Swyer Syndrome in Siblings: A Rare Presentation

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Abstract

Objective: Swyer syndrome in siblings is a rare entity. The risk for gonadal malignancies is more. Swyer syndrome running in families is a rare event.

Case Presentation: We are presenting this rare entity involving two affected siblings born to a nonconsanguineous couple. A 19 year old female presented with primary amenorrhea. The clinical findings, laboratory, radiological investigations and genetic study revealed Swyer syndrome. On follow up, we found that the elder sibling has similar presentation.

Conclusion: Early diagnosis and prophylactic gonadectomy plays an important role as chances of gonadoblastoma in these cases are high and increases with age. Psychological support and social rehabilitation should also be included in management.

Introduction

Swyer syndrome is a pure gonadal dysgenesis associated with a 46XY karyotype commonly presenting with primary amenorrhea in a phenotypic female. Inspite of having a Y chromosome, complete testicular dysgenesis is associated with a complete lack of androgenization of the external genitalia and persistent mullarian structures due to insufficient AMH production.[1] Swyer syndrome running in families is a rare event and few such scenarios were reported in the literature. It can have X linked, Y linked or autosomal inheritance.[2] Two affected siblings born to a non-consanguineous couple, presented with primary amenorrhea in the outpatient unit of North Bengal Medical College.

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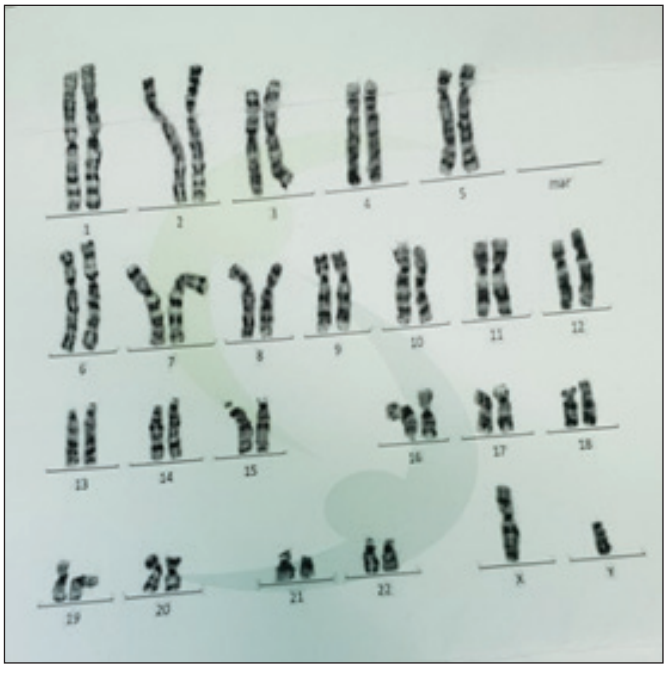
Case Presentation

A 19 year old phenotypically female patient presented to our outpatient unit with primary amenorrhea. On examination her height was 157cm, weight 48 kg, arm span 159 cm and upper segment 82 cm. Tanner stage 2 breast development. Pubic hair is tanner stage 3. On examining the breast primary areola was found (B2 Stage). External genitalia was feminine, vestibule formed, vagina patent and lined by pink rugose mucosa. No clitoromegaly noticed. No palpable swelling in inguinal or labial region. Pelvic ultrasonography showed hypoplastic uterus (31mm*7mm*8mm) and absent ovaries. No ovaries were found even in magnetic resonance imaging. Laboratory findings were consistent with hypergonadotrophic hypogonadism (Table 1). Karyotyping was done and it showed 46XY genotypic pattern. Testosterone level was



Karyotyping showing 46XY pattern

within normal limit. Patient was started on combined estrogen and progesterone preparation and she started getting withdrawal bleeding every month thereafter. Serial ultrasound was done and it showed increase in the uterine size (Table 2).

