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A rare case of primary amenorrhoea and breast development in a 46,XY 15-year-old girl

Rzadki przypadek 15-letniej pacjentki z kariotypem 46,XY, pierwotnym brakiem miesiączki i prawidłowym rozwojem piersi

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Abstract
A disorder of sex development (DSD) is defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical. Swyer syndrome is an example of 46,XY DSD with a female phenotype. It usually becomes apparent in adolescence with delayed puberty and amenorrhoea. Spontaneous breast development is very rare. A 15-year-old girl was presented due to primary amenorrhoea with breast development compatible with Tanner stage V. Hormonal tests revealed hypergonadotropic hypogonadism with low level of oestradiol. Pelvic ultrasound and magnetic resonance imaging revealed a small uterus, and no ovaries were found. In the right lower abdomen, a structure of unknown origin was visible. The chromosome analysis revealed a 46,XY karyotype. The patient was qualified for a laparoscopic bilateral gonadectomy. Postoperative histopathological examination revealed gonadoblastoma. We underline the need to consider DSD 46,XY in the presence of primary amenorrhoea, even when pubertal development is present. Germ cell tumors have a tendency to grow and metastasize rapidly. Delayed diagnosis may increase the risk of malignant transformation and cause a poor diagnosis.
Key words:
primary amenorrhoea, gonadal dysgenesis, Swyer syndrome, gonadoblastoma, disorder of sex development.

Streszczenie
Zaburzenia różnicowania płci polegają na niezgodności płci genetycznej i gonadalnej z fenotypem zewnętrznych narządów płciowych. Zespół Swyera jest przykładem DSD z kariotypem 46,XY i żeńskim fenotypem. Rozpoznanie jest ustalane głównie w wieku nastoletnim w związku z diagnostyką pierwotnego braku miesiączki i opóźnionego pokwitania. Prawidłowy rozwój piersi występuje u tych pacjentek niezwykle rzadko. Piętnastoletnia dziewczyna została przyjęta w celu diagnostyki pierwotnego braku miesiączki. W badaniu fizykalnym rozwój piersi wg skali Tannera oceniono na M5. W badaniach hormonalnych stwierdzono cechy hipogonadyzmu hipergonadotropowego z małym stężeniem estradiolu. W badaniu ultrasonograficznym i rezonansu magnetycznego miednicy małej zobrazowano małą macicę, brak prawidłowych jajników. W podbrzuszu prawym widoczna była struktura niewiadomego pochodzenia. W badaniu cytogenetycznym stwierdzono kariotyp męski – 46,XY. Pacjentka została zakwalifikowana do zabiegu usunięcia gonad. W pooperacyjnym badaniu histopatologicznym stwierdzono gonadoblastoma. Prezentowany opis przypadku podkreśla konieczność wzięcia pod uwagę zespołu Swyera w diagnostyce pierwotnego braku miesiączki, nawet w przypadku obecności drugorzędowych cech płciowych. Należy pamiętać, że nowotwory germinalne mogą szybko rosnąć i dawać przerzuty. Opóźnienie właściwego rozpoznania może zwiększać ryzyko zezłośliwienia nowotworu i niekorzystnie wpłynąć na rokowanie.
Key words:
pierwotny brak miesiączki, zaburzenia różnicowania płci, dysgenezja gonad, gonadoblastoma, zespół Swyera.

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Introduction

A disorder of sex development (DSD) is defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical [1–3]. According to the Chicago classification, DSD is subdivided into three groups on the basis of cytogenic, hormonal, gonadal histology, and clinical findings: 46,XY (primary disorder of testicular development or disorders in androgen synthesis or action), 46,XX (disorders of ovarian development, congenital adrenal hyperplasia, aromatase deficiency), and sex chromosome disorders (Klinefelter syndrome, Turner syndrome, chimerism, mixed gonadal dysgenesis) [1, 3, 4]. The overall rate of incidence is estimated at 1 : 4500 births, and that of DSD with Y chromosome material is approximately 1 : 20,000 births [4]. In patients with DSD the rate of associated congenital anomalies is significantly higher than in the general population. These abnormalities include small for gestational age, congenital cardiovascular diseases, and central nervous system disorders [1].

