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REVIEW ARTICLE

Aphallia: a review to standardize management

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Abstract
Congenital aphallia is a rare anomaly with little supporting literature and controversial management. The aim of this review is to assess the most recent literature with a focus on staged management of these cases. We performed a PubMed search of all English literature in the past 10 years using the term aphallia. Twenty-three articles were identified of which six were excluded. A further three papers meeting our criteria were found in the references to papers initially identified. We found that management can be staged in three phases: short, intermediate and long-term. We conclude that optimal short-term management centers on resuscitation and urinary diversion as necessary, intermediate-term management entails urethrorectal fistula division, urethrostomy and neophallus creation and long-term management results in successful neophalloplasty, urethroplasty, prosthetic implant and continued protection of the upper urinary tracts with a Mitrofanoff. All this within a multidisciplinary team ensuring shared decision-making with the patient and their family.

Keywords Aphallia · Urethrorectal fistula · Neophalloplasty · Urethroplasty

Introduction

Aphallia is a rare disorder with only around 100 cases reported in the literature [1]. Because of its rarity (incidence estimated to be 1 in 10–30 million births) [2–4] and the difficulties it presents to both patient and families, treatment of this condition has been controversial. We review the English literature over the last 10 years in an attempt to clarify and better understand aphallia and its management.

Methods

Ethics was obtained from the Human Research Ethics Committee for the University of the Witwatersrand (R14/49). We performed a PubMed search of the English literature using the term 'Aphallia' with the following filters: Articles published in the last 10 years (2007–2017), Human subjects and children (birth–18 years). Because of the significant shift in attitude toward managing this subset of patients with feminizing genitoplasty to raising these children as male with phallus reconstructive procedures, we decided to limit our literature search to the last 10 years, thereby helping us strategize management based on recent literature more in line with current 'standard of care'.

Results

The search rendered 23 articles. Six articles were excluded (one paper not in English, two papers on intra-vesical penises, one systematic review and two papers that did not report on interventions). A further three papers fitting our criteria were identified when assessing references to the articles already included.

Table 1 shows all applicable papers with their cases, associated abnormalities, site of the urethrorectal fistula and type of intervention.

The above studies were case reports or case series reporting 30 cases of aphallia with a maximum of four cases per publication. Patient age ranged from a gestational age of 35 weeks to 12 years old. Four cases did not comment on associated abnormalities and only 3 (10%) cases reported no

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Table 1 Summary of published articles on aphallia including the associated abnormalities and chosen intervention

Author	Type of report	*N*	Age	Associated abnormalities		Site of urethrorectal fistula	Type of intervention
				Genitourinary	Non-genitourinary		
Joshi et al. [2]	Case report	1	11 months	Oligohydramnios Nonobstructed left megaureter	Spinal cord syrinx	Presphincteric	Planned for staggered perineal urethroplasty and pseudo phalloplasty*
Aslanabadi et al. [3]	Case report	1	Day 1 of life	Right kidney hypoplasia Left kidney dysplasia	–	Presphincteric	Died pre-intervention*
Goyal et al. [5]	Case report	1	Not reported	Fused kidneys in left-to-right crossed ectopia configuration	–	Postsphincteric	Staged phalloplasty and urethroplasty
Gouvea et al. [6]	Case report	1	11 years	Not mentioned	Not mentioned	Not mentioned	Previous urethrostomy, phalloplasty and Mitrofanoff Later penile prosthesis
Macedo et al. [7]	Case report	1	6 months	Not mentioned	Not mentioned	Presphincteric	Previous vesicostomy. Perineal urethrostomy, Mitrofanoff, phalloplasty
Kane et al. [1]	Case report	1	Day 1 of life	Grade III right VUR	–	Presphincteric	Initial cystostomy Later anterior urethral transposition Planned for phalloplasty at puberty
Friedman et al. [8]	Case series	3	Day 1 of life	Right renal atrophy and partial duplication Bilateral hydronephrosis Left hydroureter Bilateral Grade V VUR Periureteral bladder diverticulum / dilated utricle receiving ectopic left ureter Urethral narrowing	Anteriorly displaced anus	Postsphincteric	Urethral dilatation Bilateral ureteral reimplantation and diverticulectomy
			Day 1 of life	Right UVJ obstruction with hydroureteronephrosis and duplication Patulous bladder neck Right-sided bladder diverticulum PUV	–	Postsphincteric	Ablation of PUV Intravesical excisional tapered right ureteral reimplantation and paraureteral diverticulectomy Later ureterolysis and right-to-left transureteroureterostomy
			Day 1 of life	Stenotic urogenital sinus Bilateral renal dysplasia (right dysplastic kidney, left MCDK) Right ureteral ectopia left ureteral atresia bladder agenesis	Anterior patulous anus Kommerell diverticulum with oesophageal ring Left inguinal hernia Umbilical hernia Mild developmental delay	Postsphincteric	Renal transplant Temporising ureterostomy Ileocaecal neobladder and Mitrofanoff with non-refluxing implantation of transplant ureter

