



Complete gonadal dysgenesis analysis in the population of Latvia: malignant outcomes and a review of literature

Alise Jakovleva^{1,2}, Zanna Kovalova^{3,4}

1) Department of Pediatrics, Faculty of Residency, Riga Stradins University, Riga, Latvia

2) Department of Pediatrics, Children's Clinical University Hospital, Riga, Latvia

3) Department of Pediatrics, Faculty of Medicine, Riga Stradins University, Riga, Latvia

4) Department of Hemato-oncology, Children's Clinical University Hospital, Riga, Latvia

Abstract

Background and aim. Complete gonadal dysgenesis or Swyer syndrome is a rare genetic disorder characterized by 46,XY karyotype and female phenotype with undeveloped streak gonads and high malignancy risk. The condition usually manifests in teenage and young adults with delayed puberty and primary amenorrhea. The purpose of this study was to investigate the incidence and potential malignant outcomes of complete gonadal dysgenesis in Latvia.

Methods. 37 patients were included in a retrospective study from 1996 to 2016. In fifteen cases, additional patient information was available. Information from medical records was collected on age at the time of diagnosis: anamnesis data, laboratory results, histology of gonads, and treatment.

Results. Complete gonadal dysgenesis with karyotype 46,XY was proven in 36 (97.3%) cases and one (2.7%) case with karyotype 47,XY,+21. The average age of patients at the time of diagnosis was 15.4 ± 8.0 years. The study included 15 cases: eight patients (53.3%) were investigated for primary amenorrhea, and incomplete development of secondary sexual characteristics, 5 patients (33.3%) with abdominal pain and lower abdominal mass, 2 patients (13.3%) were diagnosed at birth. Gonadectomy was performed in 12 cases (80%). The median time between diagnosis and gonadectomy was 0.4 ± 4.3 years. The histopathology results from the gonadal biopsy showed malignancy in 7 cases (58.3%). The most commonly diagnosed tumors were dysgerminoma and gonadoblastoma.

Conclusion. Early diagnosis of Swyer syndrome is necessary in view of the risk of malignancy that can develop at a young age. In several cases, the diagnosis of the syndrome was made only after the malignant process development. The study showed the median time between diagnosis and gonadectomy was suboptimal. Therefore, women with amenorrhea and lack of secondary sexual characteristics require careful investigation.

Keywords: disorders of sex development, gonadal dysgenesis, ovarian neoplasms

Introduction

In recent years, the issue of diagnosing rare genetic diseases has become increasingly topical in the world. The process of gender development is an extremely complex mechanism that requires a thorough understanding of gender development.

Disorders of sex development (DSD) are congenital conditions with atypical development of chromosomal,

gonadal, and anatomical sex [1]. 46,XY gonadal dysgenesis consists of various clinical conditions in which fetal gonadal development is abnormal and it includes both partial and complete forms [2]. 46,XY gonadal dysgenesis partial forms are characterized by partially developed internal ducts with a variable degree of testicular development and testicular function [2,3]. Patients with complete gonadal dysgenesis are phenotypically

DOI: 10.15386/mpr-2064

Manuscript received: 03.02.2021

Received in revised form: 26.04.2021

Accepted: 10.05.2021

Address for correspondence:
alise.jakovleva@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License

women with fully or partially developed Miller wire structures and dysgenetic gonads [1].

Complete gonadal dysgenesis or Swyer syndrome was described by G. Swyer in 1955. He presented two women with 46,XY karyotype, normal external and internal female genitalia and primary amenorrhea [4]. The exact incidence of the condition is unknown but literature data suggest that the approximate incidence ranges from 1: 80 000 [5-7] to 1: 100 000 [8-10]. According to the literature, complete gonadal dysgenesis has a high tumor development incidence in 20–30% of the cases. The presence of the Y chromosome increases the risk of germ cell neoplasms [11]. In most cases bilateral gonadoblastoma, dysgerminoma in 5% and less frequently embryonal carcinoma were found [10,12,13]. To prevent the development of malignancy, early surgical treatment is required [14].

To evaluate the prevalence of complete gonadal dysgenesis in general, a careful study of this syndrome is required in many countries of the world, including Latvia. This study will give some insight into the prevalence, diagnosis, and treatment of the complete gonadal dysgenesis. In medical literature, complete gonadal dysgenesis of Swyer syndrome patients has been chiefly reported as case presentations. In our study, we summarize some of the available cases in order to make it easier the comparison of the data.

