystic wall is represented by sclerogenic connective tissue with scar aspects. The content of cystic cavities is often transparent with yellowish tones sometimes with cholesterol crystals. In the cystic wall there are pulvirulent calcifications.

In 69.7% (23) of cases among cysts in various ratios primitive nephron insulins, monstrous solitary glomeruli, dispersed or in small groups in a mesenchymal tissue mass, in one case small cartilage islets, were attested. Signs of the pelvis also did not appear, the ureter in 57.6% (19) of cases being present in the form of a solid cord at the level of the suspected kidney hill, diminishing in a mesenchymal, conjunctival mass, the vascular device practically being poorly developed and observed.

In 30.3% (10) of the cases (Fig.1 a), b)) among dispersed cysts the presence of a fibrous renal parenchyma with the appearance similar to the limit of the norm, as well as the presence of the deformed, hypoplastic, monstrous cystic nephron , the presence of dysplastic glomerular groups and various myocardial or muscle fractures, were attested. Some glomeruli were with hyaline, proliferative or glomerulo-cystose features. Within these modifications the rudiments of the basin (fig.1 a), b)) were present, lacking communication with the cystic formations or tubulo-neural components, in the testing by injecting of the hematoxylin into the ureter.

Another characteristic established in the results of the histological exploration within DRM was its presence in parallel with the vicious interstitial-non-chronic and cystic processes of the inflammatory process. Depending on the MRD type, the inflammatory process was attested with a frequency of 45.5% (15) of cases.

Thus, it is worth mentioning that the goal of MRD therapy, including vesicoureteral reflux on this kidney or the contralateral kidney, is to protect the single functional kidney from "scarring", to allow normal growth of renal parenchyma and to maintain normal renal function. It is proven that the therapeutic concept in single-kidney vesicoureteral reflux puts the medical treatment (prophylactic antimicrobial treatment) at the forefront, monitored by the monthly urine test for 3 months; if the urine normalizes, the exam is repeated after 2-3 months.

Medical treatment included prevention of the onset or progression of renal retractions, with their potential for progressive chronic renal disease, antibiotics, nitrofurans, antioxidants, nonsteroidal preparations. Medical treatment was followed by regular bacterial urine tests.

Postoperative monitoring of the patients included in the study, particularly those with single functional kidney reflux, included clinical evaluation, urinary echography, micturition cysturethrography, intravenous infusion urography in children up to 3 years of age, uroculture, renal scintigraphy.

Features of clinical case presentation

As an example, we present a newly diagnosed MRD case in patient C.E. aged 1.5 months, medical file no. 117965, male, born 11.XI.17, hospitalized in PHI Institute of Mother and Child, Academician Natalia Gheorghiu National Center for Scientific and Practical Pediatric Surgery, Chisinau, the Republic of Moldova, with complaints: the presence of vicious pathology of the urinary system, ultrasound examination during intrauterine development, confirmed later in the postnatal period by ultrasound of the urinary system with the diagnosis of MRD on the left, trembling of the chin, tremor of the lower limbs, vomiting.

Perinatal anamnesis: Third-born child, 7th pregnancy with a complicated obstetric anamnesis (3 pregnancies with spontaneous abortion at 3 weeks, 5 and 6 months, 1 medical abortion) and extragenital anamnesis characterized by recurrent pyelonephritis. Current pregnancy has evolved with imminence of abortion in the I-II pregnancy period. At 37 weeks of pregnancy, a congenital renal ureteral abnormality - renal polycysteosis, was diagnosed sonographically. The child was born with a weight of 3200, the waist - 52 cm, the cranial perimeter - 33 cm. At birth, being certified with Apgar score - 8 points.

Anamnesis morbi: The neonatal period was without any specific features and complaints. At 10 days of life, the child was repeatedly investigated by the ultrasound of the urinary system, establishing with certainty the presence of malformation of renal-ureteral complex on the left, characterized by the increased volume aspect up to 72x38mm, the absence of parenchyma being reflected by

multiple cystic formations. The reno-ureteral complex on the right detected a 52x24mm kidney with sonographically differentiated parenchyma, the 8.6 mm cortical layer. The child was in natural food. The child's body mass was 5640kg at the time of hospitalization. At the age of 1 month and 11 days, repeated vomiting occurred in child after each feeding, in large quantities, with cheesy milk. Subsequently the vomits were repeated twice.

Clinical specificity. On 23.XII.2017, the child was hospitalized in the pediatric surgical ATI department for examination. After paraclinical examinations (EFGDS) with initiation of treatment, vomiting did not occur again. Subsequently, in improving the general condition, the child was transferred to the newborn surgery. Objectively: The general condition of the child was attested as severe - medium, after the present pathology - severe. Teguments and mucous clean, pale - rosy. Heavy breathing in the lungs. Heartbeats - sore. Sensitive abdomen in lumbar region on the left.

Paraclinic laboratory specificity (of 01.12.17). The haemolegogram showed a decrease in hemoglobin and erythrocytes, an increase of unshed to 8%, indicating the persistence of an inflammatory process in children characterized by: hemoglobin 96, g / l, (norm b - 130.0-160.0, f-120.0-140.0), erythrocyte - 3.0x1012 / l, (b-4.0-5.0, f 3.7-7.7x1012 / l), leukocyte 5.1x109 / l, (norm – 4.0-9.0 x109 / l), hematocrit – 0.28% (norm b – 40.0m – 48.0%, f.-36.0 – 42.0%), platelets - 242 x (Norm - 1 - 6%), segmentations - 37 (norm - 47-72), eosinophile - 2 (norm - 0,5-5), lymphocytes - 51 (norm - 19-37), monocyte - 2 (norm - 30-11), VSH - 6 mm / hr. (norm - b-2-10, f. - 2-15). At the recommendation of the haematologist, the treatment for iron-deficient anemia has been initiated.

Biochemical Blood Test: Protrombinic Index - 85%, (norm - 70-130%), fibrinogen - 2.89 g / l (norm - 2.0-4.0 g / l), total protein -53 g / l (norm - 64-83), urea - 2.2 mmol / l (norm - 2.1-7.1 mmol / l), creatinine - 46 mcmol / l (norm - 53-115), total bilirubin - 30.0 mcmol / l (norm 1-17mcmol / l), ALAT -21 units / l (norm 1-49), ASAT - 38 units / l (standard - 1-46units / 3 mmol / l, (norm 3.5-5.3), 132 mmol / l sodium (norm - 135-148 mmol / l), 2.32 mmol / l (standard - 2.2-2.55 mmol / l) Fe - 12.9 mcmol / l (norm - 8.9 - 30). Blood Group Rh factor - B (III) Rh factor (+), POSITIVE. Summary urine examination: flat epithelium - 6-7 in the field of vision, leukocytes - 12-15 in the field of vision.

Functional Explorations (04.12.17): Electrocardiogram: vertical AE. Tachycardia. Neuro-sonography: Medium cerebral structures are not dilated; anterior horns - 2mm, ventricle III - 2mm;

Imaging specificity (04.12.17). Ultrasound of internal organs (04.12.17), liver 54 mm, left lobe - 27 mm, port vein - 2 mm. Average echogenicity. Biliary bile inflection to the body. Pancreas 5x6x6mm. Average echogenicity. Spline 44mm. Upon examination of the reno-ureteral system, the right kidney was detected 69x28mm with the parenchyma differentiated 8 mm in thickness, the left kidney 76x46mm, the collector system on the left, in the renal parenchyma many cystic formations, the largest of 22mm. Intravenous urography - detection at 6.40 minutes after injection of contrast substance - pyelocaliceal system on the right, ureter contrasted to the right in its middle and inferior third (fig.2 A, B). To the left, the pyelocaliceal system is not contrasted at 1.5 hours after injection of the contrast substance (fig. 2 C).

Micturition cistouretrography revealed bilateral vesico-ureteral reflux, third degree, passive (fig.3 a)), bilateral vesico-ureteral reflux, grade III, active (fig. 3 b)).

Dynamic kidney scintigraphy (of 05.12.17). The right kidney is located in a typical place, with sharp, enlarged dimensions. The distribution of the radiopharmaceutical in it is uneven. The glomerular filtration process is in order. The excretion process is diminished. Radiopharmaceutical retention is found in the calcification system - basinet on the right. The left kidney is not visualized, its function is not determined.

After treatment, on the background of anti-anemic medication (Ferropol 6 drops in 24 hours) the control tests of 11.12.17, established normalization indices: Hemoleucogram: hemoglobin 116, g / l, (norm b - 130.0-160, 0, f - 120.0-140.0), erythrocytes - 3.7 x 1012 / l, (norm b - 4.0-5.0, f. 3.7-4.7x1012 / l), colour index – 0.94 (norm - 0,85-1,05), leukocytes 7.3x109 / l, (norm - 4,0-9.0 x109 / l), hematocrit – 0.28% (norm b – 40.0 - 48.0%, f.- 36.0-42.0%), thrombocyte - 232x109 / l (norm - 180.0-320 x109 / l), non-segmentations -7 (norm - 1-6% - 20 (norm - 47-72), eosinophils - 3 (norm - 0.5-5), lymphocytes - 66 (norm - 19-37), monocytes - 4 . (norm - b-2-10, f. - 2-15). Despite the insignificant normalization of hemoglobin indices, there is an increase in the non-segmentations of up to 8%, which indicates the persistence of an inflammatory process in the child.

Biochemical blood test of 11.12.17. Total protein -56.1 g / l, (norm - 64-83), urea - 1.0 mmol / l (norm - 2.1-7.1 mmol / l), creatinine - 40 mcmol / l - ALU - 18 units / l (norm - 1-49), ASAT - 24 units / l (norm - 1-46 units), total bilirubin – 8.6 mcmol / l (norm 1-17 mcmol / / l), potassium - 5.18 mmol / l, (norm 3.5-5.3), sodium - 136 mmol / l (norm - 135-148 mmol / l), calcium - standard - 2.2 - 2.55 mmol / l).

On the basis of the imaging and functional examinations of the renal urinary system, especially reno-ureteral, a diagnosis of congenital reno-ureteral abnormalities has been made: Renal multicystic dysplasia of the reno-ureteral complex on the left, nonfunctioning, with vesico-ureteral reflux III degree mixed; single-functional reno-ureteral complex at the parameters of the oblique ureteral reflux III degree mixed. Recurrent pyelonephritis. Iron-deficient compensated anemia.

On the basis of the diagnosis made on 18.12.2017, two-approaches surgery was performed. 1. Lumbotomia pe stânga. Nephrectomy on the left. (Fig. 4 a), b)) Draining of the paranephral space. 2. Over-bladder ureterectomy on the left. After processing the field of operation, a left ventricular lymphoma incision was performed. Gradually the paranephron was opened. The kidney presented by multiple cystic formations, approximately 18-20 of different sizes, with thin cyst walls, with transparent content, was detected

(fig.4 a), b)). Hypoplastic ureter did not differentiate from cyst tissue. Nephrectomy was performed. Rubber drainage. Anatomical plans rebuilt to drain. Aseptic dressing. Over-bladder ureterectomy on the left. Incision of the suprapubic region on the left. Gradually the bladder was detected. Hypoplastic ureter in the lower 1/3, proximally dilated. It was maximally mobilized. It was taken over two clamps, cut between them. Survezicular ureterectomy was performed on the left. Rubber drainage. Anatomical plans rebuilt to drain. An aseptic dressing was applied.

Morphopathological specificity, Morphopathological, postoperative, anatomical-surgical (kidney and urethral segment presentation) findings revealed a multicystic conglomerate shaped kidney with dimensions in the range of 4.5x3x2.6cm and ureter segment with lumen varied between 0.2-0.5 cm in diameter, the bladder being more dilated. In the section, the cystic conglomerate is presented by cystic formations with a diameter of 0.1 to 2.0 cm, lacking communications, with cubic epithelial or epithelial-free cover with transparent, sometimes semitransparent serous content, slightly trabecular surfaces (Fig.5-6). Among the cysts there is pseudomixomatous tissue on the account of edema, including increased consistency. Pelvic-calicular segments were attested only on histological examinations in discordant cystic-cavitary rudimentary aspects, lacking communication with attested cysts, taped with the presence of the pseudo-and pluristrated urothelium (fig. 7). Among the cystic formations there is the parenchyma with dysplastic nephron with tubular and glemerular cysts associated with polymorphometric inflammatory process predominated by lymphocytic elements sometimes with the neoformation of the pseudo-follicular structures (fig.8).

The postoperative period corresponded to the surgery performed. The child, with obvious improvement in general condition, was discharged at home to continue conservative treatment. The following recommendations were made: 1. Tab. 5 NOC 0,05 1/4 tab. x 3 times a day for 10 days, 2. Tab. Quamatel 20 mg 1/4 tab. x 1 per night for 10 days, 3. Tab. Furagin 1/4 x 3 times a day for 10 days, 4. Tab. Furagin 1/4 x 2 times a day for 10 days, 5. Tab. Furagin 1/4 x 1 daily for 10 days, 6. Vit. E 2 drops x once a day in the morning for 1 month. 7. Examination after a month with general urine analysis - once every 10 days (total - 3 analyzes), blood count (once every 2 weeks), examinations performed (intravenous urography, renal scintigraphy, micturition cistoureterography). 8. The assessment of the disability group.

The analysis of the results obtained in the study on the MRD allowed to determine two types of MRD: a) MRD with absence of basin, with or without the presence of a rudimentary ureteral segment, the presence of cartilage, this variant frequently being described in the literature, also characterized by the lack of nephron parenchyma; b) MRD with the presence of a non-communicating rudimentary pelvis with cystic formations, with dorsal ureter in the shape of a cord and with segmental morpho-functional features at the limit of the norm. This variant was characterized by the presence of the nephron stroma.

Depending on the type of MRD ranked as a result of the quantification of morphopathological features, the inflammatory process was predominantly certified in variant "b", at the level of nephronous parenchymal islets characterized by the polymorphic cell predominated by the lymphoplasmocyte with the presence of lymphoid pseudo-follicular structures. In our opinion, the presence of inflammatory process in the malformative kidney is already a criterion which does not exclude the simultaneous absence of the inflammatory process in the contralateral reno-ureteral complex, which can be taken into account as a suggestive marker for the monitoring of the patient, ie the controlled kidney.

Conclusions

1. Multidisciplinary renal dysplasia in the child is a congenital kidney malformation due to embryonic disturbances, diagnosis being determined by the ultrasound examination during the intrauterine development of the fetus in the antenatal screening programs.
2. In an asymptomatic newborn the clinical examination reveals a palpable tumor mass, and renal ultrasound determines multicystic, morphological renal dysplasia based on the vicious features of the structural components being diagnosed with 2 conventional forms and making the presence of their pelvic-calicular and rudimentary elements .
3. The precise causes of renal multicystic dysplasia to date are not well known, the presence of the inflammatory process may justify a genesis of intrauterine infectious teratogenic actions, being also an advanced secondary characteristic to pre-existing dysplasia changes.
4. Although according to literature data, vesicoureteral reflux in renal multicystic dysplasia has a frequency of 15-30%, only 3 cases have been detected in our clinic over 20 years.
5. Surgical correction in renal multicystic dysplasia is nephrectomy (in the absence of the ureter) or in vesicoureteral reflux on dysplastic kidneys supplemented with over-bladder ureterectomy.
6. The prognosis is age-dependent, the presence of vesicoureteral reflux on the contralateral kidney, rigorous pre- and postoperative surveillance, anti-hypoxanth treatment.

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THINK ABOUT THE FOUNDER EFFECT IN ENDOGAMOUS POPULATION - CONGENITAL CATARACTS, FACIAL DYSMORPHISM, AND NEUROPATHY (CCFDN) SYNDROME - TWO CASES

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Abstract

Introduction: Congenital Cataract, Facial Dysmorphism and demyelinating Neuropathy (CCFDN) syndrome is a rare, progressive and multisystem disorder with autosomal recessive inheritance, to date described in 170 individuals of Roma ancestry (founder pathological variant c.863+389C>T in CTDP1 gene with high allelic endogamous frequency (7%)). Herein we present a familial phenotype shown by two siblings, aiming to increase awareness for the specific clinical presentation for a Romanian Roma ethnic subgroup.
Materials and Methods: Medical histories were obtained as a part of the affected individual's clinical workup. Molecular analysis of CTDP1 was performed in 2nd Faculty of Medicine of "Charles" University in Prague. Results: A 11-year-old boy presented with the pathognomonic triad after experiencing an episode of acute rhabdomyolysis. His sister aged 13 exhibited a similar phenotype. They both express a complex phenotype and additionally congenital right inguinal hernia. CCFDN was suspected and confirmed through targeted molecular analysis diagnosis by of the pathological variant in CTDP1 gene.Discussions and conclusions: This work highlights the essential tools in clinical practice and genetic counseling regarding CCFDN. Is inguinal hernia an additional feature to CCFDN phenotype or only an incidental finding? Based on the high allele frequency caused by founder effect, the pathogenic variant of CTDP1 is an actionable genetic variant. An earlier diagnosis in the girl, would've allowed prevention in the following pregnancies. The couple is aware of their high risk of another offspring with CCFDN, as all Roma endogamous subpopulation should be informed about.

Key words: CTDP1 gene, founder effect, Roma ethnicity, actionable genetic variant

Introduction

A Congenital Cataract, Facial Dysmorphism and demyelinating Neuropathy (CCFDN) (OMIM 604168) syndrome is a rare, complex developmental, multisystem disorder with autosomal recessive inheritance, to date found only in population having Roma/Gypsy ancestry. Clinically, it presents with the pathognomonic triad of bilateral congenital cataract, developmental delay and later demyelinating neuropathy [1]. First described by W-Muller-Felber et al. as a subtype of Marinesco-Sjogren syndrome (OMIM 248800) in 1998 (Marinesco Sjogren Syndrome with Rhabdomyolysis [2]), it was in 1999 when Tournev I. at al. established the molecular difference between the two entities although the 2 disorders share some overlapping features (congenital cataracts, delayed psychomotor development, and ataxia [3]) and gave the disorder's name [1]. Also in 1999, Tournev's team member, Angelicheva et al., by linkage studies, assigned the CCFDN locus to chromosome 18q23-qter (telomeric region of chromosome 18q), linkage disequilibrium and highly conserved haplotypes suggesting genetic homogeneity and founder effect [4].

The complex but particular phenotypic features of CCFNN allow a relatively rapid and accessible clinical diagnosis, thus herein we aim to increase awareness for the specific clinical presentation for a Romanian Roma ethnic subgroup by emphasizing the importance of a proper anamnesis and clinical workup for the diagnosis and further management, and subsequent genetic counseling.

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Phenotype evolution	C.C., ♀, 13 year-old, 1st born		R.C., ♂, 11 year-old, 2nd born	
Antenatal information	No particular events, normal fetal movements		No particular events, normal fetal movements	
Birth related information	Full term, normal vaginal delivery, normal weight at birth (2800 g), no hypotonia- affirmative to mother	Right inguinal hernia	Full term, normal vaginal delivery, normal weight at birth (3150 g), no hypotonia- affirmative to mother	Right inguinal hernia
Neonatal period	No particular events, no feeding difficulties, normal weight gain		No particular events, no feeding difficulties, normal weight gain	
Growth	Weight at percentile 10-25% for age	Height at percentile 10-25% for age	Weight at percentile 10% for age	Height at percentile 10-25% for age
Dysmorphic facial features	Prominent midface with a well-developed nose, thickening of the perioral tissues, and micrognathia (Figure 1)		Prominent midface with a well-developed nose, thickening of the perioral tissues, and micrognathia (Figure 2)	
Ophtalmological involvement	Bilateral congenital cataracts diagnosed one week after birth, she undergone surgery in both eyes at the age of 6 years with subsequent left eye aphakia and right eye pseudoaphakia, with a re-intervention 2 years after: no improvement in her visual impairment, bilateral cecity		Bilateral congenital cataracts diagnosed in the first days of life, he undergone surgery in both eyes at the age of 4 years, with subsequent aphakia, no re-intervention, bilateral cecity	
	Bilateral convergent strabismus since birth		No strabismus in infancy, developed bilateral convergent strabismus after the first year of live	
	Bilateral persistent hyperplastic primary vitreous in the anterior chamber		-	
	Bilateral proliferative vitreoretinopathy		-	
	Bilateral horizontal pendular nystagmus		Bilateral mixed horizontal-torsional nystagmus	
	Microphthalmia		Microphthalmia	
	Microcornea (mean diameter ~9 mm)		Microcornea (mean diameter ~7 mm)	
	Micropupils with fibrotic margins		Micropupils with fibrotic margins	
			Left eye ptosis	
Parainfectious rhabdomyolysis	No episode to date		One episode (5 months ago, at the age of 10 years and 10 months)- acute severe proximal weakness and myalgia with impossibility of walking and lifting the arms greater than a 90° angle, occurred after a febrile infection, along with rhabdomyolysis, myoglobinuria, and hyperCKemia (93404 U/L at first determination, diminished in 2 weeks with proper hydration and prednisone therapy to 361 U/L).	
Peripheral nervous system involvement	Delayed motor skill acquisition from the first year of life: - she sat approximately when 1 year and 2 months old - she started walking by the age of 3 years old, with ataxia gait, affirmative to the mother		Delayed motor skill acquisition from the first year of life: - he sat approximately when 1-year-old - he started walking by the age of 1 and a half years old, with normal gait, but gaining ataxia around the age of 3 years, affirmative to the mother	
	She was initially diagnosed with spastic quadriparesis		-	
	Currently presents loss of distal tendon reflexes, no sensory impairment in hands and feet		Currently presents loss of tendon reflexes, sensory loss in feet	
	No nerve conduction velocity measurement was performed		Symmetric and distally accentuated hypomyelinating peripheral neuropathy with predominantly motor involvement shown by measuring the nerve conduction velocity (in the context of his recent episode of rhabdomyolysis, with no previous records) in left peroneal nerve (9.2 m/s (-81.7%)) and right peroneal nerve (3.4m/s (-93.2%)); diminished bilateral M-wave amplitude (0.1 mV (-98%)); prolonged distal motor latency and residual latency (21.6 ms (+978%)). Sensory nerve action potentials were unobtainable, with no sensitivity to pain showing secondary axonal loss	
	No electromyography performed		Electromyography performed for bilateral anterior tibial muscles has shown myogenic changes (in the context of his recent episode of rhabdomyolysis)	
Central nervous system and psychological involvement	Delayed intellectual development: she started to talk around age 3 years; in present, mild cognitive deficit QD=50-55 (Portage Assessment Scale) with partial autonomy, some oculogyric and gestural stereotypies and adaptation difficulties		Delayed intellectual development: he started to talk around age 2 years; mild to moderate cognitive deficit QD=50 (Portage Scale) with partial autonomy, some behavioral stereotypies, psychoaffective immaturity and adaptation difficulties	
	No brain imaging performed to date		No brain imaging performed to date	
	Epilepsy with generalized tonic-clonic seizures between the age of 1 and 3 years old, responsive to usual antiepileptic drugs (clonazepam, carbamezepine)		No seizures	
	Electroencephalogram: performed in early childhood, data unavailable		Electroencephalogram: theta rhythm, medium amplitude waves with no pathological graphic elements	
Skeletal deformities	Mild thoracic levoscoliosis		Mild lumbar dextroscoliosis	
	-		Pectus excavatum	
	Genu valgum with bilateral atrophy of the short toe extensor muscles, externally rotated feet, high arched feet (Figure 1)		Genu valgum with bilateral atrophy of the short toe extensor muscles, externally rotated feet, high arched feet (Figure 2)	
Sexual development	Appropriate for age		Appropriate for age	
Other	-		An additional cardiologic finding was described for the boy in the context of a single-episode lipothymia and this is an aortic bulb ectasia not reconfirmed in the last cardiological evaluation this year.	

Table 1. Medical data of the two siblings

Materials and Methods

Medical histories were obtained as a part of the affected individual's clinical evaluation. Neurophysiologic study of affected muscles and nerves in the proband was performed. Molecular analysis of CTDP1 was performed in Charles University in Prague and University Hospital Motol, Prague, Czech Republic, a research laboratory interested in CCFDN subgroup of patients.

Written informed consent from the guardians of the two children and authorization for disclosure of recognizable persons in photographs for publication were obtained; patients and parents were given the opportunity to review the manuscript

Results

We report a family with four children of which the oldest two (one boy age 11 years and one girl 13 years) are affected. They have two younger siblings with no sign of the disease. Parents were endogamous, but not consanguineous. Parents reported a maternal grand-grandmother having congenital cataract, possibly suggesting another affected person, however she was not available for clinical evaluation. Both paternal grandparents have congenital strabismus. Medical data of the two affected siblings is detailed in Table 1 and the phenotype can be observed in Figures 1 and 2.

Routine laboratory tests did not reveal any relevant modifications excepting for the ones expected in the context of the boy's episode of parainfectious rhabdomyolysis.

Genetic testing

Subsequent to this episode of parainfectious rhabdomyolysis and presenting these mild dysmorphic features, he was oriented to Genetics Department where the suspicion of CCFDN was for the first time brought in discussion. Targeted molecular analysis by classic sequencing confirmed homozygous status of the pathological variant c.863+389C>T in the intron 6 of CTDP1 gene in the boy.

His older sister was also diagnosed with CCFDN presenting a striking similar phenotype.

