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The risk of neoplasm associated with dysgenetic testes in prepubertal and pubertal/adult patients

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Abstract

Introduction. In patients with Y-chromosome in the karyotype, partial gonadal dysgenesis and disorders of male reproductive sex organs development are usually resected in childhood because of the high risk of germ cell tumours (GCT). In patients with Y-chromosome, complete gonadal dysgenesis and female genitalia gonadectomy is performed markedly later. However, due to the relatively low number of adult patients with preserved dysgenetic gonads, the true risk of neoplasm is unknown. The aim of the study was to evaluate the prevalence of neoplasia in dysgenetic gonads of children and adults with Y-chromosome in a retrospective study.

Material and methods. A review of medical documentation of 94 patients with disorders of sex development (DSD), Y-chromosome and gonadal dysgenesis (GD), aged 1.2–32 years (47 prepubertal, 1.2–10 years; 47 pubertal/adult, 13–32 years), was conducted. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone were determined. Bilateral gonadectomy was performed in 73.4% of patients, and unilateral gonadectomy with biopsy of the contralateral gonad in 26.4%. All gonadal tissues were subjected to immunohistochemical evaluation with antibodies against PLAP and OCT3/4 (markers of malignant germ cells, but also foetal multipotent germ cells), while gonads of prepubertal patients were examined by c-KIT, as well.

Results. Streak gonads were identified on both sides (complete GD) in 30.8%, a streak gonad on one side and an underdeveloped testis on the other (asymmetric GD) in 38.3%, and underdeveloped testicular structure on both sides (partial GD) in 30.8% of cases. Germ cell neoplasia was found in 53.2% of patients (51.1% in children, 55.3% in pubertal/adults). Invasive GCT were identified in 11.7% of cases, of which 90.9% were in pubertal/adult patients. Other neoplastic lesions included gonadoblastoma (16% prevalence) and testicular carcinoma *in situ*

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(25.5%). In younger patients FSH serum levels were increased in 81% of cases (mean 2.82 ± 2.18 IU/L), while LH in 58% (mean 1.82 ± 1.69 IU/L). Hypergonadotropic hypogonadism was diagnosed in most of the pubertal/ /adult patients (mean FSH 54.2 ± 23.3 IU/L, mean LH 21.7 ± 12.1 IU/L, mean testosterone 5.5 ± 4.5 nmol/L). **Conclusions.** Dysgenetic gonads in patients with Y chromosome have a high risk of germ cell neoplasia (ca. 50%). If they are preserved until puberty/early adulthood, they may develop overt, invasive GCT. The gonads also have poor hormonal activity (hypergonadotropic hypogonadism) in most of the pubertal/adult patients. Each of these cases must be considered individually and a decision to remove the gonad or not should be based on the comprehensive analysis of the phenotype by a multidisciplinary team of specialists in consultation with the patient and the parents. If dysgenetic gonads are not resected in childhood, these patients need careful ongoing follow-up examination, including biopsy and histopathological evaluation. *(Folia Histochemica et Cytobiologica 2015, Vol. 53, No. 3, 218–226)*

Key words: testis; gonadal dysgenesis; testicular carcinoma *in situ*; gonadoblastoma; germ cell tumours; hypergonadotropic hypogonadism

Introduction

Gonadal dysgenesis (GD) is a term used to describe the incomplete formation (organogenesis) of gonads, testes or ovaries during embryogenesis [1, 2]. The origin of this condition may be genetic or environmental [3–6].

In patients with the Y-chromosome, or Y-chromosome-specific sequences in the genotype including the presence of the *SRY* gene (sex-determining region Y), dysgenetic gonads are histologically categorised as: 1) bilateral streaks of an ovarian-like cortical stroma (complete or pure GD); 2) a streak on one side and testis-like stroma on the other (asymmetric or mixed or combined GD); 3) bilateral testes with incomplete organogenesis (partial GD) [7, 8]. In testicular dysgenesis, germ cells are absent or spermatogenesis is arrested at the level of foetal gonocytes or spermatogonia, Sertoli cells frequently remain immature and the adult type of Leydig cells rarely appears [7–11]. Disturbances in the maturation of these testicular somatic cells lead to disorders of male internal and external reproductive sex organs development. Absent or decreased secretion of testosterone by foetal Leydig cells results in differentiation disorders of the external and internal male sex organs. Disturbed secretion of antimüllerian hormone (AMH) by Sertoli cells is associated with the persistence of Müllerian ducts and the presence of female internal sex organs in patients with the male genetic sex. A further clinical consequence of deteriorated testicular development is hypergonadotropic hypogonadism observed from the pubertal period of life [10, 12, 13]. These patients are referred to the group of disorders of sex development (DSD) and classified as sex chromosomal DSD or 46,XY DSD or 45,X/46,XY DSD according to the karyotype [14].

