Prune Belly Syndrome in monozygotic male twins with pulmonary involvement A rare entity

Samira Ahmed Mustafa

Faculty of Medicine, Al Neelain University and Jaafar Ibn Auf Hospital

Ethical considerations:

- The author reports no conflicts of interest in this work

- Informed consent was taken from the parents. Using patient's knowledge for research work only was explained. Confidentiality is considered

Abstract

Prune belly syndrome is a rare, often sporadic congenital disease with diverse manifestations and may be multisystem involvement, of variable severity ranging from mild to lethal. *Etiology is unknown.* Diagnosis is possible by antenatal sonographic findings of Prune belly syndrome, and oligohydramnios. Abdominal wall appearance immediately after birth suggests the diagnosis. Despite advances in medical and surgical management, neonatal mortality remains high. The key to management is multidisciplinary approach to provide the needed individualized care. Quality Of Life (QOL) of pediatric patients was found to be profoundly affected, and interventions which positively influences the patient's reported QOL should be determined.

A fifty nine days old male infant is reported. He is the second of monozygotic twins. Maternal Ultrasound during pregnancy showed oligohydramnios. Since delivery was at home, no routine neonatal checkup was done for the twins. Although the mother noticed difficulty of breathing after birth, they were only seen by a pediatrician at 35 days when they developed fever and severe respiratory distress. The first twin died and the second twin who showed poor response to treatment

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was sent to a tertiary hospital for further management. Clinical assessment revealed severe bilateral pneumonia and the classical triad of prune belly syndrome. Mild pulmonary hypoplasia was the likely extra genitourinary manifestation which was aggravated by the chest infection. Ultrasound abdomen showed right hypo-plastic kidney and KUB showed dilatation of posterior urethra. Initial and follow up Renal Function Tests and electrolytes were normal, and in the presence of one normal kidney, these suggested satisfactory prospects for long term renal function. It is concluded that the reported twins are Prune Belly Syndrome plus with extra genitourinary (pulmonary) manifestation that does not satisfy the criteria for any well-defined genetic disease, syndrome or association.

To avoid death and to offer the necessary individualized multidisciplinary care, antenatal maternal ultrasound and hospital delivery are recommended for early detection. Research work and documentation are necessary to improve categorization, treatment and outcome of this rare disease

Key words*:* *prune belly syndrome, cryptorchidism, extra genitourinary co-morbidities, multi-disciplinary management, Quality Of Life (QOL).*

Introduction

Prune Belly Syndrome(PBS) is a rare congenital phenotypically variable disorder with mild to lethal severity and may have multi-systemic effect in the neonatal period. The reported incidence is 3.8 per 100,000 live male births (1, 2).

Classical PBS is a syndrome characterized by cardinal features of deficient or lax abdominal muscles, bilateral cryptorchidism and urinary tract anomalies. It is also called Eagle Barret Syndrome or Triad Syndrome. It is an uncommon disease, males constituting an incidence of 95 % of cases. Being a cardinal feature of PBS, cryptorchidism indicates that females are non-classical cases constituting < 5% of prune belly syndrome cases. Diagnosis is suggested by the appearance of the abdominal wall immediately after birth. Many affected infants are stillborn. Despite marked advances in neonatal care, perinatal mortality rates remain high. Pulmonary hypoplasia is the major cause of death in the first few months of life. As many as 30% of long term survivals develop End Stage Renal Disease(ESRD) due to renal dysplasia or complications of infections or reflux and may require renal transplant (1,2).

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Epidemiology and pathogenesis:

Prune belly syndrome often presents as a sporadic event. The true mechanism of its development is unknown, but accumulating evidence support a genetic component. The high concordance rate in twins (12.2 per 100,000 live birth), case reports of monozygotic twins, familial case reports and a high incidence in males all suggest a genetic contribution (2, 3,4,5). However, in monozygotic twins both concordance and discordance for PBS have been reported implying that inherited genetic mutation cannot explain the pathogenesis of the syndrome (2, 3, 6). Several familial cases of PBS support an X-linked or autosomal recessive mode of inheritance. (9). This together with the fact that females cannot have cryptorchidism had led to the thinking that females cannot be true PBS, in addition extra GU features that appear syndromic suggesting VACTRERL, a syndrome (7, 8, 9,). The disorder is 18 to 20 times more common in males than females (10). Female variance with deficient abdominal muscles and urinary anomalies but without genital anomalies have been described which may contribute to approximately 3% of all PBS cases, (4). In females abnormalities of urethra, uterus and vagina usually are present (1). Females represent < 5% of all PBS cases (3).

