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Short Communication

Persistent Mullerian Duct Syndrome: A Challenge as Great as it is Rare

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ABSTRACT

Persistent Mullerian Duct Syndrome (PMDS) is a rare condition characterized by the persistence of mullerian duct structures in genotypic and phenotypic males. Despite its rarity, PMDS poses significant diagnostic and management challenges. This commentary draws insights from the diagnosis and treatment management from the experience in treating a 37-year-old patient with PMDS in Brazil. PMDS arises from defects in Mullerian Inhibiting Factor (MIF) or its type II receptor (AMHR2), leading to the development of female reproductive structures in male individuals. Clinical presentation varies, with adults often presenting with infertility complaints or incidental findings on imaging studies.

Keywords: PMDS; Mullerian inhibiting factor; Phenotypic males; AMHR2

INTRODUCTION

In children, abnormal genitalia at birth may indicate PMDS, though diagnosis can be challenging, particularly when testicular abnormalities resemble more common conditions like cryptorchidism. Associated conditions include transverse testicular ectopia, uterine cancer, polycystic ovary, hypospadias, polysplenia, short pancreas and hypogonadism. Diagnosis typically involves clinical imaging, MIF serum measurement and molecular testing, with MRI emerging as the preferred imaging modality [1]. Surgical treatment is recommended to mitigate the risk of malignant transformation of mullerian structures, with laparoscopic approach being the gold standard. Multidisciplinary care is essential, highlighting the need for psychological support for patients navigating this complex condition. As awareness and diagnostic capabilities improve, an increase in PMDS incidence seems to be anticipated in forthcoming years. Overall, PMDS remains a challenging yet important area of study, with ongoing research needed to enhance understanding and management strategies [2].

DESCRIPTION

Persistent Mullerian Duct Syndrome (PMDS) is a rare condition with less than 200 cases recorded in literature, being first described by Nilson as late as 1939. It presents as a form of male pseudohermaphroditism, where the patient is genotypic and phenotypically male, while also developing an uterus and fallopian tubes in a plethora of combinations. I have had the privilege to assist in the diagnosis and treatment management of a 37-year-old patient with PMDS in Brazil, whence I derive the insights for this commentary [3].

Since its discovery, two main causes have been found to originate PMDS-a defect in the Mullerian Inhibiting Factor (MIF) and its type II receptor (AMHR2).

The MIF, also known as anti-mullerian hormone, is produced by sertoli cells of the male fetus, playing a major role in sexual differentiation by signaling the regression of the mullerian ducts, uterus and fallopian tubes. The production defect of MIF results in the otherwise natural development of referred structures, as would happen in the female human, characterizing PMDS in the male. The same happens in the event of AMHR2 defects, when mullerian structures tissue would not be able to receive signaling from MIF to regress female structures. Both of the known gene mutations of AMHR2 are of autosomal recessive inheritance namely the deletion of 27 pairs bases on exon 10 of this 11 exon gene, a novel deletion of 2 pairs bases on exon 6, as well as inactivation of SF1 binding site.

Due to the few reported cases of PMDS, it is difficult to precise the prevalence of MIF and AMHR2 pathological variations and the best estimates state it to be present in 88% of patients being MIF mutations accountable for approximately 50% of cases, while AMHR2 accounts for 40% and the rest could be

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categorized as idiopathic PMDS in the light of the current state of affairs [4].

While typical female organs are developed in the abdominal cavity, the individual is phenotypically male, since genitalia differentiation does not share mullerian structures. These are on the other hand determined by androgens produced by Leydig cells inducing Wolffian ducts to differentiate in male external genitalia and related structures.

Clinical presentation of PMDS in adults is usually rather poor, since the mere presence of female structures in the abdominal cavity of a man does not result in any symptomatology. The reasons that drive a patient with PMDS to seek medical care are usually due to secondary effects of the disease, namely infertility and related manifestations which was my patient's case of hematospermia-or symptoms arising from malignant transformation of mullerian structures. More often than not, it seems that PMDS is diagnosed incidentally, as the result of the observation of abnormal structures in routine medical imaging for other abdominal conditions, e.g. appendicitis. As clinical imaging becomes more readily available, we are expected to see an increase in PMDS incidence due to improved identification, since we now have a little less than 200 cases reported by 2024, while from the condition discovery in 1939 to 1993 there were only around 150 cases in literature.

However, in children there are usually abnormal clinical features concerning external genitalia from birth. PMDS often presents with ectopic testes in different patterns, the most common called PMDS-female type, where both testicles are intra-abdominal, in the ovarian position. As testicular scrotal situation is not obligatory immediately postpartum, the condition is usually not suspected at birth, although present. Other testes disposition variations can make it extremely hard to detect PMDS, as was the case with our patient, who was born with one scrotal testis and the other ectopic in what resembled a herniated sac in the pelvis, therefore considered cryptorchidism, an incomparably more common condition [5].

Fertility is usually compromised, but possible and reported if at least one testis is scrotal, since male ejaculatory structures are determined by Wolffian ducts, untouched by PMDS as seen [6].

Other than clinical imaging and MIF serum measuring, molecular testing can also be useful to establish PMDS diagnosis. Further investigation on children who present apparent cryptorchidism seems justified to exclude PMDS, especially when other structural abnormalities are noticed. The following conditions have been found to coexist with PMDS: Transverse testicular ectopia, uterine cancer, polycystic ovary, hypospadias, polysplenia, short pancreas and hypogonadism [7].

After diagnosis is established, surgical treatment is always justified considering the possibility of malignization of mullerian structures, which in spite of being fairly rare can present in aggressive forms. It seems to be the common opinion among researchers that MRI is the best imaging modal to diagnose and typify PMDS as well as to plan surgical approaches. Laparoscopic surgery is widely documented as the gold standard to treat PMDS and a few robot-assisted approaches have also been described. It seems reasonable to state that multidisciplinary attention should be provided, emphasizing the psychological condition of patients who find themselves in this challenging position.

CONCLUSION

In conclusion, PMDS is a rare condition only very recently discovered. Basic mechanisms by which it develops are robustly established but molecular findings regarding genetic mutations accountable for suppressing Mullerian structures regression are still limited, mainly due to the scarcity of cases. It seems mandatory that clinicians from different fields such as pediatricians, gynecologists, obstetricians, family doctors and general practitioners are able to identify and consider the possibility of PMDS in its often subtle presentations. Considering treatment, surgical approaches seem rather successful, while robot-assisted procedures may help establish advanced management protocols in coming years. A main concern rarely mentioned is to provide psychological support for patients. Furthermore, as medical imaging and information spreads, it is reasonable to expect an increase in incidence following detection improvement.

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