Best Practice & Research Clinical Endocrinology & Metabolism 24 (2010) 291–310

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

9

Gonadal tumours and DSD

Leendert H.J. Looijenga, PhD [a,*], Remko Hersmus, BSc, PhD student [a], Bertie H.C.G.M. de Leeuw, PhD [a], Hans Stoop, BSc, PhD student [a], Martine Cools, MD, PhD [b], J. Wolter Oosterhuis, MD, PhD [a], Stenvert L.S. Drop, MD, PhD [c], Katja P. Wolffenbuttel, MD [d]

[a] *Department of Pathology, Erasmus MC-University Medical Center Rotterdam, Josephine Nefkens Institute, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*
[b] *Department of Pediatric Endocrinology, University Hospital Ghent, Belgium*
[c] *Department of Pediatric Endocrinology, Erasmus MC-University Medical Center Rotterdam, Sophia, Rotterdam, The Netherlands*
[d] *Department of Pediatric Urology, Erasmus MC-University Medical Center Rotterdam, Sophia, Rotterdam, The Netherlands*

Keywords:
disorders of sex development (DSD)
undervirilisation
gonadal dysgenesis
germ cell tumours (GCTs)
seminoma
non-seminoma
carcinoma *in situ* (CIS)
gonadoblastoma (GB)
maturation delay
testicularisation
OCT3/4
testis-specific protein on the Y chromosome (TSPY)
stem cell factor (SCF)

Disorders of sex development (DSD), previously referred to as intersex, has been recognised as one of the main risk factors for development of type II germ cell tumours (GCTs), that is, seminomas/dysgerminomas and non-seminomas (e.g., embryonal carcinoma, yolk sac tumour, choriocarcinoma and teratoma). Within the testis, this type of cancer is the most frequent malignancy in adolescent and young adult Caucasian males. Although these males are not known to have dysgenetic gonads, the similarities in the resulting tumours suggest a common aetiological mechanism(s), –genetically, environmentally or a combination of both. Within the group of DSD patients, being in fact congenital conditions, the risk of malignant transformation of germ cells is highly heterogeneous, depending on a number of parameters, some of which have only recently been identified. Understanding of these recent insights will stimulate further research, with the final aim to develop an informative clinical decision tree for DSD patients, which includes optimal (early) diagnosis without overtreatment, such as prophylactic gonadectomy in the case of a low tumour risk.

* Corresponding author. Department of Pathology, Erasmus MC-University Medical Center Rotterdam, Josephine Nefkens Institute, Building Be, Room 430b, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. Tel.: +31 10 70 44329; Fax: +31 10 70 44365.
E-mail address: l.looijenga@erasmusmc.nl (L.H.J. Looijenga).

1521-690X/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.beem.2009.10.002

Human germ cell tumours (GCTs) comprise a heterogeneous group of neoplasms with different pathogenesis and clinical behaviour.[1] Recognition of the existence of the various subtypes is both scientifically and clinically relevant. The subtypes are characterised by a set of defined parameters, most of them related either directly or indirectly to their different origin, that is, maturation stage of the germ cell, and the associated pathobiology. This knowledge is, on the one hand, informative to investigate the pathogenesis of these types of tumours, and, on the other hand, of value to identify individuals who are at increased risk to develop such a malignancy in comparison with the general population. In fact, recent insights can be used for further development of individualised treatment protocols with the aim of optimal clinical management, both related to early diagnosis of the tumour and efficient treatment, with emphasis on prevention of both under- and overtreatment (either (prophylactic) gonadectomy, irradiation and/or chemotherapy). Proper decision making is of utmost importance because of the general young age of the patients at clinical diagnosis and the curability of the disease. This article specifically focusses on patients with disorders of sex development (DSD), of which recent observations indicate that heterogeneity exists between the various subgroups of patients regarding the risk for malignant transformation of germ cells, leading to the so-called type II GCTs. Application of the knowledge on predictive parameters will allow a better pre-selection of patients into tumour-risk groups (i.e., high, intermediate and low), and subsequent application of the most appropriate treatment modalities. It must be borne in mind that gonadectomy at an early age will preclude spontaneous puberty and fertility and necessitate lifelong hormonal supplementation. To facilitate an evidence-based decision regarding the various possible treatment approaches, understanding the biology of normal germ cells, gonadal development and the pathobiology of the type II GCTs is of great importance. Therefore, in this article, the first two sections describe many relevant aspects of normal embryonic germ cell development, both pre-gonadal and gonadal. Subsequently, the type II GCTs are introduced, including their precursor lesions, followed by a description of the parameters related to tumour risk. In this context, the most appropriate markers for (early) diagnosis are discussed. Finally, suggestions for future studies are made with the aim to further improve assessment of tumour risk in DSD with minimal burden to the patients.

Physiological pre-gonadal germ cell development

During human intra-uterine development, embryonic germ cells can be identified at weeks 5–6 gestational age, referred to as primordial germ cells (PGCs).[2] These germ cells are unique and characterised by several markers, such as alkaline phosphatase (AP), VASA, c-KIT and OCT3/4 (also known as POU5F1). PGCs are progenitors of the germ cell lineage, resulting in spermatozoa in males and oocytes in females in later life, capable of transmitting genetic information to the next generation.[3] To fulfil this special task, they have unique characteristics (recently discussed elsewhere[4] and references cited therein). PGCs begin migrating from the proximal epiblast through the hindgut and mesentery to the genital ridge (Fig. 1), for which the stem cell factor (SCF) – c-KIT pathway – is crucial.[5] PGCs express the receptor, while the SCF functions as a chemo-attractant as well as survival factor.[6–8]. Disturbances in the function of the c-KIT pathway, depending on the ligand stem SCF, results in various anomalies, including sub-infertility or infertility. Recently, Sox17 has been identified to be crucial for proper migration of PGCs as well.[9]

Physiological gonadal germ cell development

On reaching the genital ridge, PGCs are called gonocytes (Fig. 1) independent of the chromosomal constitution. Their original bi-parental pattern of genomic imprinting is completely erased. This epigenetic modification, demonstrated by the bi-allelic expression of the imprinted genes (see Ref. 10 and 11 for review), is required to allow proper development of the gender-specific germ cell lineage. The fate of the gonocytes is determined by the microenvironment, referred to as gonadal sex, (i.e., development of either testis or ovary; see Fig. 2). In this article, the term 'testicularisation' will henceforth be used for the active process of testis formation, in the broadest context. Development of gonadal sex is initiated by the chromosomal sex, that is, XY (male) versus XX (female) of the gonadal stromal compartment, which is established during fertilisation. Testis development, in fact, depends on