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A rare case of bilateral Vanishing Testicle Syndrome

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Abstract

Vanishing testicle syndrome (VTS) is due to regression of already formed testes. This could occur at any stage during or after testicular descent due any insult resulting in testicular atrophy. VTS is estimated to affect 1:1250 males. We present a rare case of a 12-year-old boy presenting with absent secondary sexual characteristics and short stature found to have bilateral vanishing testicle syndrome. His testes were impalpable at neonatal examination. At the age of 1.5 years an ultrasound scan detected the right testis in the inguinal ring, measuring 1.5 × 1 cm with features suggestive of ischaemia with likely acute or subacute torsion. The left testes was seen in the inguinal canal already atrophied by that time. Subsequently, on surgical exploration the right testis was found atrophied in the inguinal canal, and was replaced in the right sub-dartose pouch, but left testis could not be identified. Surprisingly, 4 months later laparoscopic exploration failed to identify either of the testes except for bilateral atrophied gubernaculum, indicating testicular regression. At the age of 7 years, magnetic resonance imaging confirmed the absence of either of the testes, with no remnants. On examination his height was 146.5cm, which was between the 25 th and 50 th percentile for that age, and below his mid-parental height range. He had no androgenic hair growth, testes were impalpable and had a prepubertal penis accounting to tanner stage of 1. He had hypergonadotrophic hypogonadism. Pubertal induction was done with testosterone injections which resulted in height gain and development of secondary sexual characteristics.

Introduction:

The entity Vanishing testicle syndrome (VTS) was coined by *Abeyaratne et al.* in 1969, and is also referred to as "Testicular regression syndrome" [1][2]. The two essential diagnostic criteria are; visualizing the blind-ending spermatic vessels within the retro-peritoneum or spermatic vessels and vas deferens exiting a closed internal inguinal ring, and Testis not palpated during examination under anaesthesia [2][3]. A small fibrotic nodule or nubbin with dystrophic calcification and haemosiderin deposition is usually found at the end of the spermatic cord, with or without identifiable testicular or para-testicular structures [2][3]. Cryptorchidism is reported in 1 – 4.6% full term and 1.1 – 45.3% pre-mature male infants [4]. This prevalence of cryptorchidism decreases to 1% by the age of 1 year [5]. Testes are non-palpable in 10 – 20% cases of cryptorchidism, and of these VTS accounts for 35 – 60% [6]. VTS occurs in < 5% cases of cryptorchidism [7]. VTS is estimated to affect 1:1250 males [8]. We present a rare case of bilateral VTS in a 12 year old boy who presented with short stature and absent secondary sexual characteristics with unpalpable testes.

Keywords: Vanishing testicle syndrome, Testicular regression syndrome, cryptorchidism, testicular atrophy, hypergonadotrophic hypogonadism

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Case presentation

A 12-year-old boy presented to the Endocrine clinic due to absent secondary sexual characteristics and short stature compared to his peers. He demonstrated good school performance, but was concerned about his physical appearance. He had no history of recurrent infections, mumps, malabsorption or known chronic disease. He had no exposure to radiation, denied anosmia, and was not on any long-term drugs. He had no known history of symptomatic testicular torsion, genital tract infections and denied history of perineal trauma. He had no family history of any hormonal disorders or chronic disease. He was a product of a non-consanguineous marriage following an uncomplicated pregnancy and delivery at term. His birth weight was 2.35 kg being between -2SD and -3SD below normal. According to his Child health development records, he had achieved a catch-up of weight after birth, gaining normal weight from 4 months of age onwards (Figure 1). However, he had no records of his height assessment.

His testes were not palpable in the scrotal sac at neonatal examination. At the age of 1 year and 7 months, an ultrasound scan detected the right testis in the inguinal ring, measuring 1.5 × 1 cm, with increased echogenicity of testes and epididymis with reduced central and increased peripheral vascularity. This indicated ischaemia with likely acute or subacute torsion, with no testicular atrophy at that time. The left atrophied testis was seen in the inguinal canal. Subsequently, one month later on surgical exploration the right testis was found atrophied in the inguinal canal, and was replaced in the right sub-dartose pouch, but the left testis was identified. Surprisingly, 4 months later laparoscopic exploration failed to identify either of the testes except for bilateral atrophied gubernaculum, indicating testicular regression. At the age of 7 years, magnetic resonance imaging (MRI) confirmed the absence of either of the testes, with no remnants.

