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RESEARCH ARTICLE

A RARE CASE OF OVARIAN AGENESIS AND HYPOPLASTIC UTERUS IN A PREPUBERTALGIRL WITH NORMAL 46, XX KARYOTYPE

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Abstract

Delayed onset of puberty and primary amenorrhea pose diagnostic challenges, often associated with diverse etiologies including hypothalamic-pituitary disorders, gonadal dysgenesis, and müllerian duct malformations.Historically, such syndromes have been associated with XY chromosomal components, but rare cases in karyotypically normal females (46, XX) have been reported. Comparisons with similar cases, including atypical forms of Mayer-Rokitansky-Küster-Hauser (MRKH) syndromeare made, highlighting the rarity of this condition. Despite advancements, the genetic basis remains unspecified, underscoring the need for further research. We present a unique case of gonadal agenesis and hypoplastic uterus in a 46,XX individual, without associated organ system anomalies, contributing to primary amenorrhea. Diagnostic evaluations including hormonal assessment, and pelvic MRI confirmed the absence of ovaries and severe hypoplasia of paramesonephric duct (PMND) derivatives. Treatment with 17beta estradiol successfully induced puberty, highlighting the clinical importance of timely intervention. Early detection of such cases is crucial for providing comprehensive support and improving patient outcomes.

Introduction:-

Delayed onset of puberty and amenorrhea in individuals with a normal female phenotype can result from various underlying diseases, congenital or acquired, including hypothalamic pituitary disorders, gonadal dysgenesis, or müllerian duct malformations [1]. Amenorrhea, characterized by normal secondary sexual characteristics but absence of menarche by 16 years or absence of menstrual flow by age 14 alongside the lack of normal secondary sexual characteristics, underscores the clinical landscape of these conditions [2].

The coexistence of gonadal agenesis with dysgenesis of paramesonephric duct (PMND) derivatives, as a manifestation of an atypical form of Mayer-Rokitansky-Küster-Hauser syndrome, is rarely reported [3]. Gonadal agenesis is typically associated with a 46,XY karyotype and absence of secondary sexual characteristics. Despite incomplete understanding of its etiology, gonadal agenesis is believed to arise from improper differentiation of the mesonephric and paramesonephric ducts (PMNDs) during embryonic development, resulting in a spectrum of gynecological and urological disorders [3].

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The paramesonephric (müllerian) ducts, crucial in female reproductive anatomy development, give rise to the fallopian tubes, uterus, and upper portion of the vagina. In the majority of cases involving 46,XX females with abnormal growth of PMND derivatives, the ovaries typically remain unaffected and develop normally [4].

In this document, we present a case involving gonadal agenesis and hypoplastic uterus in a female patient with a 46,XX karyotype and no associated congenital anomalies in other organs. The aim of this report is to delve into the potential origins of this rare association.

Case Report

A 17-year-old girl, with no particular medical history and no consanguinity context, was admitted to our department for primary amenorrhea. The patient did not report cyclic pelvic pain, signs of anterior pituitary insufficiency, or anosmia. Clinical examination revealed a lack of development of secondary sexual characteristics. Her height was normal with a normal BMI, Tanner stage was prepubertal with no breast development neither pubic hair, her external genitalia appeared normal for a child with no sexual ambiguity or signs of hyperandrogenism. Cognitive function evaluation was normal. Given this presentation, hormonal assessment was performed. Gonadotropins were elevated with FSH at 62 IU/mL and LH at 20 IU/mL. Estradiol level was 5 ng/mL, and prolactin level was normal at 11.28 ng/mL. The rest of the hormonal profile and immunological assessment were normal. Bone age assessed by left wrist radiography using the Greulich and Pyle method was 13 years. In light of these results, a pelvic MRI was performed, revealing the absence of both ovaries and ahypoplastic uterus measuring 18.7 x 7.5 mm. No other associated congenital malformation was detected. A karyotype was then conducted, confirming the presence of 2 normal-structured X chromosomes in all observed mitoses. Subsequently, anti-Müllerian hormone levels were measured and found to be nearly undetectable, <0.015 ng/mL. Treatment with 17beta estradiol to induce puberty was initiated for the patient, with good clinical progress and development of secondary sexual characteristics. After 18 months, the patient experienced her first menstrual period under hormonal treatment.It was emotionally traumatic for the patient and her family to have such condition what affects the productivity of life, so she had to undergo supportive psychological sessions.