Methods

Data collection

This study was based on data from the Children’s Clinical University Hospital, the largest children’s hospital in Latvia, and the Medical Genetics and Prenatal Diagnosis Clinic. The aim of the study was to explore the incidence, clinical manifestations, and treatment options of complete gonadal dysgenesis in Latvia. As far as we know, this is the first study in terms of complete gonadal dysgenesis research in Latvia.

In a retrospective, descriptive study, 41 patients were selected between 1996 and 2016. Patients with a suspected disorder of sex development were selected from the cytogenetics laboratory registry based on a 46,XY karyotype. Karyotype analysis was performed by the FISH (Fluorescent in situ hybridization) method for all patients. The study included 37 patients with female phenotype, who presented the karyotype 46,XY. Four women with mixed or partial gonadal dysgenesis (46,XY/45,X) were excluded. Based on patients’ data, diagnosis of complete gonadal dysgenesis, Swyer syndrome, and gonadal tumor, we searched available medical history and clinical examination result information in hospital databases. The clinical information of the investigation and treatment was available in 15 cases. Data were obtained from the registry of the cytogenetic laboratory, oncology department registry, hospital electronic database, medical records.

In the initial data analysis, we included patients’ age at the time of diagnosis, main complaints, medical history, laboratory parameters, histological examination results, ultrasonography findings of the gynecological pelvic floor, and applied therapy.

Statistical analysis

All statistical analyses were carried out using Microsoft Excel 2010 and the IBM SPSS Statistics program (version 22.0). The study was approved by the ethics committee of the Institutional Review Board of Children’s Clinical University Hospital.

Results

Patient characteristics

In the selection of respondents, in 36 cases (97.3%), chromosome analysis confirmed 46,XY karyotype, in one case (2.7%) patient had Down syndrome with karyotype 47,XY,+21. The youngest patient had a karyotype analysis a couple of days after birth. The oldest patient was 32 years old. The patients’ average age at the time of diagnosis was 15.4 ± 8.0 years (Figure 1).

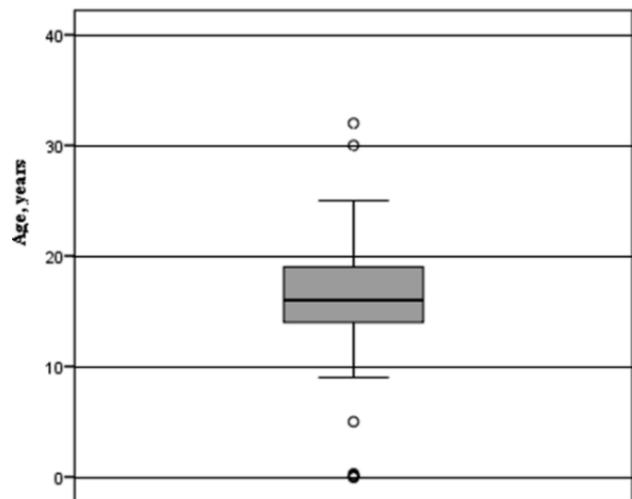


Figure 1. The average age of patients at the time of karyotype detection.

Information on the patient medical history, clinical and laboratory tests was available in 15 (40.5%) cases. The mean age of patients was 12.7 years (range 0-24 years). Five (33.3%) of 15 patients were tested for SRY (SRY locus microdeletion Yp11.3) by the FISH method - the result was negative in all cases.

Eight patients (53.3%) were investigated for primary amenorrhea and incomplete development of secondary sexual characteristics. Five patients (33.3%) were with abdominal pain and lower abdominal mass. They were hospitalized with suspicion of formation in a small groin. Two (13.3%) patients were diagnosed immediately after birth. The first patient was investigated for suspected Down

syndrome with congenital heart disease. The other patient's karyotype testing reason is unknown.

Secondary sex characteristics

Secondary sex characteristics were assessed according to the Tanner scale. Data were available in 7 (46.7%) cases (Table I).

Table I. Evaluation of secondary sex signs by Tanner's scale.

