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CASE REPORT

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Prune belly syndrome: A mini-review and case report

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Abstract

Prune belly syndrome is a multisystem disease that is clinically manifested by a combination of hypoplasia of the abdominal muscles, bilateral cryptorchidism, and congenital anomalies of the urinary system of varying severity. The prognosis for patients with Prune belly syndrome is mainly determined by the extent of renal parenchyma dysplasia. An interdisciplinary approach involving urologists, nephrologists, surgeons, endocrinologists and other specialists allows us to improve urodynamics, to achieve stable remission of chronic obstructive pyelonephritis to perform kidney transplantation in childhood with a good result.

The article provides a mini-review of the current state of the art in etiopathogenesis, classification, diagnosis and criteria for differentiating patients according to the severity of manifestations. A clinical report of a patient with Prune belly syndrome, which was diagnosed at the age of 7 months. Who developed bilateral refluxing ureterohydronephrosis on the background of severe dysplasia of the renal parenchyma. Staged surgical correction of bilateral refluxing ureterohydronephrosis and orchiopexy at the age of 1 to 3 years was carried out. However, the loss of kidney function caused transplantation at the age of 11 years. The follow-up of this patient to the age of 15 years was presented and an evaluation of the results was discussed.

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Introduction

Prune belly syndrome (Eagle-Barrett syndrome) includes a triad of signs: the underdevelopment of the abdominal wall muscles, cryptorchidism (often as abdominal retention) and congenital anomalies of the urinary system. The syndrome occurs with a frequency of approximately 1 in 29,000-40,000 newborns, 95% are boys (1,2). Clinical manifestations of the syndrome vary from severe renal dysplasia, incompatible with life, to moderate urodynamic disorders in combination with cryptorchidism and hypoplasia of the muscles of the anterior abdominal wall (1,3-6).

Perinatal mortality reaches 10-25% and directly correlates with the severity of pulmonary hypoplasia as a result of oligohydramnios due to a decrease in fetal urine production and renal parenchymal dysplasia. Combined anomalies such as gastrointestinal tract lesions, lungs and orthopedic pathology occur in 60% of cases (3,7-10). In the United States, the number of children with prune belly syndrome, that are reaching the age of 18 years old annually varies around 1500 per one year (5).

Historically, there are three theories of embryopathogenesis of Prune belly syndrome. The first theory provides explanation, that early obstruction at the level of the posterior urethra results in dilation of the urinary tract, ascites and oligohydramnios. However, this theory does not explain the neurological manifestations of the syndrome and is not always confirmed by autopsy results (1,2). Although cases of hypoplasia and even atresia of the anterior urethra have been described in Prune belly syndrome cases, as well as the presence of a vesicocutaneous fistula and complete non-obliteration of the urachus (7,10).

According to the second theory, the primary stop of normal mesodermal embryogenesis occurs due to a pathological gene regulating myogenesis (1). This event leads to smooth muscles of the urinary tract development disturbances, and results in the urinary tract dilation without organic obstruction. This theory has been further developed and confirmed in recent years by genetic research. DNA mutations (also known as genetic variants), that causes prune belly syndrome and megacystis, have been identified. Over the 10 years 14 genes that are critical for normal embryonic bladder development have been identified. These are genes encoding smooth muscle cellular transcription factors, contractile filament proteins, in addition enzymes, regulatory proteins of the cytoskeleton and enzymes and receptors of nervous tissue. The two key genes for Prune belly syndrome are the genes encoding myocardin (MYOCD) and filamin A (FLNA) (11).

A third theory involves an interruption of the yolk sac involution. During the early stage of embryonic development, the lateral fold expands, which leads to the preservation of an abnormally large yolk sac for this period of embriogenesis (12). Probably, the large size of the yolk sac leads to the bladder outlet obstruction with subsequent dilation of the upper urinary tract.

However, the majority of cases of prune belly syndrome remain genetically unexplained. It can be definitively concluded that some cases of Prune belly syndrome are caused by mutations in known genes that regulate fetal urogenital myogenesis. The identification of these critical genes in bladder malformations will allow progress in fetal screening of megacystis and guide the management of this group of fetuses. Ultrasound examination of fetal urodynamics with registration of detrusor activity, determination of reservoir capacity of the bladder, duration of the voiding cycle, amount of residual urine allows to assess the functional state of the fetal bladder and to identify the main symptom of megacystis syndrome - the absence of bladder emptying. The graphic registration of filling and emptying bladder process gives us an opportunity to get the curve of pathological type of urination, in fact, the absence of urination, which can be detected prenatally in various nosological forms (13). The differentiation of these conditions at the prenatal stage is crucial for choosing a pregnancy management strategy.