All forms of testicular GD are accompanied by an increased risk of germ cell neoplasia [15, 16]. Neoplastic lesions appear as overt, invasive germ cell tumours (GCT), which can be either seminomatous or non-seminomatous, and usually develop in young adults [17]. Preinvasive testicular carcinoma *in situ* (CIS, or intratubular germ cell neoplasia unclassified — IGCNU or testicular intraepithelial neoplasia — TIN) [17, 18] is seen not only in the testes of adult men, but also in the gonads of prepubertal children [7–9, 11, 19–21]. Other germ cell neoplastic lesions include the sex cord-derived tumours, gonadoblastoma (GB) and unclassified mixed germ cell-sex cord stromal tumours found mainly in testes with profound developmental defects [10, 22, 23].

Underdeveloped testes (in partial or asymmetrical GD) in patients with Y-chromosome, if early diagnosed, are frequently resected at prepuberty due to their potential for presumptive GCT development. However, the procedure is controversial, as some of these gonads may have adequate hormonal function and normal spermatogenic cells, and may never develop GCT [10, 11, 24]. In patients with Y-chromosome and complete GD preventive gonadectomy is performed markedly later because of female phenotype. Nevertheless, also in these cases the removal of gonads is the matter of criticism. The true risk of neoplasia in GD is in fact unknown because of the relatively low number of adult patients with preserved gonads.

The aim of our study was to determine the prevalence of neoplasia in dysgenetic gonads in children and adults with the Y-chromosome in their genotype.

Material and methods

Patients and clinical data. The study was performed with the approval of the Bioethical Committee of the Medical University of Lodz (no RNN/28/10/KE).

A review was conducted of the medical documentation of DSD patients diagnosed and treated from 1983 to 2013 in the centres of Paediatric Endocrinology, Paediatric Urology

and Genetics in Lodz and Warsaw, Poland. Ninety-four patients, aged 1.2–32 years, were included. External sex organs were qualified as female or ambiguous (undervirilised male or virilised female). Ultrasonography, later confirmed by genitography and abdominal surgery, revealed all patients to have the remnants of Müllerian ducts. The gonads were located mainly in the minor abdominal cavity or in some cases in the upper segment of the inguinal canal. All patients possessed the Y-chromosome in either 46,XY (71.3%) or a mosaic complement (*i.e.* 45,X/46,XY, 45,X/47,XXY, 45,X/46,XY/47,XXY — 28.7%).

Bilateral gonadectomy was performed in 73.4% of patients, unilateral with the biopsy of the contralateral gonad in 26.4%. The age of histopathological evaluation of gonads was as follows: 1.2–10 years (median 3.0) — 50%, 13–32 years (median: 17.0) — 50%. Gonadal tissues were fixed in formalin (mostly in younger group) or in Bouin's fixative (mostly in older group) and stored in paraffin.

Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and testosterone were determined shortly before gonadectomy. In most patients chemiluminometric immunoassay was used, while in some cases radioimmunological or immunoenzymatic. The following were taken as reference values for prepubertal children — FSH: 0.22–1.92 IU/L, LH: 0.02–0.42 IU/L and testosterone: < 0.1–0.35 nmol/L. The corresponding values for healthy adult men were FSH: 1.70–10.35 IU/L, LH: 1.54–7.00 IU/L and testosterone: 12.25–33.95 nmol/L [25].

Histology and immunohistochemistry. The gonads were cut into sections 5 μm thick, and stained with haematoxylin and eosin (H & E). Histological examination was then performed with the use of an Eclipse E600 light microscope (Nikon, Tokyo, Japan).

