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Special Issue: "focus on pediatric nephrology"

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Special issue: **"FOCUS ON PEDIATRIC NEPHROLOGY"**

In this special issue, Researchers and Specialist Registrars of University of Catania, Catanzaro and Messina (ITALY) focused on nephron-urological abnormalities in children, ranging from glomerular (nephrosic and Alport syndrome, chronic glomerulonephritis) and urologic diseases (multicystic dysplastic kidney, obstructive pathologies and stones).

Particular attention was paid to congenital syndrome, such as Vacterl, Fabry and Goldenhar syndrome and acquired conditions such as Schoenlein-Henoch disease potentially leading to renal impairment.

In addition, oxidative stress in newborns is involved in the progression of renal failure. When associated to congenital renal anomalies a dialysis treatment might be needed.

Dialysis is a treatment option for children who are experiencing kidney failure. We treated about the differences between adult and pediatric dialysis concerning physical and staffing requirements.

In this regards we reported a clinical case of a child in dialytic treatment who was used innovative topical ozone therapy for infantile atopic dermatitis.

In conclusion, aim of this report was to discuss about pediatric nephro-urological issues by reporting literature reviews and clinical cases.

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FAILURE TO THRIVE: THE IMPORTANCE OF MEASURING THE ELECTROLYTES

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Diabetes insipidus (DI) is characterized by hypoosmotic polyuria related to deficiency of arginine-vasopressin (AVP) secretion (centraldiabetesinsipidus, CDI) or renalinsensitivity to AVP (nephrogenicdiabetesinsipidus, NDI). We report a case of a child with congenital NDI.

Case report

A 1-year-old male child was admitted to our pediatric emergency room for fever that lasted for a week (T max 38.5°C) and reduced diuresis since 1 day. During pregnancy, a fetal cerebral ventriculomegaly had been revealed, resolved before birth and confirmed by a cerebral sonography during the first days of life. He was the first child from non-consanguineous parents, born at term by caesarian section because uterine inertia with normal weight, length (3750g, 52 cm) and Apgar index.

In his history, delayed gross motor milestones were reported along with failure to gain weight and length. For the generalized hypotonia, he followed a physiokinesis therapy program and for malnutrition he initially underwent to a gastroenterologic visit and celiac disease was excluded. He was studied for short stature and underwent specific laboratory investigations: somatomedin C resulted below normal value for chronological age (< 25 ng/ml), subnormal clonidine GH stimulation test(peak 8.67 ng/ml). In the normal range were thyroid hormones, TSH and cortisol.

On general physical examination in the emergency room, he appeared to be in poor general condition, dehydrated and pale. He presented doll-like facies, frontal bossing and saddle nose, mild hypotonia and ligamentous laxity. Cardiac and respiratory system examination showed no abnormalities. Length 68cm (-4.0SD), weight 7700g, head circumference 46cm.

Routine blood investigations revealed Red Blood Cell Count- 2.9 million cells/cmm, Hb 8.1 mg%,

Key words: diabetes insipidus,polyuria, polydipsia,hyposthenuria,hypernatremia,desmopressin test.

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total leukocyte 11.300/cmm, platelets 2.6×10^5/cmm, sodium 159 mEq/L, potassium 4.2 mEq/L, chloride113 mEq/L, blood urea 136 mg/dl, serum creatinine 0.7 mg/dl. Arterial blood gas analysis showed pH 7.4, HCO3 12.7 mmol/l. Liver function test, serum calcium, phosphorus, albumin, glucose, C-Reactive Protein, Vitamin B12, Folic Acid were in the normal range. The patient was admitted to our pediatric ward for further diagnostic studies.

He was investigated for his hypernatremia, serum and urine osmolarity, liquid input (1330ml/24h) and urine output (138ml/kg/24h) were measured. Urine osmolality was 318 mOsm/Kg H2O and corresponding serum osmolarity was 371,23mOsm/Kg H2O. Urinary specific gravity was 1004. MRI did not show neurohypophysis. ECG, eco cardio, abdomen sonography and sweat test were normal.

Thanks to a further, more detailed family history, it resulted that his mother, maternal aunt and maternal grand-mother suffered from polyuria and polydipsia (introducing liquid about 4-6 l/day), and they had never been investigated for these problems.

Diabetes insipidus was confirmed by repeated tests with less urine osmolarity than serum osmolarity and hypernatremia. A desmopressin test was performed, using endonasal 5 mcg twice a day for 3 days, which showed no improvement in urine osmolarity. With the above history and relevant supportive clinical investigations, the diagnosis of nephrogenic diabetes insipidus was made. Clinical diagnosis was sustained by molecular genetics which demonstrated mutations in the arginine-vasopressin receptor 2 gene (AVPR2): c.738dupG, p.Arg247Alafs*12. His mother had a genotype:c.[738dupG]; [=],p. [Arg247Alafas*12]; [(=).], as heterozygous carrier. On the basis of the genetic diagnosis, hydrochlorothiazide therapy was started.

DISCUSSION

NDI can be inherited (X-linked or autosomal) or acquired, mostcommonlyas a result of lithium treatment. NDI is a hereditary disorder, generally transmitted by sex-linked recessive genes with varyingdegrees of penetrance in females. It is a rare disorder in which there is renal resistance to the action of antidiuretic hormone (ADH), normally produced. The renal collecting duct cells do not respond to the hormone and are unable to reabsorb water. About 90% of patients with congenital NDI are males with X-linked NDI (MIM #304800) who have mutations in the vasopressin V2 receptor (AVPR2): this gene, located on X-chromosome at locus Xq28, encodes the vasopressin V2 receptor (3, 4).

To our knowledge, there are no data on the Italian national incidence of congenital NDI, but it has been estimated that the incidence of X-linked NDI in the general population of Quebec is approximately 8.8 per million male live births (5). In less than 10% of the families studied, congenital NDI has an autosomal recessive or autosomaldominant mode of inheritance with mutations in the aquaporin-2 (AQP2) gene (6).

Our patient presented mutation in AVPR2 and his mother was carrier of this mutation. His mother, his maternal aunt and maternal grandmother reported symptoms as polyuria and polydipsia but they have never attached importance to them.

It is important to diagnose DI as early as possible because hyperosmolalality and hypernatremia could lead to retarded growth and neurologic sequelae such as intracranial hemorrhage, consciousness disturbance and even mortality. Furthermore, infantile hypotonia and intracerebral calcification has been reported in untreated children (1, 2, 7). NDI usually presents itself in infancy with symptoms of polyuria with hyposthenuria, nocturnal enuresis, thirst, fever, vomiting, constipation, dehydration and failure to thrive (8, 9, 10).

Our patient presented failure to thrive during the first few months of life and for this reason, he underwent to gastroenterological tests to exclude celiac disease and endocrinological tests to exclude GH deficiency, without performing dosage of serum electrolytes and urine test.During summer period for protracted fever he arrived in pediatric emergency room. For the first time, urine test and serum electrolytes were investigated thus allowing us the diagnosis and therapy.

This case reminded us that doctors should be alert to the initial presentation of NDI. Detailed electrolyte and urine analysis are mandatory for the correct

initial differential diagnosis. An early diagnosis may allow normal growth and psychomotor development of the children with NDI and give the possibility of genetic counseling to the family.

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CONGENITAL RENAL ANOMALIES IMAGING: A VALUABLE TOOL FOR PEDIATRICIANS

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The purpose of this article is to review the main congenital anomalies of kidneys and urinary tract that can be diagnosed prenatally and postnatally by imaging technique. The incidence of congenital anomalies of the kidney and urinary tract during the past decade has been estimated to be 0.4 to 4.0 cases per 1000 births. Congenital kidney disease can evolve in chronic disease in childhood and in adulthood. A diagnostic imaging of the various congenital renal and urological conditions allows pediatricians to make a correct diagnosis and treatment. Because of the concerns about long-term effects of ionizing radiation, the most commonly and first used imaging modality for evaluation of the urinary system is ultrasound.

Congenital anomalies of the kidney and urinary tract (CAKUT) include a wide range of structural malformations resulting from defects in the morphogenesis of the kidney and of the urinary tract. The kidney and the urinary excretory system present close relationships for their embrional and functional development. Human kidney development begins in the first trimester. There are three stages of mammalian kidney development: pronephros, mesonephros, and metanephros. The first glomeruli form at 9-10 weeks of gestation and increase as nephrons between 18 and 32 weeks and complete between 32 and 36 weeks. Fetal urine represents a major contributor to amniotic fluid at about 20 weeks (1).

CAKUT are present in 3 to 7 out of 1.000 births, accounting for 20 to 30% of all anomalies detected in the prenatal period. The term CAKUT indicates a set of primitive disorders of number, size and morphology of the kidneys and/or urinary tract. These anomalies may be isolated or part of a plurimal formative syndrome. These anomalies can be the first manifestation of a complex systemic disease and can manifest in different members of the same family. For this reason, a precise genetic definition is necessary for the familial genetic counseling (2, 3). CAKUT are usually detected with prenatal sonography but many cases remain undiagnosed until adulthood. CAKUT represent a large spectrum of disease with different grades of severity and renal outcome: they range from mild, asymptomatic malformations to severe pathologies.

Key words: children, congenital anomalies of the kidney and urinary tract, diagnosis, imaging techniques

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Overall data indicate that approximately 20% of patients may have a genetic disorder or Angiotensin I converting enzyme (ACE) and angiotensin type 2 receptor (AT2R) gene polymorphisms that are usually not detected based on standard clinical evaluation, implicating many different mutational mechanisms and pathogenic pathways (4, 5). The most frequent causes of chronic renal failure (CRF) are due to renal hypodysplasia and urinary tract malformations, contributing to around 25% in this age group.

The aim of this article is to expose the role of ultrasonography (US) in the diagnosis of some of the main lesions involving the renal and urinary system during fetal period and after birth. In some cases, US is only the first exploratory imaging method and it is easy to perform.

US is valuable for evaluating renal parenchyma, renal size and growth, collecting system dilation, congenital malformations, bladder wall thickness and pre-void and post-void bladder volume (6-8). It is very important for the radiologist to identify the anatomic variants and guide obstetrics during prenatal period, and pediatricians during the post-natal period, for clinical and therapeutical approaches.

Renal agenesis/hypoplasia

About one-third of renal anomalies were detected by prenatal US, during the second trimester of pregnancy, and it is extremely important to recognize it for clinical counseling. Time of prenatal diagnosis depends on severity of the abnormality: bilateral renal agenesis (BRA), which is the most severe lethal anomaly, can be diagnosed about the 15th week of pregnancy when kidneys are not seen in normal or anomalous position associated with oligohydramnios. BRA depends on metanephric mesenchyme apoptosis. The incidence of BRA is 1 in 4000 live births, usually sporadic. Males are affected about three times more than females. After birth, the newborn presents Potter's sequence: pulmonary hypoplasia, abnormal facial features and limb deformities. Unilateral renal agenesis (URA) is associated with genital anomalies in both boys and girls (9). The incidence is 1 in 1000 live birth and can be detected by US pre and post-natally. US of the renal fossa demonstrates absence of the kidney and it is necessary to exclude renal ectopia. The contralateral kidney can be hypertrophic. Other imaging studies like scintigraphy or MRI are needed to evaluate genital anomalies.

Renal Hypoplasia (RH), a congenital defect, is usually detected by US during childhood and is characterized by small kidneys. Bilateral RH can be associated with neurological problems. Maternal diabetes (type 1, type 2 and gestational) has been evaluated extensively as a risk factor for other congenital malformations (10).

Horseshoe Kidney

Horseshoe kidneys (HSK) are the most common congenital anomaly due to a fusion defect of the kidneys, occurring during the embryonic period of intrauterine development. HSK combine three anatomic abnormalities: ectopia, malrotation and vascular changes. In most cases, the abnormality consists of two renal masses fused, in the majority of cases, at their lower poles by aparenchymal or fibrous isthmus. In rare cases, the isthmus connects the upper poles (inverted U shape).The incidence of HSK is approximately 1 in 500 in the normal population with a male preponderance of 2:1. The incidence is higher in some chromosomal disorders: Edward syndrome at approximately 67%, Turner syndrome at 14% to 20% and Down syndrome at about 1%.

HSK may be asymptomatic, sometimes associated with urinary tract infections.There is an increased incidence of ureteral duplication (UD), ureteral-pelvic junction obstruction (UPJO) and vesicoureteral reflux (VUR). Prenatal diagnosis is possible as early as the first trimester of pregnancy with US. The postnatal US may demonstrate the upper portion of each kidney in a low but otherwise normal paraspinal location and the low position of the lower pole of the kidney. Postnatal US may demonstrate the isthmus anterior to the spine. The abnormal renal axis can be appreciated with scanning, suggesting HSK. Additional imaging technique like computed tomography (CT), angiography, magnetic resonance imaging (MRI) or scintigraphy are rarely necessary (11-14).

Congenital renal dysplasia

Multicystic dysplastic kidney (MDK) is a non-

heritable disorder and is associated with obstruction of urinary drainage on the affected side; polycystic kidney diseases (PKD) are inherited, both autosomal recessive (AR) and autosomal dominant (AD) and are not associated with obstruction of renal pelvis or ureter (15).

PKD-AR belongs to a group of congenital hepatorenal fibrocystic syndromes, it is a rare disorder that affects both kidneys and liver with ectasia and fibrosis; late complications are renal failure and hepatic fibrosis. It is a cause of significant renal and liver-related morbidity and mortality in children. More than 50% of affected individuals with PKD-AR progress to end-stage renal disease (ESRD) within the first decade of life. No systematic data are available on the sensitivity and specificity of prenatal US examination in establishing the diagnosis of PKD-AR in pregnancies at risk. After birth high frequency US shows diffuse uniform involvement of the kidney with many tiny microcysts caused by collecting duct ectasia; marked nephromegaly. For the best diagnosis, an MR-urography is necessary (16, 17).

PKD-AD affects 1 in 400 to 1.000 live births and represents the most common monogenic cause of renal failure. It is a common pathology that affects kidneys, liver and pancreas. Renal and liver cysts increase over time. There are two genetical mutations: polycystin 1 gene (PK1-chromosomal locus 16p) and polycystin 2 gene (PK2-chromosomal locus 4q); mild forms depend on PKD2, while the more severe forms depend on PKD1 defects. US does not have a diagnostic accuracy during infancy, but it is used when there is an enlarged kidney due to conglomerate cysts. During adulthood multiple bilateral renal cortical and medullary cysts can be detected; number and size of cysts increase with time (18, 19).

Anomalies of the pelvocaliceal system

Caliceal diverticulum

The frequency is about 4.5 per 1000 in the urogram studies. At US it appears as a rounded fluid collection simulating solitary renal cyst. Size can increase over time from a few millimeter to several centimeters. For the diagnosis, urography and CT examinations are necessary (20).

Ureteropelvic junction obstruction

UPJ obstruction has an incidence of about 3 in 1000 live births, and it frequently occurs unilaterally and in males. UPJ is the most common cause of antenatal hydronephrosis and abdominal mass in neonate. Prenatal US has been used as an indicator of potential obstruction, with anterior-posterior diameter measurement that is dependent on gestational age, bladder fullness, and maternal hydration status. There are many causes of UPJ obstruction or stenosis including insertion anomalies of the ureters, ureteral muscular hypertrophy, peri pelvicalyceal fibrosis, and abnormal blood vessels crossing over the ureter or renal pelvis. One of the classic US findings is a disproportionate dilatation of renal pelvis (compared to calyces) with normal ureter. Calculi, infection and hemorrhage can complicate UPJ. For a more accurate diagnosis an excretory urography and renal scintigraphy are necessary (21, 22).

Ureterovesical junction obstruction

Ureterovescical junction (UVJ) is an important critical structure of the urinary tract that allows the passage of urine into the bladder. It prevents retrograde flow to the kidneys, therefore representing the most important region for the anti-reflux mechanism (23). Primary VUR is a common pediatric condition due to a congenital developmental defect in the UVJ and is observed in 30 % of children presenting with urinary tract infection. Secondary VUR depends on posterior urethral valves or neurogenic bladder.The sensitivity of US, employed as first evaluation to detect VUR and renal scarring is inferior to that of voiding cystourethrogram (VCUG) (24) and dimercaptosuccinic acid scintigraphy (25, 26).

DISCUSSION

Imaging (US, CT, scintigraphy and MRI) plays an important and increasing role in the diagnosis and follow up of renal congenital disorders. US offers a non-invasive, relatively low cost imaging modality without ionizing radiation and/or sedation in the evaluation of suspected CAKUT (27). CT and MRI maintain an important position in the investigation

of pediatric pathology, but are expensive and have inherent limitations in the child. Prenatal screening US usually identifies the majority of congenital anomalies of the urinary tract and is effective for an early detection. It is important for pediatricians that radiologists recognize the various conditions to ensure the patients a correct diagnosis, a specific therapeutic approach, follow-up and the best outcome.

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NEPHROTIC SYNDROME: IMMUNOLOGICAL MECHANISMS

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Nephrotic Syndrome (NS) is a rare diseases (around 2-7 cases per 100.000 children per year) characterized by proteinuria ≥50 mg/kg/day (or ≥40 mg/m²/h) or a proteinuria/creatininuria ratio >2 (mg/mg); hypoalbuminaemia< 25 g/l and edema. The protein leakage, with the consequent hypoalbunaemia and edema, due to podocyte alterations may be caused by genetic diseases, immunological mechanisms, infections, toxins or malignancy. However, most commonly the exact etiology is unknow. The idiopathic NS may be classified based on response to corticosteroid therapy or the hytological appearance. The first classification identifies steroid-resistant NS (no response after 4 weeks of steroid therapy); frequently relapsing NS (≥ 2 relapses in first 6 months or ≥4 relapses in 1-year); steroid dependent NS (relapses during steroid decalage or within 2 weeks from steroid therapy interruption). The hystological classification is based on light and electron microscopy after renal biopsy, which is indicated in case of onset disease before 1 year or after 12 years of age. Macroscopic hematuria: persistent hypertension and/or microscopic hematuria and/or low plasma C3 renal failure not related to hypovolemia; steroid resistence: secondary or related-syndromes NS.Minimal change disease (MCD) is the most common form of idiopahtic NS in children, with good response to steroid treatment, and it is characterized by normal glomerular appearance on light microscopy and evidence of podocyte foot alterations on electron microscopy, due to immunological related damage. Focal segmental glomerulosclerosis (FSGS) is described inidiopahtic NS, particularly in steroid-dependent or steroid-resistant forms, and is characterized by evidence of focal glomerular damage with secondary sclerosis and adhesion with Bowman's capsule; the electron appearance is the same of MCD one. Recent authors hypotizethat the FSGS is an evolution of MCD. These 2 idiopathic NS forms may be expression of the same immunological disease, with 2 different severity grades; so they may be considered different moments of the same disease spectrum. Less common idiopathic NS forms are membrano proliferative glomerulonephritis; membranous nephropathy; IgM-nephropathy; C1q nephropathy and thin basement membrane disease (1, 2, 3).

Key words: nephropathy, glomerular damage, glomerulonephritis, proteinuria, edema

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Pathophysiology: glomerular structure and glomerular damage mechanisms

The components of glomerular filtration barrier are fenestrated endothelium, glomerular basement membrane (GBM) and podocytes. The podocyte is the protagonist of this barrier. It is an epitelial cell characterized by foot processes that form a filter structure aroud glomerular capillaries (Fig. 1). Adjacent foot processes interact with each other throught particular cell-cell junctions (slit diaphragm arises) creating a diaphragm with selective filter function. The glomerular filtration must be selective and calibrated to mantain an adeguate serum protein concentration, important to obtain the right blood osmolarity.

Podocytes damage causes a loss of filter function with protein leakage and reduction of albuminaenia and consequent decrease of blood osmolarity. The consequences are the passage of fluid from vascular compartment to interstitium and the appearance of edema that is the first and most evident clinical manifestation of NS. An example of the importance of podocytes and their slit diaphragm arises comes from Finnish-type congenital NS (autosomal recessive disease). It is characterized by mutations NPHS1 gene that encodes for nephrin, an essential structural component of the slit diaphragm that regulates the actin cytoskeleton organization. Mutations of NPHS1 cause a loss of normal foot processes morphology and function with severe proteinuria that appeares in the first 6mounths of life.

Other genetic podocytopathies have been recently identifies such us NS due to mutations of NPHS2, that enconde for podocin, or mutations

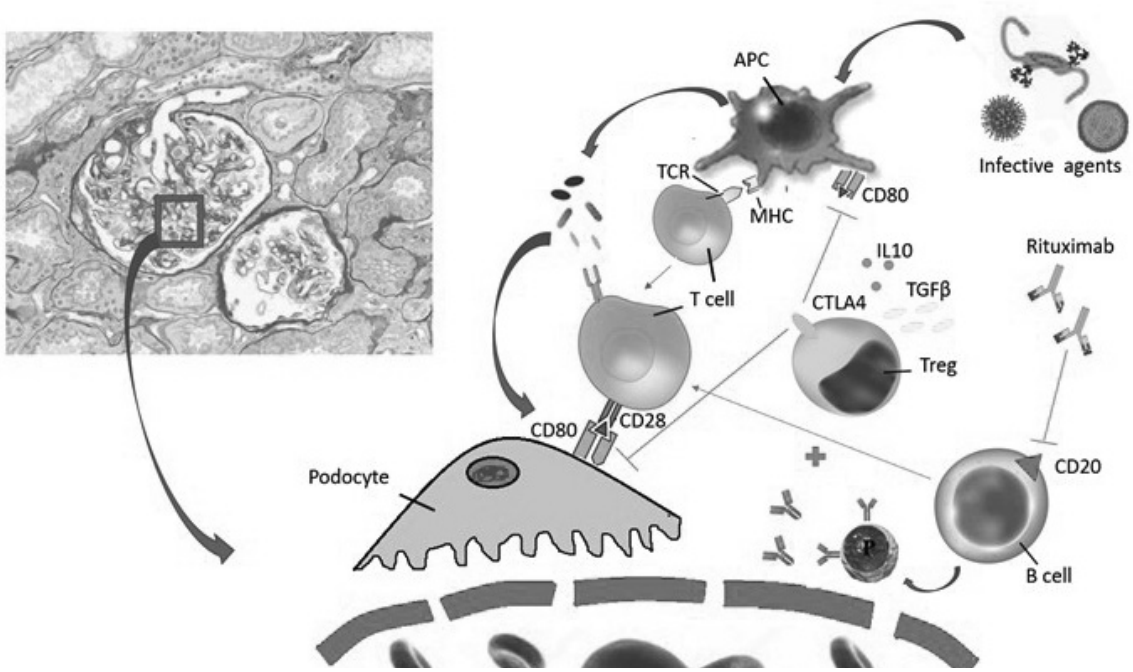

Fig. 1. *Podocytes, APCs, T and B cells partecipate in inflammation of NS, after trigger infective eventsthatactivate the APCs. APCsdetermine the T cellsactivation (MHC-TCR binding) and polarization producing specific inflammatory cytokines. CD80, expressed by podocytes and APCs, has an important role causing shape change of foot processes and T cell activation. Treg cells have an antinflammatory action through CTL4 expression and IL10 and TGFβ secretion, while B cells act on immunoglobulin dipedent and independent damage. Rituximab is a chimeric anti-CD20 monoclonal antibody that acts on B cells and reduces the Th17/Treg cells ratio.*

***Legend**: **APC** = Antigen Presenting cell; **TCR** = T Cell Receptor; **MHC** = Major Histocompatibility Complex; **IL** = Interleukine; **TGFβ** = transforming growth factor β; **Treg** = T regulatory cell; **P** = Plasma cell.*

of other genes that encode for podocyte actin cytoskeleton proteins (CD2AP, INF2), nuclear proteins (WT1), glomerular basement membrane proteins (LAMB2) and mitochondrial proteins (COQ2) (1, 4).

Glomerulonephritis is a typical immune-mediated disease. It may be a consequence of infections with loss of tollerance against self-antigens or due to vasculities with glomerular capilllaries inflammation and secondary inflammation of adjacent tissues. All components of the immune system are involved in the pathogenesis of NS: from innate immunity (Toll-Like Receptors) to umoral and cellular members of the adaptive immunity and the complement system (5, 6).

NS and Innate Immunity: Toll-Like Receptors (TLRs)

The innate immune system consists of a series of sensing elements, known as Pattern Recognition Receptors (PRRs) that respond to microbial components and trigger inflammatory responses. PRRs include TLRs located on cell surface (TLR1, TLR2, TLR4, TLR5, TLR6) or in the cytosol (TLR3, TLR7, TLR8, TLR9). The binding between Pathogen-Associated Molecular Patterns (PaMPs) and TLRs on immune cells (monocytes, macrophages and dendritic cells) activates nuclear factor-kappa B (Nf-kB), activator protein 1 (AP-1) and interferon (IFN) pathways, with consequent induction of transcription factors and cytokines production that cause the inflammatory response. Moreover, TLRs induce B cell differentiation and Immunoglobulines (Ig) production through tNf-kB pathway activation and T cells mediation (5, 7).

Some authors have studied the association between idiopathic NS and TLRs, considering that infections typically accompany the disease onset and relapses, especially viral infections. About this, there are evidences that around 70% of disease relapses are preceded by viral infections, more frequently of upper airways. In 1986, McDonald et al. identified more viral agents (respiratory syncytial virus (RSV), influenzae, parainfluenzae, varicella zoster, and adenovirus) through serological and cultural exams as triggers of idiopathic NS relapses (8). More recently, Dossier et al. show that herpes viruses such us CMV and HHV-7 ($p=0.02$) and in particular EBV ($p=0.0002$) infections are statistically significantly associated with the disease onset, studing 164 pediatric patients (9).

From these data come the hypothesis about the central role of TLRs and innate immune system in NS pathogenesis. Jamin et al. show increased TLR-3 expression on serum B cells and increased TLR-8 expression in both CD4 T cells and B cells of patients affected by idiopathic NS in remission versus patients with disease relapse. This TLRs over-expression may be a consequence of latent microbial (mainly viral) infection. After Rituximab treatment, the authors observed a normalization of TLRs expression on immune cells surface, associated with a normalization of IgG, IL6 and IFN production (7). In vitro sudies show that TLRs (TLRs 1-6 and 9) and CD80 are expressed on podocytes surface. Shimada et al. demonstrated that the administration of PolyIC (polyinosinicpolycytidylic acid), a TLR3 ligand, cause the CD80 expression on podocytes with consequent actin reorganization in foot processes (10). Similar data, with evidence of increased urinary excretion of CD80, come from mice model of NS after Poly IC stimulation (11).