Genetic counseling was offered for the affected family and consisted in:

- As known, CCFDN is an autosomal recessive disease. Thus, both parents of an affected child are obligate heterozygotes (i.e., carriers of the pathogenic variant of CTDP1 gene on one of the two alleles), but asymptomatic. Siblings of an affected person have a 25% risk to also carry the two pathogenic variants inherited from their parents, or a 50% risk to be asymptomatic carrier as their parents, or a 25% chance to not be a carrier, nor affected by the disease. On the other hand, the offspring of an individual presenting CCFDN are obligate heterozygous for the pathogenic variant. This becomes very important when the reproductive partner has also a risk to be a carrier (risk elevated at 7% by being part of the same Roma endogamous community);
- Carrier testing and genetic counseling was offered to the extended family before planning a pregnancy with an individual of Roma ethnicity

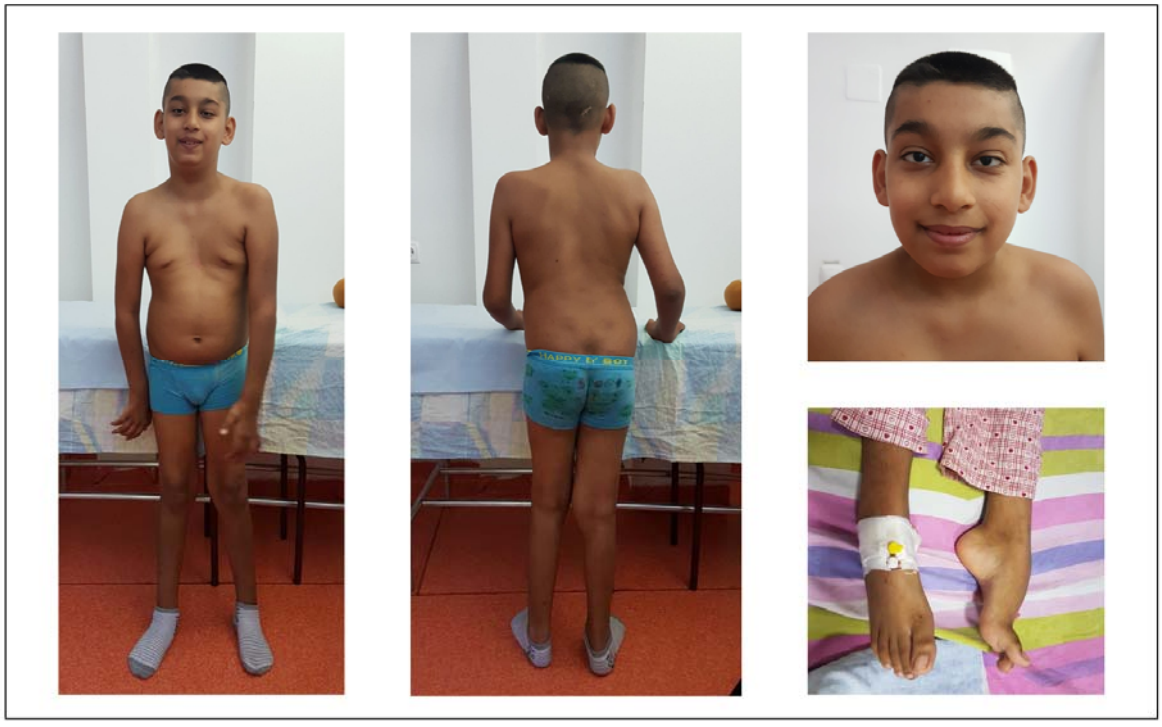

Fig. 2. Phenotypical features of patient C.R., ♂ 11 year-old

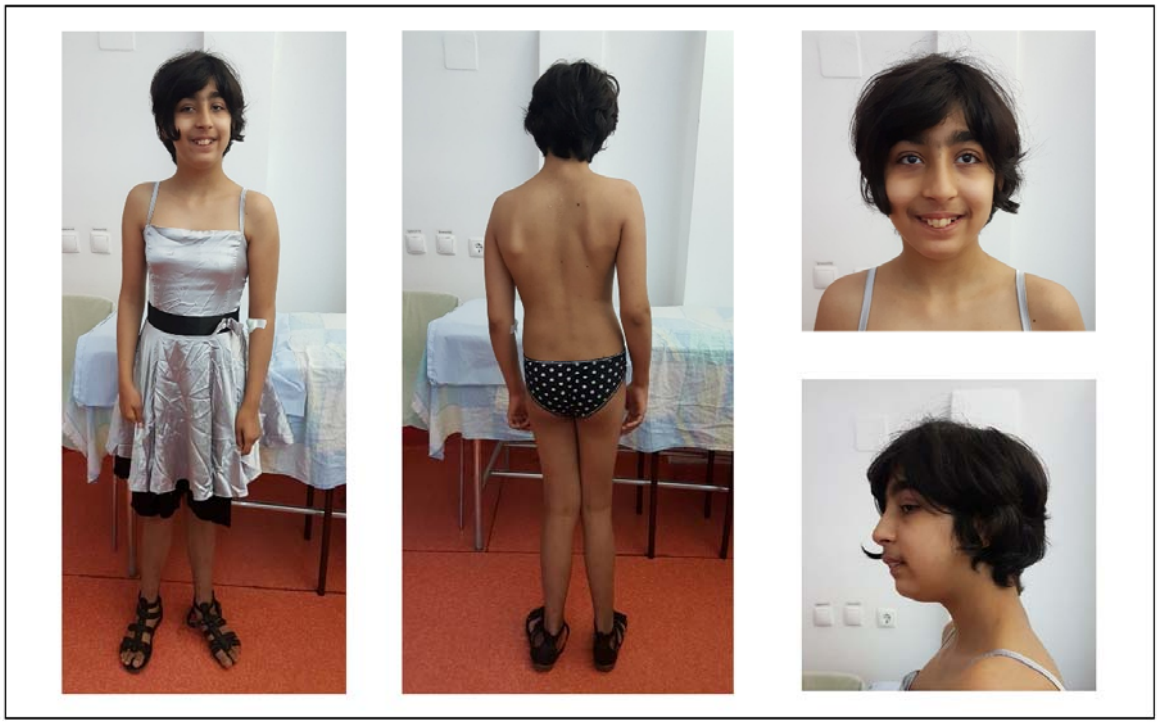

Fig. 1. Phenotypical features of patient C.C., ♀, 13 year-old.

Discussions

Apart from the pathognomonic triad described in the disorder's name, the phenotype described in literature includes additional features involving the anterior segment of the eye, the skull and face, the nervous system, and the endocrine system [5,6]:

- The eye involvement is present at birth and precedes the onset of neurological symptoms, with a severe visual impairment. The lens opacities are bilateral and often consist of anterior and posterior subcapsular opacities with clouding of the adjacent part of the lens nucleus or as total cataracts involving the entire lens. Axial length measurements may document microphthalmia and microcornea (mean diameter ~7.5 mm). Micropupils with fibrotic margins, sluggish responses to light and dilatation to mydriatics were also described as congenital. Later, some patients may develop bilateral ptosis, strabismus and horizontal pendular nystagmus. No fundus abnormalities are present [7,8]. Our two patients present the almost complete eye involvement with no ptosis yet in the girl.
- Facial dysmophism develops with age and are more evident in adult males. They include a prominent midface with an over-developed nose, thickening of the perioral tissues, forwardly directed anterior dentition, and micrognathia [9]. Both siblings here presented respect the mild facial dysmophism excepting the anomaly in dentition.
- The nervous system involvement is characterized by a symmetric and distally accentuated hypomyelinating peripheral neuropathy with predominantly motor involvement which becomes evident during childhood (invariable delay in early motor development with unsteady gait around 2-3 years of life) and progresses to severe disability by the third decade of life [3,9]. Nerve conduction velocity is normal in infancy but begins to decline around the age of 18 months, stabilizing at approximately 20 m/s at around age four to ten years. Electromyography shows myogenic changes in proximal muscles in rhabdomyolisis weakness episodes, recovered after [5,10]. The central nervous system is also affected with slow early intellectual development [10] and common cerebellar manifestations with ataxia, nystagmus, intention tremor, and dysmetria [11]. All these modifications were variable lined to brain MRI findings (from no abnormality to myelin immaturity and cerebral, cerebellar, and cervical spine hypotrophy, enlargement of the lateral ventricles, hyperintense lesions in periventricular white matter and brain stem) [11]. In our proband (C.R, ♂, 11 years old), the complex neurological

evaluation allowed us to assess the progression of CCFDN to date and assume the further evolution.

- Other involvements include reported intrauterine growth restrictions [12] (not presents in our patients) and small stature and low weight in some patients (intermittently described in the evolution of our two patients), skeletal deformities causing reduction of the respiratory capacity, secondary to the peripheral neuropathy (deformed feet and hands, thorax, spine) (both patients express all these acquired skeletal deformities), hormonal deficiency (growth hormone, hypogonadotropic hypogonadism), osteopenia [9]. The most feared part of the phenotype remains parainfectious rhabdomyolysis being a potentially life-threatening complication that leads to acute kidney failure characterized by acute severe proximal weakness and myalgia [5]. One episode of rhabdomyolysis in our boy's medical history was the essential point which suggested CCFDN diagnosis.

As already said, CCFDN diagnosis in mainly based on clinical findings. However, especially when the patient is the first in his family with this suspicion, the molecular confirmation must be done. CTDP1 is the only gene in which pathogenic variants are known to cause CCFDN. Targeted analysis identifies the pathogenic variant IVS6+389C>T in intron 6, the CTDP1 founder variant in the Roma ethnicity. CTDP1 maps to 18qter encoding a protein phosphatase whose only known substrate is the phosphorylated serine residues of the carboxy-terminal domain of the largest subunit of RNA polymerase II, indicating that CCFDN affects basic cellular processes of gene expression and developmental regulation [13].

The total number of affected individuals to date is approximately 170, all of Roma ethnicity [14]. The carrier rate for the c.863+389C>T pathogenic variant is approximately 7% among the Rudari (the Roma group most affected by the disorder) and approximately 1.4% in the general Roma population [15]. Allele frequency is extremely important for interpretation of variants and needs to be taken in account for founder effect in a given endogamous population. Cases of CCFDN were previously described by a group of paediatric neurologists in Romanian Roma ethnicity patients, but a carrier rate of the pathogenic variant in CTDP1 was not established yet [16,17].

The major differential diagnosis is the autosomal recessive Marinesco-Sjögren syndrome (MSS), similarly featuring cerebellar ataxia due to cerebellar atrophy, early-onset bilateral cataracts, chronic myopathy, variable intellectual disability and delayed motor development, along with short stature, dysarthria, strabismus, and nystagmus caused by mutations in the SIL1 gene [18]. Another similar disease is Galactokinase deficiency (OMIM 230200), an autosomal recessive rare mild form of galactosemia caused by another founder variant in Roma ethnicity (p.Pro28Thr in GK1 (GALK1)) characterized by early onset of cataract and an absence of the usual signs of classic galactosemia (feeding difficulties, poor weight gain and growth, lethargy, and jaundice. Because of the congenital cataract, Galactokinase deficiency is the main differential diagnosis of CCFDN in infants of Roma ethnic group [19,20]. As previously discussed, CCFDN was highly suspect in the proband and differential genetic diagnosis was postponed and later not needed.

Regarding the management and taking in consideration recent diagnosis of CCFDN in the two patients, recommended evaluations to establish disease's expression following initial diagnosis are to be completed with neurologic and orthopedic examinations, measurements of nerve conduction velocity for the girl, and brain MRI together with endocrinologic and bone density assessment for the two siblings.

Ethyologic treatment for CCFDN has not been discovered to date. Treatment of manifestations for the two children will respect the recommendations [14] and will focus on regular rehabilitation for peripheral neuropathy and to prevent osteopenia, corrective surgery for the secondary bone deformities, Vitamin D supplementation and hormone replacement therapy especially for the young girl if she is later diagnosed with amenorrhea. As the long-term outcome depends on the recurrence of rhabdomyolysis episodes it is very important to be aware and prevent rhabdomyolysis following viral infections and seek medical attention in emergency when suspected. If concluded, oral corticosteroid treatment for two to three weeks can result in full recovery within two to six months [5]. Other potentially life-threatening complications previously described are related to anesthesia (pulmonary edema, inspiratory stridor, malignant hyperthermia, and epileptic seizures) [21].

For follow-up, annual examinations including ophthalmologic, neurologic, and endocrine assessments were indicated.

Right inguinal hernia was our common case particularity, not previously described by any author in CCFDN. It remains the question whether there is an additional phenotype finding or just an incidental one.

Conclusions

This work highlights the essential tools in clinical practice and genetic counseling regarding Congenital Cataracts, Facial Dysmorphism, and Neuropathy. Based on the high allele frequency caused by founder effect, the pathogenic variant in CTDP1 causing CCFDN could've been and it still is an actionable genetic variant in this family. An earlier diagnosis in the girl, would've allowed a prenatal testing for the boy or at least a neurological and ophthalmological oriented fetal evaluation. The couple affirms they do not plan other pregnancies, but they are now aware of their high risk of another offspring with CCFDN, as all Roma endogamous subpopulation should be informed about. leukomalacia, intraparenchymal hemorrhage, cerebral atrophy, porencephaly, and hydrocephaly.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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PREMATURITY – A RISK FACTOR FOR CEREBRAL PALSY

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Abstract

The progress made in neonatal medicine led to a better survival rate of premature newborns of smaller and smaller gestational ages, which also led to a greater risk of complications such as cerebral palsy, whose incidence is increased to 1.5-5.6 per 1,000 live births among premature infants. The risk factors associated with prematurity in producing cerebral palsy are multiple. Of these, the most common are: corioamniotitis, fetal malpresentations, birth asphyxia, periventricular leukomalacia, intracranial haemorrhage, hypoxic-ischemic lesion. The clinical-etiological forms encountered are spastic hemiplegia, spastic tetraplegia, spastic diplexia and extrapyramidal dyskinesia. Prognosis is severely affected by the presence of epilepsy, deafness, hallucinations, strabismus, mental retardation (30-50%), attention deficit and autism. It is appreciated that 25% of patients with cerebral palsy have walking disorders. Cerebral palsy is considered a serious condition with immediate and long term sequelae that affects quality of life and social integration.

Key words: prematurity, cerebral palsy, risk factors

Introduction

Although the term cerebral palsy (CP) was first described more than a century ago, it still is a a very present subject due to its relatively high incidence among premature newborns [1].

First symptoms in the newborn and infant period are atypical, this is why some authors state that the diagnosis can be established only after the age of 3 (or 5 according to other authors) [2]. This is the case because of the association of also mental retardation in 30-50% of patients with CP and recurrent seizures (even epilepsy) in 50-60% of cases, signs that are not specific for CP [3].

Embriogenesis

The progress made in neonatal medicine led to a better survival rate of premature newborns of smaller and smaller gestational ages, which also led to a greater risk of complications. A rapid review of the principal stages of brain development may lead to a better understanding of the pathogenesis of the disease:

- 3-4 weeks of gestation – neurulation
- 2-3 months of gestation – development of the prosencephalon
- 3-4 months of gestation – neurogenesis
- 3-5 months of gestation – neuronal migration
- From the 5th month of gestation – organization of the cerebellum
- from birth to years – myelination [4].

Epidemiology

A prevalence of 1,5 – 5,6 of 1000 premature newborns [5] and 2 – 2,5 of 1000 term newborns is estimated [6]. Multiple studies show a higher risk of cerebral palsy among premature newborns (37-38 weeks of gestation), but also among postterm newborns (over 42 weeks of gestation) in comparison to full term newborns (40 weeks of gestation) [5]. Taking this into account, studies show that lesions that occur before 20 weeks of gestation can lead to neuronal migration disorders, lesions that occur betwen 26-34 weeks of gestation can lead to periventricular leukomalacia and those that occur between 34-40 weeks of gestation lead to focal or multifocal cerebral lesions [4,6].

The high incidence of CP among preterm newborns can be explained through the circulatory particularities, respectively the termination of the fetal cerebral circulation with periventricular white matter hypoperfusion. This leads to hemorrhagic lesions of the germinal matrix and/or periventricular leukomalacia. It is widely known that at 26-34 weeks of gestation, the periventricular white matter, especially at the exterior angles of the lateral ventricles, is the most vulnerable area [7,8].

Risk factors

From an etiologic point of view there are multiple risk factors associated to prematurity in producing CP. It is considered that 70-80% of cases appear mostly due to association of prenatal conditions and lesions. Studies show a correlation between an Apgar Score <5 and the high incidence of the disease [9].

The most frequently incriminated prenatal risk factors are: previous miscarriages, maternal mental retardation, maternal disease such as seizures, thyroid disorders, hypertension, maternal exposure to toxins (mercury), first trimester bleeding, multiple pregnancies [8,9].

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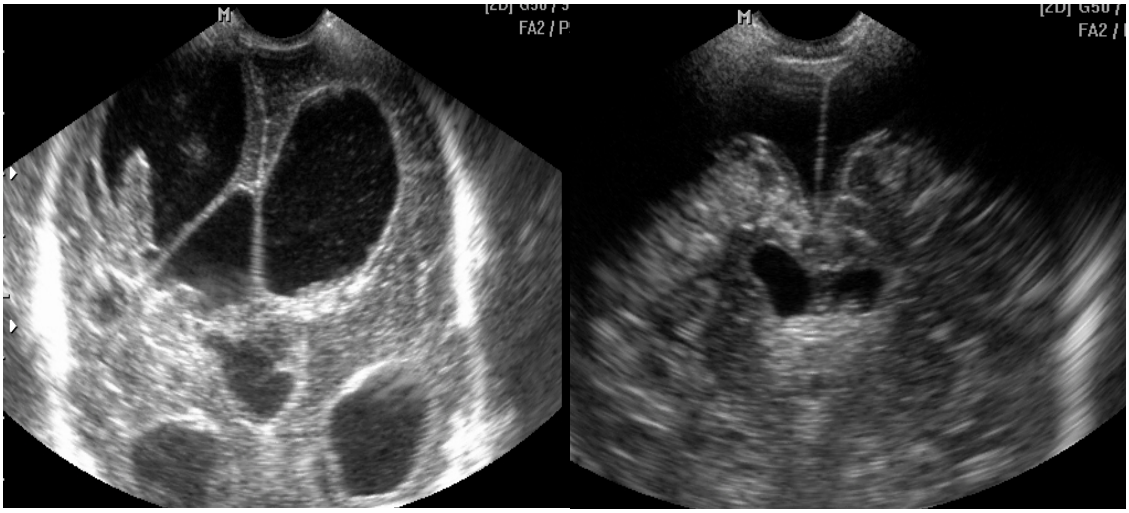

Fig. 1 and 2. Posthemorrhagic porencephaly and cerebral atrophy.

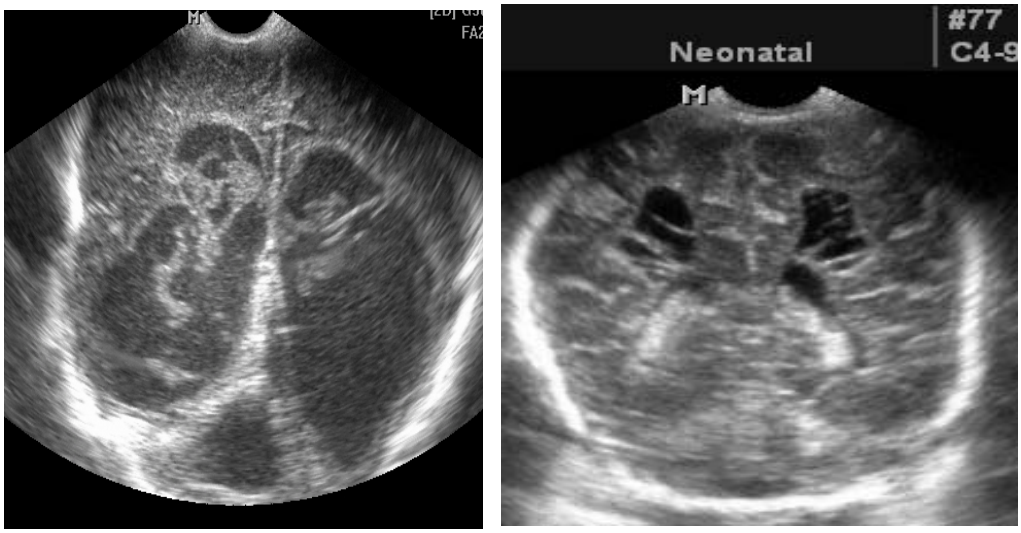

Fig. 3 and 4. Periventricular leukomalacia and severe peri/intraventricular hemorrhage (grade IV)

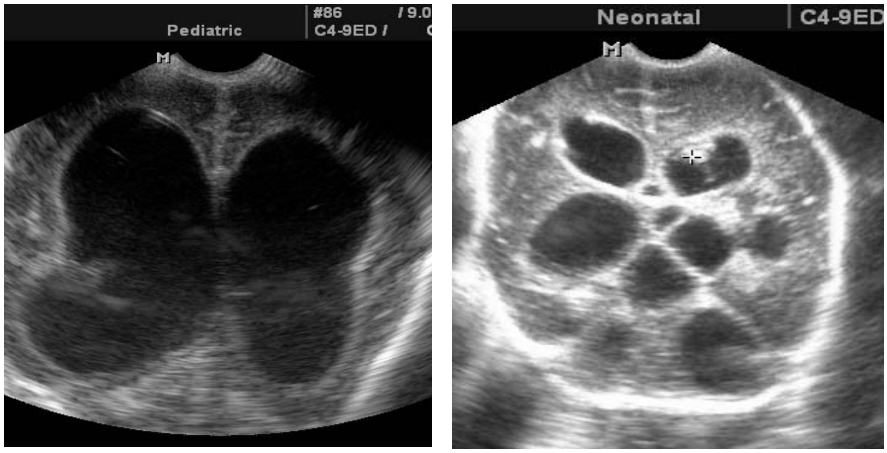

Fig. 5 and 6. Hydrocephaly and multicystic encephalomalacia.

The most common prenatal risk factors are: prematurity, chorioamnionitis, fetal malpresentations, birth asphyxia. In less than 10% of the cases, birth asphyxia cand be considered a cause of CP even if it occurs on a malformative background, growth restriction, severe maternofetal infections. Even in these cases, the classic diagnostic criteria for birth asphyxia have to be present: Apgar Score <4 at 5 minutes, fetal bradycardia, metabolic acidosis, multiple organ failure due to tissue hypoxia and early imaging changes [10].

Postnatal risk factors are also involved in the development of CP: periventricular leukomalacia (preterm newborns), intracranial hemorrhage, hypoxic ischemic lesion (meconium aspiration, pneumothorax), infections (meningitis, encephalitis, severe congential pneumonia), persistent fetal circulation (pulmonary hypertension of the newborn at term), nuclear jaundice [11].

Clinico-etiological forms

Spastic hemiplegia

The most frequent cases are congenital (70 – 90%) and only 10-30% of aquired causes [12].

It can be unilateral (the middle cerebral artery's teritory being the most frequent affected) and affect especially the left side (2 times more frequent than the right). From a neuropathologic point of view this type of lesion is produced on the basis of posthemorrhagic porencephaly (Figure 1), cerebral atrophy (Figure 2) and periventricular leukomalacia of the preterm newborns (Figure 3) [4].

Spastic diplegia

Is a controversial disease from an etiological point of view, especially for newborns at term. Among preterm newborns, periventricular leukomalacia and severe peri/intraventricular hemorrhage (grade IV) are most frequently involved. (Figure 4) [4].

Spastic tetraplegia

A severe form of cerebral palsy, that appears due to prenatal causes in 50% of cases, perinatal in 30% and postanatal causes in 30% of cases [5]. From a neuropathologic point of view the most common causes are: hydrocephaly (Figure 5), diffuse cortical atrophy, multicystic encephalomalacia – isolated or communicating with the ventricular system (Figure 6).

Extrapyramidal dyskinesia

Not so frequent in the common medical practice. Nuclear jaundice was the most frequent cause, but it's incidence decreased significantly. Other causes are: hypoxic-ischemic injury, prematurity, some cerebral degenerative diseases. Some cases caused by high bilirubin concentrations (without nuclear jaundice) are cited in specialized literature [10].

Hypoxic-ischemic lesions of the basal nuclei and talamus are more frequent among the term newborns than premature newborns [4].

Evolution and prognosis

Short term outcome is determined by the complication rate. The most common complications are: gastroesophageal reflux with aspiration pneumonia (sometimes with acute respiratory failure), absent or insufficient sucking and deglutition reflex, chronic constipation (even occlusion), chronic pulmonary disease (BPD – broncho-pulmonary dysplasia) [6].

Long term prognosis is severely affected by the presence of: epilepsy, deafness, halucinations, strabismus, mental retardation (30-50%), attention deficit, autism. 25% of the patients with cerebral palsy have walking disorders and 25% are severely affected and in need of intensive medical care [13].

Conclusions

1. Cerebral palsy is a serious condition, with immediate and long term sequelae that affect quality of life and social integration.
2. It is more frequent among preterm and postterm newborns. The most incriminated risk factors affect these age groups.
3. From a neuropathologic point of view, the most common lesions that cause cerebral palsy are: periventricular leukomalacia, intraparenchymal hemorrhage, cerebral atrophy, porencephaly, and hydrocephaly.

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DUODENAL ATRESIA - LATE RESULTS

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Abstract

Background: Duodenal atresia and stenosis are frequent cause of congenital intestinal obstruction. Current operative techniques and contemporary neonatal critical care are result of 5% decrease of morbidity and mortality rate. Late complications are not uncommon. Material and Methods: In this retrospective review has been shared the experience of Clinic for Pediatric Surgery - University Hospital "St. George "- Plovdiv for period of 20 years (1995- 2015), to identify long term results after operation for different forms of duodenal atresia. Results: Duodenal atresia or stenosis were identified in 60 patients. Late results are checked in 16. Nine children have required additional abdominal operations after initial repair including fundoplication (1), three children underwent revision of their initial repair: tapering duodenoplasty or duodenal plication (2), insufficiency of anastomosis (3) Conclusions: Late complications occur in 11 patients with congenital duodenal anomalies and associated anomalies, we have observed by 7 of them. Follow-up of these patients into adulthood is recommended to identify and describe late results.

Key words: duodenal atresia, late results, children

Introduction

Duodenal atresia and stenosis is a frequent cause of duodenal obstruction with frequency 1: 10 000 live births. Boys are affected more common than girls. Associated anomalies have observed more than 50% of cases. Down's syndrome occurs more than 30% of patients, polyhydramnion - to 50% of cases, and more than 40% are premature. Other associated anomalies could be found such as - pancreatic anomalies, esophageal atresia, malrotation, congenital heart anomalies, Meckel's diverticulum, imperforate anus. Anomalies of biliary tract are rarely observed.

In recent years, early postoperative survival rate has improved from 60% to 90%. With contemporary neonatal intensive care and improved operative techniques, the early morbidity and mortality rate is very low- around 5%. A few reports suggest that the late complications may occur around 15% of patients. The true incidence of long term complications and late results after initial repair of duodenal atresia is unknown. The availability of such information would be helpful for long- term care plan for these patients as they progress into childhood and adolescence.

Materials and Methods

For a 20- years period (1995- 2015) 60 infants with different forms of duodenal atresia have been operated in Clinic for Pediatric Surgery - University Hospital "St. George "- Plovdiv, Bulgaria. Late results checked in 16

Results

This study includes late results in 16 patients with different forms of duodenal atresia or stenosis. There are 9 girls and 7 boys. The oldest patient was 20 y.o, and the youngest - 2 y.o. Associated anomalies are observed in 7 patients: Down's syndrome- 3 patients, cardiac desieases -2 patients, craniostenosis- 1 patient, disorder of NPD- 1 patient. Late results are described on Table 1.