Immunohistochemical staining for foetal multipotent germ cells (gonocytes)/malignant germ cells, was carried out in all patients using monoclonal antibodies against placental like alkaline phosphatase (PLAP) (Novocastra Laboratories, Newcastle, UK), and against octamer transcription factor 3/4 (OCT3/4) (Santa Cruz Biotechnology Inc., Dallas, Texas, USA). Polyclonal antibody against the c-Kit proto-oncogene (c-KIT, Santa Cruz Biotechnology Inc.) was performed only in the gonads of prepubertal children. The primary antibody was diluted to 1:25 (PLAP), 1:200 (OCT3/4) or 1:50 (c-KIT) in 0.05 M Tris-buffered saline, pH 7.4. For the qualitative detection of antigens in fixed paraffin-embedded tissue sections, the Impress polymerized reporter enzyme staining system (Vector Laboratories, Peterborough, UK) was used for PLAP and OCT3/4, and the Novocastra Novolink Polymer Detection System (Leica Biosystems, Nussloch, Germany) for c-KIT. Five histological sections were examined for each gonad.

A testicular CIS (a part fixed in formalin and part in Bouin's fluid) from an adult patient served as a positive control for PLAP, OCT3/4 and c-KIT. For the negative control, the primary antibodies were replaced with 0.05 M Tris-buffered saline, pH 7.4.

Statistical analysis. Basic statistical analyses (mean, standard deviation, median) were performed using Statistica 8.0 software (StatSoft, Krakow, Poland). Confidence interval was set at 95%.

Results

The group of patients was divided into two subgroups: 1) prepubertal patients (age: 1.2–10 years) and 2) pubertal/adult patients (13–32 years). All patients from the younger group presented Tanner stage I of puberty, while the older patients presented various stages of secondary sexual characteristics. The start of puberty in the older group was confirmed by the activity of the hypothalamus-pituitary axis (increased FSH and LH serum levels), and the results in both, young and old, subgroups are given in Table 1. FSH levels were higher in 81% of younger patients and all pubertal/adult patients compared to the corresponding normal values. LH was elevated in 58% of younger patients and in 83.8% of pubertal/adult patients. Testosterone levels were at prepubertal values in all

Table 1. Gonadotropin and testosterone concentration in the blood of patients with gonadal dysgenesis and Y-chromosome

Age group (years)		Age (years)	FSH [IU/L]	LH [IU/L]	Testosterone [nmol/L]
1.2–10 n = 47	Mean ± SD Median Range	4.14 ± 2.38 3.0 1.17–10.0	2.82 ± 2.18 2.2 0.1–8.37	1.82 ± 1.69 1.34 0.30–5.6	0.44 ± 0.39 0.35 0.01–1.86
Normal prepubertal values	Range		0.22–1.92	0.02–0.42	< 0.1–0.35
13–32 n = 47	Mean ± SD Median Range	18.09 ± 4.39 17.00 13.00–32.00	54.24 ± 23.26 57.00 17.00–105.00	21.75 ± 12.08 23.00 4.4–50.00	5.55 ± 4.46 4.80 0.38–13.40
Normal adult values	Range		1.70–10.35	1.54–7.00	12.25–33.95

Range provides 95% confidence interval. Abbreviations: n — number of cases; FSH — follicle-stimulating hormone; LH — luteinizing hormone