The main factor determining the prognosis for patients with prune belly syndrome is the severity of the urinary system damage, particularly, the extent of renal dysplasia (1,5,8,12). A classification that takes into account the severity of the clinical manifestations of Prune belly syndrome was proposed by Woodard in 1998 (14) and involves three categories of patients. Category I includes newborns who has oligohydramnios due to severe renal dysplasia or functional bladder obstruction followed by pulmonary hypoplasia and Potter syndrome. The outcome in this category of patients is antenatal fetal death or death in the neonatal period caused by renal failure.

Category II presents a complete triad of symptoms. The severity of kidneys and urinary tract damage varies. Pulmonary hypoplasia may occur in a small part of cases. The clinical course may be stabilization of renal function at or slightly below normal, but existing anomalies of the urinary system and associated urodynamic disturbances and recurrent infection can lead to loss of kidney function.

Category III patients have mild or incomplete Prune belly syndrome with less or no renal dysplasia,

ureterohydronephrosis, and vesicoureteral reflux, and normal lung function. Emptying of the bladder occurs adequately, which prevents recurrence of urinary tract infection and helps preserve kidney function.

To estimate the quality of life of patients in categories II and III according to Woodard, Wong et al. published in 2019 a new system for assessment the severity of the clinical manifestations of the syndrome - RUBACE (R-renal, U-ureter, B- bladder, A- abdomen, C- cryptorchidism, E-extraurinary) (2).

Lopes R.I. et al. (2021) proposed to distinguish 3 additional categories of patients with prune belly syndrome: isolated Prune belly syndrome, syndromic, including additional genetic syndromes (Duchenne muscular dystrophy, Pierre Robin syndrome, VACTERL or Megacystis, microcolon, hypoperistaltic syndrome (MMIHS)), as well as "Prune belly syndrome +", which can include other unusual conditions (hepatoblastoma, hearing loss, infantile stroke with damage to the optic nerve, early gout with type 2 diabetes mellitus and pancreatic atrophy or mydriasis) (1).

Case description

Patient K., currently a boy 15 years old, was admitted for the clinical examination at the age of 7 months due to his mother had noted the weight loss, an increase in the size of the abdomen and urination in large portions. There was bilateral pelvis expansion of the fetus prenatally revealed at the 24th week of gestation by ultrasound. The child was born at term with birth weight 2000g, height 45 cm. A significant increase in the size of the abdomen, "flabbiness" of the skin of the anterior abdominal wall, weight deficiency, multiple stigmas of disembryogenesis (hypertelorism, epicanthus, antimongoloid type of the eyes form, low-lying, deformed auricles, strabismus), and also manifestations of renal rickets or "osteoid hyperplasia" ("rachitic rosary", "bracelets", an increase in the frontal tubercles, severe muscle hypotension) were noted. The abdomen is significantly enlarged, flattened, the anterior wall is "wrinkled". The muscles of the anterior abdominal wall are poorly developed, the intestinal loops contour throw the skin, the lower poles of both kidneys are palpated. According to the clinical manifestations and the results of urological examination (hypoplasia of the muscles of the anterior abdominal wall, bilateral refluxing ureterohydronephrosis (Figure 1), bilateral cryptorchidism in type of inguinal retention), a diagnosis of prune belly syndrome was confirmed. During the first year of life a continuously relapsing course of chronic obstructive pyelonephritis took place, the bladder was constantly drained by the urethral catheter.

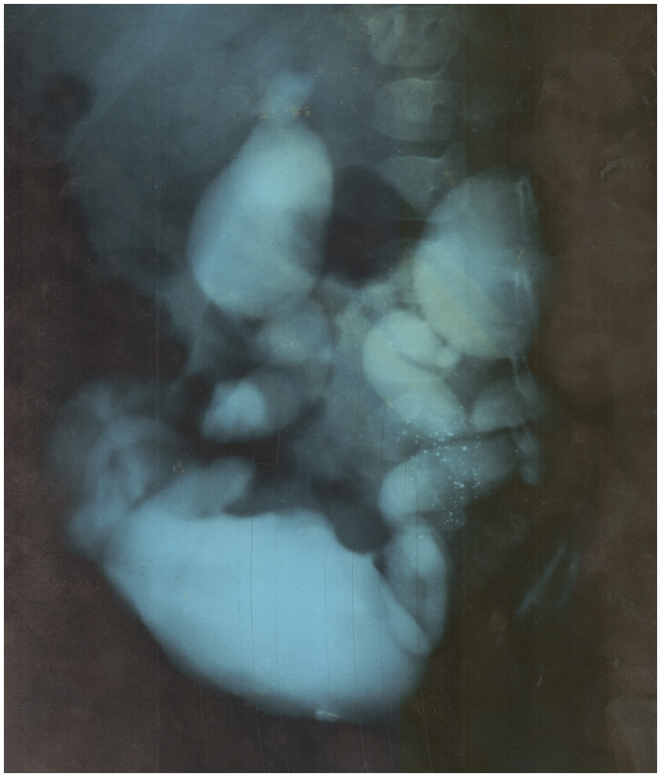

Figure 1: Cystogram of the patient K. Bilateral refluxing megaureter. The bladder is irregularly shaped, hypotonic