CD80 (also called B7-1) is a trasmembrane protein of immune cells (Antigen-Preseting Cells (APCs), Natural Killer (NK) cells and B cells) that binds its ligand CD28 on T cells surface activating them. On podocyte, CD80 expression causes shape change of foot processes with consequent appearance of proteinuria. Microbial agents, via TLRs and cytokines, induce CD80 expression both on immune cells and podocytes. The CTLA-4, expressed by Foxp3+ T regulatory (T reg) cells, down-regulates CD80 expression (12, 13). TLR-3 and -4 are the most studied TLRs in NS and the CD80 (on immune cells or

in urine sample) has been proposed as marker of disease activity and severity. Mishra et al. studied 70 idiopathic NS patients with steroid-sensitive and steroid resistent forms of disease. Higher values of TLR-3, TLR-4 and CD80 mRNA in peripheral blood mononuclear cells (PBMCs) have found patients with active steroid more sensitive to NS than in those with the steroid-resistent form. Lower levels of these markers have been found in controls. Urinary CD80/creatinine ratio was higher in patients with active NS than in the controls and patients with steroid-sensitive NS in remission ($p < 0.001$). Higher values have been found in steroid-resistent NS than in steroid-sensitive group. TLR3 and CD80 mRNA and control urinary CD80/creatinine ratio were higher in patients with biopsy-proven MCD (14).

NS and acquired immunity: the role of T cells

A dysregulation of T cells function is another pathogenetic mechanism of NS. T cells polarization is regulated by APCs. Trigger events, such as infections (mostly viral), vaccinations or allergic episodes, cause APCs activation with release of cytokines and differentiation of naive T cells into Th1 cells [when exposed to interleukin (IL)-12]; Th17 in case of exposure to IL-6, IL-23 and transforming growth factor beta (TGF-β); Th2 when is released IL4. The same trigger events are involved in NS exacerbations. There is evidence about a possible protective role of CD4+ T cells: a reduction of CD4+ T cells and an increase of CD8+ T cells were observed in the acute phase of NS and a subtraction of CD4+ T cells in mouse models made the renal damage worse (15).

Increased levels of serum Th17 cells and IL17, and local kidney production of IL-17 and IL-1β have been found in NS patients. Wang et al. have demonstrated that recombinant human IL-17 (rmIL-17) increases the expression of Fas, Casepase-8 and Casepase-3, but has no effect on that of FasL, with consequent podocyte apoptosis and glomerular barrier damage (15, 16). A recent article of Yan et al. shows that IL17 receptor is persistently expressed on podicytes surface. In presence of IL17, Nod-like receptor protein 3 (NLRP3) inflammasome is activated with consequent podocyte apoptosis (caspase-1 activation), and production and release of IL1 that cause local inflammation. The result is the glomerular filtration barrier disruption (17). The role of NLRP3 inflammasome in podocyte damage has already been shown in many studies (also in other pathological conditions such as Aldosterone-induced podocyte damage or hyperhomocysteinemia) (18, 19).

Other studies have shown a dysregulation between regulatory T cells (Treg) and effector cells (Th1 andTh2) activity (20). The Treg cells act in controlling the inflammation through production and secretion of specific cytokines such as IL-10 and TGFβ, and inhibiting APCs activation. The expression on Treg cells surface of CTLA-4 (also known as CD152) causes the down-regulation of CD80/86 on APCs (and on podocytes) and the inhibition of their activity. Therefore, the balance between Treg and effector T cells activity is important in NS pathogenesis, according to Prasad et al. that demonstrated increased levels of Treg cells and their cytokines (IL10 and TGFβ) and reduced values of Th1 and Th2 cells during remission phase of pediatric NS patients, while during relapse this report was reversed with increased frquency of Th1 and Th2 cells and decreased levels of Treg cells (21).

Similarly, Tsuji et al. demonstrated the presence of increased Tregs levels during remission and significantly lower values of the same cells at NS onset than in healthy children. These data were associated with increased serum CTLA-4 concentration at remission compared with onset (22). CD80, that is downregulated by CTLA4, is instead increased during relapse in blood samples and on podocytes surface (23). Whereas Jaiswal et al. studied steroid-sensitive vs steroid-resistent NS patients, showing that Treg cells percentage is lower in the second group than in the first one, while Th1 and Th2 cells percentage is higher in steroid-resistent NS patients (24).

NS and acquired immunity: the role of B cells

The role of B cells in NS pathogenesis has become clear for effectiveness in therapy with Rituximab, a chimeric anti-CD20 monoclonal antibody. One of the first reports come from Benz et al. which used Rituximab to treat an idiopathic thrombocytopenic purpura in a 16-year-old child with steroid-resistent NS, with good response both on thrombocytopenia and on NS (25). B cells act on immunoglobulin dipedent and indipendent damage, activating T cells through expression of costimulatory molecules and cytokines. CD20 is expressed on B cells surface in more differentiation stages, with only exceptions of lymphoid stem cells and antibody-secreting plasma cells. There is evidence of efficacy in Rituximab therapy in frequently relapsing/steroid-dependent NS and steroid-resistent NS without response to immunosuppressive therapies (26). Rituximab reduces the Th17/Treg cells ratio, resulting in reduction of IL17 production and increase of IL10 and TGFβ release (26). Numerous studies presented that an imbalance in Th17/Treg ratio, with prevalence of Th17 activity and reduced Treg control function on inflammation, is an important pathogenetic mechanism in NS and is associated to clinical severity, glucocorticoid sensitivity and prognosis of the disease (27-30).

Recent studies have furhermore demonstrated a link between Treg and Th17 cells differentiation. In absence of proinflammatory cytokines, FOXP3 (marker of Treg cells) can inhibit RORgammat (a transcriptor factor) function and drive Treg differentiation; while, in presence ofproinflammation cytokines, FOXP3 is inhibited and the Th17 differentiation pathway is induced (30).

DISCUSSION

The interplay between innate immunity, adaptive immunity, infective triggers and podocytes constitutes the pathogenetic mechanism of NS and is still not well elucidated. The role of each component (TLRs, APCs, Th1, Th2, Th17 and Treg cells, B cells, cytokines, podocytes) is different for every patient. Further studies are needed to better understand the role of innate and acquired immunity in the pathogenesis of the disease. It will be important to identify new laboratory markers that allow us to identify the main immunological protagonist for each patient, to personalize the therapy and make it more focused and effective.

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ALPORT'S SYNDROME

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Alport's syndrome (AS, OMIM 301050) is a hereditary disorder characterized by progressive renal failure, hearing impairment and ocular changes. It is clinically and genetically heterogeneous and in its natural history, renal disease progresses from microscopic haematuria to proteinuria, and finally to progressive renal insufficiency. AS is caused by an inherited defect in a type IV collagen, a structural material, expressed in many tissues that is essential for the normal function of different parts of the body. In most of cases, about the 85%, Alport's syndrome is X-linked and is originated by mutations in the *COL4A5* gene. In the remaining cases, it may be inherited in either an autosomal recessive, or rarely in an autosomal dominant manner. Mostly, the condition is caused by mutations in the *COL4A3* or *COL4A4* genes. Coexisting mutations in *COL4A3, COL4A4, COL4A5* or *COL4A6* were found to cause an Alport's syndrome phenotype with digenic inheritance. Diagnosis of the condition is based on family history, clinical signs, and specific procedures such as a kidney biopsy. The diagnosis can be confirmed by genetic testing. Treatment may include use of a hearing aid, hemodialysis, and peritoneal dialysis to treat those with end-stage renal failure, and, as the last step, kidney transplantation. Firstly described by Arthur C. Alport's, in 1927, over the years it has become a pathology of high scientific interest. At the moment, thanks to advances in diagnostic techniques, it is possible to make an early diagnosis avoiding irreversible damages and life -threatening complications.

Alport's syndrome (AS) (OMIM 301050) is a hereditary disorder characterized by progressive renal failure, hearing impairment and ocular changes caused by an inherited defect in type IV collagen, a structural material expressed in ears, eyes and kidney tissues. About 85% of the cases are X-linked, followed by mainly autosomal recessive cases; autosomal dominant inheritance is not common. The Alport's syndrome was described in 1927, by Arthur C. Alport's; he observed familiar cases of hereditary congenital haemorrhagic nephritis, deafness and ocular changes. He also observed how the disease

Key words: Alport's syndrome; chronic kidney disease; collagen IV genes; lenticonus

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was heterogeneous and was mostly predominant and severe in males than in females (1, 2).

Alport's referred to the disease as hereditary, but did not analyze the pattern of inheritance. Finally, Govan concluded that Alport's syndrome can be diagnosed if one of three characteristic features is seen: anterior lenticonus; macular flecks; or peripheral coalescing flecks. He considered that the absence of these changes does not preclude the diagnosis, especially in young patients or women (3).

From 1927 to today, much progress has been made in the knowledge of this syndrome, from the clinical, genetic and therapeutic point of view.

Genetics

Alport's syndrome is caused by a structural defect of type IV collagen, originated by mutations in the *COL4A3, COL4A4* and *COL4A5* genes (4-6), located on two different chromosomes: chromosome 2 and X (Fig. 1). Mutations in *COL4A5* gene are associated with X-linked Alport's syndrome, which represents approximately 85% of cases and is more severe in males than in females. The *COL4A3* and *COL4A4* genes mutations are associated with both autosomal recessive and dominant Alport's syndrome (7). These genes encode the a3, a4, a5 chains of collagen type IV, which are associated in networks that interact with laminin-521, agrin, nidogen, and other proteins; they form the structural skeleton of basement membranes such as the glomerular basal membrane (GBM). These alpha chains are expressed in different tissue (8) (Table I).

As a result, of the disorder in the type IV collagen, there are defects in the basement membranes of different tissues; for instance, due to the GBM thinning in the kidneys, blood and proteins pass into the urine. Over time, the kidneys become scarred, causing end-stage kidney disease. Type IV collagen is also an important component of the organ of Corti and its alterations may result in abnormal inner ear functions, which can lead to hearing loss. In addition, type IV collagen is part of the structural framework of the eye, mutations found in AS may affect the retina. To understand how the disease affects different organs, it is important to remind that the actual evidence suggests that the accumulation of type V and type IV collagen chains occurs as a compensatory mechanism

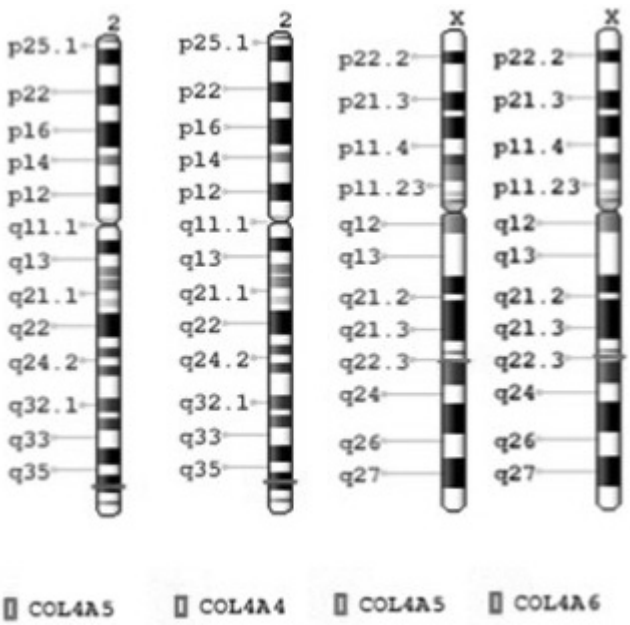

Fig. 1. *COL4A3, COL4A4, COL4A5, COL4A6 chromosomal position.*

to the loss of alpha 3, 4, 5 chains. Therefore, type V and type VI collagen chains occupy the full GBM, causing an alteration on glomerular homeostasis and its permeability (9-10).

Clinical manifestations

Clinical manifestations of the syndrome are usually milder in females and involves several organs:

Renal disease

The hallmark finding of Alport's syndrome is microhaematuria/gross haematuria.The presence of haematuria seems to be different between males and females, in fact it is usually persistent in males and intermittent in females. Kidney biopsy reveals the irregular thickening of GBM as lamellation; tubulo-interstitial damage may be present (11). Proteinuria is also present in AS and requires differential diagnosis compared to other causes of proteinuria at a young age (12). It progresses with age, especially in males with X-linked AS and in males and females with autosomal recessive AS; usually it is absent in childhood.

Ocular lesion

Anterior lenticonus, in which the central portion of the lens protrudes into the anterior chamber, is pathognomonic of AS. When present, anterior lenticonus is bilateral in approximately 75% of individuals. Other ocular lesions also associated with AS are macular flecks and peripheral coalescing flecks that typically become evident in late adolescence or early adulthood.

Deafness

The development of sensorineural deafness is one of the most common signs in Alport's syndrome, hearing loss is usually bilateral. When the hearing defect is detected before the age of 10 years, it is usually progressive. In adults, the deafness is usually not progressive and many patients retain some hearing capacity (13).

Aneurysms of the thoracic and abdominal aorta

Some cases of aneurysms of the thoracic and abdominal aorta have been described in a small number of males with Alport's syndrome (14-15).

Leiomyomatosis

There are family reports of leiomyomatosis of the esophagus and tracheobronchial tree. All of the individuals developing this sign have been found to have deletions that span the 5' ends of the COL4A5 and COL4A6 genes. Furthermore, in these families, females presented uterus leiomyomas and sometimes

Table I. *Type IV collagen genes, chromosomal location, tissue distribution and inheritance. GBM: Glomerular basement membrane; TBM: tubular basement membrane.*

Gene	Chromosomal location	Alpha (IV) chain	Tissue distribution	Inheritance
COL4A3	2	Alpha-3 (IV)	GBM-distal TBM, Descemet membrane, Bruch membrane, anterior lens capsule, lungs cochlea	autosomal recessive and dominant
COL4A4	2	Alpha-4 (IV)	GBM-distal TBM, Descemet membrane, Bruch membrane, anterior lens capsule, lungs cochlea	autosomal recessive and dominant
COL4A5	X	Alpha-5 (IV)	GBM-distal TBM, Descemet membrane, Bruch membrane, anterior lens capsule, lungs cochlea	X-linked
COL4A6	X	Alpha-6 (IV)	Distal TBM, epidermal basement membrane	X-linked

associated clitoral hypertrophy or involvement of the labia majora (16).

Genotype-phenotype correlations

Genotype-phenotype correlations are not clearly established yet. In X-linked Alport's syndrome, COL4A5 mutations that interfere with the synthesis of the a5 (IV) chain, such as deletions, frame shift mutations, and nonsense mutations, are associated with a severe disease phenotype in hemizygous male subjects while the effects of splicing and missense mutations on a3, a4 and a5 (IV) expression and clinical phenotype are more variable (17). In X-linked Alport's syndrome, end stage renal disease (ESRD) usually appears before age 30, and frequently it is associated with progressive sensorineural deafness and specific ocular lesions such as perimacular flecks and lenticonus. Females have variable clinical features depending on X chromosome inactivation (18).

Homozygous mutations of COL4A3 or COL4A4 cause autosomal recessive Alport's syndrome (ARAS). As in X-linked Alport's syndrome, sensorineural deafness and ocular lesions are frequently present and are associated with renal disease in patients with ARAS. If similar severity of disease in male and female siblings is found, autosomal recessive inheritance may be suggested, especially in parental consanguinity, or microscopic haematuria in the father or in both parents of a severely affected male. ESRD is common in the autosomal recessive form (19).

Autosomal dominant (ADAS) inheritance is very rare and results from heterozygous COL4A3 or COL4A4 variants, the phenotype can vary significantly (20). Because of a variable expression and an incomplete penetrance, the features are different. Clinical findings may be: complete absence of detectable symptomatology, isolated asymptomatic haematuria or progressive renal disease, sensorineural deafness, and ocular abnormalities (21). ESRD and ocular lesions, that are common in X-linked and in autosomal recessive AS, are unusual in autosomal dominant type but have been reported. Sensorineural deafness is less common in people with heterozygous mutations in COL4A3 and COL4A4 than in people with X-linked or autosomal recessive Alport's syndrome and tends to manifest later in life. Recently, a splice site mutation resulting in skipping of exone 21 in the COL4A3 gene was found in ADAS (22).

Coexisting mutations in COL4A3, COL4A4, COL4A5 or COL4A6 were reported to cause an Alport's syndrome phenotype with digenic inheritance (23). In the case of a combination of a

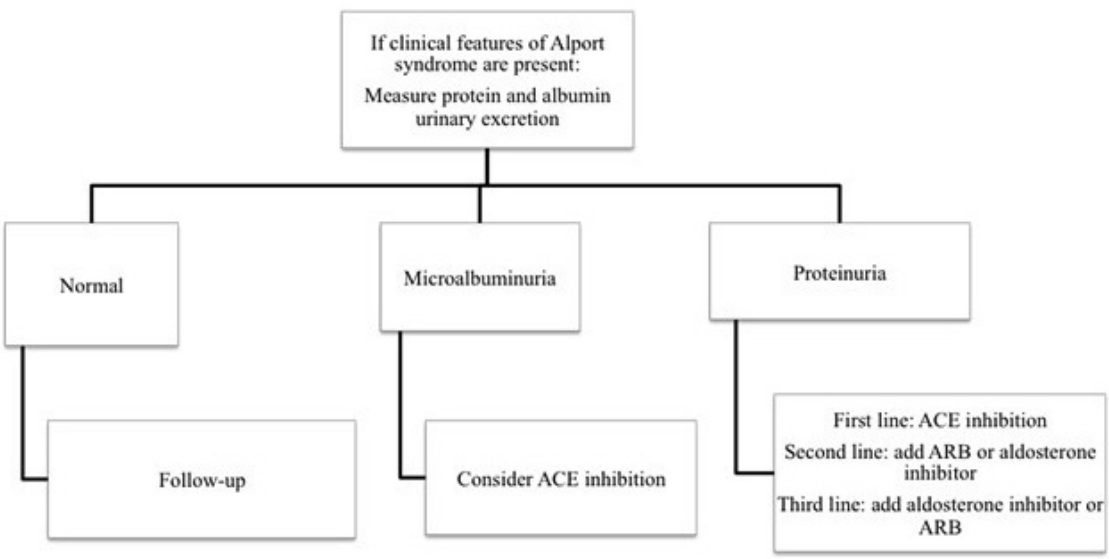

Fig. 2. *Treatment flow-chart based on clinical findings.*

COL4A5 mutation with a mutation in COL4A3 or COL4A4, the pattern of inheritance does not resemble any mendelian process and family-specific risk assessment is needed (24).

Diagnosis

Alport's syndrome diagnosis is based on both clinical and genetic criteria. The syndrome should be suspected in patients with renal manifestations such as persistent glomerular haematuria, proteinuria or renal failure; but also extrarenal manifestations such as progressive deafness, retinopathy, or a positive family history (25). The diagnosis of AS is confirmed after the renal biopsy if there is a lamellated GBM or with the demonstration of a pathogenic mutation in the COL4A5 gene or two pathogenic COL4A3 or COL4A4 mutations (26).

Initially diagnosis of AS was based on clinical criteria that included haematuria, hearing loss and ocular changes, supplemented with pedigree data and tissue studies. Pedigree data consist of suggestive family history of haematuria, deafness, and ESRD. From the 1990s to 2000, the Sanger sequencing of *COL4A3*, *COL4A4*, and *COL4A5* genes allowed diagnosis of AS over a long time with predictable results. Recently, next-generation sequencing (NGS) of these genes and whole exome sequencing improved mutation identification and lowered the cost of sequencing (27). These innovations are modifying the diagnostic evaluation of patients and families with suspected Alport's syndrome. The guidelines on the diagnosis and management of Alport's syndrome recommend that all individuals with likely AS should undergo genetic testing, to confirm the diagnosis and mode of inheritance, and predict the risk of renal failure (28).

Course and treatment

Proteinuria, hearing loss, lenticonus, retinopathy, and reduced levels of GBM collagen IV a5 are all correlated with an earlier onset of renal disease and worse prognosis, especially in males. Hearing loss is progressive and can be treated with auxiliary acoustic devices. Usually, the retinopathy does not affect vision and does not require treatment; the lenticonus also worsens but can be corrected with lens replacement.

Some recent findings in animal models of Alport's syndrome suggest a number of potential targets for therapeutic intervention. Attention has focused on early initiation of angiotensin blockade, which is remarkably effective in murine Alport's syndrome and, according to retrospective analyses, seems to slow down the rate of progression in human Alport's syndrome. Starting angiotensin blockade while renal function is still normal has been reported to have a greatest impact on timing of ESRD (29). The "Early Protect" trial in Europe has shown that earlier introduction of therapy may have additional benefit to prevent the progression to ESRD (30).

Renal transplantation is usually offered to patients with AS who develop ERSD. The allograft survival in these patients is similar to other renal diseases (31).

Recently, some findings in pediatric patients with Alport's syndrome suggest that urinary epidermal growth factor may be a promising biomarker of the decline of the renal function, helping to identificate the ones that need special clinical care (32).

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CLINICAL COURSE OF A PEDIATRIC SERIES OF MULTICYSTIC DYSPLASTIC KIDNEY

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To the Editor,

Multicystic dysplastic kidney (MCDK) is part of the spectrum of CAKUT (Congenital Anomalies of Kidney and Urinary Tract) and actually it is one of the clear ones to diagnose. Renal dysplasia as a whole is found in 1:1000 live births. The actual definition of MCDK includes complete lack of normal renal tissue. MCDK is also characterized by replacement of normal renal tissue with numerous cysts which do not inter-communicate, with varying degrees of loss of normal cortico-medullary differentiation and with a hypoplastic or completely obstructed ureter. Its incidence is estimated to be 1 in 4300 births (1), although in most literature (2) it seems to be 1 in 2,400. Commonly, the diagnosis is made early, by fetal ultrasound. The genetic defect and the pathogenetic mechanism are still unknown. It has been suggested which genes may be involved in determining MCDK, such as HNF-1B, PAX-2, c-RET, the WT1, GDNF, which play a role in regulation of ureteric bud. This genetic abnormality, manifested as sporadic non-hereditary disorder and reported only in rare cases in twins and members of the same family, leads to an alteration in the pathogenic mechanism of the interaction between the ureteric duct and metanephricblastema (3-5).

The multicystic kidney may be associated with urogenital malformations. According to Ranke's study, (6) the incidence is 56% of cases and urologic malformation is found in 43% while in the remaining 13% there are abnormalities of the genitalia. Regarding urologic malformations, the vesicoureteral reflux with febrile urinary tract infections (7), is most frequently found in the contralateral kidney, affecting 17-20% of cases. A smaller percentage has other urological abnormalities, such as the megaureter, hydronephrosis, ureteral duplication, renal hypoplasia, imperforate valves of the urethra and perineum. Among genital malformations in females ipsilateral agenesis of the duct of Muller, cloacal malformations or of the urogenital sinus and imperforated vagina are found; in males, however, ipsilateral cryptorchidism, agenesis of the ipsilateral vas deferens, seminal vesicles and hypospadias are found.

Key words: multicystic dysplastic kidney, non-hereditary disorder, ureteric duct, children

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The aim of this study was to perform a retrospective evaluation of our patients with multicystic kidney, considering all the possible variables, such as evolution of multicystic kidney, presence of associated malformativeuropathy or pathognomonic complications of this disease, and evaluation of sonographic diameters of the contralateral kidney.

Patients & methods

In our study, 32 children with unilateral multicystic kidney were enrolled observed from January 2007 to December 2017, and aged between two months and thirteen years. The parent(s) of each child provided written informed consent.

All statistical analyses were performed using standard SPSS package (version 12.0 for Windows). The significance of differences between the categorical variables was assessed by a Likelihood Ratio Tests. A *P*-value of <0.05 was set as the threshold for statistical significance. Data are expressed as percentages.

Of the 32 patients, 18 were males and 14 were females (M/F ratio 1.2).The diagnosis of MCDK was made through renal ultrasonography, which documented the presence of cysts of variable magnitude and volume, in the absence of renal parenchyma and confirmed by the finding of scintigraphic mute kidney. Children were sedated with melatonin (8, 9). In 23 (71.8%) of 32 cases the diagnosis was made prenatally, while in the remaining nine (28%) multicystic kidney was detected by ultrasound scans performed post-natal. The left kidney was involved in 15 cases, and the right in 17 cases (ratio L/R 0.88) (Fig. 1).

Eight children (25%) had associated uropathymulticystic kidney, and, out of these, 2 (6.25%) had vesicoureteral reflux, diagnosed by colour-dopplercistosonography with echocontrast.

All patients were placed in conservative treatment ultrasound scans performed every six months for the first three years and then every twelve months. For ultrasound scans the maximum longitudinal diameter of the kidneys was rated and the values obtained were compared with the renal growth curves (kidney length versus height) according to Dinkel et al. It was seen that compensatory hypertrophy of the contralateral kidney is larger than the 95 percentile. Auxological checks (height, weight), biochemical

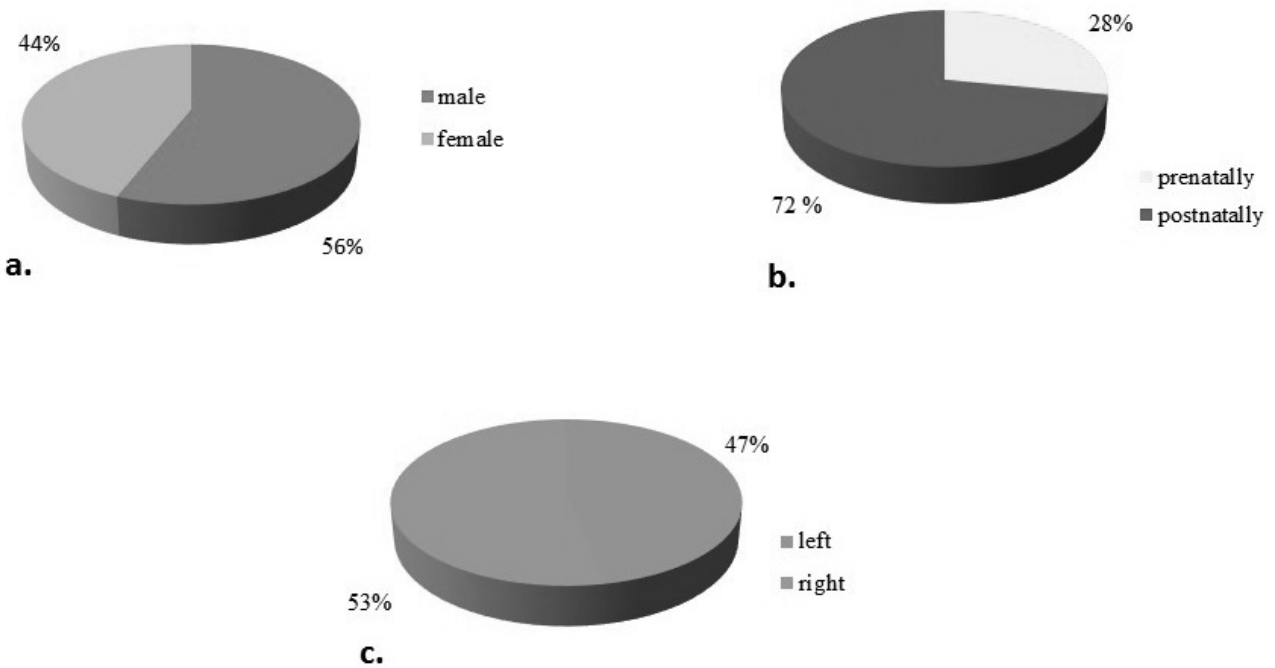

Fig. 1. ***a****: gender distribution (M/F ratio 1:2);* ***b****: Time of diagnosis;* ***c****: Localization of disease (ratio L/R 0.88).*

checks (creatinine, creatinine clearance according to Schwartz, urinalysis, urine culture, microalbuminuria and proteinuria) and blood pressure checks were also carried out on the patients. The blood pressure values obtained were compared with reference values of the second report, "Task Force on Blood pressure control in children" (10).