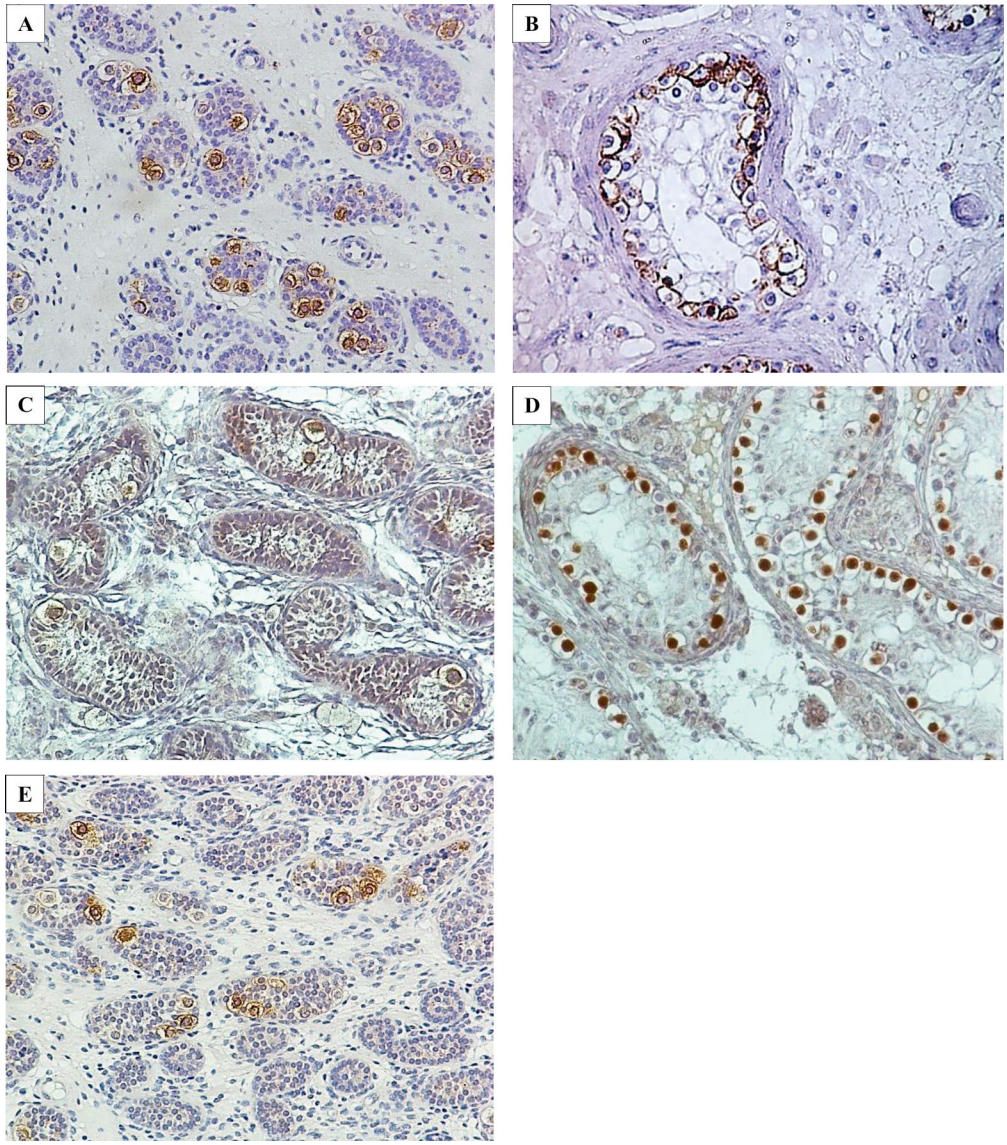

Figure 1. Dysgenetic gonad of prepubertal child (**A**, **C**, **E**) and adult men (**B**, **D**) with disorders of sex development. Positive reaction with antibodies against PLAP (**A**, **B**), OCT3/4 (**C**, **D**), c-KIT (**E**) in germ cells. The brownish staining of cytoplasm (PLAP and c-KIT) and nuclei (OCT3/4) confirms the diagnosis of testicular carcinoma *in situ*. Note the wide intertubular spaces specific for dysgenetic testes structure. Magnification × 200.

children, and either low (80.7%) or normal (19.3%) in pubertal/adult patients.

All of the gonads displayed features of dysgenesis under histopathological evaluation (Figure 1). Of the whole group, 29 (30.85%) were patients with complete GD, 36 (38.30%) with asymmetric GD and 29 (30.85%) with partial GD. In the whole documentation we found 6 patients with ovotestes. Three patients were not included to this study because were younger than 1 year. In the next 3 patients ovocytes were not found in the wider than normal cortical part of gonad, and, therefore, ovotestis was not recognised, but partial GD.

The numbers of different types of germ cell neoplasia found in the dysgenetic gonads are given in Table 2. Diagnoses of GB and overt GCT were based on specific histological features [22]. Overt GCT included seminomatous (one 7-year-old patient and 4 pubertal/adults) and non-seminomatous (1 — immature teratoma, 5 — mixed GCT) tumours. The mixed GCT contained elements of embryonal carcinoma, yolk sac tumour, teratoma and seminoma.