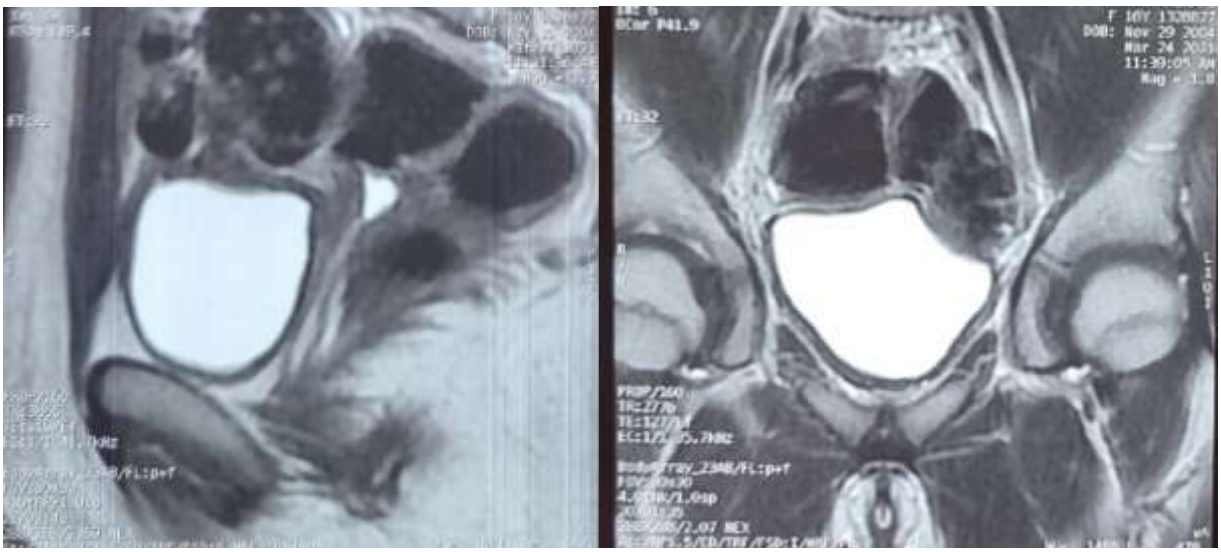

Figure 1:-Pelvic magnetic resonance imaging of the present case showing severe uterine hypoplasia and absence of ovaries.

Discussion:-

In the case discussed here, primary amenorrhea and the persistent characteristics of sexual infantilism were attributed to the hypergonadotropichypogonadal state in the female, as evidenced by subsequent investigations. MRI revealed a complete absence of the ovaries, along with severe hypoplasia of the fallopian tubes, uterus, and vagina. This condition, defined as bilateral gonadal absence and developmental defects of paramesonephric duct (PMND) derivatives, invariably pointed towards a primary congenital disability.

Historically, gonadal agenesis syndromes were described as having an XY chromosomal component. Only a few

cases have been reported in the literature describing bilateral ovarian agenesis with developmental defects of PMND derivatives in a karyotypically normal female (46, XX)[6].

Supposedly, Levinson et al. reported the first case of its kind in 1976; It was an atypical form of Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome described in a case involving bilateral gonadal absence with dysgenesis of PMND derivatives and a left-sided double ureter[6]. Other cases reported in the literature arecompared with the present case in Table 1.

More frequently observed is the coexistence of PMND anomalies with normal ovarian development, as exemplified by the MRKH syndrome, whereas the complete lack of PMNDs and vagina has rarely been reported [3,6]. Kdous et al. reported a case of gonadal agenesis with MRKH syndrome, but further analysis is needed to determine whether this association was a form of manifestation of MRKH syndrome or a different clinical entity itself[9].

