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Impact and frequency of extra-genitourinary manifestations of prune belly syndrome

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Summary

Introduction—Extra-genitourinary (extra-GU) manifestations are serious comorbidities beyond the genitourinary (GU) anomalies of prune belly syndrome (PBS). It was hypothesized that there is an underestimation of the reported frequency and understated impact on quality of life (QOL) of extra-GU comorbidities in people with PBS who survive the newborn period. To assess this, the extra-GU manifestations of PBS in a contemporary cohort of living patients were compared to those that have previously been described in the literature. Second, the impact of extra-GU manifestations of PBS on the QOL of the patients and their families were assessed via a non-validated open-ended survey.

Methods—From 2010-2013, living people with PBS were prospectively recruited at Children's Health Dallas or at three PBS Network National Conventions. The family/subject was asked to complete a detailed PBS questionnaire, non-validated QOL survey, and provide medical records for review. Clinical data were extracted from medical records for local patients. The frequency of extra-GU manifestations was compared between the contemporary, living cohort and a historical cohort derived from PubMed publications.

Results—Of the 706 identified publications on PBS, seven historical studies that were published a mean of 30 years ago met inclusion criteria and tabulated the frequency of extra-GU PBS manifestations. Clinical data from the present institution were available for 65 living patients: 99% were male and the mean age was 10 years (1 month-45 years). They had a statistically significantly higher incidence of gastrointestinal (63%), orthopedic (65%), and cardiopulmonary

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(49%) diagnoses when compared with the historical cohort of 204 PBS subjects from the literature (Fig. 1).

A total of 43 people completed the QOL survey: 11 males with PBS and 32 family members. Of these, 47% listed at least one non-GU problem (i.e. lung disease, skeletal problems, constipation) as negatively affecting their QOL; 42% listed at least one GU problem (i.e. self-catheterization, recurrent UTIs) as negatively affecting their QOL; 56% reported musculoskeletal surgery and 21% reported gastrointestinal surgery/medication as positively impacting on their QOL.

Discussion—In this largest reported series of living people with PBS, the frequency of gastrointestinal, orthopedic, and cardiopulmonary diagnoses was found to be significantly higher than previously published. These findings are very important for the urologist, as non-GU manifestations of PBS, such as cardiopulmonary disease and constipation, may affect the medical and surgical treatment of the PBS patient.

The present study also sought to identify what aspects of PBS matter the most to those affected by and living with PBS. As expected, the QOL survey of PBS revealed that the majority felt that GU problems negatively affected their QOL. However, nearly 50% of the respondents indicated that a non-GU aspect of the disease also had a negative effect on QOL and that treatment of these conditions improved their QOL.

Conclusions—In this large contemporary series, surviving people with PBS had a significantly higher incidence of orthopedic, gastrointestinal, and cardiopulmonary diagnoses than previously reported in PBS publications. As urologists are often the most frequently seen physicians of these complex patients, it is extremely important to be aware of and prepare for the high incidence of comorbidities that may directly impact on the treatment and QOL of these patients.

Introduction

Prune belly syndrome (PBS) is classically characterized by three cardinal features: bilateral undescended testicles, a dilated urinary tract, and deficient abdominal wall musculature [1]. Unfortunately, the syndrome has high morbidity, with 20-30% of affected children dying within the first few months of life [2]. Despite advances in prenatal care and neonatal resuscitation, a 2010 publication reported that the US perinatal death rate remains high at 29% [3].

Pediatric urologists are infrequently consulted to evaluate and treat the fetus with PBS or the neonate that succumbs to PBS. More frequently, they care for the surviving child. For children with PBS, pediatric urologists are one of the more frequently visited surgical specialists, as these children ultimately require bilateral orchiopexy as well as urinary tract reconstruction and, often, abdominoplasty. As the understanding of genitourinary (GU) manifestations has improved, pediatric urologists have recognized that PBS represents a spectrum of abnormalities ranging from partial absence of abdominal wall musculature with bilateral cryptorchidism and mild urinary tract dilation, to the patient with renal dysplasia/chronic kidney disease, massive hydronephrosis, high-grade VUR, and severe bladder dysfunction. However, extra-GU manifestations affecting the gastrointestinal, orthopedic, and cardiopulmonary organ systems can also have high morbidity [1], and many chronic extra-GU disorders, such as constipation and asthma, may directly affect the medical and

surgical care that urologists provide these children. It is likely that contemporary providers under-appreciate the prevalence of these comorbidities, as publications tabulating the frequency of extra-GU manifestations of PBS are hampered by small sample sizes, reliance on autopsy studies, and being >20 years old [1,2,4-8].