CIS was indicated not only by histological features, but also by positive immunohistochemical reactions with antibodies against PLAP and OCT3/4 in all gonads, as well as against c-KIT in those of prepubertal

Table 2. Germ cell neoplasia in dysgenetic gonads of patients with Y-chromosome

Group	Gonad	GB n	CIS n	GCT n	Total n (%)	Total in GD types n (%)
Age: 1.2–10 years						
Complete GD n = 6	One	1	0	1	2 (33.3)	4 (66.7)
	Both	2	0	0	2 (33.3)	
Asymmetric GD n = 21	One	1	6	0	7 (33.3)	7 (33.3)
	Both	0	0	0	0	
Partial GD n = 20	One	0	2	0	3 (15.0)	13 (65.0)
	Both	1	9	0	10 (50.0)	
Total n (%)		6 (12.8)	17 (36.2)	1 (2.1)	24 (51.1)	
Age: 13–32 years						
Complete GD n = 23	One	3	0	4	7 (30.4)	12 (52.2)
	Both	5	0	0	5 (21.7)	
Asymmetric GD	One	1	3	4	8 (53.3)	8 (53.3)
n = 15	Both	0	0	0	0	
Partial GD n = 9	One	0	2	2	4 (44.4)	6 (66.7)
	Both	0	2	0	2 (22.2)	
Total n (%)		9 (19.1)	7 (14.9)	10 (21.3)	26 (55.3)	

Abbreviations: n — number of cases; GB — gonadoblastoma; GD — gonadal dysgenesis; CIS — testicular carcinoma *in situ*; GCT — germ cell tumour

children (Figure 1). Only samples which expressed these immunohistochemical diagnostic markers, and displayed a distinctive pattern of atypical germ cells with the characteristics of the gonocytes (bigger than normal spermatogonia, large cytoplasm, hyperchromatic nuclei with prominent nucleoli, big irregular clumps of heterochromatin), and were located near the basal membrane in the seminiferous epithelium were classified as neoplastic CIS cells.

The total risk of germ cell neoplastic lesions was 51.1% (24/47) in prepubertal children, 55.3% (26/47) in pubertal/adult patients and 53.2% (50/94) in the whole group. The risk of neoplasm was 55.2% (16/29) (children — 4/6, 66.7%, pubertal/adults — 12/23, 52.2%) in patients with the complete GD, 41.7% (15/36) (children — 7/21, 33.3%, pubertal/adults — 8/15, 53.3%) in those with asymmetric GD and 65.5% (19/29) (children — 13/20, 65%, pubertal/adults — 6/9, 66.7%) in those with partial GD. Overt GCT were revealed in 11.7% (11/94) of cases, most of them (90.9%) in pubertal/adult patients with all types of GD. GB was found in 16% (15/94) of patients (children — 6/47, 12.8%, pubertal/adults — 9/47, 19.1%), while CIS in 25.5% (24/94) (children — 17/47, 36.2%, pubertal/adults — 7/47, 14.9%). GB was the most prevalent in patients with complete GD (11/15, 73.3%), while CIS was most common in patients with partial GD (15/24, 62.5%). In asymmetric GD the neoplastic lesions were found only in underdeveloped testes.

Besides the germ cell neoplasia, sertolioma composed of cells with features of foetal/prepubertal Sertoli cells was identified in 2 (2.1%) adult patients, one in a streak gonad and one in a patient with partial GD.

Discussion

Testicular cancer represents 1–1.5% of male neoplasms, with an incidence of 0.3–1% new cases per year in the general population of European countries, mainly in young adults [26–29]. Although the risk of GCT in dysgenic gonads in patients with Y-chromosome is known to be high, the precise risk has not been determined. Based on an epidemiological analysis of GCT established and suspected risk factors, Dieckmann and Pichlmeier [15] attribute levels of evidence to each of the putative risk factors. GD was assessed as high risk (up to 25% cumulative risk) but because of rare, heterogenous cases and small case series which were regarded as only level IV in the formal hierarchy of evidence. They established also that risk factor with the highest level of evidence (level I) is the presence of undescended testes (cryptorchidism), in which a cause might be GD [30, 31]. Our previous study found that adult patients with cryptorchidism may demonstrate the histological features of GD,

i.e. decreased seminiferous tubule diameter, thicker tubular membrane, increased intertubular space or the presence of tubules with immature Sertoli cells, and an increased incidence of germ cell neoplastic lesions (11.1%) [32].

