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Growth morbidity in patients with cloacal exstrophy: a 42-year experience☆

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ABSTRACT

Purpose: Cloacal exstrophy is associated with multiple comorbidities that affect growth. This report describes long-term growth outcomes in a large cohort of patients with cloacal exstrophy and explores associated comorbidities.
Methods: Records of 71 patients with cloacal exstrophy who were treated between 1974 and 2015 were reviewed, and 62 patients with growth data from 2 to 20 years of age were included. Genetic sex, gender of rearing, and all heights, weights, and comorbidities were noted for each patient. Height-for-age, weight-for-age, and body mass index z-scores (HAZ, WAZ, and BMIZ) were determined using US Centers for Disease Control 2000 growth data, and average patient z-scores were calculated.
Results: There were 904 height and 1301 weight measurements available for 62 patients. 31 were genetically 46,XY, 21 of whom underwent gonadectomy in infancy and were raised female. 46,XX patients, 46,XY male patients, and 46,XY female patients all had median HAZ and WAZ substantially lower than the general population, with median HAZ less than −2, while maintaining normal BMIZ. Short bowel syndrome and enterocystoplasty with intestine were associated with lower z-scores for all parameters.
Conclusions: Patients with cloacal exstrophy have significant multifactorial long-term growth failure. These benchmark data can be used to further optimize management.
Level of evidence: 2b

Cloacal exstrophy is a complex congenital anomaly with an incidence of approximately 1/300,000 live births [1]. Although there is considerable variability, cloacal exstrophy classically consists of an omphalocele, imperforate anus, exstrophy of two small hemibladders (between which exists a lateral cecal fissure), and genital malformation. The terminal ileum often prolapses through the exposed cecum, and the hindgut is foreshortened [1,2]. As current survival has improved to nearly 100%, long-term outcomes are of paramount importance [3].

Patients with cloacal exstrophy frequently have comorbidities that affect growth and anecdotally struggle with growth failure. Approximately one quarter of patients with cloacal exstrophy are affected by short bowel syndrome (SBS) of varying severity [4]. Almost all patients have some degree of spinal dysraphism, ranging from tethered cord to lipomyelomeningocele. Skeletal abnormalities may affect the spine, pelvis, and lower extremities, with spinal abnormalities (including extra vertebrae, scoliosis, kyphosis) affecting 22–60% of patients, and lower limb anomalies, most commonly congenital talipes equinovarus, seen in 17–26% of patients [4].

Previous studies on the impact of enterocystoplasty on growth outcomes have had mixed findings, with some studies documenting an adverse effect and others demonstrating no effect after adjustment for confounding variables [6]. Abnormalities of the upper urinary tract are seen in up to two thirds of patients, and lower urinary tract