Table 1 (continued)

Author	Type of report	*N*	Age	Associated abnormalities		Site of urethrorectal fistula	Type of intervention
				Genitourinary	Non-genitourinary		
Gerard-Blanluet et al. [9]	Case report	1	Post-mortem (35/40)	URSMS (complete urogenital aplasia with imperforate anus, urethral atresia, bilateral renal cystic dysplasia, persistent urogenital horns) Right inguinal testis Oligohydramnios	Bilateral clubfeet Potter sequence Single umbilical artery Unilateral lung agenesis Thoracic hemivertebrae 14 left ribs	Urethral atresia	Termination of pregnancy at 35 weeks gestation*
Bahe et al. [10]	Case report	1	6 days	Bilateral hydronephrosis and hydroureter	–	Not mentioned	Vesicostomy at initial presentation
Willihnganz-Lawson et al. [11]	Case report	1	5 years	Horseshoe MCDK Ureteral and bladder atresia	–	Postsphincteric	Peritoneal dialysis Previous cadaveric renal transplant with cutaneous ureterostomy Later takedown of ureterostomy Phalloplasty
Rattan et al. [12]	Case series	3	Day 1 of life	Unilateral renal agenesis	Imperforate anus	Postsphincteric	Urethral dilatation Planned for later phalloplasty*
			Neonate	Right ectopic pelvic kidney	–	Postsphincteric	Planned for perineal urethrostomy*
			6 months	–	–	Presphincteric	Parents refused treatment
Shamsa et al. [13]	Case report	1	18 months	–	–	Presphincteric	Previous open cystostomy Stone removal Perineal urethrostomy
Coquet-Reinier et al. [14]	Case report	1	Day 2 of life	Bilateral grade II VUR	–	Postsphincteric	Feminizing genitoplasty
Descamps et al. [15]	Case series	2	Day 1 of life	Not mentioned	Not mentioned	Postsphincteric	Feminizing genitoplasty Later phalloplasty and staged urethral reconstruction
			Day 1 of life	Bladder exstrophy	–	Not mentioned	Feminizing genitoplasty Augmentation cystoplasty and bladder neck tightening Urinary diversion Later phalloplasty and testicular implants
Nakano et al. [16]	Case report	1	Day 1 of life	URSMS (imperforate anus, covered cloacal exstrophy, bifid scrotum, vesicointestinal fistula, duplicated colon, caecum and appendix SSBS) Patent urachus	Mild bilateral radial dysplasia Wide pubic diastasis	Urethral atresia	Cystostomy

Table 1 (continued)