In two of the children as a late result of surgical treatment, we have observed gastric outlet obstruction has been determined, in two of these cases the contrast persists in the stomach more than 6h. after the procedure. After the first 12h. of the contrast investigation, no offset has been found in the stomach of all the patients. In two of the cases, after eating of dry food abdominal discomfort has been established by the parents. Gastroesophageal reflux is found in 2 of the patients. Three patients have defecated once per 2-3 days, which we have accepted as a constipation.

We have analyzed the latest results in 16 patients and we have compared them to the following indicators:

1. Food.

In 13 of the cases (81.2%) there are no problems neither complaints with the feeding after discharging. In 3 of the cases (18.8%) the liquids are more tolerated since they have an inability to take hard meals. (Table 2.)

2. Stool.

Defecation is one of the main criteria for checking. In 10 (62.5%) of the followed patients, the defecation is regular with normal consistency. We have found that in three of them, the stools were irregular during the first 1- 2 years after the operative treatment. Very often the children have a stimulated stool.

Example 1: Patient B.X., 2 y.o, has been operated as a newborn because of a membranous form of duodenal atresia. According to anamnesis, during the first year the child has had every day stimulated defecations. The GIT contrast study doesn't detect pathological changes in the duodenal region and the rest of the gastrointestinal tract (Figure 1). There is no evidence of contrast in the stomach (Figure 2) at the first hour.

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Late results	No
Gastroesophageal reflux disease	2
Megaduodenum	3
Gastric outlet obstruction	2
Abdominal discomfort	2
Constipation	3
Without complaints	5
All	16

Table 1. Late results.

	Frequency	%
Common food	13	81,2
Liquid food	3	18,8
Total	16	100,0

Table 2. Feeding at home.

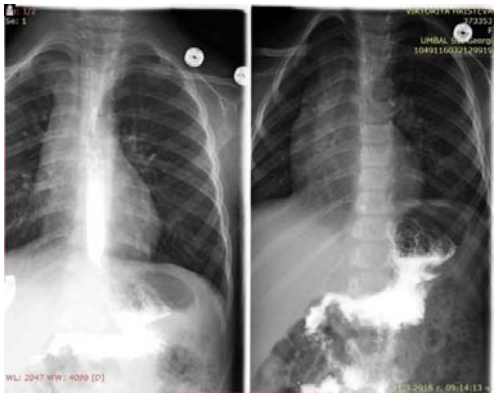

Fig. 1 The contrast material passed smoothly from the stomach to the duodenum, presented a normal shape and dimensions.

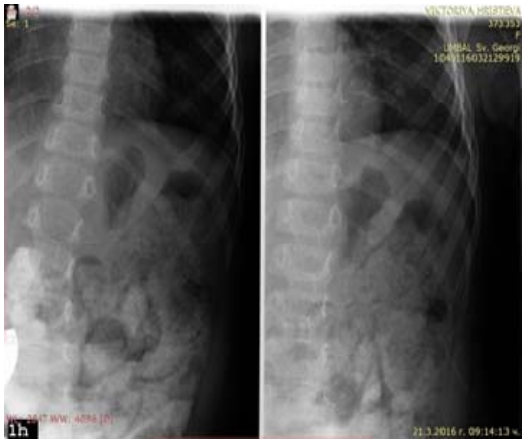

Fig. 2. No contrast material in the stomach after the 1st hour.

Vomiting	Frequency	Percent
Yes	13	81.3
No	3	18.7
Total	16	100

Table 3. Vomiting.

Passage description	Frequency	Percent
Without specifics	12	75
With specifics	4	25
Total	16	100,0

Table 4. Passage description.

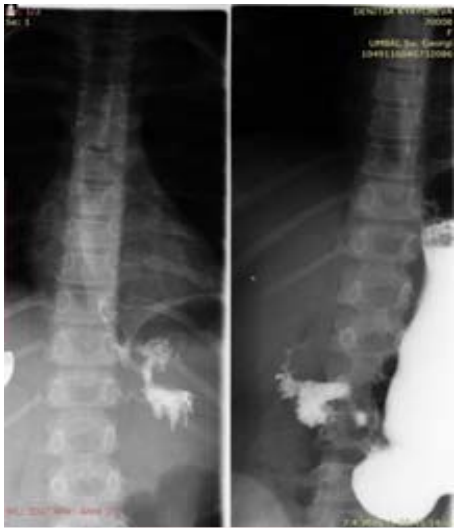

Fig.3. After introducing the contrast-stomach extended to the pelvis is visualized.

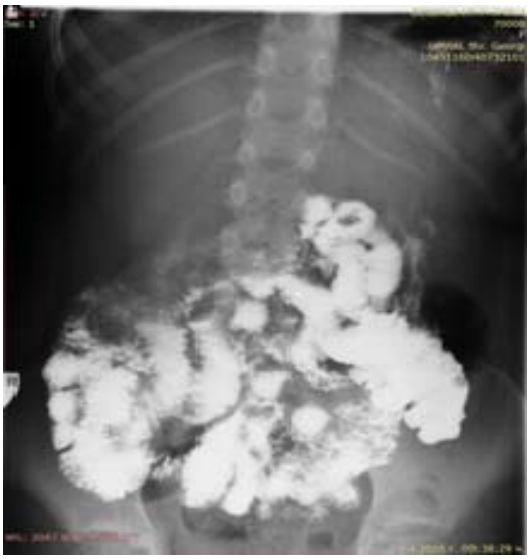

Fig. 4. At the second hour, the small intestine is completely in the right half of the abdomen.

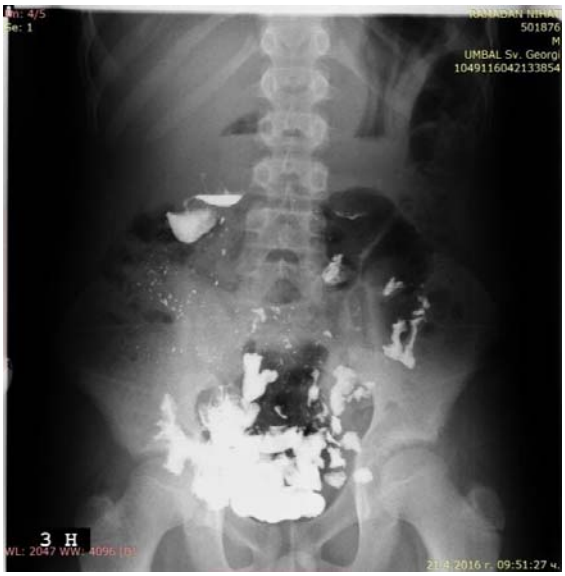

Fig. 5. 3 hours after the start of the study, a small part of contrast is visualized in the duodenum.

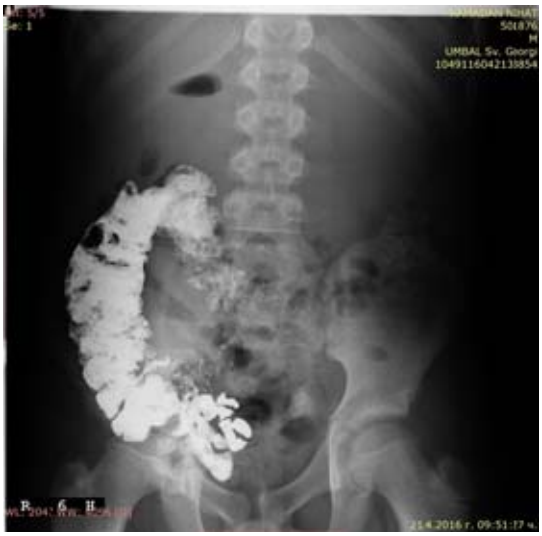

Fig. 6. 6 hrs. contrast reaches Colon transversum, and a small amount is in the terminal ileum.

In two (12.5%) patients defecations are irregular, and they needed enema stimulation every day. In these patients have been detected associated anomalies as craniostenosis and Down's syndrome.

1. Vomiting.

Vomiting is the other important symptom which is checked. In three of the cases (18.7%) vomiting is fixed after extra quantity feeding. (Table 3.)

2. GI contrast investigation.

GI contrast imaging is the main diagnostic method we use in all patients. It gives us the information of GIT condition and detects some possible pathology. (Table 4.)

Our 16 patients are followed by a contrast GIT investigation. In four of them (25%), we have detected deviations such as: megaduodenum, stomach dilatation, intestinal malrotation and GIT dismotility due to persistence of contrast in stomach and small intestine 3h after initiation of study.

Example: Patient D. K., 7 y.o. As a newborn, the child is operated because of a membrane form of duodenal atresia and Bride de LADD. When performing the contrast test, we found a strongly prolonged stomach reaching the pelvis without visualizing the bulbus duodeni, as well as malrotation of the intestine. (Figure 3,4)

Example: Patient R.N. 10 y.o. As a newborn child is operated because of duodenal atresia by performing duodeno - ileo anastomosis. According to the anamnesis, the child was eating well and has developed normally with regular defecation. From the contrast study a curved stomach was found. The contrast forms are horizontal level in the bulbus duodeni area and at the third hour a small amount of contrast is still in the duodenum (Picture 5). At the sixth hour the contrast reaches the transversal colon, but a small portion still appears in the field of the terminal ileum (Picture 6).

Discussion

The late results by our patients out of the given study are quite good. The oldest patient in our study is 20 years old female and she has no problems with feeding, body weight and stools. No megaduodenum and gastric outlet obstruction in contrast study is discovered. She is without associated anomalies. The youngest patient in our study is 2 y.o girl, she is operated because of duodenal obstruction - membrane form with no complications in the early postoperative period. She eats and gains weight normally. Defecations are problematic only with enemas and medicaments. Associated anomaly of this patient is Down's syndrome. Another patient is 5y.o. girl, who underwent operative treatment for duodenal atresia with duodeno - duodeno anastomosis, with no complications in early postoperative period. She has a cardiac defect as associated anomaly. Without vomiting till this moment, but she eats only liquid foods and lags behind the NDP. The patient has normal defecations.

Long - term problems may also occur because of other structural or chromosomal anomalies, the most common of which is trisomy 21. (2) Combination with Duodenal atresia or stenosis, malrotation and trisomy 21 can be found at rate of 10-20%. Relatively high mortality rates for duodenal obstructions associated with trisomy 21 have also been reported. That is unlikely in our cases. The effect of Down's syndrome on the death rate in our cases did not correlate with results reported in other studies. This rate may have significantly higher incidence of congenital heart anomalies. In later series, decreasing mortality rates have been reported. The overall survival rates of infants with anomalies associated with duodenal obstruction have improved over at the past several decades.

Early postoperative survival after the repair of duodenal atresia has steadily improved over the past 40 years, from approximately 60% to over 90% in practice, owing to improved neonatal and anesthesia management, total parenteral nutrition and more aggressive treatment of associated anomalies [3].

According to Nicola Lewis, long-term follow-up of these patients with different forms of duodenal atresia reveals that most of these children are asymptomatic with a normal nutritional status. Approximately 12% of patients develop late complications. Late deaths occur in approximately 6% of patients, and 50% of these are related to complex cardiac conditions. Fewer than 10% of patients require fundoplication for gastroesophageal reflux, and fewer than 10% require revision of the initial repair. (4)

Our results are comparable to those of the authors. When analyzing the late results of our patients, we have identified a absence of subjective complaints in a most of them. They have a normal nutritional status.

According to Escobar MA, Ladd AP, et al. Late complications occur in 12% of patients with congenital duodenal anomalies and the associated late mortality rate is 6%, which is low but not negligible.(5)

In our study we have found late complications in 20% of patients with duodenal atresia.

Intestinal malformations are common anomalies of the newborn and they must be treated in experienced centers. Reports of long-term follow-up and associated complications are insufficient and leading to misinterpretation of clinical symptoms later in childhood. To prevent treatment errors, it is important to keep in mind the late complications of duodenal atresia.

This study contributes to the treatment of duodenal obstructive pathology and its late postoperative results. Long lasting follow up of these patients gives an important information of quality of life of patients with this congenital anomaly.

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THROMBOCYTOPENIA- SHORT REVIEW OF THE ETHIOLOGIC AND THERAPEUTIC APPROACH

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Abstract

Thrombocytopenia is defined as a platelet count less then150.000/mmm3. Thrombocytopenia can be often asymptomatic or may present as an incidental finding during routine evaluation or during laboratory investigations performed for other reasons. Clinically is suspected when a child develops symptoms like petechial rash, easy bruising or bleeding, or mucosal hemorrhage. Bleeding risk generally increases with a low platelet count, because circulating platelets fulfill many critical hemostatic functions :adhesion to sites of vascular injury, secretion of mediators of hemostasis (eg, thromboxane, adenosine 5 diphosphate, serotonin, and histamine) cause firm aggregation via fibrinogen binding and increase local vasoconstriction, platelets are also necessary for normal clot retraction. The system used most often to categorize the different causes of thrombocytopenia is based on the underlying pathologic mechanism leading to the thrombocytopenia, that is, either increased destruction or decreased production of platelets or increased splenic sequestration (capturing of circulating platelets in the spleen). An important role is attributed to the history of the disease, that should document the timing and severity of present and past bleeding symptoms. Other components of the history may provide clues to the underlying etiology of thrombocytopenia. Physical examination and laboratory findings complete and establish the etiology of thrombocytopenia. Management of thrombocytopenia in an individual patient should be guided by an understanding of its cause and predicted clinical course. Correction of the cause may not be possible (eg, congenital thrombocytopenias) or may not be necessary (eg, mild-to-moderate ITP).The principal management goal in all patients who have thrombocytopenia is to maintain a safe platelet count as to prevent significant bleeding, not to achieve a normal platelet count. What constitutes a safe platelet count in a particular patient varies, depending on the cause of the thrombocytopenia and consideration of all other aspects of hemostasis. For patients who have significant bleeding symptoms treatment is essential.

Key words: thrombocytopenia, child, etiology, bleeding, laboratory findings, treatment

Introduction

Thrombocytopenia is defined by the decreased number of blood platelets below the threshold of 150,000 per mm3. Thrombocytopenia may be the consequence of the following four pathogenic mechanisms:

- ***platelet production deficit***
- ***accelerated platelet destruction***
- ***abnormality of total platelet mass distribution***
- ***artefactual thrombocytopenia***

1***) Decrease in platelet production*** can be seen in the following situations:

- primary malignancies (leukemias), bone marrow infiltration, bone marrow insufficiency (aplastic anemia), viral infections (HIV, EBV, CMV, rickettsia, etc.), cyanogenic heart diseases, nutritional deficiencies; ineffective thrombopoiesis of genetic cause:

- thrombocytes with small dimensions: Wiskott Aldrich syndrome;

- platelets with normal dimensions: TAR (thrombocytopenia -absent radius), Congenital amegakaryocytic thrombocytopenia, familial platelet disorder with propensity to myeloid malignancy;

- giant platelets: Bernard-Soulier disease, MYH9-related disorders, Paris Trousseau syndrome, X Linked thrombocytopenia with dyserythropoiesis

2) ***Increased platelet consumption.***

a. ***Immune Causes:*** Immune Thrombocytopenic Purpura (ITP) - the most common cause of thrombocytopenia in children, Neonatal alloimmune thrombocytopenia, Evans Syndrome, collagenosis and autoimmune diseases

b) ***Non-immune causes:*** drug toxicity (heparin, vancomycin, trimethoprim-sulfamethoxazole), measles-mumps-rubella vaccine, platelet activation and increased consumption (disseminated intravascular coagulation, hemolytic and uremic syndrome, sepsis, thrombotic thrombocytopenic purpura, Kasabach-Merrit syndrome), mechanical destruction by hemodialysis, apheresis, cardiopulmonary bypass

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3) ***Platelet mass distribution abnormality (platelet sequestration)*** from hypersplenism encountered in infections, inflammation, red blood cell disease, storage diseases (eg portal hypertension in advanced liver cirrhosis, leukemia, lymphomas). This mechanism can also be seen in the case of hemangiomas or in the case of hemodilution (recent blood transfusion in large quantities).

4) ***Artifactual or false thrombocytopenia*** is a laboratory abnormality determined mainly by the presence of giant platelets or platelet agglutination (pseudo thrombocytopenia). Agglutination of platelets occurs in the presence of anticoagulant agglutinins (immunoglobulin A, M, G). This phenomenon is commonly encountered when blood collection is made in a container containing an EDTA-type anticoagulant.

Clinical manifestations and evaluation of thrombocytopenia in children

Evaluation of clinical manifestations/medical history

Anamnesis may provide important details on the timing / modality of occurrence and possibly the history of haemorrhagic events. The association of systemic signs and symptoms, family history, and personal pathological antecedents should be analyzed accurately. Drug history, any prodromal diseases (background diseases, history of respiratory infections), past blood counts, food survey, trips in endemic areas (malaria) may suggest the etiology of thrombocytopenia.

Clinical examination may reveal bleeding into the skin: skin purpura (petechiae, ecchymosis) - small dots, generally pinpoint, smooth, flat, painless, purple and do not blanch under pressure; rarely they can be pruritic; vibices - linear layout in the flexion folds, rarely hemorrhagic spots are filled with blood serosity, the rash having the character of serous bubbles. Bleeding in the mucous membranes (oral/nasal mucosa, soft palate, gums, lingual mucosa, conjunctival mucosa) such as epistaxis, gingivorrhagia, oral haemorrhagic blisters are common manifestations found in thrombocytopenia, regardless of etiology.

Clinical examination requires a correct inspection and classification of the haemorrhagic signs, their location and monitoring their dynamics. The presence of adenopathy, splenomegaly and / or hepatomegaly raises the suspicion of leukemia, lymphoma, chronic liver disease with Portal Hypertension, possibly viral infections. Sensorineural deafness-macrotrombocytopenia-cataract manifestations orientates towards the diagnosis of Fechtner syndrome, congenital leukoplakia- dyskeratosis.

The history of arthralgia / arthritis, prolonged febrile syndrome suggests a possible vasculitis or collagenosis (Systemic lupus erythematosus), and the association of skeletal abnormalities of absent radius type determines the diagnosis of TAR (Thrombocytopenia with absent radii) syndrome; the presence of skeletal abnormalities or spots café au lait in combination with thrombocytopenia, can be seen in Fanconi anemia. Other skin changes such as eczema accompanied by a history of recurrent infections (immune deficiency) determine the diagnosis of Wiscott-Aldrich syndrome; the presence of vascular tumors is encountered in Kasabach-Merritt's syndrome. Intracranial haemorrhage is the most serious consequence of thrombocytopenia and involves an increased risk of neurological complications

Laboratory evaluation of thrombocytopenia

Complete blood counts should be considered as a whole because the platelet count and the mean platelet volume(MPV) should be correlated with the white line and the red line.

Analyzing thrombocytopenia according to the mean platelet volume may reveal the following diseases:

- Low MPV(<7 fL): Wiscott Aldrich syndrome, X-linked thrombocytopenia
- normal MPV (7-11fL): Congenital amegakaryocytic thrombocytopenia, Thrombocytopenia with absent radii syndrome, Amegakaryocytic Thrombocytopenia associated with radioulnar synostosis, familial platelet disorder with propensity to myeloid malignancy
- MPV> 11fL: MYH9-related diseases; Bernard Soulier's syndrome, DiGeorge syndrome; ParisTrousseau syndrome; von Willebrand type 2B disease; X-linked thrombocytopenia with dyserythropoiesis / thalassemia.

Peripheral blood smear is a reference investigation on the estimation of platelet count, their morphology, the presence / absence of platelet aggregates; possible abnormalities of the white and red lines. The presence of blasts suggests a leukemic process; sometimes blasts are difficult to distinguish from atypical lymphocytes (sometimes present in immune thrombocytopenia or immune thrombocytopenic purpura) in the case of an infection in the near history.

The presence of small hypochromic red blood cells can be found in massive bleeding and the presence of schizocytes suggests a microangiopathic process (disseminated intravascular coagulation, hemolytic and uremic syndrome, thrombotic thrombocytopenic purpura), the presence of spherocytes is orientates to an autoimmune hemolytic anemia, which in the presence of immune-mediated thrombocytopenia establish the diagnosis of Evans syndrome.

A medulogram is not routinely recommended in the investigation of isolated thrombocytopenia if there is no suggestive symptom for infiltration / medullary insufficiency. This investigation is indicated in patients with chronic stable thrombocytopenia with a presumptive diagnosis of immune thrombocytopenic purpura at 6-12 months after debut.

Other tests such as coagulogram, Coombs test, D dimer, fibrin degradation products, antinuclear antibodies(AAN), anti-CMV antibodies, EBV, HIV, HCV, serum immunoglobulins, abdominal ultrasound / tomography, platelet kinetic studies / spleen scintigraphy are required in case of association of signs and symptoms specific to suspected etiology.

Both from the clinical and laboratory point of view, the elements of gravity which should be carefully analyzed can be determined,: the association at the onset or during evolution of haemorrhagic phenomena that interest the abdomen, oral haemorrhagic blisters, hematuria, retinal haemorrhage, meningocerebellar haemorrhage as well as the

association of hemostasis abnormalities or platelet counts below 10,000/mm3.

Platelet count is closely linked to the risk of bleeding, so it is imperative to correlate thrombocytopenia with the type of clinical manifestations. Thus, the absence of clinical manifestations necessitates a repeat of the complete blood count, and the harvesting method may detect the existence of technical errors or the use of EDTA (artefactual thrombocytopenia).

In general, the risk of bleeding does not increase until the platelet count falls significantly below 100,000/mm3. For example, surgical bleeding solely due to a decreased platelet count typically does not occur until the platelet count is less than 50,000/mm3 and spontaneous bleeding typically does not occur until the platelet count is less than 20,000/mm3.

Therapeutic approach of thrombocytopenia
General principles

The therapeutic management of thrombocytopenia should be individualized according to etiology and clinical evolution, and sometimes correction of the thrombocytopenia cause is not possible or not necessary.

The primary goal is to maintain platelet counts at a safe level to prevent bleeding, and the level of platelet safety varies from one patient to another and is dependent on the cause of the thrombocytopenia;

Patients at high risk for bleeding require immediate treatment, and in the case of asymptomatic thrombocytopenia or with minimal symptomatology, therapy may be required if the thrombocytopenia is severe or if the risk of bleeding is elevated.

Restriction of physical activity is indicated in moderate and severe thrombocytopenia, precautions are required for possible trauma, avoiding contact sports. Also, antiplatelet or anticoagulant medication (aspirin, ibuprofen or other non-steroidal anti-inflammatory drugs) should be avoided.

Invasive procedures - a platelet count of more than 50,000 / mm3 is safe for most invasive procedures, but if the risk of bleeding is major, the safety level more than 100,000 / mm3. Corticotherapy in short dose (Prednisone 2mg / kgc, 7 days) or a single dose of IG IV (1g / kg) is sufficient to increase the number of platelets prior to procedures requiring haemostasis. Platelet concentrate administration in emergency situations is indicated because it provides prompt and satisfactory, but short-term hemostasis.

Critical bleeding management - Severe thrombocytopenia with massive bleeding requires a platelet concentrate, regardless of etiology. Intracranial haemorrhage is the most serious complication of severe thrombocytopenia with neurological symptoms and imaging is imperative, sometimes craniotomy being necessary. Patients with immune thrombocytopenic purpura and life threatening bleeding may receive pulse therapy with methylprednisolone (30mg / kg / day) besides platelet concentrate.

Therapeutic approach of neonatal thrombocytopenia.

Special attention should be paid to thrombocytopenia during the neonatal period.

In most cases, thrombocytopenia resolves spontaneously without any complications.

Platelet concentrate transfusion is reserved for cases with active bleeding or hemorrhagic signs: umbilical cord bleeding, numerous petechiae or extensive ecchymosis, cephalhematoma, or asymptomatic neonates with severe thrombocytopenia.

Newborns with allo-immune ITP have an increased risk for cerebral haemorrhage, (possibly intrauterine), which is why transfontanelar ultrasound is performed. The presence of intracerebral haemorrhage requires the administration of high doses of platelet concentrate, especially if platelets <100,000 / mm3. The administration of platelet concentrate is indicated in any required surgical intervention, even if the platelet values are more than 100,000 / mm 3; This intracerebral hemorrhage requires administration of high doses of platelet concentrate, in particular if the values of platelets <100,000 / mm3.

The risk of intracranial hemorrhage is greatly increased in the immediate perinatal period, it is necessary to maintain the values more than 50,000 / mm3 in the first 72-96 hours of life; after the first 96 hours of life, the decision for platelet concentrate transfusion depends on the clinical manifestations of each newborn.

Conclusions

1. Thrombocytopenia should be suspected in all patients with history of petechiae, bruising or bleeding, but can also be detected in asymptomatic patients.
2. Thrombocytopenia has as its mechanism in either increased destruction or removal of platelets from the circulation, or in the decrease in their production;
3. Physical examination corroborated with the history of the disease and the judicious use of laboratory data can accurately determine the etiology of thrombocytopenia;
4. Therapeutic management of thrombocytopenia is based on etiology and clinical evolution, the main aim being to obtain a safe level of platelets.
5. Neonatal thrombocytopenia resolves spontaneously, without complications, in most cases; establishing etiology requires specific treatment. Management of neonatal thrombocytopenia with high risk of life-threatening hemorrhage requires urgent administration of platelet concentrate, and diagnostic evaluation is continued thereafter.

