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Mullerian agenesis coexisting with gonadal dysgenesis in a lady with 46, XX karyotype: A rare case report

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Abstract
Mullerian agenesis also known as Mayer-Rokitansky-Kauster-Hauser (MRKH) syndrome is a congenital disorder associated with aplasia of the upper part of vagina, cervix in a female with normal karyotype (46, XX) and well developed secondary sexual characteristics. This was a rare case of combined Mullerian agenesis and gonadal dysgenesis in an eighteen-year-old Nigerian lady who presented with primary amenorrhoea and poorly developed secondary sexual features. She had no history of cyclical abdominal pain, and attempts at penetrative vaginal intercourse. Physical examination revealed a phenotypical female with height and weight of 155cm and 42 kg respectively. Hormone profile revealed markedly elevated Luteinizing Hormone (LH) and Follicle stimulating Hormone (FSH); and raised testosterone, normal prolactin and thyroid function test. Magnetic resonance imaging revealed an absent uterus, tubes and ovaries. Chromosomal studies revealed normal female karyotype 46, XX. Intravenous urography, ultrasonography and skeletal survey showed no associated renal and skeletal abnormalities. Hormone replacement therapy with estrogen was instituted for development and maturation of secondary sexual characteristics followed by serial vaginal dilatation to enhance sexual activities. Patient is on follow up and doing well. MRKH syndrome is a rare case and can coexist with gonadal dysgenesis. This knowledge would be helpful to clinicians in the diagnosis and management of primary amenorrhoea.

Keywords: anomalies, mayer-Rokitansky-Kauster- Hauser syndrome, dysgenesis, primary amenorrhoea, RSUTH

Introduction
Primary amenorrhea is defined as the failure to initiate menses by the age of 14 years in the absence of secondary sexual characteristics or the absence of menses by the age of 16 regardless of the presence of normal growth and development of secondary sexual characteristics [1]. Mullerian agenesis also known as Mullerian agenesis also known as Mayer-Rokitansky-Kauster-Hauser (MRKH) syndrome is a congenital disorder associated with non-development of the upper part of vagina, cervix in a normal phenotypic female (46, XX) and well developed secondary sexual characteristics. It is second only to gonadal dysgenesis as a common cause of primary amenorrhoea [2]. MRKH is a rare condition that affects 1 in 4,500-5000 women and often associated with genitourinary and skeletal systems abnormalities [3, 4]. The aetiology of MRKH is poorly understood and its genetic basis appears heterogenous [2].
Gonadal dysgenesis on the other hand, involves absence of the ovaries or ovarian underdevelopment. It is characterized by impuberism, primary amenorrhea, hypergonadotropic hypogonadism [5]. Individuals with gonadal dysgenesis have varying karyotype such as 46, XX; 45, X0, deletion and/ or mosaicism of X chromosome and occurs in 1 in 2000-2500 women [6].
Although association of MRKH and gonadal dysgenesis in an individual has been reported, it is extremely rare to find a case of MRKH coexisting with gonadal agenesis and poorly developed secondary sexual characteristics. We report such a case in an eighteen-year-old Nigerian lady who presented to Rivers State University Teaching Hospital (RSUTH) for care.

Case Report
We report a case of an eighteen-year-old Nigerian lady who presented to the Gynaecology Clinic of Rivers State University Teaching Hospital (RSUTH) with primary amenorrhoea, incomplete breast development and scanty hair distribution in the axillae and pubic region. She had no history of cyclical abdominal pain, and attempts at penetrative vaginal intercourse.

There were no significant past medical history and family history of similar symptoms. She had a female phenotype, normal intelligence with no abnormal facies.

At presentation, her weight was 42 Kg, height was 155cm (BMI: 17.43Kg/M^2), the breast and pubic hair development were at Tanner stage 3 and 2 respectively. She had normal vital signs. Her abdomen was neither tender nor distended. She had normal labia majora and clitoris, poorly developed labia minora, patent introitus, depth of about 3cm with blind end. Uterus was not palpated on digital rectal examination.

