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A rare association of Craniopharyngioma and Meyer-Rokitansky-Kuster-Hauser Syndrome in a patient with primary amenorrhea and delayed puberty – A Case Report

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Abstract

Background: Meyer-Rokitansky-Kuster-Hauser Syndrome (MRKH) is a congenital abnormality of the uterus and the upper two-thirds of the vagina in women showing normal development of secondary sexual characteristics with a normal karyotype of 46, XY. Craniopharyngioma is a rare intracranial neopalsm found in sellar/suprasellar region with two distinct histologic phenotypes – adamantinomatous and papillary. It has insidious onset of symptoms and presents as headche, visual impairment and hormonal imbalances secondary to compression of adjacent pituitary manifesting commonly as sexual dysfunction in adults and growth failure in children. This case report presents a 20 years female with primary amenorrhea and absence of secondary sex characteristics, headache and visual field defect who was subsequently diagnosed as adamantinous craniopharyngioma with multiple pituitary hormones deficiency with Type 1 MRKH. Patient underwent transsphenoidal resection and replacement of levothyroxine and corticosteroid with further plan of reassessing pituitary gonadal axis, creation of a neovagina, addressing puberty induction and infertility (in vitro fertilization and surrogacy). It is too early to say that there may be an association between craniopharyngioma and MRKH. Whether craniopharyngioma and MRKH share a similar etiology is unclear. With inreasing genetic testing, in the future, we may get some correlation.

Key Words : Meyer-Rokitansky-Kuster-Hauser Syndrome, craniopharyngioma, primary amenorrhea, delayed puberty

Introduction

Meyer-Rokitansky-Kuster-Hauser Syndrome (MRKH) or Mullerian agenesis is a congenital abnormality of the uterus and the upper two-thirds of the vagina in women showing normal development of secondary sexual characteristics with a normal karyotype of 46, XY. The reported prevalence of the disease is 1 in 4500 female births. It is caused by an interruption in the development of the mullerian duct system during the embryonic period at 5th and 6th weeks of gestation.[1] MRKH is classified as: MRKH-1 (isolated utero-vaginal aplasia) and MRKH-2 (associated with extra genital manifestations).[2] Craniopharygioma is a rare intracranial neoplasm arising from the epithelial remnants of the Rathke's pouch, found mostly in the sellar or suprasellar region.[3] Histologically, craniopharyngioma is a low grade tumour (WHO grade 1) and has two distinct phenotypes – adamantinomatous craniopharyngioma and papillary craniopharyngioma.[4] Craniopharyngiomas

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account for 1–3% of all primary intracranial neoplasms in adults and 5 – 10% of intracranial neoplasms in pediatric population. In one study, annual incidence of craniopharyngioma was 0.19 per 100,000 persons.[5, 6] The disease demonstrates a bimodal age distribution, with one peak occurring in patients 5-14 years of age and another in 50-74 years of age.[7] Papillary craniopharyngiomas are more common in adults, while adamantinomatous craniopharyngiomas predominate in children.[8] The most commonly reported clinical manifestations include headache, visual impairment, nausea and vomiting, along with hormonal imbalances that lead to sexual dysfunction in adults and growth failure in children. Among the hormonal disturbances, growth hormone deficiency is the most prevalent.[4]

We present a case of adamantinomatous craniopharyngioma with MRKH in a 20-year-old-female with multiple pituitary hormones deficiency and bilateral hemianopsia

Case History

A 20-year-old female presented to Endocrine OPD with primary amenorrhea and absence of breast development, along with no axillary or pubic hair development. She was born at term through normal vaginal delivery at home with normal female genitalia. She achieved all her developmental milestones normally, compared to her peers. There is no history of consanguinity in parents. She complained of gradually progressive headache for 3 years, that was exacerbated by straining and on looking downwards, often waking her up from sleep and was occasionally associated with nausea. She also had gradually progressive narrowing of field of vision for the last 3 years, with normal central field of vision. For the last 3 years, there is history of easy fatiguability during daily activities, poor memory and concentration (hampering her scholastic performance in school), decreased appetite, and generalized body swelling. She has normal bowel and bladder habits. She has normal sense of smell.

There is no history of infertility, menstrual disorder, urogenital abnormalities or malignancy in the family.

On examination, her vitals were normal. Height is 158 cm, weight is 47 kg, and BMI is 18.8 kg/m2. She had achieved target height in terms of mid parental height.