It was hypothesized that there are underestimations of the reported frequency and impact on quality of life (QOL) of extra-GU comorbidities in children with PBS who survive the newborn period. To assess this, the present study compared the extra-GU manifestations of PBS in a contemporary cohort of living people who had survived the newborn period to those that had previously been described in the literature. Second, it assessed the impact of extra-GU manifestations of PBS on the QOL of these people and their families via a non-validated open-ended survey.

Materials and Methods

Historical prune belly syndrome cohort

A PubMed search using the terms ‘prune belly syndrome’, ‘PBS’, and ‘Eagle-Barrett syndrome’ was performed to identify studies during the period 1967-2013 that described the frequency of extra-GU manifestations in people with PBS of all ages – living and deceased. The decision to review a paper was based on a review of the study abstract. Publications that exclusively reported urologic data, surgical outcomes, or newborn subjects were excluded. The overall frequency of each extra-GU manifestation of PBS was calculated by averaging the individual frequencies of each manifestation from all identified studies to derive the historical cohort data.

Contemporary, living prune belly syndrome cohort

With IRB approval, living people with PBS from 2010-2013 were prospectively recruited into a DNA/tissue repository at Children's Health Dallas or at three PBS Network National Conventions. Deceased people with PBS and those who did not survive the newborn period (defined as the first 30 days of life), and non-English speakers were excluded. The family/person with PBS completed a comprehensive PBS medical health questionnaire (available on request) and provided medical records for retrospective review of the person with PBS. Clinical data on the frequency of extra-GU manifestations of PBS were extracted and calculated from the questionnaire, outside medical records, and medical records for local subjects. The clinical information that was reported in the questionnaires was crossed referenced with outside hospital records, when possible, to ensure accuracy.

To document which aspects of PBS negatively affect QOL in people with PBS and their families, an open-ended non-validated prune belly syndrome quality of life (PBSQOL) survey was created and administered to those with PBS and their family members at the August 2013 national meeting of the Prune Belly Syndrome Network in St. Louis, MO, USA. The PBSQOL survey posed three open-ended questions requiring anonymous, unbiased, free-text responses about how the disease and medical care affected their QOL (Appendix). The PBSQOL survey was distributed to people with PBS >10 years old and family members to be completed anonymously in private; it was hoped that this would

remove any potential bias of the providers directly asking questions. Each question was on a separate sheet of paper, which allowed documentation of as many lines of free-text responses to each question that were required. The responses were reviewed and categorized into thematic domains and expressed as a percentage of responders.

Statistical analysis

The frequency of extra-GU manifestations was compared between the historical and contemporary, living cohorts with Fischer's exact test via GraphPad statistical software.

Results

Of the 706 identified publications on PBS, seven historical studies met inclusion criteria and tabulated the frequency of extra-GU PBS manifestations (Table 1). One contemporary study by Routh et al. was reviewed but excluded from the analysis as it only studied newborns with PBS [3]. The selected studies for review were published a mean of 30 years ago (19-39 years). When combined, the seven publications included a total of 204 PBS subjects ranging from newborns to adult survivors. Combining these studies, the historical cohort of PBS subjects had the following weighted average frequency of extra-GU comorbidities: 36% gastrointestinal disorders, 50% orthopedic diagnoses, 24% cardiopulmonary diseases, and 20% developmental delay (Fig. 1).

Of the 95 cases of PBS in the Children's Health DNA/tissue repository, 27 had incomplete clinical data and three were deceased in the newborn period, leaving 65 living subjects for analysis. The subjects were a mean age of 10 years (1 month-45 years) and 99% were male. These living patients had a statistically significantly higher incidence of gastrointestinal (63%), orthopedic (65%), and cardiopulmonary (49%) diagnoses when compared with the historical cohort of 204 PBS subjects from the literature (Fig. 1).

Table 2 compiles the complete list of extra-GU manifestations seen in the contemporary cohort of living patients. The most common diagnoses for each organ system were: constipation (58%), scoliosis (25%), and asthma (22%). With regards to other diagnoses, there was a trend towards a higher number of PBS patients with developmental delay compared with previously published studies; however, the difference was not statistically significant (Fig. 1). In addition, 17% (11/65) had a neurologic comorbidity, with the most common being hearing loss (11%).