Author	Type of report	*N*	Age	Associated abnormalities		Site of urethrorectal fistula	Type of intervention
				Genitourinary	Non-genitourinary		
Bothra et al. [17]	Case report	1	4 years	Bilateral grade III hydronephrosis Left VUR Right hydroureteronephrosis	–	Presphincteric	Perineal urethrostomy
Sharma et al. [18]	Case report	1	Day 1 of life	Oligohydramnios URSMS (imperforate anus, bilateral renal agenesis)	Single umbilical artery Depressed nasal bridge Endocardial cushion defect Prominent cerebral ventricles with bulky choroid plexus Pulmonary hypoplasia	Not mentioned	Non-operative (supportive) care
Mane et al. [19]	Case report	1	7 years	Poorly developed scrotum Bilateral UDTs Grades I and III VUR Bilateral hydronephrosis Unilateral medial renal rotation Urachal fistula	–	Postsphincteric	Single stage feminizing genitoplasty
Amiri et al. [20]	Case series	3	Day 1 of life	Bilateral hydronephrosis Left VUR	Limited hip abduction	Presphincteric	Planned for phalloplasty*
			Day 1 of life	Multicystic, atrophic kidneys Patent urachus Bilateral VUR	Oligohydramnios Low-set ears Saddle nose Hepatomegaly Superiorly located umbilicus Short sacrum Bilateral clubfoot Mild TI and small PDA	Urethral atresia	Cystostomy Died pre-penile intervention*
			Day 1 of life	Bifid scrotum Mild left VUR	Mild TI	Postsphincteric	Parental refusal

Table 1 (continued)

Author	Type of report	*N*	Age	Associated abnormalities		Site of urethrorectal fistula	Type of intervention
				Genitourinary	Non-genitourinary		
De Castro et al. [21]	Case series	4	6 months	–	Not mentioned	Presphincteric	Phalloplasty + urethroplasty. Later removal of distal urethra and scrotal urethrostomy (planned for scrotoplasty + glanuloplasty / new distal urethroplasty)
			17 months	Right multicystic dysplastic kidney Megacystis and megaurethra Bilateral undescended testes	Hirschsprung's Disease	Presphincteric	Phalloplasty + urethroplasty Vesicostomy Later re-do glanuloplasty
			3 years	Enlarged, irregular and hard right testis	Not mentioned	Presphincteric	Previous bilateral loop ureterostomies + attempt at urethral relocation Phalloplasty + urethroplasty
			12 years	Not mentioned	Not mentioned	Presphincteric	Phalloplasty + urethroplasty

* Planned interventions that had not yet taken place at the time of the published report

N number of patients in paper, *VUR* vesicoureteral reflux, *PUV* posterior urethral valves, *UVJ* ureterovesical junction, *URSMS* urorectal septum malformation sequence, *MCDK* multicystic dysplastic kidney, *SSBS* severe short bowel syndrome, *UDT* undescended testis, *TI* tricuspid insufficiency, *PDA* patent ductus arteriosus

associated abnormalities. Position of the urethrorectal fistula was pre-sphincteric in 12 patients (40%), post-sphincteric in 11 patients (36%) and complete urethral atresia with no communication was described in three patients (10%). There was no position reported in four patients (13%). Eight patients (27%) had planned interventions that were not carried out at the time of publication. Two patients (7%) refused treatment. Four patients underwent feminizing genitoplasties of which two patients later went on to gender identify as male with subsequent phalloplasties performed. Eighteen patients (60%) required multiple surgical procedures.

Table 2 assessed only the papers that dealt with phalloplasty with or without urethroplasty.

Of the ten cases reported in Table 2, three patients (30%) had 'interim' phalloplasties necessitating future reconstructive phalloplasty. Five patients (50%) underwent simultaneous urethroplasty and phalloplasty although only one patient (10%) did not need further urethroplasty intervention and only one patient (10%) had a good cosmetic outcome. Seven patients (70%) underwent De Castro technique phalloplasty.