A study of 15 PBS children in Sudan revealed that male to female ratio was 4: 1, a higher female ratio than what is reported in literature. The researchers could not explain their finding but they thought that some cases might have been missed as their study was only a case series study (11).

Homozygous, putative loss of function mutations of CHR M3 have been reported in a family with several males affected by PBS-like disease. Heterozygous whole gene deletions of Hepatocyte Nuclear Factor 1B (HNF 1B) have been reported in a rare patient with PBS, but as whole gene deletion HNF 1B also extended to adjacent genomes, the final phenotype is unlikely to be ascribed to HNF 1B itself (12,13,14). According to Ganberg CF, despite PBS case reports of multi-exonic HNF 1B deletions, functionally significant mutations detectable by coding and splice site sequencing of HNF 1B are uncommon in PBS. The VGIG HNF 1B mutation was detected in one (3%) of 34 patients with PBS in this large scale screening, which was observed to be functionally normal. Further genetic studies are warranted which can ultimately lead to prevention and improved treatments for this rare but severe disease (15).

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DNA variations in 4 autosomal genes CHR M3, HNF 1B, ACTA2 AND ACTG2 have been associated with 5 sporadic PBS cases and one PBS multiplex consanguineous kindred. DNA variants in these Autosomal genes would manifest theoretically in females as near equal frequency as in males which is not the case (5,6,8,9).

Boghussin NS. et al in their study identified several Copy Number Variants (CNVs) that included genes in mesodermal muscles and urinary tract development and differentiation, all systems that are affected in PBS. Their findings supported a genetic contribution to PBS etiology. The BMP signaling pathway is a well-known contributor to mesodermal differentiation and formation. Thus identifying CNVs in BMPR 1B and NOG gene areas, both regulators of the BMP pathway, strengthens the hypothesis that abdominal mesoderm development leads to PBS phenotype. They recommended that further research on the genetic factors identified, particularly of BMP signaling, and genes associated with mesodermal development is warranted. (16).

Clinical features and diagnosis:

The routine implementation of maternal sonography has rendered prenatal diagnosis of PBS possible(17,18, 19). Prenatal sonographic findings of PBS may include: lower urinary tract obstruction, hydroureteronephrosis, megacystis, irregular abdominal circumference and oligohydramnios which may be detected as early as 11-12 weeks, but may not be consistently identified until later in pregnancy (20). Oligohydramnios and pulmonary hypoplasia are common complications in the perinatal period (9). Abdominal wall appearance of the neonate immediately after birth suggest PBS regardless of whether the diagnosis was known prenatally (2). Ramnik V Patal.. et al studied non-identical twins delivered by CS at term because of prenatal UltraSound (U/S) suggestive of the possibility of PBS. No abnormality was detected on the second twin, with normal echocardiography and chromosomal study. At birth the first twin was noted to have grossly distended abdomen, with wrinkled skin with visibly dilated ureters and kidneys and has bilateral undescended testes, suggestive of PBS. His U/S showed normal thickness of the bladder wall and no key hole sign and MCUG showed bilateral vesicoureteral reflux and urinary tract dilatation. His urea nitrogen and creatinine were high but returned to normal after 3 months of prophylactic antibiotic cover and he was thriving

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well. Their comment was that PBS in one of the twins is rare and that most males are infertile and that prenatal diagnosis is possible (21).

In their studies about congenital disorders of human urinary tract, Adrian SW. et al stated that PBS describes a constellation of signs present from the antenatal period featuring a massively distended bladder that fails to empty fully and overlying abdominal wall that is thinner than normal. It nearly always occurs in boys when the signs include undescended testicles (22).