Her full blood count and renal function test were normal. Serum gonadotrophins were markedly increased (LH: 15miu/ml, FSH: 40miu/ml), serum estradiol was low: 25.2pg/ml, progesterone was low: 0.9ng/ml, testosterone was elevated at 1.2ng/ml, thyroid function test and serum prolactin levels were normal.

An abdominopelvic ultrasound scan done revealed urinary bladder, absent uterus and adnexal structures (Figure 1). Karyotyping done using GTG banding technique showed 46, XX (Figure 2). A magnetic resonance imaging (MRI) also done in the Radiology Department of RSUTH revealed absent uterus, ovaries and the fallopian tubes (Figure 3). Skeletal survey showed no skeletal abnormalities.

A diagnosis of Mullerian agenesis with coexisting gonadal dysgenesis and poorly developed secondary sexual characteristics was made. Hormone replacement therapy with estrogen was instituted for development and maturation of secondary sexual characteristics followed by serial vaginal dilatation to enhance sexual activities. Patient has achieved tanner stage 3 breast development. She is still on follow up and doing well.

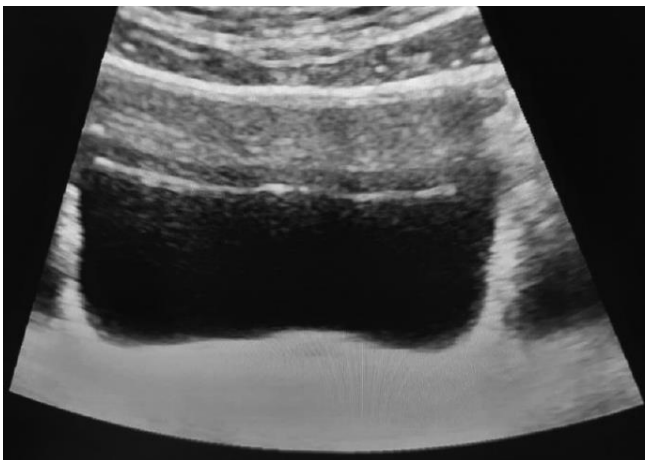

Fig 1: Grey Scale Trans- abdominal ultrasound Scan (Transverse)