Patient No.	Breasts	Pubic hair
2.	II/III	III/IV
3.	I/II	II
4.	III	III/IV
5.	I	I
6.	I	I
10.	I	III
15.	IV	—

Each patient's data are numbered from 1 to 15; thereby, the given tables' data can be tracked for each particular patient. The exact age of the patients at the time of the investigation is not known. All patients had amenorrhea. Gynecological pelvic floor ultrasound findings were available for six (40%) patients. All the patients had reduced uterus size.

Surgical treatment

Data of patient age were collected at the time of diagnosis and at the time of treatment initiation, and performed gonadectomy respectively. Gonadectomy was performed in 12 cases (80%). Two (13.3%) patients were scheduled for surgery. For one patient, no information

was available. The median time between diagnosis and gonadectomy was 0.4 ± 4.3 years (Figure 2).

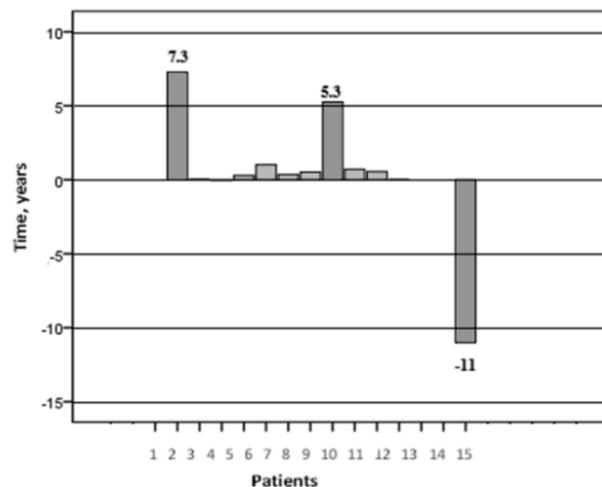


Figure 2. The time period from diagnosis to gonadectomy.

In two (13.3%) cases, gonadectomy was performed late, respectively 7.3 and 5.3 years after diagnosis. In one case (6.7%), karyotype analysis was performed 11 years after ovarian tumor (dysgerminoma) treatment (Figure 2. shown as a negative time).

Histological and laboratory results

In our study, we analyzed histological responses and laboratory tests. Results were available in 9 (75%) cases out of 12 (Table II).

Table II. Results of histological and laboratory parameters.

Nr.	Histology		Laboratory results					
	Right gonad	Left gonad	FSH mU/mL	LH mU/mL	E ₂ pg/mL	T ng/mL	AFP IU/mL	βHCG IU/mL
1.	—	Gonadoblastoma + Dysgerminoma	8.51 (0.23-2.6)	0.196 (0.7-0.9)	5.66 (6-27)	0.20 (0-0.13)	2.4 (ng/mL) (0-6.7)	2.0 (ng/mL) (0-2)
2.	Dysgerminoma	—	39.52 (2.1-11.1)	6.1 (0.1-11.9)	23.01 (5-70)	0.261 (0.02-0.25)	15954 (0-4.6)	0.064 (0-5.0)
3.	Dysgerminoma	Gonadoblastoma	170 (1.48-11.7)	32.6 (<11)	14.5 (26-192)	0.15 (0.06-0.8)	1630 (0-5.0)	25 (0-5.0)
4.	Gonadoblastoma	Gonadoblastoma	60.1 (<11.3)	37.6 (<11)	20.46 (5.10-42.5)	0.226 (0.02-14.9)	0.97 (0-5.0)	—
5.	Streak gonad	Streak gonad	96.8 (<11.3)	20 (1.7-11.0)	—	1.22 (0.10-1.2)	—	—
6.	Gonadoblastoma + Dysgerminoma	—	94.5 (1.34-9.9)	26 (1.7-11.0)	5 (14-124)	—	—	—
7.	—	Fibrous tissue with calcification	1091	40.6	18.51 (14-124)	0.46 (0-0.73)	—	—
11.	Teratoma	Gonadoblastoma	—	—	—	—	—	—
14.	—	Dysgerminoma	—	—	—	—	—	—

FSH – follicle stimulating hormone, LH – luteinizing hormone, E₂ – estradiol, T – testosterone, AFP – alpha fetoprotein, βHCG – beta choriogonadotropin.

Seven (58.3%) patients developed an oncological process. The most commonly found gonadal tumors were dysgerminoma and gonadoblastoma. There were two cases of different histological types of tumor in the histology of bilateral malignant tumors and cases with mixed histological subtype in one gonad.