Urinary tract abnormalities include massive dilatation of the ureters and upper tracts, and very large bladder with patent urachus or urachal diverticulum. Most patients have vesicoureteral reflux. The prostatic urethra usually is dilated and the prostate is hypoplastic. The posterior urethra may be dilated resulting in mega urethra. Rarely there is urethral stenosis or atresia. The kidneys usually show various degrees of dysplasia and the testes are intra-abdominal. Malrotation of the bowel often is present. Cardiac abnormalities occur in 10% of cases. More than 50% of cases have abnormalities of the musculoskeletal system including limb abnormalities and scoliosis (1).

Renal dysplasia and dysfunction is common in PBS population with approximately 40-50% of patients ultimately requiring renal replacement therapy, (RRT). Early end stage renal disease(ESRD), is thought to be secondary to renal dysplasia, whereas kidney failure occurring later is often attributed to parenchymal damage from repeated infections and the increased pressure transmitted to the upper tract generated from incomplete emptying. Presence of one normal kidney on U/S and a nadir serum creatinine of < 0.7 mg/dl in infancy are prospectives of satisfactory long term renal function (22,23).

Impact and frequency of Extra- Genitourinary (extra- GU) manifestations of PBS was studied by GM Grimstoy,… et al in their large contemporary series which compared cohorts of PBS survivors and published literature. They stated that Extra- GU manifestations are serious co-morbidities beyond the GU anomalies of PBS. They mentioned that there is under estimation of the reported frequency and under stated impact on quality of life of Extra GU manifestation of PBS patients who survive the newborn period. The study showed that the surviving people with PBS have a significantly high incidence of orthopedic (65%), gastrointestinal (63%), and cardiopulmonary (49%) diagnoses, than reported in previous publications. They also stated that it is extremely important for urologists to

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beware of, and prepare for high incidence of co-morbidities which may directly impact on the QOL of these patients (24).

Oligohydramnios and pulmonary hypoplasia are known complications of PBS in the perinatal period which can lead to still birth or early demise. Being the most serious early presentation of PBS, resulting in stillbirth or death in the early months of life in one third of patients, pulmonary hypoplasia is the least reported manifestation in surviving PBS patients (1,2,9,12).

Pulmonary hypoplasia involves a decrease in both the number of alveoli and the number of airway generations. The hypoplasia may be bilateral in the setting of bilateral lung constraint as in oligohydramnios or thoracic dystrophy, or unilateral in the setting of pleural effusion with fetal hydrops or congenital diaphragmatic hernia that produce an impairment of normal lung development which is more severe in the ipsilateral side than in the contralateral side where the mediastinum is displaced. In these conditions which physically constrain the developing lung/ lungs, airway and arterial branching are inhibited, thereby limiting the capillary surface area. Pulmonary hypoplasia usually present in the newborn due either to respiratory insufficiency or persistent pulmonary hypertension. Later presentation by tachypnea with stress or respiratory viral infection can be seen in infants with mild pulmonary hypoplasia who might need only oxygen or may be mechanical ventilation to support gas exchange (25).

To improve PBS research and treatment it is hypothesized that a more expansive, twofold classification system will better describe the phenotypic diversity of PBS. Current study designs are hindered by the wide heterogeneity of phenotype and the absence of any unified method to classify phenotypic severity, making it difficult to compare patients and their outcome (7,26).

According to Woodard, prune belly syndrome is a rare congenital disease of unclear etiology, with a complex and a wide spectrum of severity and with diverse multisystem involvement. Also, no standard strategies for treatment of PBS exist despite advances in medical and surgical management of PBS, and that newborn mortality remained as high as 10 – 25%. Furthermore, the small sample size (case series), the case reports and the retrospective studies hindered the development of advanced standardized approaches. So, Woodard categorized the newborns into three groups based on clinical,

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parameteral and immediacy of life supporting surgical management required by the child, (2,7). (table1)

Table (1): Spectrum of Prune Belly Syndrome by Woodard

Category	Characteristics
Category 1 (20%)	Renal dysplasia Severe Oligohydramnios Pulmonary hypoplasia Potter's Features
Category 11 (40%)	Full Triad Features Moderate or Unilateral Renal Dysplasia No Pulmonary Hypoplasia May Progress to Renal Failure
Category 111 (40%)	Incomplete mild Triad Features Mild to Moderate Uropathy No Renal Dysplasia surgical l Stable Renal Function No Pulmonary Hyopoplasia