Forty-three people completed the PBSQOL survey: 11 males with PBS and 32 family members. The mean age of the males with PBS was 22 years (8-46 years). A total of 47% of the respondents listed at least one non-GU problem (i.e. lung disease, skeletal problems, constipation) as negatively affecting their QOL (Table 3). A total of 42% of respondents listed at least one GU problem (i.e. self-catheterization, recurrent UTIs) as negatively affecting their QOL (Table 3). In addition, 56% reported a musculoskeletal surgery (i.e. abdominoplasty, club foot repair) and 21% reported a gastrointestinal surgery or medication as positively impacting their QOL (Table 3).

Discussion

The challenge of treating the complexity of urologic disease in PBS is often compounded by difficulty in drawing evidence-based conclusions from experience, as even the largest institutions may only treat 10-20 PBS patients over several decades [3]. Thus, little is known regarding the outcomes of contemporary PBS patients, as very few modern publications exist [3]. This is especially relevant to non-GU manifestations of PBS, the frequency of which is based on small studies published 20-30 years ago [1,2,4-8].

In addition to being historical outcomes, existing publications often include autopsy studies and subjects that deceased in the first few months of life. In the present study, it was hypothesized that the inclusion of these subjects in the tabulation of the frequency of non-GU PBS comorbidities would overestimate the incidence of severe, possibly fatal, associated anomalies such as bilateral renal dysplasia and pulmonary hypoplasia, and underestimate the incidence of non-life-threatening non-GU comorbidities such as orthopedic and gastrointestinal diseases. The goal of the present study was not to describe the frequency of non-GU manifestations in all people with PBS, as this does little other than guide providers in perinatal counseling. Rather, the driving force behind the design and execution of this study was to identify the frequency of non-GU PBS comorbidities in those that survived the newborn period and, thus, ended up in the office of the pediatric urologist, often requiring multiple major urologic surgeries.

In this largest reported series of living people with PBS, the frequency of gastrointestinal, orthopedic, and cardiopulmonary diagnoses was found to be significantly higher than previously published. Although it is tempting to attribute this to improved newborn survival, this is likely not the case. In the seven historical studies, the pooled percentage of PBS subjects that deceased in the first few months of life was 27% [1,2,4-8]. A recently published study of 133 PBS subjects, utilizing administrative data from 2000-2006, noted an in-hospital mortality of 29% [3]. Thus, PBS still has a significantly early mortality rate, and improved newborn survival does not explain these findings. It is more likely that a higher frequency of non-GU comorbidities was found in the contemporary cohort because all of the subjects were living and, thus, had time to develop and be diagnosed with more extra-GU manifestations of the disease.

Although seemingly straightforward, these high frequencies of non-GU manifestations of PBS should be very important to urologic providers. Constipation was diagnosed in 58% of the contemporary patients. The association between bladder and bowel dysfunction has previously been well recognized, with several studies in children documenting that constipation is associated with UTIs, enuresis, VUR, and upper tract dilatation [9]. As these are common urologic problems associated with PBS, it is extremely important to assess the bowel habits of these patients with a targeted history and proper clinical examination, as constipation may not be recognized and reported by the parents [9]. Because of the lack of abdominal wall musculature, constipation may also require more aggressive treatment in these patients, and poorly managed constipation could diminish the outcomes of abdominoplasty surgery.

Cardiopulmonary comorbidities were noted in 49% of contemporary PBS patients. The most common of which (reactive airway disease) affected nearly a quarter of the patients. This is extremely important knowledge for the peri-operative and anesthetic management of these patients who often require long and complex urologic reconstructive surgeries. Because of the absence of abdominal muscles and limited movement of the diaphragm, anesthesia is thought to be more hazardous for PBS patients because of the potential respiratory difficulties [10,11]. In addition, respiratory infections are common due the inability to cough effectively and consequent retention of secretions [10]. Finally, PBS patients have been noted to have micrognathia, which may result in difficulties with intubation [12].

Historical studies have also reported respiratory failure and death following general anesthesia in PBS patients [10,13,14]. Thus, PBS patients require careful pre-operative assessment and any existing respiratory infections must be thoroughly treated prior to elective surgery [10]. Although many of these concerns may be addressed by anesthetists, urologists must be aware of the presence of cardiopulmonary comorbidities when planning for appropriate level operating rooms and recovery beds (i.e. ICU), as well as preparing the patient and family for a potentially prolonged hospital recovery. For moderately and severely affected PBS cases, postoperative aggressive pulmonary toilet and pain control are prudent, as narcotics may cause respiratory depression during the recovery period [10]. In addition, single-dose antibiotics may be considered, even for short procedures, because of the increased risk of postoperative respiratory infections [4].