On examination his height was 146.5cm, which was between the 25th and 50th percentile for that age. He had a body mass index (BMI) of 17.5 kg/m^2. His upper body and lower body height was proportionate and had no skeletal deformities. His mother's height was 154.3cm and father's height was 173.4cm with a calculated mid-parental height ranging from 162 – 178 cm. He had no pubic, axillary or facial androgenic hair growth, with a tanner stage of 1. His testicles were not palpable bilaterally in the scrotal sac or in the inguinal canals. His penile length was 5cm and was pre-pubertal. He had no discolouration of scrotal skin and tanner stage for genitalia was 1. He had no gynecomastia, abnormal facies or rashes. His lungs were clear, had no hepatosplenomegaly, and no cardiac murmurs.

A repeat ultrasound scan did not identify testes in the scrotum, inguinal canal or abdomen. His skeletal age assessment was appropriate for his chronological age. His renal functions and liver functions were normal. His Insulin like growth factor-1 (IGF-1) was 221.9 ng/ml (64 – 508 ng/ml) being normal for his age. He had hypergonadotrophic hypogonadism with a testosterone of 0.092 ng/ml (0.1 – 3.5 ng/ml), luteinising hormone (LH) of 43.93 mIU/ml (for age – 0.4 – 7 mIU/ml, for tanner stage 1 – 0.02 – 0.3 mIU/ml), follicle stimulating hormone (FSH) 112.38 IU/ml (for age – 2 – 9.2 mIU/ml, for tanner stage 1 – 0.26 3 mIU/ml). Inhibin B levels were not affordable. Thyroid stimulating hormone (TSH) was 1.79 μIU/ml (0.4 – 4 μIU/ml).

He did not require growth induction with growth hormone as he did not have growth hormone deficiency. He was started on pubertal induction with 3 monthly pubertal assessment for response to treatment. He was given intramuscular (IM) testosterone 50 μg monthly injection for 6 months.

3 months after pubertal induction his penile length increased to 7cm, with a pubic hair tanner stage of 1, and his height increased to 148 cm (0.5 cm per month) (Figure 2)(Figure 3). 6 months after commencing pubertal induction he noticed early morning erections, and mild appearance of facial hair. His penile length increased to 7.5 cm, genital and pubic hair tanner was 2, and height was 151.3 cm (1.1 cm per month) (Figure 2)(Figure 3). In 6 months, his testosterone injection dose was increased to 100 μg monthly, with the aim of gradually increasing it by 50 μg every 6 months until reaching a maximum dose of 250 μg monthly. Repeat ultrasound scan in 6 months detected no testicular tissue in scrotum, inguinal canal or abdomen. Ultrasound scan was planned to be repeated annually to detect reappearance of testicular tissue or malignant potential.

Discussion

This 12 year old boy presented with absent secondary sexual characteristics and was found to have bilateral non-palpable testes. Non-palpable testes in a phenotypical and karyotypical male could be due to many differential diagnoses including retractile testes, cryptorchidism, testicular agenesis, or vanishing testicle syndrome (VTS) [2]. If testes are visualised by laparoscopy or other imaging modality along the embryonic descending pathway it would indicate

