Original Study

A Complete Gonadal Dysgenesis Case with Mental Retardation, Congenital Hip Dislocation, Severe Vertebra Rotoscoliosis, Pectus Excavatus, and Spina Bifida Occulta

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A B S T R A C T

Background: 46,XY, or Swyer syndrome, is a complete gonadal dysgenesis. Patients usually presents with primary amenorrhea with underdeveloped secondary sex characteristics. Phenotypes of these patients are female. In this report, a Swyer syndrome case is reported with novel clinical features that are classified as connective tissue disorders. This case and the 2 other previously reported Swyer syndrome cases with ascendant aortic aneurysm and diaphragmatic hernia are suggest that the Y chromosome has an important role in the structure of connective tissue.

Case: Here we report a case of a 17-year-old with clinical features of 46,XY complete gonadal dysgenesis including external female genitalia, hypoplastic uterus, hypergonadotrophic hypogonadism, incomplete secondary sex characterics, primary amenorrhea, and normal male karyotype. In addition, she had mild mental retardation, severe rotoscoliosis, pectus excavatus, spina bifida occulta, hip dislocation, and long, slender extremities. She had a rudimentary uterus and streak gonads; after giving her cyclic estrogen and progesterone pills, she was able to menstruate.

Summary and Conclusion: In this report, a Swyer syndrome case was discussed regarding clinical features, especially those are not characteristic for Swyer syndrome after a review of the literature.

Key Words: Swyer syndrome, Gonadal dysgenesis, Primary amenorrhea, Vertebral deformities

Introduction

Swyer syndrome, or 46,XY complete gonadal dysgenesis (CGD), is a rare disorder with an estimated occurrence rate of 1/20,000 first described by Swyer in 1955 in 2 phenotypically female cases.[1,2] Patients with 46,XY CGD present normal female phenotype; however, they do not develop secondary sexual characteristics at puberty, do not menstruate, and have streak gonads.[3] Swyer syndrome results from a failure of one of the earliest stages of differentiation in a genetic male, usually during the first 8 weeks of fetal life.[4]

Several animal models have been used to identify the responsible genes that play a role in gonad differentiation.[5] Mutations in SRY and SOX9 account for approximately 20% of 46,XY CGD patients, whereas other causative genes including DAX1 (NR0B1), SF1 (NR5A1), WNT4, DHH, and MAP3K1 are responsible for fewer than 30% of cases; the underlying genetic basis in the remaining 50% of patients remains unclear.[6] With that information in mind, 46, XY CGD patients have a high risk of gonadoblastoma, dysgerminoma, and choriocarcinoma.[7] Dysgenetic gonads are characterized by their high propensity toward malignancy, and especially dysgerminoma, which occurs in about 30% of patients.[8] Therefore, prophylactic gonadectomy should be considered. These patients can also have some additional diseases such as congenital diaphragmatic hernia and ascending aortic aneurysm.[9,10]

Our case had notable findings such as congenital hip dislocation, severe rotoscoliosis, spina bifida occulta, pectus excavatus, and mental retardation together with 46,XY CGD female phenotype.

Case

A 17-year-old single girl was admitted to our gynecology department with a complaint of primary amenorrhea. She also had mental retardation (IQ score was 64), spina bifida occulta, enuresis nocturna, surgically treated severe rotoscoliosis, and surgically treated congenital hip dislocation. Her visual examination revealed mild myopia.

Her family history was not remarkable. She had a brother with surgically treated congenital hip dislocation. She was investigated for enuresis nocturna. Lumbosacral vertebral x-ray showed rotoscoliosis and a fusion defect at the S1 vertebral arcus (spina bifida occulta). We performed abdominal CT and 3-dimensional volumetric image reconstruction, and these images supported our diagnosis of

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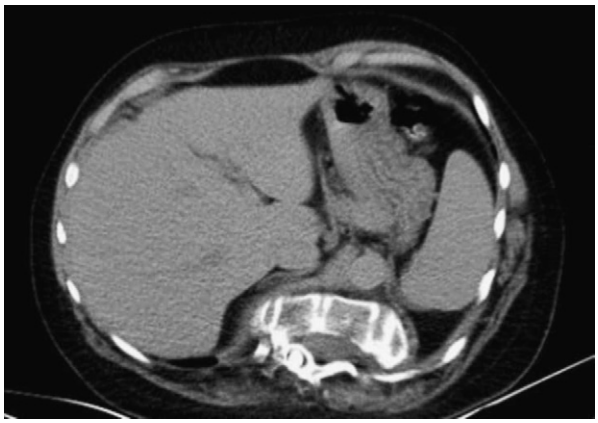

Fig. 1. Abdominal computed tomography of columna vertebralis.

rotoscoliosis (Figures 1 and 2). She had eunuchoid body shape. Her breasts were not well developed. Her pubic hair was developed as female type, but rare. Her vulva was normal with labia majora and minora, and she had a normal clitoris. The vaginal introitus was narrow, and the vagina was poorly developed. Her karyotype was analyzed from a peripheral blood sample using the GTL band technique, and it was determined that she had 46,XY chromosomal structure. Her ultrasonography report showed a rudimentary uterus, 30 × 10 mm in size.