Swyer syndrome is an example of 46,XY DSD with a female phenotype. It is a rare condition with an incidence rate estimated at 1:80,000 births [1, 5, 6]. Patients have normal to tall stature, bilateral dysgenetic gonads, and the presence of müllerian structures. Pubertal development is delayed. The most common symptom that encourages patients with Swyer syndrome to consult a physician is primary amenorrhoea. This disorder is defined as either a lack of menarche by 14 years of age in the absence of secondary sexual characteristics or lack of menses by 15 years of age in the presence of normal growth and secondary sexual characteristics [7–9]. Approximately 2.5% of adolescents experiencing primary amenorrhoea suffer from Swyer syndrome [7].

It must be kept in mind that in every case of DSD with Y chromosome and female phenotype, there is an increased risk of gonadal germ cell tumours, compared with the general population [4, 5]. Gonadal neoplasms occur in 15-55% of complete gonadal dysgenesis patients [10, 11]. The current evidence strongly recommends prophylactic gonadectomy in patients with 46,XY DSD at the time of diagnosis.

Case report

A 15-year-old girl was admitted to the Department of Child Endocrinology due to primary amenorrhoea. The girl's medical history included birth from the first pregnancy, by vaginal delivery at 40 weeks of gestation with a birth weight of 3920 g, body length of 60 cm, and Apgar score of 10 at five minutes. The child's psychomotor development was normal. Until admission she did not require hospitalisation or specialist treatment. A growth spurt had been observed about 1.5–2 years before admission. Breast enlargement had been noted a year before admission. The family history was irrelevant. The girl's mother experienced menarche at 15 years of age.

Upon admission to the Department of Child Endocrinology the patient was in good general condition. In the physical examination obesity (the body weight of 89 kg [> 97c] and the height of 171.4 cm [> 97c], body mass index [BMI] = 30.3 kg/m^2) and stretch marks on the thighs were noted. The development of breasts was of Tanner stage B4 and pubic hair of Tanner stage P4. No apparent abnormalities within external genitalia or other evidence of virilisation were observed. Laboratory findings revealed normal biochemistry. Hormonal tests were as follows: hypergonadotropic hypogonadism with low level of oestradiol and testosterone (follicle stimulating hormone 48.68 mIU/ml, luteinising hormone 25.79 mIU/ml, oestradiol 16.79 pg/ml [ranges shown in Table I], testosterone 14.21 ng/dl [normal range: 6-86 ng/dl]). Pelvic ultrasound revealed a uterus that showed modest oestrogenisation, which was, however, insufficient to make the endometrium visible. No ovaries were found. In the projection of a right gonad a solid structure with a vague ultrasound image was found. To verify the results of the ultrasound examination, magnetic resonance imaging was performed – the uterus dimensions were appropriate for the age (6.0 × 1.8 × 3.2 cm). In the left gonad projection, a small structure with vesicles up to 3 mm was visible. The right gonad was not visible, while a 7 mm thick tissue lesion was found in that area. Fallopian tubes were present. In the right lower abdomen, a structure of unknown origin and with dimensions of 22 × 14 × 15 mm was visible. In the course of further diagnostic tests, the chromosome analysis revealed a 46,XY karyotype, using a technique of analysing peripheral leukocytes (50 metaphase cells counted). Hormonal tests showed euthyreosis and morning hyperprolactinaemia with normal daily profile of prolactin. Chorionic gonadotropin subunit β and α-fetoprotein serum concentrations remained within normal limits (1.28 mIU/ml [normal range: 0–5 mIU/ml] and 1.51 IU/ml [normal range: 0–7 IU/ml], respectively). The bone age was assessed as 14-–15 years according to the Greulich & Pyle method. After completing a detailed assessment, the patient was qualified for a laparoscopic bilateral gonadectomy. Postoperative histopathological examination revealed *gonadoblastoma* within the right dysgenetic gonad and the foci of *gonadoblastoma* in the left gonad. No structures characteristic for ovarian or testicular tissue were found. The patient is currently under constant observation in an outpatient setting. The patient is currently receiving transdermal oestradiol replacement therapy to prevent hypoestrogenism and will begin administration of progesterone preparation. The patient was informed about vitamin D deficiency prevention and adequate calcium supplementation.