RESULTS

During the period of our observation we documented in 18 of the 32 children (56.25%) complete involution of multicystic kidney, in 5 cases (15.6%) a decrease in volume of multicystic kidney was documented, while in 9 cases (28.1%) dimensions were unchanged during a follow-up ranging between 1 and 94 months with an average of 40 months. Eight children with MCDK had associated genitourinary malformations: in 2 cases vesicoureteral reflux; in 2 other cases contralateral renal dysplasia; in 1 case, respectively, renal ectopia, ureterocele, bladder diverticulum, and hypospadias. In cases with associated anomalies, we observed a complete involution of multicystic kidney in 2 (25%), a partial regression in 3 (37.5%) and in 3 others (37.5%) no changes in multicystic kidney diameters were shown (Fig. 2).

No patient presented with urinary tract infections, because they had undergone antibiotic prophylaxis.

In children without associated anomalies, 16 had complete involution (66.6%); 2 a partial involution (10%) and 6 no change (30%). There was, therefore, a statistically significant difference in the natural history of multicystic kidney between patients with or without associated genitourinary anomalies. The only relevant fact, but not statistically significant given the small sample, was that in both patients with vesicoureteral reflux there were not any modifications of MCDK despite a period of very long follow-up, 156 months in one case and 93 months in the other case (Fig. 2). The growth of the contralateral kidney in cases of MCDK with other malformations was seen in only 4 cases (50%) out of 8, documenting a compensatory hypertrophy (DL>95%); by contrast, in the absence of associated anomalies, in 24 cases (95.8 %) compensatory hypertrophy was detected (Fig. 2). During the period of follow-up hypertension and abnormal creatinine

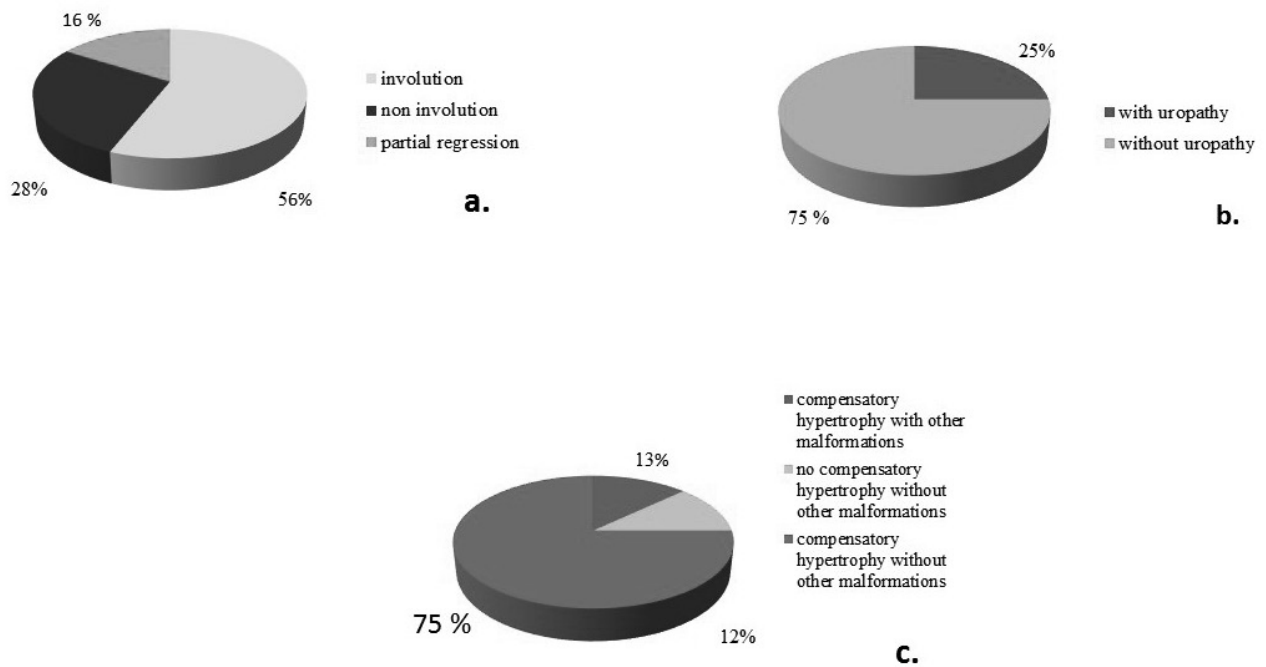

Fig. 2. ***a****: Natural history of disease;* ***b****: Prevalence of uropathy;* ***c****: Incidence of compensatory growth in enrolled patients.*

and creatinine clearance was not documented in any child; microalbuminuria was detected in only 3 cases (9.37%), where vesicoureteral reflux was present.

DISCUSSION

Multicystic dysplastic kidney is a developmental abnormality in infants and children. There is a particularly accredited pathogenetic hypothesis according to which the early ureteral obstruction, around the 5th-6th week of gestation, may stop the development of the blastema with renal cysts, some of which would come to be replaced by fibrous tissue within the renal parenchyma. The latter provides the basis of multicystic disease and hydronephrosis, which have the same pathogenic mechanism, consisting of ureteral obstruction and a consequent increase in intrarenal pressures that develop at different gestational ages, which would be responsible for the two diseases. Therefore, within the 14th-20th week of gestation this would lead to a framework of multicystic dysplasia, characterized by retention of fluid within the nephrons, causing the formation of cysts in the nephrogenic subcapsular region, while at later stages, from 18 to 35 weeks of gestation, the obstruction, associated with increased renal pressure, would cause the onset of hydronephrosis (11).

However, recently, the vascular insult due to early obliteration of the supplying renal artery has been neglected since the genetic pathogenesis of CAKUT, involving the earliest interaction between the ureteric bud and the metanephricblastema, which are considered most applicable to all these malformations (4).

Clinically, MCDK involves a condition comparable to unilateral renal agenesis, the multicystic kidney being a kidney, which is non-functional, non-vascularized, and therefore not working. Consequently, the long-term prognosis of renal function is closely related to the contralateral kidney and the presence of renal abnormalities associated with the contralateral kidney may expose the patient to the risk of developing renal failure in the medium to long term (12).

Over the years, management of the disease has undergone significant changes. In the late 1980s, in fact, many authors considered that MCDK could expose the patient to major complications, such as neoplastic degeneration and/or the onset of hypertension, related to abnormal activation of ectopic foci of the renin-angiotensin within the dysplastic tissue, and recommended elective nephrectomy as a treatment in the neonatal period.

Over time, many authors have taken a conservative approach, showing that in some cases at ultrasound follow-up spontaneous involution was observed. Gordon, in a study of 1998 (13), documented that in 2 of 11 children treated conservatively, there was a spontaneous involution. As regards the risk of neoplastic degeneration, the conservative approach has shown that the incidence of malignancy is low (up to 1997 only 9 cases were reported). Considering that the risk of Wilms tumour in the paediatric population is one in 10,000 children, in the United States 3-10 cases per 10,000 children with MCDK have been reported, with an increased risk of 0.03 to 0.1%. Regarding the onset of hypertension in children with MCDK, the incidence is estimated at 0.8%, as evidenced by the register of multicystic renal dysplasia, maintained by the Urology Section of the American Academy of Pediatrics, in which in about 441 cases only 4 cases of hypertension during conservative follow-up were described. Seeman et al. (14) pointed to a higher prevalence of hypertension in patients with MCDK with contralateral kidney abnormalities.

The therapeutic conservative choice that we undertook, enabled us to evaluate the natural history of the disease, both with reference to the timing of involution of the multicystic kidney, and with reference to the contralateral kidney with regard to its compensatory growth, as assessed by ultrasound.

The results of the study, with a follow-up period of 40 months, show a spontaneous regression rate comparable to that reported in the literature data and confirm that complete involution occurs more frequently within the second year of life. The conservative approach allowed us to learn about the natural history of MCDK. Longitudinal studies of ultrasound follow-up of renal multicystic renal dysplasia in the last 20 years have documented that

involution of dysplastic kidney is part of its natural history, understoodas a progressive resorption of kidney, asitisnotvascularized. It sfunctiona ldecline does not change the prognosisat a distance, becauseitisrelated to the functionality of the contralateral kidney. Strife et al., (15) in a series of 48 children from 1979 to 1990, documented a decrease in the size of the multicystic kidney in 67% of cases. Rabelo et al. (16) have documented that MCDK conservatively treated at 18 months reached the 5th percentile for length, at 108 months it is reduced to half the maximum length documented at birth, and at 122 months it sees spontaneous involution. Only in 1%, the length of the kidney with MCDK remains unchanged.

In a review of literature, in studies with a series of at least 30 patients and with follow-up of at least 24 months, 48% of all cases showed a reduction of MCDK and 20% complete involution. In a meta-analysis on the incidence of vesicoureteral reflux (VUR) and dilatation of the caliceal-pelvic system (CPD) in children with MCDK, it was evident that VUR was affected in 17.5% and CPD in 13.8%. Caldeira et al. (1) in a series of 36 children from January 1995 to December 2009 showed that contralateral nephro-urologic pathology was identified in 10 cases (28%): 7 children with VUR (grade $\geq$ IV in 3), 2 with ureteropelvic junction obstruction (UPJO) and 1 with mild pelvic dilatation. There was involution of dysplastic kidney in 27 cases (75%), partial in 24 and total in 3. The involution rate was higher in the first 36 months. There was a progressive compensatory hypertrophy of the contralateral kidney, with the highest rate in the first two years of life. There was resolution of VUR in 5 of the 7 reflux units (3 spontaneous and 2 after ureteral reimplantation). Two children with UPJO underwent surgery. There were no cases of hypertension or decreased glomerular filtration rate or malignant degeneration. Rabelo et al. (16), in a meta-analysis of 9 studies with at least 24 months of follow-up, report for a series total of 614 patients complete involution without acknowledgment ultrasound in 121 cases (20%), while in 296 cases, equal to 48%, a reduction in the size of renal dysplasia detected with ultrasound scans was shown. However, considerable variability in the timing of the data shows spontaneous involution of MCDK and compensatory growth of the contralateral kidney (17- 19) As regards the first aspect, in fact, Rottemberg et al. (20) show that in 40% of cases there was complete involution at an average age of 1.6 years, while Kessler et al.(21) showed the highest percentage of reported complete involution amounted to 73.6% after a mean follow-up of only 9.6 months.

Regarding compensatory growth of the contralateral kidney, the reaching of the 95 percentile length for age is at a mean of 30 months; however, other studies have documented that the presence of single kidney compensatory growth occurs in the uterus and in 44% of cases is already present at 29 weeks of gestation. Some authors (22-24) have demonstrated that the kidney has a single accelerated growth between 0 and 22 months. The mechanism by which the compensatory hypertrophy is established remains unclear, but it is conceivable that this is stimulated by hyperfunction of functioning nephrons and not by the gradual decrease of the multicystic kidney.

The results of our study confirm that in the presence of abnormalities of the contralateral kidney, particularly of VUR, both the rate of spontaneous involution and the growth of the contralateral kidney in relation to the age of the patient are reduced in a statistically significant manner. This finding is supported by Feldeberg et al. (25), who showed the compensatory hypertrophy of the contralateral kidney in a different way; in fact, in addition to MCDK, there were other abnormalities of the genito-urinary tract with a substantially different prognosis and with several degrees of renal insufficiency in 50% of cases. By contrast, in our series, no pathognomonic complication of MCDK is reported, such as neoplastic degeneration and hypertension; there was evidence of microalbuminuria in only 3 cases, presumably an expression of renal hyperfiltration.

From the analysis of our series, supported by literature data (26-28), we show that within the general pathognomonic features of multicystic dysplasia, such as the percentage of spontaneous involution and compensatory hypertrophy of the contralateral kidney, there are individual variables

that require a careful follow-up on a case-by-case basis. However, individual variables, presumably, would be cancelled or minimized by a long-term follow-up, seeing as spontaneous involution of multicystic kidney is estimated within 10 years. The creation of an international registry on renal cystic dysplasia would show the true incidence of the disease and a precise evaluation of various aspects related to the disease (29).

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Authors' contributions: GD: Study conception and design of the manuscript; SM: Writing up of the first draft of the paper; LM: Conceived of the case and helped to draft the manuscript; RC: Critical revision of the article; CS, EG: Conceived of the study and participated in its coordination. All authors read and approved the final manuscript.

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CONSERVATIVE MANAGEMENT IN CONGENITAL SEVERE BILATERAL HYDRONEPHROSIS RELATED TO URETERO-PELVIC JUNCTION OBSTRUCTION

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We report our experience in conservative management of patients with prenatal and neonatal diagnosis of severe bilateral ureteropelvic junction obstruction (UPJO), focusing on the actual predictors of renal function impairment or sponta-neous resolution. Between 1996 and 2006, 20 patients with bilateral severe hydronephrosis related to UPJO were included in the study. Indications for surgery were an increased hydronephrosis, decreased renal function, onset of symptoms. Conservatively treated patients were followed up for 3 months to 10 years with renal ultrasound, DTPA diuretic, urine culture. At first renal scan, 22 out of 40 renal units had a poor, 10 an intermediary and 8 a good drainage. Pyeloplasty was required in 10 of the 40 kidneys, while 30 out of 40 kidneys were followed conservatively. At the end of follow up, sieric normalized creatinine and estimated glomerular filtration rate were normal in all patients. Our data showed that bilateral severe hydronephrosis related to UPJO can be safely managed in a similar manner of a unilateral case. A poor drainage could be considered a negative predictive factor in the feasibility of a conservative management.

It has been previously reported that congenital ureteropelvic junction obstruction (UPJO) spontaneously resolves in 70-80% of cases before the second year of life without any decrement of the renal function or worsening of drainage (1-7).

However, the management of pediatric patients with antenatal or neonatal diagnosis of bilateral UPJO is still controversial. In particular, some authors (2-7) disagree with conservative management because both differential renal function (DRF), calculated by renal scan, ad ultrasonography did not correctly reflect renal impairment. Nonetheless, other Authors (3) reported in previous studies a safe and reliable conservative management in more than 50% of newborns with antenatal or a neonatal diagnosis of bilateral UPJO. The aim of the study was to report our experience in conservative management of patients with prenatal and neonatal diagnosis of severe bilateral UPJO, focusing on the actual predictors of renal function impairment or spontaneous resolution.

Key words: bilateral ureteropelvic junction obstruction, bilateral hydronephrosis, 99mTc-DTPA renal scan, pyeloplasty

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MATERIALS AND METHODS

Between 1996 and 2006, 20 (12 males and 8 females) neonates with bilateral severe hydronephrosis related to UPJO were followed up at our Department. 16 out of 20 (80%) patients had an antenatal ultrasonographic diagnosis of bilateral hydronephrosis, while in 4 (20%) the diagnosis was suspected during a neonatal ultrasound screening. In patients with an antenatal suspect, diagnosis of bilateral severe hydronephrosis was confirmed by post-natal ultrasound examination performed within the first month of life. Hydronephrosis was graded from 1 to 4 according to the Society for Fetal Urology grading system and patients with hydronephrosis ≥ grade 3 were included in the study (2). Patients were excluded from the study if they had ipsilateral or contralateral reflux, duplex system, fused kidney, solitary kidney, arterial dilatation, or anatomical or neuropathic abnormality of the lower urinary tract. Voiding cystourethrogram in males and cystosonography in females was used to exclude patients with vesicoureteral reflux or secondary causes of hydronephrosis.

Prophylactic low dose antibiotics were administered to all patients during the first year of life or until hydronephosis significantly improved. Urine culture was performed monthly during the first year of follow-up and repeated in the successive period in case of temperature or urinary symptoms (8). Follow-up consisted of renal ultrasound every 3 months in the first two years and every 6 months in the successive period. DTPA diuretic renography was performed every 3 months in the first 2 years, every 6 months in the third year and annually repeated until the hydronephrosis resolution or decreasing grade 2. The DTPA renogram lasted for 40 min and consisted of an injection of 200 MBq 99mTc-DTPA initially and 0.5 mg/kg furosemide at20 min.

Data analysis involved manually drawing regions of interest around each renal unit. To assess DRG results, patients were subdivided into three categories: better drainage - T½ less than 10 min; intermediary drainage - T ½ between 10 and 20 min; poor drainage - T ½ greater than 20 min (6). In order to ensure the global renal function, serum creatinine was analyzed every month for the first two years and every two months during the successive period of follow up. Moreover, the estimated glomerular filtration rate was calculated (9). Surgery was recommended if DRF of the UPJO-affected kidney was below 40%, if there was a progressive deterioration of split renal function > 10%, if there was worsening of hydronephrosis on repeated ultrasound, in case of impairment of estimated global renal function greater than 10 ml/min or an alteration of normalized serum creatinine or if there was any symptom such as pain, urinary infection, stones, hypertension or hematuria. After surgery, renal sonography and 99mTc-DTPA diuretic scan were performed at 6 months, 1 years and 4 years respectively to assess renal function, upper tract anatomy and drainage. In conservatively treated patients, follow-up was 13.3 ± 3.1 years, ranging from 11 to 16 years.

RESULTS

A grade 3 hydronephrosis was found in 29 (72.5%) of the 40 kidneys with hydronephrosis, in 11 cases hydonephrosis was grade 4. Only in 5 renal units function was less than 40% (25-39%). In the last 35 kidneys function ranged from 40 to 75%. At first renal scan, 22 out of 40 renal units had a poor drainage, 10 an intermediary and 8 a good drainage.

Surgical group

Pyeloplasty was necessary in 10 of the 40 kidneys (25%) (two patients underwent to a bilateral and six to monolateral pyeloplasty). In particular, 5 renal units belonged to males and 5 to females (including two bilateral cases). At sonography, six renal units had a grade 4 and four a grade 3 hydronephrosis. All the patients requiring surgery showed an obstructive pattern. Indication for surgery was an increased hydronephrosis in four patients (from grade 3 to grade 4) while a decreased renal function in five (one patients presented both an increased hydronephrosis and decreased renal function).

Two patients underwent surgery for a loss of renal function at 6 months. The mean age at operation of other six patients was 25.4 ± 11.7 months (range from 12 to 48 months). Bilateral pyeloplasty was performed in two times. Age of surgery ranged from 6 to 28 months (mean 23.5 ± 12.7 months). Contralateral not surgically treated kidneys (6 renal units) (five grade 3 and one grade 4) showed a decrease in hydonephrosis during follow-up. (of the

five to grade 3, four became grade 2 and one grade 1, the one with grade 4 became grade 3).

Conservative group

Twelve (7 males and 5 females) out of 20 patients (60%) were followed conservatively. During follow-up, no one patients of this group showed a decrease of DRF, an improvement of hydronephrosis or onset of symptoms. Hydronephrosis resolved in 10 out of 24 renal units, while improving in 2. In patients with grade 4, hydronephrosis improved in all study cases, until grade 2 in two renal units and to grade 3 in one . At the end of follow up, sieric normalized creatinine and estimated glomerular filtration rate were normal in all patients.

Chi-square test showed a significant relationship between a poor drainage at the first renal scan and a possibility of efficient conservative management ($p = 0.004$) while the grade of hydronephrosis at first sonography was not significantly related to need of surgery ($p = 0.307$).

DISCUSSION

With the advent of prenatal ultrasound, the management of hydronephrosis considerably changed (14). In particular, it allowed pediatrics to early discover also asymptomatic hydronephrosis and to know the natural history of this urological abnormality (10-15). The common clinical scenario of spontaneous improvement of hydronephrosis in children with congenital suspected UPJO drove physicians to try a conservative management, supported by the evidence that a delayed maturation of ureteropelvic junction (15) could promote a spontaneous resolution of most cases of congenital hydronephrosis (16-17).

On this basis, a watchful-waiting approach has been successfully tried also in unilateral asymptomatic UPJO with a poor urine drainage at renal scan, following-up these patients with scheduled ultrasound and renal scan in order to strictly monitor the renal function (18). However, if the management of unilateral UPJO is still debated, a conservative approach of congenital bilateral UPJO is more controversial for the risk of global renal function impairment that can lead to chronic renal failure. In this regards, while some Authors (19) recommended early bilateral synchronous pyeloplasty or at least an early unilateral pyeloplasty without initial conservative management in all patients with severe bilateral UPJO, others (5, 20) suggested that initial management with close follow-up could be a proper approach.

In this regards, Onen et al. (5, 20) reported that only 35% of total renal units with prenatally diagnoses primary high grade bilateral hydronephrosis required a pyeloplasty while the remaining 65% of renal units might be conservatively followed-up, showing in a long-term resolution or improvement of the hydronephrosis. In our study, we also limited surgery in asymptomatic patients with severe bilateral hydronephrosis only in case of impairment of DRF, worsening of the grade of hydronephrosis on repeated ultrasound or at the onset of symptoms, strictly monitoring the estimated glomerular filtration rate and the serum creatinine. So far, our findings are in accordance as previously reported by some authors that a non-operative observation could be considered a safe procedure also in bilateral moderate to severe UPJO. However, while DRF is a reliable marker of renal function in unilateral abnormality of kidney (21), it is difficult to impart the meaning to the change of DRF in case of bilateral anomalies (22).

In this regards, DRF could be in the normal range even in case of simultaneous bilateral renal function deterioration. For this reason, even if changing of the DRF has been reported to be an indication for pyeloplasty also in bilateral UPJO, a strict evaluation of global renal function in mandatory in order to establish a prompt surgical treatment as previously suggested, in particular in the first two years of life (5).In fact, during the first 24 months of life, it has been reported that obstruction of ureteropelvic junction is more likely to become evident (5). Also in our experience, a pyeloplasty was indicated during the first two years of life in 7 out of 10 (70%) and before the age four in the remaining patients.

Moreover, our data suggest that the natural history of a spontaneous resolution of hydronephrosis does not change in bilateral UPJO and it was possible

to adopt a conservative management in 70% renal unit in severe bilateral UPJO. Furthermore, all cases requiring surgery had a poor drainage at the first renal scan. An obstructive pattern at renal scan seems to be significantly correlated to a renal function impairment or worsening of the grade of hydronephrosis.

In conclusion, in our experience bilateral UPJO can be managed in a similar manner of a unilateral UPJO, also in case of congenital severe hydronephrosis. However, a poor drainage is considered a negative predictive factor in the future resolution of the obstruction. In order to prevent a global renal impairment, a close follow-up is strongly suggested (23).

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PEDIATRIC UROLITHIASIS

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Urolithiasis is a well-known condition that can affect any part of the urinary tract. With a rate of 3-5% the incidence of upper urinary tract for long has been higher in adults (1-3), but recently it has increased among children reaching 3,3% . Indeed, more than 1% of all urinary stones are seen in patients aged < 18 years (4). Pediatric urolithiasis is endemic in Turkey and Far East and it is probably due to malnutrition and racial factors (5). The spontaneous stone passage is more likely in children than in adults, indeed ureteral calculi spontaneously pass into 41-63% of children (1). Rate of stone passage depends on size and stone location in the urinary system. Stones sized <5 mm have a passage rate ranging from 40% to 98%, whilst stones >5 mm have between 55% and 50% (6). In the last decade, the use of alpha blockers has proven well efficacious in helping spontaneous passage of distal ureteric stones in adults (7-9). The latest EAU guidelines support their use in adults while remain vague about their use in childrenbecause of unclear safety and efficacy (4). In search of evidence supporting or not the use of medical expulsive therapy in children we reviewed the literature dealing with the management of urolithiasis in pediatric patients. The primary aim of the present study was to evaluate the efficacy of medical expulsive therapy (MET), defined as stone expulsion rate, with a-blockers compared to a control group. The secondary aim was to assess the safety, defined as side effects rate, of MET compared to a control group.

MATERIALS AND METHODS

An electronic literature search was performed using MEDLINE and COCHRANE databases. The MEDLINE research was made through PubMed using the combination of the terms 'urolithiasis' OR 'urinary calculi' OR 'urinary stones' AND 'alpha blocker' OR 'medical expulsive therapy' OR 'medical treatment' OR pharmacological treatment. Only studies recovered in a second research using

Key words: urolithiasis, pediatric, pharmacological therapy

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the words “pediatric”or “children” were analyzed.

Only published randomized controlled trials (RCTs) on patients younger than 18 years old were included, comparing either an a-blocker to a control group. Only studies using either a placebo or analgesics serving as controls were included. Were excluded retrospective studies and “studies reporting only abstracts”. Unpublished studies were not included in the analysis. The characteristics of analyzed studies are reportedin Table I.

Five RCTs were preselected and included in this review (10-14). The RCTs we found are the only existing in literature, as a matter of fact, the Cochrane, who made the search using different database, reviewed the same ones (15). Methodological quality evaluation performed by GRADE is represented in Table II.