In some cases, laboratory data showed increased serum concentrations of tumor markers: alpha-fetoprotein. Patients had altered levels of sex hormones. Laboratory tests showed elevated luteinizing hormone, follicle-stimulating hormone, and decreased estradiol levels. These data are consistent with the complete gonadal dysgenesis diagnostic criteria, but these changes may be associated with tumor hormonal activity.

Hormone replacement therapy was used in six (40%) cases. The following medication was used: estradiol, combined oral contraceptive containing ethinylestradiol, drospirenone, and gestodene, ethinylestradiol. Adjuvant chemotherapy, according to MAKEI protocol, was performed in three (20%) patients.

Down syndrome patient with complete gonadal dysgenesis

The child was born to a 33-year-old mother from the second pregnancy, the first labor. Due to suspicion of congenital heart disease, amniocentesis was performed, which identified a 21-chromosome trisomy. Childbirth was spontaneous in 38-39 weeks of gestation, birth weight 2890 g, length 51 cm, evaluation on the Apgar score 8/9/9 points. After birth, the baby's condition is stable. The child visually corresponds to the characteristic facial features of Down syndrome. Heart auscultation found the 4/6 grade systolic murmur on all valves. At the age of 5 days, the patient was transferred from the regional hospital to the Children's Clinical University Hospital.

At the age of 11 days, the geneticist performs a karyotype analysis using the FISH method. 47,XY,+21 karyotypes were detected. The pediatric cardiology consult revealed Ebstein anomaly, ventricular septal defect, infundibular pulmonary stenosis, heart failure (NYHA II). The patient is under regular observation by cardiologists. At the age of 4 years, the patient undergoes diagnostic angiography with balloon dilatation of the pulmonary valve. Correction of congenital heart disease is planned in the future.

A gynecological examination found that the child's external genitals were anatomically female type. Based on karyotype analysis, complete gonadal dysgenesis is considered. It is recommended to perform a gonadectomy at the age of 5-6 years due to the high risk of gonadal tumors.

At the age of 6 years, the patient underwent an MRI of the abdominal organs, which revealed that the uterus was small, did not have any structural changes, the ovaries were not visualized. During the development of this study, gonadectomy for this patient was scheduled. It is currently known that at the age of 7, a laparoscopic bilateral

salpingooferectiony is performed. The postoperative period was without complications. Unfortunately, the results of the histological examination are not available. The patient is recommended to have a gynecological exam once a year. It is planned to start hormone replacement therapy at the age of 12.

Discussion

In recent years, significant progress has been made in managing disorders of sex development, but the information available is still limited [15].

Genetic characteristics

Determining the genetic etiology of 46,XY gonadal dysgenesis has been challenging [3]. In 30% of the patients with sex development disorder has 46,XY karyotype [16]. The diagnosis should be made immediately after birth, prenatal screening, or family screening [6,17]. As molecular genetic examinations become more accessible, accurate diagnoses are more frequent [18,19]. Medical professionals from different sectors should also carefully investigate teenage and young adults who have not started puberty until the age of 14 [6]. Approximately 3.4% of all patients with primary amenorrhea are XY females; therefore, girls with primary amenorrhea and delayed puberty require routine karyotype analysis [12,20].

46,XY gonadal dysgenesis is heterogeneous and can result from defects of any gene involved in the process of gonadal formation [2]. Complete gonadal dysgenesis is a difference in sex development typically associated with mutations in genes responsible for testicular development [11]. In the second month of pregnancy, the initial stage of testicular formation requires the function of several genes, the most important of which is SRY (Sex-determining region Y chromosome) [21]. SRY gene mutation is approximately 10-20% of complete gonadal dysgenesis cases [1,20]. SRY gene expression is crucial in initiating male sex determination by triggering undifferentiated gonadal tissue to transform into testes. The absence of SRY gene expression or mutation of this gene results in testicular formation failure, and bipotential gonad develops as an ovary or streak gonads [5,22]. Approximately 40% of all 46,XY gonadal dysgenesis cases result from mutations in the SRY, NR5A1 (encoding steroid factor-1), and MAP3K1 genes [3]. In some cases, the cause of complete gonadal dysgenesis is unknown or related to mutations in other genes by sex differentiation, such as genes DHH, DEAH37, SOX9, WT1, and NROB1 (DAX1) on the X chromosome [5,15,20,21]. If such a gene is mutated, the bipotential gonads cannot differentiate in the testicles [21]. Most of the cases are sporadic mutation, but in literature, some familial cases have also been described [23].

