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A Rare Case of Persistent Müllerian duct syndrome

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Abstract

Persistent Müllerian duct syndrome (PMDS) is a rare type of 46XY DSD (Disorders of Sex Development) caused by a deficiency in anti-Müllerian hormone (AMH) or a defect in AMH type II receptor. We present 10years old child who reared as male and presented to paediatric surgery department with bilateral undescended testes. Past history of bilateral Fowler Stephen stage-I procedure done in August 2023. Physical examination revealed empty scrotum, normal sized penis and absence of gonads even in the inguinal region. Height and weight were appropriate for the age. Haematological and Biochemical parameters of the child were normal. Hormonal analysis revealed elevated AMH levels. Ultrasonography abdomen and pelvis showed hypoplastic uterus, bilateral pelvic gonads and bilateral mild hydroureteronephrosis. MRI (Magnetic Resonance Imaging) pelvis report showed gonads in parametrium, Horse Shoe Kidney and uterus is not visualized. In view of ambiguity of the both the imagings we have gone for diagnostic laparoscopy. Diagnostic laparoscopy revealed hypoplastic uterus, bilateral pelvic gonads, bilateral vas deferens and gonadal biopsy sent for HistoPathological Examination (HPE). HPE confirmed that microscopic features suggestive of testes. Karyotype analysis detected a 46,XY chromosome pattern. finally we diagnosed the child as 46 XY DSD with PMDS.

Keywords: Persistent mullerian duct Syndrome, Anti Mullerian hormone, Anti Mullerian hormone receptor type 2, bilateral undescended testes, laparoscopy.

1. Introduction

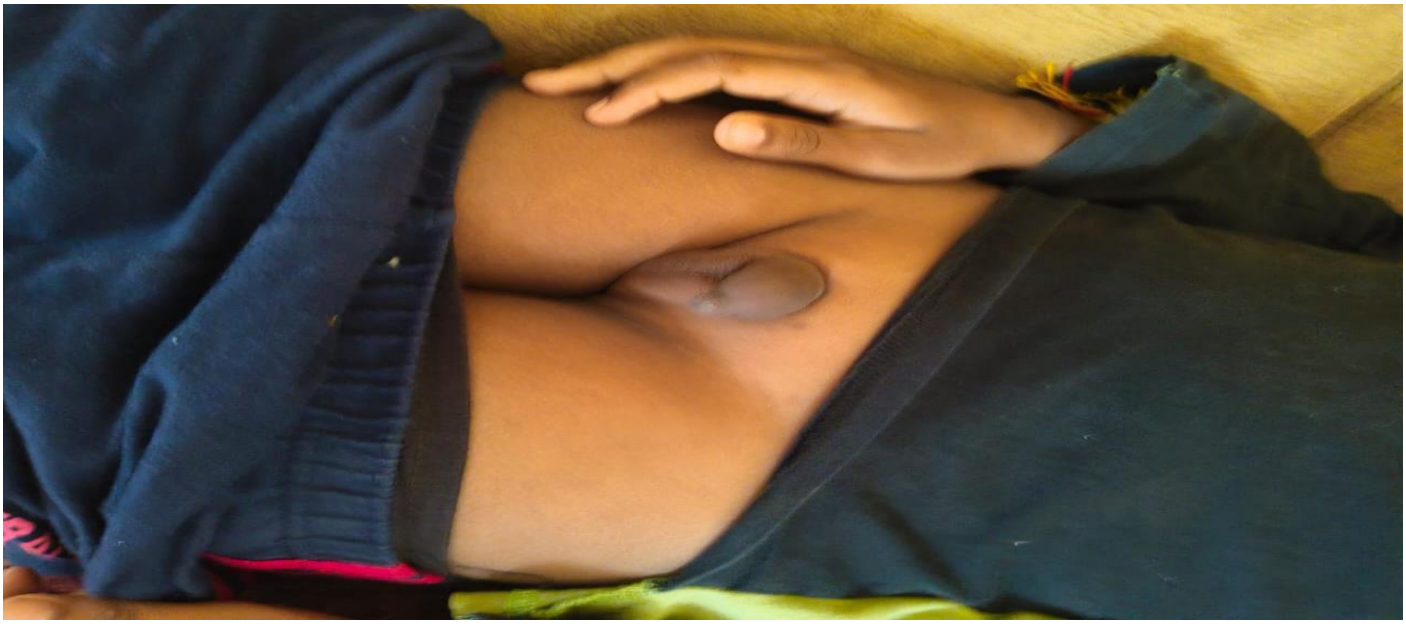
Persistent Müllerian duct syndrome (PMDS) is a rare form of internal male pseudohermaphroditism characterized by Müllerian duct (MD) derivatives in the genotypes and phenotypes of males with a 46,XY karyotype (**1,2**). Normally, Sertoli cells begin to produce anti-Müllerian hormone (AMH) during week 7 of gestation, causing MD regression. However, MDs remain in patients with PMDS, due to a deficiency of AMH or a defect in the AMH type II receptor (AMHR-II) (**1**). PMDS is complex and anatomically variable, which makes diagnosis challenging. Patients with PMDS are categorized into three types, according to the position of the testes and uterus.