Discussion

Aphallia is defined as an absent phallus with an ectopic urethral opening, usually associated with a well-developed scrotum and bilaterally palpable testis. The absent phallus is characterized by absence of all three components of the phallus, namely the two corpora cavernosa and the corpus spongiosum [3, 8, 10, 14]. As the defining factor is absence of the corpora, aphallia may also occur in female patients although it is thought to be less common and more difficult to diagnose [8]. This is most likely attributable to a high association with bladder agenesis and higher in-utero mortality [8]. Aphallia may also be an association of the urorectal septum malformation sequence (URSMS) spectrum of disorders [9, 18]. As such, aphallia must be considered on a spectrum ranging from an isolated disorder where the rest of the genitourinary tract has a normal configuration, to a symptom of a broader spectrum of congenital malformations, which is the case, in over 50% of patients [9, 18, 22]. These include anomalies of the genitourinary, gastrointestinal and musculoskeletal systems and sometimes with more severe anomalies incompatible with life [9, 18, 22].

The aetiology of aphallia is unknown but has been described as a sporadic malformation [11]. Genetic work based on murine models has shown association with abnormalities in the Sonic Hedgehog (SHH) gene, which is critical in bladder and bowel development, with impaired signaling of fibroblast growth factor [8]. Aberrant signaling of retinoic acid within the SHH pathway has also been found to be associated with impaired genital tubercle development via inhibited vasculogenesis [8].

Table 2 Phalloplasties, urethroplasties and outcome

Author	Phalloplasty–interim/final	Technique	Urethroplasty	Outcome of phalloplasty
Joshi et al. [2]	Interim	For creation of phallic structure at 18 months and functional phallus at puberty (using vascularised flap around prosthesis)	Planned for perineal urethrostomy before phalloplasty*	
Goyal et al. [5]	Interim	Parascrotal flap phallo-urethroplasty	Staged urethroplasty at later stage	Good skin sensation, position and appearance Adequate length for age Standing micturition and continence Good psychosocial functioning
Gouvea et al. [6]	Final	De Castro phalloplasty perineal urethrostomy and Mitrofanoff	–	Thinner penile shaft Excellent initial outcome
Macedo et al. [7]	Final	De Castro phalloplasty	Perineal urethrostomy	Some degree of penile retraction in length
Willihnganz-Lawson et al. [11]	Final but possible need for future reconstruction	De Castro neophalloplasty	Previous catheterisable stoma created	Regression of distal neophallus, Some loss of conical glanular shape High satisfaction
Descamps et al. [15]	Final	Pedicled anterolateral thigh flap phalloplasty	Staged urethral reconstruction begun at time of phalloplasty	Wound dehiscence at distal tip of neophallus
De Castro et al. [21]	Interim-for cosmetic reoperation	Quadrangular abdominal skin flap phalloplasty + bladder/buccal mucosa free graft urethroplasty	Initial urethroplasty at time of phalloplasty but later distal urethra removed and scrotal urethrostomy performed	Progressive meatal and urethral stenosis
	Final	Quadrangular abdominal skin flap phalloplasty + bladder/buccal mucosa free graft urethroplasty Later re-do glanuloplasty	Simultaneous urethroplasty	Good cosmetic outcome
	Final	Quadrangular abdominal skin flap phalloplasty + bladder/buccal mucosa free graft urethroplasty	Simultaneous urethroplasty	Epispadic urethral meatus due to partial dehiscence of dorsal urethral sutures
	Final	Quadrangular abdominal skin flap phalloplasty + bladder/buccal mucosa free graft urethroplasty	Simultaneous urethroplasty	Epispadic urethral meatus due to partial dehiscence of dorsal urethral sutures

* Planned interventions that had not taken place at time of publication

During the fourth week of gestation, a mesenchymal prominence within the cloacal membrane proliferates to form the genital tubercle [8]. Aphallia is likely due to failed development, hence absence of the genital tubercle, related in part to inadequate development of caudal mesenchyme or an early insult in cloacal maturation [8]. In the more severe aphallia associated malformations, the problem may originate with a defect in the induction of cloacal differentiation [9] occurring in early embryogenesis as a defect in blastogenesis [18]. This occurs at the same time as organogenesis of other systems, which explains the wide range of associated malformations seen, principally in URSMS, which may be partial or full [9, 18]. Partial URSMS is characterized by a single perineal opening draining a common cloaca with any number of associated systemic malformations (GU, GIT, MSK), whereas full URSMS is characterized by absence of both perineal and anal openings, usually associated with severe pulmonary hypoplasia and oligohydramnios secondary to severe associated renal anomalies, and is not compatible with postnatal life [9, 18].