Clinical characteristics

Women with 46,XY karyotype, Y chromosome short arm deletion, and SRY gene mutation inhibit anti-Müllerian hormone and testosterone and hence the

testicular development, resulting in poorly developed dysgenetic streak gonads with weak hormonal and reproductive activity [1,15,23,24]. An affected individual presents with primary amenorrhea and undeveloped secondary sex characteristics because of the inability of the gonads to produce hormones [12].

Patients have hypergonadotropic hypogonadism: elevated gonadotropins, normal female levels of androgens, and low estrogen levels [14,20]. Tumor markers including AFP, β -hCG, and LDH are associated with germ cell malignancy [15]. Hormone analysis can make the differential diagnosis. In androgen insensitivity syndrome, the androgens are elevated to male levels, but in complete gonadal dysgenesis, the levels are elevated compared to female levels [25]. Our study included the results of secondary sex characteristics (Tanner stage), laboratory results that were performed before gonadectomy and hormone replacement therapy.

Complete gonadal dysgenesis patients have normal or tall body proportions, small or undeveloped breasts, and pubic hair. The external genitalia is females type with normal or reduced vagina and fallopian tubes. The uterus

is small or rudimentary. The gonads are dysgenetic strips consisting of fibrous tissue [1,11,12].

The present study showed that the average age of women with suspected cases of 46,XY sex development disorder was 15.4 years, though in the patients who were diagnosed and treated for complete gonadal dysgenesis it was 12.7 years, which is a relatively better indicator, like in other studies. Michala et al. and Ben Temime et al. reported median age at diagnosis for the 46,XY gonadal dysgenesis to be 17.2 years, and 17.6 years respectively [26,27]. Therefore, due to the high risk of developing gonadal tumors, the diagnosis should be made as soon as possible [6].

Malignancy

46,XY gonadal dysgenesis has a significant risk factor for type II germ cell tumors [2]. The presence of Y chromosome is associated with a high incidence of gonadoblastoma and dysgerminoma [11]. The risk of tumors in complete gonadal dysgenesis patients is approximately 20-30% [28]. Malignancy increases with age: 5% at age 15; 27.5% at age 30 and > 50% after 40 years of age [28].

Table III. Comparison of patient parameters between previous studies.

	Our study	Michala et al. (2008) ^[26]	Malhotra et al. (2015) ^[34]	Ben Temime et al. (2009) ^[27]	Behtash et al. (2007) ^[35]	Da Silva Rios et al. (2015) ^[1]	Zhu et al. (2016) ^[36]
Total patient No/cases	15	29	8	5	3	1	1
Age at presentation (mean)	12.7	17.2	16.19±2.85	17.6	18,6	18	16
Main Complaints	Primary amenorrhea Abdominal pain	Delayed Puberty	Primary amenorrhea Delayed Puberty	Primary Amenorrhea	Primary amenorrhea Abdomina pain	Primary amenorrhea	Primary amenorrhea Pelvic mass
Karyotype	46,XY 47,XY,+21 (1)	46,XY 46,XY+SRY gene (8)	46,XY/45X (1)	46,XY	46,XY	46,XY	46,XY
Abdomen examination	Abdominal mass (5)	—	Abdomen soft (6) Palpable mass (2)	Abdominal mass (1)	Abdominal mass (3)	—	—
Vaginal examination	Small uterus (6)	—	Normal vagina (7) Anteverted uterus (1)	Hypoplastic uterus (5)	Normal genitalia (1)	Eutrophic vagina Small cervix	Normal Genitalia
Imaging (USG, MRI, CT)	—	Uterus 62 mm (mean) (8)	Small uterus (8) Streak gonads (8) Adnexal mass (2)	Small uterus (5)	Abdomino-pelvic mass from right ovary (3)	Pelvic tumor 9,5cm Ø	Normal uterus Solid mass 9 cm Ø
Surgery	Gonadectomy (12)	Bilateral gonadectomy (28)	Laparoscopic gonadectomy (5) Laparotomic gonadectomy (3)	Adnexectomy (5)	Laparoscopic gonadectomy (2) Laparotomic gonadectomy (2)	Bilateral salpingectomy Oophorectomy Hysterectomy	Laparoscopy gonadectomy
Histo-pathology	Streak gonads (1) Dysgerminoma (2) Gonadoblastoma (1) Gonadoblastoma + dysgerminoma (3) Teratoma + gonadoblastoma (1) Fibrous tissue (1)	Streak gonads (12) Dysgerminoma (7) Gonadoblastoma (3)	Streak gonads (4) Dysgerminoma (3) Right gonad: dysgerminoma Left gonad: streak gonad (1)	Streak gonads (3) Gonadoblastoma +Dysgerminoma (1) Gonadoblastoma (1)	Right gonad: dysgerminoma Left gonad: streak gonad (3)	Right gonad: dysgerminoma Left gonad: streak gonad	Right gonad: Immature teratoma + dysgerminoma + yolk sac tumor Left gonad: mature teratoma + gonadoblastoma
Treatment	HRT (6)	HRT (28)	HRT (8)	HRT (5)	HRT (3) CT (1)	HRT CT	CT

