Abstract

The risk of germ cell cancer is elevated in many DSD patients, although not to the same extent. A number of risk factors have been identified recently, but their interplay and relative impact is currently not fully clear. Until the advent of reliable screening tools for the detection of pre-invasive cancer lesions, managing germ cell tumour risk focuses on the question if and when to perform biopsy or gonadectomy in most patients and how to interpret the histological findings.

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Keywords: DSD; Germ cell tumor; Risk; Gonadectomy

1. Introduction

Several DSD conditions are associated with an increased risk for the development of germ cell cancer (GCC), specifically the so-called type II germ cell tumours of the testis and dysgenetic gonad, here further referred to as GCC. Identified risk factors include the presence of the $GBY$ region (probably limited to the presence of TSPY) in the (gonadal) karyotype, disturbed gonadal development, being an incomplete testicularisation of the gonad in a 46,XY or 45,X/46,XY individual, maturation delay or block of germ cells as identified by amongst others a prolonged expression of the pluripotency transcription factor Octamer binding protein 3/4 (OCT3/4) in the germ cells and aberrant immunohistochemical detection of the ligand for...
Fig. 1. Factors of malignant transformation. The risk of malignant transformation, leading to an invasive GCC is likely related to various parameters, including environmental as well as genetic/chromosomal anomalies. These may interfere with the physiological maturation of primordial germ cells. Four parameters are required to allow malignant transformation. These include the presence of the \textit{GBY} region (probably only TSPY) in the patient’s karyotype, the presence of immature gonadal tissue and of embryonic germ cells (characterized by OCT3/4 amongst others), and the expression of the c-KIT ligand (SCF). This specific constitution is the prerequisite for the formation of the precursor lesion, either GB or CIS/IGCNU, depending on the level of testicularization of the gonad, which is in part reflected by the patient’s phenotype and can be described by the External Masculinization Score. Based on this knowledge, clinical intervention can be planned, varying between no action at all (in case of absence of risk factors), surveillance, gonadectomy (or irradiation).

Modified from [1].

C-Kit (KITLG), alternatively called the stem cell factor (SCF) (reviewed in [1]) (Fig. 1). The first step in the development of GCC is the retention of a pluripotent stage of the primordial germ cells (PGC)/gonocytes, most likely due to failure of Sertoli cells to support GC in the accomplishment of their intrinsic maturation program during a critical phase in fetal life; ultimately leading to abnormal clonal expansion many years later [2]. Precursor lesions in a testicular context can be identified as carcinoma in situ (CIS) or testicular intraepithelial neoplasia (TIN), whereas gondoblastoma (GB) is the typical precursor lesion in the dysgenetic gonad [3–5].

Recently, powerful genome wide association studies have linked several susceptibility genes to GCC development (KITLG, SPRY4, DMRT1, BAK1, TERT, ATF7IP, TGFBR3, BMP7 and LRRC50). Interestingly, these risk SNPs are the most prevalent alleles in the Caucasian population, in contrast to African and Asian populations who, as expected, have a lower risk for GCC [6–11]. Additionally, aberrant epigenetic reprogramming of PGC/gonocytes due to subtle micro-environmental influences during early fetal life can interfere with the maturation program. Indeed, the endogenous hormonal (androgen and estrogen) milieu, as well as exposure to (xeno)estrogens have been shown to modify the embryonic germ cell epigenetic program [12]. The above described risk factors have been integrated in the so-called genenvironmental hypothesis for the development of GCC. Combining these data suggests that the risk for GCC in DSD patients should be seen as a continuum, determined by the additive effects of the underlying condition and known and hitherto unidentified environmental modifiers [2]. However, this hypothesis needs further confirmation.