Her breasts and pubic hairs are Tanner's stage 1. There's no axillary hair. She is otherwise grossly normal.

Her lab reports showed eosinophilia, low LH, low FSH, low Growth hormone and low FT4.

Her lab reports are shown in table 1.

Table 1

S.no.	Investigations	Value	Reference
1	Hb (g/dL)	13.2	12-16
2	TLC (cells/µL)	7820	4,000-11,000
3	DLC (%) Neutrophil Lymphocyte Monocytes Eosinophils Basophils	 42 45 2 11 0	 40-70 20-40 2-10 1-6 0-2
6	S. creatinine (mg/dL)	0.9	0.7-1.2

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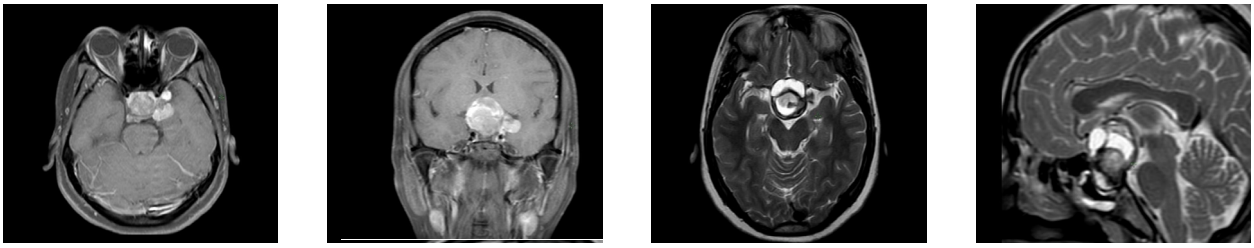
7	S. Na^+ (mEq/L)	138.8	135-145
8	S. K^+ (mEq/L)	4.36	3.5-5.5
9	S. Ca^{++} (mg/dL)	9.4	9-11
10	S. Albumin (g/dL)	4.3	3.5-4.5
15	FSH (mIU/mL)	<0.66	Follicular phase: 1.098 – 11.6 Mid cycle peak: 5.14 – 23.4 Luteal phase: 1.38 – 9.58 Post menopause: 21.5 - 131
16	LH (mIU/mL)	<0.216	Follicular phase: 2.58 – 12.1 Mid cycle peak: 27.3 – 96.9 Luteal phase: 0.833 – 15.5 Post menopause: 13.1 – 86.5
17	Estradiol (pg/ml)	73.398	Follicular phase: 26.6 – 161 Pre ovulatory phase: 187 – 382 Luteal phase: 32.7 – 201 Post menopause: 5.37 – 38.4
18	Total testosterone	<0.170 nmol/L	0.198-2.67 nmol/L
19	FT3	2.73 pg/mL	2.77-5.27 pg/ml
20	FT4	0.19 ng/dL	0.78-2.19 ng/dl
21	TSH	3.672 mIU/L	0.40-4.04 mIU/L
22	8 AM serum Cortisol	<0.5 ug/dL	5-22
23	GH	0.1 ng/mL	Upto 8

X-ray left hand showed bone age of 12-13 years. Ultrasonography revealed no uterus, however, bilateral ovaries were normal. Dynamic MRI scan of pituitary showed a heterogeneously enhancing well defined lesion of dimension 39 x 35 x 33 mm in the Sella turcica with suprasellar extension without separate visualization of pituitary. The lesion was involving bilateral internal carotid artery (left > right), invading left temporal lobe laterally, abutting the bilateral thalamus and basal ganglia anterosuperiorly. MRI image is shown in figure 2.



On MRI of abdomen and pelvis, cervix and upper two thirds of vaginal canal were not visualized; small blind ending lower third of vaginal canal was seen. Both ovaries were normal in size and signal intensity with no mass lesions seen. Figure 3 shows her MRI abdomen and pelvis.