Table I. *Characteristics of analyzed studies.*

	Intervention	Control	Follow-up duration	Detection of stonepassage
Elgalaly 2017	Silodosin4 mg at bedtime Ibuprofen on demand for pain episode relief (20 mg/Kg/day in 2 doses)	Placebo Ibuprofen on demand for pain episode relief (20 mg/Kg/day in 2 doses)	4 weeks with evaluation at 2 and 4 week	visual confirmation of the stone and subsequently confirmed radiologically
Aldaquadossi 2015	Tamsulosin 0,4 mg >5 ys, 0,2 mg< 2 ys at bedtime +Ibuprofen	Ibuprofen 4-10 mg/kg orally every 6-8hours (for intractable pain Ketorolac 0,5-1 mg/kg intramuscularly)	4 weeks with weekly clinical evaluations	Spontaneous stone expulsion rate confirmed by plain film and USS.
Erturhan 2013	Doxazosin 0,03 mg /kg daily at bedtime	Ibuprofen 20 mg/Kg/day in 2 doses (up to 40mg/kg in 4 dose for intractable pain)	3 weeks with weekly evaluations	Stone passage was assessed using KUB radiography and ultrasonography and non contrast-enhanced spiral computed tomography.
Mokhless 2012	Tamsulosin 0.4 mg>4 ys m 0,2mg< 2 ys + - ibuprofen		4 weeks	Filter the urine, KUB or NCCT to confirm passage of stone.
Aydogdu 2009	Doxazosin 0,03 mg/kg daily at bedtime	Ibuprofen 20 mg/kg/day in 2 doses	3 weeks	Filter the uri

Statistical analysis

The numerical data were expressed as mean and standard deviations (SD) and the categorical variables as number and percentage.

Comparisons between groups were performed by Student's unpaired t test for the mean time to expulsion and mean pain episodes. Z-test was applied to perform comparisons between proportions with reference to expulsion rate. $P<0.050$ two sided was considered to be statistically significant. The number needed to treat (NNT) or the number needed to cause harm (NNH) was calculated both for 5-10 mm and for whole population. Statistical analyses were performed using Excel 10 and Primer for Windows.

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RESULTS

The five studies included patients randomized into two groups, totaling up 245 patients; 125 were in the intervention group (alpha-1 adrenergic antagonist) and 120 in the control group (ibuprofen or placebo). Population characteristics are shown in Table III.

The incidence of ureteral stone expulsion was 84% in the alpha-1 adrenergic antagonist group (105 of 125 patients) and 60% in the control group (72 of 120 patients) ($p < 0.0001$, RR =1.40). The alpha-1 adrenergic antagonists increased the probability of calculus expulsion by 24%, needing to treat 4 patients to achieve this benefit (NNT=4, ARR 0.24) and reduced the mean time to stone expulsion (p=0.05). Moreover, the mean number of daily pain episodes in treated patients was less than in the treated group, but not significantly (P = 0.05). The number of daily pain episodes was evaluated only in 4 studies (10, 12, 14).

Sixteen of 125 treated patients and 6 of 120 patients of the control group reported adverse side effects as headache, dizziness, somnolence, nausea and nasal congestion (p= 0.03, RR= 2.56), needing to treat 13 patients to have side effects (NNH=13, ARR 0.08).

Three of five studies stratified the population for the stone size 5-10 mm and evaluated the free stone rate in 37 children treated with the alpha-1 adrenergic antagonist versus 32 patients treated with ibuprofen or placebo. Also in this subgroup the expulsion rate was higher in the treated group, but not significantly (p= 0.08) and the NNT was 4.8 (ARR 0.20). The number of daily pain episodes was not evaluated in any studies.

DISCUSSION

The management of symptomatic urolithiasis depends on size, position and composition of stones.

Table III.

	Stone size (mm)	Patients included in the results	Expulsion rate n (%)			Mean interval to expulsion (d)			Mean number of daily pain episodes		
			I	C	p	I	C	P	I	C	p
Elgalaly 2017	0-10	37	16/18 (88.8)	14/19 (73.6)	**.4**	7.0	10.4	.02	2.3	4.7	.001
	5-10	NS	-	-	-	-	-	-	-	-	-
Aldaquadossi 2015	0-10	63	27/31 (87)	20/32 (63)	.025	7.7	18	.001	1.6	2.5	.03
	5-10	47	-	-	-	-	-	-	-	-	-
Erturhan 2013	0-10	45	17/24 (70.8)	6/21 (28.6)	.005	NA	NA	.001	NA	NA	.023
	5-10	24	8/15 (53.3)	1/9 (11.1)	.03	NA	NA	NA	-	-	-
Mokhless 2012	0-10	61	29/33 (87.8)	18/28 (64.2)	.01	8.2	14.5	.001	1.4	2.2	.02
	5-10	26	11/13 (84,6)	7/13 (53,8)	.08	8.8	16	NA	-	-	-
Aydogdu 2009	0-10	39	16/19 (84)	14/20 (70)	**NS**	5.9	6.1	NA	-	-	-
	5-10	18	6/9 (67)	7/9 (78)	**NS**	6.1	6.3	NA	-	-	-
totale	0-10	245	105/125 (84)	72/120 (60)	.0001	7.2±0.99	12.2±5.14	<.001	1.8±0.47	3.13±1,37	.0797

NA= not available, NS= not signif.

Pharmacological treatment includes analgesics, steroids, alpha blockers or calcium blockers, while surgical techniques are ureterorenoscopy, intracorporeal lithotripsy, percutaneous antegrade ureteroscopy, laparoscopic ureteral stone removal.

High morbidity due to recurrence, surgical complications, and high probability of spontaneous passage of the stone must be considered when choosing the treatment for children (17, 19). It is well known that spontaneous stone clearance depends on size, with an expulsion rate of 60% for 5-7 mm stones and 39% for >8 mm stones (20-22).

Since 1998 the use of alpha blockers and other medication, known as MET, has spread in urological setting. Their use is justified by the fact that the urinary smooth muscle contains alpha 1- adrenergic receptors, which are more concentrated in the distal ureter while in the mid and upper tract their density is lower (17). The blockage of α-adrenoreceptors reduces the muscle tone and help the spontaneous stone passage.

The 2015 EAU guidelines on urolithiasis support the use of alpha-blockers and Nifedipine for distal ureteral stones with renal colic and do not recommend the use of corticosteroids neither in mono nor in combination therapy. Neverthless to date the existing literature has been inconsistent in its support of MET for children.

In this analysis, 3 of 5 studies found a stone expulsion rate (SER) significantly higher in the group of patients with 0 -10 mm stone sizethat received MET. These studiesregistered less pain episodes intreated group (10,13,14). On the contrary Aydogdu and Elgalayfound no differences between treated and controls (11, 12).

Aydogdu, Erthuran and Mokhless also evaluated SER and Time to stone expulsion for patients with 5-10 mm stone size, but only Erthuranfound significantly higher SER for treated patients(11, 13, 14). No statistical significance in time to stone expulsion was found in any study.

With regard to drug related side effects,all these studies reported low incidence of mild symptoms only, including headache, dizziness, nasal congestion and somnolence (10,12, 14).Erthuranreported that onlyone patient abandoned the study because of vomiting, nausea and somnolence (13). Moreover, we calculated the NTT for stone sizedbetween 0-10 mm, that resulted from 2 up to 4.These results are in line with a big multicentre RCT, dealing with noninvasive management of ureteral stones (24) .The subgroup analysis of 5-10mm stone size revealed an higher rate of stone passage in patients treated with Tamsulosin with an NTT of 4.5. A multi-institutional retrospective cohort study analyzed results from 274 patients from 4 institutions and found higher odd of spontaneous stone passage in patients receiving Tamsulosin than in control group receiving analgesic (18).

Because of the low quality of evidence, Cochrane meta-analysis on the management of nephrolithiasis in children has found considerable uncertainty regarding efficacy and adverse events associated with MET to UUTC. The few data about children are probably due to the rarety of urolithiasis in children, but also to the fact that MET is often underprescribed as demonstrated by a retrospective analysis of 1323 patients (1).

By contrast, studies on adults found stronger evidences about METefficacy. A systematic review,on a total of 2768 adult patients,found that MET (especially alpha-blockers) shortened the meanexpulsion time and increased expulsion rate for distal ureteric stones. The NTT was 14 for distal ureteric stones with an ARR of7,4%.Nevertheless, theauthors suggest to balance this result with thelikelihood of developing side effects (6,6 %), even if non severe side-effects were reported (6).

Finally, our analysis was limited by biases affecting the included studies, such as different processes of selection and randomization. Additionally, blinding was not described in any of the RCTs, potentially leading to detection biases. Other limitation were the variety and dosages of alpha-1 adrenergic antagonists and the difference of methods for measuring stone expulsion. Indeed, some studies analyzed the expulsion rate through imaging studies, while other ones analyzed it through urine filtration that is a less sensitive method (TableII).

Although the data are still scanty, the high success rate, the low frequency of adverse events and the substantially lower costs compared to surgical treatments, suggest that, in the absence of

contraindications, MET is the first line treatment that should be considered for stones of 5-10 mm.

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MONOSYMPTOMATIC ENURESIS: THE THERAPEUTIC WEAPONS

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Nocturnal enuresis (NE) was defined by the World Health Organization (ICD-10) and the American Psychiatric Association (DSM-5) as bed-wetting in children aged >5 years. In cases of mental retardation, the developmental age may be equivalent to 5 years. In this review, we focus on the current knowledge about the etiology of enuresis and the most recent therapeutical options. Both non-pharmacological and pharmacological therapies are included, although the relative effectiveness of each remains uncertain. To date, motivational, alarm and drug therapies are the mainstay of treatment. Alarm therapy remains the first-line treatment modality for NE, while desmopressin is the most commonly used medical treatment.

Nocturnal enuresis (NE) was defined by the World Health Organization (ICD-10) and the American Psychiatric Association (DSM-5) as bed-wetting in children aged >5 years (1, 2). In cases of mental retardation, the developmental age may be equivalent to 5 years. According to DSM-5, the NE may negatively affect child's psychosocial development by interfering with the development of self-confidence and the ability to socialize. Besides having implications for the patient, this condition can be stressful for the entire family (3).

It was observed that the prevalence at 5 years of age was 20%, decreasing spontaneously with age in approximately 15% of cases every year and that it was more common in boys than in girls (M:F=1.5-2:1) (4, 5).

The International Children's Continence Society (ICCS) classified NE as primary (75-90%) if the nocturnal urinary control was never achieved, or secondary (10-25%) if the NE followed a period of at least 6 months of normal urinary control. The secondary one was generally associated with underlying pathologies (6, 7).

Depending on the presence of other lower urinary tract symptoms, NE was further classified into monosymptomatic (MNE) or non-monosymptomatic (NMNE). The MNE was nighttime wetting only, while the NMNE was associated with daytime incontinence, urgency and holding maneuvers. The MNE is the most common form, accounting for about 70% of presentations (7).

Key words: enuresis; urinary control; alarm system; desmopressin

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Etiology

To date, the true etiology of the primary NE remains unclear; it probably involves genetic, physiological and psychological factors. Although primary nocturnal NE may be polygenetic, some authors suggested that genes 8q, 12q, and 13q are responsible for the tendency to develop enuresis (8). Half of patients has a positive family history: if one parent was enuretic, each child has a 44% risk of enuresis; if both parents were enuretic, each child has a 77% likelihood of enuresis (7). In the same way, concordance rates are higher among mono- than di-zygotic twins (68% *vs* 36%) (9). Main causes of enuresis are shown in Table I.

Diagnosis

The initial diagnosis of NE is based on the subjective information provided by the patient or his caregivers. Parents are requested to observe and record on a diary when and how much their child voids and drinks, as well as any associated symptoms (11). Daytime associated voiding symptoms may be incontinence, high voiding frequency (>8 micturition/ day), voiding urgency, and low voided volumes.

Table I. *Main causes of enuresis.*

Primary enuresis
• Genetic influences • Defective sleep arousal – Non REM dreaming phases • sleep apnoea and upper airway obstructive symptoms • Low overnight vasopressin levels • Low functional bladder capacity • Obstructive airway disease • Obesity • Behavioral disorders - Attention deficit hyperactivity disorder (ADHD) • Constipation
Secondary enuresis
• Psychological trauma or strees • Sexual abuse • Diabetes insipidus • Brain tumors • Psychiatric conditions • Drugs

Second step is a careful physical examination. Each child should be examined at least once to exclude any kidney disease, genitalia alterations, spinal cord defects, and other neurological disorders (12). A urine dipstick examination may provide important clues on urinary osmolarity or glycosuria, possible first signs of insipidus and mellitus diabetes respectively. Urinalysis is usually negative in children with MNE, but is important to rule out a lower urinary tract dysfunction thatmay need further radiological workup (13, 6). In regards to radiological investigations, the ultrasonography (US) is not routinely indicated in cases of primary MNE, but it should be performed on all patients with daytime incontinence to detect renal or bladder abnormalities. In children with recurrent or febrile urinary tract infections, or where US has demonstrated increased bladder wall thickness, voiding cystourethrography should be performed to exclude bladder dysfunction (14). Further radiological examinations, such as uroflowmetry, pelvic floor electromyography, urodynamics studies, cystoscopy and spinal MRI, should only be performed in specific cases.

Treatment

The NE treatment uses several approaches. The choice of treatment depends on co-existing disorders, subtype of enuresis (MNE or NMNE), severity of the problem, child's motivation and motivation and abilities of their parents.In such cases, the spontaneous resolution rate has been shown to be 15% (15). We analyzed primary MNE treatments.

Co-existingdisorders treatment

It is proven that if there are co-existing disorders, such as constipation and obstructive sleep apnea syndrome (OSAS), the early diagnosis and treatment of these improves enuresis. Constipation could be related to NE by a neuronal connection due to the common embryonal origin of the bladder and rectum. Another hypothesis is large stool masses may compress the bladder causing a reduction in functional capacity (10). Constipation can be assessed in children using the Rome IV criteria. Several studies reported that 34% of children with constipation and/or encopresis have NE, overactive bladder or dysfunctional voiding (16, 17). Constipation can be treated with an adequate fluid and fiber intake, laxatives and a toileting regime involving regular toilet sits after meals and a supported toilet posture to enhance motor control for bladder/ bowel emptying. In NE children with constipation, a successful treatment of the constipation can lead to a resolution of NE in 63% of patients without any other treatment (18).

The association between NE and OSAS is supported by the decrease or complete resolution of bed-wetting after adenotonsillectomy or treatment with intranasal corticosteroids (19, 20). Several studies showed that children with NE and OSAS have elevated brain natriuretic peptide (BNP) levels and lower antidiuretic hormone (ADH) levels than healthy children, with normalization after surgical correction (21). Probably, upper airway obstruction may lower intrathoracic pressures during sleep, leading to cardiac distention and the release of atrial natriuretic (ANP) and brain natriuretic peptide (BNP) that inhibit the antidiuretic hormone (ADH) activity causing natriuresis and diuresis. Moreover, a recent systemic review, that included almost 900 patients, demonstrated that a complete resolution of NE after adenotonsillectomy was observed in 54% of patients, which is significantly higher than the expected annual spontaneous remission rate of 15% (22). In the same way, children with allergic rhinitis and more severe respiratory manifestations appear to be more prone to developing primary nocturnal enuresis (23).

NON-PHARMACOLOGICAL THERAPY

First-line treatment of MNE involves education and giving information on enuresis. It is important for families to understand that enuresis is the fault of neither the child nor the parents (24).

Urotherapy and Lifestyle advice

Urotherapy involves educating the child and family about appropriate and adequate daytime fluid intake, voiding regularly during the day. The child should be encouraged to drink a non-excessive amount (approx. 50 ml/kg body weight/day, up to 2

l per day) and minimize beverages (such as cola or chocolate milk) that can reduce bladder contractions and diuresis (25). Fluids should be restricted 2 hours before bed and the child should be encouraged to empty the bladder completely before going to bed. A calendar of dry and wet nights is useful. Bladder diaries with frequency volume charts are also useful. The child should participate in the morning clean up as a natural, non-punitive consequence of wetting.

Alarm system

Alarm therapy conditions the child to inhibit urination during sleep or to wake to void when the bladder is full. Parents need to help the child to wake up completely. There are many types of alarms. Bed pads, bed bells, and oscillators that vibrate when wet have all been shown to have similar effects (6). The alarm has to be used every night without interruptions. Alarm therapy must be continued for at least 14 consecutive dry nights for a maximum of 16 weeks before being discontinued. The effect should be evaluated after a period of 6-8 weeks of use. Response is not immediate, but if there is no improvement after 6 weeks, it is reasonable to stop therapy or to add other treatment components (medication, behavioral therapy) (16). Sometimes, repeating the treatment after an appropriate interval is effective for some patients who failed to respond to the initial course of treatment (26). Treatment success rates are reported to be between 65-75% after 10-12 weeks of therapy (27).

The most common reason for alarm failure is the child's inability to wake to the alarm stimuli. For this reason, parental supervision and support for the child are generally needed for successful alarm training (22). Winter is also associated with higher failure rates of alarm therapy for enuresis. Contraindication to the alarm therapy may be severe problems in the parent–child interaction or other psychological disorders, NMNE with an overactive bladder, because in this case the alarm will sound several times every night.

Transcutaneous parasacral electrical neural stimulation (TENS)

Electrotherapy has recently been reported as an alternative treatment of NMNE, but it has also been used to treat MNE with a response in almost 50% of patients. Neuromodulation has been shown to enhance beta-adrenergic activities to cause detrusor relaxation, reduce cholinergic activity and alter other neurotransmitters. A recent study showed that the combination of TENS and behavioral therapy decreases the percentage of wet nights compared to behavioral therapy alone in children with MNE (37% vs 62%) (28, 29).

PHARMACOLOGICAL THERAPY

Desmopressin

In children with MNE, desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) is the second-line treatment option after alarm therapy. This synthetic analog of arginine vasopressin, acts on the distal tubules of the kidney and increases water reabsorption in the collecting ducts, producing a more concentrated and lower volume of urine. The use of DDAVP is appropriate in enuretic children with low ADH production or in case of alarm therapy failure (13). Moreover, it can be very useful to prevent enuresis for short periods such as at summer camps and sleepovers (12). DDAVP is available in tablet, fast-melting oral lyophilisate form or nasal spray, but the last one should be avoided as it may cause hyponatremia (30). Oral DDAVP may be started with a dose of 0.2 mg administered 1 h before bedtime. After 7-14 days of inefficient treatment, the dose can be titrated by 0.2 mg up to a maximum of 0.6 mg (12, 24). The therapy should be carried out for 3-6 months after which the drug may be gradually reduced and stopped (24). The success rates reported are between 60 and 70%, but the recurrence rate is as high as 50 - 90%. Desmopressin should be combined with fluid restriction otherwise, it can cause water intoxication with hyponatremia and convulsions. Other side effects are rare and include abdominal discomfort, nausea, headache and epistaxis.

Imipramine

Imipramine is a third-line treatment alternative in the hands of specialists (30). The tricyclicsact by inhibiting the reuptake of serotonin and noradrenaline

from synaptic alpha receptors, increasing bladder capacity through a weak anti-cholinergic effect and also decreasing detrusor muscle contractions through an antispasmodic effect. Imipramine is effective in almost 40% of patients with enuresis, but the relapses after the discontinuation of therapy are 75% (32). Moreover, it is cardiotoxic at high dosages, and ECG before starting treatment is recommended to rule out a long QT syndrome (24). The potentially lethal side effects may be ventricular dysrhythmias, seizures and coma. If imipramine therapy is selected, the family must be counselled about the dangers of accidental ingestion, safe storage of the drug and supervision of the child taking the medication.

Anticholinergic drugs

Anticholinergic treatment is intended to prevent involuntary detrusor contractions. In children with MNE, monotherapy with anticholinergics is not recommended, but it may be used combined with other established therapies such as enuresis alarms, desmopressin and imipramine (33). Side effects, due to the anti-cholinergic action of the drug, are flushing, blurred vision, constipation, tremor, decreased salivation and decreased ability to sweat.

DISCUSSION

This systematic literature search was carried out by guideline and position papers from the European Society of Pediatric Urology, the ICCS, Pubmed researches and Cochrane library. As demonstrated by a Cochrane review of 22 randomized controlled trials involving 1125 children, long-term alarm therapy was more effective in treating nocturnal enuresis than desmopressin or tricycles therapy (34). By comparing alarm and desmopressin therapy, a similar finding between the two interventions was demonstrated during the treatment, but a significantly more frequent relapses after desmopressin therapy (35). In the same way, comparing alarm with imipramine therapy, the number of patients achieving a complete response was higher for standard alarm therapy (33% vs 83%) and the relapse after cessation of treatment was lower for alarm therapy (100% after imipramine versus 58% after alarms) (33). Despite the success rates of alarm therapy, this intervention has a high attrition rate. These findings emphasize the importance in assessing a child and family's willingness and tolerance to commence treatment that requires active long-term intervention before success in bedwetting is achieved.

Desmopressin was also compared with tricyclics. There was no statistically significant difference between the two drugs in the mean number of wet nights at the end of treatment, in the number achieving a complete response at the end of treatment and in the mean number of wet nights at follow-up after cessation of treatment (32). Moreover, some authors have suggested that the combination of desmopressin and oxybutynin not only increases the success rate, but also decreases the rate of recurrence (6).

Finally, a Cochrane review analyzed 24 randomized controlled trials about complementary intervention and demonstrated the presence of weak evidence to support the use of hypnosis, psychotherapy, acupuncture, chiropractic and medicinal herbs (36).

Although enuresis in itself is pathologically benign and has a high rate of spontaneous remission, it affects child's quality of life and self-esteem, influencing his social, emotional and psychological well-being. Consequently, it is important to identify effective interventions for treating enuresis. Although many different interventions have been tried for treating nocturnal enuresis, the relative effectiveness of each remains uncertain. To date, motivational, alarm and drug therapies are the mainstay of treatment. Alarm therapy remains the first-line treatment modality for NE, while desmopressin is the most commonly used medical treatment. Alarm monotherapy alone is not less effective than alarm combined with desmopressin or alarm combined with tricyclics (32). Desmopressin has an initially high response rate and is best for episodic use (such as overnight camping). Anticholinergics and imipramine may be considered for resistant cases. Alternative medicine is commonly used in some areas of the world, but its safety and efficacy has yet to be proven with well-designed studies.

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RENAL ANOMALIES IN NEWBORNS WITH VACTEREL ASSOCIATION: CASE SERIES AND LITERATURE REVIEW

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VATER association was first described in 1973 as a non-random combination of the following congenital abnormalities: vertebral defects (V), anal atresia (A), tracheo-esophageal (TE) fistula with esophageal atresia, and radial and renal dysplasia (R) (1, 2). Successively, cardiac malformations (C) and limb defects (L) were also included with the resulting acronym of VACTERL (3, 4). Furthermore, it was proposed to consider vascular anomalies (V), comprising single umbilical artery as part of the disease. Its incidence is estimated to be approximately <1-9/100000 infants (5). The definition of the disease is extensively debated but the most widely accepted one requires the presence of at least three component features for diagnosis (6). The etiology of these anomalies remains largely unknown, and the causes have been found to be heterogeneous and pathogenetically unrelated (7). VACTERL association can be considered as a biological entity caused by teratogenic effects on the determination of cell fate and patterning, leading to a spectrum of birth defects affecting multiple organ systems (8, 10). Urinary tract anomalies are frequently observed. These abnormalities may affect the structure and function of kidneys and/or bladder. Isolated ureteral anomalies are rarely present.

We hereby present two patients affected by VACTERL association with renal manifestations. Our two cases demonstrate how renal involvement is characterized by heterogeneous clinical variability and can result in different diagnostic and therapeutic implications.

CASE SERIES

Case report 1

Infant 1 was born from non-consanguineous parents at the 39th week of gestation, by caesarian section, weight 2.840 g. Ultrasound screening in pregnancy showed no abnormalities. On newborn physical examination, anal atresia with rectovaginal fistula was noted. After a few hours from birth, a chest

Key words: congenital abnormalities, atresia, renal anomalies, malformations, VATER

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X-ray revealed the tip of the nasogastric tube at the level of the second thoracic vertebra. A diagnosis of trachea-esophageal fistula was made. Furthermore, cardiac ultrasound examination revealed atrial septal defect associated with mild pulmonary hypertension. Based on the combination of anal atresia, tracheo-esophageal fistula and cardiac malformation VACTERL association was diagnosed. She underwent surgical closure of trachea-esophageal fistula on the second day of life. Heart disease was initially treated with diuretics and ACE inhibitors drugs.

At 1 month of age, surgical treatment of atrial septal defect was carried out. Surgery for recto-anal fistula closure was scheduled for the age of 4 months. At 3 months of age, the child was hospitalized for fever, vomiting and poor feeding. Laboratory tests, including a urine culture, were performed and revealed a urinary tract infection. Ultrasonography showed increased renal parenchymal echogenicity. Antibiotic treatment was successfully practiced. At the age of 6 months, she had a second urinary tract infection episode. After resolution of this second episode, according to recent clinical practice guidelines, antibiotic prophylaxis was started.

The patient underwent voiding urosonography, which revealed non-obstructive 3rd degree vesicoureteral reflux in the left ureter. Posterior urethral valves were not detected. ^{99m}Technetium dimercaptosuccinic acid (DMSA) scan was performed, demonstrating renal scarring in the left kidney. Antibiotic prophylaxis was continued and nephrological follow-up was established. To date the patient's health has not worsened clinically.

Case report 2

Infant 2 was born at the 38th week of gestation by caesarian section. The mother was healthy and had not received any teratogenic medications. There was no family history of consanguinity or congenital malformations. The baby cried immediately after birth with an Apgar score of 9/10 at 1 and 5 min. The newborn's weight was 2.510 g. At birth, he exhibited a single umbilical artery and imperforate anus. At the first life of day, tracheo-esophageal fistula with esophageal atresia was detected by chest X-ray. He underwent surgical treatment for trachea-esophageal fistula with atresia and ano-rectal malformation on the second life of day. During hospitalization, he had oliguria and high blood pressure (100/65 mmHg), and laboratory investigations revealed a progressive decline of renal function. At the 7th day of life, creatinine was 5.1 mg/dl, blood urea nitrogen 256 mg/dl, serum sodium 129 mEq/l, and serum calcium 7.5 mg/dl. Blood gas analysis showed pH 7.26, bicarbonate serum 15.2 mmol/l, base deficits 10.4 mmol/l. Urinalysis showed high levels of protein. Based on these results, we made a diagnosis of acute kidney failure in VACTERL patient. Ultrasonography was performed, revealing lobulated renal contour with multiple internal cysts of varying sizes and shapes; the renal parenchyma appeared fibrous. The patient was initially treated with fluids restriction, sodium bicarbonate infusion and antihypertensive agents. Despite this medical management, his clinical condition worsened, and the patient presented with a severe combined respiratory and metabolic acidosis which require intubation and mechanical ventilation. Peritoneal dialysis was contraindicated since the child was at high septic risk due to recent history of surgical treatments. Then, at 8 days of age, he underwent hemofiltration. He was supported with parenteral nutrition, calcium and phosphate supplementation. Urine output gradually increased, and serum creatinine levels reached 1.4 mg/dl. Hemofiltration was discontinued after 16 days of renal support. Two days later, he was extubated and started to advance to complete oral alimentation. The infant was discharged from hospital at 50 days of life and received close nephrological follow-up.

