Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

Annales d'Endocrinologie 75 (2014) 67–71

Annales d'Endocrinologie
Annals of Endocrinology

Journées Klotz 2014

Germ cell cancer risk in DSD patients

Risque de cancer des cellules germinales chez les patients présentant un DSD (désordre de la differentiation sexuelle)

Martine Cools

Department of pediatrics and genetics, Ghent university hospital, Ghent university, building 3K12D, De Pintelaan 185, 9000 Ghent, Belgium

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.

Keywords: DSD; Germ cell tumor; Risk; Gonadectomy

Résumé

Le risque de cancer des cellules germinales est élevé chez de nombreux patients présentant un désordre de la différentiation sexuelle (DSD), cependant à un degré variable. Un certain nombre de facteurs de risques ont été identifiés récemment, mais leur interaction et leur impact relatif ne sont pas complètement élucidés. Jusqu'à la mise à disposition d'outils fiables de dépistage des lésions pré-néoplasiques, la prise en charge du risque de tumeurs germinales testiculaires sera centrée sur la question de l'indication de la biopsie et/ou de la gonadectomie, l'âge auquel les réaliser et l'interprétation des résultats histologiques.

Mots clés : DSD (désordre de la differentiation sexuelle) ; Tumeur des cellules germinales ; Risque ; Gonadectomie

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

DOIs of original articles: http://dx.doi.org/10.1016/j.ando.2014.03.007,http://dx.doi.org/10.1016/j.ando.2014.04.010, http://dx.doi.org/10.1016/j.ando.2014.03.004, http://dx.doi.org/10.1016/j.ando.2014.04.006, http://dx.doi.org/10.1016/j.ando.2014.04.011, http://dx.doi.org/10.1016/j.ando.2014.03.008, http://dx.doi.org/10.1016/j.ando.2014.03.010, http://dx.doi.org/10.1016/j.ando.2014.04.002, http://dx.doi.org/10.1016/j.ando.2014.04.004, http://dx.doi.org/10.1016/j.ando.2014.03.001, http://dx.doi.org/10.1016/j.ando.2014.03.003, http://dx.doi.org/10.1016/j.ando.2014.03.009, http://dx.doi.org/10.1016/j.ando.2014.03.011, http://dx.doi.org/10.1016/j.ando.2014.04.001, http://dx.doi.org/10.1016/j.ando.2014.04.005, http://dx.doi.org/10.1016/j.ando.2014.03.002
E-mail address: martine.cools@ugent.be

http://dx.doi.org/10.1016/j.ando.2014.04.003
0003-4266/

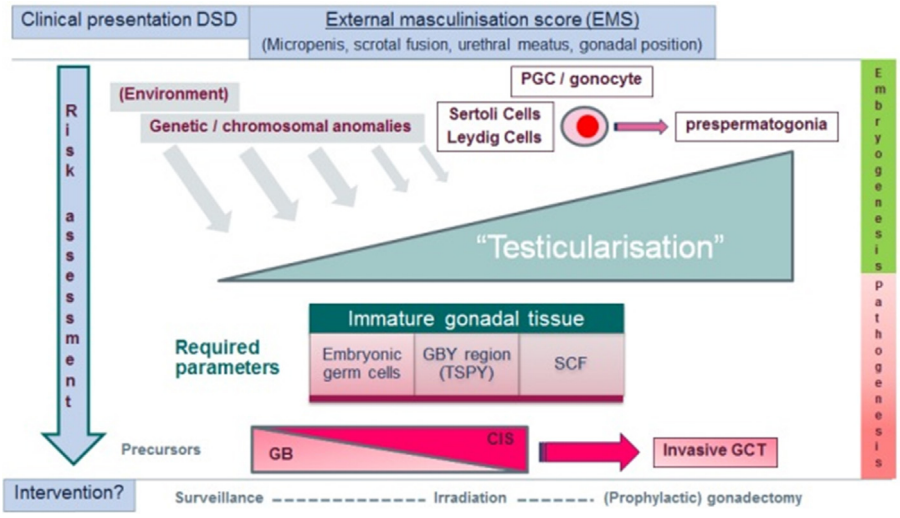

Fig. 1. Factors of malignant transformation. The risk of malignant transformation, leading to an invasive GCC is likely related to various parameters, including environment as well as genetic/chromosomal anomalies. These may interfere with the physiological maturation of primordial germ cells. Four parameters are required to allow malignant transformation. These include the presence of the *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 maturational 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 genvironmental 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 genvironmental 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