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The persistent Müllerian duct syndrome: a rare cause of cryptorchidism

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Abstract. The persistent Müllerian duct syndrome is characterized by the retention of Müllerian derivatives in patients otherwise normally virilized. Clinically, the persistence of uterus and tubes leads either to cryptorchidism or inguinal hernia, depending on whether or not the Müllerian derivatives can be mobilized during testicular descent. The condition is usually discovered at surgery, however preoperative sonography could allow the diagnosis to be made preoperatively. The molecular basis of the persistent Müllerian duct syndrome is heterogeneous, and is reflected by wide variations in the serum concentration of anti-Müllerian hormone. Some cases are apparently due to end-organ resistance, and are associated with normal serum levels of the hormone. Others, characterized by absent or low hormone concentrations, can be explained by mutations of the gene coding for anti-Müllerian hormone, which are distributed along the whole length of the coding region.

Key words: Anti-Müllerian hormone (AMH) – Müllerian-inhibiting substance (MIS) – Intersex – Male pseudohermaphroditism – Uterus

As shown by the seminal experiments of Alfred Jost [8], the fetal testis imposes masculinity on the reproductive tract by a dual mechanism. Testosterone, produced by the Leydig cells, masculinizes the external genitalia and maintains the Wolffian ducts, which develop into the vasa deferentia and epididymes. Another hormone, anti-Müllerian hormone (AMH), also called Müllerian-inhibiting substance or factor, a glycoprotein secreted by immature Sertoli cells, causes the regression of Müllerian ducts, which would otherwise differentiate into uterus, tubes and the upper part of the vagina. Male pseudohermaphroditism – defective virilization in a patient bearing testes – can affect both steps or selectively interfere with either testosterone or AMH-dependent steps of sex differentiation. Defective external virilization combined with retention of Müllerian derivatives is always related to anatomical testicular lesions, such as testicular dysgenesis, since no single biochemical defect can interfere with the production or action of testosterone, a steroid hormone, and AMH, a glycoprotein. In contrast, molecular lesions affecting the production or action of testicular hormones can account for male pseudohermaphroditism limited to a single facet of male differentiation.

Genetic defects of steroidogenic enzymes, 5α-reductase or the androgen receptor have been known for a long time to be involved in male pseudohermaphroditism with normal Müllerian regression. In contrast, the molecular basis for the isolated persistence of Müllerian ducts has been elucidated only recently. The disorder has been named "internal male pseudohermaphroditism", "hernia uteri inguinalis" or "persistent Müllerian duct syndrome" (PMDS). Reportedly a rare condition, described in approximately 150 publications, now that correction of cryptorchidism is systematically carried out in early infancy, a increasing number of cases are being discovered by pediatric surgeons, and a review of the clinical and molecular features of this syndrome appears in order.

Clinical and radiological signs of the Persistent Müllerian Duct Syndrome

PMDS is nearly always discovered at surgery for cryptorchidism. In some cases, bilateral cryptorchidism is the only symptom, however, in most cases, unilateral cryptorchidism is associated with an inguinal hernia, containing the Müllerian derivatives, on the opposite side. The following features could alert to the possibility of PMDS:

- similar symptoms in older brothers
- lack of signs of intestinal obstruction in cases of apparently incarcerated hernia

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Abbreviations: AMH = anti-Müllerian hormone; *PMDS* = persistent Müllerian duct syndrome

– negative correlation between cryptorchidism and inguinal hernia: when the inguinal hernia is reduced, the testis exits from the scrotum. This sign is not absolute, however: in some cases, the inguinal canal contains only the hernia, the homolateral testis is at the internal inguinal orifice.
– presence of transverse testicular ectopia, with both testes on the same side of the scrotum, separated by the hernia;

Whenever PMDS is suspected prior to surgery, sonographic examination may be helpful, however, the uterus must be sought for not only in its normal retrovesical position, but also in the inguinal canal, in case of an inguinal hernia. Except in the cases where the Müllerian derivatives are firmly held into the pelvis by the round ligament, the position of the uterus can vary from one day to another in the same child, and may also vary within the same sibship [3].

Apart from cryptorchidism, the external genitalia are by definition normal in PMDS. The presence of hypospadias excludes the diagnosis, and suggests that testicular dysgenesis is responsible for the combined defects in androgen and AMH-dependent steps of fetal sex differentiation.

Biological data

By definition, PMDS affects only the AMH-dependent steps of male sex differentiation, therefore testosterone concentration and response to hCG stimulation are normal for the child's age. Assay of immunoreactive AMH in serum by an ELISA technique [5] yields variable results [6]. AMH is present in the serum of normal boys at a mean ± SEM concentration of 43 ± 3.7 up to two years of age, and decreases slowly until puberty. A precipitous fall in AMH serum concentration is observed when the child reaches the P3 stage of pubertal maturation, corresponding to a serum testosterone concentration above 10 ng/dl [7]. Thus the AMH status of PMDS can only be assessed in prepubertal boys.