Table 1

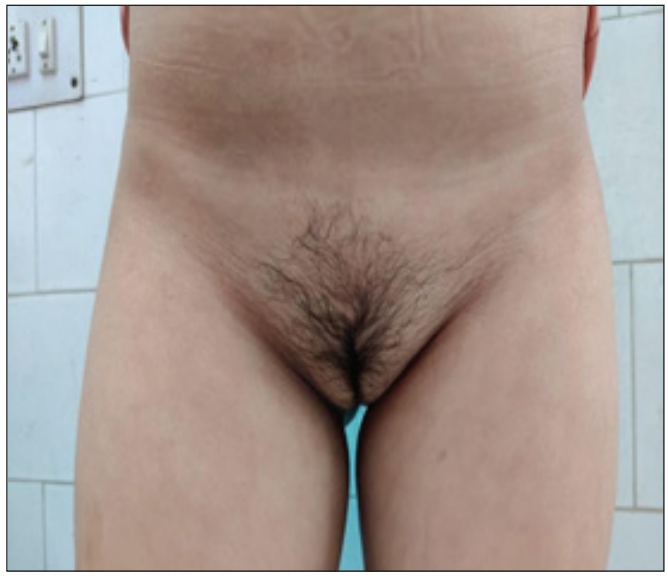
Test	level
FSH	18.7mIU/mi
LH	11.7mIU/ml
TSH	2.4mIU/ml
Testosterone	0.34ng/ml

Laparoscopy showed small uterus,cervix, normal tubes and streak ovaries. Pouch of douglas was normal. LDH was 103mIU/ml (normal 89-200), AFP, HCG were also normal. Since there was no evidence of any tumour gonadectomy was not done.

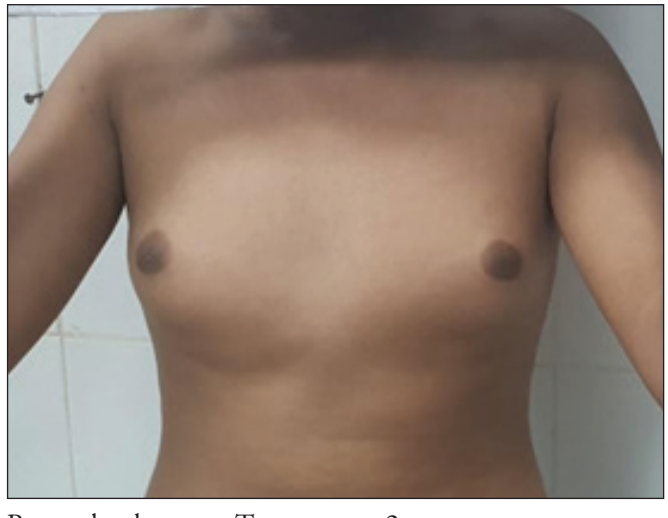
Table 2

Date	Size of uterus
14/11/2019	31x7x8mm
28/11/2019	40x20x10mm
31/1/2020	48x22x11mm
8/2/2020	52x23x12mm
21/3/2020	51x25x23mm
25/4/2020	53x27x30mm

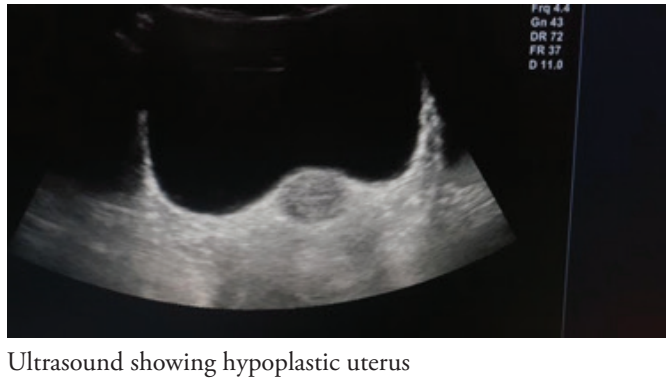
Her elder sister also had similar complaints and was investigated. She was found to have similar findings with internal genital organs, streak ovaries and 46XY