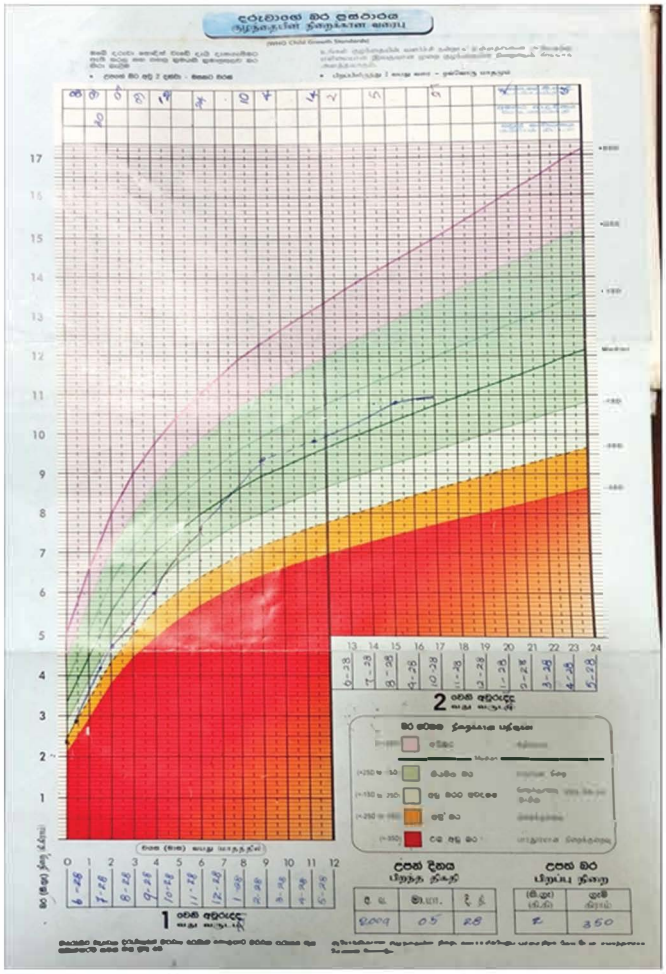

Figure 1: Child health development record showing weight monitoring since birth

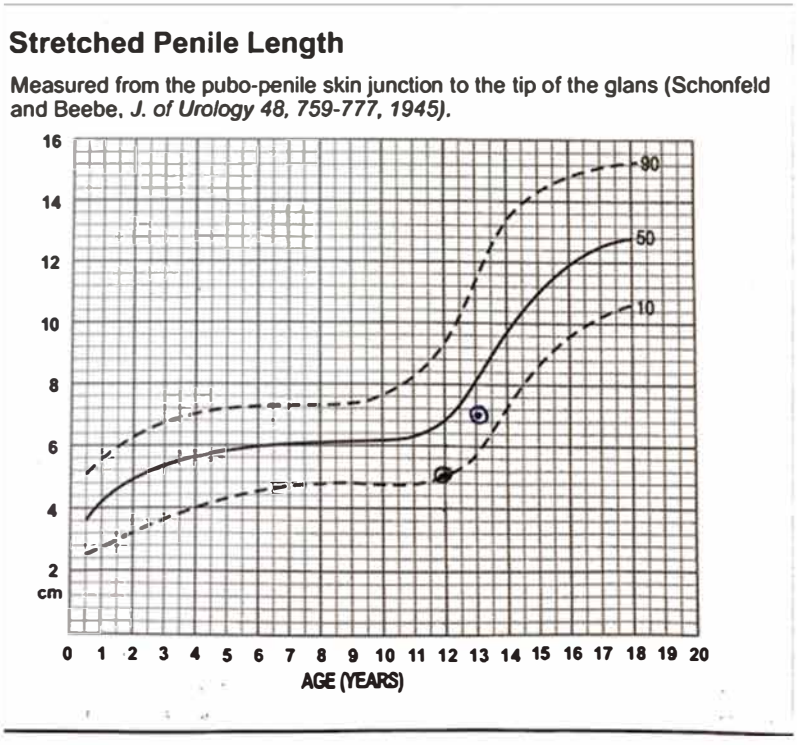

Figure 2: stretched penile length response to testosterone

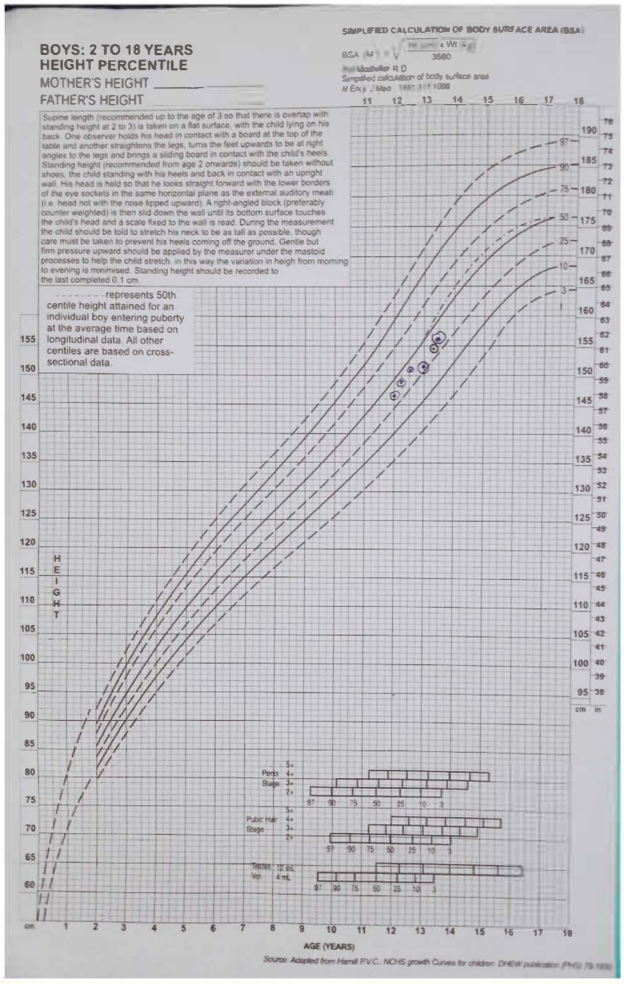

Figure 3: height response to testosterone

cryptorchidism, and if visualised in another location it would indicate ectopic testes [2]. Testicular agenesis is due to non-formation of testicular tissue during embryogenesis, and is rarer than VTS [3]. In the case of bilateral testicular agenesis, the individual would be a phenotypic female with male XY genotype, and will have persistence of mullerian structures due to the absence of mullerian inhibitory hormone [3]. VTS is due to regression of already formed testes.

VTS can present with a range of phenotypes and clinical manifestations. Though patients with VTS usually have a male phenotype, the phenotypical spectrum can range from normal male, through phenotypical male with micropenis, and intersex to phenotypical female. The degree of masculinization and where the patient stands in the phenotypical spectrum, depends on the duration of testicular function prior to its regression, based on the extent and timing of the intrauterine or extrauterine insult leading to testicular regression in relation to sexual development. The extent of the insult leading to regression can result in either unilateral or rarely bilateral testicular regression, or partial or complete loss of testicular tissue. The timing of the insult leading to regression can range from early and late embryonic, and early, mid and late fetal or early neonatal events [3]. A study by *Gou et al.* showed that 63.8% of thoses diagnosed with VTS are less than 36 months old [9]. *Spires et al.