DISCUSSION

Renal anomalies have been described in 50-80% of patients affected by VACTERL association (5, 11). Urinary manifestations can be classified into structural and non-structural defects. Structural anomalies mainly concern kidney and bladder morphology. Structural renal abnormalities include unilateral renal agenesis, dysplastic kidneys, multicystic kidneys, horseshoe kidney, renal atrophy, ectopia or hypoplasia. Structural bladder anomalies comprise bladders with diverticula,

bladder duplication, enlargement, and dysplasia. Non-structural urinary defects include isolated vesicoureteral reflux, isolated hydronephrosis without evidence of obstruction, and neurogenic bladder. These non-structural urinary manifestations could be secondary to malformations affecting other organ systems, such as ano-rectal malformations or lower vertebral anomaly (12). Kolon et al., in 2000, reported a prevalence of 63% of underlying vesicoureteral reflux in the setting of a normal renal ultrasound (13). To date, structural anomalies seem to be more evident, occurring in between 65% and 75% of urinary anomalies in VACTERL association. Most of these structural malformations are associated with vesicoureteral reflux (13, 14). Salomon et al. reported a high frequency of genito-urinary anomalies in conjunction with renal anomalies. Of these, genito-urinary fistulae represent the most observed manifestations. Other genito-urinary anomalies include cloacal anomalies, didelphys uterus and hypospadias, cryptorchidism, ambiguous genitalia and micropenis (15).

Several recent studies have investigated the likely genetic mechanism underlying renal anomalies in VACTERL association. Ngan et al. have demonstrated a crucial role of Sonic hedgehog signaling in the development of renal abnormalities in mutant murine models. *Shh, Gli2* and *Gli3* genes are involved in the Sonic hedgehog signaling pathway. According to this theory, the precise type of renal anomaly could be secondary to the severity and nature of the genetic lesion in relation to hedgehog signaling (7).

In humans, various allelic phenotypes have been associated with heterozygous mutations of *Shh, Gli2* and *Gli3*; however, none of these syndromic phenotypes completely resembles the classic human VACTERL association. Ludwig et al. have reported that all the identified human disease genes for the VATER/VACTERL association, namely *FGF8, FOXF1, HOXD13, LPP, TRAP1, ZIC3,* had been associated with "renal" phenotypes (16). *FGF8* mutations had been described in five patients with VACTERL association including horseshoe kidney and in one patient presenting with right-sided renal dysplasia (17). A heterozygous de novo *FOXF1* missense mutation was found in a patient with a VACTERL association who presented with left-sided renal agenesis (18). A heterozygous 21 pair de novo deletion in *HOXD13* gene was described in a VACTERL patient with bilateral hydronephrosis and hydroureter (19). *LPP* gene haploinsufficiency was detected in a patient with VACTERL association including a renal phenotype characterized by hypoplastic kidneys (20). Mutations in the gene encoding TNF receptor-associated protein 1 (*TRAP1*) were described in three families with VACTERL association comprising right duplex kidney and right renal agenesis (21). *ZIC3* mutations had been detected in several VACTERL patients with unilateral renal anomalies, such as multicistic kidney, renal agenesis, unilateral vesicoureteral reflux, ectopic kidney (18, 22).

It is thought that urinary anomalies may not immediately be recognized in VACTERL patients since the initial focus is often directed at those conditions that can be life-threatening for the infant, such as severe congenital cardiac defects, anorectal malformations or tracheo-esophageal fistula with atresia (23). Moreover, despite other features of VACTERL association, which could be associated to relatively obvious clinical signs, most renal anomalies may be recognized only with careful imaging. Early diagnosis is important as clinical course and prognosis depend on the severity of the malformations observed. Renal ultrasound is considered the first choice of examination in the suspicion of VACTERL association. If the ultrasound examination shows evidence of obstruction, further investigations, such as voiding cystourethrogram/urosonography, serial ultrasound testing, and Tc-99m DMSA/MAG-3 renal cortical scan may be required (12, 24). Routine ultrasound examination in pregnancy could lead to a prenatal diagnosis of renal anomalies related to VACTERL association. Debost-Legrand et al. reported the detection of 45% of renal malformations in a group study of ten VACTERL patients ascertained prenatally through ultrasound examination and confirmed after birth (25).

Vesicoureteral reflux can predispose to urinary tract infections and renal scarring, leading to progressive renal damage and impaired renal

function. According to recent clinical practice guidelines for pediatric urinary tract infection, antibiotic prophylaxis is recommended in the presence of urinary tract dilation and suspected obstruction until the diagnosis is confirmed and proper treatment is given, as well as for patients with high-grade vesicoureteral reflux only (26).

Ahn et al. described a 15-year follow-up period of twelve VACTERL patients, diagnosed at birth, with chronic kidney disease stage 2-5. Eight of them progressed to end-stage renal disease at a mean age of 8.5±2.5 years. Six patients were initially treated with dialysis (14). The choice of dialysis modality for these patients is debated. Peritoneal dialysis represents the most common dialysis modality prescribed worldwide to children aged < 5 years with end renal stage disease. Advantages of peritoneal dialysis over hemodialysis include better preservation of residual renal function, avoidance of the need for vascular access, less strict dietary and fluid restrictions, ability to provide dialysis at home, and less disruption to daily activities (27, 28). However, due to peritoneal dialysis complications, such as abdominal adhesions, it appears that hemodialysis is the preferred modality for VACTERL patients who are frequently burdened with multiple abdominal surgeries. Hemofiltration with the addition of a dialysis circuit in hemofilter may be considered in patients who are hemodynamically unstable, have multiorgan dysfunction and require pressor support (29). Kidney transplantation represents a prominent choice of treatment for these patients. Patients who have congenital urologic anomalies have been shown to be at increased risk for urinary tract infection, surgical complications, graft dysfunction, and graft loss (30, 31). Therefore, management of the lower urinary tract before and after transplantation should be considered. Koo et al. reported 18 patients with severe dysfunctional lower tract anomalies who underwent kidney transplantation. Eleven underwent bladder augmentation or continent urinary diversion, two patients had an intestinal conduit and five had a transplant into the native bladder. They reported a patient survival rate of 81% during a 4.4-year follow-up period post transplantation (32).

Seven out of twelve patients described by Ahn et al. underwent kidney transplantation; 85.7% were treated with extensive urological surgical interventions that included augmentation cystoplasty procedures. Nevertheless, they had a poor transplant outcome, since mean creatinine 2 years post-transplant was 65.8±6.3 vs 87.8±7.1 ml/min per 1.73 m² in controls (14). Adams et al. described their experience with kidney transplantation in patients affected by VACTERL association. They observed a high rate of urinary tract infections following renal transplantation. Therefore, they remarked the importance of antireflux ureteral implantation and urinary tract infection chemoprophylaxis as symptomatic infections of the urinary tract might facilitate rejection episodes and cause chronic allograft dysfunction (33, 34). Multiorgan involvement severely complicates outcome after transplantation since VACTERL patients often require major surgeries on two or more organ systems (35-37).

The rarity of the disorder makes it difficult to carry out large trials regarding the renal course in VACTERL patients. Further reports of diagnostic examinations, timing of therapeutic procedures and the various complications that can arise during treatment are mandatory to improve outcomes of VACTERL association patients (38).

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RENAL INVOLVEMENT IN PAEDIATRIC FABRY DISEASE

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Anderson-Fabry Disease (AFD) is a rare, X-linked inborn error of glycosphingolipid catabolism caused by a deficient or absent activity of the lysosomal enzyme, α-galactosidase A, resulting in the progressive multisystem lysosomal accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb3). Among the wide spectrum of clinical signs and symptoms and the life-threatening complications of Fabry disease, renal failure causes significant morbidity and mortality. Various evidence shows that the accumulation of Gb3 in different renal cells is present since the first years of life, many years and usually decades before manifest symptoms and signs of renal involvement. Early renal damage can be demonstrated by clinical signs as microalbuminuria and proteinuria, developing as early as in the second decade of life. A decline in GFR is uncommon at paediatric ages but may be seen as early as adolescence. Renal biopsy is rarely used in paediatric patients with Fabry disease although evidence shows that it may be considered a valid tool for the diagnosis of early and potentially reversible nephropathy, as well as for the evaluation of the effectiveness of enzyme replacement therapy (ERT). Although there is consensus in considering the early initiation of ERT as the only tool able to prevent the progression of nephropathy, the issue on the correct timing for the onset of ERT in pediatric age remains open in the management of this chronic and progressive disease.

Anderson-Fabry Disease (AFD) [Online Mendelian Inheritance in Man (OMIM) 301500] is a rare, X-linked inborn error of glycosphingolipid catabolism caused by a deficient or absent activity of the lysosomal enzyme, α-galactosidase A (α-Gal A) (1). The α-Gal A deficiency results in the progressive lysosomal accumulation of glycosphingolipids, mainly globotriaosylceramide (Gb_3) in cells from various organs, thus explaining the multisystemic disease, and the wide spectrum of clinical signs and symptoms that begin to appear in pediatric age (2, 3) (Table I) up to organ complications that limits patients' life expectancy.

Among the life-threatening complications of

Key words: Fabry disease, renal damage, α-galactosidase, Gb

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Fabry disease, renal failure causes significant morbidity and mortality, especially today that Enzymatic Replacement Therapy (ERT) is available. It is important to fully understand the nephrological aspects of the disease, above all to understand if there is a phase of renal involvement in which the damage caused by the accumulation of Gb3 can be made reversible by a timely start of therapy.

Renal involvement and assessment of renal damage

Although the symptoms and signs (evident proteinuria and hypertension to more serious cases of renal failure) of renal involvement are generally absent in paediatric age, becoming evident in young-adult age, different evidence shows that the accumulation of Gb3 in different renal cells is present from the first years of life and usually decades before manifest proteinuria and/or elevated serum creatinine is found (4, 5).

α-Gal A deficiency results in accumulation of Gb_3 in all kidney cell types (6), with a broad spectrum of morphological changes of glomerular, tubulointerstitial, and vascular compartments (4). These potentially irreversible histologic changes can be detected in renal biopsy specimens from children with AFD before the first appearance of clinical signs, such as microalbuminuria (4).

Early renal involvement can be demonstrated by clinical signs such as microalbuminuria and proteinuria, developing as early as in the second decade of life (4, 7, 8). In clinical practice, microalbuminuria is considered a helpful, non-invasive and easily performed marker to evaluate renal disease even in young children. Wilcox *et al.* described that microalbuminuria or proteinuria are present in almost all adult Fabry registered patients for whom this was measured, suggesting that in adults, microalbuminuria cannot prove to be of strong predictive value, because not all patients, especially female patients will necessarily progress to an advanced form of renal disease (9). The same authors reported a prevalence of albuminuria or proteinuria of 10% in Fabry registered children (10).

Early onset of microalbuminuria in children can be considered a more precise indicator of serious Fabry nephropathy, as the result of increased glomerular leakage of albumin due to damage of the filtration barrier or decreased tubular reabsorption of filtered albumin (11). However, other studies with a larger number of patients, are required to confirm whether microalbuminuria can be considered as a predictive sign of incipient renal damage due to the accumulation

Table I. *Early signs and symptoms of classic Fabry disease.*

Acroparesthesias
Fabry crises
Gastrointestinal symptoms
Angiokeratomas
Whorled corneal opacity, retinal vascular tortuosity
Heat, cold and/or exercise intolerance
Hypohidrosis or anhidrosis
Microalbuminuria, mild proteinuria and urinary sediment containing globotriaosylceramide
Urinary hyperfiltration
Impaired heart rate variability
Arrhythmias
Mild valvular insufficiency

of Gb3. Tondel et al (4) suggest that in pediatric Fabry patients with signs of early renal disease such as albuminuria, a prompt renal biopsy may be required in order to assess and characterize the extent of renal damage, thus proving an important diagnostic tool. Nevertheless, it must be considered that advanced lesions have been detected in biopsies from patients with AFD and normo-albuminuria (4, 7).

About proteinuria, it may start around 10 years old (12), and although it usually precedes signs of decline in renal function, a fraction of patients with AFD develop a Glomerular Filtration Rate (GFR) loss before proteinuria (9).

A decline in GFR is uncommon at paediatric ages but may be seen as early as adolescence (13, 14). The timing detection of an early decline in GFR is essential since especially in relation to a better prognosis that can be obtained following an earlier initiation of the enzyme replacement therapy, before the damage due to the accumulation of Gb3 in the renal parenchyma become irreversible. For this reason, the identification of the most correct way to calculate paediatric GFR has been a major challenge for years. Renal function in children with FD have usually been evaluated using estimated creatinine-based GFR (eGFR). The original and widely used Schwartz formula (15) substantially overestimates GFR and has a low accuracy, whereas the new abbreviated Schwartz formula (16) correlates with a mean GFR overestimation of 5.3 ml/min/1.73 m2, being only slightly superior to the Counahan-Barratt formula (17). This shows that abbreviated Schwartz formula should be used in the routine follow-up of children with AFD replacing the original Schwartz formula (18). Even if measured GFR (mGFR; iohexol-GFR) offers the best combination of precision, safety, and accuracy (19), it requires long procedures so that it is only rarely used (20).

In addition to the renal manifestations described above, some authors described parapelvic cysts, a distinguishing feature of renal Fabry disease, suggesting that the presence of PC in renal patients should alert physicians to consider the diagnosis of FD, primarily in subjects with an unclear family history of renal disease and in the presence of other stigmata of the disease (21).

Role of renal biopsy

Renal biopsy, as a useful tool to identify the histological changes resulting from the accumulation of Gb3 in the renal parenchyma, is rarely used in paediatric patients with Fabry disease, neither for diagnostic purposes nor for monitoring the effects of therapy. In children with known Fabry disease, diagnostic renal biopsy is rarely performed and generally, its use is confined to patients with unusual clinical features such as early onset of heavy proteinuria or gross hematuria (11). Moreover, especially in young male patients, renal biopsy is never used to decide whether and when to start ERT, despite the potential usefulness of baseline biopsies, prior to initiation of ERT, in defining the severity of renal involvement, in addition to the possibility of determining the efficacy of therapy through follow-up biopsies after the start of the ERT. This is even more valid in the young Fabry women, for whom, due to a more varied and often more nuanced symptomatology than in males, doubts often arise about whether and when to start the ERT.

Evidence shows that histological alterations, especially in kidney podocytes, can be found in patients with normal values of microalbuminuria and proteinuria, underlining that renal functional alterations alone do not allow the early diagnosis of Fabry nephropathy (4, 5, 22-24), unlike renal biopsy. In addition, renal biopsy can be useful in order to exclude other causes of renal involvement in cases with atypical presentation, such as a very early evidence of high proteinuria or a rapid decline of renal function. In particular, Tondel et al indicated that early segmental podocyte foot effacement might represent a ‘silent window’ that precedes the development of overt proteinuria in the early phases of a slowly progressive chronic disease like Fabry disease (23). This justifies the use of renal biopsy as a tool for the diagnosis of early and potentially reversible nephropathy, as well as for the evaluation of the effectiveness of ERT. Furthermore, kidney biopsies may be useful in the assessment of additional vascular and interstitial involvement and for additional renoprotective therapy (25).

Effects of ERT on renal involvement in paediatric Fabry disease

Although ERT has been available for over 15 years, the issue about when therapy should be started remains still open, as well as, if there is a marker that may allow us to identify a "reversibility window" of the lesions already established as a consequence of Gb3 accumulation. Early treatment of children has been shown to prevent the progression of nephropathy during 5 years treatment in young Fabry patients with normo- or microalbuminuria (25). Evidence shows that mesangial and endothelial cell deposits are reversible (5,26), although, the clearance of Gb3 deposits alone has not been shown to guarantee long-term prevention or stabilization of Fabry nephropathy (26). Although there is consensus in considering the early initiation of enzyme replacement therapy as the only tool for slowing down or preventing progressive renal involvement and of other organs (27), the issue on the correct timing for the onset of ERT in pediatric age remains open in the management of this chronic and progressive disease (28-29).

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URETEROCYSTOPLASTY (BLADDER AUGMENTATION) IN A 16 YEAR-OLD BOY WITH GOLDENHAR SYNDROME

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The use of the dilated ureter for bladder augmentation is universally accepted for its lower rate of complications compared to the use of gastrointestinal segments. We report the case of a 16 year-old boy affected by Goldenhar syndrome who presented with neurogenic bladder with small-capacity, 5° grade vescico-ureteral reflux (VUR) with megaureter and bilateral hydronephrosis. Bladder augmentation using the distal dilated ureter, transuretero-ureterostomy left to right and Mitrofanoff's appendicovescicostomy were performed. Six months after surgery voiding cystourethrogram (VCUG) revealed a compliant bladder with a functional capacity of 400 ml. Ureterocystoplasty is a safe and effective method of augmenting small capacity urinary bladder. We suggest using the ureter, when available, instead of using gastrointestinal segments.

Bladder augmentation is an important tool in the management of children requiring reconstructions for congenital malformations like neurogenic bladder or obstructive uropathies (1).

Actually, the major tissue used for bladder augmentation is the gastrointestinal one, but it is associated with numerous complications: increased mucus production, infection, stone formation, perforation, metabolic disturbances and rarely even malignant changes. The ideal substitute for bladder augmentation should be the bladder tissue itself, which has unfortunately been unavailable in cases of small capacity urinary bladder. The second best substitute is the ureter, which possesses an urothelial lining backed by a thick, smooth muscle and is devoid of the complications associated with the use of gastrointestinal segments (2). The typical patient undergoing ureterocystoplasty has a dilated ureter secondary to severe VUR. If the affected kidney is non-functional, a concurrent nephrectomy is performed. If the kidney retains function, drainage of the kidney is provided via transuretero-ureterostomy (3).

Herein, we report the case of a 16-year-old boy with Goldenhar syndrome suffering from neurogenic bladder, bilaterally severe dilated ureter by VUR and bilateral hydronephrosis.

Key words: bladder augmentation, ureterocystoplasty, neurogenic bladder

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Case report

A 16-year-old male patient with Goldenhar syndrome presented in our department with impaired bladder emptying, a history of urinary tract infections (UTI) and diagnosis of neurogenic bladder, bilateral severe dilated ureters by VUR and bilateral hydronephrosis. The laboratory result showed a normal blood analysis except the creatinine which was 3.4 mg/dl and blood urea nitrogen (BUN) which was 68 mg/dl. An abdominal ultrasonography revealed bilateral hydroureteronephrosis with grossly dilated ureter and bladder wall thickening. His abdominal CT revealed diffused 4° grade bilateral hydroureteronephrosis. The renal pelvis presented a diameter of 40 mm bilaterally with renal calices of 30 mm, the ureters appeared extremely dilated (30 mm on the left and 20 mm on the right) and showed a tortuous course.

Fig. 1. *Preoperative VCUG showing 5° grade VUR on the left.*

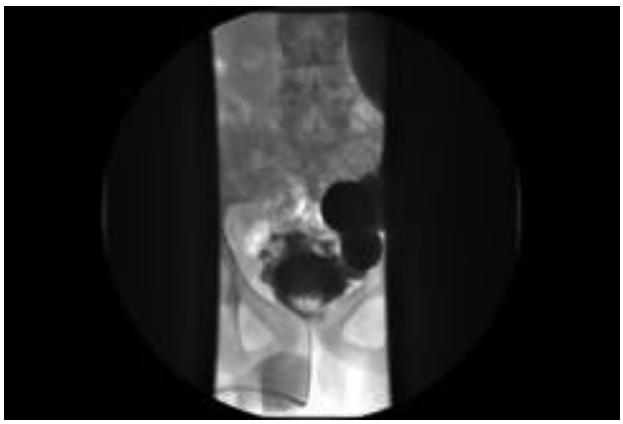

Fig. 2. *Preoperative VCUG showing small-capacity bladder.*

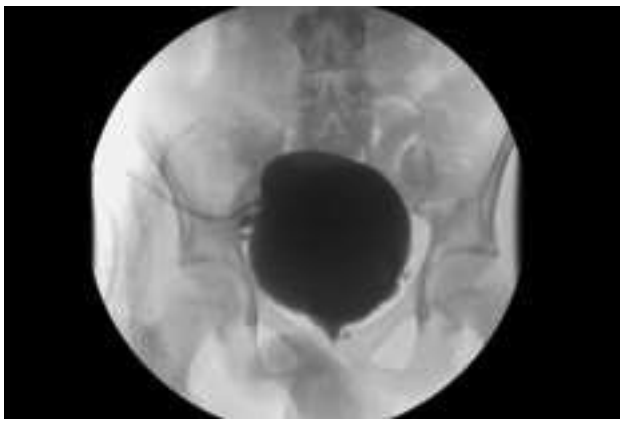

Fig. 3. *Postoperative VCUG showing a bladder capacity > 400 ml.*

The bladder presented a diffusely thick and inhomogeneous wall. Abdominal magnetic resonance imaging confirmed the TC report. His voiding cistouretrogramma (VCUG) showed a vesico-ureteric reflex of 5° grade on the left associated with the megaureter (Fig. 1, 2). His 99Tc-DMSA scan showed multiple scars on the left and renal function of 23% on the left and 77% on the right. The patient was managed by bladder augmentation using dilated distal left ureter, uretero-ureterostomy left-to-right, and Mitrofanoff's appendix-vescicostomy.

Procedure

A midline transperitoneal approach was used. The markedly dilated and tortuous left ureter was visualized (diameter >30 mm). The bladder was opened on the anterior surface starting from the bladder neck and moving in the posterior direction up to the trigone, along the sagittal plane, into two halves. An uretero-ureterostomy left-to-right was created after positioning of a JJ ureteral stent. Distally to uretero-ureterostomy, the left ureteric sheath along with its vascularity was preserved while the ureter was being detubularized. The detubularized left ureter was folded and stitched to obtain a bladder augmentation. Before completing bladder augmentation a urinary and suprapubic catheter was positioned; the cecal appendix was used to create a Mitrofanoff's vescicostomy with anti-reflux technique on the right side of the bladder.The bladder wall was closed and bladder capacity was tested showing a volume >300 ml. Intraoperatively a Meckel diverticulum was found and excised.

The postoperative period was free of adverse events and he was discharged on the third post-operative week. The serum creatinine and BUN reduced to normal range value (respectively 1.30 mg/dl and 40 mg/dl). Two months after surgery he underwent urinary US that showed an evident reduction of hydronephrosis. He subsequently underwent VCUG which showed absence of VUR and a bladder capacity of approximately 400 ml (Fig. 3). DSMA renogram, done 6 months after surgery showed a renal function stable relatively compared to pre-operative values. After a follow up of 8 months the patient is continent and clean and he catheterizes through the Mitrofanoff every 4 h during the day and has not had any problem of incontinence nor infections, moreover he leads a normal social life.

DISCUSSION

The use of a dilated ureter to augment the bladder was first described by Eckstein and Martin (4) but no reports followed it until 1993 when the separate reports of Bellinger(5) and Churchill et al. (6), have provided excellent short-term results in patients with favorable anatomy. Ureterocystoplasty is a reasonable choice for patients with a small-capacity, poorly compliant urinary bladder and a unilateral poorly functioning kidney and megaureter. The major advantages of bladder augmentation with uroepithelium, respect to ileal or colic segments, are mainly related to the absence of mucus production, with a decreased likelihood of urinary infection, lithiasis and absence of metabolic complications like hyperchloremic acidosis or abnormalities of calcium and phosphorus balance due to active intestinal absorption of chloride and ammonium from the urine (7, 8).

Because the augmentation material contains no heterotopic tissue, the reported risk of late bladder neoplasia in enterocystoplastyshould theoretically be decreased(9, 10). The most important concern regarding ureteral tissue is that a large enough ureter is not always available for proper bladder augmentation. In conclusion, ureterocystoplasty is a safe and effective method of augmenting small capacity urinary bladder. However, case selection is important since it is indicated only in a particular subset of patients having a small capacity bladder with an enormously dilated ureter. In cases of a non-functioning kidney, it must be removed and the ureter in its entire length can be used for bladder augmentation. When there is a residual renal function, the ipsilateral kidney can be preserved by dividing the megaureter and using the distal part for ureterocistoplasy and proximal part for transuretero-ureterotomy.

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UNUSUAL PRESENTATION OF HENOCH-SCHÖNLEIN PURPURA

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Henoch Schonlein Purpura (HSP) is a systematic IgA-mediated vasculitic disease that affects the small vessels of the skin, the joints, the gastrointestinal tract and the kidneys (1). It is the most common childhood vaculitis, with an incidence estimated at 3-26 per 100,000 children, and with a male-to-female ratio of 2:1 (2-6). The 90% of patients are under 10 years of age, with a mean age of 4 years (4). It seems to be most common in fall and winter in children, and summer and winter in adults (7). Recent studies suggested a strong genetic predisposition in individuals with immunoglobulin Avasculitis (IgAV) associated to HLA class II region. Clinically, the non-thrombocytopenic purpura often located on lower extremities and buttocks is the essential element for the diagnosis of HSP. Treatment is supportive, because the disease is usually benign and self-limited. Indeed, in children, the prognosis is good, with a self-limited course and without any complications and after a median follow-up of 12 months, complete recovery was obtained in 83% of the IgAV patients (4, 8). The aim of our study is to describe some atypical presentations of the HSP in children.

Case 1

In December 2016, an eight-year-old female patient was admitted to our hospital with a one-week history of progressive abdominal pain, nausea, and vomiting. She was afebrile and had no arthralgias, diarrhoea, or other complaints. Additionally, she had positive history for recurrent urinary tract infections caused by ureteral bladder reflux. On examination, her vital signs were normal. Abdominal examination revealed moderate mesogastric tenderness, but no peritoneal irritation signs. Laboratory evaluation, including full blood count, serum electrolytes, liver and kidney function tests, serum IgA, were normal. Her urinalysis showed glycosuria, nitrites +++ and E. Coli was found in the urine culture, so antibiotic therapy was started. Control urine culture performed during antibiotic therapy was sterilized. Due to the persistence of abdominal pains of left hypochondrium, an abdominal ultrasound (US) was performed and oriented for an ileo-mesenteritis. During the hospitalization, the child remained afebrile, and the vital signs were normal.