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A CLINICOPATHOLOGIC AND IMAGISTIC REVIEW OF THREE CHILDREN WITH WILMS TUMOUR

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Abstract

Wilms tumour, also known as nephroblastoma, is the most common pediatric abdominal malignancy that occurs in early childhood with peak incidence between 2 and 4 years of age. The majority are unilateral, less than 5 % occurring bilaterally. The clinical presentation is typically with a painless left or right upper quadrant abdominal mass. In the following presentation we want to discuss the diagnostic clinicopathologic and imagistic workup of three male patients aged 1 to 2 years old with Wilms' tumor admitted in the Hematology Oncology Department of Pediatrics I Clinic, in Targu Mures in the second half of 2017

Key words: nephroblastoma, childhood, clinicopathologic

Introduction

Nephroblastoma is the second most common abdominal tumor in children. It represents approximately 6% of all pediatric cancers and accounts for more than 95% of all tumors of the kidney in the pediatric age group. Young children in the age range of 3 – 4 years are normally affected by this disorder (1). The majority of Wilms tumors are sporadic, however in a few of them, it occurs associated with syndromes including aniridia, hemihypertrophy or genitourinary malformations (cryptorchidism, hypospadias, horsshoe kidney) (2). Roughly 20% of all Wilms tumors carry WT1 mutation located on the chromosome 11p13, and most of these patients associate congenital anomalies and syndromes such as WAGR Syndrome, Denys Drash and Beckwith-Wiedemann (3,4,5). Normally, only one kidney is affected with Wilms tumor; however, in about 5% of the cases, both kidneys may have tumors. Most children with Wilms tumor present with increasing size of the abdomen or an asymptomatic abdominal mass that rarely crosses the midline, though it can extend inferiorly to the pelvis; also fever, vomiting, nausea, loss of appetite, microscopic hematuria and high blood pressure may be present (6,7). Once it's discovered a complete physical examination followed by a complete blood count, liver and kidney functions and specific tumor markers should be performed. Imaging studies include ultrasonography, CT and/or MRI, also radiographic examination of the chest is required to determine the presence of pulmonary metastases (8). Willms tumor must also be differentiated from a variety of malignant abdominal and pelvic tumors such as neuroblastoma, non-Hodgkin lymphoma, rhabdomyosarcoma, germ cell/teratoma, hepatoblastoma. Once the diagnosis is confirmed, accurate staging is imperative because appropriate therapy, as well as prognosis, is based on tumor stage (9). The histological type of the tumor has implications for therapy and prognosis: favorable histology refers to classic triphasic Wilms tumor composed of three elements: blastema, epithelia and stroma, unfavorable histology refers to the presence of anaplasia (8). Anaplasia is present in about 5% of Wilms tumors and is more common in older children, reaching a peak at approximately 5 years of age. Anaplasia can be focal or diffuse, with the focal subtype being somewhat more favorable (10). One of the main controversies in the treatment of children with unilateral Wilms tumor is whether or not to administer preoperative chemotherapy. The International Society of Pediatric Oncology (SIOP) recommends giving Vincristine and Dactinomycin chemotherapy before nephrectomy and classifies the pretreated renal tumors in low-risk tumors, intermediate-risk tumors (epithelial, stromal, mixed, focal anaplasia) and high-risk tumors (blastemal type, diffuse anaplasia, clear cell sarcoma, rhabdoid tumor) (11,12). The role of surgery in the therapy of Wilms tumor is very important because a well-performed procedure will accurately determine the stage of the disease and future therapy: Stage I the tumor is confined to the kidney and by definition, is excised completely with the capsular surface intact; Stage II the tumor is also confined to the kidney, but the capsule is penetrated or tumor is present in the perirenal soft tissue; Stage III tumor has post surgical residual non-hematogenous extension (lymph nodes); Stage IV tumor is characterized by hematogenous metastases (lungs, liver); and Stage V is characterized by bilateral renal involvement (8,13,14).

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Complete blood count	Case 1	Case 2	Case 3
Leukocytes (10^9/L)	19,6	8.48	9,65
Neutrophyls (10^9/L)	13,58	3,15	3,15
Erythrocytes (10^{12}/L)	3,9	4,6	4,1
Hemoglobin (g/dl)	10,7	11,7	11,1
Platelets (10^9/L)	67,7	176	231
Reticulocytes (‰)	23	19	12
Biochemical analysis			
Sedimentation rate (mm/h)	59	35	30
C- reactive protein (mg/L)	2	0.99	5
AST (U/L)	54	449	37,7
ALT (U/L)	7	706	15,5
Ureea (mg/dl)	18,96	28,31	31
Creatinine (mg/dl)	0,43	0,39	0,30
Glucose (mg/dl)	86	95	100
Serum Calcium (mmol/l)	2	1,98	2,06
Alkaline phosphatase (U/L)	106	246	368
Serum Total Proteins	4.02	11,56	16,12
Urinalysis	Microscopic hematuria	Microscopic hematuria	Hypostenuria

AST=Aspartate Aminotransferase, ALT=Alanine Aminotransferase
Table 1. Laboratory Findings of Case Reports

Tumoral markers and serology	Case 1	Case 2	Case 3
Vanillylmandelic acid (mg/24h urine)	2,58	1,18	2,46
Neuron Specific Enolase (ng/ml)	216,7	29,63	23,53
Serum Copper µg/dl	154,3	156,6	-
Ig G Anti EBV antibodies	Positive	Negative	Positive
Ig M Anti EBV antibodies	Negative	Negative	Negative
Anti HCV antibodies	Negative	Negative	Negative
Antigen HBs	Negative	Negative	Negative
Ig G Anti CMV antibodies	Negative	Positive	Negative
Ig M Anti CMV antibodies	Positive	Negative	Negative
Ig G Anti Toxoplasma antibodies	Negative	Negative	Negative
Ig M Anti Toxoplasma antibodies	Positive	Negative	Negative
HSV type 1, 2	Positive	Negative	Negative
HIV	Negative	Negative	Negative

EBV=Epstein Barr Virus, HCV=Hepatitis C Virus, HBV=Hepatitis B Virus, CMV=Cytomegalo Virus, HSV=Herpes Simplex Virus, HIV= Human Imunodeficiency Virus
Table 2. Laboratory Findings of Case Reports

The patency of the (inferior vena cava) IVC should be established prior to the resection; if it is not patent, preoperative chemotherapy should be administered (15). The chemotherapy guidelines proposed for stage I and II tumors with favorable histology, Vincristine and Dactinomycine, for stage III and IV tumors with favorable histology – Vincristine, Dactinomycine and Doxorubicine plus radiotherapy (3). For tumors with unfavorable histology, Vincristine, Dactinomycine, Doxorubicine and Cyclophosphamide is administered together with radiotherapy (3,16). The prognosis for patients with Wilms tumor is quite good, compared to the prognosis for most types of cancer. The patients who have the best prognosis are usually those who have a small-sized tumor, a favorable cell type, have less than two years old and have an early stage of cancer that has not spread (17). Long-term survival approaches 90% in localized disease (13,18).

Case series

The following presentation takes into consideration the overall clinical, pathological and imagistic characteristics for the diagnosis of Wilms tumor.

Case 1: First is a 2 year old male patient diagnosed in July 2017. The onset of the disease was one week before admission with poor appetite, followed by abdominal pain and vomiting. From the emergency room he receives symptomatic treatment at home, but the general condition worsens, associating fever above 38oC so the mother returns to the emergency room. Here an abdominal ultrasound reveals an 8 cm inhomogeneous tumor with calcifications in the left renal parenchyma. The suspicion of Wilms tumor is raised for which he is hospitalized in the Hematology-Oncology Compartment. Clinical examination and anamnesis at admission reveal no personal history of illnesses before this age, poor general state, normal colored skin, normal colored pharynx and tonsils, bilateral painless submandibular lymph nodes. Palpable large, firm mass in the left abdominal flank, with increased sensitivity of this area, liver in normal limits, spleen difficult to asses due to the abdominal tumor, poor appetite, slow intestinal transit (stools once every three days), bilateral cryptorchidia, dysuria, weight: 14kg. Over the course of admission, another abdominal ultrasound is performed for a much detailed description of the characteristics of the tumour and the findings were: liver 88.5/48mm, homogeneous echostructure, increased echogenicity, spleen within normal range, right kidney with normal size for age, left kidney occupied by a 118/78.6mm inhomogeneous, well defined tumor, with Doppler signal accentuated at the periphery, left kidney with disorganized structure and grade 2 hydronephrosis. A contrast CT scan is performed on the thorax, abdomen and pelvis showing absence of suspected lung nodules and no pathological lymph nodes on the mediastinal or axillaries level with minimal left pleural effusion. Abdomen CT scan revealed an inhomogeneous density mass with approximately 88/93/124mm, with areas of necrosis, with compressive effect on jejune and descending colon, without images of left renal vein thrombosis and IVC involvement, sub hepatic, perisplenic free fluid and in Douglas recess, retroperitoneal lymph nodes up to 8 mm (Figure 1). Laboratory tests as seen in Table 1 and Table 2 performed also for the differential diagnosis, confirmed the diagnosis of Wilms tumor, thus cytoreductive treatment is initiated with Vincristine and Dactinomycine D (4 weeks). The abdominal ultrasound 20 days after initiation of cytoreduction reveals a reduction in tumor size at 107/68mm. During this period of time a series of investigations were performed in order to establish the loco-regional invasion and possible secondary determinations of the tumor: cardiology examination with ultrasound parameters, neuropsychiatry examination and ophthalmologic exam within normal limits. To complete the set of laboratory tests a bone marrow exam was performed that did not show tumor invasion. One month after diagnosis, left nephrectomy is performed followed by tumor biopsy and the histopathology examination reveals a triphasic Nephroblastoma with predominance of the mesenchymal component (85%), the blastematic component below 66% (intermediate risk). The examined tumor tissue also presents extensive areas of necrosis (<50%) and the tumor infiltrates the fibrous pseudo capsule and tears up the renal capsule without infiltration of the basin and kidney hilum. There is no angio-lymphatic invasion. Afterwards the patient followed treatment according the Nephroblastoma SIOP stage I protocol for low/ intermediate risk with Dactinomycine, Vincristine and Epirubicin.

Case 2: Second case is a 1 year old male patient diagnosed in July 2017. The onset of the disease is about 3 weeks prior to admission, with persistent fever (2 weeks), poor appetite and altered general condition, for which he receives antipyretic treatment. Pediatric reevaluation discovers hepatic cytolysis, Ig M EBV positive and abdominal ultrasound reveals a tumor in the left kidney. He is admitted at Hematology-Oncology Department of Pediatrics I, Targu Mures, where investigations continue. Anamnesis reveals he was born prematurely at 35 gestational weeks through c-section, SGA (small for gestational age) weighing 1920g, subsequently hospitalized for transient neonatal hypoglycemia. Clinical assessment at admission reveals: influenced general condition, pale skin, capillary refill time ~ 3 sec, bilateral submandibular lymph nodes, painless, laterocervical and inguinal palpable lymph nodes, symmetrical bilateral vesicular murmur, no rallies, rhythmic heartbeats. Distended abdomen, apparently painless at palpation, umbilical hernia, liver at about 2 cm below right costal rib, palpable spleen, present intestinal transit, normally conformed external genitalia, weight 10 kg. The abdominal ultrasound reveals hepatomegaly with liver of 86/41mm, spleen with normal size for age, right kidney with normal size for age, left kidney occupied by a 99/46mm tumor, presenting fine septa to the upper pole, not exceeding the renal capsule, with present Doppler signal. Also a CT scan of the thorax, abdomen and pelvis is performed showing a well defined parenchymal tumor developed in the left kidney, native homogenous, discreetly inhomogeneous post contrast, with iodophylia slightly pronounced at the tumor capsule, with fine septa, other abdominal, thorax and pelvis structures with normal appearance (Figure 2).

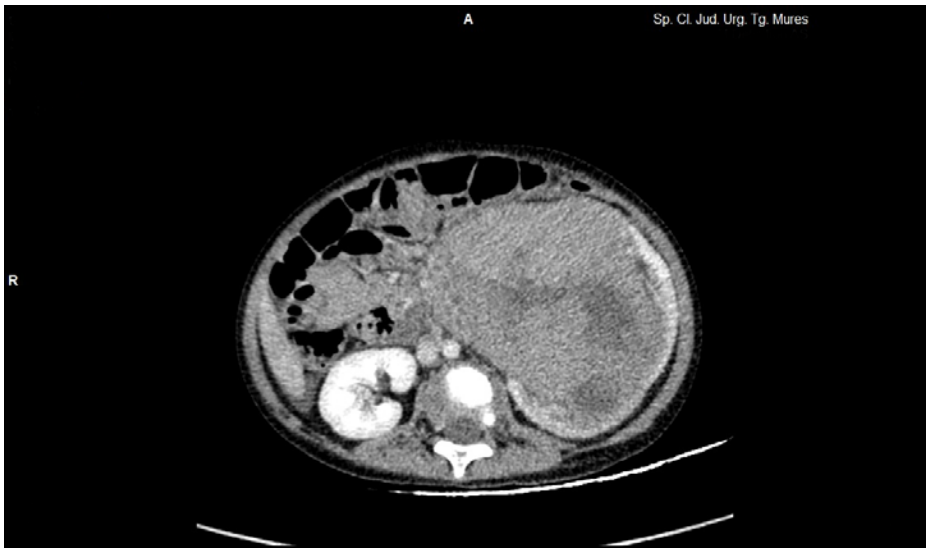

Fig. 1. (Case 1): Enhanced axial CT section of the abdomen demonstrates a very large inhomogeneous density mass arising from the left kidney displacing the remaining renal parenchyma, with areas of necrosis and compressive effect on jejune and descending colon. No involvement of the renal vein or IVC.

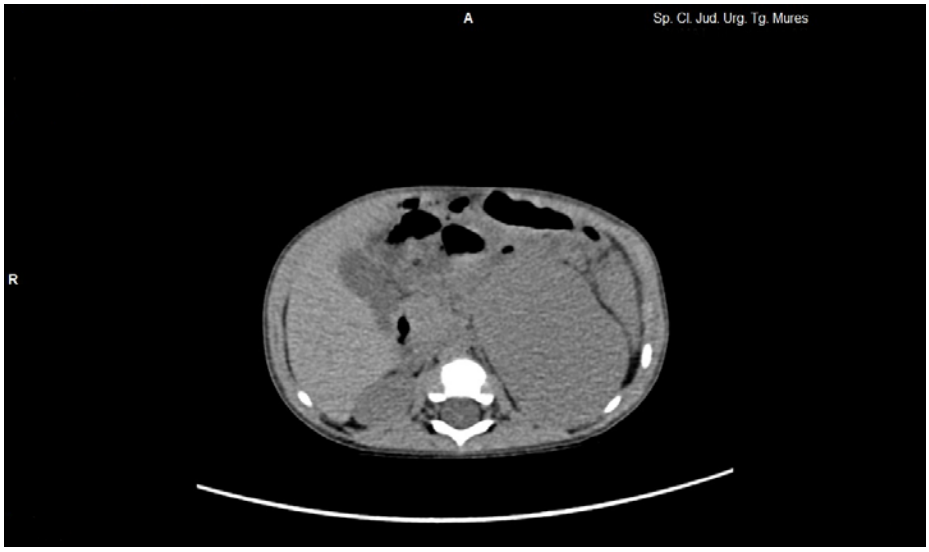

Fig. 2. (Case 2): Unenhanced axial CT section of the abdomen demonstrates a well defined native homogenous parenchymal tumor developed in the left kidney, without involvement of the renal vein or IVC.

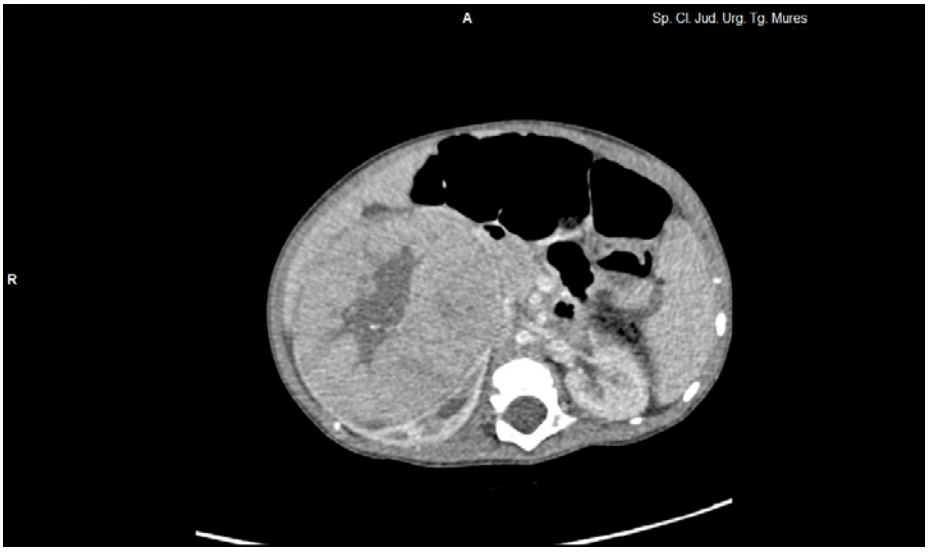

Fig. 3. (Case 3): Enhanced axial CT section of the abdomen confirms the presence of a right kidney tumor with central necrosis and hemorrhagic areas, exerting a compressive effect on IVC but still permeable.

Laboratory tests as seen in Table 1 and Table 2 performed also for the differential diagnosis, confirmed the diagnosis of Wilms tumor, so chemotherapy is initiated according to the SIOP 93-01 protocol, stage I, cytoreductive phase. Abdominal ultrasound 10 days after initiation of cytoreduction reveals a reduction in size of tumor at 91/44mm. Investigations were performed in order to establish the regional invasion and possible secondary determinations of the tumor: cardiology examination with ultrasound parameters, ophthalmologic exam within normal limits, neuropsychiatric examination diagnosed a mild hypotonia, also bone marrow exam was performed that did not show tumor invasion. After 4 weeks from the diagnosis left nephrectomy is performed, the total weight of the tumor and left kidney being 77g. The histopathology result classifies the tumor as a high-risk, stage I monophasic Nephroblastoma with more than 66% blastematic component. The tumor does not infiltrate the fibrous capsule, renal capsule and kidney. No angio-lymphatic invasion or tumor necrosis is observed. The surgery is followed by chemotherapy treatment (high grade stage I, no radiotherapy) with Etoposide and Carboplatin alternately once every three weeks with Epirubicinum and Ifosfamidum.

Case 3: The third case is a 1 year old patient diagnosed in October 2017. The onset of the disease is characteristically with an asymptomatic abdominal mass discovered by the parents the previous day. The patient is admitted to the Pediatric Hematology-Oncology Department of the Pediatrics I Clinic in Targu Mures for further investigations. Personal history reveals he was born prematurely at 34 weeks of gestation through Caesarean section (for pelvic presentation) with birth weight: 2560g. Physical examination on admission reveals a good general state, pale skin, dolichocephalism, anterior fontanel of 1.5/1cm, facial dysmorphism with micrognathia and viciously inserted dentition, no palpable lymph nodes, rickets rosary on thorax with flared bases, rhythmic heartbeats. Abnormal, globular abdomen, sensitive on the right abdominal flank, palpable tumor on the right abdominal flank with the lower edge to the right iliac fossa, liver hardly accessible due to the formation, non-palpable spleen, capricious consumption, intestinal transit present, normal external genitalia, weight 9.5kg. During hospitalization the abdominal ultrasound revealed a rounded-oval shape tumor of 98/98mm, exceeding the median line with a maximum diameter of 103 mm, with peripheral Doppler signal present. The renal structure of 38/18 mm is visualized at the upper pole, 7 mm pylon; the tumor exerts a compressive effect on large vessels, also retroperitoneal lymph nodes of 11mm are seen. Abdominal CT scan confirmed the presence of a right kidney tumor with dimensions of 95/88/93mm, with central necrosis and hemorrhagic areas, exerting a compressive effect on IVC but still permeable (Figure 3). Laboratory tests as seen in Table 1 and Table 2 performed also for the differential diagnosis, confirmed the diagnosis of Wilms tumor. Chemotherapy is initiated according to the SIOP 93-01 protocol for nephroblastoma, cytoreductive phase (Dactinomycine + Vincristin). In order to establish the regional invasion and possible secondary determinations of the tumor cardiologic examination was performed with normal ultrasound parameters, ophthalmologic exam within normal limits, neuropsychiatric examination was normal, also bone marrow exam was performed that did not show tumor invasion. Thoracic X-ray and cranial CT scan were negative.

Cytogenetic and molecular biology examination showed no variation in the number of copies at the level of the examined regions and no methylation defects have been revealed at the level of the examined regions at 11p15 level. At 4 weeks after diagnosis the repeated abdominal CT shows a reduction in tumor size (83/76/82mm) with the persistence of compressive effect on IVC, with bilateral nephrogram present. Afterwards total right nephrectomy is performed + tumor excision (total weight 234g), tumor biopsy and mesenteric ganglion biopsy and appendectomy. The histopathology examination confirms the diagnosis of the Wilms tumor (triphasic nephroblastoma with predominance in relatively equal proportions of the epithelial and blastematic component, with reduced mesenchymal component, associated with focal anaplasia), the tumor tissue infiltrates the capsule, but does not extend to the kidney itself or to the hilum. The mesenteric lymph node and appendix examined with the histological structure preserved. In the absence of secondary determinations, treatment is initiated according to the SIOP 93-01 Protocol for Nephroblastoma stage I.

Once the chemotherapy will be complete, all three patients will be followed for recurrence with chest CT scans and chest X-rays and with abdominal ultrasound, every 3 months for the first 3 years and then every 6 months for the next 2 years, blood tests and urinalyses will also be performed at each visit..

Discussions

Wilms tumor diagnosis includes a thorough history and clinical examination to identify possible genetic syndromes, genitourinary malformations, and genetic risk factors, and requires corroboration with paraclinical, imagistic and histological examination. Wilms tumor often becomes quite large before it is noticed, most of the times it's discovered by the parent or doctor during a physical examination. It is important to note that having a risk factor such as genetic predisposition, birth anomalies/defects or congenital anomalies does not mean that one will have the condition. But a risk factor increases the chances of having Wilms tumor compared to an individual without the risk factors (19). Therefore clinical examination is very important to establish these risk factors. In the presentation above one of the patients had criptorchydia, and case number 3 had dolichocephalism, anterior facial dysmorphism with micrognathia and viciously inserted dentition therefore Beckwith-Widemann syndrome was suspected but the genetic tests were negative. In the diagnostic work-up our clinic follows the main diagnostic tests used in detection of Wilms tumor, including physical exam with evaluation of family history, blood analysis such as complete blood count, creatinine levels, blood urea tests, urine analysis, abdominal ultrasound, abdomen CT scan, chest x-rays and bone scans if the tumor has metastasized. Definite diagnosis can only be made by surgical resection and biopsy followed by pathologist examination and staging. The imagistic workup includes abdominal ultrasonography that determines whether the mass is cystic or solid and whether the renal vein or vena cava is involved and abdominal CT or MRI that determines the extent of the tumor and spread to regional lymph nodes, the contralateral kidney, or liver (20). The ultrasound of the first case describes an inhomogeneous, well defined left kidney tumor and grade 2 hydronephrosis. The ultrasound of the second case describes hepatomegaly and a left kidney tumor not exceeding the renal capsule. And the ultrasound of the third case describes a rounded-oval shape right kidney tumor exerting a compressive effect on large vessels. Although many of the features seen on CT/MRI can also be identified on ultrasound, they are required to adequately stage the disease, and are established in protocols for Wilms tumour staging in North America and Europe (20). The abdominal CT examination of the first case revealed an inhomogeneous density mass with areas of necrosis, without images of left renal vein thrombosis and IVC involvement. The abdominal CT exam of the second case revealed a well defined parenchymal tumor developed in the left kidney, native homogenous and discreetly inhomogeneous post contrast. And the abdominal CT scan of the third case revealed the presence of a right kidney tumor with central necrosis, exerting a compressive effect on IVC. Diagnosis of Wilms tumor is typically made presumptively based on the results of the imaging studies, so nephrectomy rather than biopsy is done in most patients at the time of diagnosis. Biopsy is not done because of the risk of peritoneal contamination by tumor cells, which would spread the cancer and thus change the stage from a lower to a higher one requiring more intensive therapy. During surgery, loco-regional lymph nodes are sampled for pathologic and surgical staging (21). Because appropriate therapy, as well as prognosis, is based on tumor stage, accurate staging of patients with Wilms tumor at the time of diagnosis is very important. Classic Wilms tumor has a triphasic appearance, (stromal, epithelial, blastemal) however all three elements are not required to have a diagnosis of Wilms tumor (22). Case 1 presented has the best prognosis out of all, because of the classic triphasic composition, unlike case 2 that has a monophasic type with more than 66% blastematic component, and case 3 that has a triphasic nephroblastoma associated with focal anaplasia. Because case no 3 has focal anaplasia and genetic anomalies a cytogenetic analysis of his DNA was performed in order to establish genetically determined anomalies such as Beckwith-Wiedemann syndrome located at the level of the chromosome 11p15 and no methylation defects have been revealed.

As of 2004, there are significant differences between the treatment protocols American practice favors surgery followed by chemotherapy, European oncologists use preoperative chemotherapy and stage the tumor at the time of surgery rather than at the point of initial imaging studies. The International Society of Pediatric Oncology (SIOP) recommends giving Vincristine and Dactinomycin chemotherapy before nephrectomy for localized renal tumors. Following this protocol all three cases received preoperative chemotherapy, surgery and postoperative chemotherapy. Approximately 80-90% of children with a diagnosis of Wilms tumor survive with current multimodality therapy. Patients who have tumors with

favorable histology have an overall survival rate of at least 80% at 4 years after the initial diagnosis, even in patients with stage IV disease (10).

Conclusions

Any abdominal mass in a child must be considered malignant until diagnostic imaging such as ultrasonography or CT and laboratory findings define its true nature. Ultrasound is a very useful and cheap examination used to localise the kidney tumor and also distinguish from other causes of renal masses. Abdominal CT scan is the investigation of choice required to adequately stage the disease. Abdominal ultrasound is also used as a good parameter for evaluating the reduction in tumor size after performing cytoreduction. Histological examination of the tumor is the most important determinant of diagnosis and prognosis and can classify the tumors as having a favorable histology or an unfavorable histology, which is associated with a worse prognosis. The outcome is also reflected by the stage of the tumor at the time of diagnosis. Accurate staging is essential for the determination of the need for radiotherapy and the administration of appropriate chemotherapy regimen. Pretreatment with chemotherapy contributes to the reduction of the tumor, making it easier to remove, preventing the rupture of a large tumor into the peritoneal cavity. Wilms tumor has a very high cure rate, particularly when detected as a localized tumor

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LATERAL HUMERAL CONDYLE FRACTURES IN CHILDREN – CASE SERIES AND REVIEW OF LITERATURE

Tepeneu N.F.[1,2]

Abstract

The three most common elbow fractures classically reported in pediatric orthopedic literature are supracondylar (50–70%), lateral condylar (17–34%), and medial epicondylar fractures (10%). The mechanism of injury varies, but the most commonly described mechanism involves a fall on an outstretched hand with varus, valgus or rotational force or a combination thereof. The vectors of force and the degree of chondro-osseous development dictate the type of injury incurred.14 cases of lateral humeral condylar fractures between the years 2013 and 2018 were reviewed. A review of the literature was also conducted to see the most frequent injuries and complications.

Key words: trauma, humerus, lateral humeral condyle fracture, children

Introduction

The three most common elbow fractures classically reported in pediatric orthopedic literature are supracondylar (50–70%), lateral condylar (17–34%), and medial epicondylar fractures (10%).

The mechanism of injury varies, but the most commonly described mechanism involves a fall on an outstretched hand with varus, valgus or rotational force or a combination thereof. The vectors of force and the degree of chondro-osseous development dictate the type of injury incurred.

Material and methods

14 cases of lateral humeral condyle fractures between the years 2013 and 2018 were reviewed.