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The RUBACE score is a practical, organ/system level, numerically continuous phenotyping tool, designed to quantitatively grade PBS severity and categorize patients into one of the following groups: Isolated PBS (the classical PBS triad), Syndromic PBS (with extra genitourinary features which meet criteria for a known genetically defined disease, syndrome or association) and PBS-plus(with extra genitourinary features that fall short of a known genetically defined disease, syndrome or association) It also lays the groundwork on which genotype / phenotype correlations and standardized quality studies assessing medical and surgical treatment outcome will be built(26) .

The abbreviation RUBACE sub category grading and severity scoring denotes:

- R : Renal scoring as assessed by GFR
- U : Ureter sub score
- B : Bladder outlet severity
- A : judgement of Abdominal wall laxity
- C : definition and categories of Cryptorchidism
- E : the five Extra- genitourinary sub scores (neurologic, cardiac, gastrointestinal, musculoskeletal and respiratory (27).

Management and Outcome:

Major treatment objectives are: preservation of renal function and upper urinary tract, polyuria management, adequate bladder emptying and improvement of quality of life in addition to the long term follow-up of the urinary tract. Infants need individualized care according to the phenotype severity. Some patients require abdominal and urinary tract reconstruction, and others require as little as bilateral orchidopexy (28).

Routine implementation of maternal U/S has rendered prenatal diagnosis of PBS possible. Early accurate diagnosis allows not only for the prompt multidisciplinary management of newborns in a

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tertiary center at birth resulting in improved survival, but also allows for the option of voluntary termination if desired (2).

Intrauterine intervention in the second or third trimester gestation with decompression of urinary tract using vesico-amniotic shunting exist. (22,23,26). Although shunting may be effective in correcting oligohydramnios, there remains a lack of standardization and its ability to achieve adequate renal function is variable while pulmonary function cannot be assured despite restoration of normal amniotic fluid level (12,26).

Many neonates with PBS have difficulty with effective bladder emptying because the bladder musculature is poorly developed and the urethra may be narrowed. When no obstruction is present, the goal of treatment is prevention of UTI with Antibiotic prophylaxis. When Obstruction of the ureters or urethra is demonstrated temporary drainage procedures such as vesicotomy, can help to preserve renal function until the child is old enough for Surgery. Some children with PBS have been found to have classic or atypical Posterior Urethral Valves (PUVs). Urinary Tract Infection(UTI) occurs often and should be treated promptly. Children often require orchidopexy which can be difficult in these children because the testes are located high in the abdomen and surgery is best accomplished in the first six month of life. Individually tailored urinary tract surgery and abdominal wall reconstruction is often needed by these Children (1,2). Reconstruction of the abdominal wall offers cosmotic and functional benefits (1).

The prognosis ultimately depends on the degree of pulmonary hypoplasia and renal dysplasia. One third of children with PBS are stillborn or die on the first few months of life because of pulmonary hypoplasia. As many as 30% of long term survivals develop End Stage Renal Disease (ESRD) from dysplasia or complications of infections or reflux and eventually require renal transplantation. Renal transplantation in these children offers good results (1).

As with most complex congenital anomalies, the key to management of PBS is multidisciplinary approach providing individualized care. Long-term surveillance of urinary tract is crucial, as bladder dynamics and renal function can change overtime. As scientific and technological advances are expected to improve with time, the overall survival and life-expectancy of PBS patients is expected

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to improve. The challenge remains to develop best practice standards and provide comprehensive care while mitigating potential negative disease sequelae. PBS has been shown to profoundly affect the physical, emotional and social Quality Of Life (QOL) in pediatric patients, highlighting the need to determine which interventions positively influence patient's reported QOL(2 ,29).

Case history and examination:

Here is reported a 59 days old infant. He is the second of a monozygotic twins, from west Sudan. The twins were products of a full term pregnancy and a normal vaginal delivery at home. Maternal sonography during pregnancy showed oligohydramnios. The mother noticed fast breathing in both twins shortly after birth. At 35 days they developed high grade fever and shortness of breath. Unfortunately the first twin died on the same day while the second twin was referred to a tertiary hospital in Khartoum after 20 days admission in a local hospital with poor response. The patients had no difficulty in voiding and they needed no emergency procedures to the urinary tract.