(1) – number of patients, HRT - hormone replacement therapy, CT – chemotherapy.

In 46,XY disorder of sex development SRY, WT1, SOX9 gene abnormalities in the early stages of Sertoli cell differentiation disrupt sex determination and are associated with a high risk of gonadoblastoma [2,18]. The Y chromosome region, known as the GBY (gonadoblastoma Y locus), is a prerequisite for malignant transformation [2,18]. Uehara et al. described that SRY gene abnormalities might play a role in the formation of gonadal tumors, especially dysgerminoma [29]. Uehara et al. study showed that patients with SRY abnormalities meta results revealed gonadal tumors frequency of 52.5% [30]. Dysgerminoma has high malignant potential and typically presents with abdominal pain (70-80%) and abdominal mass [1]. Dysgerminoma is bilateral in 15% of cases and often infiltrates adjacent organs, with distant metastasis and frequent recurrences [10,28]. Survival rates of 46,XY gonadal dysgenesis and dysgerminoma dependent on the tumor stage: stage I 96.9% and stage II–IV 53.9% [10]. Dysgerminoma differential diagnosis includes diffuse large B cell lymphoma, poorly differentiated carcinoma, embryonal carcinoma, yolk sac tumors, and gonadoblastoma [15,31]. Some coexistence cases of dysgerminoma with gonadoblastoma and gonadoblastoma with choriocarcinoma have been reported in the literature (Table III) [28].

Treatment

Laparoscopic bilateral gonadectomy is the standard recommendation as soon as the diagnosis is confirmed [17].

Our study shows that in 80% of the cases gonadectomy was performed. This is a good indicator, but the study showed that the average time from diagnosis to gonadectomy was 0.4 years. In two cases, the surgery was 7.3 and 5.3 years after the diagnosis, indicating that not only diagnostics but also the treatment is started too late despite the exact diagnosis. Some studies have shown that many women are late in making an accurate diagnosis, often for several years after their first presentation, possibly due to normal phenotypic appearance [32].

Chemotherapy is administered to patients with recurrent and metastatic disease [14]. Hormone replacement therapy is crucial for female cycle regulation to induce menstruation, develop secondary sex characteristics, preventing hypoestrogenemia and osteoporosis, and improving the patient's psychological condition [28,33].

Fertility

The issue of fertility is also essential. Pregnancy is possible by IVF (In vitro fertilization) using donor eggs and hormonal support during the early antenatal period [5,32]. Y genotype does not affect the normal uterine and endometrial response so that patients may have a successful pregnancy despite an underdeveloped uterus [23,32]. According to available literature, most pregnancies in patients with complete gonadal dysgenesis required cesarean section due to their anatomical features of the possible androgenic shape of the pelvis and hypoplastic uterus that may prevent

normal dilatation and childbirth and inability to react to oxytocin and prostaglandins [23,25,32,33]. Fertility securing for these patients could be a challenge in Latvia.

Strengths and limitations of our study

Our study detected a relatively large number of women with karyotype 46,XY, and select patients with complete gonadal dysgenesis. As already mentioned, most studies have been chiefly reported as case presentations. However, the present study has limitations because it is retrospective. Not all data are available for all patients, not all patients have undergone surgery or histological results, and no data are available on long-term outcomes for quality of life and sexual functioning.