There were 10 male and 4 female patients. 8 patients were treated with a long arm cast and 6 patients with open reduction and osteosynthesis with screw, Kirschner wires or a combination of both. The osteosynthesis material was buried under the skin in all 6 patients.

There were no notable complications in both groups with good clinical outcome. 1 patient developed a wound infection which responded well to antibiotics. 2 patients had a decrease in range of motion of the elbow after conservative treatment with long arm cast. They responded well to physiotherapy.

A review of the literature on this complex subject was also conducted using the key words “trauma”, “humerus”, “lateral humeral condyle fracture”, “children”.

Results

Lateral humeral condylar fractures are the second most common pediatric elbow fractures after supracondylar humeral fractures [1, 2]. They comprise about 10–20% of all childhood elbow fractures having the annual incidence of 1.6/10,000 partly because of the increasing number of young athletes participating in highly competitive athletics [3].

Fractures involving the lateral condyle in the immature skeleton can either cross the physis or follow it for a short distance into the trochlear cartilage.

Associated injuries

Fractures of the lateral condylar physis rarely are associated with injuries outside the elbow region and unlike supracondylar humeral fractures, fractures of the lateral condyle rarely are associated with neurovascular injuries. Within the elbow region, the associated injuries that uncommonly occur with this fracture include dislocation of the elbow (which may be a result of the injury to the lateral condylar physis rather than a separate injury), radial head fractures, and fractures of the olecranon, which are often greenstick fractures. Acute fractures involving only the articular capitellum are rare in skeletally immature patients but are serious injuries that need to be recognized and treated appropriately.

Mechanism of injury

Two mechanisms have been suggested: “push-off” and “pull-off.” The pull-off or avulsion theory has more advocates than the push-off mechanism.

The mechanism of injury includes either avulsion forces from the lateral ligaments with the elbow extended, or impaction of the radius on the capitellum after a fall on an outstretched arm [4].

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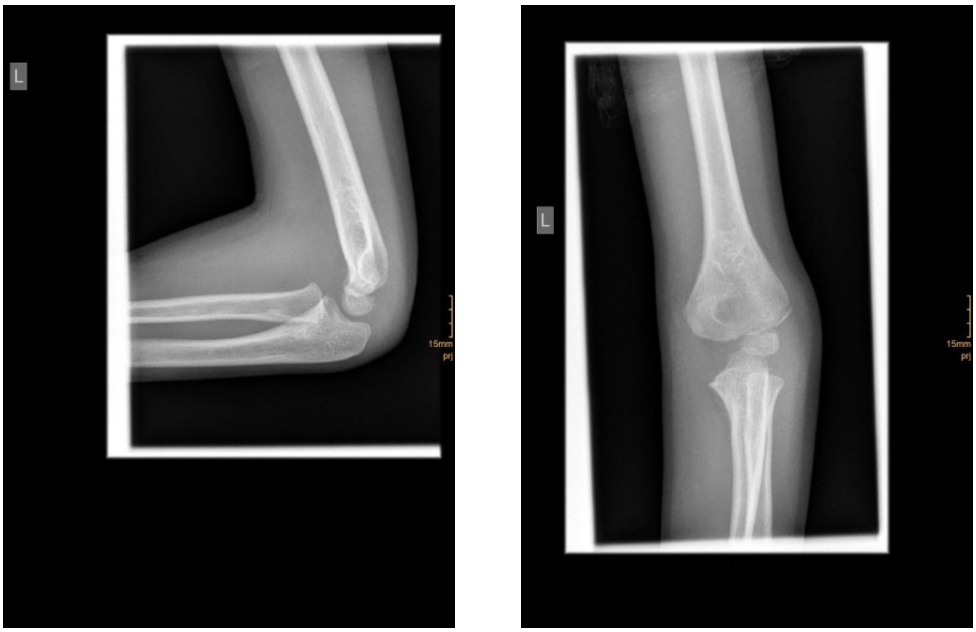

Fig. 1. 6 year old male patient with a undislocated left lateral condyle fracture which was succesfully treated with a long arm cast (personal collection)

Clinical presentation

Compared with the marked distortion of the elbow that occurs with displaced supracondylar fractures, little distortion of the elbow, other than that produced by the fracture hematoma, may be present with lateral condylar fractures. The key to the clinical evaluation of this fracture is the location of soft-tissue swelling and pain concentrated over the lateral aspect of the distal humerus.

Imaging investigations

Diagnosis is made based on radiographs and it may be difficult in children [5]. The radiographic appearance varies according to the fracture line's anatomic location and the displacement stage

The degree of displacement may be seen on the true lateral view. In determining whether the articular hinge is intact (i.e., stage I vs. stage II), the relationship of the proximal ulna to the distal humerus is evaluated for the presence of lateral translocation. Oblique views are especially helpful in patients in whom a stage I displacement is suspected but not evident on AP and lateral views.

Arthrography or MRI evaluation has been suggested to identify unstable fractures in the acute setting and to aid in preoperative planning for those with late displacement, delayed union, or malunion. MRI can be a very useful diagnostic aid to guiding treatment, especially with delayed unions.

Classification of lateral humeral condylar fractures

The Milch classification, based on whether or not the fracture extends through (type I) or around (type II) the capitellar ossific nucleus, is used infrequently because of its poor reliability and poor predictive value. Salter and Harris classified lateral condylar physeal injuries as a form of type IV injuries in their classification of physeal fractures. A true Salter– Harris type IV injury through the ossific nucleus of the lateral condyle is rare. Although lateral condylar fractures are similar to Salter–Harris type II and IV fractures, treatment guidelines follow those of a type IV injury: open reduction and internal fixation of displaced intra-articular fractures. Weiss et al. modified this classification based on fracture displacement and disruption of the cartilaginous hinge [6]. They classified the lateral humeral condyle fractures in 3 types: type I, less than 2 mm of displacement; type II, 2 mm or more of displacement and congruity of the articular surface; type III, more than 2 mm of displacement and lack of articular congruity.

Treatment

Non-displaced and stable fractures may be treated by cast immobilization with close follow-up, but fractures displaced >2 to 3 mm may indicate surgical fixation [7, 8]. Surgical treatment can be done either by closed reduction and percutaneous osteosynthesis or open reduction and osteosynthesis.

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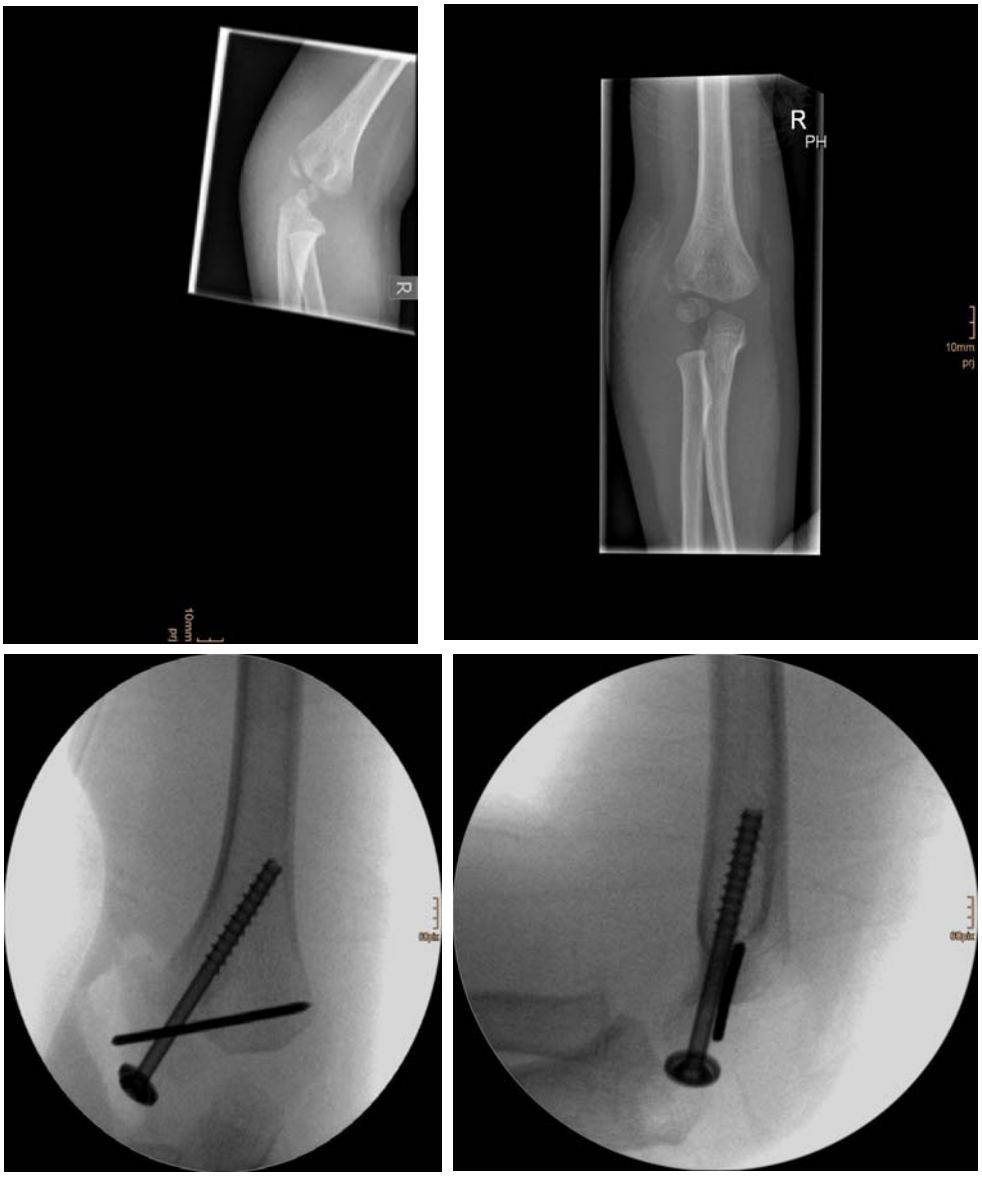

Fig. 2. 6 year old male patient with a dislocated right lateral condyle fracture which was treated by open reduction and osteosynthesis with a screw and a Kirschner wire (personal collection)

Classification of lateral humeral condylar fractures

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Treatment

Non-displaced and stable fractures may be treated by cast immobilization with close follow-up, but fractures displaced >2 to 3 mm may indicate surgical fixation [7, 8]. Surgical treatment can be done either by closed reduction and percutaneous osteosynthesis or open reduction and osteosynthesis.

Surgical fixation is either by screw, smooth K-wires or both. The K-wires can be buried under the skin or not.

The idea behind burying K-wires is to reduce infection rates because it is felt that the wires have to stay in for a minimum of six weeks to prevent non-union. Some studies show no cases of non-union in either the buried or unburied wires group and infection rates that were comparable. In addition some of the cases with buried wires became effectively unburied. So that is why some authors concluded there is no justification in burying wires, which requires an additional general anaesthesia for removal [9].

Regarding pin orientation, most authors favor a divergent construct for greater stability.

For 2-pin constructs, maximizing pin divergence at the fracture site provided greater stability in torsional loading and valgus loading. The addition of a third pin in a divergent orientation increases stability compared with 2-pin constructs in valgus, internal, and external rotation loading. The pins must be placed in a bicortical manner, with maximum divergence and spread at the fracture site [10].

Complications

Many complications are known to be associated with childhood lateral condylar humeral fractures, with poor outcomes often related to delayed or inadequate initial treatment [5,11].

Lateral humeral condylar fractures are the most common injuries that involve the growth line around the elbow region [12]. There are also intra-articular fractures, which may affect bone healing and the joint surface [13]. These fractures more commonly result in decreased range of movement more than any other elbow fractures [14]. Up to 20% of patients with lateral condylar fractures show a cubitus varus deformity and >10% show a cubitus valgus deformity [15,16,17].

Discussion

Fractures involving the lateral condylar physis occur early, with the average age around 6 years [18,19]. All the physes of the distal humerus are vulnerable to injury, each with a distinct fracture pattern. Next to those of the distal radius, injuries to the distal humeral physes are the most common the first 2 to 3 years of life [19,20,21].

Fractures concerning the medial condylar physis are rare and occur most often in children 8 to 12 years of age [22].

The diagnosis of lateral condylar physeal injuries may be less obvious both clinically and on radiographs than that of supracondylar fractures, especially if the fracture is minimally displaced..

Further, the fracture line usually lies posterolaterally and may not be captured in the conventional radiographs[1].

Oblique views of the distal humerus are very helpful in making accurate diagnosis and defining the extent of fracture displacement for treatment decisions Such cartilaginous anatomy affects the prognosis of the lateral humeral condylar fractures: growth disturbance can occur in the form of a partial lateral growth plate closure or partial closure of the centre of the physis[23].

The central insult between the lateral condylar physis and the trochlea can result in a deep groove, forming the typical “fishtail deformity”[16].

Regardless, the extremity should be evaluated for concomitant injuries of forearm, wrist, or hand, and the radiographs should be inspected for additional fractures about the elbow.

Humeral condyle fractures can be associated with elbow joint dislocations, although dislocations of the elbow joint in children are not common. Of all elbow injuries in skeletally immature patients, Henrikson [24] found that only about 3% of all were dislocations. The peak incidence of pediatric elbow dislocations typically occurs in the second decade of life, usually between 13 and 14 years of age when the physes begin to close [25]

The largest proportion of elbow dislocations (44.5%) occur in conjunction with sports activities; football/ rugby, wrestling, and basketball being the most common sports for males and gymnastics and skating being the most common sports for females [25]. Almost 60% of medial epicondyle fractures are associated with elbow dislocations in this age group. As with all joint dislocations, the principles of treatment include promptly obtaining a concentric reduction of the elbow joint while identifying and treating all associated injuries. The ultimate goal is allowing protected motion and rehabilitation with the goal of restoring full elbow motion without recurrent instability.

Because of the location of critical stabilizing factors and surrounding neurovascular structures, elbow dislocations should be considered based on the direction of dislocation and the associated fractures which may be present. As the mechanism of injury, the associated injuries, and imaging differ based on the nature of the injury, these factors should be considered for each dislocation pattern.

Diagnosis of these traumatic entities is done by clinical examination and paraclinical investigations.

Trauma is a common indication for elbow imaging in children. Fractures in the developing pediatric elbow occur frequently and can be challenging to diagnose radiographically.

Although some fractures are quite apparent, knowledge of the normal developmental appearances and the radiographic clues to injury are necessary to optimize detection of more occult fractures. Sometimes a CT or better yet a CT with 3D reconstruction can help in the diagnosis and treatment of these fractures. A intraoperative arthrography is sometimes also useful.

The most important problem in the treatment of humeral condyle fractures is the pseudarthrosis that can happen in the framework of a conservative treatment of displaced fractures, rarely after operative treatment with K-wires or screws. A rather academic problem is the obligatory growth disturbance of a partial stimulation of the lateral part of the growth plate. This leads to radial overgrowth and thus to a more or less distinct varus deformity.

The extent of varus deformity is dependent on the time till consolidation, which is longest in conservatively treated fractures and shortest in those treated with compression screw osteosynthesis. An additional academic problem is the so-called fishtail deformity that becomes radiological visible at the end of growth. This deformity has no clinical

significance. Pseudarthrosis, varus and fishtail deformity are a result of increasing instability of primarily or secondarily displaced fractures of humeral condyles. Cubitus valgus and tardy ulnar nerve palsy are considered the main complications of nonunion lateral humeral condyle. The treatment of nonunion of the lateral humeral condyle with <1 cm of displacement is generally recommended, if care is taken to avoid damage to the vasculature of the lateral condylar fragment [26].

Conclusion

Fractures of the distal humerus in children pose special problems which need to be addressed by a person specialized in pediatric traumatology. Conservative and operative treatment is possible, specific for each type of fracture.

Specific complications can occur after such fractures which in turn can pose problems which need special expertise in order to be solved.

The most common prenatal risk factors are: prematurity, chorioamnionitis, fetal malpresentations, birth asphyxia. In less than 10% of the cases, birth asphyxia cand be considered a cause of CP even if it occurs on a malformative background, growth restriction, severe maternofetal infections. Even in these cases, the classic diagnostic criteria for birth asphyxia have to be present: Apgar Score <4 at 5 minutes, fetal bradycardia, metabolic acidosis, multiple organ failure due to tissue hypoxia and early imaging changes [10].

Postnatal risk factors are also involved in the development of CP: periventricular leukomalacia (preterm newborns), intracranial hemorrhage, hypoxic ischemic lesion (meconium aspiration, pneumothorax), infections (meningitis, encephalitis, severe congential pneumonia), persistent fetal circulation (pulmonary hypertension of the newborn at term), nuclear jaundice [11].

Clinico-etiological forms

Spastic hemiplegia

The most frequent cases are congenital (70 – 90%) and only 10-30% of aquired causes [12].

It can be unilateral (the middle cerebral artery's teritory being the most frequent affected) and affect especially the left side (2 times more frequent than the right). From a neuropathologic point of view this type of lesion is produced on the basis of posthemorrhagic porencephaly (Figure 1), cerebral atrophy (Figure 2) and periventricular leukomalacia of the preterm newborns (Figure 3) [4].

Spastic diplegia

Is a controversial disease from an etiological point of view, especially for newborns at term. Among preterm newborns, periventricular leukomalacia and severe peri/intraventricular hemorrhage (grade IV) are most frequently involved. (Figure 4) [4].

Spastic tetraplegia

A severe form of cerebral palsy, that appears due to prenatal causes in 50% of cases, perinatal in 30% and postanatal causes in 30% of cases [5]. From a neuropathologic point of view the most common causes are: hydrocephaly (Figure 5), diffuse cortical atrophy, multicystic encephalomalacia – isolated or communicating with the ventricular system (Figure 6).

a***Extrapyramidal dyskinesia***

Extrapyramidal dyskinesia

Not so frequent in the common medical practice. Nuclear jaundice was the most frequent cause, but it's incidence decreased significantly. Other causes are: hypoxic-ischemic injury, prematurity, some cerebral degenerative diseases. Some cases caused by high bilirubin concentrations (without nuclear jaundice) are cited in specialized literature [10].

Hypoxic-ischemic lesions of the basal nuclei and talamus are more frequent among the term newborns than premature newborns [4].

Evolution and prognosis

Short term outcome is determined by the complication rate. The most common complications are: gastroesophageal reflux with aspiration pneumonia (sometimes with acute respiratory failure), absent or insufficient sucking and deglutition reflex, chronic constipation (even occlusion), chronic pulmonary disease (BPD – broncho-pulmonary dysplasia) [6].

Long term prognosis is severely affected by the presence of: epilepsy, deafness, halucinations, strabismus, mental retardation (30-50%), attention deficit, autism. 25% of the patients with cerebral palsy have walking disorders and 25% are severely affected and in need of intensive medical care [13].

Conclusions

1. Cerebral palsy is a serious condition, with immediate and long term sequelae that affect quality of life and social integration.
2. It is more frequent among preterm and postterm newborns. The most incriminated risk factors affect these age groups.
3. From a neuropathologic point of view, the most common lesions that cause cerebral palsy are: periventricular leukomalacia, intraparenchymal hemorrhage, cerebral atrophy, porencephaly, and hydrocephaly.

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DOES PRENATAL DIAGNOSIS AND EARLY POSTNATAL CARE OF POSTERIOR URETHRAL VALVES IMPROVE THE OUTCOME?

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Abstract

Introduction: Posterior urethral valves are severe congenital obstructive uropathies that could lead to renal failure and end stage renal disease despite the progresses in prenatal and postnatal diagnosis and management. Aim of the study: The aim of this paper is to study the relation between certain parameters and the long-term outcome of infants with and without a prenatal diagnosis of posterior urethral valves.

Material and methods: Records of all children with posterior urethral valves treated in our center from January 2000 to December 2014 were retrospectively reviewed and statistically analyzed. Results: 31 patients were analyzed; no significant relations between the existence of the prenatal diagnosis of posterior urethral valves and the long time impairment of the renal function were revealed ($\chi 2=3.02$, p=0.08, 95%CI); a multivariable statistic analysis showed that high postnatal age at diagnosis and treatment was a risk factor predictable for poor outcome through renal function impairment (HR=5.139 → 95%CI: 2.01-6.18). Conclusion: Our data shows no relations between the existence of prenatal diagnosis of posterior urethral valves and their outcome, but a smaller age at the moment of treatment was observed in the prenatal group, with lower rates of renal function impairment.

Key words: congenital obstructive uropathy, posterior urethral valves, prenatal diagnosis

Introduction

Posterior urethral valves (PUV) are one of the most severe forms of congenital obstructive uropathy, with a reported incidence of 1/ 3000-8000 male newborns (1). Despite the advances in prenatal detection of these malformations and in the possibilities of medical and surgical management, posterior urethral valves continue to be a common cause of renal failure, leading to dialysis and renal transplantation. The outcome of 13-64% of all of these patients is to end stage renal disease (ESRD) (2).

Currently the diagnosis of PUV is made during the fetal period, by routine prenatal ultrasound. This will allow parental counseling during pregnancy, early medical and surgical postnatal treatment, avoiding postnatal infectious complications. There are multiple controversies regarding the consequences of prenatal diagnosis on the postnatal outcome of these infants, and the relation between age at diagnosis and the risk of progress towards ESRD.

The aim of our study is to evaluate the characteristics, diagnostic tools, treatment options and long term outcome of children with or without prenatally detected PUV treated in our institution.

Materials and methods

Records of all children with PUV treated in our center between January 2000 and December 2014 were retrospectively reviewed. Data like annual incidence, demographic information, gestational age at diagnosis, birth weight, diagnosis circumstances, treatment and outcome were analyzed. All data were statistically processed and deemed relevant at a value of $p<0.05$.

Results

A total number of 31 patients with PUV were identified, including 12 cases (38.7%) with prenatal diagnosis. The annual incidence of the cases showed a relative homogenous distribution in time, but still with a slightly tendency of increasing starting from 2008. Also, from the 12 cases prenatally diagnosed, only two were identify before 2008, all other (10 cases) being diagnosed and treated between 2008 and 2014.

Regarding origin environment we found no differences between rural and urban area: 51.6% of all cases came from urban areas and 48.4% from rural areas.

Mean gestational age was 37.35 weeks +/- 1.4SD, and none of these boys were preterm baby. Mean birth weight was 3100g, with a minimum of 2000 grams and a maximum birth weight of 3950 grams. (Table 1)

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Mean GA lot	Mean -95%	Mean +95%	SD	SEM	Min	Max	Q25	Median	Q75
37.35	36.84	37.87	1.40	0.25	35.00	39.00	36	37	39

Table 1. Gestational age

	n	%
Evaluation of a prenatal hydronephrosis	8	25.8%
Urinary tract infections	12	38.7%
Urosepsis	5	16.1%
Acute urinary retention	4	12.9%
Neonatal occlusion	2	6.5%
Incidental	1	3.2%
Arterial hypertension	1	3.2%
Total	31	

Table. 2. Postnatal diagnosis

Vesicoureteral reflux	Count	%
Absent	12	38.71%
Present	19	61.29%
gr IV left	3	9.68%
gr IV bilateral	2	6.45%
gr V left /right	7	22.58%
gr V right, IV left	2	6.45%
gr V bilateral	5	16.13%
Total	**31**	

Table. 3. Associated vesicoureteral reflux

MULTIVARIATE ANALYSIS	Beta	SE	Wald	Sig. p	Hazard Ratio Exp(β)	95% CI for Exp(B) Lower	Upper
Diagnosis age	0.094	.039	5.889	.015	**5.139**	2.018	6.184
Prenatal diagnosis	1.637	1.141	2.059	.151	**1.098**	0.549	48.071

χ2 statistic test = 1.577 df = 7; p = 0.0628; 95%CI.
CI – Confidence Interval, df-degree freedom, HR-Hazard rate SE-standard error

Table 4. Multivariable statistic analysis of evolution to end stage renal disease risk vs. diagnosis age

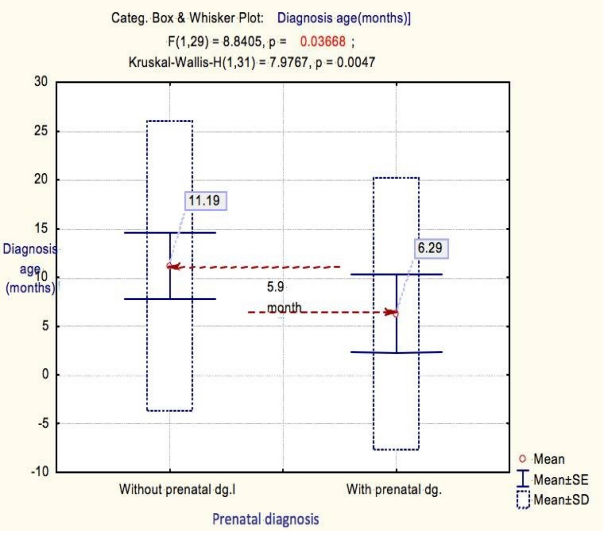

Fig. 1. Diagnosis age according to prenatal diagnosis

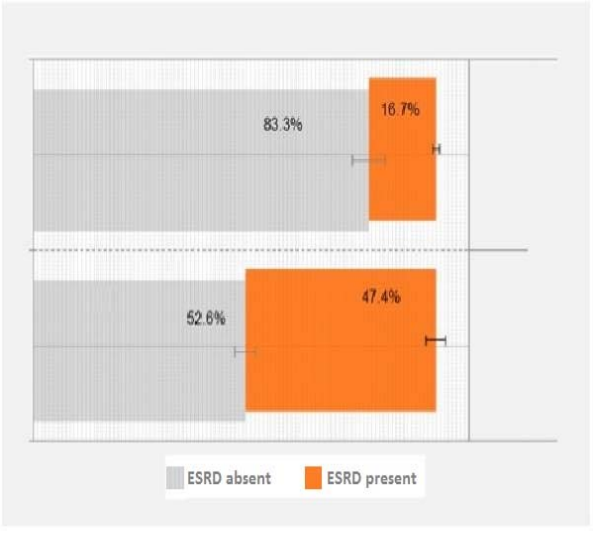

Fig. 2. Prenatal diagnosis vs. chronic renal

The mean gestational age at diagnosis, in the case of the 12 patients prenatally detected, was 31.42 weeks +/-3.03SD, with a minimal gestational age of 25 weeks, and a maximum of 36 weeks. The Q25 quartile indicates that 75% of the cases were late diagnosed during pregnancy, around 30 weeks of gestational age.

The prenatal diagnosis was suggested in all cases by dilatation of the fetal urinary pathways. In 10 cases (83.35%) the ultrasound identified bilateral ureterohydronephrosis, while in 2 cases (16.7%) a megacistys was also found. A direct sign of urethral obstruction ("key-hole sign") was not found in any of the 12 fetuses.