Diagnosis is made clinically with the absence of the phallus in a child with normal karyotype on genetic testing. The absence of the phallus should not be mistaken for a concealed or rudimentary penis, micropenis, male pseudohermaphroditism or intra-uterine amputation of the penis [10].

Aphallia may be classified in three ways:

1) As a disorder of sex development of the non-hormonal/non-chromosomal type [23].
2) Skoog's anatomical classification related to the position of the ectopic urethra in relation to the anus, and the number of associated anomalies [2, 9, 12, 24].
    a. Post-sphincteric (fistula below the dentate line or anywhere on the perineum). This is the most common subtype (60%) and is commonly associated with a skin tag. It has the highest survival rate (87%) and the lowest incidence of associated anomalies (1.2 per patient) [9, 24].
    b. Pre-sphincteric (fistula above the dentate line, i.e., a urethrorectal fistula). This group makes up 28% of the aphallia population and has 36% mortality in the neonatal period related to associated life-threatening malformations [9, 24].
    c. Urethral atresia. This occurs least commonly (12%) and is uniformly fatal. It also has the highest number of associated malformations (4 per patient) [9, 21].
3) Evans' prognostic classification based on the presence or absence of major associated anomalies [2, 12, 25]
    a. First group—This occurs in 16% of cases and is associated with renal aplasia, renal dysplasia and other caudal abnormalities and has a high mortality [2, 25].
    b. Second group—72% of cases. This group has fewer associated malformations and has a lower mortality rate [2, 25].
    c. Third group—the remaining 12% of cases are not associated with any specific pattern of anomalies [2, 25].

Aphallia should, thus, be considered a developmental field defect. Although it does occur in an isolated form (with a good prognosis), it can be associated with multiple other anomalies with high mortality [25]. Overall, more than half aphallia patients will have an associated anomaly [2, 13], which can be broadly divided into genitourinary and non-genitourinary [13] (Table 1).

Management of this rare disorder has been controversial. As recently as 1997, the recommended surgery and only available reconstructive option for these children was feminizing genitoplasty. This was based on the belief that 'raising these patients as male can be disastrous', and that 'it is better to be incompletely female than inadequately male' [26]. This management strategy comprised a bilateral orchidectomy within the first few days of life, to prevent early post-natal androgen imprinting, followed by vaginal interposition and hormonal therapy at puberty [11, 26]. These patients experienced a high rate of gender dysphoria [2, 11] due, in part, to prenatal androgen imprinting that had already taken place. Prenatal and early neonatal androgen imprinting has been studied in animal models, pregnant females on hormone therapy and in children with congenital adrenal hyperplasia proving that exposure of the fetus to testosterone affects sex-typed interests in childhood (including toy, playmate and activity preferences) as well as sexual orientation in later life tending toward male typical behavior and gynephilia (erotic interest in females) [27]. Extrapolating from surgical management of patients with disorders of sex development, sexual designation should be based on the gender that provides the best prognosis in terms of reproductive function, capability of sexual function, appearance of the external genitalia and self-identity of the patient with a specific gender [4]. Therefore, although feminizing genitoplasty has still been recommended for infants and newborns in case reports as recent as 2015 [10], it is now generally accepted, and the opinion of these authors, that a normally genetic male with aphallia should be supported surgically as a male until the patient is old enough to gender identify.