2. Estimating GCC risk in the individual patient

2.1. Underlying condition and localisation of the gonad

DSD patients have an increased risk for GCC only if they have Y chromosomal material in their (gonadal) karyotype. A risk estimation per condition, based on an extensive meta-analysis of published series was presented in 2006 [13]. From this review, it became clear that GCC is much more prevalent (30–50%) in conditions associated with gonadal dysgenesis (GD), i.e. conditions with defective testicularisation of the gonad, as compared to 46,XY disorders of hormone synthesis or action (<1–15%), where testis development is normal. Whereas the latter conditions are associated with a transient phase of delayed maturation of GC, GD rather leads to a block in GC maturation [3,5,14–16]. It has been shown in cases with 45,X/46,XY DSD that the degree of testicularisation is – to a certain extent – reflected in the patient’s phenotype: a low external masculinisation score (EMS) is the result of a poorly differentiated gonad. This finding, combined with knowledge on the patient’s underlying condition, can be used as a predictor of GCC risk in the clinical setting (Fig. 1) [17,18]. An abdominal or inguinal position of the gonad represents an additional independent risk factor [19]; in a recent meta-analysis, isolated cryptorchidism has been associated with a relative risk for GCC of 2.9 [20].

For a number of very rare conditions, such as testosterone biosynthesis disorders, in which prophylactic gonadectomy in accordance with the sex of rearing is typically performed in the majority of patients at an early age, insufficient data are available to reliably predict lifelong tumour risk. The same is
true for more recently described conditions, such as NR5A1 mutations, in which only one CIS lesion and no invasive GCC have been reported so far [21]. It is expected that, with recent improvements in and more widespread availability of diagnostic facilities, and with more children with this condition being raised male, additional data will become available in the future.

Controversy exists around GCC risk in complete androgen insensitivity syndrome (CAIS). On the basis of data mainly obtained in prophylactic gonadectomy material of prepubertal children, this risk has been estimated less than 1% (13), leading to the suggestion to postpone gonadectomy until adolescence in order to allow spontaneous breast development [22]. This low risk has been attributed to massive apoptosis of germ cells in the first years of life [13,14,23,24]. However, recent observations indicate that in most gonadal samples obtained in postpubertal CAIS women, a limited number of germ cells persist, organized in small isolated groups (unpublished data). Recent evidence suggests that the lack of androgen action itself might have a protecting effect on germ cell tumour proliferation [25]. So far, no series have been published that focus on GCC risk in adult CAIS women, although combining data from historic case series suggests an incidence of CIS in adult CAIS women with retained gonads of around 5% [26,27] (and unpublished data); although a risk of 14% was mentioned by others [28]. This needs further evaluation, in which inclusion of the susceptibility alleles (see above) is of great interest.

2.2. Patient age

GB has been reported in very young children with GD, whereas CIS appears to arise mainly in postpubertal testes [13]. The role of androgens and/or puberty in the progression of a germ cell delayed in its maturation towards clonal expansion and formation of CIS remains speculative. An interesting finding in this context is that proliferation of germ cells in human GCC cell lines is androgen dependent and can be repressed by TSPY, through trapping of androgen-bound androgen receptor in the cytosol [25].

3. Gonadectomy or not?

The decision if and when to perform gonadectomy in the individual patient is based on a GCC risk assumption, the likelihood that hormones in concordance or disharmony with the sex of rearing will be produced during puberty, and patient/parent preferences. The development of large multi-center studies are a necessary step for the development of general guidelines. Further details regarding the decision making process with regard to gonadectomy in individual DSD patients and per condition can be found in a number of recent publications [29,30].


4.1. Self-examination

Boys and men with DSD and scrotal testes are advised to perform self-examination by palpation of their testes once a month from puberty onwards. In case of any abnormal finding, an ultrasound (US) is the next step. A Dutch App has been developed to instruct man (http://www.zaadbalkanker.nl/zaadbalkanker/zelfonderzoek).

4.2. Imaging

In view of its low cost and safety, US is the first choice for imaging retained gonads in a scrotal or inguinal position [31]. As in other men with increased risk for GCC, annual follow-up by US is recommended from late puberty onwards. CIS cannot be visualized directly by US but an irregular aspect of the testis parenchyma may be suggestive. The role of US in the detection of early testicular GCC lesions is revised in detail [32]. Although no specific studies in DSD patients are available, the presence of microlithiasis, especially in combination with an inhomogeneous testis parenchyma, is highly sensitive but not specific for CIS [33].