Regarding the postnatal diagnosis circumstances we found that the most frequent symptoms were those related to the urinary tract infection (38.7%) and urosepsis (16.1%). Only 8 cases from the 12 with prenatal diagnosis were transferred to our department immediately after birth for diagnostic confirmation of a suspected fetal urethral obstruction (25.8% of all cases). (Table 2)

Mean age at diagnosis was 9, 3 months+/-14,4SD, with a maximum of 48 months. 50% of all cases were diagnosed under the age of 2 months, while 25% of the patients were older than 14 months at diagnosis. For children with a history of fetal ureterohydronephrosis we found a mean diagnosis age of 2.3months+/-13.8 SD, smaller with 5.9 months comparing with the group without prenatal diagnosis (p=0.0047).(Fig.1)

At admission in our department blood and urinary test were performed in all cases. A renal ultrasound was also performed, and in case of a confirmed ureterohydronephrosis, a bladder catheter was placed to relieve bladder outlet obstruction. If necessary, antibiotic therapy was initiated for the treatment of the urinary tract infection (according to the antibiotic susceptibility of the identified germs), and after it, a diagnosis voiding voiding cystourethrography was performed. Beside the urethral obstruction, in 61,3% of the cases, the cystography also identified the presence of associated vesicoureteral reflux. (Table 3.)

After the imaging confirmation of the urethral obstacle, all children, except 4 cases, underwent surgical treatment. One of the cases was referred to us at the age of two years, with ESRD, which required dialysis. The outcome was unfavorable, with death due to multiple complications (including cardiac impairment). The other three cases were diagnosed in the infancy but in all three the urethral obstruction was associated with urosepsis and high degree vesicoureteral reflux. In one case the family didn't agree with the endoscopic procedure. In all the cases without surgical treatment the outcome was toward exitus; the pathological examination showing important degrees of renal and pulmonary hyperplasia. From the remained 27 cases, the treatment was represented only by endoscopic ablation of the urethral obstacle in 67.7% of the cases, endoscopic ablation associated with cystostomy in 6.5% of cases, with ureterostomy in 6.5% of cases, with pyelostomy in 3.2% cases, and endoscopic ablation with the need for a peritoneal dialysis catheter in one patient.

The outcome was unfavorable in eleven cases (35.5%) which developed a form of renal function impairment. Only two of the cases with prenatal diagnosis evolved through end stage renal disease, representing 16.7% from all cases with renal impairment. Our results revealed no statistical significant correlation between the presence of the prenatal diagnosis and the long time impairment of the renal function ($\chi 2$=3.02, p=0.08, 95%CI). (Fig.2)

On the other hand, a multivariable statistic analysis showed that high postnatal age at diagnosis and treatment was a risk factor predictable for poor outcome through renal function impairment (HR=5.139 → 95% CI: 2.01-6.18), while again, prenatal diagnosis didn't correlate with chronic renal disease (HR=1.09 → 95%CI: 0.54-48.07). (Table4.)

Discussion

PUV are one of the most frequent causes of congenital low urinary tract obstruction. They produce a wide range of urethral obstruction with variable severity, and thus, they represent a spectrum of diseases, ranging from mild obstruction with minor effect on renal function to severe diseases with premature renal insufficiency. Severe urethral obstruction can lead to devastating congenital anomaly that can be lethal in utero or during the perinatal period. They are usually associated with severe dilatation of the urinary pathways that will lead to a high rate of prenatal diagnosis of the malformation. Mild forms of the disease will be nearly subclinical, presented later in life with signs of urinary tract infection or micturation abnormalities (3). Recent progress in fetal ultrasonography lead to a progressively increase in the prenatal detection of congenital urethral obstructions.

Gestational age for the newborns affected by the PUV is generally normal. Bilgutay et al. reveal in a study on 104 cases of urethral obstruction a prematurity rate (defined as gestational age less than 37 weeks) of 33% (4). In another series of 31 patients, in 2015, Roy and coworkers found a median for gestational age of 38 weeks (5). Our results are in concordance with these data, as in our group gestational age was 37 weeks ± 1.4 DS (minimum 35 weeks, maximum 39 weeks). The Q25 quadrille indicates that 75% of the pregnancies ended at a gestational age older than 36 weeks.

The widespread of fetal ultrasound has significantly increased in time the frequency of prenatal diagnosis in PUV, with reported incidence varying from 50% to 70% of the cases. Thakkar et al. reported in 2014 an incidence of 51% on a series of 71 cases (6). Our data revealed an incidence of 38.7% of prenatal suspicion of PUV; most of the cases prenatally suspected for urethral obstruction were children born after 2008 (10 of 12 cases), situation that can be justified by the increased use of obstetrical ultrasound in the last decade and also by the advances made in the medical technologies.

Medium gestational age at diagnosis in our group was 31.4 weeks (minimum 25 weeks, maximum 36 weeks) with 75% of the cases being identified at a gestational age older than 30 weeks. Prenatal diagnose in PUV can be suspected starting from 18th-19th week of gestation; most commonly the diagnosis is establish at 20th-38th week of pregnancy

(7). Different scientific reports proved that the earlier the prenatal diagnosis is suspected during fetal life (especially before 24 weeks of gestation), the bigger is the risk to an unfavorable outcome, to end stage renal disease (8).

The effect of prenatal diagnosis in posterior urethral valves is controversial. There are some authors who showed that patients with prenatal diagnosis have a higher risk to developed end stage renal disease (9), while others suggesting an improving of long term outcome for patients with fetal diagnosis (10). Reinberg et al. found in a series of 8 cases with prenatal diagnosis that 64% developed renal failure, showing that a poor prognosis was associated with prenatal diagnosis (11).

Our study didn't find a strong statistical correlation between the prenatal diagnosis and long time evolution to ESRD. Only 16.7% of all cases that developed ESRD had the urethral obstruction identified prenatally, fact that can lead to the idea that prenatal diagnosis will be associated with a low risk for developing renal function impairment. There are multiple reports in the literature that support the idea that the prenatal diagnosis didn't improve outcomes (12), (13), probably because more severe forms of the urethral obstruction are likely to show signs during the fetal period. Our results, which are in contradiction with these opinions, can be explained by a low rate of prenatal diagnosis in our series (38.7%), related to an inconsistent access to prenatal screening. On the other hand, we noted that only 8 neonates (66%) from the 12 with prenatal diagnosis were referred to our department for the postnatal investigation of a fetal renal abnormality. The other 4 cases were presented later in the infancy, as a result of acute urinary tract infection.

In our series, prenatal suspicion of a urethral obstruction was associated with a smaller age of postnatal treatment comparing with cases without fetal diagnosis. The mean age of definitive diagnosis, and beginning of treatment for prenatal group was 2.3 month, with 5.9 month smaller than the one in the group without postnatal diagnosis. Age at presentation and age at surgery are other subjects of controversy. A study in 2010 reported that posterior urethral valves diagnosed after one year of age are associated with a low risk of developing renal impairment, as chronic kidney disease developed in 48% of patients diagnosed before 1 year of age vs. 25% in patients diagnosed after 1 year of age (14). On the other hand, there are multiple reports that support the idea of a poor outcome associated with late presentation. Ansari et al. found that evolution to chronic kidney disease was more frequent (41% vs. 30%) in cases that underwent valve ablation after and before 2 years of age respectively.

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Conclusions

Our data shows no relations between the existence of the prenatal diagnosis of PUV and their outcome. However prenatal diagnosis was related to a lower age at the time of diagnose and postnatal treatment. Our study has some limitations as it is a retrospective study that includes a small number of patients from a single institution. Further studies will need to be conducted, with the analyses of other multiple risk factors implied in the long term outcome of these patients..

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OBESITY IMPACT ON REPRODUCTIVE FITNESS

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Abstract

Obesity has a worldwide high prevalence and it increases every year especially in developed countries. The ethiology is large including life style changed, reduced physical activity together with higher caloric intake and use of fast food. It became an epidemy with important and severe complication for reproductive system. It is difficult to treat the anovulatory infertility in obease womens because they have a low success chance after assisted reproductive treatment and they need higher doses of gonadothropin. This patient's category is characterized by low answer of ovarian stimulation and high risk of miscariege. The literature proved that weight loss improves the fertility. The patients should be informed about the impact of obeasity and overweight for pregnancy and the importance of weight lost before any infertility treatment.

Keywords: obeasity, infertility, assisted reproductive technology

Introduction

The obesity is a worldwide important health problem, that became more frequent among women of reproductive age. It consists in anormal and excessive accumulation of fat in the whole body, with severe impact for patients's health. According to World Health Organization (WHO), the overweight condition is defined as a body mass index (BMI) 25- 30 kg/ m2; to be framed as obease, a patient needs to have a BMI greater than 30 kg / m2. (1) Obesity is a complex, multifactorial disease affecting a third of worldwide population. (2) Is considered that, in 2023, about 38% of adults will be overweight and 20% obease. (3,4)

Obeasity involved also social, psychological and demographic problems. It's complications like, diabetes, arterial coronary artery disease, osteoarthritis and various malignancies (endometrial, breast or colon cancer) are lifethreting severe pathologies. Another obeasity impact is for reproductive system, especially in womens. It is associated with anovulation, menstrual disorders, infertility, difficulties in assisted reproduction or spontaneous abortion. (1)

Due to lower rates of implantation, increased risk of abortion and increased maternal and fetal complications during pregnancy, obese women have a lower chance of giving birth to a healthy newborn. (1)

This present paper aims to present the effects of obesity on fertility and the effective management of infertility in obese and overweight womens as well as the relationship between obesity and the occurrence of congenital malformations in newborns.

Epidemiology

The prevalence of obesity has significantly increased throughout the world, especially in developed countries due to a change in lifestyle including reduced physical activity, changes in nutritional style and increased caloric intake. (5) The etiology is multifactorial and involves several factors, such as endocrine disorders, hormonal disturbances, psychological disorders and the use of drugs (steroids and antidepressants). In the US and most European countries, 60% of women are overweight (≥ 25 kg / m2), and 30% are obese (≥30 kg / m2), 6% of whom have morbid obesity ≥35 kg / m2). (1,5,6)

Different European studies have shown that there are large differences in the prevalence of obesity among countries. A study from 2008 showed a low prevalence of obesity in French population (4- 6.2%), and at the opposite are the Czechs with an obesity rate of 30 to 32%.(7) It has been established that an increased prevalence of obesity exists in the southern regions of Italy and Spain and Eastern European countries, western and northern European countries have lower obesity rates. (7)

Obesity and reproduction

The relationship between obesity and reproductive function is known but further studies are still needed to elucidate pathogenic mechanisms. The negative effects of obesity for reproductive function are also well known. The first signs of reduced reproductive fitness in obese women are anovulatory cycles and /or subfertility. (8) It is difficult to explain how obesity affects the reproductive system..

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Obesity can affect reproductive function, by affecting the ovaries and the endometrium. Luteinising hormone (LH), estrone, androstenedione, triglycerides, insulin and low density lipoprotein levels are elevated, and high density lipoprotein levels are low in obese women. Due to these changes, the HPG axis deteriorates and various gynecological effects occur. (1)

Because of low pregnancy rates, increased rates of abortion and pregnancy complications, birth rates are low in obese women. (1) The methabolic profile of obese womens is characterized by hyperandrogenemia, insulin resistance and elevated leptin levels. Although adipose tissue is required for reproductive function and for normal development, excessive adipose tissue causes some reproductive disorders. It aggravates polycystic ovarian syndrome (PCOS) and anovulation and can cause hypothalamic hypogonadism.

Anovulation produces changes in the level of adiponectin and HPG axis as well as steroidogenesis in obese women. Adipokines are signaling molecules produced by adipose cells, correlated with inflammation and signaling disorders that can affect cellular metabolism. (8) Leptin, alpha tumor necrosis factor (TNFα), resistin, glargine, visfatin, interleukin 6 (IL-6), free fatty acids, adiponectin, chemerin are adipokins that can be correlated with the adverse effects induced by obesity (8)

Adipose tissue also affects follicular development by inhibiting gonadotropin secretion, by converting androgens to estrogen in adipose tissue. Therefore, almost all adipokines appear to have effects on reproduction by causing insulin resistance. Hyperinsulinemia and insulin resistance are causes of obesity, accompanied by hyperandrogenemia and alteration of steroidogenesis.

Leptin inhibits the production of estradiol in granular cells and insulin-induced ovarian steroidogenesis, acting on receptors in the teat cells. Another effect of leptin on reproductive functions is the regulation of early embryonic development. This may explain poor reproductive performance in obese women. (1,9)

Adiponectin-induced signaling is important for preimplantation embryonic development and process of implanting the zygote. (10)

Resistin and ghrelin are also involved in the pathophysiology of obesity and associated endocrine disorders, but the mechanism of action has not been fully elucidated. Resistin is a protein secreted by adipose tissue. It has been demonstrated that resistin induces insulin resistance and production of antibodies that are resistant to insulin sensitivity. (11)

Visfatin is secreted by several types of cells, including adipocytes, bone marrow, lymphocytes, muscles, liver, trophoblasts and fetal membranes. Visfatine exhibits insulin mimetic effects, increases glucose uptake in adipocytes and muscle cells and decreases the release of glucose from hepatocytes. The association between visfatin and obesity as well as the action of insulin are not fully understood. (12)

Chemerina is another adipokine that interferes with the adipocytes and glucose metabolism. Chemerin levels increase during metabolic syndrome and are also associated with obesity and type 2 diabetes. Chemerina interferes with follicular steroidogenesis stimulated by foliculostimulant hormone (FSH) and plays an important role in polycystic ovary pathogenesis. (13)

Lipotoxicity is another mechanism by which obesity can affect reproductive tissue. (8,14,15) In obesity, there is an excess of saturated long chain fatty acids due to increased secretion by adipocytes as well as by diet. When adipocytes can no longer store these fatty acids, other cells will store fat, which will induce an increase in the production of reactive oxygen species that causes mitochondrial dysfunctions, endoplasmic reticulum stress and apoptosis. At the reproductive tissue level, this mechanism will be used to treat granulosa cells and oocytes, resulting in oocyte maturation disorders as well as their quality abnormalities. (15, 16)

Another mechanism leading to hyperandrogenemia is hyperinsulinemia via IGF-1, secreted by human ovarian tissue and its receptors are located in the ovary. Insulin can bind IGF-1 receptors, as well as its own receptor. It causes decreased production of IGFBP-1 and SHBG in the liver and increased levels of serum androgen in obese women. Polycystic ovary is also a metabolic disorder characterized by hyperandrogenemia. Previously, the polycystic ovary was known only as a hyperandrogenic condition, possible etiologic factor for infertility. However, current data show that the polycystic ovary is associated with an increased risk of metabolic disturbances, insulin resistance (IR), hyperinsulinemia (HI), decreased glucose tolerance and obesity. In women with polycystic ovaries, weight loss decreases androgen levels and improves insulin resistance. (17,18)

The mechanism by which hyperandrogenemia and/or hyperinsulinaemia causes anovulation was not fully understood. Because of improving steroidogenesis due to insulin and its interaction with LH, it stops the follicular growth. Thus, premature luteinisation and follicular arrest develops and lead to obesity-induced menstrual cycle and oligoanalubital disorders.

In conclusion, the excess of estrogen and androgen plays a key role in the development of anovulatory cycles in obese patients.

Obesity, risk factor for infertility?

Infertility is defined as a lack of pregnancy, despite regular unprotected sexual intercourse after one year or therapeutic insemination in women under the age of 35 and after 6 months in women aged 35 years and over. (19) Although many overweight women are able to become pregnant, there is an increased prevalence of infertility in obese women.

Among the recognized causes of infertility are chromosomal abnormalities, inflammatory and autoimmune diseases, polymorphisms of thrombophilia related genes. In the Western Region of Romania, several studies have been conducted focusing on the incidence of chromosomal anomalies in infertility patients, the presence of cytogenetic abnormalities in spermatic fluid as well as the incidence of cytogenetic anomalies diagnosed in the fetal period. (20,21)

Studies have shown that the time required to achieve a spontaneous pregnancy in the general population is increased, but decreases in obese women, including those with normal ovulatory function. (22) The risk of infertility is three times higher in obese women than in normal weight women and their fertility appears to be affected both in natural and assisted. (23) The probability of pregnancy is reduced by 5% per unit of BMI exceeding 29 kg / m2. (24) Obesity causes infertility through various pathways, including by impairment of follicular development, qualitative and quantitative development of ovocytes, fertilization, embryo development and implantation.(25) Obstetricians have shown that anovulatory infertility and menstrual disorders are higher in overweight and obese women. (1)

Can obesity be correlated with un increased risk for miscarriage?

There was a correlation between obesity and significant increases in fetal as well as maternal death, preeclampsy, diabetes, fetal developmental anomalies, and other congenital anomalies during pregnancy. (26)

It is difficult to establish a correct link between abortion for women with spontaneous pregnancies, due to the fact that first trimester abortion may or may not be recognized, especially for women with non-fixed periods. In the event when assisted reproduction techniques are called upon, a much more accurate risk analysis of obesity, spontaneous abortion, pregnancy evolution and post-natal evolution is a possibility. Association between obesity and spontaneous abortion has been signaled in several studies, in general population, as well as in pregnancy assisted women.(27) A study involving 1644 women suffering from obesity with a control lot (3288 normoponderal women) has shown a higher risk of abortion of any kind. (28) Although there are some studies showing an increase of abortion risk in pregnant obese women, other studies have not found such correlation between the two pathologies. (28–30)

Embrionary chromosopathy, the most common form of spontaneous abortion during the first trimester of pregnancy does not apper to have an increased incidence for overweight women. Endocrine imbalances, such as polycystic ovary, hyperthyroidia, and insulin resistance are most common in overweight women. These conditions are known to cause spontaneous abortions.

In conclusion, endocrine anomalies, embrio quality and uterin receptivity could determin spontaneous abbortions in obese patients.

Does obesity influence embrionary development?

Maternal metabolic imbalances as well as ovocites quality have consequences on embryons. Weak embryons can develop due to ovocytes quality, as well as uterus quality. In-vitro experiments have shown that exposure at high concentration of palmitic acid of the pre-implant embryos leads to abnormal expression of IGF-1 in the embrio. The embrios exposed to palmitic acid had groth restriction and developed metabolic syndrome. (31) Furthermore, another study has shown that embrio's insulin resitance is associated with an increased risk for spontaneous abortion and that the use of metformin has been shown to reduce such risk. (32) Although a direct ethiopathogenic correlation between embryo resistance to insulin and spontaneous abortion in obese women has not been established, there are studies that support the idea of metformin use for improved quality of fetal development. (33)

Does obesity have consequences over the uterus receptiveness and zygot implantation?

One of the proposed mechanisms is endometrial influence induced by obesity which affects the implantation process, more so than fertility and early pregnancy development. Several reports over the potential endometer role in infertility occurrence during obesity have been done by taking ovocytes from healthy donours which have been administered to women with various BMI. (30) The results showed that the pregnancy success rate was significantly lower in obese women compared to women of normal weight.(30) There are different studies however, in which no such correlation could be established, namely obesity and zygot implantation. (34,35) Obese women have shown a significant difference in gene expression during zygot implantation window, especially for women with polichistic ovary. (36)

Could obesity influence the result of assisted reproduction?

Some studies have shown that overweight or obese women have poorer results after in vitro fertilization (IVF) compared with women of normal weight. A link between obesity and weak quality of embryos at women under 35 years old has been established, and young obese women have fewer chances of cryopreserved embryos. (37) Obese women with ovary stimulation need higher doses of gonadotropine administered during a longer period of treatment. (38)

Infertile obese women in need of assisted reproduction show some difficulties during treatment such as low ovarian response during ovarian stimulation, low ovocyte recovery, low ovocyte and embryo quality, low concentration of human chorionic gonadotrophine, low estradiol level, low number of mature ovocytes and embryo transfer. (1)

BMI is negatively associated with estradiol level of preovulatory follicle, which leads to reduced estradiol levels with increase in BMI. (39) Obesity is generally correlated with lack of follicular development as well as ovocyte number reduction and gonadothropine resistance. (40,41) Gonadothropine resistance can be induced by leptine, since an increase in leptine concentration in serum as well as in the follicular liquid in obese women determines a decrease in estradiol secretion at the granulous cells level which act as gonadothorine inhibitor when in high concentrations. (42) There is justification for high doses of gonadothropine administered to obese women which resides from differences of absorbtion, distribution and clearance rates in gonadothropine secreted by excess fat tissue. (39)

Recent meta-analyses investigated the influence of obesity over pregnancy rates after the fertility treatment. The results showed that overweight and obese women exhibit a significant reduction in pregnancy rate, and abortion rates were significantly higher compared to normal BMI women.((38,43) A different study with higher cohorts of patients wich received ovules from donors have shown a reduction of implantation chances, lower pregnancies onset, and a lower chance of healthy baby deliveries at obese women, but there was no significant difference regarding the abortion risk between normal weight and obese women. (30)

Obesity and infertility treatment characteristics.

Treatment of un-ovulatory condition in obese women is difficult, since obese women have a lower reproduction chance after assisted fertilization procedures and higher doses of gonadothropine are needed, there is a weak ovarian stimulation response and higher risk of spontaneous abortion.

Weight loss among the overweight and obese women proved to be beneficial for the reproduction rates, including fertility. (46) Therefore, it is important to determine which patients can benefit from weight loss as well as weight loss interval and ART program.

Weight loss of over 10-15% in obese patients have shown to lead to an increase in the pregnancy rate in the absence of fertilization treatment by 30%, and if there is an undergoing of drug therapy, chances increase by 50%. (47,48) In patients that have undergone surgical operations such as biliopancreatic diversion, 47% of the women with prior operation infertility have sustained pregnancy after the operation, which facilitated weight loss. Another important aspect to mention is the beneficial effect of weight loss for the pregnant woman as well as for the fetus. It was observed that weight loss is important for normalization of weight modification during gestation as well as for reducing the risk for macrosomia. (49)

The British Fertility Society recommends clinicians to counsel their patients with regards to their weight loss prior to commencement of any fertilization program, by indicating that no fertility stimulation treatment should be administered to women with BMI higher than 35kg/m2, and preferably up to BMI of 30kg/m2.(50)

The majority of overweight and obese women have an overweight and obese life partner, which represent an additional risk factor for achieving pregnancy. (51) Obese men have exhibited a lower sperm count, and there is a positive correlation between weight loss and sperm count as well as percentage of morphologically normal sperm. (52)

Nevertheless, in the event that weight loss will continue for an extended period of time, the patient may enter in a phase catabolic fertility, since advanced age is one of the determing conditons for deteriorating infertility factors.(1)

Conclusions

Overweight and obese patients should receive counselling with regards to the importance of weight loss prior to pregnancy and should be encouraged to enter weight loss programs before treatment for improving obstetrical results. The majority of fertility clinics have a protocol for the initiation of assisted fertility treatment, but there are no proof based indications on the fertility treatment for overweight or obese infertile women. Weight loss for obese women is considered essential as there are numerous scientifical reports ahowing that the chances of pregnancy rates significant increases if these women achieve weight reduction. There are several proposed mechanisms to explain the way obesity can lead to infertility. However, the exact physiopathology is not clearly understood.

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OPERATIVE SETTINGS: CUSTOM MADE - VERSUS STANDARD SURGICAL DRAPES

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Abstract

Surgical drapes are used as a method to keep sterility and asepsy in the operating settings of a surgical procedure. Nowadays disposable surgical drapes are included in standard size kits. The study includes 96 patients operated in the "Louis Țurcanu" Emergency Clinical Hospital for Children Timișoara and it was conducted in between September 2017 - March 2018. The research aims to explore other feasible option to the standard surgical drapes kits. A custom made surgical drape model was conducted by using age related classes anthropometric measures.

Key words: Surgical drapes, children, operating room

Introduction

The operating room is one of the most demanding healthcare sites. It implies both large maintenance costs and a growing need for adaptability [1] by adjusting to the technological progress. Thus it is prone to large quantities of waste. One of the most disputed surgical settings regards the surgical drapes used.

There are two types of surgical drapes: reusable or disposable. The reusable drapes are made of a woven material and are laundered and sterilized for the next surgical procedure. On the other hand, disposable drapes are usually made of non-woven material and are incinerated after each operation [2].

There is considerable variation in design and performance characteristics within each of these two broad categories, which reflects the necessary trade-offs in economy, comfort and degree of protection required for particular surgical procedures [3].

It remains unclear which drape type is superior at preventing infections and, internationally, this has resulted in a lack of consensus on which drapes to use, despite attempts to develop guidelines [2].

However, single-use surgical drapes tend to gain popularity over the reusable, woven material drapes

Purpose

The aim of the present paper is to emphasize the importance of custom made surgical drapes divided by age related classes for the Pediatric Surgical Ward. This measure is cost-effective by reducing surgical drapes acquisition costs, reducing wastes from a pediatric surgical department and being easier to use when adapted to the patient dimensions and needs in a Pediatric operating room..

Materials and Methods

The data was collected on surgical cases performed in the Clinic of Paediatric Surgery and Orthopaedics of the "Louis Țurcanu" Emergency Clinical Hospital for Children Timișoara. The study was conducted between 1st September 2017 and 31 March 2018 and included 96 patients operated in the Clinic. Data was collected prospectively, including data regarding the patients and data related to the operative settings used during the surgical procedures.

Inclusion criteria were selected in order to choose a sample of relatively homogeneous patient population. Patients over 18 years old, patients for whom more than one kit of surgical drapes were used, patients standing procedures involving special surgical drapes were excluded.

Patients' data included age of each child and anthropometric measurements such as weight (W), height (H), and thoracic circumference (TC). Imagistic measurements were also used (antero-posterior thoracic diameter).

The thoracic circumference of each patient was collected by measuring the chest perimeter at the level of the xiphoid notch [4]. The antero-posterior diameter was calculated by measuring the depth of the chest on chest X-rays from the level of the carina (6th intercostal space) on a maximal inspiratory image [5].

Standard surgical drapes' settings were measured and analyzed. The standard drapes kits used in the clinics comprise two lateral fields measuring 75x90 cm each (LF), a drape used to cover the Mayo table measuring 78x145 (Mayo), a drape used for the dressing of the surgical instrument table measuring 150x190 cm (Instr.Table), a proximal drape measuring 140x240 cm (ProxDrape) and a distal drape measuring 180x182 cm (DistDrape). The total amount of fabric used to isolate a patient (StdPatientDrape) was calculate by formula in Fig. 1.