At the age of 1 year, a bilateral ureterocutaneostomy was performed to drain the upper urinary tract. Subsequently, an antireflux operation (reimplantation of the right ureter according to the Cohen method) was performed, the drainage of the left ureter by using a ureteral stent due to stenosis of the skin part of the ureterocutaneostomy on the left side. In the period between 1-2 years orchiopexy on both sides was performed. The perioperative period was complicated by relapses of chronic obstructive pyelonephritis, hemorrhagic and bullous cystitis were noted, and courses of antibiotic therapy (cephalosporins), instillation of the bladder with antiseptic solutions were required.

The signs of impaired renal function such as polyuria, hypoisostenuria were registered from birth, at the age of 1-2 years the nitrogen metabolism remained at the level of the upper limit of standard values. Despite the conservative and staged surgical treatment, renal dysfunction progressed (polyuria up to 2 l/day, hypostenuria 1002-1005, persistent proteinuria, intermittent glucosuria, rickets-like changes in the skeleton).

At the age of 3 years old, an increased level of the blood urea nitrogen was noted. According to nephroscintigraphy, a violation of the secretory-excretory function of both kidneys was

confirmed, chronic kidney disease was diagnosed. Nephroprotective, immunoreplacement, membrane stabilizing therapy was performed, correction of protein and electrolyte metabolism and also constant control of the level of urea and creatinine were carried out. However, there was a steady downward trend in the level of glomerular filtration rate (GFR). At the age of 10 years old, GFR was 25 ml/min, the child was consulted at the department of kidney transplantation. In case of a persistent decrease in GFR less than 15 ml/min/1.73 m2 the renal replacement therapy was recommended. Preparation course for donor kidney transplant from own mother has begun.

At the age of 11 years old, at the National Research Center for Children's Health of the Ministry of Health of Russia, the child underwent nephrectomy on both sides, allotransplantation of the right kidney from a related donor (mother) into the left renal position was performed. The graft function is immediate. The postoperative period was uneventful, the suboptimization of nitrogen metabolism (creatinine up to 95 μmol/l, urea up to 7.3 mmol/l, increase in GFR up to 56.6 ml/min/1.73 m2) was observed.

10 months later, during a routine examination, signs of graft dysfunction were revealed. They were manifested in the edematous syndrome, arterial hypertension, proteinuria up to 200 mg/day, and a decrease in the thickness of the cortical layer of the kidney parenchyma according to ultrasound examination. A biopsy of the kidney graft was performed, a thickening of the basement membrane, lymphoid infiltration, and tubulitis were revealed. Correction of conservative therapy (dose of tacrolimus) was made, therapy with diuretics was intensified with a positive effect. Repeated biopsy revealed moderate subcapsular sclerosis with atrophy of 5% of the tubules. Similar episodes of graft dysfunction occurred four times during the next 4 years.

Currently, the patient is 15 years old, his physical condition is satisfactory, the physique is hypersthenic (height 165 cm, weight 63 kg). The function of the donor kidney is assessed as partially intact, relatively satisfactory, however, the indicators of azotemia slightly exceed the upper limit of the norm (urea 8.4 mmol/l, creatinine 133 μmol/l). Duplex scanning of the renal arteries revealed no hemodynamic disturbances in the renal graft. The maximum blood flow velocity at the level of the segmental branches of the common renal artery was about 50 cm/s, at the level of the arcuate branches - about 20 cm/s. Vascular resistance index (RI) is about 0.53-0.59 (Figure 2).

Urination is not violated, the amount of residual urine is within normal limits. The patient is under constant supervision of a nephrologist, urologist; cytostatics, antihypertensive agents and immunoglobulin were carried out.