* reporteda 26 year old male who was diagnosed with VTS, 11 years after orchidopexy for cryptorchidism [7]. *Kathar Hussain et al.* reported a male diagnosed with VTS at the age of 40 years, which is the oldest reported case to our knowledge [10]. We reported a case of VTS which likely occurred at the age of 24 months, and was then formally diagnosed at the age of 12 years. He is a normal male in the phenotypical spectrum with absent secondary sexual characteristics. Despite bilateral cryptorchidism, he had a normal sized right testis for age by 1 year and 7 months. USS at that time showed features suggestive of acute or sub-acute right testicular torsion, with left testicular atrophy. This indicates the right testis possibly underwent torsion at or slightly before 1 year and 7 months.The left testis might have undergone torsion and started regression before the right as it was already atrophied by then. The left testis was undetectable by 20 months of age, and the right testis was undetectable by 24 months of age, indicating the occurrence of bilateral vanishing testicle syndrome.

The embryonic differentiation to a male fetus is triggered mainly by the SRY gene located in the Y chromosome and SOX9 gene which initially differentiates the gonadal ridge into testicular tissue comprising Leydig cells and Sertoli cells [11]. The epididymis, vas deferens, and seminal vesicle develop separately from the Wolffian ducts under the influence of testosterone produced by Leydig cells [11]. SRY gene triggers Sertoli cells to produce Mullerian inhibitory hormone by which Mullerian structures are regressed by the 6th to 8th week [11]. Since testicular regression in VTS occurs after completion of these steps of embryonic development, all those with VTS will have absence of Mullerian structures, in the presence of wolffian structures with or without varying degrees of regression.