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$$StdPatM < ientDrape = LF * 2 + ProxDrape + DistDrape.$$

Fig. 1. Formula to calculate the amount of fabric

$$BSA = \sqrt{height\ x\ weight\ x\ 0.016667}\ [6]$$

Fig.2. Formula tocalculatethe area occupied by a patient

$$1)\ \frac{BSA}{2} * \frac{1}{TableSA};$$

$$2)\ \frac{BSA}{2} * 1/StdPatientDrape$$

Fig. 3. Impact of the body surface of the patient over the total area of the operating room table (1) and total surface of the surgical drapes (2)

$$PatientNeed = (\pi APTD^2 + 2\pi APTD * H)1/2\ .$$

Fig.4. strict need of fabric calculation

$$Transition = (2 * L * 50cm) + (2 * Wi * 50cm).$$

Fig. 5. Formula for need for fabric taking into consideration the pseudo-semi-cylindrical shape of a laying patient

Custom drapes = PatientNeed+Transition

Fig. 6. Formula for modified surgicaldrapes

The surgical table used for the procedures measured 174 cm in length (L) and 60 cm in width (Wi). The surface area (Table SA) was calculated accordingly.

In order to estimate the area in square meters occupied by a patient, for each child of the study was calculated his/her Body Surface Area by using the Mosteller formula in Fig. 2.

Two indices of impact of the body surface of the patient over the total area of the operating room table, and the total surface of the surgical drapes were calculated using these two formula in Fig. 3.

We imagined further a mathematical model calculating the need for fabric taking into consideration the pseudo-semi-cylindrical shape of a laying patient, two anthropometric measurement (H, APTD), and a transition sterility zone. In order to calculate the strict need of fabric to cover the patient (PatientNeed) we used the following formula in fig. 4.

We imagined further a mathematical model calculating the need for fabric taking into consideration the pseudo-semi-cylindrical shape of a laying patient, two anthropometric measurement (H, APTD), and a transition sterility zone. In order to calculate the strict need of fabric to cover the patient (PatientNeed) we used the following formula in fig. 5.

Finally, the proposed a modification to the standard side of the drapes calculated by the formulain fig. 6

Results

The sample included 96 children aging from 0 months until 18 years. The patients have been grouped in six age related classes: Newborns “0”, one to six months “1-6 mo”, seven months to one year “7mo-1yr”, one year to six years “1-6 yrs”, six years to fourteen years “6-14 yrs”, fourteen years to eighteen years “14-18 yrs”.

Average height, average weight, and average anteroposterior thoracic diameters (APTD) have been calculated and the results are shown in the graph below (Fig. 7).

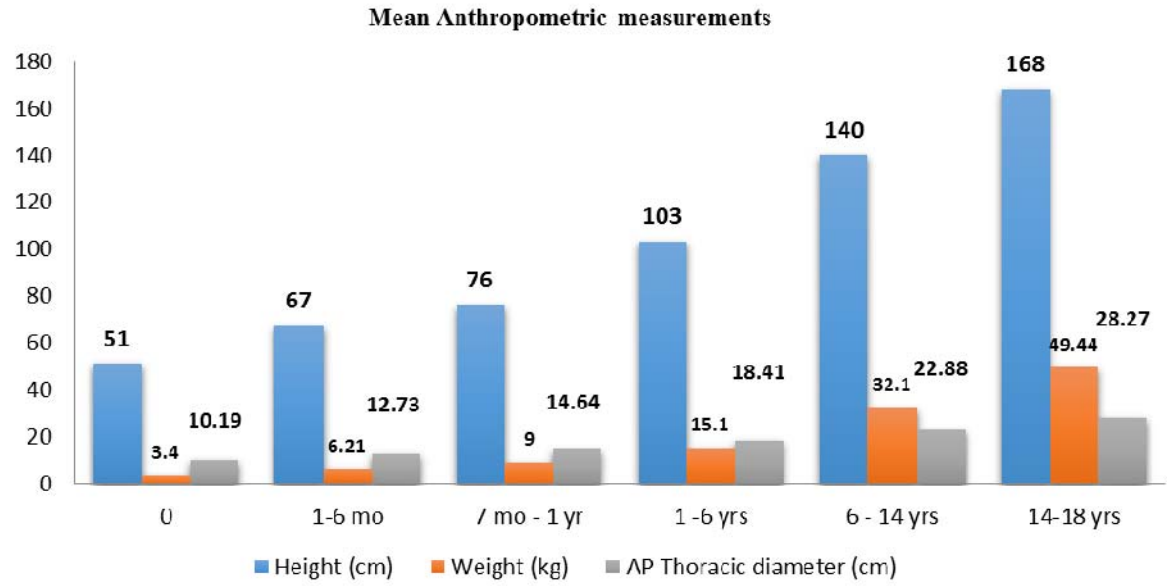

Fig. 7. Mean Anthropometric measurements

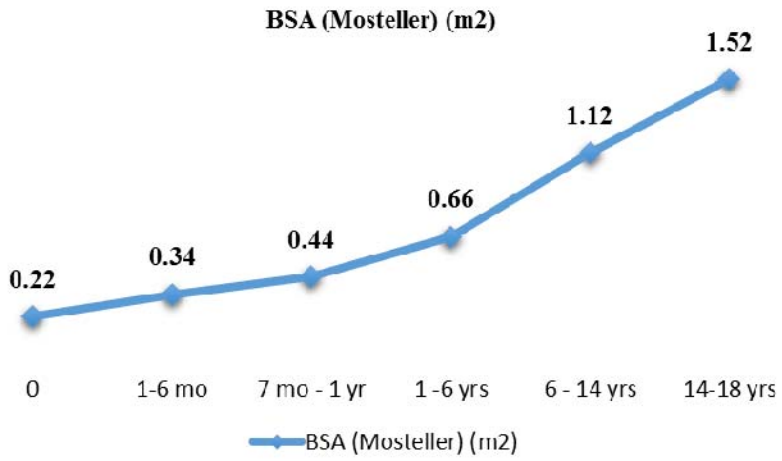

Fig. 8. BSA (Mosteller) (m^2)

Drapes / class	Newborns	1-6 mo	7mo-1yr	1-6 yrs	6-14 yrs	14-18 yrs
Lateral (cm)	48/40	49/41	51/42	53/44	57/47	61/51
Proximal (cm)	97/92	99/93	101/95	106/100	113/107	121/115
Distal (cm)	129/97	131/99	134/100	140/105	151/113	162/122

Table 1. Proposed size forthe surgical kits

The index describing the impact of the body surface of the patient over the total area of the drapes was calculated for each age group. Values of 0.026, 0.041, 0.052, 0.071, 0.134, 0.182 were calculated for each of the six age related group respectively.

The proportion of the surface of the table occupied by the children during procedures was calculated for each age category resulted in values of 10.55%, 16.34%, 20.96%, 31.60%, 53.72%, 73.03%. for each group.

The result of the transition zone is 2.340 sqm and it is the same for each class of age. Considering the relative small surface percentage of the used surgical drapes within the draping of a patient, we proposed creating custom made surgical drapes divided by age related classes for the Pediatric wards. As a consequence six surgical drapes dimension according to the age related class were calculated: 2.52sqm, 2.63sqm, 2.72sqm, 2.99 sqm, 3.43sqm, 3.96 sqm.

Thus, respecting the classical fashion of four drapes operating field we have designed 6 surgical kits made out of four drapes based on the standard proportions as shown in table 1.

Discussions

Standard kits of surgical drapes are costly and not specifically designed for paediatric patients' needs.

The variability of the dimensions in the paediatric patient makes the axiom "one size fits it all" not a feasible method of draping the patient in the paediatric surgical ward. This statement is supported by the fact that according to our calculations (BSA/2*1/StdPatientDrape) the age group with the largest dimension the proportion of the surface of the drape occupied by the patient is less than 19%.

It is estimated that the operating theatre accounts for a large proportion of hospital waste therefore operating room waste reduction should be considered as a method of decreasing costs in the paediatric surgical ward [7].

The proposed model allows the surgical unit to arise significant financial savings, environmental benefits by cutting down the material used for draping the patient. A reduction of the fabric needed coincides as well with a lower probability of surgical drapes having contact with free oxygen in the operating room therefore reducing the risk of fire in the operating theatre setting [8]. Furthermore the model, including the transition sterility zone could provide an effective method of combined patient need and reduced risk of surgical site infection. Our proposal is to implement a feasibility study to test the applicability of the model in the paediatric surgical ward.

Conclusions

The choice of an efficient surgical draping system can be a dilemma with a relevant impact on a Paediatric Surgical Ward. The amount of fabric needed must answer the necessities of asepsis, sterility, feasibility and cost-effectiveness required for the well functioning of a surgical unit.

Nonetheless the theoretical nature and further applicability studies needed to implement the imagined draping system, the custom made surgical drape model can be considered an answer to the request of flexibility, economy, strictness, security and environmental compatibility required in a modern surgical ward.

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HEALTH STATUS OF FIRST PERMANENT MOLARS IN CHILDREN FROM ROMANIA- A RETROSPECTIVE OBSERVATIONAL STUDY

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Abstract

First Permanent Molars represent an important indicator of the status of oral health of children. They are the first permanent teeth to make their eruption in the oral cavity and influence the development of the maxilla and the mandible. Our study wishes to assess the oral status of these teeth in children between 7 and 15 years of age. A retrospective observational study was designed using complete dental charts from 1213 children. DMFT index for all four first permanent molars was analyzed. Data was interpreted by simple descriptive statistics. Results present a high prevalence of caries among studied children, prevalence that increases in correlation with age. Mandibular first molars are more affected than maxillary ones. Intensification of programs to increase awareness of the importance of oral hygiene is advised. Prevention measures for dental decay in children and young adolescents are mandatory.

Keywords: DMFT index, First permanent molar, Oral health in children,

Introduction

Unfortunately in present times tooth decays remain a globally widespread health problem which has direct impact on

the quality of life. When the individual suffering from dental caries is still in a developmental stage, such as children and adolescents their health and growth are affected because caries can be associated with lack on weight gain if they remain untreated[1]. The World Health Organization (WHO) estimates that one third of world population doesn't have access to health care and in countries with low-income dental restorative treatments don't represent a priority for the healthcare system. In countries with a better developed healthcare system the prevalence of dental caries has been reduced in the 20th century, however tooth decay remains as a sign of an economic problem and a major public heath challenge in developing countries [2].

The most susceptible tooth to dental caries is the first permanent molar as it emerges early, usually at the age of 6, children might not be well accustomed to correct toothbrushing at that age and parents might mistake it for a deciduous tooth and ignore the first sign of caries and therefore this tooth is more prone to premature extraction even before 15 years of age [3]. The first permanent molar is essential in maintaining a normal masticatory function and dento-facial harmony. When affected by tooth decay, before treating the first permanent molar there are multiple factors to be considered such as the degree of pulp maturation, the status of the developing dentition, the severity of crown destruction, the level of the pain on a visual scale, the cooperation of patient and parents, the ability to withstand the treatment under local anesthesia. More often than not, some clinicians are more inclined to early extraction due to a rather poor prognosis after treatment and supporting the mesial eruption of second molar in the place of the first permanent one[4].

Nowadays, there is a world-wide movement of raising the awareness regarding heath issues and within this movement oral health education is very important. However it is a must that correct information in respect with the health status of the communities is delivered, so the prevention programs are adapted to the society's needs.

The present study wishes to provide information regarding the health status of permanent first molars using the DMFT index in populations from two regions in Romania.

Materials and Methods

The study consisted in a retrospective analysis of dental charts from children and adolescents that have been treated in the Clinical Regional Hospital and Faculties of Dentistry in Cluj-Napoca and Timisoara during a period of two years 2016 and 2017. Data was gathered during the first four months of 2018. The approval of the protocol for this study was given by the Ethics Committee from the "Iuliu Haţieganu" University of Medicine and Pharmacy from Cluj-Napoca, Romania.

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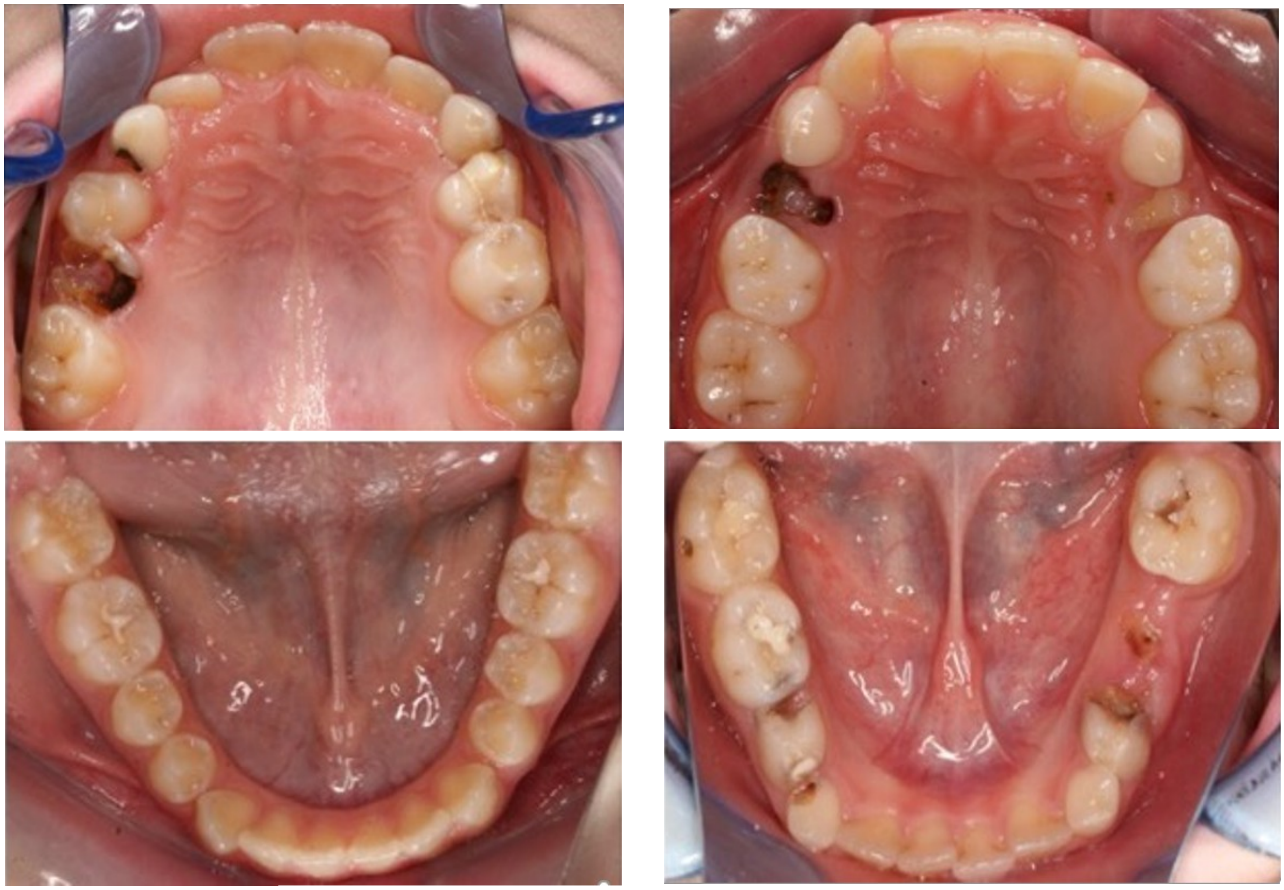
The inclusion criteria for the dental charts to be part of the study were:

- Age of patient between 7 and 15 years of age, patient must have had permanent residence in Romania for more than 5 years
- Patient presented for treatment for the first time between 1st of January 2016 and 31st of December 2017
- Charts were completed and/or verified by an attending specialist and were complete with initial dental and periodontal status, initial intra-oral photographs (figure 1), initial panoramic radiographs



Picture 1. Examples of examined maxillary and mandibulary arches.

All charts that were incomplete, that were of patients who previously benefitted from dental treatment in the same dental clinic, or were under the supervision of residents and have not yet been verified by the attending specialist were dismissed from our study. Patients that have not had a permanent residence in Romania for 5 years or more were excluded from the study as it was considered that they may have benefitted from a National Prevention Program in their former country of residence and therefore results including them might be biased. A comparison between urban and rural based patients was done but not a comparison between the two regions as all data gathered between the two clinics was processed together.

1213 charts of patients from the two Dental Clinics were included in this study. There was observed that from 9743 new charts of fatients between 7 and 15 years that were registered in the two Oral Healthcare units only 1213 had complete records with photographs and panoramic investigations.

Teeth that had sealants in pits and fissures were considered sound if there was no sign of marginal microleakage, otherwise they were considered with decay. Teeth presenting extensive sealants in pits and fissures were considered having fillings.

The description of the included population for our study is described in Tables 1 and 2.

Gender/ Living environment	Urban	Rural	Total
Female	349	279	628
Male	327	258	585
Total	676	537	1213

Table 1- Description of the population incthough luded in the study regarding their gender and living environment.

Gender/ Age	Age 7	Age 8	Age 9	Age 10	Age 11	Age 12	Age 13	Age 14	Age 15	Total
Female	72	65	47	56	68	75	89	87	69	628
Male	53	72	39	45	71	83	79	82	61	585
Total	125	137	86	101	139	158	168	169	130	1213

Table 2 -Description of the population in regard with their age and gender.

Throughout the study a number of 4852 permanent molars from our 1213 patients were assessed. The study did not take into consideration the physiological age of eruption of teeth therefore, even if the first permanent molar was not fully erupted in the oral cavity for example at the age of 7, if it's presence was shown on the panoramic radiograph it was taken into account for the study. Their assessment was done using the DMFT index (Decay, Missing, Filling Teeth Index).

The gathered data was analyzed and interpreted using simple descriptive statistics with the help of Microsoft ™ Excell 365 Software.

Results

Within the 1213 patients there were 2 who were diagnosed with agenesis of first permanent molars, and both cases had this condition present in the lower jaw, bilaterally and both cases were of male gender. The missing teeth were counted in the Missing component of the DMFT index although they were not extracted.

Distribution of the examined teeth in respect with age of patients is shown in Figure 1. There has been found a normal distribution of children in regard with the age although the percentages of children between 12 and 15 years old were slightly higher. DMFT index for first permanent molars were assessed for children according to each age as shown in Figure 2.

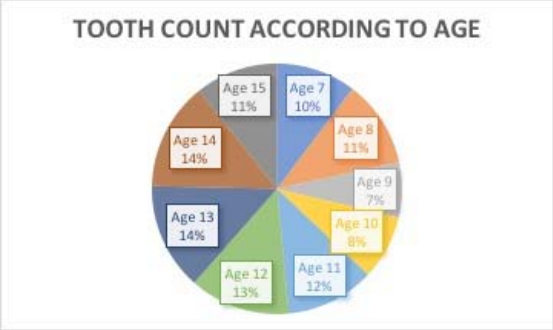


Figure 1. Distribution of examined teeth according to age.

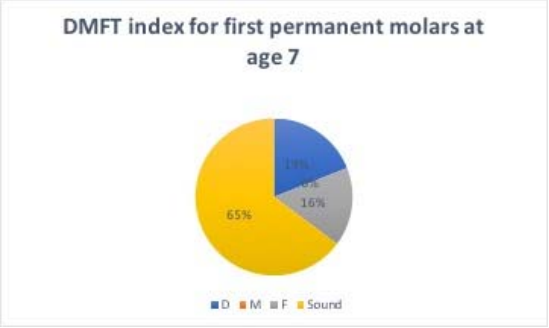


Figure 2. DMFT index assessment for children of 7 years of age.

DMFT index for first permanent molars in each quadrant was compared at different ages as seen for examples in figures 3 and 4 where DMFT index for tooth 1.6 (Upper first right permanent molar) was assessed at ages 7 and 15. It was observed that in children older in age there is a decrease of the percentage of healthy and sound 1.6 and an increase of the percentage of teeth with fillings and teeth that were missing.

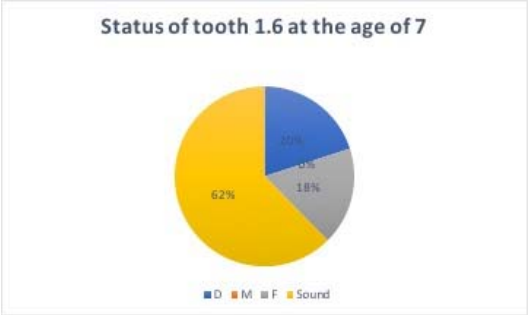


Figure 3. Status of tooth 1.6 in patients with 7 years of age.

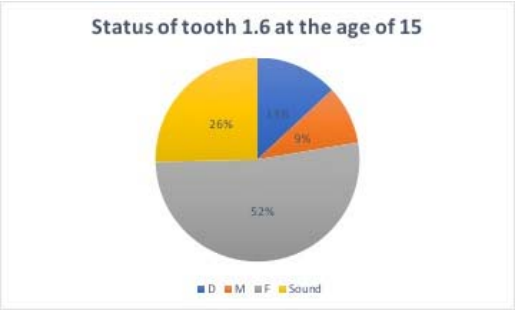


Figure 4. Status of tooth 1.6 in patients with 15 years of age.

The overall DMFT index for the first permanent molars in children between 7 and 15 years of age showed that 35% of teeth were healthy and sound not presenting any signs of caries or fillings, 43% of teeth were affected and have already been treated, 16% presented active carious lesions that demanded treatment in the future and 6% of the first permanent molars have already been extracted. This means that in children of our studied age groups there is a prevalence of 6% of early permanent molar extraction due to carious complications and a prevalence of 65% of caries as only 35% were sound teeth (figure 5).

Authors find encouraging the fact that overall prevalence of treated first permanent molars was three times higher than the active caries prevalence as it represents a sign that the communities are active in seeking dental treatment in order to reduce the prevalence of extraction.

DMFT Index was studied for each of the four permanent molars in respect with age and a comparison between the different ages has been conducted. As seen in figures 6 to 14 there has been observed that in children of a higher age the percentage of sound teeth decreases in all four quadrants. It has also been observed a difference between the upper quadrants and the lower quadrants as there seem to be more affected lower first permanent molars that upper ones. Starting from the age of nine there is a clear tendency that lower molars are less healthy than the upper ones. Also it has been observed that if in children of 7 years of age there were no missing first permanent molars, in elderly children that is no longer the case and there has also boon observed a strong correlation ($p<0.039$) between the age and the increase of prevalence for fillings and extractions.

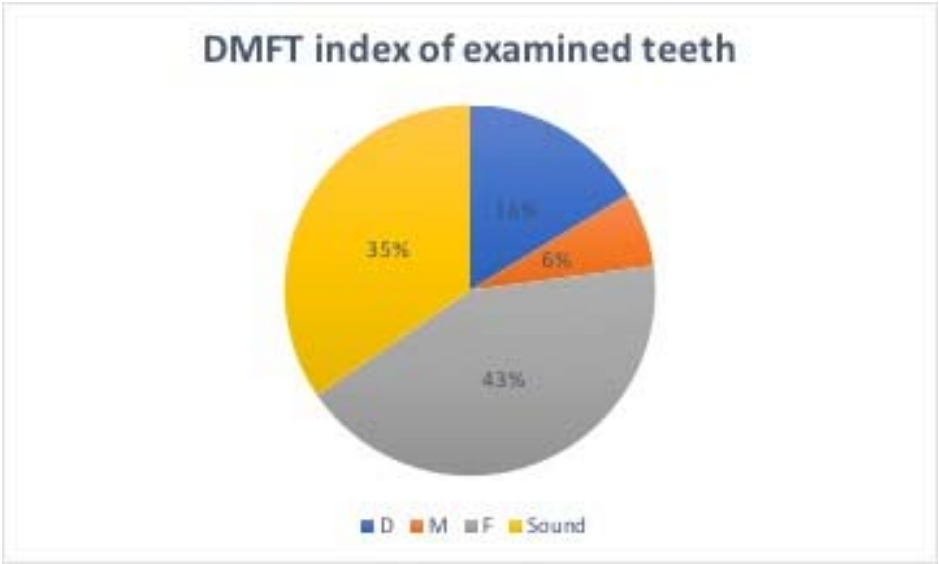


Figure 5. DMFT index assessment for al 4852 examined teeth.

Figure 6. Status of First Permanent Molars at different ages.

There have not been found any significant differences between children from urban and rural environment. Allthough it was suspected to be one of this study's null hypothesis it has been denied by our ANNOVA tests. Even if there was observed that at an early age (7-9 years old) more patients (67 %) were from the urban environment the percentages between the two populations in regard with the DMFT index for the first permanent molars were similar. Patients from 10 to 15 years of age had a more normal distribution in respect with their living environment and also similar percentages in the DMFT index.

Another null hypothesis of our study was that there would be significant differences between patients of different genders and this hypothesis has also been rejected by our study.

While assessing the overall DMFT index assessment at different ages (Figure 7) we can observe that there is an abrupt decrease in the health of first permanent molars between the ages of 8 and 9 and afterwards this situation is somewhat constant. Also, the number of fillings is abruptly increasing between 10 and 12 years of age and decreases after the age of 14. The percentages of carious lesions are somewhat constant from 7 to 15 years of age showing that there is a constant preoccupation from patients and healthcare providers to treat the increasing carious lesions. Unfortunately there was observed a slow but constant increase in the percentage of missing molars due to early extraction between 8 to 15 years of age meaning that some carious lesions are suffering from early complications.

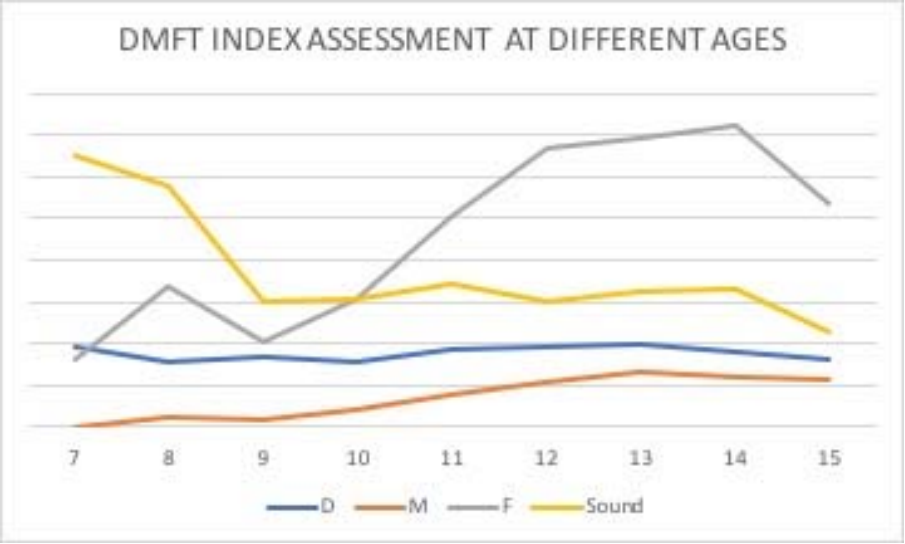


Figure 7. DMFT index status at children of different ages between 7 and 15.