Key words: Henoch Schonlein Purpura, vasculitis, atypical presentation

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For the persistence of abdominal pains of a colonic type in the sixth day, an abdominal US was repeated and showed the presence of a small concentric parietal thickening of an intestinal loop, probably duodenal. This finding was confirmed by abdominal TC that excluded other causes of abdominal pain. A pediatric gastroenterological consultancy was performed and therapy with ceftriaxone was started. In the following days, persistence of abdominal pains of a colonic type, always localized in the left hypochondrium and appearance of purpuric and petechial manifestations in the lower limbs. For this reason, HSP was suspected, and prednisone was started with regression of abdominal pain.

In the 12th day, resumption of abdominal pains of a colic type associated with vomiting and rectorrhage for which plasma infusion was performed, increased cortisone dosage (methylprednisolone 30 mg/kg/day) for 3 days and subsequently reduced to 2 mg/kg/day with resolution of gastrointestinal symptoms. Examinations performed in pre-discharge (Hemoglobin values, total proteins, renal function) were normal. The abdomen ultrasound repeated at the discharge documented resolution of the previously objectivated picture of the duodenum. The girl is now in good health and she is periodically followed at our clinics.

Case 2

In October 2017, a previously healthy 12-year-old girl was transferred from a district general hospital to our center, 3 weeks after she had been diagnosed with steroid-dependent idiopathic nephrotic syndrome. At the admission, the physical examination showed edema of the lower limbs, eyelid and sovrapubic area. The urine analysis showed Proteinuria 4.78 g/24h, Creatinuria 113.4 mg/dl, microalbuminuria 80 mg/L, and the working diagnosis of steroid-dependent nephrotic syndrome was adopted. During the hospitalization, we continued the therapy with

Table I. *Typical features of HSP.*

Rash (especially involving the legs)	95-100% of cases
Abdominal pain and vomiting	35-85%
Joint pain and swelling(especially involving the knees and ankles)	60-84%
Subcutaneous edema	20-50%
Scrotal edema	2-35%
Renal findings (Acute glomerular lesions, including mesangial hypercellularity, endocapillary proliferation, necrosis, cellular crescents, and leukocytein filtration)	45-50%
Bloody stools	rare
Intracranial hemorrhage; bilateral subperiosteal orbital hematomas; adrenal hematoma; acute pancreatitis as the sole presenting feature (rare); cystic changes of the ovaries.	rare

prednisone (60 mg/day) already started at the center of origin and we practiced hyposodic diet and water restriction, with monitoring of water assumption, diuresis and blood pressure. Given the confirmation of a cortico-resistance, kidney biopsy was performed and while waiting for the histological report, therapy with immunosuppressive therapy (Tacrolimus 10 mg/day) was started with improvement of proteinuria (2.4g/24h) and kidney function (creatinine 1.0 mg/dl, azotemia 45 mg/dl, protein 4.9 g/dl, albumin 2.1g/dl). Two days after discharge, during the outpatient check, petechial manifestations were observed on the lower limbs, the biopsy resulted positive for IgA on direct immune fluorescence and HSP was diagnosed. Therefore, Tacrolimus was stopped and high-dose methylprednisolone was performed. In the following months, therapy with mycophenolate and ACE inhibitors was started, while the steroids were reduced to suspension. Today, after 8 months from diagnosis, the girl practices only ACE inhibitors and the last urine analysis were normal.

Case 3

In November 2016, a 3-year-old girl was admitted to our clinic for pain in the lower limbs and swollen knees. She was previously healthy, but the mother reported cough and cold 10 days earlier. At the admission, the physical examination showed erythematous macules on her lower limbs, roundish eczematous lesions on her back, on her thorax and on her right arm. Laboratory assessment revealed a C-reactive protein of 2xN, with a normal complete blood count, albumin, prothrombin time and partial thromboplastin time. The urine examination was normal, while occult blood was positive in the feces, even if she had no abdominal pain. On the second and third day of hospitalization, edema occurred on the lumbar region, on the scalp and on the periorbital region, with spontaneous resolution in 24 h. Palpable purpura on her lower extremities had a polymorphic evolution: erythemato-ponfoid lesions, nodular and finally ecchymotic. Haematological causes were excluded by lymphocyte typing. The

Table II. *Diagnostic criteria for HSP.*

EULAR/PRINTO/PRES 2010	Palpable purpura, nonthrombocytopenic/petechiae (mandatory) + ≥ one of the following:
	Diffuse abdominal pain
	Histopathology: typical LCV with predominant IgA deposits or proliferative glomerulonephritis with predominant IgA deposits
	Arthritis or arthralgias
	Renal involvement (proteinuria: >0.3g/24hor >30mmol/mg of urine albumin to creatinine ratio on a spot morning sample; and/or hematuria, red blood cell casts: >5 red cells per high power field or ≥2 + on dipstick or red blood cell casts in the urinary sediment).

HSP was diagnosed because of clinical signs and blood in the feces. Abdominal US was negative. On the fifth day, for the onset of gait with an enlarged base, pain and limited mobilization of inferior limbs, electroencephalogram (EEG) and Computed Tomography (CT) were done. The EEG revealed the presence of anomalies of brain in the right occipital region, and the CT incidentally revealed a type I Arnold-Chiari malformation, confirmed by magnetic resonance imaging (MRI). In addition, the MRI angiography revealed vasculitis of left temporal artery and thickening of ipsilateral temporal muscle. In the following 12 days, brain symptoms and abdominal involvement progressively resolved without any therapy. The patient was discharged healthy, and now he practices a regular follow-up at our outpatient clinic.

DISCUSSION

HSP is a generalized vasculitis involving the small vessels of skin (95-100%), gastrointestinal (GI) tract (35-85%), kidneys, joints (60-84%), and, rarely, lungs and central nervous system (CNS) (8, 9). The typical clinical features are summarized in Table I. Although palpable purpura is considered the hallmark of HSP, skin findings are not the presenting feature in almost 25% of patients (10). We presented 3 clinical cases of atypical presentation of HSP occurred in the last 20 months.

Case 1 - abdominal involvement is frequent in HSP and it occurs in more than half of patients, but it precedes purpuric lesions of several days only in 12-19% of cases (11, 12).

In order of frequency, the small intestine, the jejunum, the stomach, the ileum and the colon are the most commonly involved traits of the gastrointestinal system (13). The most common symptoms are pain or nausea without any complications, while the intestinal bleeding is rare and occasionally it may require transfusion. Laparotomy may be necessary in case of intussusception, infarction and perforation (14).

Severe gastrointestinal bleeding in patients with HSP is associated with poor prognosis. It requires intensive medical treatment and close follow-up. Our patient was under steroid treatment with prednisone when HSP complicated with GI bleeding but responded to high dose of Metilprednisolone.

Steroid treatment may be beneficial, but there are few data on the management of steroid-resistant HSP with GI bleeding. In some cases of severe GI bleeding, IVIG and plasmapheresis were useful. Recently, i.v. cyclophosphamide monodose was proposed as treatment for HSP patients with severe gastrointestinal involvement who do not respond to high-dose steroids (15).

Case 2 - Renal involvement usually occurs within the first 3 weeks of the disease, but may rarely precede the appearance of purpura. It ranges from isolated microscopic hematuria, proteinuria, or nephritic-nephrotic syndrome (> 3 g/24 h in adults and > 40 mg/m2/h in children) to acute, rapidly progressive glomerulonephritis. Moreover, it is known that the degree of proteinuria is not only a sign of renal damage, but also an accelerator of the progression of kidney disease (16). Nephrotic proteinuria (NP) in HSPN often is linked to a poor prognosis. Indeed, it is known that chronic renal failure develops in 5% of children with hematuria and/or minimal proteinuria, in 40% of children with nephritis syndrome and in over 50% of children who have shown both nephrotic syndrome and nephritic syndrome. Moreover, the risk of HSPN increases with age. In particular, cases of children over 10 years of age were more likely to progress to HSPN (17) and recently a study of 202 pediatric patients with HSPN showed that patients older than 10 years had a significantly different clinical presentation with decreased renal function, and more chronic lesions compared with younger ones (18). Immediate onset of corticosteroid therapy significantly reduced the odds of developing kidney disease. Furthermore, the association of oral prednisolone with cyclophosphamide seems to be useful. Recently, mycophenolate mofetil (MMF) was proposed as an alternative therapeutic option, because some studies showed that patients treated with MMF had a significant improvement within 1 month from the start of therapy (19).

Case 3- The involvement of the central nervous system (CNS) is rare in PSH and is mostly reported in patients with a severe course of the disease or in adults.

The pathogenesis of HSP-associated encephalopathy is probably due to vasculitis that affects small blood vessels and causes micro-thrombosis in the brain. Clinical signs and symptoms of CNS involvement are alteration of consciousness (58%), focal neurological deficit (26%), visual disturbances (24%), seizures (14%), language disorders (10%) (20). Few cases of posterior reversible encephalopathy syndrome (PRES) have also been described in HSP (21). The diagnosis of vasculitis of the central nervous system is generally based on TC or MRI images showing cerebral hemorrhages, infarcts and edema, rarely confirmed by histopathology. The conventional brain angiography does not show abnormalities in the patients with CNS. Instead, in a single case, MRI angiography showed irregularities on segments of the middle and posterior cerebral arteries, but this technique is subject to artifacts (22). Generally, patients with CNS vasculitis are treated with corticosteroids, but our case had a spontaneous resolution.

CONCLUSIONS

In conclusion, most children with HSP will have classical manifestation of the disease but diagnostic confusion can occur in those with atypical or absent cutaneous features at the onset. Several sets of diagnostic criteria for HSP have been proposed, but EULAR/PRINTO/PRES criteria showed a better sensitivity and specificity (Table II). Generally, the treatment is supportive, but steroid and/or immuno-suppressants therapies are indicated in case of kidneys, intestinal or nervous complications (3, 5, 8). Progressive impairment of renal function, bowel perforation, and central nerve system involvement are rare but major morbidity of HSP (5, 6).

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RENAL OXIDATIVE INJURY IN NEWBORNS

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Free radicals (FRs) are molecular species with an unpaired electron in the outer shell, which renders them highly reactive and unstable. FRs are oxygen- and nitrogen-derived metabolites, collectively termed reactive oxygen species (ROS) and reactive nitrogen species (RNS), produced in aerobic organisms. The accumulation of these reactive FRs beyond the capacity of the endogenous antioxidant defense system results in damage to proteins, lipids and DNA (fragmentation, base modifications and strand breaks) with a wide range of biologically destructive effects that compromise cell function, leading to cell death via apoptosis or necrosis (1, 2).

ROS play an important role in the pathogenesis of several diseases during the perinatal and neonatal period, also in the pathophysiological processes of renal diseases (3). Foetuses and preterm neonates are more vulnerable to oxidative stress (OS) damage than full-term infants due to organ structural and functional immaturity, overloading of aerobic metabolism with rapidly growing energy demand, excessive ROS production, and the lack of antioxidant systems that come to maturity during the first year of life (4). The combination of immature antioxidant defence systems and elevated levels of ROS place the infant at increased risk for oxidative damage (5).

Recent studies also elucidate the role of OS in neonatal renal damage. In neonates, in particular if preterm, OS is triggered by oxygen therapy during neonatal reanimation and stabilization, and the known inadequate detoxifying mechanisms of neonates. Newborn infants are highly susceptible to renal ischemia, and when OS is prolonged and persistent, acute tubular or cortical necrosis develops with further parenchymal edema and sloughing of necrotic tubular epithelial cells into the tubular lumen. Possibly, it is all due to the immaturity of the newborn kidney at the time of birth with continuation of functional maturation in the postnatal period (6). In particular, OS mediates a wide range of renal impairments, from acute renal failure, rhabdomyolysis, obstructive nephropathy, hyperlipidemia, and glomerular damage to chronic renal failure and hemodialysis (6).

Nephrogenesis is usually completed at about 34-36 weeks' gestation. Therefore, preterm neonates, particularly vulnerable to OS as they possess low concentrations of antioxidant molecules, are often born at a time when nephrogenesis is still ongoing.

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In children born preterm, increasing frequency of reduced kidney size, impaired renal function, and hypertension indicate that renal development may be impaired after birth (7). Besides, these neonates, compared to older infants, have certain physiological characteristics that increase the potential risk of acute kidney injury, including major susceptibility to hypo-perfusion, higher vascular resistance, elevated plasma renin activity, and decreased reabsorption of sodium in the proximal tubules (8).

Clinical and experimental evidence of renal damage mediated by oxidative injury can be grouped under glomerular, tubulo-interstitial, and endothelial modification (9, 10). Oxidative noxa may alter both the structure and function of the glomerulus, mainly because of the effect of ROS on mesangial and endothelial cells. The glomerulus is considerably more sensitive to oxidative injuries induced by hyperlipoproteinemia, mainly associated with the glomerular accumulation of low-density lipoprotein (LDL), than other nephron segments, such as the proximal tubule (11, 12).

Both native and oxidized (LDL-ox) forms of LDL may be involved in the pathogenesis of the glomerular damage mediated by OS. Subsequently, oxidation of LDL by mesangial cells could occur, thereby activating the apoptosis pathway of endothelial cells, mesangial cells proliferation and leukocyte infiltration, all processes that culminate in the final and irreversible condition of glomerulosclerosis (13).

Authors have observed that ROS production, as detected by dichlorofluorescein fluorescence in vital sections of the cortex, was significantly higher in the kidney of pups exposed to lipopolysaccharide (LPS) as compared with controls, revealing that the main damaging effect was related to OS induced by LPS (14). Although the molecular mechanisms involved in the apoptosis of resident cells during renal diseases have not been clarified, other molecules, including hydrogen peroxide, participate in the initiation of the glomerular cell apoptosis pathway (15).

Another mediator of renal damage by OS is TGF-ß, a noted cytokine involved in angiogenesis, inflammation, modulation of protease activity, and apoptosis. This molecule also affects a number of extracellular matrix proteins, such as collagen, fibronectin, and elastin, inhibiting their degradation and stimulating synthesis of their receptors. Consequently, this cytokine plays a key role in progressive renal fibrosis through the accumulation of extracellular matrix proteins by glomerular epithelial, mesangial, and tubular epithelial cells (16-18).

Oxidative injury is associated with proximal tubule injury in kidneys of neonates. It has been documented that an early life exposure to hyperoxia in rats leads to hypertension and a 25% reduction in nephron number in adulthood. Furthermore, hyperoxia also creates mild increases in renal tubular necrosis, dilatation, regeneration and interstitial inflammation (19).

Innovative approaches to identify early neonatal renal damage using specific urinary biomarkers have emerged over the past few years, showing great promise for developing prevention therapeutic strategies; although several studies have shown that some urinary biomarker concentrations depend on gestational age and birth weight (20). Biomarkers most frequently explored in both term and preterm infants include neutrophil gelatinase-associated lipocalin, cystatin C, interleukin-18, and kidney injury molecule-1 (21).

The critical perinatal susceptibility to OS could indicate that a prophylactic use of antioxidants could help prevent or at least reduce OS-related diseases in newborns. Antioxidants may play a key role against glomerular inflammatory processes, through a diminution of the activity of inflammatory enzymes and cytokine secretion, or by inhibiting their activity (22).

It has been documented that selenium deficiency induces renal OS and renal injury via TGF-ß, and that selenium supplementation prevents OS and structural injury, thereby underlining the role of selenium-dependent glutathione peroxidase activity in renal antioxidant defenses (23).

Recently, the use of antioxidant melatonin has been increasingly proposed as an agent to counteract OS (24). The protective role of this indolamine has been reported in various experimental models of tissue damage by reducing OS and lipid

peroxidation. Due to its liphophilic properties, melatonin can easily cross cell membranes and displays a direct scavenger activity against ROS and RSN. Many of its actions are produced through activation of melatonin receptors, while others are due to its role as a powerful antioxidant with a key role in the protection of nuclear and mitochondrial DNA. High-affinity melatonin receptors located primarily in the kidney, blood vessels, eye, brain, and gastrointestinal tract have been documented (25). Authors reported the protective effects of melatonin on partial unilateral ureteral obstruction induced oxidative injury in rat kidney mediated via reduction in the expression of iNOS, p38-MAPK, and NFkB (26). Besides, it has been observed that melatonin can reduce organ damage during renal ischemia/ reperfusion by increasing glutathione and reducing lipid peroxidation in the early and late reperfusion phase (27).

Melatonin, as adjuvant therapy, has been widely used for decades in some countries and no long-term toxicity has been reported. Melatonin has shown to be effective in studies performed on neonatal disorders characterized by excessive inflammatory reaction and oxidative damage (28). Moreover, it has an excellent biosafety profile and therefore, due to its wide spectrum of properties, would appear to be a potentially beneficial molecule for therapeutic uses in the management of neonates with OS-related disorders. Numerous studies agree that short-term melatonin therapy is highly effective in reducing complications in the neonatal period with a remarkably benign safety profile, even when neonates are treated with pharmacological doses (29-33). No animal study of antenatal or postnatal melatonin treatment has shown any serious side effects (34) and no significant toxicity or treatment-related complications with long-term melatonin therapy in children and adults have been reported (35). Thus, melatonin could be considered as a synergic treatment and might result in a wide range of health benefits, helping to limit complications during this critical period.

Additional studies and biochemical investigations are required to define the most effective antioxidant co-therapies and to better specify the molecular mechanisms of their beneficial actions to reduce renal damage mediated by oxidative injury, to treat it promptly with all the medical devices in possession and to mitigate its progression.

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CARDIAC DYSFUNCTION IN CHILDREN WITH ESSENTIAL OBESITY: PRELIMINARY DATA

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Obesity in children has been recognized as a major underlying factor of the pathogenesis of several diseases and a reduced life expectancy. This study aims to verify if clinical parameters, such as waist circumference and/or body mass index and biohumoral and inflammatory parameters can help predict cardiac structural and functional alterations, through an echocardiogram test in obese children and adolescents. Children were prospectively enrolled at the AUOC outpatients' department of Emergency Paediatrics, University Hospital, Messina, from June to December 2017. Clinical, metabolic parameters and an inflammation marker (HMGB1) were evaluated and a transthoracic echocardiogram was carried out. Twenty-two obese subjects were prospectively enrolled.HMGB1 values were 12.6 ± 2ng/ml, significantly higher compared to a previously studied healthy control group. A significant positive correlation was found both between total cholesterol levels and HMGB1 values (r=0.846, p=0.000) and between LDL cholesterol and HMBG1 values (r=0.663, p=0.001). No correlation was found between clinical, biohumoral and echocardiograph parameters. In obese children cardiac parameters obtained from echocardiogram tests may be in the normal range. However, other parameters may be altered in the early phase, showing that infantile obesity can compromise myocardial functions, even in the absence of comorbidities. Furthermore, the evaluation of concentrations of HMBG1 could explain how an initial inflammation can trigger the condition of meta-inflammation.

Obesity in children, defined as a body mass index (BMI) at or above the 95th percentile for age and sex (1) and characterized by an increase in body weight that results in excessive fat accumulation, has been recognized as a major underlying factor of the pathogenesis of several diseases (e.g., metabolic

Key words: obesity; children; HMGB1; echocardiogram test; inflammation

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syndrome, diabetes mellitus, idiopathic intracranial hypertension, nocturnal enuresis, cardiovascular and liver diseases, and cancer) (2-4), all-cause mortality, and a reduced life expectancy (5, 6).

Since the mid-1980s, obesity and attendant co-morbidities have been an emergent problem in public health, in both developed as well as developing countries (7). Moreover, it has been reported that children and adolescents who are obese are likely to be obese as adults (8) and are therefore more at risk for adult health problems (9).

Literature reports on an increased risk of developing cardio-vascular disease (CVD) in obese children and adolescents, above all if concomitant with arterial hypertension, dyslipidaemia, insulin-resistance (IR) or type 2 diabetes mellitus (T2DM) (2).

The study aims to verify if clinical parameters, such as waist circumference (WC) and/or BMI, and biohumoral and inflammatory parameters can help predict cardiac structural and functional alterations, on carrying out an echocardiogram test in obese children and adolescents.

MATERIALS AND METHODS

Children and adolescents included in this study were prospectively enrolled at the AUOC outpatients' department of Emergency Paediatrics, University Hospital, Messina, from June to December 2017. Criteria for inclusion were:

1) Caucasian children and adolescents;

2) Age between 6-16 years old;

3) Simple obesity (BMI >+2.0SD);

4) Absence of systemic, renal, cardiac, endocrine, neuropsychiatric and genetic disease.

Information on medical history were collected for all subjects, after obtaining informed consent from parents, and a complete clinical exam carried out, following study protocol. The patients were weighed, undressed, on precision weighing scales; height was measured in an upright position, barefooted, using a wall stadiometer (SECA Modell 220).

BMI was calculated in Kg/m^2 and compared with standards for gender and age (10). WC was measured with patients in an upright position, after normal exhalation, with a tape measure half way between the lower rib margin and the top of the iliac crest (11). BIM and WC were transformed into z-scores and compared with standard measurements for gender and age (12). Obesity and abdominal obesity were defined as >+2.0 SD. Blood pressure (mmHg) was evaluated with three measurements using a manual blood pressure cuff, with the patient in a resting position. Systolic and diastolic pressure values were evaluated based on percentiles for gender and age (13).

Metabolic parameters and an inflammation marker were evaluated in the morning, after 12 h overnight fasting, and included blood sugars, insulin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, uric acid, HMGB1 and microalbuminuria. Values obtained were compared with reference values for paediatric age (14, 15). To evaluate insulin resistance (IR) HOMA-IR was used: glucose (mg/dl) x insulin (mU/ml)/22.5 (16); 2.5 was used as cut-off value to distinguish subjects with normal or elevated HOMA-IR(17). Hyperinsulinism was defined as fasting insulin >15mU/ml.

A transthoracic echocardiogram was carried out. For all subjects enrolled in the study, images were obtained for the 4 chambers of the heart, wall thickness of the interventricular septum, thickness of the posterior left ventricle and diameter of left ventricle; the results were evaluated comparing them to the American Society of Echocardiography's Guidelines (17). A colour Doppler transthoracic echocardiogram was obtained using the Hitachi Aloka, Arietta s60, Hitachi Europe, echocardiograph. B-Mode images were obtained of the parasternal short axis view at papillary muscle level. M-mode images were obtained of the parasternal long axis view. 2-D and 3-D data were acquired for all patients:

- Left ventricle: end-diastolic diameter, wall thickness of interventricular septum, posterior

wall thickness, relative wall thickness, 4 chamber (CH) ejection fraction;
- Left atrium: 4CH end-diastolic area, indexed end-diastolic volume;
- Tricuspid valve: tricuspid annular plane systolic excursion (TAPSE);
- Aorta: ascending aorta diameter, diameter of aortic sinuses.

All cardiac dimensions and left ventricular systolic and diastolic functions were evaluated following the American

Society of Echocardiography Guidelines (18). Statistical analysis was performed with NCSS for Windows (version 4.0) and data are expressed as median, mean and SD (M±SD). Spearman's test was carried out, considering <0.01 significant.

RESULTS

Twenty-two obese subjects (22M) were prospectively enrolled between the ages of 6-15.9 years (median 10.6): weight ranged from 43.6 to 87.7 (median 55.2); BMI was between 24 to 31.5 (median 27) +2.1 and +3.9 SD (median 2.8); WC was 50 to 92.4 cm (median 27). Systolic blood pressure was from 120 to 131 mmHg (median 126.5) and diastolic from 75 to 84 mmHg (median 80.) HMGB1 values were 12.6 ± 2.7ng/ml (range 10.8- 13.9), which were significantly higher compared to a previously studied healthy control group (3.7±1.2ng/ml) (19).

Patients' results are reported in Table I (clinical), Table II (biohumoral) and Table III (echocardiograph). A significant positive correlation was found both between total cholesterol levels and HMGB1 values (r=0.846, p=0.000) and between LDL cholesterol and HMBG1 values (r=0.663, p=0.001). No correlation was found between clinical, biohumoral and echocardiograph parameters.

DISCUSSION

Infantile obesity is a major risk factor for developing diabetes mellitus T2 and cardiovascular disease (CVD) in adult age. In young adults, it has been shown how early cardiac dysfunction

Table I. *Clinical Data.*

	Mean	Median	Standard Deviation	PERCENTILES	
				25°	75°
AGE (years)	10.80	10.65	3.08	8.15	13.93
WEIGHT (kg)	63.18	55.25	23.51	43.63	87.75
BMI (kg/m²)	28.18	27.05	4.91	24.00	31.48
BMI-SD	2.89	2.85	.53	2.50	3.25
SBP (mmHg)	127.09	126.50	8.54	120.00	131.25
DBP (mmHg)	79.18	80.00	5.65	75.00	84.25
WC (cm)	80.61	78.00	11.01	70.00	92.38
WC-DS	3.53	3.40	.81	2.98	4.05

Table II. *Biohumoral Data.*

	Mean	Median	Standard Deviation	PERCENTILES	
				25°	75°
Glucose (mg/dl)	86.18	86.50	8.76	79.00	90.25
IRI (µU/ml)	14.27	12.65	5.85	10.45	17.13
HOMA-IRI	3.03	2.80	1.20	2.28	3.60
GOT (UI/l)	21.6	23.00	5.63	16.75	25.50
GPT (UI/l)	22.00	18.50	11.74	13.50	26.75
GGT (UI/l)	12.68	12.50	4.40	9.00	14.50
TOTAL CHOLESTEROL (mg/dl)	168.64	169.00	22.75	145.25	186.50
CHOLESTEROL-HDL (mg/dl)	52.68	51.00	13.66	43.25	60.25
TRIGLYCERIDES (mg/dl)	82.64	69.00	36.16	54.00	105.00
PCR (mg/dl)	.41	.35	.27	.18	.63
FT4 (µg/dl)	11.32	11.05	1.80	10.28	12.27
TSH (µUI/ml)	2.62	2.45	1.14	1.88	3.05
CREATININE (mg/dl)	.54	.55	.11	.48	.60
SODIUM (mEq/l)	138.32	138.50	2.50	136.00	140.00

Table III. *Echocardiograph data*.