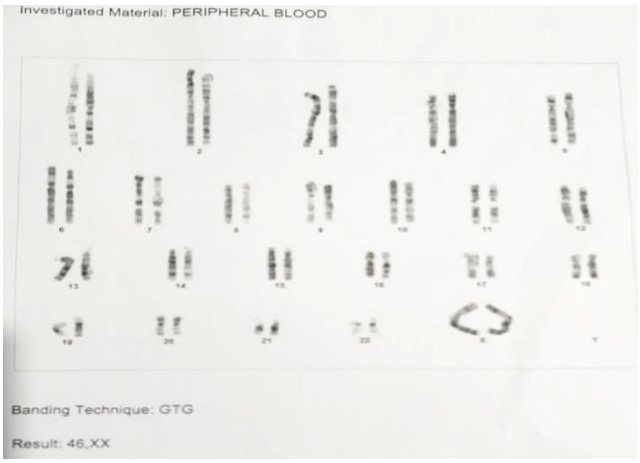

Fig 2: Karyotyping done using GTG Banding Technique

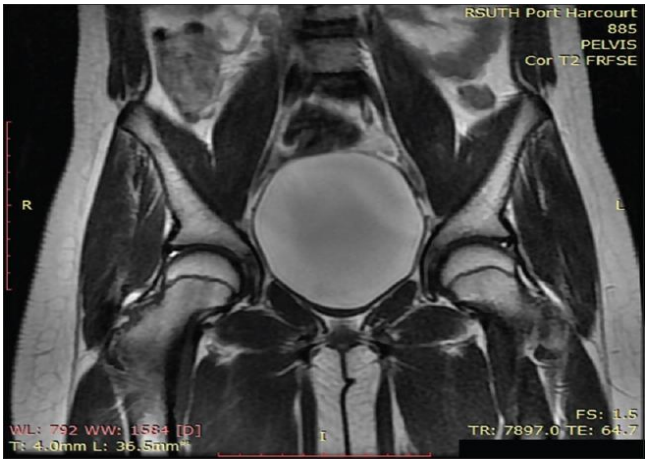

Fig 3: Coronal Magnetic Resonance imaging of the patient's pelvis (T_2-weighted)

Discussion

A case of 18-year-old Nigerian lady with Mullerian agenesis coexisting with 46, XX gonadal dysgenesis and poorly developed secondary sexual characteristics is reported. Mullerian agenesis also known as Mayer-Rokitansky-Kauster-Hauser (MRKH) syndrome is a congenital disorder characterized by aplasia of the uterus, cervix and upper part of the vagina in a female with normal secondary sexual characteristics and normal karyotype (46, XX). This condition has also been named Mullerian aplasia (MA), Genital Renal Ear Syndrome (GRES) or congenital absence of uterus and vagina (CAUV) [5, 7]. Two categories of MRKH have been reported. Category 1 is known as Rokitansky sequence or isolated-characterized by absence of vagina, uterus with symmetrical remnants in some cases and normal tubes and ovaries. While category 2 (atypical form) is characterized by absent uterine remnants, aplasia or hypoplasia of one or both tubes and other systems abnormalities [8, 9].

In Gonadal dysgenesis there is absence of the ovaries or ovarian underdevelopment and characterized by impuberism, primary amenorrhea, hypergonadotropic hypogonadism [5, 10]. Gonadal dysgenesis usually occurs in association with 46,XY karyotype and absence of secondary sexual characteristics [11]. Our patient had poorly developed axillary and pubic hairs, no ovaries and uterus. Coexistence of both conditions is thought to occur coincidentally and independent of any chromosomal aberration [10, 12-14]. Our patient had both syndromes (Mullerian agenesis and gonadal dysgenesis).

Although different karyotype (Mosaics and or deletions) have been reported in literature [12, 14, 15], our patient had a normal female karyotype (46,XX). Ting and Chang reported two mosaic cell lines 45,X/46,X,del(X)(p22.2) in a Chinese lady [12].

Renal and skeletal anomalies usually coexist with mullerian duct agenesis [11, 16]. While unilateral renal agenesis and horse-hoe kidney occur in about 35% of cases of MRKH, skeletal anomalies like scoliosis, spina bifida coexist in over 24% of cases [17]. However, in present case, there were no associated renal or skeletal anomalies.

In isolated MRKH, creation of a neovagina is the first line of treatment in order to enhance sexual activities. This can be done non-surgically, which is the treatment of choice or surgically [4]. However, hormonal therapy targeted at development of secondary sexual characteristics and prevention of osteoporosis in individuals with combined MRKH and gonadal dysgenesis have been reported [9, 14, 18]. This management option was instituted for our patient. She was placed on hormone

replacement therapy with estrogen for development and maturation of secondary sexual characteristics followed by serial vaginal dilatation to enhance sexual activities.

Fertility options for patients with MRKH syndrome with coexisting gonadal agenesis is a major challenge and should be addressed during the counselling session. However, adoption and surrogacy with donor's egg are available options for them. This should be offered during counselling session.

Conclusion

Combined Mullerian agenesis and gonadal dysgenesis abnormalities is an extremely rare condition in phenotypically normal female. Hormone therapy is useful for development and maturation of secondary sexual characteristics. Knowledge of coexistence of these syndromes and the associated psychosocial and fertility challenges will be helpful in making diagnosis and instituting appropriate management. Although fertility remains a major challenge in individuals with these syndromes, surrogacy with donor's ovum and adoption are available options for them.

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