Pubic hair development Tanner stage 3

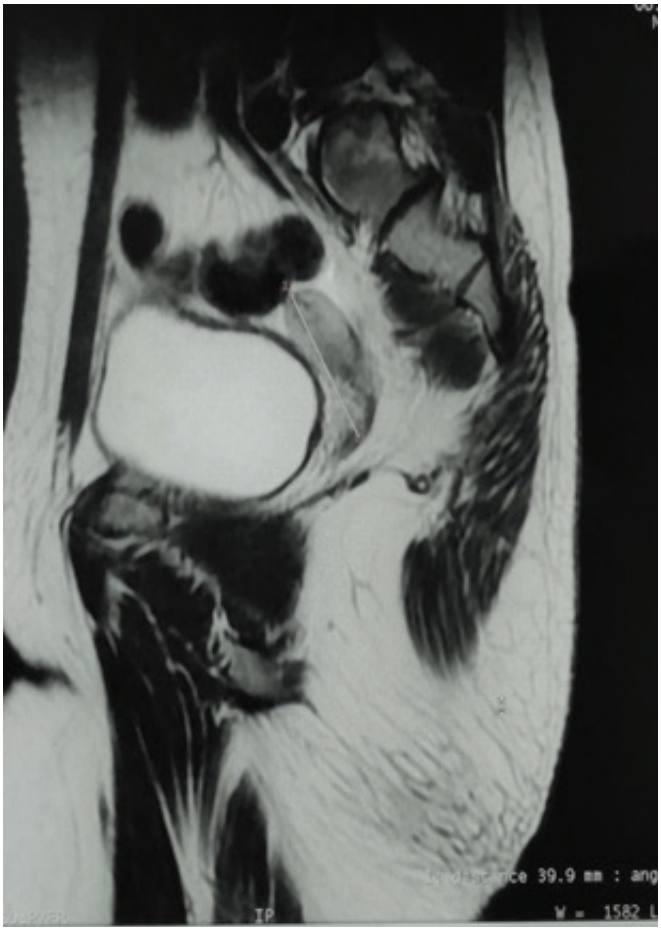


Breast development Tanner stage 2

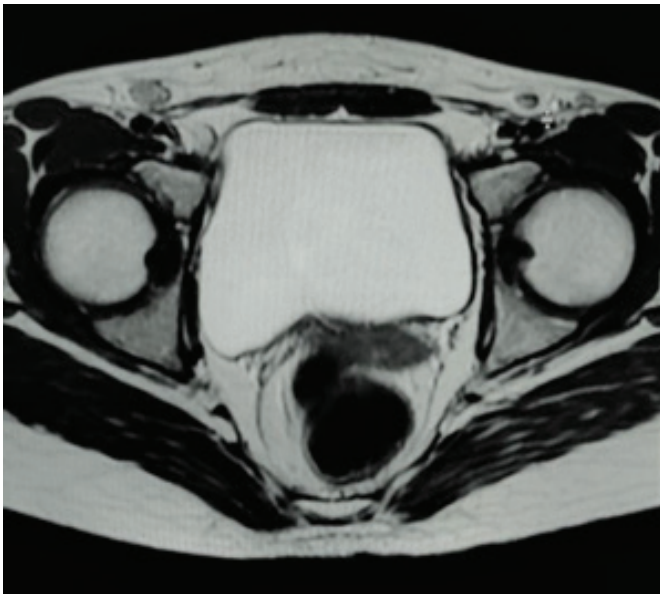


Ultrasound showing hypoplastic uterus

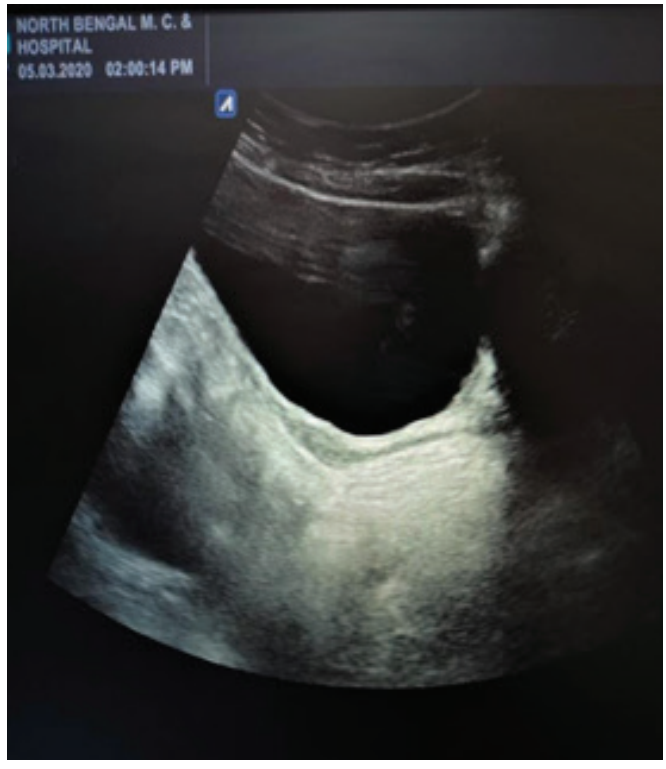
karyotype. LDH was 112, AFP & HCG were also normal. She did not have any swelling in the ovaries and hence prophylactic gonadectomy was not done. Being tea garden workers, both are alive and well at the time of reporting.