As such, management can be divided into short, intermediate and long-term treatment phases [2]. From the most recent literature (Tables 1, 2), management can be divided as follows:

1) Short term—supportive care of life-threatening complications and associations of aphallia usually presenting in the neonatal period (resuscitation of compromised airway, breathing and circulation according to protocolled algorithms). Most pertinent is relief of urinary obstruction if present, this with the creation of a vesicostomy. Urinary obstruction may not always be present (as in cases of a urethro-perineal fistula) and would therefore, not need urinary diversion at this stage.
2) Intermediate term—division of the urethrorectal fistula with perineal urethrostomy with or without temporary phallus formation. This is preferably fashioned from scrotal skin to allow use of other sites for neophallus creation at puberty, allowing the imprinted male to outwardly identify as male from an early age (usually before toilet training).
3) Long-term—definitive phalloplasty and urethroplasty, with or without creation of a Mitrofanoff.

Successful creation of a neophallus should allow the patient to appear outwardly male, urinate standing up and perform adequately from a sexual perspective, usually with the help of a prosthesis.

When specifically considering the phalloplasty, the reconstructive techniques can be divided into microsurgical and non-microsurgical procedures [4]. Non-microsurgical procedures essentially constitute flap surgery, with techniques that are technically easier and simpler to perform but are generally performed as temporizing procedures, necessitating more definitive reconstructions during puberty. These more definitive procedures usually utilize microsurgical free flap techniques in combination with implantation of prostheses. This staged approach is necessary as rotational flap procedures performed in early life may not grow appropriately in relation to the patient and may not accommodate prosthesis implantation [4, 6]. The reason that these flap phalloplasties are used preferentially in infants is that construction of a permanent adult-sized neophallus in a paediatric patient is undesirable and this technique spares tissues used for microsurgical free flap phalloplasty for use at a later stage.

Non-microsurgical options for phalloplasty include groin, abdominal and scrotal flaps [4]. Although the De Castro flap (abdominal wall flap based on vascular supply from the superficial epigastric arteries) has been reported as a temporary reconstructive or pseudophallus option [11], it has been reported to grow adequately with the patient and has allowed prosthetic implantation allowing 'erectile' function [6].

Microsurgical procedures are complex with a much longer intra-operative time and necessitate multidisciplinary team management [4]. They are designed as a single-stage procedure to be performed in adulthood with the concomitant insertion of a penile prosthesis. Microsurgical procedures used in the past include osteocutaneous fibular flap, myocutaneous latissimus dorsi flap and the radial forearm flap [4].

Although many options exist for phalloplasty, the greatest reconstructive challenge in aphallia patients is the urethroplasty. Again, many options exist but the most commonly used option is the combined use of groin skin to create the posterior urethra and a buccal mucosal graft to fashion the anterior urethra. However, the majority of patients ultimately require a Mitrofanoff channel to adequately decompress the bladder and protect the upper tracts [4]. It is vitally important to understand which aspect of the reconstructive surgery is most important to the patient and their family to properly manage expectations. Long-term follow-up is essential but there is a distinct lack of information regarding the long-term outcomes of these patients. This is a major limitation to this review.

Conclusion

Because of the rarity of aphallia and its reconstructive complexity, management of this condition remains a challenge. Its management should be approached as a multidisciplinary team consisting of paediatric surgeons, paediatric urologists and plastic surgeons as well as nephrologists and psychologists. One conclusive statement that can be made is that feminizing genitoplasty should be avoided at all costs. When appraising the small number of cases reported it seems that the De Castro technique for non-microsurgical flap phalloplasty is the most commonly used technique with the best outcome. This flap is reported to grow with the patient, allows simultaneous urethroplasty with acceptable outcomes, and the potential for penile prosthesis implant at a later stage remains. It has the advantage of using skin and tissue in the surrounding area and so spares any area that may need to be used at a later stage for microsurgical free flap phalloplasty. All interventions should be undertaken with the end goal of meeting and managing patient expectations and protecting upper urinary tracts.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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