Conclusions

Early diagnosis of complete gonadal dysgenesis is crucial for a view of the malignancy risk that can develop at a young age and can prevent significant health problems: delayed puberty, development of oncological processes, and psycho-sexual trauma. A multidisciplinary team of doctors is significant to ensure careful examination, observation, karyotype investigation, and appropriate management. Crucially important is the prophylactic surgical removal of streak gonads to prevent gonadal tumor development and long-term complications. Creating specialized centers and a database is required.

Considering that the data availability of patients that were analyzed in the study is limited, it is difficult to assess the overall situation of 46,XY complete gonadal dysgenesis in the Latvian population. Further research on complete gonadal dysgenesis and other sex development disorders should be carried out.

Acknowledgments

We gratefully acknowledge all involved Children's Clinical University Hospital pediatricians and subspecialty physicians for their contribution and whose advice and recommendations helped in the design of the study.

References

1. Da Silva Rios S, Monteiro IC, Braz dos Santos LG, Caldas NG, Chen AC, Chen JR, et al. Case of Swyer Syndrome Associated with Advanced Gonadal Dysgerminoma Involving Long Survival. *Case Rep Oncol.* 2015;8:179–184.
2. Domenice S, Arnhold IJP, Costa EMF, Mendonca BB. 46,XY Disorders of Sexual Development. Update: May 3, 2017. . Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279170/>.
3. McElreavey K, Jorgensen A, Eozenou C, Merel T, Bignon-Topalovic J, Tan DS, et al. Pathogenic variants in the DEAH-box RNA helicase DHX37 are a frequent cause of 46,XY gonadal dysgenesis and 46,XY testicular regression syndrome. *Genet Med.* 2020;22:150–159.