Discussion

Our study investigates the health status of first permanent molars among children between 7 and 15 years of age of Romanian population. The study was focused on the first permanent molar as it plays an important role in maintaining oral and general heath of the individual. They are the first permanent teeth to erupt in the oral cavity and have a great influence over the eruption of other permanent lateral teeth[5,6]. Also, the first permanent molars are the largest teeth in the oral cavity and support the maximum occlusal forces. They have important influence in the vertical development of the face, the occlusal height and vertical aesthetic proportions. They also represent the best dental anchorage for orthodontic treatments [7,8]. All this characteristics render the first permanent molars as key elements in the normal development on the individual. Due to their physiological functional and morphological particularities they are more vulnerable and represent a good starting point in assessing the oral status of children[7].

The study was done by examining the dental charts of children at one point in their development. A longitudinal study where observations of the charts could be done throughout several consecutive years would provide better understanding of the dynamics in oral health status. In our study 35% of the examined molars were free of caries but DMFT index for first permanent molars has increased with the increase in age among the studied group. Our results are in agreement with similar studies [7,9,10] conducted in developed and developing countries throughout the world. The increase of the number of affected teeth in correspondence with the increase of age can be explained by the fact that caries being a cumulative and continuous process have increased in time. Another finding, that was consistent with studies conducted by Șerban, Maxim and Balan [10 in other regions from Romania is that mandibular first permanent molars appear to be more affected by decay than maxillary ones an explanation being the difference in morphology where the mandibular first permanent molars exhibit more pits and supplementary grooves that are retentive for food and therefore promote more caries. Another explanation can be the fact that mandibular first permanent molars erupt usually before their maxillary

counterpart and therefore are exposed longer to the oral flora.

Conclusions

A high prevalence of caries affecting the first permanent molars was observed in children between 7 and 15 years of age.

The elder the patients were the higher the prevalence of caries and the higher the DMFT index was.

Mandibular first molars are prone to be more affected than maxillary first permanent molars.

There was no statistically significant difference found in the DMFT Index between children from urban and rural environment.

There was no statistically significant difference found in the DMFT index between male and female patients.

The increase in percentage of teeth with fillings show interest within the population in regard with their oral health status.

Authors recommend intensification of preventive dental health programs in schools. Such educational programs may consist of following; awareness programs for children and parents, regular check-ups in schools, application of fissure sealants, topical fluoride and home care instructions.

Conflict of interests

The authors declare they have no conflict of interest with conducting and publishing this study.

Acknowledgment

All authors are considered to have equal contribution in the development of this study and writing of the article.

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LATE DIAGNOSIS OF GANGLIONEUROBLASTOMA IN AN INFANT

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Abstract

The neuroendocrine masses that synthesize vasoactive intestinal peptide (VIP) are named VIPomas.Watery diarrhea, hypokalemia, achlorhydria syndrome (WDHA) occurs frequently in adults with pancreatic tumors. WDHA syndrome in children is mainly induces by VIPomas localized in mediastinum or retroperitoneum. Chronic diarrhea in infants is a common condition for addressability to pediatric gastroenterologists. The causes are multiple and the delay in reaching the final diagnosis can lead to fatal complications. The authors present an infant with recurrent watery diarrhea, subocclusion manifestations, hyperchloremic metabolic acidosis and hypokalemia triggered by a retroperitoneal VIPoma that was diagnosed by abdominal ultrasound and tomography. Laboratory investigations indicated an elevated VIP serum level. Tumor excision restored the normal stool consistency, corrected the imbalance of serum electrolytes and normalized VIP level. The diagnosis of N-MYC negative ganglioneuroblastoma was confirmed by immune-histochemical assessment. This paper describes the clinical and histo-genetic aspects of this rare clinical condition.

Key words: infant, diarrhea, vasoactive intestinal polypeptide, ganglioneuroblastoma

Introduction

Verner and Morrison reported in 1958 chronic watery diarrhea with hypokalemia triggered by pancreatic masses.[1] The patients with Verner-Morrison syndrome usually associate reduced gastric secretion or achlorhydria and severe diarrhea similar to that induced by Vibrio cholerae.[2] For this reason, the syndrome was named ”pancreatic cholera”.[2] Some authors proposed the acronym WDHA for watery diarrhea, hypokalemia and achlorhydria[3], albeit the term WDHHA (watery diarrhea, hypokalemia, hypochlorhydria and acidosis) would be more appropriate accounting the loss of bicarbonate.[3] Several publications of case series have described the concomitance of recurrent watery diarrhea with pancreatic masses.[4, 5, 6] This syndrome is mainly associated with pancreatic tumors in adult patients. Only in rare cases it can be triggered by extra-pancreatic tumors as retroperitoneal histiocytoma, adrenal pheochromocytoma, bronchogenic carcinoma or medullary thyroid carcinoma.[7]

In infants, it is extremely rare for a vasoactive intestinal polypeptide (VIP) synthesizing mass to belong to the pancreas. More often, WDHA syndrome in children is determined by VIPomas originating in the mediastinum and retroperitoneum.[5] Although being reported in childhood, pancreatic non–beta-cell hyperplasia is very scarce among pediatric patients.[8, 9] There were only a few case series published regarding this topic. [8, 9]

A vast array of gastrointestinal disorders may induce recurrent diarrhea in pediatric patients. In a minority of cases, diarrhea is a consequence of active intraluminal liquid outpouring, known as secretory diarrhea. Due to important diagnostic implications, the identification of such pathologic cases comes as a necessity. Recurrent secretory diarrhea without an obvious intestinal cause may be due to an occult tumor mass that produces VIP.

In this paper, the authors describe an infant diagnosed with electrolytes imbalance–low kalium level and chronic secretory diarrhea caused by a retroperitoneal VIP producing tumor which was immune-histochemically confirmed to be a N-MYC negative ganglioneuroblastoma. Tumor excision restored the normal stool consistency, corrected the imbalance of serum electrolytes and normalized VIP level. The authors obtained the written informed consent from the parents of the child to publish this case report.

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Case presentation

An 11 months old female patient was referred to our hospital with a history of watery diarrhea, malnutrition and important abdominal distension, without vomiting. For one month, the infant presented recurrent diarrhea with seven to eight watery stools daily without pathological products (mucus or blood).

The child originates from a rural environment, the mother being aged 42 years old and the father 40 years old. No relevant familial history for chronic diseases was noted. The female child was the eighth born infant by natural birth, with the gestational age of 38 weeks, weighting 3100 grams and being given an APGAR score of nine points. The child was vaccinated according to the national program. She has been breastfed for one month and was then switched to formula. Also, complementary feeding has been properly initiated at the age of four months. The infant has no significant medical history. During the first ten months of life, she presented a normal intestinal function. However, at the age of ten months, watery diarrhea occured, without fever or vomiting.

Before hospital admission, during four weeks of outpatient investigations the diagnosis of cow's milk protein allergy was established. Dairy were excluded and the infant started a semi-elemental diet containing hydrolyzed proteins without lactose, but the trial of cow's milk exclusion had been unsuccessful. Empiric administration of Furazolidon for an alleged parasitosis was useless. The infant received oral rehydration solution repeatedly, but the diarrhea persisted.

Upon admission, the infant's height was 70 cm (5th percentile according to age) and the weight was eight kg (25th percentile according to age). Physical examination indicated normal blood pressure (80/55 mmHg) and regular heart rate of 85 beats/minute.The infant presented facial flushing, important abdominal distension without liver or spleen enlargement or abdominal mass detected through palpation. Laboratory tests showed mild hypokalemia and metabolic acidosis. There were no abnormal results of routine biochemical investigations and blood cell count.We ruled out infectious enterocolitis, intestinal parasitosis, cow's milk protein allergy, celiac disease and exocrine pancreas insufficiency/mucoviscidosis. Diarrhea persisted even after implementation of modular, elemental amino-acid based diet.

Due to the persistence of an important abdominal distension, X rays examination of the abdomen was performed showing enlarged small and large intestine with air-fluid levels without a lumen-occluding mass (Figure 1).

An abdominal ultrasound, followed by abdominal computed tomography (CT) scan showed a calcified tumor with a size of six/four cm in the retroperitoneal left lateral area, anterior to the L1-L4 lumbar spine and aorta, without contact with the left kidney. The pancreas did not present any abnormalities (figure 2).

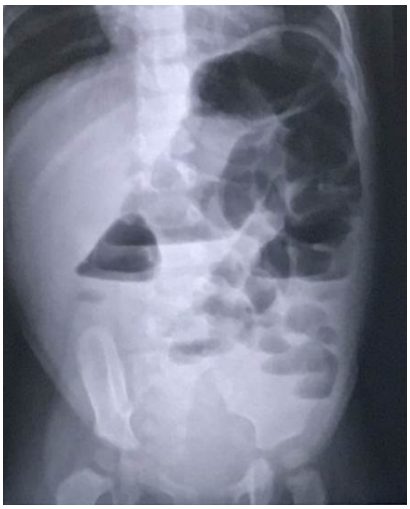


Figure 1: Radiological imaging showing enlarged small and large intestine with air-fluid levels without a lumen-occluding mass.

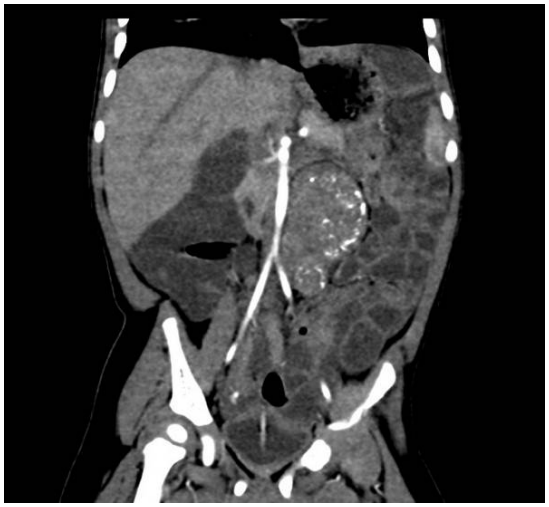


Figure 2: CT scan depiction of the retroperitoneal tumor with calcifications.

Additional endocrinological evaluation was applied in order to ensure an accurate diagnosis. The thyroid did not show any signs of disfunctionality. Serum hormone levels was assessed and the results showed high values of VIP =180 pmol/l (normal range <30 pmol/l). In addition, the 24 urinary vanillylmandelic acid levels were normal as well as those of the homovanillic acid. However, neuron specific enolase showed elevated levels - 25,77 ng/ml (normal range <16,3 ng/ml), raising the suspicion of a possible VIP secreting ganglioneuroblastoma.

The infant was referred to the Department of Pediatric Surgery. Surgical exploration showed an encapsulated retroperitoneal tumor measuring of six/four cm, anterior to the L1-L4 lumbar spine and aorta, without contact with the left kidney. The aspect of the pancreas did not present any notable changes. Tumor excision was then performed.
Figure 3 shows the macroscopic aspects of the tumor.

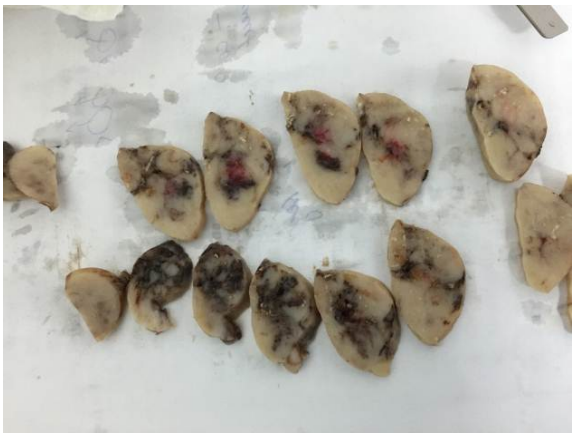
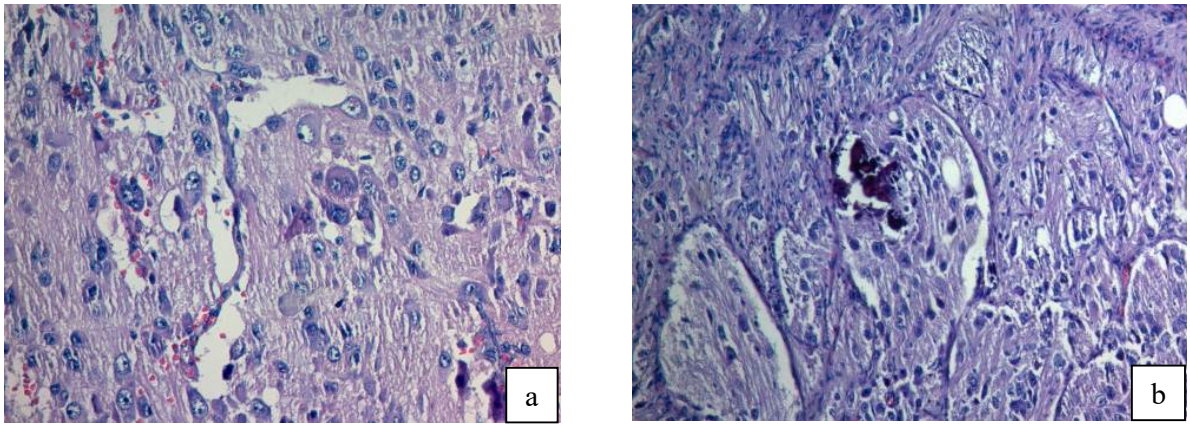


Figure 3: Macroscopic aspects of the tumor reveal a brown color, an elastic consistency and visible calcifications on each section.

Histological examination of the tumor established the diagnosis of ganglioneuroblastoma intermixed with stroma rich (Shimada Classification [10]), International Neuroblastoma Staging System (INSS) [10] stage two localized tumor, with incomplete gross removal, positive lymph nodes, MKI (mitosis-karyorrhexis index) low < 100. The tumor exhibited a lobular/solid growth pattern. The tumor cells were characterized by an abundant basophilic cytoplasm, with large, round to ovoid nuclei. Prominent nucleoli were noted along with alternative areas of euchromatin and heterochromatin, slightly mimicking a "salt and pepper appearance". Other tumor cells were characterized by eccentric nuclei, distinct cell borders and a rich, eosinophilic cytoplasm. A low amount of hemorrhage was present amongst the tumor cells along with moderate areas of dystrophic calcification. Figure 4a and Figure 4b reveal the microscopic aspect of the tumor on Haemotoxylin and Eosin (H&E) stained specimens.



Figures 4a and 4b: Depiction of the enlarged nuclei of tumor cells exhibiting visible nucleoli and the rich, eosinophilic cytoplasm. Amongst tumor cells, slight areas of hemorrhage have been observed (4a). Note the lobular/solid growth pattern of the tumor with the presence of moderate areas of dystrophic calcification (4b). H&E stained specimen x40 magnification.

In order to establish the final diagnosis and exclude other similar lesions, additional immunohistochemical analysis was applied using the following panel of markers: NSE, Synaptophysin, NF 200, S100, GFAP, Chromogranin and CD99. Vimentin was used as an internal control marker and exhibited a positive stromal reaction. NSE, Synaptophysin and NF 200 exhibited a moderate to strong reaction in the tumor cells. The pattern of reaction was cytoplasmic and presented a diffuse, heterogeneous distribution. S100 and GFAP presented a strong immunohistochemical reaction in the ganglion cells and in stroma. Additionally, S100 was positive in the cytoplasm of Schwann cells. Neuroblasts proved to be isolately positive for Chromogranin. CD99 was evaluated as negative overall. The immunohistochemical features of the tumor are revealed in Figures 5a, b, c and d.

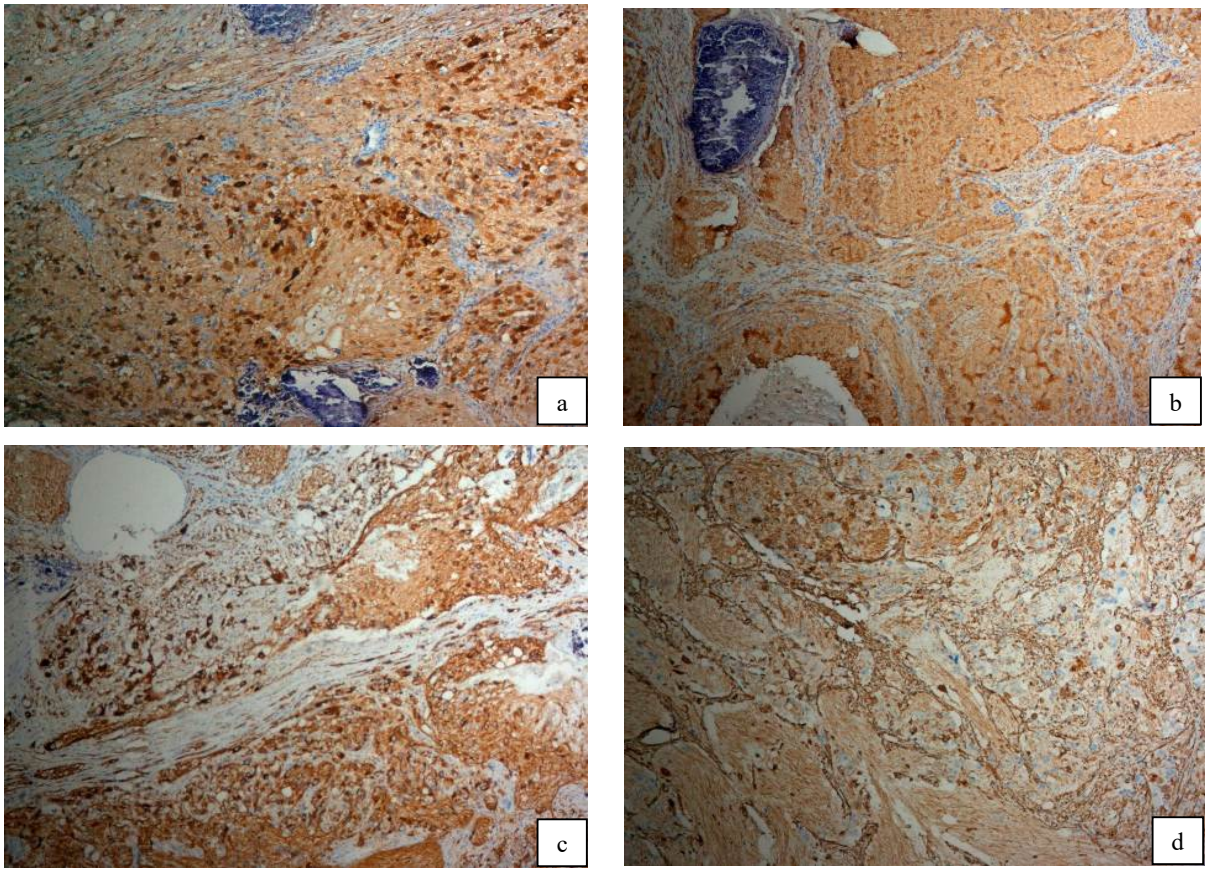


Figure 5a, 5b, 5c, 5d: Protein S100 exhibited a strong, positive reaction in both Schwann cells and ganglion cells (5a). NSE was intensely expressed in the tumor cells, with a cytoplasmic pattern of reaction (5b). Note the intense, diffuse, rather homogeneous expression for NF 200 in the tumor cells (5c). GFAP exhibited a moderate to strong positive expression in the ganglion cells (5d). Specimen x10 magnification.

Further molecular biology tests were performed. The N-MYC gene status was assessed by fluorescence in situ hybridization (FISH) technique and the result was negative.

The evolution after surgical tumoral excision was favorable. The stool consistency restored to normal and laboratory test showed correction of serum kalium levels. Subsequently, there was no diarrhea recurrence after the follow up period. The plasma concentration of the vasoactive intestinal polypeptide remained at low levels on regular measurements following surgical intervention.

Discussions

Although rare, Werner-Morrison Syndrom is a well-known clinical and pathological condition induced mainly by VIP-secreting masses.[1] The majority of VIPomas diagnosed in children are ganglioneuromas or ganglioneuroblastomas, developed from the neural crest of the adrenal medulla or sympathetic ganglia. Ganglioneuromas are benign tumors characterized by well differentiated structure, while ganglioneuroblastomas display variable degree of differentiation and have an uncertain prognosis.[11] These tumors may originate everywhere the sympathetic nerve tissue exists. The adrenal glands (35%), retroperitoneal ganglia (30-35%), posterior mediastinum (20%), pelvis (2-3%) and head and neck (1-5%) represents the most frequent localizations. More rarely, these tumors are found in anterior mediastinum, thymus, lung or kidney. [12]

Ganglioneuromas, ganglioneuroblastomas and neuroblastomas differ from one another according to the cells maturation stages. Being composed of mature cells, ganglioneuromas are considered benign tumors. Ganglioneuroblastomas are more immature masses, bearing a higher potential of invasion. These tumors usually develop in infants and toddlers, the medium age at onset being around two years. Patients diagnosed with ganglioneuroblastomas present a relatively good prognosis considering that these masses may spontaneously regress or maturate into ganglioneuromas. Regression develops in 1-2% of cases and the reason is uncertain.[11]

Initially, a hypothesis has been released in the 1960s, supporting the idea that watery diarrhea was provoked by synthesis of high level of catecholamine, a well-known fact that was associated with neural crest masses.[13] Later, in the 1970s, researchers have proved that these tumors also secreted VIP.[14] VIP is characterized by a 3381 molecular

weight and consist of a sequence of 28 amino acids, appertaining to the secretin-glucagon class.[15] In physiological situations, VIP is synthesized at the level of central nervous system and in the neural plexus of the digestive, urogenital and respiratory tract, acting as a neurotransmitter. [15]

VIP overexpression causes diarrhea and its receptors overexpression may induce malignant proliferation. At the gastrointestinal level, VIP leads to relaxation in smooth muscle cells of vascular and nonvascular structures and regulates intraluminal transport of electrolytes and water. Food consumption triggers intestinal dilatation and secondary VIP releasing. Intestinal cyclic adenosine monophosphate (cAMP) synthesis is stimulated by VIP hormone, promoting important intraluminal secretion of kalium along with other electrolytes and water. The patients with neuroendocrine masses that synthesize high levels of VIP hormone experience significant watery diarrhea with secondary dehydration, failure to thrive and facial flushing.[16]

VIP concentration was raised in the hereby presented case report. Moreover, hypokalaemia was documented. About 90% of children with a neuroblastoma will present an excessive homovanillic and vanillylmandelic acid production. If vanillylmandelic acid along with other catecholamine levels are within normal ranges, the diagnosis of neuroblastoma is less probable; however, this diagnosis cannot be excluded.[17] The neuroendocrine tumors do not synthesize catecholamines permanently. Therefore, the secreted hormones and their metabolites may have unsteady peaks with fluctuating levels in the blood and urine.[18] Neuron specific enolase (NSE) is a well-represented isoenzyme synthesized in neuroendocrine tumors and neurons, described as a 78 kD gamma-homodimer.[19] NSE concentration in other organs, with the exception of erythrocytes, are non-detectable.[19] Having a high specificity for the above mentioned organs and tissues, NSE serum or cerebrospinal levels are increased in almost all disorders that associate neuronal destruction. Also, patients with tumors derived from the neural crest usually present elevated NSE levels. In almost 70% of cases with small cell lung carcinoma high NSE levels were detected at the onset of the disease.[20] NSE may also present high serum levels in certain neuroendocrine malignancies as carcinoid tumors (66% of patients), islet cell tumors (up to 40% of patients) or neuroblastoma (with unknown prevalence of patients that associate elevated serum levels). [20,21]

In this case, vanillylmandelic and homovanillic 24 urinary levels were normal, but neuron specific enolase serum level was elevated, indicating, along with the elevated VIP serum levels, the diagnosis of VIP producing ganglioneuroblastoma that was further certified by histopathological examination and imunohistochemical staining.

According to the International Neuroblastoma Risk Group (INRG) classification[22], this patient was included into the low risk group based on histological criteria, degree of differentiation, age and N-MYC negative test.

In this case, the initial suspicion was referring to a gastrointestinal condition. This fact delayed the correct diagnosis. The infant underwent four weeks of different medical explorations as an outpatient and the period starting from hospital admission to diagnosis was of two weeks time. Empiric administrations of various medications and special diets for unproved digestive disorders were useless. Early recognition of secretory diarrhea would have facilitated a rapid diagnosis and would have avoided unnecessary tests.

In certain cases infectious gastroenteritis (viral or bacterial) may induce intraluminal secretion. But chronic secretory diarrhea due to infectious causes is scarce. There are some rare genetic conditions that occur in the neonatal period and are characterized by the presence of secretory diarrhea due to electrolyte transport inherited errors as congenital sodium or chloride diarrhea. These are easily ruled out when the persistent watery diarrhea occurs later in infancy.

In this case, the symptoms occurred at the age of 10 months old, allowing us to initially rule out the diagnosis of congenital electrolyte transport defects.

Later in childhood, secretory diarrhea may appear in context of other gastrointestinal conditions as short bowel syndrome or inflammatory bowel diseases. However, in these disorders, the intestinal injury as cause for persistent diarrhea is easily recognized.

Conclusions

Secretory diarrhea may be the only inaugural symptom of a VIPoma and consequently appropriate explorations and treatment strategies must be initiated for early diagnosis.

This report describes an atypical case of VIP-secreting ganglioneuroblastoma in an infant that presented diarrhea as the main clinical sign. In case of a child with chronic watery diarrhea of unknown etiology it is recommended to carry out both gastrointestinal explorations and abdominal imagistic tests in order to establish whether or not a tumor is the cause of intraluminal secretion.

From a morphological perspective, the examined tumor presented particular features that made the differential diagnosis a difficult step. Neuroblasts lacked the specific pseudo rosettes layout and cystic degeneration was absent. We did not notice the presence of neuromelanin pigment inclusions, that are documented in literature as being rare.

Ganglioneuroblastomas are controversial clinical and pathological entities, the morphologic and immunohistochemical distinction between ganglioneuromas, neuroblastomas and Schwannomas with neuroblastoma-like features being regarded as a difficult diagnostic approach. The final diagnosis of such rare pathologic cases is complex and mostly based on the integration of the clinical presentation of the patient, with imaging examination, histopathological routine analysis and additional immunohistochemical evaluation of the specimens.

Acknowledgments

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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.