Looijenga et al. [33] classify the risk for GCT development in the gonads of patients with DSD and Y-chromosome into high, intermediate, low and unknown levels. However, this analysis was based on a limited number of studies. Patients with GD, those who were positive for testis-specific Y-encoded protein (TSPY) and those with intra-abdominal gonads were included in the high-risk group (risk 15–60% based on the literature) [9, 12, 33]. In our patients, as the dysgenetic gonads were located in the minor abdominal cavity or in the upper segment of the inguinal canal, a high risk of GCT was suspected. Unfortunately, TSPY could not be identified in gonads fixed in Bouin's fixative. Nevertheless, germ cell neoplasia could be recognised undoubtedly in about 50% of pubertal/adult patients with GD. Moreover, the incidence of germ cell neoplasia seemed to be similar in younger subgroup.

CIS cells were more frequent in the younger (36.2%) then the older subgroup (14.9%). However, there are difficulties in the diagnosis of malignant germ cells in children. CIS cells originate from developmentally arrested foetal germ cells (gonocytes) [4, 16, 34]. A number of studies show that the arrest of germ cell differentiation is the key event, which may be followed by malignant transformation and invasive GCT development, usually occurring in young adults [16, 32, 35]. CIS cells have some morphological features of gonocytes, but also display a series of antigens present normally in the foetal period of life, some of them up to the first year after birth [35, 36]. After this age, foetal antigen expression is used as an immunohistochemical marker of malignant germ cells. PLAP, OCT3/4 and c-KIT have been proposed as the best immunohistochemical markers for malignant germ cells [37, 38]. While there is no doubt as to their significance in pubertal or adult men, this is not so obvious in prepuberty. Cools et al. [11] claim that not all germ cells expressing foetal antigens are real neoplastic cells in very young male patients with undervirilisation. In these patients, germ cells may undergo delayed maturation, resulting in the prolonged expression of such embryonic markers as PLAP, OCT3/4 and c-KIT. The location of the germ cells positive for these antigens in the centre of seminiferous tubules is an additional sign of their immaturity. Normally, the gonocytes differentiate into pre-spermatogonia, and as part of that process, they move to the basal lamina of the seminiferous tubule and stop expression of the embryonic genes. Nevertheless, Chemes et al. [8] claimed that infantile CIS may have both basal and central location because germ cell distribution is not yet restricted by a permeability barrier.

The methods used in the present study fulfil the required criteria to differentiate normal germ cells with delayed maturation and neoplastic CIS cells, however, we did not perform the examination of DNA ploidy in germ cells, what might eventually confirm the results. Chemes et al. [7, 8] note wide cytological variation in aneuploid germ cells, ranging from normal-looking large infantile spermatogonia to gonocyte/CIS cells. As the earliest recognizable change in germ cell neoplastic transformation is thought to be DNA polyploidy of foetal germ cells, so they propose careful histopathological examination of cytological signs of malignancy, their topographic distribution, immunohistochemical markers and the use of DNA densitometry to confirm the presence of neoplastic tendencies in infantile germ cells. In our previous study among 70 patients from various high-risk groups of GCT, the incidence of neoplastic lesions was found to be the highest in children with GD (43.5%) [39], and the aneuploid DNA content, with pattern typical of GCT cells, was found in 42–98% of germ cells in the dysgenetic testes of prepubertal children [21]. The neoplastic transformation of germ cells in the dysgenetic gonads of prepubertal children was revealed also by double immunolabelling with antibodies against PLAP and RBM (germ cell-specific RNA-binding motif protein encoded by the Y-chromosome) [40, 41]. The RBM protein is expressed in normal male germ cell nuclei of pubertal and adult testis, as well as foetal ones from the second trimester of gestation [42]. The study demonstrated normal germ cells to be RBM-immunopositive, and PLAP-positive germ cells to be RBM-immunonegative.