There was no consanguinity between parents and they have two elder normal siblings.

On admission the child was wasted but not dysmorphic. Weight for hieight was –2SD below the mean for age and sex. Respiratory rate was 71/ min and his oxygen saturation was always low. BP was normal.

Chest examination: showed signs of respiratory distress and right lung mainly middle and lower lobes showed reduced air entry, and harsh vesicular breathing, with crackles bilaterally.

Abdomen: was distended with lax and thin abdominal muscles with a defect in the right hypo chondrium, through which the abdominal contents herniate. Liver span is 12 cm. not tender Fig (1).

No abnormality was detected in other systems (Orthopedic, GIT, Cardiac or CNS).

The clinical diagnosis of Prune belly syndrome with pulmonary hypoplasia complicated by severe pneumonia was made.

Chest X-ray is attached, and CT chest with contrast showed: large bilateral cavitory pneumonia; The upper cuts of the abdomen showed hepatomegaly and Small hypoplastic right Kidney (fig2,3).

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U/S Abdomen → Small 3.4 right kidney. No stones. Enlarged compensatory 6.1 left kidney; Normal urinary bladder, no stones ; empty scrota; Left testis seen Intra abdomen(1.0cm) at the level of the internal ring; Right testis not seen in the inguinal region or intra abdomen.

KUB: → Dilatation of posterior urethra.

Complete blood count was unremarkable.

Renal Function tests and electrolytes were normal. Urine analysis was clear.

Investigations for Tuberculosis were negative.

The child was put on Oxygen therapy and IV antibiotics, started empirically then according to cultures, with supportive treatment, but the patient was showing slow improvement. He was Oxygen dependent for four months then he was safely weaned off oxygen. Follow up chest X-rays showed resolution of pneumonia but right upper lobe collapse. At 7 month of age the patient was thriving well. He had normal renal function. He was send for orchidopexy and abdominoplasty, he is on regular follow-up by the Nephrologist, and he was reviewed by the urologist. At 10 months of age his blood pressure was normal and he has a normal renal function. He has no signs of respiratory distress and chest X-ray was normal.

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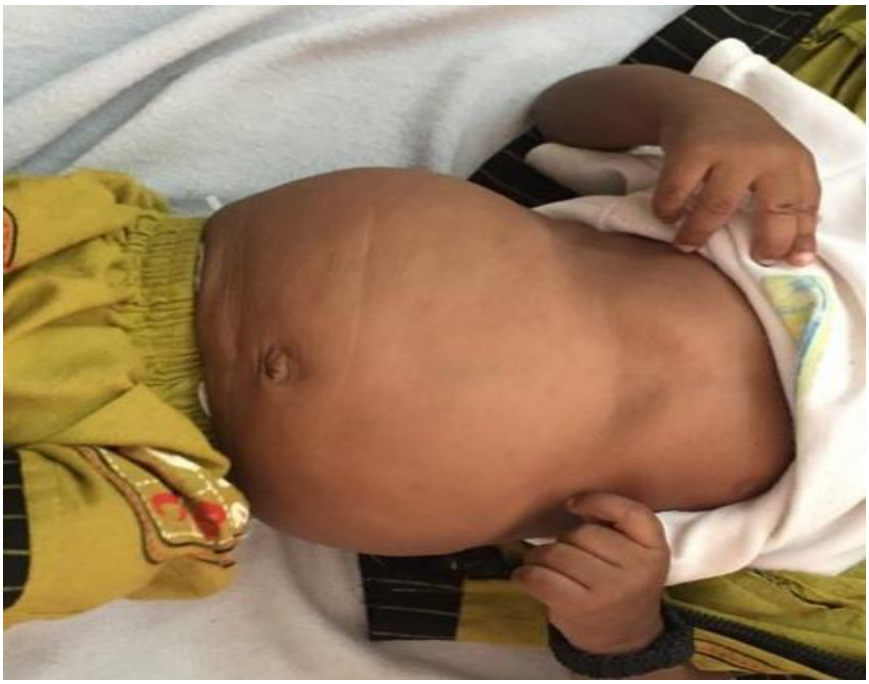