In some patients, no immunoreactive AMH can be detected in serum, even in very early childhood (Fig. 1).

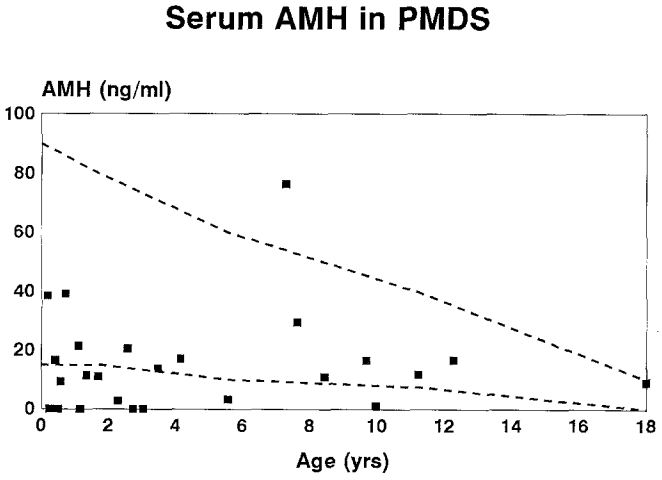

Fig. 1. Serum AMH in patients with the persistent Müllerian duct syndrome. The normal range is enclosed within the dotted lines

More rarely, AMH concentration is normal or elevated. In the former case, PMDS is probably due to a mutation of the gene coding for AMH on chromosome 19 [2], in the latter, end-organ resistance is the most likely explanation for the condition. In other patients, AMH is detectable in serum, but at a decreased concentration, suggesting that the hormone is unstable. In patients with detectable AMH, study of the anti-Müllerian activity of a testicular biopsy may be informative, to distinguish between defects of the AMH protein and putative AMH receptor. The testicular biopsy of the patient is co-cultured with the reproductive tract of a rat fetus [11], normal regression of the Müllerian duct indicates that the biopsy is endowed with anti-Müllerian activity and suggests end-organ unresponsiveness. However, interpretation of this test may be difficult, because it is not quantitative and has obviously not been performed on normal testicular tissue. Furthermore, not all mutations of the AMH gene are expected to totally destroy anti-Müllerian activity and conversely, lack of adequate survival of testicular tissue in organ culture can lead to non-specific decrease of its anti-Müllerian activity.

Molecular biology of PMDS

For all these reasons, analysis of the AMH gene itself is the best way to distinguish between mutations of the AMH gene itself and end-organ insensitivity. Since the AMH receptor has been neither isolated nor cloned, it is not yet possible to obtain molecular evidence for AMH insensitivity in target organs. The first mutation of the AMH gene has been described [9] in a Moroccan sibship, and consisted in a stop mutation on the 5th exon. Since then, other mutations have been identified [1, 4]. Up to now, no prevalent pattern has been observed, the gene appears highly polymorphic and stop missense are distributed along the whole length of the gene (Fig. 2) this could be partly due to the unusually high GC content of the coding regions of the gene.

Family history

PMDS is an inherited disorder, usually transmitted as a recessive autosomal trait, in keeping with the autosomal lo-

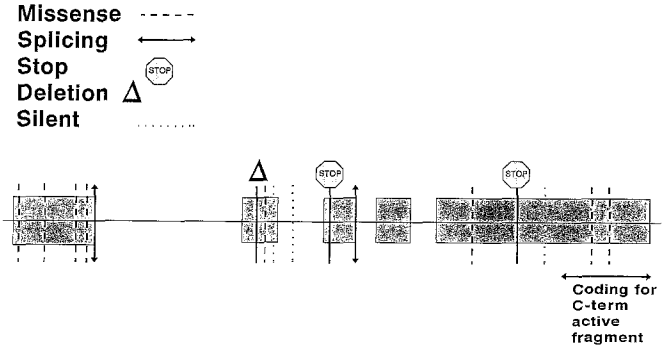

Fig. 2. Mutations of the AMH gene associated with the persistent Müllerian duct syndrome. Both homozygotes and complex heterozygotes were encountered

cation of the AMH gene [2]. A dozen reports of familial cases have been reported in siblings. However, in two instances, the genetic transmission was compatible with an X-linked trait [10, 12]. Since the molecular basis for PMDS in these patients was not ascertained, it is possible that the disorder was due to end-organ insensitivity, and not to an AMH gene defect. Cloning and mapping of the AMH receptor will hopefully resolve this question.

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