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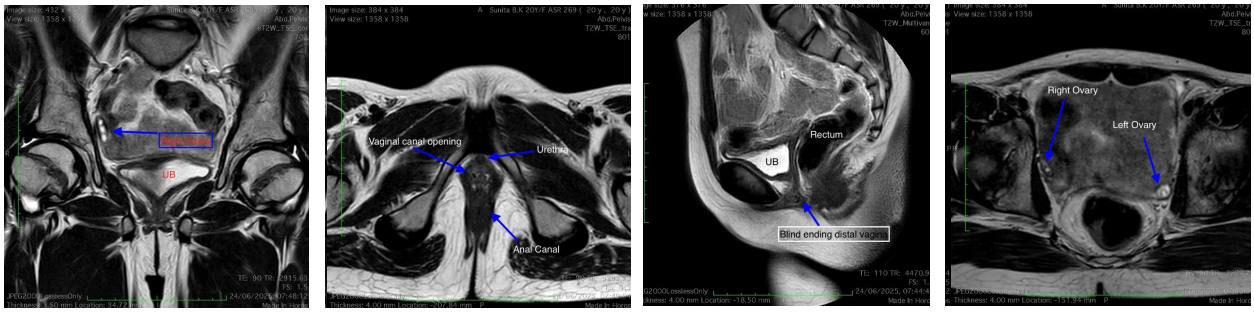
Figure 3



Visual field assessment by perimetry showed bitemporal hemianopia. Her karyotyping showed a normal 46 XY genotype.

Patient underwent endoscopic endonasal transsphenoidal surgery. Histopathological examination confirmed the diagnosis of adamantinomatous craniopharyngioma (WHO grade 1).

Diagnosis of Primary amenorrhea and delayed puberty secondary to craniopharyngioma with multiple pituitary hormone deficiencies causing hypogonadotropic hypogonadism, central hypothyroidism, central adrenal insufficiency, possible GH deficiency with Mayer-Rokitansky-Kuster-Hauser syndrome - type 1 was made.

After surgery, visual field has improved, as assessed by confrontation testing. She is being prescribed physiological dosages of corticosteroid replacement for adrenal insufficiency and levothyroxine replacement for central hypothyroidism. Further plan for the patient is to assess for the pituitary gonadal axis, puberty induction, creation of a neovagina, and addressing infertility (in vitro fertilization, surrogacy).

Discussion

Mullerian agenesis, also called Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome, is a congenital abnormality of the uterus and the upper two-thirds of the vagina in women showing normal development of secondary sexual characteristics with a normal 46, XY karyotype. The reported prevalence of the disease is 1 in 4500 female births.1 Most of the cases are sporadic, but familial cases have been reported, suggesting it is autosomal dominant with incomplete penetrance and variable expressivity. The exact etiology is not known till now. Chromosomal abnormalities have been reported affecting various chromosomes.9 Mutations in the gene encoding anti-mullerian hormone receptor (AMH-R) and estrogen receptor have been proposed to cause MRKH syndrome. The WNT-4 gene has been confirmed to be associated with some cases of MRKH syndrome with hyperandrogenism.10 In our patient, we didn't do genetic testing due to issues of local availability and financial constraints on patient's behalf.

There are two variants of MRKH. Type 1 MRKH presents with isolated utero-vaginal aplasia, also referred to as the Rokitansky sequence. Type 2 MRKH is more common and presents with incomplete utero-vaginal aplasia associated with other abnormalities, also referred to as Mullerian duct aplasia, Renal dysplasia, and Cervical Somite Anomalies (MURCS), or Genital-Renal-Ear Syndrome (GRES).[2]

MRKH Syndrome is the second most common cause of primary amenorrhea after

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ovarian failure. A typical case presentation of MRKH includes primary amenorrhea, a normal female phenotype with a 46, XY karyotype, and normal functioning ovaries. Breast development, axillary hair, and pubic hair develop normally. The external genitalia look normal. Diagnosis is confirmed by radiological findings (ultrasonography, MRI), and Celioscopy. Hormone levels (FSH, LH, Estradiol) are normal in MRKH.[11]

The diagnosis of MRKH syndrome in our patient was made because of the absence of a uterus and the upper two-thirds of the vagina on pelvic MRI and ultrasonographic examination with a normal karyotype of 46, XY. Absence of breast, pubic and axillary hair development can be explained by hypogonadotropic hypogonadism secondary to non-functioning pituitary adenoma, which also caused neurological symptoms in the form of headache and visual field defect. Hypogonadotropic hypogonadism is not a feature of MRKH. Easy fatiguability, decreased appetite, poor scholastic performance and generalized body swelling can be explained by central adrenal insufficiency and central hypothyroidism.

This may be the first reported case of a craniopharyngioma with MRKH. It is too early to say that there may be an association between craniopharyngioma and MRKH, and presence of both these disorders in our patient might just be coincidental. Whether craniopharyngioma and MRKH share a similar etiology is unclear. With inreasing genetic testing, in the future, we may get some correlation.

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