4. Swyer GI. Male pseudohermaphroditism: a hitherto undescribed form. *Br Med J*. 1955;2:709–712.
5. Ostrer H. Swyer syndrome. *NORD's Rare Disease Database*. Years published 2008,2012,2016,2019. . Available from: <https://rarediseases.org/rare-diseases/swyer-syndrome/>.
6. King TF, Conway GS. Swyer syndrome. *Curr Opin Endocrinol Diabetes Obes*. 2014;21:504–510.
7. Hanlon AJ, Kimble RM. Incidental gonadal tumors at the time of gonadectomy in women with Swyer syndrome: a case series. *J Pediatr Adolesc Gynecol*. 2015;28:e27–e29.
8. Bastian C, Muller JB, Lortat-Jacob S, Nihoul-Fékété C, Bignon-Topalovic J, McElreavey K, et al. Genetic mutations and somatic anomalies in association with 46,XY gonadal dysgenesis. *Fertil Steril*. 2015;103:1297–1304.
9. Akyürek N, Atabek ME, Eklioğlu BS, Yuca SA. 46 XY Gonadal Dysgenesis. *Eur J Gen Med*. 2012;9:292–294.
10. Park JW. Swyer syndrome with dysgerminomas: ambiguity of pathologic diagnosis. *Current Gynecologic Oncology*. 2019;17:189–192.
11. Chand MT, Turner S, Solomon LA, Jay A, Rabah R, Misra VK. A Case of 45,X/46,XY Mosaicism Presenting as Swyer Syndrome. *J Pediatr Adolesc Gynecol*. 2020;33:577–580.
12. Jorgensen PB, Kjartansdóttir KR, Fedder J. Care of women with XY karyotype: a clinical practice guideline. *Fertil Steril*. 2010;94:105–113.
13. Elagwany AS, Eltawab S, Abouzaid ZS. 46, XY complete gonadal dysgenesis (Swyer syndrome): Report of two different cases. *Apollo medicine*. 2016;13:63–66.
14. Kumar NP, Venugopal M, Mathews A, James FV. Mixed Germ Cell Tumour in a Case of Pure Gonadal Dysgenesis (Swyer Syndrome) - A Case Report. *Cureus*. 2016;8:e459.
15. McCann-Crosby B, Mansouri R, Dietrich JE, McCullough LB, Sutton VR, Austin EG, et al. State of the art review in gonadal dysgenesis: challenges in diagnosis and management. *Int J Pediatr Endocrinol*. 2014;2014:4.
16. Massanyi EZ, DiCarlo HN, Migeon CJ, Gearhart JP. Review and management of 46,XY disorders of sex development. *J Pediatr Urol*. 2013;9:368–379.
17. Berra M, Liao LM, Creighton SM, Conway GS. Long-term health issues of women with XY karyotype. *Maturitas*. 2010;65:172–178.
18. Cools M, Looijenga LH, Wolffenbuttel KP, Drop SL. Disorders of sex development: update on the genetic background, terminology and risk for the development of germ cell tumors. *World J Pediatr*. 2009;5:93–102.
19. El-Sherbiny M. Disorders of sexual differentiation: I. Genetics and pathology *Arab J Urol*. 2013;11:19–26.
20. Rocha VB, Guerra-Júnior G, Marques-de-Faria AP, de Mello MP, Maciel-Guerra AT. Complete gonadal dysgenesis in clinical practice: the 46,XY karyotype accounts for more than one third of cases. *Fertil Steril*. 2011;96:1431–1434.
21. Priya PK, Mishra VV, Choudhary S, Rizvi JS. A Case of Primary Amenorrhea with Swyer Syndrome. *J Hum Reprod Sci*. 2017;10:310-312.
22. Du H, Taylor SH. Principles of Developmental Genetics (Second Edition). Chapter 27 - Development of the Genital System. Academic Press. 2015, p. 487-504. . Available from: <https://www.sciencedirect.com/science/article/pii/B9780124059450000272>.
23. Gupta A, Bajaj R, Jindal UN. A Rare Case of Swyer Syndrome in Two Sisters with Successful Pregnancy Outcome in Both. *J Hum Reprod Sci*. 2019;12:267–269.
24. Patnayak R, Suresh V, Jena A, Rajagopal G, Vijayalakshmi B, Reddy AP, et al. Swyer syndrome: a case report with literature review. *JNMA J Nepal Med Assoc*. 2012;52:72–74.
25. Mannaerts D, Muys J, Blaumeiser B, Jacquemyn Y. A rare cause of primary amenorrhoea, the XY female with gonadal dysgenesis. *BMJ Case Rep*. 2015;2015:bcr2014206609.
26. Michala L, Goswami D, Creighton SM, Conway GS. Swyer syndrome: presentation and outcomes. *BJOG*. 2008;115:737–741.
27. Ben Temime R, Chechia A, Attia L, Ghodbane I, Boudaya F, Makhlof T, et al. Swyer syndrome: report of 5 cases. *J Gynecol Obstet Biol Reprod (Paris)*. 2009;38:220–225.
28. Milewicz T, Mrozińska S, Szczepański W, Białas M, Kiałka M, Doroszevska K, et al. Dysgerminoma and Gonadoblastoma in the Course of Swyer Syndrome. *Pol J Pathol*. 2016;67:411–414.
29. Uehara S, Funato T, Yaegashi N, Suziki H, Sato J, Sasaki T, et al. SRY mutation and tumor formation on the gonads of XP pure gonadal dysgenesis patients. *Cancer Genet Cytogenet*. 1999;113:78–84.
30. Uehara S, Hashiyada M, Sato K, Nata M, Funato T, Okamura K. Complete XY gonadal dysgenesis and aspects of the SRY genotype and gonadal tumor formation. *J Hum Genet*. 2002;47:279–284.
31. Han Y, Wang Y, Li Q, Dai S, He A, Wang E. Dysgerminoma in case of 46, XY pure gonadal dysgerminoma (Swyer syndrome): a case report. *Diagn Pathol*. 2011;6:84.
32. Chrysostomou A, Tsuari M. Successful pregnancy in a patient with Swyer syndrome, or pure 46, XY gonadal dysgenesis. *SAJOG*. 2019;25:9-11.
33. Tulic I, Tulic L, Micic J. Pregnancy in patient with Swyer syndrome. *Fertil Steril*. 2011;95:1789.e1-2.
34. Malhotra N, Dadhwal V, Sharma KA, Gupta D, Agarwal S, Deka D. The laparoscopic management of Swyer syndrome: Case series. *J Turk Ger Gynecol Assoc*. 2015;16:252–256.
35. Behtash N, Karimi Zarchi M. Dysgerminoma in three patients with Swyer syndrome. *World J Surg Oncol*. 2007;5:71.
36. Zhu HL, Bao DM, Wang Y, Shen DH, Li Y, Cui H. Swyer's Syndrome with Mixed Ovarian Malignant Germ Cell Tumor and Ovarian Gonadoblastoma. *Chin Med J (Engl)*. 2016;129:1752–1754.