The parents of the patient signed written informed consent for the publication of this case report.

Discussion

Complete gonadal dysgenesis (CGD) – Swyer syndrome – was described for the first time in 1955 by G. Swyer [11]. Characteristic features of this disorder are as follows: female phenotype, male karyotype, unambiguously female external genitalia, delayed puberty, and the presence of müllerian structures with streak gonads [1, 11]. The affected person usually

Table I. Normal ranges of gonadotropins and oestradiol

	Patients' results	Normal range	
LH	25.79 mIU/ml	Follicular phase	2.4–12.6 mIU/ml
		Ovulation	14.0–95.6 mIU/ml
		Luteal phase	1.0–11.4 mIU/ml
		Postmenopausal	7.7–58.5 mIU/ml
FSH	48.68 mIU/ml	Follicular phase	3.5–12.5 mIU/ml
		Ovulation	4.7–21.5 mIU/ml
		Luteal phase	1.7–7.7 mIU/ml
		Postmenopausal	25.8–134.8 mIU/ml
Oestradiol	16.79 pg/ml	Follicular phase	12.5–166 pg/ml
		Ovulation	85.8–498 pg/ml
		Luteal phase	43.8–211 pg/ml
		Postmenopausal	<5.0–54.7 pg/ml

FSH – follicle stimulating hormone; LH – luteinising hormone

has a tall stature, which may be caused by the effect of the Y chromosome or delayed epiphyseal closure due to the deficiency of sex steroids [1]. Generally, due to the absence of hormonal activity of ovaries, there is no appearance of breast development and menarche. Usually, this disorder is identified in adolescence, during the diagnosis of primary amenorrhoea and delay in pubertal signs [12].

The most relevant aspect of this article is the presence of breast development in a girl with Swyer syndrome, which could mask gonadal dysgenesis and delay the diagnosis. According to the best of our knowledge, spontaneous breast development in patients with 46,XY CGD was reported in isolated cases [6, 10, 13–17]). However, the breast development was not adequate in all the reports and did not achieve Tanner stage V, as in our patient. Catli *et al.* reported a case of a 46,XY CGD teenager with adequate breast development and irregular menstrual periods [6]. There has also been a case of Swyer syndrome reported with adequate development of secondary sexual features and secondary amenorrhoea [10]. Meyer *et al.* reported a case of a female with primary amenorrhoea, well developed breasts and one spontaneous vaginal bleeding event [17]. Usually, it is believed that the hormonal activity of tumours within the dysgenetic gonad is responsible for the stimulation of breast development. Fukamatsu *et al.* [18] reported a case of *gonadoblastoma* secreting male and female sex steroids. In such a case, virilisation is possible if mainly androgens are synthesised. However, when oestrogen synthesis dominates, female secondary sexual characteristics develop [18–21], although it should be kept in mind that breast development in patients with Swyer syndrome is not always evidence of gonadal malignancy [10, 15]. A case of CGD with spontaneous breast development despite low oestradiol level, clinical features of hypoestrogenaemia (i.a. osteoporosis) and no gonadal tumours were also described [15]. Hypotheses concerning the origin of oestrogens in girls who suffer from Swyer syndrome say that the production of female sex hormones is possible through the streak gonads. In such a case they can be a source of oestrogen and the reason for adequate breast development [6, 10, 15]. An overlap between non-mosaic Swyer syndrome with 46,XX/46,XY mosaicism is very rare. In this variant, more gonadal functions have been retained and patients are virilised [1]. Moreover, peripheral conversion of androgens to oestrogens and an increased sensitivity of breast tissue to oestrogens are also possible [6, 10, 15]. In such cases, allegedly correctly progressing puberty may delay the diagnosis. It seems that in the analysed case, the aforementioned mechanisms (production of oestrogens through the streak gonads, peripheral conversion of androgens, and an increased sensitivity of breast tissue to oestrogens) could have led to the breast development.