In the most prevalent form, a boy presents with bilaterally undescended testes and the uterus and fallopian tubes and testes are in the pelvis accounting for approximately 60-70% of cases. The second most prevalent form , a hernia containing a partially descended or scrotal testes and the ipsilateral fallopian tube and uterus in the same hernia sac known as Hernia Uteri Inguinale accounting for 20-30% of cases and the third prevalent form both the testes are located in the same hernial sac along with mullerian structure known as Transverse Testicular Ectopia accounting for 10% of cases.(**3,4**).

The incidence of PMDS is low, with only 150 cases documented globally so far (**5**). Due to a lack of distinctive clinical features in its early stages, PMDS is typically diagnosed in children when they are tested for other diseases, including cryptorchidism or inguinal hernia, or in adults when they are tested for sterility or oligospermia. The impact on fertility in adults with PMDS diagnosed and treated during childhood remains unknown. However, according to two case reports, delayed diagnosis at adulthood may cause infertility (**6,7**). At present, the treatment of PMDS consists of repairing the external genitalia, which keeps MD structures in the abdomen intact (**4**). We report a rare case of 10 year old child reared as male diagnosed with PMDS, and we review the relevant literature on the diagnosis and treatment of PMDS.

2. Case History:

We report a rare case of 46 XY DSD (Disorders of Sex development) with persistant mullerian duct syndrome diagnosed in our Super Speciality Hospital, Government Medical College, Ananthapuramu. 10 year old child reared as male presented with bilateral undescended testes. Past history of bilateral Fowler Stephen stage-I procedure done in August 2023. physical examination showed empty scrotum , no palpable gonads even in inguinal region , normal sized penis and no external stigmata suggestive of any syndrome. Child height and weight are appropriate for the age. In view of ambiguity of external genitalia child referred to endocrinology department for further evaluation. We clinically made a diagnosis as 46 XY DSD and started evaluating the child in those lines. As a part of initial evaluation we did hormonal evaluation and karyotyping. Clinical photographs of the patient are (Figure 1 & 2).



Haemotological and Biochemical parameters and surgical profile of the child are as follows (Table 1).

Table 1:

Haemotological and Biochemical parameters and Surgical Profile	**Value Obtained**
HB %	12.3 gm/dl
Total WBC Count	5600 cells/mm³
Polymorphs	50%
Lymphocytes	36%
Eosinophils	4%
Monocytes	10%
Platelet Count	3.26laks / mm³
Blood grouping and Typing	B +ve
Bleeding Time	2 minutes
Clotting Time	4 minutes
Random Blood Sugar	81mg/dl
Blood Urea	24mg/dl
Serum Creatinine	0.7mg/dl
Human Immuno Deficiency Virus 1 & 2	Non Reactive
Hepatitis B surface antigen	Negative
Hepatitis C Virus	Negative

Hormonal analysis and Karyotyping revealed elevated AMH levels and rest of the Hormones are normal and Karyotyping revealed 46 XY(Table 2) .