Fig (1): PBS patient with distended, lax and deficient abdominal muscles

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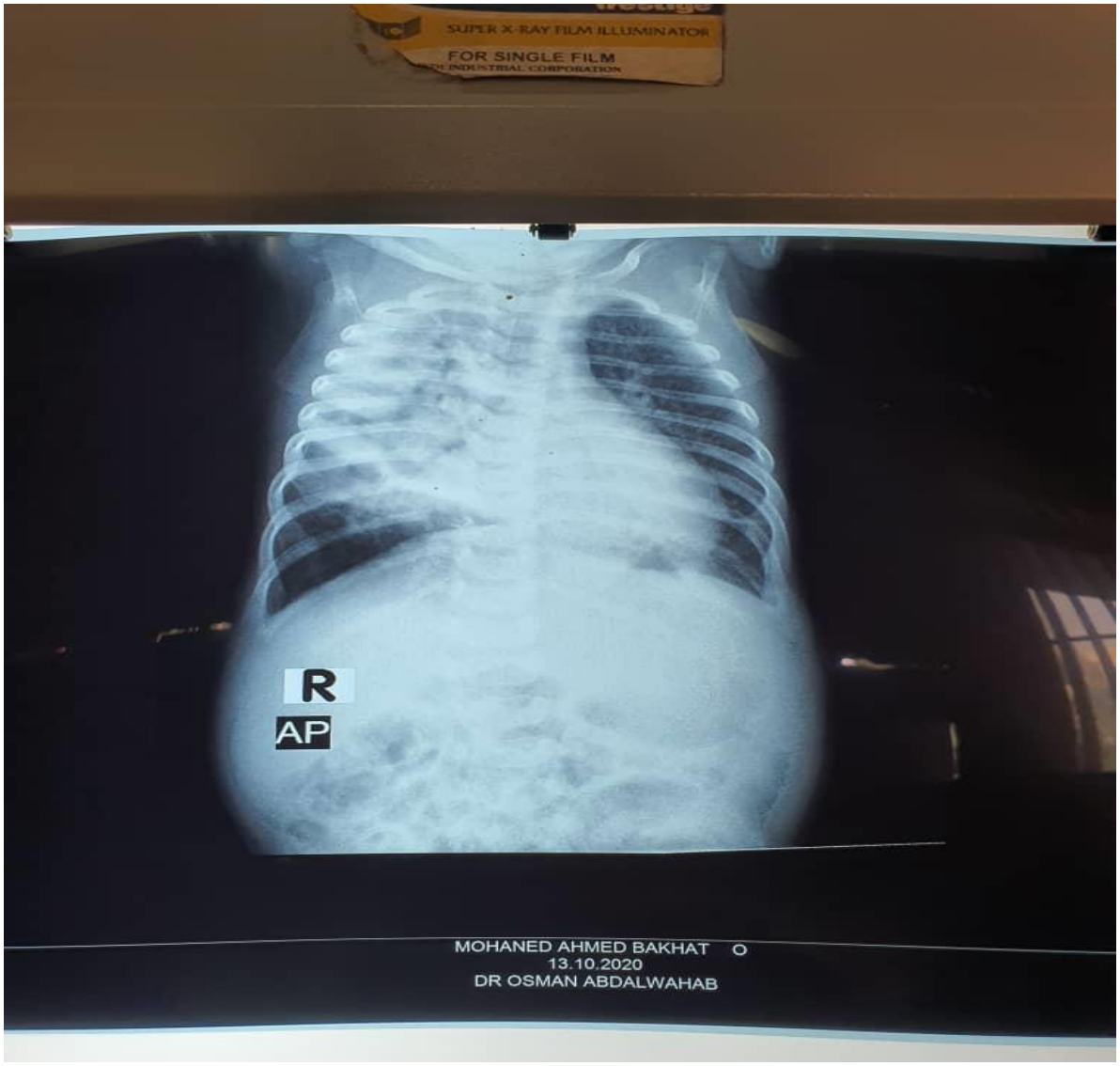