In physiological development, expression of the *sex determining region Y* (SRY) gene located on the Y chromosome, initiates a genetic cascade that causes the undifferentiated gonad to develop as a testis. In case of improper expression of this fragment, the testes do not develop and the Müllerian ducts persist

to form the fallopian tubes, uterus, and upper third part of the vagina [1, 22]. Only in 10–20% of patients with Swyer syndrome was a mutation in *SRY* confirmed [1, 6, 10, 11]. Moreover, there are still new reports of new mutations inactivating *SRY* [11, 23]. In the remaining 80–90% of cases other mutations are probably responsible for the symptoms of gonadal dysgenesis. The reason for the occurrence of 46,XY DSD may be mutations in the following genes: *SOX9*, *WT1* (Wilms' tumour suppressor gene), *SF1*, *DAX1*, *DHH*, *FGF9*, *DMRT1*, *M33*, *WNT4*, *FOXL2*, *RSPO1*, *LHX9*, *EMX2*, *LIM1*, and others (e.g. MAP3K1 gain-of-function mutation) [2, 3, 22, 24]. However, in approximately 50% of the cases, the underlying genetic cause remains unknown [6].

A routine karyotype should be requested in all individuals experiencing primary amenorrhoea, who have been diagnosed with hypergonadotropic hypogonadism and/or ovarian tumour [1, 8]. If virilisation signs are observed and testosterone and its metabolites levels are elevated, a urinary steroid profile analysis should be considered [1].

In the case of 46, XY karyotype in a patient with primary amenorrhoea, Swyer's syndrome, congenital adrenal hyperpla-

Table II. Diagnosis of primary amenorrhoea [26, 27]

Pregnancy test serum TSH and PRL level	Pregnancy test positive, abnormal TSH or PRL levels	Treat as appropriate
FSH and LH levels	Low	Functional hypothalamic amenorrhoea Constitutional delay of puberty Primary GnRH deficiency Anorexia nervosa
	Normal	Outflow tract obstruction Late onset of CAH
	Elevated	Hypergonadotropic hypogonadism (karyotyping analysis needed)
Oestradiol	Low	Poor ovarian function
USG imaging	Absent or abnormal uterus	Karyotyping analysis needed
	Normal uterus	Outflow obstruction
Karyotype	46,XX + hypergonadotropic hypogonadism	Premature ovarian insufficiency/failure
	46,X + hypergonadotropic hypogonadism	Turner syndrome
	46,XX + absent or abnormal uterus	Müllerian ducts agenesis
	46,XY + absent or abnormal uterus	Androgen insensitivity Swyer syndrome 5α-reductase deficiency
AMH	Elevated	Functional hypothalamic amenorrhoea PCOS
	Low	Primary ovarian failure
Free testosterone levels, DHEA-s	Elevated (urinary steroid profile analysis should be considered)	Hyperandrogenism PCOS Ovarian or adrenal tumour CAH Cushing syndrome
Oestradiol	Low	CAH