Orthopedic comorbidities were noted in 65% of the contemporary PBS patients. These may have a variety of effects on the surgical management of these patients. Facial abnormalities such as Potter's facies may affect the fit of oxygen masks [11]. Pectus excavatum may restrict pulmonary volumes and require positive pressure ventilation [11]. Care must be taken with positioning PBS patients in the dorsal lithotomy position, as congenital hip dysplasia and dislocations are often present [11]. Finally, orthopedic diagnoses such as scoliosis and clubfoot may make postoperative ambulation more challenging for the PBS patient.

In addition to being a concern for the provider, the present study sought to identify what aspects of their disease matters the most to those affected by and living with PBS. Most standardized and validated QOL surveys ask broad, general questions that are not disease-specific or disease-related enough to show an association with the disease or disease intervention. In addition, existing QOL study tools assume that physicians know what is important to those affected by PBS. Considering these limitations, an open-ended QOL survey was selected to initiate patient-centered outcomes for PBS.

To date, there is only one existing QOL report of people with PBS, which surveyed 22 adults using the RAND 36-Item Health Survey to assess health-related QOL [15]. The majority of the adults scored above the average established standard population norms for: physical function, lack of limitations due to physical and emotional problems, energy, mental health/sense of emotional wellbeing, social function, and body pain [15]. While it is reassuring that people with PBS had a health-related QOL similar to the reference

population, this report did not shed light on what specific aspects of PBS positively or negatively affected QOL.

As expected, the present survey of PBS patients and their families revealed that the majority felt that GU problems negatively affect QOL. However, nearly 50% of the respondents also stated that a non-GU aspect of the disease had a negative effect on QOL. In addition, patients and their families reported that the correction of musculoskeletal problems through abdominoplasty and/or orthopedic surgeries was the most common way that health providers have improved their QOL. These findings highlight that it is important for healthcare providers to identify any non-GU manifestations of PBS; they also emphasize how treatment of these aspects of the disease may significantly improve QOL. The ultimate goal of this survey was to generate domains for inclusion in a patient-centered, clinical PBS Assessment Tool (PBSAT), which will be nationally administered during routine healthcare visits and be used to offer targeted educational, clinical and psychosocial resources to each PBS child/youth and their parents.

This study of the long-term outcomes of a rare GU disease was hampered by the use of a non-validated QOL survey and dependence on potentially incomplete data collection gathered from many hospitals. Although the medical questionnaires were completed by the patients and their families and, thus, subject to recall bias and inadequate medical understanding, the answers were secondarily validated by retrospective review of medical records in >30% of the cases.

Strengths of this study included the large sample size of living patients, representing a wide age range, as well as inclusion of QOL data.

It is well known that people with PBS have a wide range of GU manifestations of the disease. However, this study emphasized that these complex patients often have a wide range of gastrointestinal, orthopedic, and cardiopulmonary diagnoses and that these comorbidities may negatively affect their QOL. Urologists, who often coordinate the required multidisciplinary care of PBS patients, must be well aware of these comorbidities, as these ailments will likely effect the treatment of urologic diseases, tolerance of long anesthetics, and recovery from surgical procedures.

Conclusions

In this large contemporary series, surviving people with PBS had a significantly higher incidence of orthopedic, gastrointestinal, and cardiopulmonary diagnoses than reported in previous PBS publications. As urologists are often the most-frequently seen physicians of these complex patients it is extremely important to be aware of and prepare for the high incidence of comorbidities, which may directly impact on the treatment and QOL of these patients.

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Appendix

Open-ended PBS QOL survey

Question 1: What are the things about having **Prune Belly Syndrome** that negatively affect your quality of life or the quality of life of your child?

Question 2: What treatments, surgeries, procedures, medications, etc. that your healthcare providers and/or doctors have recommended have had a POSTIVE impact on your quality of life or the quality of life of your child?

Question 3: What treatments, surgeries, procedures, medications, etc. that your healthcare providers and/or doctors have recommended have had a NEGATIVE impact on your quality of life or the quality of life of your child?