Table 2:

Hormones & Karyotyping	Value Obtained
T3	1.15 ng/ml
T4	11.81 µgm/dl
TSH	2.494 µIU/ml
FSH	1.62 µIU/ml
LH	0.42 µIU/ml
Testosterone	0.235 ng/dl
Estradiol	<5 pg/ml
Prolactin	8.97 ng/ml
AMH	>25.20 ng/ml
Karyotyping	46 XY

As a part of evaluation we did ultrasound abdomen and pelvis revealed hypoplastic uterus with bilateral pelvic gonads with bilateral mild Hydroureteronephrosis. Right gonad measuring 2.5X1.8X0.99 cm and volume 2.3ml and Left gonad measuring 2.4X2.6X1.4 cm and volume 5.7 ml.

As we didn't come to any conclusion we did MRI (Magnetic Resonance Imaging) pelvis which revealed evidence of 14X12 mm hyperintense leson noted in parametrium at the level of internal Iliac vessels. Both kidneys fused at the lower poles at midline forming horse shoe kidney. Uterus is not visualized.

As the findings are inconclusive in both ultrasonography and MRI pelvis we have gone for diagnostic laparoscopy by our hospital Paediatric surgery Department. The diagnostic Laparoscopic findings are hypoplastic uterus, bilateral fallopian tubes, bilateral vas deferens, bilateral pelvic gonads. We have sent biopsy of the gonad for histopathological examination (HPE), which revealed findings suggestive of testes (Table 3).

Table 3 :

Clinical Diagnosis	DSD
Nature of specimen	Gonad sent for HPE
Gross of appearance	Received single grey white soft tissue bit measuring 0.5X0.3X0.2 cm
Microscopic features	Section studied shows tissue consisting of primitive seminiferous tubules lined by sertoli cells with spermatogonic cells. In between tubules the interstitial cells are seen. Few intervening areas showing limphocytic collection, congested and dilated blood vessels.

Finally we diagnosed the case as 46 XY DSD with PMDS which is very rare in our population.

3. Discussion

PMDS was first described by Nilson (**8)** in 1939 as a rare type of male pseudohermaphroditism characterized by the presence of MD derivatives in genotypic and phenotypic males with a 46,XY chromosome pattern (**1,2,5**). It is caused by a defi ciency in AMH or a defect in AMHR-II (**9-11**). The patterns of PMDS inheritance include X linkage, autosomal dominant and autosomal recessive inheritance (**11**). In total, there have been approximately 150 cases of PMDS reported in adults, the majority in the US, Europe and the Middle East (**5**).

The internal genital canal consists of MDs and Wolffian ducts prior to sex differentiation during the first 7 weeks of gestation. The sex differentiation of a normal male depends on testosterone, dihydrotestosterone and AMH (**12**). AMH is a member of the transforming growth factor β superfamily with and is the first hormone to be synthesized by Sertoli cells (**5,13**). Its physiological function is to induce MD regression during male sex differentiation. Due to the existence of the sex-determining region Y (SRY) gene in males, undifferentiated gonads develop into testes and immature Sertoli cells begin to secrete AMH to induce the regression of the MDs at the end of week 7 of gestation.

The development of a normal male requires testosterone, which is secreted by Leydig cells, to facilitate the development of the epididymis, vas deferens and seminal vesicles (**12**). A deficiency in AMH or a defect in AMHR-II in male embryos leads to the development of PMDS. The secretion and function of testosterone are not influenced during PMDS and therefore, the development of the derivatives of the Wolffian ducts and external genital differentiation occurs normally. Therefore, patients with PMDS exhibit a 46,XY chromosome pattern and MDs are present, although they exhibit a normal male phenotype. The cryptorchidism phenomenon of PMDS may be explained by decreased levels of insulin-like 3 (INSL-3), or because the Müllerian duct construct mechanically pulls the testes, thereby preventing testicular descent. However it is hypothesized that mechanical pulling by mullerian duck construct may be the reason for cryptorchidism.

PMDS is primarily caused by mutations in the AMH and AMHR-II genes (**14,15**). The AMH gene is located on chromosome 19p13 **(8**), with mutations occurring in approximately 50% of patients with PMDS. The AMHR-II gene is located on chromosome 12q13 (**8**) with mutations occurring in approximately 50% of patients with PMDS (**14,16**). The cause of PMDS is unclear in approximately 10% of patients (**14**).

