



## CASE REPORT

## PENILE AGENESIS ASSOCIATED WITH TREACHER COLLINS SYNDROME

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Penile agenesis or aphallia is a rare congenital anomaly occurring with a frequency of 1:10 -1:30 million newborns. Fewer than 100 cases have been reported worldwide. Associated urogenital malformations and the presence of oligohydramnios with pulmonary hypoplasia determine the infant's viability. Extra-urogenital anomalies have been described in the cardiovascular, gastro-intestinal and musculoskeletal systems.

We report our experience with two patients, one of whom constitutes the first described case of aphallia with associated mandibulofacial dysostosis (Treacher Collins syndrome). A brief review of the literature is included and treatment options for survivors are discussed.

### CASE REPORTS

#### Case 1

The patient presented after breech delivery at 34 weeks' gestation to a 17-year-old gravida 1 mother. An antenatal ultrasound in the third trimester had revealed oligohydramnios, bilateral nephromegaly with cystic dysplasia of both kidneys and no visible bladder. The family history revealed a pair of stillborn twins born to the mother's sister. The cause of death was unknown.

At birth the baby was asphyxiated with Apgar scores of 4 and 6 at 1 and 5 minutes respectively. The birth weight was 1 670 g. Absence of the penis was noted, with normal scrotum, normal midline raphe and slightly posterior displacement of the anal opening. Meconium and minimal amounts of urine were passed via the anus. Both kidneys could be palpated as multilobulated flank masses extending into the pelvis. The left gonad was in the scrotal sack, the right gonad could be felt in the inguinal canal. Further physical findings included a small

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chest, dolichocephalus with prominent occiput, epicanthic folds, posterior angulation of the ears, a short neck, proximal insertion of the thumbs and subluxation of wrists and elbows possibly as a consequence of oligohydramnios.

A chest radiograph revealed 13 pairs of ribs. Abdominal ultrasonography demonstrated multicystic dysplasia in both kidneys. A bladder could not be identified. Chromosomal analysis showed a normal 46 XY karyotype. On day 3 of life the baby died as a consequence of pulmonary hypoplasia.

An autopsy confirmed multicystic dysplasia of both kidneys. There was a duplication of the left ureter with ramification into a third ectopic and equally multicystic pelvic kidney in lieu of an absent bladder. Both testes were histologically normal.

#### Case 2 (Fig. 1)

This baby was born at term after a normal vaginal delivery to a 23-year-old gravida 1 mother. Birth weight was 2 450 g. The complete absence of a phallus was noted at birth together with a normal scrotum, a midline raphe, and an anal opening in normal position with an anterior anal skin tag. Meconium and urine were passed via the anus. The right gonad was in the inguinal canal, the left could not be palpated.

In addition, features of mandibulofacial dysostosis were apparent with downward-slanting palpebral fissures, lower lid colobomata, malar and mandibular hypoplasia and micrognathia. The infant's mother displayed similar facial features and gave a history of similar appearances in her own father and sister.

An abdominal ultrasound revealed kidneys of normal size with dilated pelvis bilaterally, distended ureters, and a thickened bladder wall suggestive of obstructive uropathy. A Tc-99m diethylenetriaminepentaacetic acid (DTPA) scan confirmed impaired renal excretion. A proctoscopy revealed a vesicorectal fistula entering the rectum 1.5 cm proximal to the anal opening. Laboratory investigations found a slight impairment of renal function, a normal 46 XY karyotype without anomalies on chromosome 5, and a normal postnatal testosterone surge. The karyotype of the baby's mother showed a normal 46 XX pattern with a normal chromosome 5.

A vesicostomy and a colostomy were placed on day 5 of life. The left testis was found in the abdomen during surgery. Female gender reassignment was considered and discussed with the family. At 3 weeks of life a bilateral gonadectomy was performed preserving the scrotal skin for a vaginoplasty at a later stage. Both testicles were histologically normal. After discharge from hospital the baby was lost to follow-up.

### DISCUSSION

Only about 90 cases of penile agenesis have been reported in the English literature. The underlying pathomechanism is



Fig. 1. Patient 2 after the placement of a vesicostomy and colostomy.

thought to result from an impaired proliferation of mesenchymal cells from the cloacal eminence forming the genital tubercle, a process that starts during the fourth week of embryological development.<sup>1</sup> Early changes are likely to affect the cloacal eminence as well, leading to a proximal urethro-intestinal communication and associated urogenital anomalies. Later changes lead to a more distal urethral opening at the anal verge without associated proximal anomalies. Scrotum and testes are usually well developed and the testicular function appears to be normal.<sup>2,4</sup>

Even earlier changes, occurring during the third week of embryological development, affect the caudal mesodermal migration from the primitive streak to the formation of the cloacal folds. Defects range from penile agenesis with imperforate anus and absence of median raphe to complete caudal regression syndrome with sirenomelia.<sup>5,7</sup>

Skoog and Belman<sup>8</sup> have suggested a classification of aphyllia according to the site of the urethral meatus. Sixty per cent of the patients under review had a postsphincteric urethral opening located at the anal verge on an anterior peri-anal appendage. Associated urogenital anomalies were few and mortality was low (13%). Twenty-eight per cent of patients had a presphincteric urethral opening in the form of a prostatic fistula. Associated anomalies occurred in one-third of cases and mortality was 36%. Complete urethral atresia occurred in 12% of cases. All of these patients had major urogenital anomalies, and all of them died as a consequence of pulmonary hypoplasia following oligohydramnios. Our first patient falls into the category of urethral agenesis, major urogenital anomalies and early demise. The second case demonstrates a postsphincteric urethral meatus, no major urogenital anomalies and survival.