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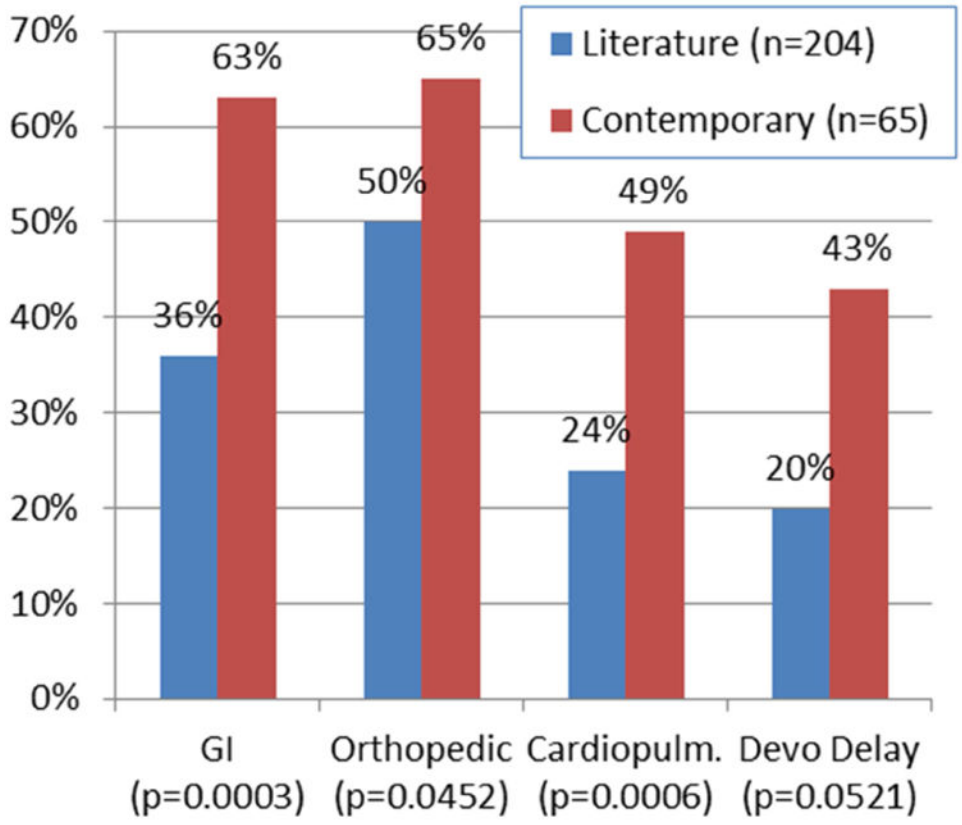

Fig. 1.

Comparison of extra-genitourinary manifestations of prune belly syndrome in the contemporary vs historical cohort.

Table 1

Publications included in the historical cohort detailing extra-genitourinary prune belly syndrome manifestations (*n*=204).

Author	Journal	Year	*N*
Rogers et al[8]	*J of Ped*	1973	20
Carter et al[1]	*Urology*	1974	10
Goulding et al[2]	*Urology*	1978	30
Geary et al[6]	*J of Urol*	1986	25
Lattimer et al[7]	*J of Urol*	1987	50
Manivel et al[5]	*Pediatr Pathol*	1989	29
Brinker et al[4]	*J Bone and Joint Surgery*	1995	40
Total			**204**

Table 2

All extra-genitourinary manifestations of prune belly syndrome in the contemporary, living cohort (*n*=65).

Diagnosis	*N*	%
Cardiopulmonary		
Asthma/reactive airway disease	14	22
Recurrent infections/pneumonia	10	15
Pulmonary hypoplasia	9	14
Patent ductus arteriosus	5	8
Patent foramen ovale	4	6
Atrial septal defect	4	6
Pneumothorax	3	5
Gastrointestinal		
Constipation	38	58
Malrotation	7	11
Bowel obstruction	6	9
Gastrostomy tube	6	9
Hepatoblastoma	2	3
Gastroschisis	1	2
Imperforate anus	1	2
Orthopedic		
Scoliosis	16	25
Clubfoot	14	22
Other orthopedic deformities	14	22
Pectus excavatum/carinatum	12	18
Congenital hip dislocation	10	15
Sacral agenesis	1	2
Neurologic		
Hearing loss	7	11
Seizures	3	5
Brain tumor	1	2
Tethered cord	1	2
Spina bifida	1	2

Table 3

Factors that positively and negatively affect quality of life in people with prune belly syndrome and families.

Factors that negatively affect quality of life	**%**
Genitourinary problems (UTIs, cathing, etc)	42
Big belly	35
Being ‘different’/social issues/teased/staring	35
Inability to play sports	33
Developmental delays/attention deficit hyperactivity disorder	21
Skeletal problems	19
Constipation	16
Lung disease	14
Renal disease	12
Factors that positively improve quality of life	**%**
Musculoskeletal surgery	56
Genitourinary surgery	47
Gastrointestinal surgery/medications	21
Kidney transplant	14