Fig (2): Chest X-ray in PBS patient with mild pulmonary hypolasia and bilateral pneumonia

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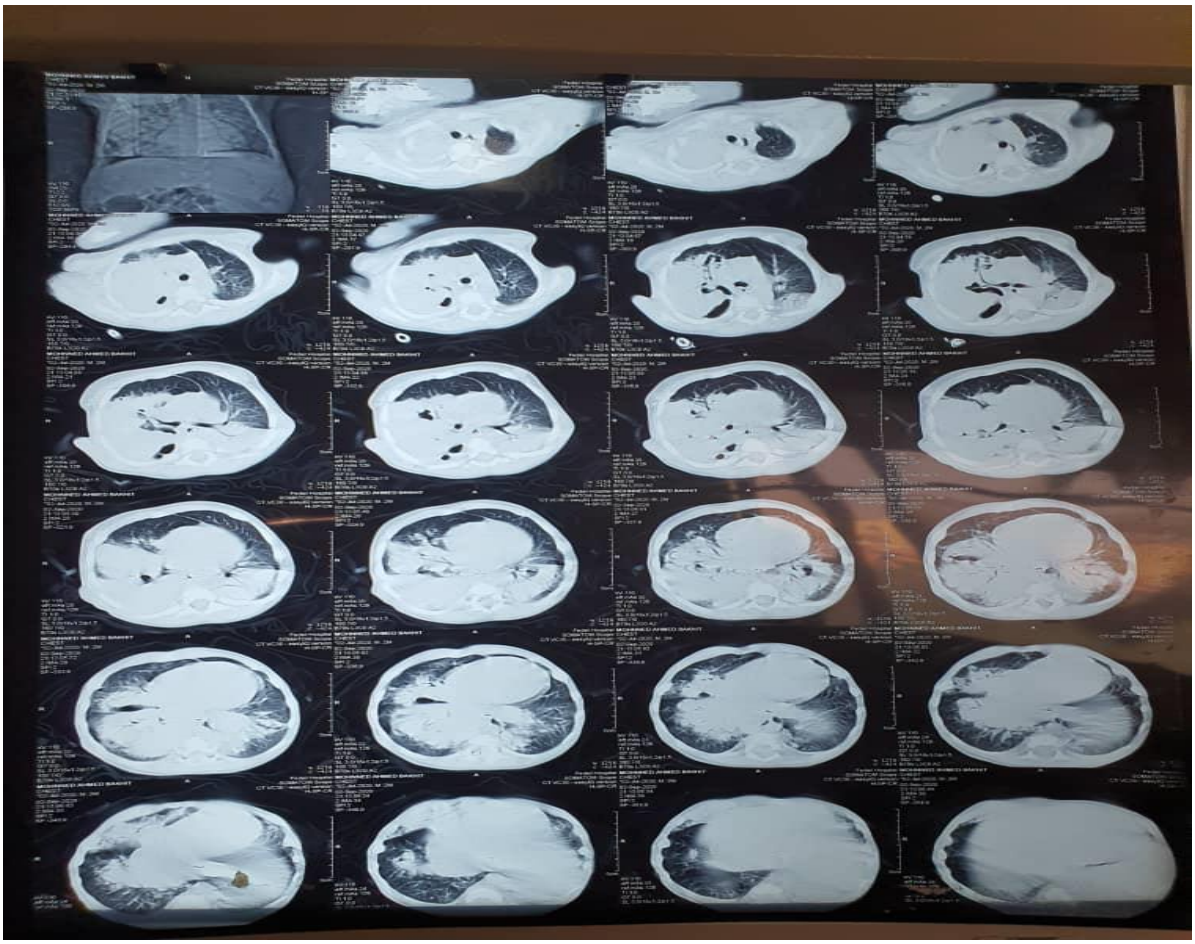

Fig (3): CT with contrast in PBS patient with pulmonary hypoplasia and bilateral pneumonia

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Discussion

Prune belly syndrome is a rare congenital disorder of variable severity which could be associated with serious extra-genitourinary co-morbidities. The twins reported are monozygotic. Our twins are similar to many PBS cases in whom the twins are monozygotic and both twins are affected, but different from the case reported by Ramnik V Patal, …et al who reported PBS in non-identical twins, in whom only one of the twins is affected (21).