	Mean	Median	Standard Deviation	PERCENTILES	
				25°	75°
TD DIAMETER (mm)	39.77	39.50	4.33	36.00	42.00
LV-IVS (mm)	6.91	7.00	1.11	6.00	8.00
POSTERIOR WALL (mm)	6.86	7.00	.71	6.00	7.00
RWT	.34	.34	.02	.33	.35
EF (%)	64.55	65.00	1.97	64.75	65.00
TS AREA (cm²)	13.84	14.00	1.95	12.88	15.00
AA DIAMETER (mm)	22.73	23.00	3.03	20.00	25.25

is associated to hypertension, obesity, and IR, while few studies have been published regarding paediatric age. It has shown how continued obesity in paediatric age can induce morbidity and mortality in adult age (20). Obesity leads to dilation of the left ventricle (LV), increasing LV filling pressure. Due to the stress load, the volume of the dilated chamber causes the left ventricle wall to thicken, in a non-proportional way. Consequently, the myocardium compensates by increasing its contractile muscle cells, and therefore the myocardium mass; the end product of this process is ventricular hypertrophy. LV hypertrophy is a determining risk factor for many CVDs in obese children.

Obesity not associated with hypertension may be a clinical condition where cardiac function does not have any confounding effects except obesity itself, as in our clinical records. However, a complete clinical approach to the obese child should include measurement of systolic-diastolic blood pressure and heart rate to check for hypertensionat an early phase. Obesity is a determining factor independent of diastolic dysfunction, but physiopathology is still unclear. Endothelial dysfunction, caused by various pro-inflammatory cytokines, free fatty acids, nitric oxide and IR, contributes to CVD in obese children (21).

The present study has shown that infantile obesity is characterized by low level chronic inflammation, observed in the indication of HMGB1 as a marker for inflammation. In particular, we have verified that HMGB1 values were higher compared to healthy control children and, in obese children, correlated with total cholesterol and LDL cholesterol values; an

increase in serum lipids values is a CV risk factor. No other correlation was found between HMGB1 and other biohumoral, clinical and echocardiographic data. Various studies have shown a strong relationship between obesity, BMI and inflammation (22, 23). Metabolic syndrome is a cluster of risk factors for the development of CVD which includes reduced glucose tolerance, hypertension, elevated levels of triglycerides, reduced levels of HDL cholesterol, and obesity. Insulin resistance may lead to structural and functional alterations in the LV. In literature, there are studies which show a statistically significant correlation between LV size and BMI and HOMA-IR obese children (24, 25). A further study reports a significant correlation between HOMA-IR and left atrium end-diastolic volume and LV, with no correlation with IR and BMI (26).

Our study has some limitations which must be mentioned: it is a one-centre study with an extremely small cohort, without a control group. A larger study with a higher number of subjects could reduce this bias and give more reliable results. At the same time, the lack of adult confounding factors (smoking, advanced CVD, chronic conditions, etc.) in our young participants lends a certain advantage in clarifying the interconnections found (27). Early indications of inflammation markers such as HMGB1 may improve prevention strategies and provide a useful tool for the diagnosis and treatment of infantile obesity and its complications.

In obese children and adolescents, cardiac parameters obtained from echocardiogram tests may be in the normal range. However, other parameters may be altered in the early phase, showing that infantile obesity can compromise myocardial functions, even in the absence of comorbidities. An analysis of HMBG1 shows how an initial inflammation can trigger the metabolic process, i.e. a meta-inflammation. This should encourage paediatricians to deal with this public health issue.

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HEMODIALYSIS IN CHILDREN: HOW, WHEN AND WHY

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End-stage renal diseases requiring chronic dialysis are rare in childhood and adolescence, but they are associated with high mortality and impaired quality of life (1, 2). The most common disease that causes chronic kidney disease (CKD) is primary glomerular disease (GD), followed by congenital abnormalities of the kidney and urinary tract, cystic, hereditary or congenital disorders and, more rarely, secondary GD. However, patients with secondary GD, urologic disorders, and metabolic diseases have greater mortality risk than patients with primary GD (3). Here, we focused on the different options of treatment available, and specifically we compared peritoneal dialysis and hemodialysis, showing pros and cons between them.

Transplantation is the choice of primary treatment in children with end-stage renal diseases but waiting times for donor kidney transplants may be long (4). While waiting for the transplant or when it is not possible, peritoneal dialysis (PD) or hemodialysis (HD) are available (5,6). The registry data showed that mortality is 4 times greater in children younger than 5 years old at dialysis initiation compared to older children, and 1.5 times greater in dialysis children started 5 to 12 years compared to older children (3, 7).

Hemodialysis

HD principles are similar for adults and children, but there are technical aspects of the procedure and complications that are unique to the pediatric population.The extracorporeal circuit consists of arterial and venous lines and the dialyser. High quality vascular access is essential. In children, there are three types of vascular access that can be used: native arterio-venous fistulas (AV), central venous catheters with subcutaneous tunnel (CVC) and synthetic AV grafts. The arterio-venous fistula (AV) is preferable to a CVC due to the lower risk of infections, longer duration over time and lower hospitalization. Although the CVC with tunnel is a temporary access, it is the most used, especially for starting HD (8). Synthetic AV grafts is the last option when other accesses have failed or when the child weigh is less than 15 kg.

Key words: kidney disease; transplantation; hemodialysis; peritoneal dialysis

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Dialysers and lines should be adapted to the size of children. A child can tolerate 8-10% of the total blood volume in the extracorporeal circuit. However, in some infants, even the smallest circuit may exceed the safe limit of extracorporeal volume (9).

Conventional HD is usually performed in the center three times a week for 3-5 h per session. It is known that the intensified dialysis session with a longer dialysis time, such as a nocturnal program, or with more frequent short daytime sessions, results in better control of blood pressure, phosphate, nutrition and growth. Furthermore, the development of new simpler dialysis machines allows the use of home intensified HD as an option for children with appropriately educated caregivers (10).

The main cause of death in children on dialysis is cardiovascular disease (CVD). Hypertension, due to excess fluid, is the most important CVD risk factor. Some authors reported that 60-70% of children on dialysis received antihypertensive medication (11). Frequently pediatric dialysis patients had also left ventricular remodeling and hypertrophy. Another complication associated with an increased risk of death is malnutrition.Guidelines recommend a normal carbohydrate intake and an increase protein intake to restore the amino acids loosed into the dialysate (12). Sometimes, either oral or enteral supplementation may be needed. Finally, bone and joint pain and fractures are an almost universal consequence of abnormal mineral metabolism in children on dialysis.

Peritoneal dialysis

The PD offers a cost-effective approach. The benefits of PD include a less restricted diet, the ability to perform dialysis treatments at home and no need for vascular access and repeated venipuncture. The dialysate is introduced through a Tenckhoff catheter positioned surgically into the pelvis, while the peritoneal membrane acts as a dialyzer. Dialysis exchanges can be performed manually or by delivery of the machine (cycler) (13).

Continuous ambulatory peritoneal dialysis (CAPD) is the manual form of PD. In this type of dialysis, the patient or caregiver attaches and inserts a bag of sterile dialysis fluid into the peritoneal cavity four times a day, followed, after a time generally no less than 5 hours, by draining the dialysate.

Automated peritoneal dialysis (APD) employs the use of a cycler. It is the preferred mode for pediatric patients because it allows a wide range of treatment options (intermittent nocturnal PD, continuous cyclic PD and tidal PD) and the risk of peritonitis is lower in patients receiving APD compared to CAPD. Generally, multiple automatic exchanges are performed at night while the patient is sleeping. The number of cycles and concentration of the osmotic agent within the dialysate can be adjusted according to the requirements for the removal of toxins and fluids.

Complications of PD can be subdivided into non-infectious, including an increase in intraperitoneal pressure, complications related to the technique or to the catheter and other complications such as pain, hemoperitoneum, Encapsulating peritoneal sclerosis, malnutrition and metabolism problems, and infectious complications such as peritonitis and catheter infections (14).

DISCUSSION

Despite the technical progress that has facilitated the treatment of even younger children, dialysis should be considered a second-choice renal replacement therapy, due to high morbidity and mortality that increases with decreasing age and is maximal before the age of two.Moreover, risk of death is highest during the first year of dialysis. Mortality does not depend on dialysis modality, while it is influenced by the type of diseasecausingend-stage renal disease (ESRD), (with glomerulonephritis having the worst prognosis), the presence of comorbidities, low socioeconomic status and access to transplantation.

Although, PD is the most common dialysis treatment modality used to treat pediatric patients, HD is recommended as first option in infants with metabolic disorders and those with clinical contraindications for PD. Furthermore, it is necessary to consider both the immediate impact and the potential long-term sequelae of central vascular access positioned precociously in HD patients, especially in infants.

As for morbidity, growth retardation and cardiovascular involvement, due to mineral and bone disorder, are the major cause of concern. Several studies have shown that in children many cardiovascular risk factors related to dialysis are modifiable (9).

The treatment of bone disorder is not easy, both with the risk of calcium deficiency, which means greater risk of fracture, than for excess of calcium, which seems related to vascular calcification. Growth can be optimized by paying attention to the correction of fluid, electrolyte and acid-base balance, metabolic bone disease, anemia, nutrition, and growth hormone resistance.

In conclusion, children have special needs and characteristics that they must consider carefully when dialysis begins. For now, no comparative study suggests the superiority of PD or HD in the outcome of children with ERSD. Considering pros and cons between HD and PD, dialysis mode should be chosen based on patient and family preferences, core philosophy and availability of desired mode.

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LOCAL THERAPY WITH OZONE IN THE MANAGEMENT OF THE EXIT SITE IN A PATIENT UNDERGOING PERITONEAL DIALYSIS

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The natural history of children with end stage renal disease is dialysis until a transplant can be done. There are two types of dialysis: hemodialysis and peritoneal dialysis (1). Peritoneal dialysis is preferred in young children because getting the vascular access for hemodialysis is challenging (2). Catheters should be surgically placed in a paramedian or lateral abdominal region with an extremity located in Douglas' pouch.

Infection is one of the most significant complications of pediatric peritoneal dialysis (PD). The 2017 Annual Data Report from the United States Renal Data System (USRDS) reported that infection is the primary cause for hospitalization and the second-most common cause of death in children receiving PD (3). Peritonitis is the most common significant complication of CPD (Chronic peritoneal dialysis) in the pediatric population (4, 5). Peritonitis contributes to major morbidity because of loss of peritoneal membrane function and technique failure, especially in children with recurring episodes of infection (6, 7). Peritoneal dialysis catheter exit site and tunnel infections are a serious cause of peritonitis and catheter failure (8).

A multicenter quality improvement study directed from 2011 to 2014 described a rate of exit site and tunnel infections of 0.25 per dialysis year (8). In this study, peritonitis evolved in 6 percent of the cohort, and catheter removal was demanded in 9 percent of the cases.

Treatment of catheter exit site infections generally consists of oral antibiotics in line with culture results. Intraperitoneal antibiotics are included only if improvement is not seen rapidly. Prevention of exit site infections is the main goal of exit site care, which consists of aseptic care, daily valuation and disinfecting of the exit site and confinement of the catheter. Cleansing should be achieved with a non-cytotoxic and non-alcoholic antiseptic agent, such as sodium hypochlorite or chlorhexidine.

For many years, the ozone, a highly unstable gas with strong oxidizing power, has been used for medical treatment. Its intense oxidizing capacity has been tested in order to demonstrate its disinfectant and sanitizing properties (9). Ozonides are a class of chemical compounds in which ozone is stabilized by the reaction with unsaturated fatty acids of oils. Ozonides have been used as local formulation with germicidal effects (10). Ozonated olive oil has been reported to be non-toxic, accelerate wound

Key words: end stage renal disease, pertonealdyalisis, peritonitis, ozonated olive oil

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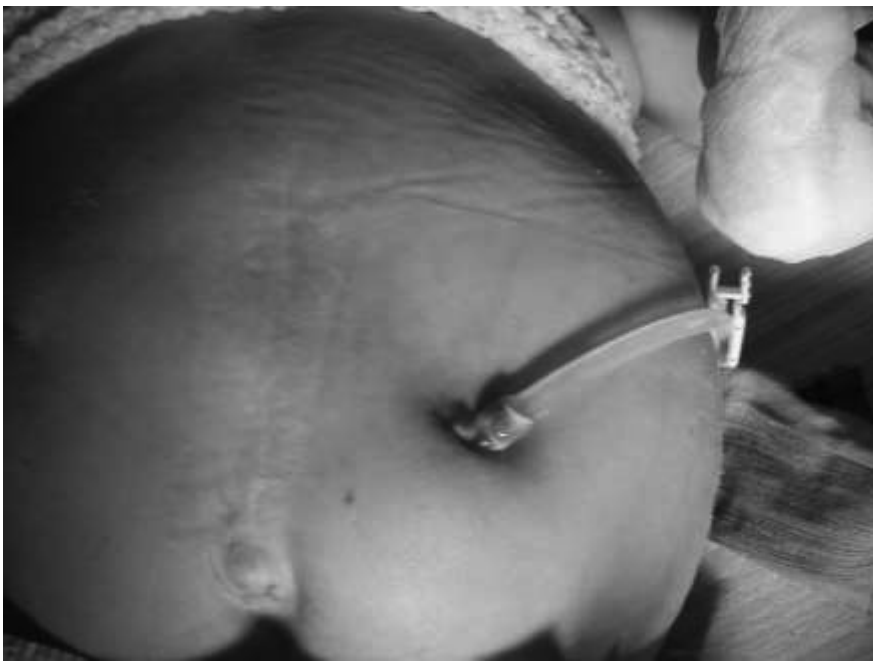

Fig. 1. *Exit site in a 4- year old child affected byrenal cystic dysplasia treated with peritoneal dialysis.*

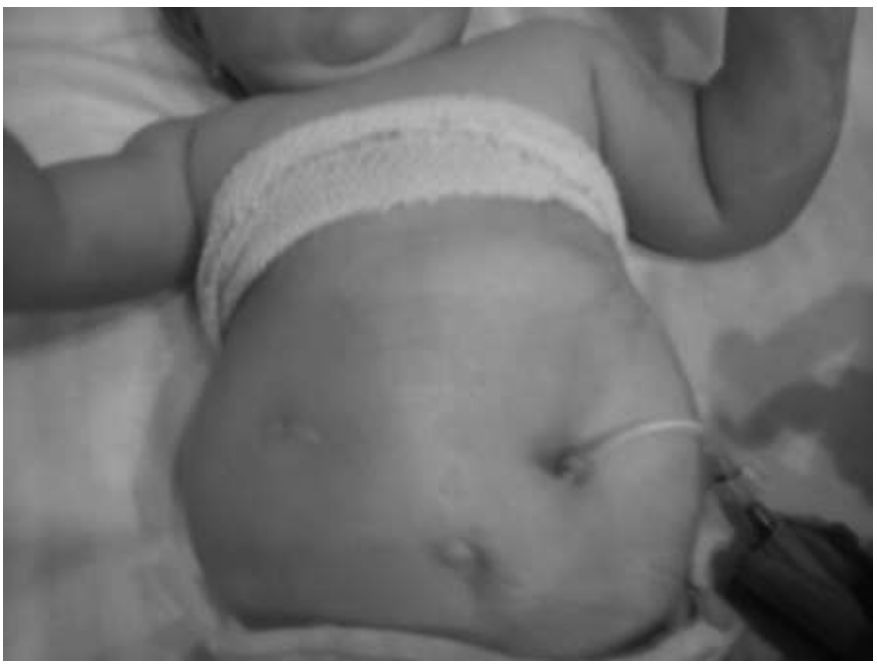

Fig. 2. *Exit site after one-week treatment with ozonated olive oil/vitamin E acetate.*

healing and utilize anti-inflammatory effects (11). In contact with skin and mucosae, ozonated olive oil, in environments such as ischemic, hypoxic, or damaged tissues, releases molecular oxygen inducing the production of radical species with production of moderate oxidative stress. These effects stimulate the liberation of growth factors, activation of local antioxidant mechanisms, and tissue repair (12). Some studies have revealed the therapeutic use of ozonated oil on skin disease (13, 14).

In end stage renal disease, patients undergoing peritoneal dialysis in our center were set a protocol that includes the use of ozonated olive oil/vitamin E acetate to treat damaged skin in case of inflammation, itching and redness in order to promote tissue regeneration.

We want to report a case of a 4-year-old child affected by renal cystic dysplasia treated with peritoneal dialysis. Based on the assumption that catheter-related exit site infection is a major risk factor for the development of peritonitis, we initiated the protocol mentioned above once noticed inflammation around the exit site. After cleansing the exit site with 0.9% sodium chloride solution, we covered the area treated with a sterile bandage soaked in ozonated olive oil/vitamin E acetate. This medication was carried out every other day. The following figures show the exit-site before (Fig.1) and after one week treatment with ozonated olive oil/vitamin E acetate (Fig. 2).

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LAPAROSCOPIC NEPHRECTOMY IN CHILDREN WITH WILMS TUMOR. CONSIDERATIONS AFTER 10 YEARS OF EXPERIENCE

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Despite laparoscopy in children is considered safe and is routinely used for several procedures, even in neonates and in pediatric oncology, its role in the treatment of pediatric renal tumors is still controversial. This study analyzes the results of laparoscopic nephrectomy for Wilms Tumor (WT) in pediatric age compared with open nephrectomy after 10 years of experience in a single centre. From 1993 in our center of reference for pediatric oncology, 30 patients with WT have been treated. We performed 21 open nephrectomy and in the last 10 years 9 laparoscopic nephrectomy. In all patients treated laparoscopically, the same technique made by the same equip was used. Compared with patients treated by open surgery, we did not find a significant difference in terms of outcome and survival. In the open surgery group, two patients had lung relapse while in the other group there was one local relapse. These three children obtained and maintained a second complete remission with chemotherapy. Open surgery complications were a tumor rupture in two cases, and an episode of pancreatitis 10 days after surgery. In the laparoscopic group, there were two conversions to open surgery not considered as complications but a surgical choice for cystic areas present in the tumor. As far as complications and oncologic outcomes are concerned, both techniques showed similar results. In experienced hands, laparoscopy proves to be an attractive alternative to open surgery for pediatric renal tumors.

Laparoscopy in children has been used for 20 years now and is considered a safe approach for several procedures, even in pediatric oncology as biopsy and excision of adrenal neuroblastoma or metastasis (1-4). Nonetheless, its role in the surgical treatment of pediatric renal tumors is still controversial. To date the literature reports only a few articles about laparoscopic nephrectomy for renal tumors. In 2006 and 2009

Key words: Wilms tumor, nephrectomy, laparoscopy

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(5, 6), Duarte et al. first reported on laparoscopic nephrectomy in a series of patients with Wilms' Tumor (WT) as a safe and feasible method in pediatric age. In the same period, only a few centers started to perform laparoscopic radical nephrectomies in children with renal cancer and from that date only a small series have been reported (7-10). Particularly, Romao et al., published a retrospective cohort study of 45 children treated for primary renal tumors (11). Moreover, Laparoscopic nephrectomy (LN) has been successfully used to treat unilateral metastatic (12), non-metastatic (5, 6, 13-15) and juxtarenale WT (16) after preoperative chemotherapy. However, the laparoscopic approach remains poorly developed due to the fear of complications such as tumor rupture, that could increase the risk of peritoneal dissemination and subsequent local recurrence, thus increasing the burden of adjuvant therapy. The criteria for the use of laparoscopy in WT have not been defined yet. It has been suggested to include tumor dimensions smaller than or equal to 10% of the patient's height (6), a good shrinkage of the tumor with neoadjuvant chemotherapy, and non-centrally located tumors (15).

A randomized multicentric trial, including a very large number of cases and comparing laparoscopy with open surgery might be suitable to clarify the efficacy and long-term outcome. In our retrospective analysis of children with WT, successfully treated with laparoscopic nephrectomy, we describe the characteristics of the patients and the tumors,

Table I. *Laparoscopic data.*

Age (y)	7,06	10,5	1,8	1,8	5,01	2,05	1,5	5,1	9,1
Stage	III	II	III	II	III	I	III	I	I
Side	Left	Left	Left	Left	Right	Right	Left	Left	Right
Weight (gr)	170	235	400	unknown	250	unknown	unknown	unknown	unknown
Diameter at diagnosis pre- chemio (cm)	16	5	13	8.2	14	7.8	6.6	7	5.5
NAC	Yes	No	Yes	No	Yes	No	No	Yes	No
Diameter post NAC	13	NA	8.5	NA	7	NA	NA	3.5	NA
Histological diameter (cm)	13	5	8.5	8.2	7	8	5.8	3.5	unknown
Lymph node sampling	2	1	1	2	3	2	1	1	unknown
Surgery Time (min)	250	270	240	190	240	180	120	130	120
Bowel activity (days)	3	2	1	1	1	2	2	2	2
Hospitalization (days)	8	8	7	5	7	8	7	5	7
Conversion in open	No	Yes	No	No	No	Yes	No	No	No
Relapse	No	No	No	No	Yes, local	No	No	No	No
Outcome	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive

(NAC: neoadjuvant chemotherapy).

including follow up as well as outcome analyzing risks and benefits compared with patients treated by open nephrectomy, in an attempt to determine which technique could be more appropriate in specific patients. Finally, we attempted to identify the best choice for laparoscopic nephrectomy.

MATERIALS AND METHODS

This retrospective analysis includes all the children with unilateral WT operated by laparoscopic nephrectomy at our institution from 2007 to 2017 (Table I). Data collected include: preoperative information such as age, tumor size, neo-adjuvant chemotherapy; intra-operative details, such as extension of tumor and the number of lymph nodes sampled; postoperative data, such as tumor histology/staging, pain treatment, length of hospital stay, short- and long-term surgical complications, length of follow-up and recurrence (Table II). Indications for laparoscopy were based on the operating surgeon, tumor size, and surgeon's advice about the feasibility of the procedure based on preoperative imaging studies, child's age and family agreement. This latter was obtained through informed consent following full disclosure of risks, the potential benefits and paucity of pediatric data for laparoscopic resection.

Technique

Laparoscopy was performed using general endotracheal anesthesia. The patient was placed in

Table II. *Clinical data laparoscopic and open group.*

Variable	Open surgery (n= 21)	Laparoscopy (n =9)
Age, median (range)	3.81 years (0.55–8.41)	5.01 years (1.59-9.15)
Gender, n (%) Male	9 (42.85%)	6 (66.6 %)
Female	12 (57.15%)	3 (33.4%)
Stage, n (%) Stage I	7 (33.3%)	3 (33.3%)
Stage II	4 (19.04%)	2 (22.2%)
Stage III	6 (28.6%)	4 (44.4%)
Stage IV	4 (19.04%)	0 (0%)
Right tumor, n (%)	10 (47.6%)	3 (33.3%)
Left tumor, n (%)	11 (52.4%)	6 (66.6%)
Neo-adjuvant chemotherapy (%)	7/21 (33.3%)	4/9 (44.4%)
Pre chemoterapy size, median (range)	12.5 cm (8.2-19)	13.5 cm (7-16)
post chemoterapy size, median (range)	6.75 cm (4-9)	7.75 cm (3.5-13)
Surgery time median, (range)	185 minutes (95–270)	193 minutes (120-270)
Median tumor size after surgery, n (range)	10 cm (4.5-16)	7.5 cm (3.5–13)
Adrenal gland spared, n (%)	18 (85.7%)	9 (100%)
Lymphnodes sampled, n patients; median (range)	11; 1.5 (1-11)	8; 1 (1-3)
Complications	1 pancreatitis	none
Bowel activity, median (range)	3.5 days (1.1-5)	2 days (1-3)
Days in Hospital after surgery, median (range)	7 days (5-14)	7 days (5-8)
Death, n (%)	0 (0%)	0 (0%)
Relapse, n (%)	Pulmonary 2 (9.5%)	Local 1 (11.1%)

(NAC: neoadjuvant chemotherapy).

supine position and turned 45 degrees to facilitate the procedure. An orogastric tube and a urinary catheter were inserted. An open transumbilical approach was used in all cases for a Hasson trocar insertion. A 12-14-mmHg pneumoperitoneum was created and the abdominal cavity laparoscopically evaluated with 30-degree telescope, before the introduction of the other Trocars, according to tumor location. Generally, three 5mm operative ports were used, one of these always placed along the subsequence Pfannestiel incision (Fig. 1).

Once the tumor was identified, a careful search for other suspect localizations of the disease was performed. Respectability was assessed by evaluating anatomical location, fixation of the tumor and involvement of contiguous organs. Mobilization of the right or left colon was necessary in order to approach the retroperitoneal space. The ureter was identified, ligated just proximal to the bladder with Hem-o-lock clips. Using the proximal arterial stump as a handle, dissection of the posterior and lateral attachments of the specimen was carried out preferably with the LigaSure® device. In all cases, we used an endoscopic stapler or Hem-o-lock clips to close renal vessels. The tumor was dissected and extracted without morcellation through the Pfannenstiel incision made in continuous of a trocar insertion; only in 2 cases endobag due to small tumor size we used were used (Fig. 2). After nephrectomy, a lymph node sampling was performed if required using LigaSure® device. In all cases, an abdominal drain was left in place. We always start the nephrectomy with the section of the ureter that we use as for traction during the renal dissection to minimize manipulation of tumor and reduce the risk of rupture and dissemination. We compared this group of patients with another group treated by open surgery from 1993 to present.