The patient in the current case report presented with bilateral undescended testes , empty scrotum with normal penis with no palpable gonads in the inguinal region with no hypospadis , which differs from the symptoms identified in adult with PMDS, which include sterility, oligospermia and inguinal hernia. During ultrasonographic examination of abdomen and pelvis, revealed hypoplastic uterus, bilateral pelvic gonads supporting the diagnosis of PMDS. Next we have gone for MRI pelvis which showed gonads in parametrium.as both the imagins are inconclusive we did diagnostic laparoscopy in our case . diagnostic laparoscpy helped us to diagnose our case as it revealed bilateral mullerian derivatives and bilateral male internal genitalia and pelvic gonads which helped us to diagnose the case as PMDS. A karyotyping test was subsequently performed to determine the chromosomal sex and the results determined that the patient's chromosome karyotype was 46, XY. Based on the clinical features

and laparoscopy of the patient, it was suspected that the patient had PMDS. As the AMH levels are elevated in our case we are suspecting the case as AMH Receptor type-II mutation.

In cases of cryptorchidism, the testes typically descend spontaneously for those less than 2 years, therefore it is recommended that orchidopexy performed in children more than 2 years. In our case the child was 10 years old with undescended testes. Past history of Fowler Stephens orchiopexy done in 2023. Fowler-Stephen orchiopexy is usually done for undescended testes particularly high intra pelvic gonds. It is a two staged procedure. Stage I is ligation of spermatic vessels which allows collateral vessels supply development to the testes. Stage II procedure is moving testes down after collateral circulation develops which usually takes 6 months after Stage I procedure.

It has been demonstrated that there is an improvement in the fertility of patients with intra-abdominal testes that undergo surgery prior to puberty. If the cord is long enough, an orchidopexy may be performed so that the spermatic cord brings the testicle down to the scrotum and the testicle can be fixed there. Follow-up should then be performed following surgery. If the cord is too short or separation of one of the arteries is unsuccessful in creating a longer cord, the testicle may be placed under the skin in the groin region and gonado tropin treatment may be used so to promote testicular descent. If testicles remain undescended, orchiectomy should not be considered. If the testicle was located in the groin, it is easier to be observed in case malignant transformation and other complications. Fertility is maintained in only 14% of patients with intra-abdominal testes who are diagnosed and treated following puberty (**17**). The malignant transformation rate is also increased compared with those treated prior to puberty, therefore, an orchiectomy may be considered. The overall incidence of malignant transformation is 15% . The higher the position of the testes, the higher the risk of malignant transformation in patients with PMDS with crypt orchidism, however, there is no difference in the malignant transformation rate between the two sides of the ectopic testes . The results of previous reviews demonstrate that malignant transformation occurs 6-18 years following cryptorchidopexy. However, there is no correlation between onset of malignant transformation and surgical treatment or patient age . This indicates that the risk of malignant transfor mation is congenital and does not depend on external causes. Treatment of the remnants of MD remains controversial. Previous studies have demonstrated that children with PMDS require removal of MD remnants due to malignant tumors identified in Müllerian remnants and the MD being connected with the seminal vesicle causing urinary tract infections, periodic hematuria, stones and urination disorders. However, other studies have suggested retaining Müllerian remnants to prevent damage to the vas deferens and disruption of collateral blood supply to the testes. A long-term management strategy includes assessment of testicular function and monitoring of malignant transformation at an earlier stage. A total of 30 cases of malignant transformation have been identified in patients with PMDS (**2**). The majority of malignant tumors are identified in ectopic testes and few originate from the Müllerian remnants. Only one patient has been reported to develop adenocarcinoma of endocervical origin and one other patient developed clear cell adenocarcinoma. Testicular tumors include seminomas, embryonic cell carcinoma, yolk sac tumors and teratomas, of which seminomas are the most common (**2**).

4. Conclusion:

In Conclusion, we report a rare case of 46XY DSD with PMDS dignosed in our Super Speciality Hospital. Although imaging like Ultrasonography and MRI have a role in the diagnosis of 46XY DSD, Diagnostic Laparoscopy has a more immense value in the diagnosis of 46XY DSD where the Mullerian duct derivatives could be visualized more precisely then imaging as in our case. So, we recommend Diagnostic Laparoscopy in patients with 46XY DSD in whom suspecting PMDS. To conclude we recommend Diagnostic Laparoscopy in all patients with 46XY DSD with Ambiguity of external genitalia where we can visualize internal genital structures more precisely.

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