Although MRI may have a role in the evaluation of suspected testicular lesions, it is not able to detect testicular CIS or microlithiasis [31,34]. However, MRI is thought to be superior to US in visualising intra-abdominal gonads and in differentiating between undescended and vanished testes [31]. Of interest, a recent study evaluated the role of MRI in 24 postpubertal women with CAIS and retained gonads in an abdominal or inguinal position. MRI was able to reliably detect cysts and Sertoli cell adenomas but could not depict any of the CIS lesions found in three patients at subsequent gonadectomy and histological analysis. If MRI imaging is able to detect early invasive GCC was not clear from this study as no such cases were available. US data were equally not available for comparison in this study [35].

4.3. GCC markers in serum and semen

Invasive GCC (especially non-seminomas), but not CIS lesions, may secrete proteins. Therefore, serum detection of β-HCG and α-fetoprotein (AFP) is essential in the work-up of suspected malignancy but will not allow the detection of CIS or GB [36].

As mentioned above, the ejaculate of men with CIS may contain tumour cells which can be detected by morphology and immunohistochemistry. The newest markers (OCT3/4, AP2-γ), if applied in a selected population, reach high specificity but need optimization with regard to sensitivity [32,37]. Automated screening tests have been developed recently [38]. However, these techniques are not incorporated (yet) in a routine clinical setting, and may be far less sensitive in the earliest stages of CIS [32]. Evidently, ejaculate can only be obtained from late puberty onwards.

Serum detection of specific microRNAs, belonging to the miR-371-3 and miR-302 clusters, might represent a promising future biomarker for invasive GCC and CIS in the general male population as well as in DSD patients. The miR371-3 and miR302 clusters are consistently and specifically overexpressed in GCC and CIS, regardless of histological subtype except teratoma, (gonadal or extragonadal) tumor site and patient age, and
have been shown to play a role in tumorigenesis [39–42]. A quality controlled test for targeted serum detection of miR371-3/367 (TSMiR) for the diagnosis and follow-up of testicular GCC has recently been proposed, yielding a sensitivity of 98% – which largely outperforms traditional tests based on the serum markers AFP and β-HCG [43]. Systematic evaluation of the value of this TSMiR test for the diagnosis of GCC and even screening for CIS (and GB) in high-risk populations, such as DSD seems now justified.

4.4. Genetic screening

As stated above, a number of GCC susceptibility genes have been identified recently. Current data indicate that carriers of a combination of multiple susceptibility alleles have the highest risk. While genetic screening in the general population may not be useful given the low incidence of GCC, the development of such a screening program in a selected population with other, independent risk factors such as DSD, might be promising [8]. However, whether genetic susceptibility adds to GCC risk in DSD patients or other risk populations remains to be established.

5. Conclusions

Evidence from epidemiological data and translational and clinical research has provided a first base for the management of retained gonads in DSD patients in recent years. However, given the practice of prophylactic gonadectomy in most cases in the past, data on GCC risk in adults are still lacking. Currently, no non-invasive imaging or biochemical screening methods exist that allow the detection of CIS, although promising tools, based on genetic risk and tumour gene expression profiles are being developed. The applicability of these tools in adolescents and adult with DSD remains to be investigated. Until that time, managing the risk of tumourigenesis focuses on the question if and when to perform a biopsy in cases with lower risk and prophyactic gonadectomy in the highest risk cases and/or in those with hormone production opposite to the sex of rearing. Patients are now fully informed and involved in this decision making process.

Disclosure of interest

The author declares that he has no conflicts of interest concerning this article.

Acknowledgement

This manuscript is the result of a close collaboration of the author with Leendert Looijenga and Katja Wolfenbuttel, Erasmus Medical Center Rotterdam, the Netherlands. The research as outlined above has been performed in Rotterdam, under the supervision of Prof L Looijenga.

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