Sagittal section MRI showing hypoplastic uterus



Axial section MRI showing hypoplastic uterus



Sagittal section of ultrasound image showing hypoplastic uterus

Discussion

Phenotypic female with unambiguously female genitalia, normal mullerian structures (uterus, tubes, vagina), primary amenorrhoea and 46XY karyotype were first described by Swyer.[3] They have streak gonads. Mutations in SRY gene Yp11.[3] happen in 15-20%,[4] although mutations in desert hedgehog gene (DHH) 12q 13.1, NR5A1 9q33, CBX2 17q25, and 9p24.[3] have also been reported.[5] NROB1(DAX1) mutation involving Xp21.[3] may act antagonistically to SRY and result in sex reversal with adrenal hypoplasia.[6] NROB1 gene mutation is inherited in an X-linked pattern, hence from mother, while SRY mutation is exclusively inherited from father.[7] Paternal germ-line mosaicisms for SRY missense mutation may produce two populations of sperms with one normal and another carrying mutations leading to sex reversal in one sibling and XY normal in another.[8] DHH-autosomal recessive, require two mutated copies one from each parent, to develop Swyer syndrome. Consanguineous parents have a higher chance to overtly express a recessive condition.[9]

In a XY fetus, development of testes at 8 weeks requires action of SRY gene. With defective SRY, TDF is not formed, the indifferent gonads fail to differentiate into testes, and hence, no AMH or testosterone.[10] Wolffian ducts fail to develop and by default Mullerian system persist.[10] Because of lack of DHT, urogenital sinus fails to virilize, labio-scrotal swellings do not fuse resulting in female external genitalia.[11] Without

AMH, the Mullerian ducts develop into normal internal female genital organs (uterus, tubes, cervix, vagina).[12] Inability of the streak gonads to produce estrogens and androgens appropriately, secondary sex characters are stunted.[13] Limited adrenal androgen exposure result in sparse pubic hair.[13]

Hypergonadotropic primary amenorrhoea with female phenotype and 46XY karyotype, may also indicate androgen insensitivity syndrome, but presence of uterus, tubes, vagina, excludes the possibility.

Incidence for this condition varies between 1 in 20,000 to 1 in 80,000, and in sisters is rarer, indeed.[14]

The diagnosis is based on clinical, radiological and genetic evaluation. It should be differentiated from other causes of primary amenorrhea such as Turners syndrome, XY/XO mosaicism, XX gonadal gysgenesis and Kallmann syndrome.[15] Diagnosis of Turner syndrome can be ruled out by clinical examination. Patient with Turner syndrome may have short neck with webbed appearance, low hair line, low set ears and shield chest, karyotypically 45X0 with streak gonads.[16] Mixed gonadal dysgenesis may present with ambiguous genitalia, further radiological imaging may reveal one side testes and other side ovary.[17] Presentation of Kallmann syndrome is primary amenorrhea with anosmia.[18] Here the genotype is 46XX.

Swyer syndrome is associated with SRY gene mutations. Most of the mutations occur in the HMG box.[19]

Dysgenetic gonads have a tendency to develop into a pre malignant or malignant changes (gonadoblastoma, dysgerminoma, embryonal carcinoma) than streak gonads especially if they are intra-abdominal. The significant risk is 20 to 30%.[20] Gonadectomy even prophylactic, is indicated soon after the diagnosis. Extensive search for rudimentary gonads is needed.

Hormone replacement therapy can be given as in this case it showed improvement in uterine development.

The gender of upbringing in the reported cases was female. Although infertile, clients may become pregnant and carry to term with donor egg

Long term prognosis of Swyer syndrome is good once the gonadectomy is done. In patients with streak gonads regular follow up is advised.

Conclusion

The treatment of Swyer syndrome is multi-disciplinary. The patient is provided psychological support. This case is relevant as it is a rare and both sisters were affected. Early diagnosis would allow for conservative treatment which may help to reduce the emotional trauma and improve the patient outcome. Prophylactic gonadectomy is suggested to reduce the risk of gonadoblastoma.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands the name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed. Financial Support and Sponsorship - Nil. Conflict of Interest - None stated.

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