Evans *et al.*<sup>9</sup> have suggested a different classification according to the presence or absence of major associated anomalies. The most commonly quoted anomalies are renal aplasia or dysplasia. However, the normal development of

renal blastema depends not only on renal development genes, a co-ordinated interaction between the developing ureteric bud and the surrounding extracellular matrix, and the presence of renal growth factors, but also on unobstructed urinary flow. Renal anomalies, particularly hypoplasia or dysplasia, may therefore be a consequence of obstructive uropathy due to penile agenesis rather than an independent association.<sup>10-12</sup>

The classification of Skoog and Belman<sup>8</sup> is more a reflection of the time of embryological development at which the insult occurs. The development ranges from complete caudal regression syndrome to penile agenesis with proximal urogenital-intestinal communication and major anomalies, to penile agenesis with distal communication and few anomalies.

Extra-urogenital anomalies are rare. Agenesis of the penis has been described as part of urorectal septum malformation sequence in infants of diabetic mothers,<sup>9,13</sup> as part of VATER association,<sup>14</sup> with spinal dysraphism<sup>9</sup> and with gastro-intestinal anomalies.<sup>15,16</sup> Our patient is the first described with associated features of Treacher Collins syndrome.

Treacher Collins syndrome is a dysplasia of the first and second bronchial arch structures inherited in an autosomal dominant fashion. The responsible gene defect has been mapped to 5q31.1-33.1. Ten distinct gene mutations have been identified, all resulting in a premature termination codon.<sup>17,18</sup> Phenotypic characteristics are bilateral hypoplasia of malar, mandibular and maxillary bones, downward-slanting palpebral fissures with lower lid colobomata, maldevelopment of the auricular pinnae, tympanic membrane and ossicular malformation with conductive hearing loss.<sup>19</sup> Spontaneous mutations are common, and Treacher Collins-like syndromes have been described without identifiable chromosomal abnormalities.<sup>20,21</sup>

Orr *et al.*<sup>22</sup> studied mice with caudal regression, bladder agenesis and anal atresia, and found a significant increase in craniofacial anomalies with microstomia, macroglossia, and cleft or arched palates, suggesting a direct or indirect relation between cranial and caudal development. Similar associations have not yet been described in humans.

Therapy for patients with penile agenesis currently includes female gender reassignment, gonadectomy in the neonatal period to avoid the postnatal testosterone surge with possible male gender imprinting, secondary vaginoplasty using scrotal skin or sigmoidal replacement, and anterior urethral transposition, followed by female hormone therapy at puberty.<sup>23-26</sup> Although surgically possible and cosmetically adequate, this approach may lead to serious gender-identity problems and long-term psychosexual morbidity in the affected genetic males.<sup>27-31</sup> Equally important is the burden placed on families to make a surrogate decision for gender reassignment of their infants,<sup>32</sup> particularly in a society where special value is assigned to male offspring. We fear that this may be the reason why our surviving patient disappeared from follow-up.



Attempts at male gender preservation have been made. Ciftci *et al.*<sup>32</sup> reviewed 18 cases reared as males. Functional and cosmetic outcome of penile reconstructive surgery was poor in all cases, none of the patients had been able to sustain satisfying heterosexual relationships, and most patients had difficulty accepting themselves as male. Urinary tract infections and obstructive uropathy were frequent complications. Until new surgical techniques improve the functional and cosmetic outcome of penile reconstruction, female gender reassignment may be the preferable approach, but severe psychosexual morbidity must be anticipated and dealt with.

## CONCLUSION

Penile agenesis remains a rare condition. Associations with other malformation syndromes may arise as more patients are described. The viability of the infants largely depends on the amount of dysplasia in the urogenital tract and on the development of pulmonary hypoplasia due to the oligohydramnios sequence. Distal urethro-rectal communication with adequate urinary drainage without renal anomalies carries a good prognosis. In these patients, surgical gender reassignment together with good psychosocial support provides a reasonable long-term treatment option.

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## LETTER FROM SOUTHAMPTON

### YES, WEAKLY FROM SOUTHAMPTON

Dear Aunt Ethel

The chorus of a Kipling 'Just So' song begins:  
 'Yes, weekly from Southampton  
 Great steamers white and gold  
 Go rolling . . .'

This tramp steamer is reeling a little, after two weeks in the port in question. For locums abroad, nonchalance and stoutheartedness are prerequisites. Walk with kings nor lose the common touch, to extend Rudyard.

Thus one doesn't bat an eyelid when met at Heathrow and whisked off to the Southampton General Hospital in a gleaming great Jaguar. Nor does the upper lip quiver even slightly as one's residence for five weeks looms murkily into sight. Stalag 9 no less: semi-permanent scaffolding, confiscated by the NHS when the contractor went bust; searchlights,

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