In other study [9] we found that within a group of 46 young patients with DSD aged from 3 months to 19 years the incidence of neoplastic lesions (mostly bilateral) was 90.9% in those with partial GD, 76.9% (mostly unilateral) in those with asymmetric GD and 23.1% (unilateral) in those with complete GD. Less disturbed testicular organogenesis was found to predispose the patient more toward germ cell neoplasia. Chemes et al. [8] have described the similar findings in their recent publication. They suggested that disrupted Sertoli cell function in severe dysgenesis may not only fail to elicit gonocyte differentiation but also compromise their viability and proliferative capacity. This observation was confirmed also in milder forms of GD in adult patients [26]. Nevertheless, the results of the present study do not indicate significant differences in the incidence of germ cell lesions in either

complete or partial GD, except the finding that the neoplastic lesions were found only in underdeveloped testes, but not streak gonads, of asymmetric GD.

The present study also indicates that overt GCT are more frequent in pubertal/adult patients than in prepubertal children (21.3% *vs.* 2.1%). This confirms the observation that GCT predominantly occur from puberty, when CIS cells start proliferation and give rise to invasive neoplasia [27]. Furthermore, the preinvasive germ cell lesions existing in 34.04% (GB — 19.1%, CIS — 14.9%) pubertal/adult patients may transform into invasive GCT. It has been previously revealed that 50% of the testes bearing the precursor lesion will progress to invasive cancer within 5 years and 70% will do so within 7 years [34]. Moreover, increased serum levels of FSH were seen in all patients from the older subgroup, while LH levels were raised and testosterone levels lowered in most of these patients. There are suggestions that low testosterone secretion and the associated increased secretion of gonadotropins may induce the formation or maintain neoplastic lesions in dysgenetic testes [16]. Both FSH and LH were found to be positively correlated with the number of CIS cells in children with GD [43]. Other clinical studies have shown that in adult men, FSH and LH may influence the number of premeiotic germ cells, including CIS cells [44–47].

Because of the commonly known high risk of GCT occurring in the dysgenetic gonads of patients with Y-chromosome after puberty and their poor hormonal and gametogenic function, gonadectomy has been recommended before puberty [2, 48]. However, prophylactic gonadectomy may deprive some boys of natural maturation [10], and in some rare cases, their chance for fertility [49]. Biopsy of dysgenetic gonads in childhood in order to detect neoplastic cells is performed rarely (including this study). The biopsy is controversial because of the low gonadal volume and the potential risk of worsening the function of the already compromised testis. However, there are suggestions that dysgenetic gonads should be biopsied during orchiopexy or genital surgery in DSD children [50]. The predictive value of the biopsy sample for the further development of neoplastic lesions depends on the availability of specific immunohistochemical markers, as well as the histological characteristics [51]. This enables early diagnosis without overtreatment, such as prophylactic gonadectomy in the case of low tumour risk. Moreover, recent reports show that testicular biopsy performed in boys does not have adverse effects such as antisperm antibodies production or testicular microlithiasis in adulthood [52]. The prepubertal biopsy of dysgenetic testes seems reasonable, because nowadays it is possible to apply the methods of assisted reproduction even if single spermatids are found intratesticularly [53]. Patients with relatively good development of testes and preserved hormonal function demonstrated by a good response to hCG stimulation (milder forms of partial GD) have better prognosis to maintain testicular function in adulthood, however, they are usually infertile [54, 55]. In case the premalignant changes are found, gonadectomy is recommended [51]. The decision may be additionally supported by low testosterone production and low volume of gonads. In adult patients with a higher risk of testicular GCT (*i.e.* DSD, undescendent testes, GCT in the contralateral testis) it is no doubt that biopsy should be recommended, especially, when increased FSH concentration, low testicular volume, poor semen parameters and/or microcalcifications are found [56].

Conclusions

In conclusion, dysgenetic gonads in patients with Y-chromosome have a high risk of germ cell neoplasia (ca. 50%). If they are preserved until puberty/ /early adulthood they may develop overt, invasive GCT. The gonads have also poor hormonal activity (hypergonadotropic hypogonadism) in most of the patients. However, each case must be considered individually and a decision to remove the gonad or not should be based on the comprehensive analysis of the phenotype by a multidisciplinary team of specialists in consultation with the patient and/or the parents. If dysgenetic gonads are not resected in childhood, these patients need careful ongoing follow-up examination, including biopsy.

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