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Fullerton: Conception/Design, data acquisition, analysis and interpretation, participated in drafting, gave final approval.
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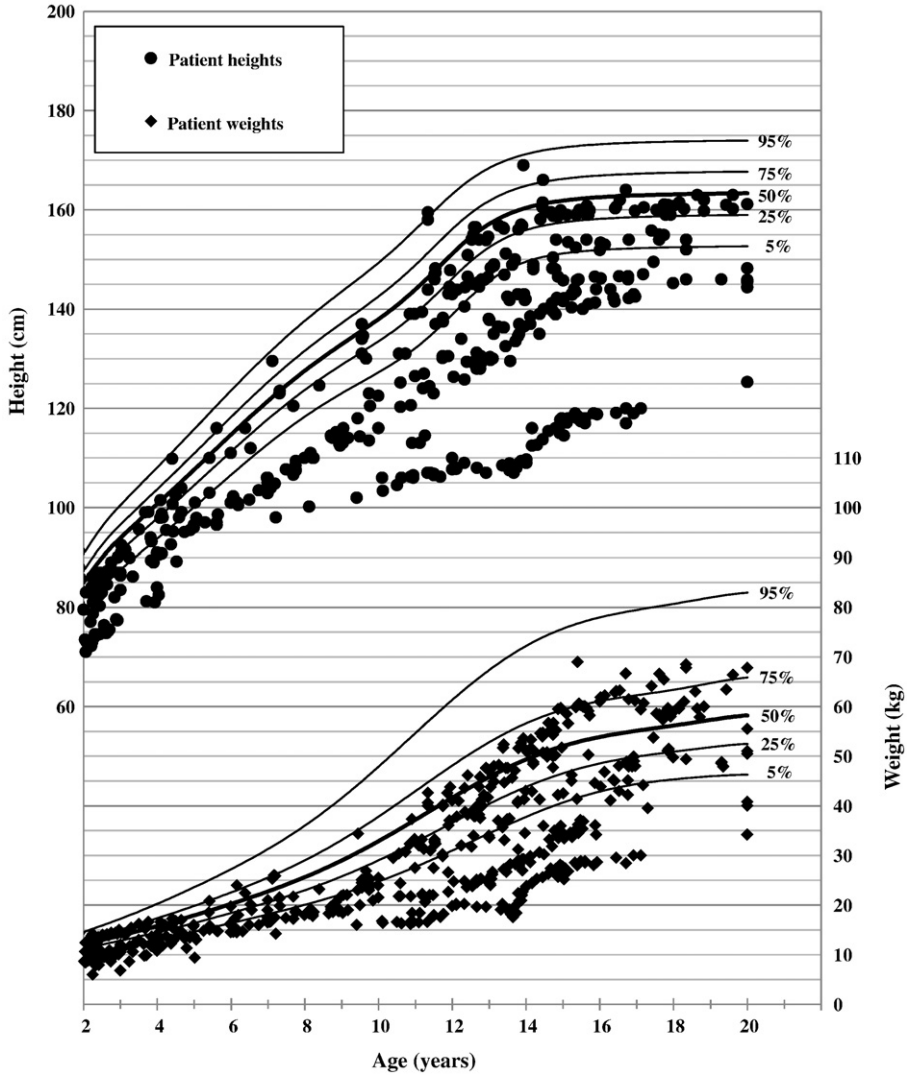

Fig. 1. 46,XX patient stature and weight with CDC 2000 **female** growth curves [12].

reconstruction may be complicated by metabolic and infectious sequelae [5]. Mild to moderate metabolic acidosis is reported in 15% of patients with incontinent urinary conduits and in approximately half of patients with continent urinary diversions, likely because of the longer segment of bowel used and the longer dwell time of urine within the pouch [5]. Gastrocystoplasty does not result in metabolic acidosis, and also has the advantage of enteral sparing for patients who have relatively short bowel [6].

Acidosis in turn impacts growth because of its effect on calcium homeostasis and direct effects on the growth hormone-IGF-1 axis. It results in increased urine calcium loss (as calcium is committed to H^+ as a buffer), increased intestinal sulfate absorption, which inhibits renal tubule calcium reabsorption, and the direct activation of osteoclasts causing growth disturbance and reduced bone mineral density [5,7]. Acidosis also blunts the release of growth hormone, and animal models have shown suppressed serum IGF-1, hepatic IGF-1 mRNA and hepatic growth hormone receptor mRNA, and decreased gene expression of IGF-1 at the growth plate of the long bones [8].

Patients with cloacal exstrophy often have conditions that can impair their ability to physiologically compensate for the metabolic derangements associated with enterocystoplasty. Renal insufficiency is an important risk factor for uncompensated acidosis, and the majority of patients have upper urinary tract anomalies, including renal agenesis, pelvic kidneys, horseshoe kidneys, fusion anomalies, hydronephrosis, or ureteral anomalies [5]. A predilection for renal impairment may be compounded by recurrent urinary tract infections [4]. In addition, patients may have high gastrointestinal losses because of congenitally short colon, small intestine, or ostomy, contributing to metabolic derangements. Growth disturbances because of acidosis can be reversed with adequate alkali therapy to correct metabolic acidosis [9].

This report is the first to describe long-term growth outcomes in a large cohort of patients with cloacal exstrophy and explores comorbidities that may be associated with growth failure.

1. Methods

1.1. Study design

With IRB approval (IRB-P00017268), the Boston Children's Hospital records of 71 patients with cloacal exstrophy treated at this institution and at Massachusetts General Hospital between 1974 and 2015 were reviewed, and patients who had height and weight recorded between 2 and 20 years of age were included in the study. Of the 62 included patients, 44 patients were followed by a single surgeon (WHH) with extensive expertise in the field. Genetic sex, gender of rearing, and all available height and weight measurements were collected for each