Table 1:- Comparison of the present case with other cases reported in the literature all with bilateral gonadal agenesis.

Cases reported by different authors	Age at diagnosis	Secondary sexual characteristics	Internalgenitalia	Associated congenitalstructural anomaly
Medina et al. [11]	Patient A: 20 years Patient B: 24 years	Absent secondary sexual characteristics	Rudimentary PMND derivatives but all components present	None
Chan et al. [13]	17 years	Poorly developed secondary sexual characteristics	Hypoplastic uterus with absence of fallopian tubes	None
Megarbane et al. [15]	Patient no. 1: 17 years Patient no. 2: 16 years	Absent secondarysexualcharacteristics	Hypoplastic uterus with absence of fallopian tubes	Malformed fifth lumbervertebrae in patient no.2
Mutchinick et al. [3]	17.5 years	Absent secondarysexualcharacteristics	Rudimentary PMND derivatives but all components present	Atrial septal defect
Dede et al. [12]	18 years	Absent secondarysexualcharacteristics	Rudimentary uterus with normal fallopian tubes	None
Miolo et al. [10]	16 years(Dizygotictwins)	Presence of axillary and pubic hair, no breastdevelopment	Rudimentary PMND derivatives but all components present	None
Al-Obaidi et al. [14]	Patientno.1: 25 years Patient no. 3: 16 years	Absent axillary and pubic hairs with Tanner stage 1 of breastdevelopment	Hypoplastic uterus with absence of fallopian tubes	None
Nandy et al. [5]	12 years	Tanner stage 1 of secondary sexual characteristics with no breast development	Hypoplastic PMND derivatives	None
Present case	17 years	Absent	Hypoplastic	None

		secondarysexualcharacteristics	uterus	

From an embryological and developmental perspective, both gonads and the PMNDs originate from the coelomic epithelium. Specifically, PMNDs arise from cranio-caudal invaginations of thickened coelomic epithelium at the upper end of the urogenital ridge. Then, in the female embryo, the absence of testicular testosterone leads to the involution of the Wolffian duct, whereas the absence of Müllerian-inhibiting substance allows for the growth of the paramesonephric system and its differentiation[7].

Certain syndromes can mimic the clinical scenario of the present case, such as Turner syndrome, Swyer syndrome, Frasier syndrome, Androgen insensitivity syndrome, and Kennerknecht Vogel syndrome. The major discriminating factor is that they have karyotypes other than the typical 46, XX found in normal females. Usually, the development of the uterus, fallopian tubes, and vagina is normal in Turner's syndrome. However, some cases of mosaicism or rearrangements/deletions of the X chromosome have been described having Müllerian derivatives aplasia in association with gonadal dysgenesis[8].

So far, no genes have been identified to elucidate these conditions, which are distinguished by the association of gonadal agenesis and varying degrees of PMNDs abnormalities[10]. The Homeobox (HOX) family of developmental genes, expressed during the differentiation of the Müllerian tract, plays a crucial role in regulating the development of the genital tract.In certain reported cases, sequence analysis of coding regions of HOX genes failed to uncover any mutations in patients exhibiting different forms of MRKH [16]. Thus, changes in the spatial and temporal transcription of HOX genes might play a role in the development of these uncommon associations.The limitation of this current case report lies in the inability to conduct molecular evaluation due to resource unavailability.

It would be accurate to classify the current case as a female counterpart within the spectrum of XY gonadal agenesis syndrome, grouping it under pure XX gonadal dysgenesis.

Conclusion:-

The absence of gonads accompanied by agenesis/hypoplasia of the PMNDs derivatives within a patient with a 46,XX normal karyotype is not commonly documented. Larger datasets are required to establish the underlying cause of this condition. Early detection of such cases can facilitate the provision of emotional support to patients in advance and enable the implementation of appropriate supportive treatments, such as hormone replacement therapy, cognitive behavioral therapy, and vocational training, at the earliest possible stage, aiming to enhance the quality of life.

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