Maternal sonographic study during pregnancy revealed oligohydramnios. but no urinary anomalies were detected. No clinical assessment was performed at birth as delivery was at home. The mother noticed difficulty in breathing in both twins, but no medical advice was sought until 35 days of age when both twins developed fever and severe respiratory distress. The first twin died and the second twin was admitted to hospital where he was discovered to have severe pneumonia and the classical features PBS. This is inconsistent with recommendations of Woods, Amanda G, RN, MSN. et al., who stated that PBS and its multi systemic effect on the newborn infant needs special attention to be paid to presentation, clinical features, complete physical assessment, nursing care of PBS infants and family support (30).

Genitourinary manifestations are among the cardinal features of PBS. Urinary tract anomalies are of variable degrees and severity. The genitourinary manifestations in the reported twin are bilateral cryporchidism, urinary tract abnormalities in the form of small dysplastic (hypoplastic) right kidney with enlarged hypertrophied left kidney. KUP showed dilatation of the posterior urethra.

The posterior urethra may be dilated resulting in mega urethra. The kidneys usually show various degrees of dysplasia (1). The GU phenotype of PBS is variable and does not necessarily correlate with the degree of abdominal wall flaccidity. Renal dysplasia and dysfunction is common in PBS population and/or scarring from urinary tract infections resulting from ureteric obstruction, VUR, or bladder dysfunction. Forty-to-fifty percent of patients require renal replacement therapy and _15% require renal transplantation (12, 22).

Unlike the reported twin, Khair AEM, Ali EMA, Medani SA, Maaty HS from Sudan in their study of 15 PBS cases showed that most of the patients (80%) had hydronephrosis and hydroureters (11).

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The likely extra-genitourinary manifestation in the reported twins is pulmonary hypoplasia secondary to oligohydramnios, a complication the mother was not aware of its implications. Oligohydramnios and pulmonary hypoplasia are known complications of PBS in the perinatal period which can lead to still birth or early infantile death (1,2,9,12).

Later presentation by tachypnea with stress or respiratory viral infection can be seen in infants with mild pulmonary hypoplasia who might need oxygen or may be mechanical ventilation to support gas exchange (25). This late presentation precepitated by infection is similar to our reported twin, who needed oxygen therapy and was oxygen dependent for many months (25).

As stated by Mehmet Satar, Ferda Özlü. et al. respiratory problems and respiratory infections in PBS could be explained by the abdominal musculature hypoplasia, resulting in impaired cough mechanism. The author reported the first use of corset in a newborn infant with PBS who had respiratory problems and chronic constipation secondary to ineffective Valsalva ability because of abdominal muscle hypoplasia, after which his symptoms resolved (31).

Grimsby GM, et al. stated that PBS could be associated with serious extra genitourinary co-morbidities and they expressed clearly that urologists should involve a multi disciplinary team in the management of PBS patients because of the diversity and severity of extra- genitourinary manifestations (24).

Although long term surveillance of the urinary tract is essential up to adulthood, because functional dynamics can change over time, according to Noh PH, Cooper CS, …et al, our reported twin is expected to have a satisfactory long term renal function, in view of one normal kidney with a normal renal function and electrolytes and a creatinine level of <0.7mg/dl (22, 27).

Conclusion and recommendations:

PBS is rare congenital disease with a broad spectrum of severity and multisystem diverse involvement, affecting mainly boys. There are no standardized or evidence-based guidelines for managing PBS. Efforts are being done to e phenotypically and if possible genotypically categorize

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related groups of these patient to help research work and treatment of this potentially serious disease. QOL has been shown to be markedly affected by the disease in all aspects.

Routine maternal U/S during pregnancy for early detection and hospital delivery whenever pregnancy is detected to be complicated are recommended. Team work management approach for any child with PBS comprising neonatologist, nephrologist, urologist, cardiologist, pulmonologist, orthopedic surgeon and psychologist and social worker is necessary for immediate and long-term treatment and follow-up. Active prospective research work on clinical, genetic and management aspects of PBS is recommended.

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