The patient's puberty was at term, at the age of 12.5 years. The formula of sexual development at this moment is G4P4. The testicular volume is about 12 cm3 on the right and 10 cm3 on the left side. This fact could mean discrepancy between the volume of the gonads and the stage of sexual development. On

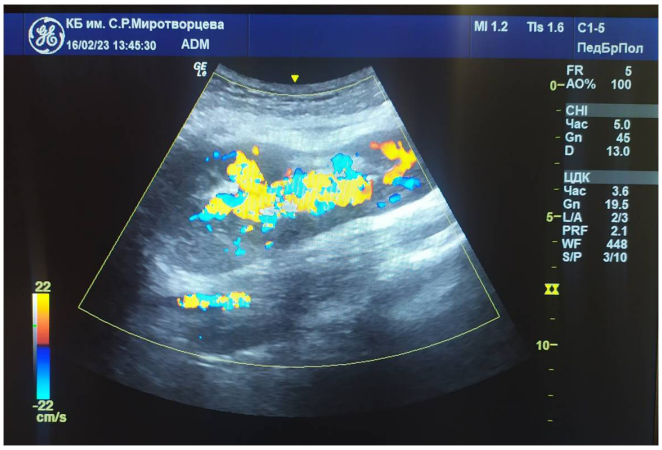

Figure 2: Ultrasonogram of a kidney graft in color Doppler mode

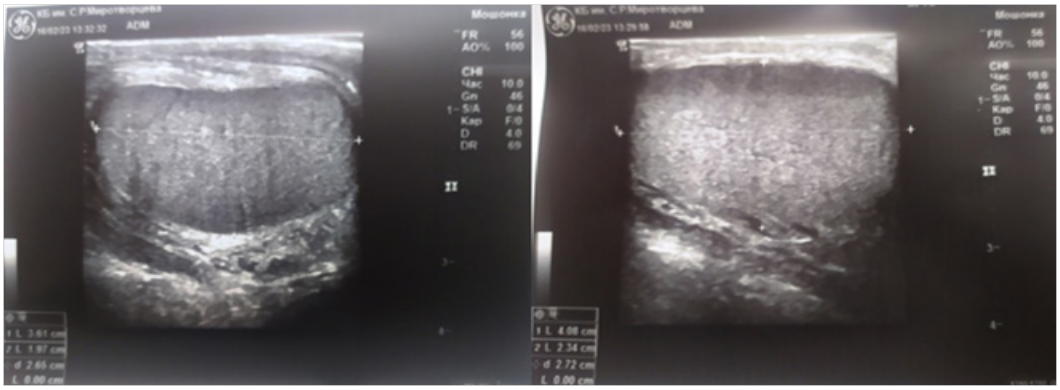

Figure 3: Ultrasonograms of the gonads of patient K. The testicles are reduced in size, the echostructure of their parenchyma is heterogeneous

ultrasound examination the right testicle has more volume (11.4 cm3) than the left testicle (9.6%) by about 16%. The heterogeneity of the echostructure of the testicular parenchyma, reduced intratesticular blood flow was revealed predominantly on the left. Thus, ultrasound signs of testicular hypotrophy were revealed (Figure 3).

The underdevelopment of abdominal wall muscles according to the RUBAC scale we rated at 1 point, the patient is able to perform exercises to strengthen the abdominal muscles. Abdominoplasty was not performed.

Discussion

At the time of the initial examination, patient K. could be assigned to category II according to the Woodard scale (1998), according to the RUBAC scale (Lopes RI et al., 2021), the patient had 13 points, extra-urogenital manifestations of the syndrome were not detected. Correction of urodynamic disorders was carried out in accordance with the EAU-ESPU-Guidelines for pediatric urology (12). Normalization of the urodynamics of the lower urinary tract made it possible to achieve stable remission of chronic obstructive pyelonephritis, which in turn provided the best conditions for kidney transplant in childhood.

The comparative analysis of the kidney transplant results in pediatric patients with prune belly syndrome, congenital obstructive uropathy (mainly posterior urethral valves), and patients with hypo-, dysplasia of the kidneys based on European Society for Pediatric Nephrology/ European Renal Association-European Dialysis and Transplant Association (ESPN/ERA-EDTA) Registry data published in 2017, patients with prune belly syndrome were required renal replacement therapy significantly earlier than patients with obstructive uropathy and renal parenchymal dysplasia. The ten-year survival of patients with PBS after kidney transplant was also slightly lower than in two other groups (85%, 94%, and 91%, respectively) (14,15).

The gonadal hypotrophy and the absence of sexual development violation are nonspecific and typical for patients who underwent orchiopexy for cryptorchidism, as we suggest. It is assumed that the process of normal testicular migration into the scrotum in fetuses with prune belly syndrome is hindered by the following factors: low intra-abdominal pressure due to underdevelopment of the muscles of the anterior abdominal wall, also a large bladder volume, which contributes to the extraperitoneal position of the inguinal canal and the abnormal development of gubernaculums (16). At the same time, recent studies show that bilateral cryptorchidism in PBS does not affect the development and growth of the testicles during fetal development (17).