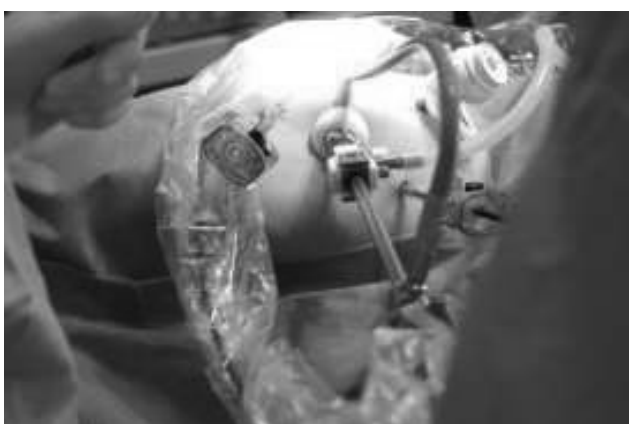

Fig. 1. *Trocars setup for laparoscopic nephrectomy.*

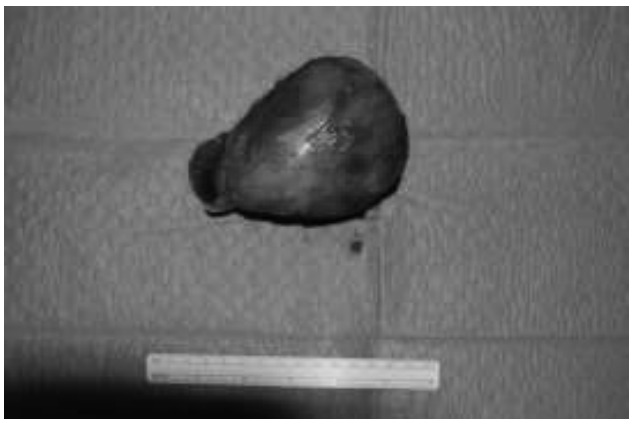

Fig. 2. *Surgical specimen.*

RESULTS

Thirty children were enrolled in the study. We operated 9 patients by laparoscopy, 3 were female, mean age was 4.8 years (range 10.5-1.5). The tumor was on the left kidney in 6 cases. Table I reports their characteristics. Three children were stage I, two stage II and 4 stage III. Only 4 out of 9 children received neo-adjuvant chemotherapy obtaining a significant volume reduction. Due to absence of anaplasia and according to WT 2003 protocol, histology was favorable to all of them and confirmed after revision. Lymph node samples (1-3 per patient) were resected in 8 out of 9 cases and they all resulted negative for neoplasia. Two of these 9 laparoscopic procedures were converted into traditional surgery due to the presence of cystic areas into the tumor in both cases. The group of patients treated with open nephrectomy consisted of 21 children, nine males with median age 3.81 years, (range 0.55-8.41). In 10 patients, the tumor was located in the right kidney. Diffuse one-place was observed in 2 cases. Seven patients (33.3%) were stage I, four stage II (19%), six stage III (28.5%) and four stage IV (19%) for lung metastasis. One stage III case and two stage IV cases presented renal vein thrombosis. One third of all open surgery patients received neo-adjuvant chemotherapy obtaining a significant volume

reduction. Lymph node samples obtained in 11 cases (1-11 per patient) were positive for neoplasia in 3 patients. A tumor rupture in the peritoneal cavity occurred in two cases; in another case, the tumor was contiguous to the liver and consequently the dissection involved the hepatic parenchyma; one patient experienced an episode of pancreatitis 10 days after surgery. The adrenal gland was spared in 18 patients (85.7%). The median weight of tumors resected in open surgery was 375 gr (range 200-1250) while for the laparoscopic group it was 242.5 gr (range, 170-400). Median surgical time was 193 minutes (range 120-270) for the laparoscopy group and 185 minutes (range 95-270 minutes) for the open surgery group.

Patients who underwent laparoscopic treatment had a median time of return of bowel function of 2 days (range, 1-3), with a discharged median on the seventh postoperative day (range 5-8), while in the other group channeling occurred at a median time of 3.5 days (range 2-5) and the discharged median time was 7 days (range 5-14) after surgery. In the open surgery group, two patients had a lung relapse – one stage IV, 1 month after surgery and the other, stage I, two months after surgery. In the other group, there were one local relapse (omentum) 11 months after surgery and 3 months of stop therapy, removed laparoscopically. These three children obtained and maintained a second complete remission with chemotherapy.

DISCUSSION

In the last decade laparoscopy has become a valid alternative to open surgery for many pathologies, including tumor surgery. In general, laparoscopic surgery is an appealing practice because it reduces patient discomfort and hospital length of stay, produces fewer sequelae, less evident abdominal scars and comparable cure rates. To date, it is a method successfully utilized in many centers to treat renal malignancies in adults (16-20). On the contrary, this application has been considered critical in children, particularly for renal tumors. Such diffidence was related to the risk of complications in a setting where traditional surgery had been effective and safe in almost all patients. Consequently, the isolated experience of laparoscopic surgery for WT that appeared about 20 years ago was not welcomed (5-8, 12, 13, 18, 21-23).

A comparison of the two surgical techniques has been reported recently. Romao et al. have conducted a retrospective cohort study on 45 consecutive children nephrectomised for primary renal tumors over a 5-year period; 13 in laparoscopy and 32 in open surgery. After a median follow-up of 18 months for laparoscopic nephrectomy and 33 months for open surgery, there was 1 recurrence among the laparoscopy patients and 4 in the other group, respectively. No tumor ruptures occurred with both techniques, procedure length was similar, while hospital stay and post-operative recovery were shorter for laparoscopic nephrectomy (11).

Duarte et al described 32 children with unilateral WT; 17 were operated in laparoscopy and 15 in open surgery. One case of preoperative rupture was reported in the open surgery group. Transfusions were not required in either group. One out the 17 patients (5.9%) operated in laparoscopy and 2 at the other 15 (13.3%) operated in open surgery presented a local relapse. The 5-year event-free survival rate was better for the laparoscopic group (93.3% *vs* 79.6%) though not statistically significant. Both techniques showed similar immediate and long-term results (12).

Varlet et al. described a retrospective multicentric study of 16 children who underwent laparoscopic radical nephrectomy over a 7-year period. Maximum diameter was 8 cm. With a median follow-up of 42 months (range 12-77), fifteen children had no recurrence, while one had a local recurrence without intraoperative tumoral rupture. No small bowel obstruction occurred. Varlet et al summarized indications for renal tumor surgery: trained laparoscopic surgeons, small tumors under 8 cm of diameter, especially if, at the time of surgery the CT scan does not reveal any crossing of the lateral edge of the vertebra (13).

Our experience spans over a period of 20 years. Obviously, the comparison between 20-year-old cases with recent ones is no easy task, but our main was

not to prove the efficacy and the safe of laparoscopic nephrectomy but to find the right indication to perform it. We have seen some advancement in laparoscopic surgery only in the last 10 years. Even so, when laparoscopic interventions became more frequent, there were still no clear criteria about the choice of the operatory technique. A first remark is that, in our series, the number of patients operated by laparoscopy is not negligible compared to the published series. Unlike the open surgery group, the patients who underwent laparoscopy were younger and their tumor weight was lower, although only less than half of them had received preoperative chemotherapy, according to the "surgery indications" of the Italian protocol AIEOP TW 2003, that we have followed for the last 12 years (24). The three patients with renal vein thrombosis were treated by open surgery. The right kidney was involved in 10 and in 3 patients in the open and laparoscopic group respectively.

Concerning the lymph node sampling, an essential part of Wilms tumor surgery as the histological evidence of tumor infiltration in even one single lymph node makes the case a stage III (25). In our cases, when required the lymph nodes sample was performed by laparoscopy without complications and limitations. The adrenal gland was spared in all laparoscopic patients and in 3 belonging to the open surgery group. The time of intestinal channeling and evacuation was definitely shorter in the patients of the laparoscopy group, which represents a clear advantage. Two cases from the laparoscopy group were converted to open surgery, which did not jeopardize the outcome. Postoperative complications were resolved. Pancreatitis occurred in a child treated with open surgery and a small bowel sub-occlusion presented in another one. Only 1 patient treated with laparoscopy, stage III for infiltrated margins, presented a local relapse treated laparoscopically. In the open surgery group, two patients had lung relapse. The most common pediatric renal malignancy, WT, is well known for presenting with large palpable masses, which render laparoscopic procedures less appealing and tumor rupture more likely in the absence of size reduction with neo-adjuvant chemotherapy.

The protocols for the surgical management of pediatric renal tumors is different in the two big groups, National WT Study (NWTS) and International Society of Pediatric Oncology (SIOP), respectively, applied in north America and in many other countries, particularly in Europe. In North America, patients are routinely treated with upfront surgical resection followed by postoperative chemotherapy and sometimes radiation therapy based on risk stratification which includes surgical staging, pathology and tumor biology information (COG). Conversely, according to SIOP philosophy, preoperative chemotherapy is administered to all patients and then followed by surgical resection. Therefore, at the time of surgery, tumors are usually smaller. Furthermore, chemotherapy often leads to the development of a "fibrous capsule" allowing for a more comfortable handling of the mass and making tumor rupture less likely to occur. This is of great importance in those children who present large renal masses.

Pediatric oncology literature reasons that both protocols have some merit and show acceptable outcomes. Nevertheless, based on stage migration and size reduction, it appears that preoperative chemotherapy could prove potentially advantageous for families and surgeons interested in pursuing laparoscopic resection. Not surprisingly, the largest laparoscopy series to date have followed this approach (5, 6, 8, 12). The fact that this is a single-centre trial and that WT is a rare disease account for the small sample size, impedes to reach reliable conclusions in terms of the safety profile of these procedures and their potential to offer oncological outcomes similar to those of open surgery. This also opens the way to the criticism typical of this kind of study.

The potential benefits of laparoscopic treatment are now well known, the reduction of postoperative pain due to minimal trauma to the tissue, shorter length of postoperative ileus, rapid wound healing, hospital stay and cosmetic damage reduced. Of course, the last two advantages are debatable in children with cancer, but some time to reinstitute chemotherapy faster could be a real benefit. After 10 years of experience, we treated only 9 patients in

our center by laparoscopy because even if there are some advantages and expert hands, the laparoscopic nephrectomy technique is feasible obtaining good results, critical selection of patients is required that we consider as a key point in this treatment.

We would like to formulate some suggestions for the best choice for the laparoscopic approach (Table III). Laparoscopy could be the best choice not only for syndromic patients. The tumor must be monolateral and strictly related to an emisoma to permit the positioning of the trocar and the acceptable working space. The maximum size limit of the tumor is difficult to assess as it depends on the weight of the child. Varlet et al. (13) never treated tumors exceeding 8 cm in diameter by laparoscopy. Nevertheless Duarte et al. (6), and in our experience, resections of tumors up to 13 cm are reported without any complications. Open surgery should be preferred when the CT scan does not reveal any crossing of the lateral edge of the vertebra (13). An evident volume reduction after neoadjuvant chemotherapy could be an indication for laparoscopy.

Due the lack of guidelines and recommendations, we believe it could be useful to reduce the indication of laparoscopic nephrectomy for small and non-cystic tumor. All oncological criteria must be respected during laparoscopic surgery, the sampling of linphonode, if required, could be performed with accuracy with the use of an energy devise. The abdominal cavity exploration to find small peritoneal tumor implants is essential (especially in the deep pelvis).

Contraindications for laparoscopy, and sometimes for open surgery, include caval or renal thrombosis, tumor rupture (even if peritoneal metastases could be removed under laparoscopy), necrotic and/or cystic tumors, syndromic patients due to the increased neoplasia trend (WAGR, Beckwith-Wiedemann, Denys-Drash) and bilateral tumors.

Finally, conversion in open surgery must not be considered a failure of procedure if to continue the nephrectomy laparoscopically could represent a risk.

Both approaches showed similar results in relation to complications and outcome. It can therefore be inferred that in experienced hands laparoscopy can be an attractive alternative to open surgery in selected cases of pediatric renal tumors, particularly for early-detected lesions or following chemotherapy. In order to avoid unnecessary complications, trained laparoscopic surgeons can safely perform laparoscopic radical nephrectomy in children with WT or other renal cancer. In the laparoscopy group, the length of surgery and the incidence of intraoperative rupture were not increased; postoperative recovery was quicker and hospital stay short. The main reasons for preferring

Table III. *Suggestions for best selection of patients to undergo laparoscopic nephrectomy in WT.*

No syndromic patients
Position and size of tumor related to only an emisoma
Monolateral tumor
Absence of caval or renal thrombosis at time of surgery
Solid tumor
No tumoral rupture before surgery
No evident necrosis inside the tumor

the laparoscopic approach are to diminish the risk of small bowel obstruction and improve cosmetic results on the abdominal wall in cases of small tumors, which, in addition to the shortened length of hospital stay, contribute to a decrease in the sequelae of WT treatment. A longer follow-up is mandatory to confirm the comparability between the oncological outcomes of laparoscopy with those of conventional open surgery.

The main objective in the future could be to improve laparoscopic procedures in pediatric oncology overall in the treatment on Wilms tumor maintaining safety and efficacy to get better results and respecting where possible the renal parenchima and renal function as reported in literature (26).

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LAPAROSCOPIC TRANSPOSITION OF LOWER POLE CROSSING VESSELS IN CHILDREN WITH EXTRINSIC PELVI-URETERIC JUNCTION OBSTRUCTION: A WORTHY ALTERNATIVE TO DISMEMBERED PYELOPLASTY

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Pelviureteric junction obstruction (PUJO) due to intrinsic or extrinsic causes is a common problem in childhood. Extrinsic compression by a lower pole-crossing blood vessel can present symptomatically in older children. In these cases, laparoscopies Vascular Hitch can represent a valid alternative to pyeloplasty dismembered. We analyzed the data of 4 children affected by extrinsic PUJO treated at our institution with the laparoscopic Vascular Hitch procedure modified by Chapman. Surgical indications included presence of clinical symptoms, worsening of intermittent hydronephrosis, signs of obstruction on the MAG-3 scan, clear or suspected images of polar crossing vessels on CT scan or Uro-MRI. All procedures were completed laparoscopically. No complications occurred. Mean follow-up was 13 months with resolution of symptoms and PUJ obstruction and significant improvement of hydronephrosis in all cases. When blood vessels crossing lower pole represent the pure mechanical cause of UPJ obstruction the laparoscopic Vascular Hitch procedure represents an excellent alternative to dismembered pyeloplasty. It is less technically demanding then pyeloplasty and is associated with a lower complication rate. The main challenge is to intraoperatively ascertain the absence of associated intrinsic stenosis.

Pelviureteric junction obstruction (PUJO) is a functional impairment of urinary transport from the renal pelvis into the ureter. It may be caused by intrinsic disorganization or by extrinsic compression mainly due to a lower pole-crossing blood vessel. Aberrant blood vessels may be responsible for intermittent PUJO; in such cases, there is generally a normal antenatal history, a late onset of clinical signs, intermittent symptoms, intermittent hydronephrosis on imaging and normal renal function.

Nowadays the gold standard in the management of PUJO is Dismembered Pyeloplasty first described by Anderson and Hynes in 1949 (1). An alternative approach to pure extrinsic PUJO was described in the same year by Hellström et al., involving displacement and anchoring the lower

Key words: vascular hitch, extrinsic uretero pelvic junction obstruction, crossing vessels, laparoscopy, hydronephrosis

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pole vessel in a more cranial position on the anterior pelvic wall using vascular adventitial sutures (2). In 1959, Chapman further modified this technique by securing a more superior position of the lower pole vessels within a wrap of the anterior pelvic wall without the need for vascular adventitial sutures. This procedure, easily performed laparoscopically, obviates to open the collecting system, eliminates the need for drainage and ureteral stenting and has shown to be safe, feasible and reliable (3).

MATERIAL AND METHODS

From June 2013 to June 2018, 73 patients affected by PUJO were treated at our institution, 69 of which underwent One-tracer-assisted pyeloplasty (OTAP) or laparoscopic pyeloplasty.

From September 2016 to October 2017, 4 patients (3 boys and 1 girl) affected by extrinsic PUJO were treated with laparoscopic transposition of aberrant crossing vessels (CV).Mean age at presentation was 12 years (range 6-18 years). None of the patients had a prenatal diagnosis of hydronephrosis and were all studied by renal ultrasonography (US) and mercaptoacetyltriglycine (MAG-3) renogram. A patient underwent CT scan locating a polar inferior crossing vessel compressing the renal pelvis, and another one Uro-MRI. Surgical indications included presence of clinical symptoms, worsening of intermittent hydronephrosis, signs of obstruction on MAG-3 renogram, decrease in relative renal function and clear or suspected images of polar vessels on CT scan or Uro-MRI. All patients, except one, presented with intermittent colicky flank pain. In one case the diagnosis was incidental, following a routine abdominal US. All patients had high-grade hydronephrosis (III-IV°) according to the Society of Fetal ultrasound (4) (Table I).

Table I. *Patients' characteristics.*

Patients characteristics	
Patients	n= 4
Age at surgery (years)	12 (6-18)
Male/female	3/1
Side of lesion: right/left	2/2
Initial clinical signs: flank pain/others	3/1
Preoperative US pelvis A-P diameter	43 (20-73)
Preoperative MAG-3 ipsilateral renal function	44% (31-54)

The surgical procedure adopted in all cases was "Hellström Vascular Hitch modified by Chapman" (2, 3). We always used an optical port of 10 mm with a 30° laparoscope and two 5-mm working ports. We preferred a transperitoneal approach that allows a better access to the renal pelvis. By partial ipsilateral colon flexure mobilization or creating a window in the mesocolon, the renal pelvis was exposed. In all cases we found a lower pole crossing vessel (CV) compressing the PUJ (Fig. 1). The CV was mobilized observing a decrease in size of the renal pelvis (Fig. 2).The PUJ was carefully observed to exclude any intrinsic stenosis and free urine passage was noticed through the PUJ after vessel transposition, hydration and IV furosemide administration. A loose wrap of the anterior pelvic wall was created around the vessel using two interrupted 3/0 or 4/0-poly-ethylene terephthalate nonabsorbable sutures (Fig. 3).

RESULTS

All procedures were completed laparoscopically without open conversion. Mean operative time was 100 minutes (range 85-115 minutes). Mean hospital stay was 6.2 days (range 5-7 days). Postoperative course was uneventful in all patients. No complications occurred. Mean follow-up was 13 months (range 9-22 months). All

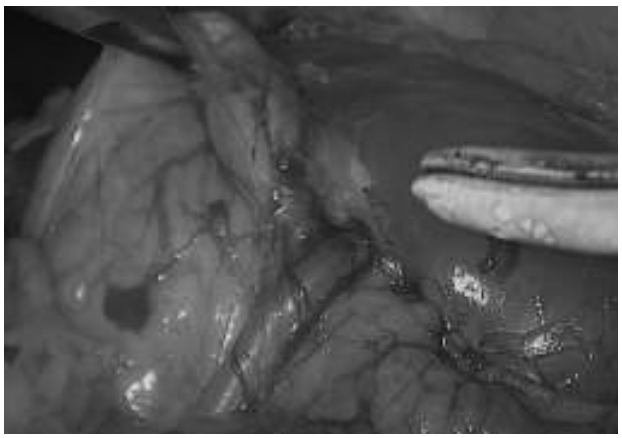

Fig. 1. *View of the crossing vessel.*

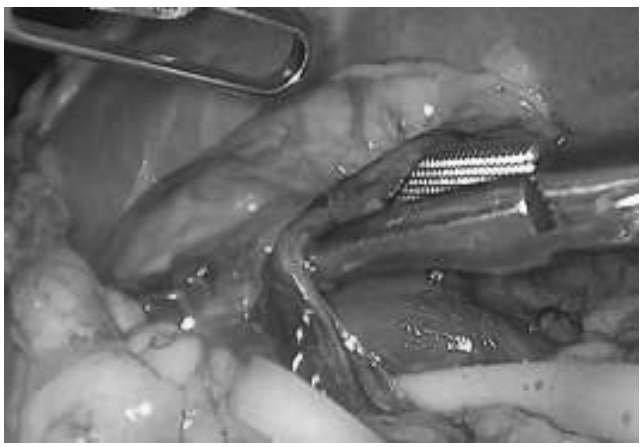

Fig. 2. *Decrease in size of the renal pelvis after CV mobilization.*

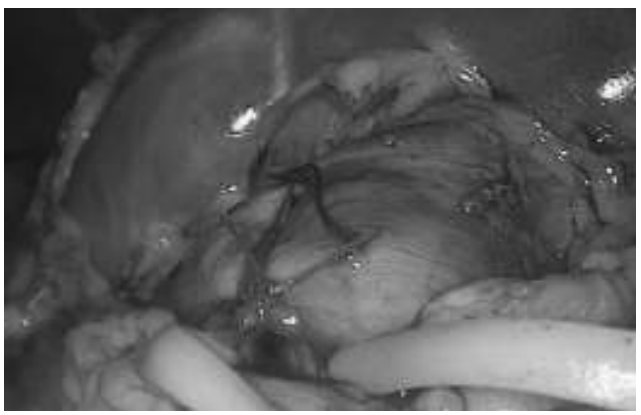

Fig. 3. *Loose wrap of the anterior pelvic wall around the CV.*

patients remained symptoms free during the follow-up period. They were all evaluated with US and MAG-3 scan that showed a significant improvement in hydronephrosis and enhanced drainage in the absence of PUJ obstruction (Fig. 4, 5). The success rate was 100%.

DISCUSSION

The incidence of crossing vessels in the aetiology of PUJO in children has been reported as ranging from 11% to 15% (5), but raise to 58% in a series of older children with symptomatic PUJO and normal prenatal US (6, 7). Dismembered pyeloplasty with the relocation of the vessels posterior to the pelvis, as described by Anderson and Hynes (1), has long remained the standard of care in children with PUJO and lower pole crossing vessels (LPCV). However, there is increasing clinical evidence that some PUJO can be purely due to extrinsic compression. A large proportion of obstructed patients with crossing vessels have minimal hystopathologic changes at the level of the PUJ. This permits to assume that LPCV can be the sole mechanical cause of obstruction (8-10).

The "Vascular Hitch" (VH) approach described by Hellström (2) and modified by Chapman (3) was first reported in children by Pesce in 1999 (11) who treated 61 children by open VH with excellent outcomes. In 2006Godbole et al. (12) first described the use of laparoscopy for this procedure with a successful outcome in up to 95% of 20 patients after a follow-up of 22 months. A series of 70 patients published by Villemagne et al. (10) in 2015 showed a successful outcome in 96% of patients with a median follow-up of 52 months. A few other publications have also reported good results with the complete resolution of symptoms in 95-100% of cases (10, 13-20).The key for success with this technique is appropriate patient selection. A careful clinical history is essential for correct patient choice. LPCV causing extrinsic obstruction generally remains undetected on routine antenatal US. Patients frequently present with intermittent colicky flank pain and with marked hydronephrosis that resolves after they become asymptomatic.

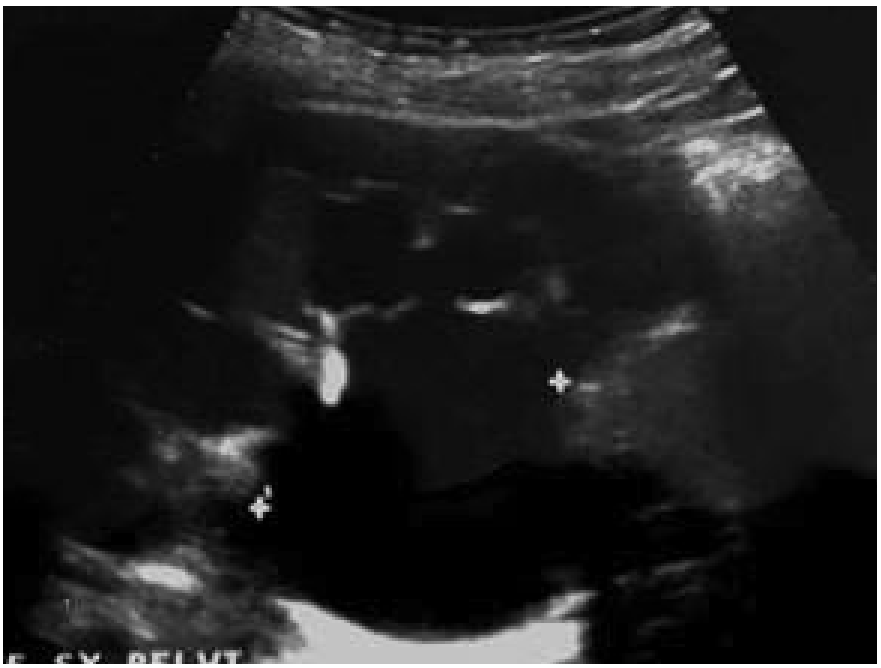

Fig. 4. *Pre-operative US showing marked hydronephrosis.*

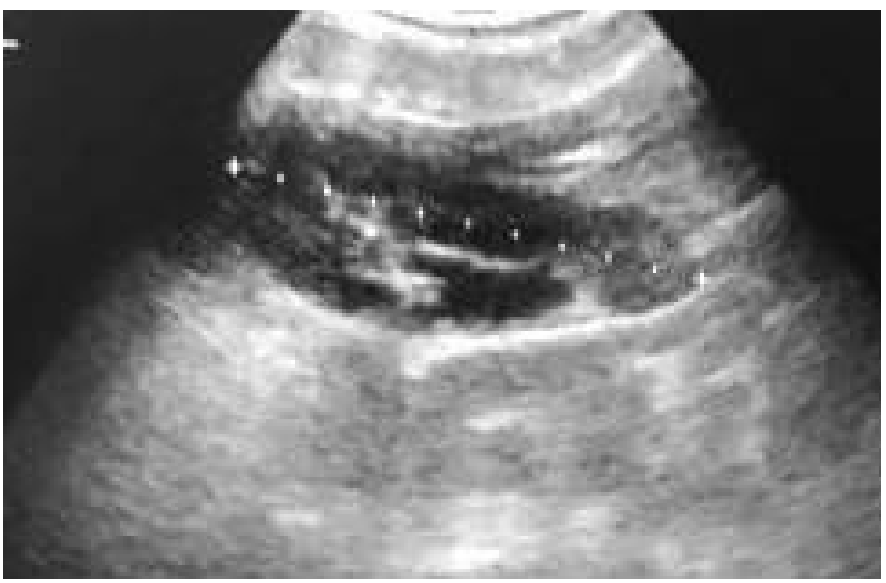

Fig. 5. *Post-operative US showing significant improvement in hydronephrosis.*

Eventually they generally present with a normal renal function despite a late diagnosis.

A combination of imaging techniques (US, MRI, CT scans) allows accurate detection of abnormal crossing vessels at the PUJ; however we cannot be absolutely sure that abnormal vessels are actually obstructing the PJU instead of merely represent an incidental finding. Therefore, the main challenge remains to intraoperatively rule out any suspicion of concomitant intrinsic PUJ stenosis.This can be done by careful examination of the PUJ after emptying following an intraoperative hydratation test with diuretics, after vessel mobilization. After IV furosemide administration, the operator will observe rapid emptying of the bloated renal pelvis followed by normal ureteral peristalsis. If there are concomitant intrinsic PUJ abnormalities, pelvis dilatation remains. In conclusion, we believe that Laparoscopic Vascular Hitch is less technically demanding then pyeloplasty. It results in a lower complication rate, reduced hospitalization and a success rate >90%. Adequate patient selection is crucial and the ultimate choice of surgical technique between dismembered pyeloplasty and vascular transposition should be made intraoperatively.

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