TSH – thyroid-stimulating hormone; PRL – prolactin; FSH – follicle stimulating hormone; LH –luteinising hormone; GnRH – gonadotropin-releasing hormone; CAH – congenital adrenal hyperplasia; AMH – anti-müllerian hormone; PCOS – polycystic ovary syndrome

sia (CAH) (from deficit of the 17α-hydroxylase/17–20 lyase enzyme), and complete androgen insensitivity syndrome (CAIS) should be considered in the differential diagnosis [17, 25]. Deficiency of 17α-hydroxylase/17–20 lyase is a rare form of CAH, caused by loss-of-function mutations in *CYP17A1*. It appears in adolescence or in adult life. XY children with this form of CAH develop female phenotype; however, they have a histologically normal testis. Due to the accumulation of mineralocorticoids, a characteristic symptom in these patients is difficult-to-treat hypertension [17, 26]. Patients with CAIS are phenotypically female with female gender identification. Gonads are found high in the inguinal canals or in the pelvis, and müllerian structures are absent. Hormonal tests usually show elevated oestrogen and androgen levels [5, 25]. The androgen insensitivity is caused by the androgen receptor mutations [2]. Table II shows the diagnostic tests in cases of primary amenorrhoea [26, 27].

Because of the possibility of neoplasm transformation in patients with 46,XY karyotype and dysgenetic gonads, bilateral gonadectomy should be performed as soon as the diagnosis is made [1, 4, 5, 7, 10, 19, 22, 28]. According to various authors, the occurrence of tumours in Swyer syndrome varies from 15% to as much as 55% of cases, with the incidence increasing with age [1, 4, 11, 20]. Among all DSD, in patients with 46,XY CGD the tumour presence and malignancy risk are the highest. Therefore, Swyer syndrome is considered the most threatening disorder [4]. The most common tumours include *gonadoblastoma* and *dysgerminoma*. *Gonadoblastoma* almost always develops in DSD with the presence of Y chromosome material, and more than 80% of cases involve patients with a female phenotype [20]. *Gonadoblastoma* is a tumour originating from persistent undifferentiated cells of a dysgenetic gonad. Its development is associated with the expression of the testis-specific protein, Y-linked gene (TSPY), and with the presence of *SRY*, *SOX9*, and *WT-1* mutations [1]. Despite being a benign tumour, it may progress further and could be a precursor to malignant germ cell malignancy – usually *dysgerminoma* [1, 4, 19, 20, 28]. It is estimated that half of *gonadoblastoma* will have malignant transformation [5]. The tumour can be uni- or bilateral. There have also been reported cases of concomitant occurrence of *gonadoblastoma* and *dysgerminoma* within one gonad [11]. Diagnosis is made most often in the pubertal age. However, a case of a three-month-old child with mixed gonadal dysgenesis and concomitant *gonadoblastoma* has been described [28]. If *gonadoblastoma* is diagnosed, the prognosis is very good. However, if the features of malignant transformation are found, then the survival rate decreases [20].

Patients with CGD are always reared as female, according to the phenotypic sex, and are unlikely to have gender dysphoria [5, 12]. The case of the described patient was similar. However, psychological care is advisable [4]. Moreover, patients with 46,XY and gonadal dysgenesis require sex hormone treatment. It helps to induce and maintain adequate breast development and menstruation, and to achieve an optimal peak bone mass. For this purpose, oestrogen and progesterone supplementation is used until menopausal age [1]. Despite of the lack of female gonads, pregnancy is possible because these patients have normal müllerian structures; it is possible via ova donation and *in vitro* fertilisation. Because of the genetic background of Swyer syndrome, familial screening should be considered [11, 19].

In conclusion, phenotypic female 46,XY DSD is a rare disorder, diagnosed most often in adolescence. Our observation underlines the need to consider DSD 46,XY in the presence of primary amenorrhoea, even when pubertal development is present. Normal breast development may mask gonadal dysgenesis and delay diagnosis. It has to be kept in mind that germ cell tumours have a tendency to grow and metastasise rapidly. Delayed diagnosis may increase the risk of malignant transformation and cause a poor diagnosis and reduced survival rates. In the described case, genetic analysis did not reveal any of the known mutations connected with CGD. Despite that, prophylactic gonadectomy was performed due to the high risk of malignancy in every case of 46 XY with gonadal dysgenesis. Early sex hormone treatment helps to induce and maintain typical pubertal and psychosexual development, and to achieve an optimal peak bone mass.

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