There are 2 phases of testicular descent. The transabdominal phase which occurs between 8th and 15th week of gestation is controlled by Insulin-like 3 (INSL3) produced by Leydig cells [12]. Mutations of genes regulating the production of INSL3 have been found in some patients with cryptorchidism [12][13]. The inguinoscrotal or final descent phase, in which the gubernaculum migrates from the groin to scrotum completes by the 35th week [11]. The genitofemoral nerve, under the control of androgens, releases calcitonin-related peptide that influences gubernaculum migration [11]. Failure of any of these stages can lead to interruption of testicular descent, resulting in cryptorchidism. The transient or long term intra-abdominal location of the testicle in cryptorchidism could result in germ cell degeneration and loss due to increased temperature, and could result in VTS [12]. *Ueda et al.* verified that cryptorchidism with a closed internal ring will result in VTS 100% of the time regardless of the position of the vas and vessels [14]. VTS is thought to result from late antenatal or perinatal vascular accident, thrombosis, or testicular torsion. This hypothesis is supported by the presence of hemosiderin-laden macrophages in surgically removed specimens, consistent with the venous congestion and haemorrhagic infarction secondary to torsion [12]. Though this patient had no known antenatal insult, he had low birth weight which might indicate a possible antenatal defect which might have resulted in the earlier onset of regression of the left testes.

he incompletely descended testis is more prone to torsion during the fetal and perinatal period than the completely descended testes [2]. Cryptorchidism is commoner in the right side, but the left testis is more prone to VTS. This is because of its early descent compared to the right, and because the left spermatic vein drains into the left renal vein, in the absence of venous anastomosis across the midline until the 16th week of gestation, which may predispose to kinking, due to an unusually mobile left kidney [2][15]. It has been identified that true unilateral VTS with mono-orchidism is associated with a contralateral descended testicular length of 1.8 cm or more [16]. Likewise, our patient's right testis was more high riding in position, and the left testis regressed earlier. Bilateral VTS is extremely rare. *Capatina et al.* reported case of a patient detected to have bilateral VTS on laparoscopic exploration at the age of 8 years [17]. A study of 52 cases with VTS showed left sided testicular remnant in 41 cases, right sided in 9 cases and, it was bilateral in only two cases [18]. We present a rare case of bilateral VTS.

The main-stay of treatment in this patient is firstly; testosterone replacement to achieve growth to age appropriate height and development of secondary sexual characteristics, and secondly; screening for remnant testicular tissue with a probable risk of progressing to malignancy. The onset of puberty is associated with an increase in height velocity. Sex hormones regulate pubertal growth in two methods. Testosterone stimulates growth hormone – Insulin like growth factor (GH-IGF) secretion via its conversion to oestrogen which interacts with oestrogen receptors in the hypothalamus and anterior pituitary gland. In addition, both testosterone and oestrogen directly interact with androgen receptors and oestrogen receptors in the growth plate cartilage [19]. Testosterone replacement was successful in increasing height velocity and gradual development of secondary sexual characteristics in our patient.

The cryptorchid testes is estimated to have a 3% to 7% increased risk of testicular malignancy [20][21]. Intra-abdominal testes have a 6 fold higher risk of developing testicular tumour compared to cryptorchid testes in another location [22]. Cryptorchidism can still have some risk of testicular malignancy even after orchidopexy, but this risk can be 32 fold higher if orchidopexy is delayed after puberty [21]. The nubbin in VTS is found to show viable germ cell (GC) or seminiferous tubule (SFT) in 0 – 16% of the excised remnant [23]. A review evaluating multiples studies in VTS showed SFT in an average of 11.5%, and GC in an average of 4% [12]. The presence of viable GC or SFT in VTS theoretically carries a risk of malignant potential [3]. However, there has been only one reported case to date of intratubular germ cell neoplasia in a remnant atrophic testicle in VTS in a 9-year-old boy. This was however not supported immunohistochemically [24]. The optimal management of testicular remnant in VTS is debatable. While some recommend surgical

removal of the remnant, some prefer conservative management owing to their low risk of malignant transformation [25]. A recent study proposed that inguinal and scrotal testicular remnants may not need removal, while intraabdominal remnants may necessitate removal as they contain more elements and are difficult to monitor [9].

Conclusion

VTS should be suspected in a boy with delayed puberty, short stature and empty scrotum. VTS though usually unilateral, can rarely be bilateral. The onset of regression of the testis can be inferred by the testicular size for age prior to progression to atrophy, and the age at which imaging may show features suggestive of acute or subacute torsion. Pubertal development and height gain can be achieved in VTS by testosterone replacement.

Abbreviations

VTS Vanishing testicle syndrome
IGF-1 insulin like growth factor – 1
GC germ cell, SFT - seminiferous tubule

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