Hormone assays were done, which showed estradiol < 10 pg/mL, FSH 63.8 mIU/mL, LH 16.6 mIU/mL, and prolactin 6.4 ng/mL. After giving her cycling estrogen/progesterone medical therapy, she had menstruated, and her breasts developed after drugs. These results confirmed her clinical diagnosis of primary amenorrhea with gonadal dysgenesis. We proposed removal of dysgenetic gonads because of the risk of gonadoblastoma development, but she refused. We continue to follow the patient closely with the department of endocrinology.

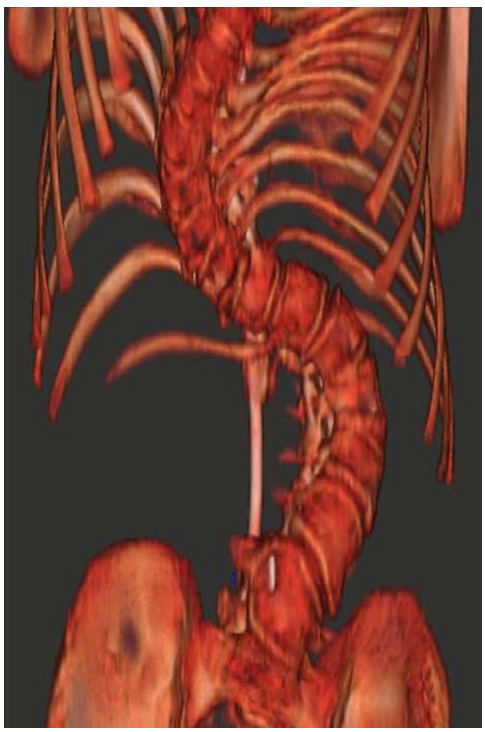

Fig. 2. Three-dimensional volumetric image reconstruction of rotoscoliosis.

Summary and Conclusion

Our patient had pectus excavatus, severe rotoscoliosis, mild mental retardation, congenital hip dislocation, and spina bifida occulta. Among these abnormalities, pectus excavatus, severe rotoscoliosis, and congenital hip dislocation suggest a connective tissue problem compatible with previously reported clinical features of aorta aneurysm and diagraphmatic hernia in different patients.

46,XY CGD is a rare disorder with an occurrence of 1:20,000.[1] Patients with female phenotype with 46,XY karyotype are classified into 4 groups of (1) androgen insensitivity syndrome, (2) mixed gonadal dysgenesis, (3) partial gonadal dysgenesis, and (4) complete gonadal dysgenesis. Differential diagnosis in these patients depends on their clinical features and genotype. The most common complaint in these patients is primary amenorrhea. They have complete female phenotype with underdeveloped secondary sex characteristics. Most have tall stature compared to other females, which is explained by the fact that chromosome Y has loci that affect height.[11] Different from androgen insensitivity syndrome patients, these patients' müllerian structures are intact. The uterus is usually rudimentary; our patient had a uterus of 30 × 10 mm. 46,XY CDG patients can menstruate both spontaneously and by cyclic estrogen-progesterone administration. Our patient needed estrogen-progesterone administration to menstruate. On the other hand, since these patients have streak gonads, they should not get pregnant except through oocyte donation. In the literature, there are a few cases of live births by oocyte donation.[12] It should be kept in mind that 46,XY CGD patients have a high risk of gonadoblastoma, dysgerminoma, and choriocarcinoma.[7] Dysgenetic gonads are characterized by their high propensity toward malignancy, and especially dysgerminoma, which occurs in about 30% of patients.[8] Therefore, prophylactic gonadectomy should be considered. These patients show hypergonadotropic hypogonadism, and they have android pelvic structure and a high risk of osteoporosis because of the lack of estrogen.[13]

Approximately 65% of scoliosis cases are idiopathic, approximately 15% are congenital, and approximately 10% are secondary to a neuromuscular disease.[14] In addition, scoliosis may arise from several diseases such as Marfan syndrome, Ehlers Danlos syndrome, and others. Regarding identifying the etiology of scoliosis in our patient, we planned to perform MRI, however, our patient had a metal device that was not compatible with MRI on her spine since a surgical fixation of vertebra. Therefore, it is still unclear whether her scoliosis depends on a tethered cord or not. Although she had spinal deformity (scoliosis), she did not show lesions, hairy patches, dimples, or fatty tumors on the lower back; foot deformity; weakness in the legs; low back pain; and incontinence, which are characteristic features of tethered cord. Nevertheless, she had spina bifida, to which tethered cord is closely linked. On the other hand, diastematomyelia, another cause of scoliosis, was excluded by

computed tomography. Among syndromes associated with scoliosis, only Marfan syndrome was considered a differential diagnosis, as she had tall stature in addition to scoliosis. However, neither clinical nor laboratory evaluations supported the diagnostic criteria for Marfan syndrome.[15]

To date, patients with novel clinical features different from the characteristic phenotype of 46,XY PGD, such as a congenital heart anomaly (bicuspid aorta, ascending aorta aneurysm) and diagraphmatic hernia, have been reported in the literature.[9,10] In addition to these features, our patient had mental retardation, congenital hip dislocation, severe vertebra rotoscoliosis, pectus excavatus, and spina bifida occulta, which, to best of our knowledge, have not so far been reported in patients with Swyer syndrome. Among these features, aorta aneurysm and diagraphmatic hernia from previous literature and congenital hip dislocation, severe vertebra rotoscoliosis, and pectus excavatus from the current case bring to mind a connective tissue problem in these patients. Reports of further cases with similar findings are needed to bring out more about the relationship between Swyer syndrome and connective tissue anomalies.

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