Conclusions

Prune belly syndrome is a congenital multifactorial disease, the diagnosis at the prenatal stage seems to be a particularly urgent task. Indications and timing of kidney transplant are determined by the initial state and the rate of decline in renal function. In our opinion, the main task is to distinguish PBS from other causes of megacystis at the prenatal stage, the normalization of the urodynamics of the lower urinary tract in the shortest possible time to slow down the loss of renal function and to prevent the decline in graft function. It is obvious that extraurogenital clinical manifestations of the syndrome aggravate the patient's condition and require a staged surgical correction of defects, but they do not generally affect the indications for renal replacement therapy.

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References

1. Lopes RI, Baker LA, Dénes FT. Modern management of and update on prune belly syndrome. J Pediatr Urol. 2021;17(4):548-54.
2. Wong DG, Arevalo MK, Passoni NM, Iqbal NS, Jascur T, Kern AJ, et al. Phenotypic severity scoring system and categorisation for prune belly syndrome: application to a pilot cohort of 50 living patients. BJU Int. 2019;123(1):130-9.
3. Grimsby GM, Harrison SM, Granberg CF, Bernstein IH, Baker LA. Impact and frequency of extra-genitourinary manifestations of prune belly syndrome. J Pediatr Urol. 2015;11(5):280.e1-6.
4. Seidel NE, Arlen AM, Smith EA, Kirsch AJ. Clinical manifestations and management of prune-belly syndrome in a large contemporary pediatric population. Urology. 2015;85(1):211-5.
5. Arlen AM, Kirsch SS, Seidel NE, Garcia-Roig M, Smith EA, Kirsch AJ. Health-related quality of life in children with Prune-belly Syndrome and their caregivers. Urology. 2016;87:224-7.
6. Arlen AM, Nawaf C, Kirsch AJ. Prune belly syndrome: current perspectives. Pediatric Health Med Ther. 2019;10:75-81.
7. Alkhamis WH, Abdulghani SH, Altaki A. Challenging diagnosis of prune belly syndrome antenatally: a case report. J Med Case Reports. 2019;13:198.
8. Achour R, Bennour W, Ksibi I, Cheour M, Hamila T, Hmid RB, et al. Prune belly syndrome: Approaches to its diagnosis and management. Intractable Rare Dis Res. 2018;7(4):271-4.
9. Radhakrishnan J, Alam S, Chin AC. Prune Belly Syndrome: Errors in Management and Complications of Treatment. Journal of Progress in Paediatric Urology. 2014;17(1):6-14.
10. Sarhan OM, Al-Ghanbar MS, Nakshabandi ZM. Prune belly syndrome with urethral hypoplasia and vesico-cutaneous fistula: A case report and review of literature. Urol Ann. 2013;5(4):296-8.
11. Houweling AC, Beaman GM, Postma AV, Gainous TB, Lichtenbelt KD, Brancati F, et al. Loss-of-function variants in myocardin cause congenital megabladder in humans and mice. J Clin Invest. 2019;129(12):5374-80.
12. Menovshhikova LB, Shaderkina VA, Garmanova TN, Bondarenko SG, Shaderkin IA. Klinicheskie rekomendacii po detskoj urologii-andrologii. M.: Izdatel'skij dom «Uromedia»; 2017.
13. Deriougina LA, Goremykin IV, Krasnova EI, Rozhkova DV. Prenatal'naja diagnostika sindroma megacistis i ego klinicheskoe znachenie. Detskaja hirurgija. 2015;1: 39-41.
14. Woodard JR, Smith EA. Prune belly syndrome. In: Walsh PC, Retik AB, Vaughan Jr ED, Wein AJ, editors. Campbell's urology. 6th ed. Philadelphia: WB Saunders; 1998. p. 1917e38.
15. Yalcinkaya F, Bonthuis M, Erdogan BD, van Stralen KJ, Baiko S, Chehade H, et al.. Outcomes of renal replacement therapy in boys with prune belly syndrome: findings from the ESPN/ERA-EDTA Registry. Pediatr Nephrol. 2018;33:117–24.
16. Logsdon NT, Sampaio FJB, Favorito LA. The role of intra-abdominal pressure in human testicular migration. Int Braz J Urol. 2021;47(1):36-44.
17. Pires RS, Gallo CM, Sampaio FJ, Favorito LA. Do prune-belly syndrome and neural tube defects change testicular growth? A study on human fetuses. J Pediatr Urol. 2019;15:557.e1-e8.