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Frequency of gonadal tumours in complete androgen insensitivity syndrome (CAIS): A retrospective case-series analysis

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Summary

Background
Complete androgen insensitivity syndrome (CAIS) is an X-linked recessive disorder of sex development (DSD) where affected individuals are phenotypically female, but have an XY karyotype and testes. The risk of gonadal tumour development in CAIS may increase with age; incidence rates have been reported to be 0.8–22% in patients who have retained their gonads into adulthood. Consequently, gonadectomy has been recommended either during childhood or after puberty is complete, although there is no consensus on the optimal timing for this procedure.

Objective and hypotheses
To establish the frequency of histological abnormalities in CAIS in relation to the age at gonadectomy.

Method
Data were collected from the Cambridge DSD database on patients with CAIS ($n = 225$; age range 3–88 years) who had undergone gonadectomy, and their age of gonadectomy, gonadal histology and immunohistochemistry.

Results
Evaluable data were obtained from 133 patients. Median age at gonadectomy was 14.0 years (range: 18 days–68 years). Pubertal status was: prepuberty, $n = 62$; postpuberty, $n = 68$. Thirteen cases were aged >20 years at gonadectomy. The pattern of histology is summarised in the Summary table.

Discussion
In this large case series of CAIS patients who had undergone gonadectomy, while the combined malignant and premalignant gonadal histology prevalence was 6.0%, the findings confirm the low occurrence of gonadal malignancy in CAIS, with a frequency of 1.5%. The two cases of malignancy were postpubertal. Germ cell neoplasia in situ (GCNIS) was observed in six cases, of which one occurred prepuberty and five postpuberty. The study highlighted difficulties in diagnosis of GCNIS and the need for histological analysis in expert centres.

Conclusion
The results support the current recommendation that gonads in CAIS can be retained until early adulthood. The small number of individuals with gonadectomy after age 20 years do not allow firm conclusion regarding later adulthood. Therefore, it is recommended that the option of gonadectomy be discussed in adulthood. Some form of regular surveillance of the gonads is then recommended, although none of the available options are ideal.

Summary table Abnormal histology.

Benign tumour
$n = 6$ Sertoli cell adenoma (SCA)
$n = 8$ testicular hamartoma (TH)
$n = 2$ mixed SCA + TH
Germ cell neoplasia in situ (GCNIS) (age at gonadectomy)
$n = 6$ (2 years 9 months, 16 years, 17 years,*17 years, 20 years,*53 years)
*Associated with benign changes
Malignant tumour (age at gonadectomy)
$n = 1$ malignant sex cord stromal tumour (68 years)
$n = 1$ seminoma (30 years)

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Introduction

Complete androgen insensitivity syndrome (CAIS) is an X-linked recessive disorder of sex development (DSD) caused by inactivity of the androgen receptor in response to androgens, due to a mutation of the androgen receptor (*AR*) gene [1]. Affected individuals have an XY karyotype, but an external female phenotype and labial, inguinal or intra-abdominal sited gonads, which are testes [2]. Management of CAIS includes a decision on whether and when to remove the gonads because of the risk of developing gonadal malignancy [3].

The risk of gonadal tumour development in CAIS may increase with age; incidence rates of 0.8–22% have been reported in patients who have retained their gonads into adulthood [4,5]. However, the data on adults with CAIS include historical cases where the diagnosis was uncertain. Invasive germ cell tumours of the gonad (including seminoma/non-seminomas, dysgerminoma/non-dysgerminomas) predominate, and are usually preceded by a non-invasive 'carcinoma in situ' (CIS) or intratubular germ cell neoplasia unclassified (IGCNU) phase. The term CIS and IGCNU will now be replaced by germ cell neoplasia in situ (GCNIS), as proposed by the World Health Organization Classifications of Tumours of the Male Genital Organs [6]. It has been reported that 50% of GCNIS progresses to invasive germ cell tumour within 5 years [7]. Currently, there are no clinically useful biomarkers available to guide clinicians in predicting tumour risk other than direct gonadal histology and immunohistochemistry.

Given the risk of gonadal malignancy in patients with CAIS, recent practice has advocated gonadectomy either in childhood or soon after puberty [8]. However, optimal timing for this procedure has become increasingly controversial, given the purported benefits of natural testosterone production (and its subsequent aromatisation to oestrogen) for patient well-being and quality of life [2]. As a result, many patients and families with CAIS are choosing to defer gonadectomy well into adulthood or to decline this option altogether [5].

The secular trend towards delayed or no gonadectomy has raised concerns that patients may now be at increased risk of developing gonadal malignancy. It is difficult to quantify the risk, given that the prevalence and incidence of early gonadal malignancy changes and tumour development are unclear. Consequently, a retrospective review was undertaken of the gonadal histology reports available from CAIS patients who had their gonads removed, in order to establish the frequency of histological abnormalities in relation to age and timing of gonadectomy.

Patients and methods

The resource that was used for this study was the Cambridge DSD database [9]. It contains detailed information on clinical phenotype, results of biochemical and genetic tests and descriptive reports of histological and immunohistochemical analyses of gonadectomy specimens. For the purpose of this study, the diagnosis of CAIS was based on typical clinical and biochemical features, and confirmed by analysis of the *AR* gene in the majority of cases. Full sequencing of the coding region, including intron/exon boundaries, was performed as previously described [10].

Information regarding patient age at gonadectomy, position of gonads at time of diagnosis, histology report, immunohistochemistry findings and *AR* mutation was analysed. Histological studies were performed at the local hospital and the reports obtained from the referring clinician. Standard immunohistochemistry, including placental alkaline phosphatase (PLAP), was performed in the majority of cases. For some of the cases where tissue from gonadectomy was available, the pathology was reviewed as previously described [11]. The terms 'carcinoma in situ' (CIS) and 'intratubular germ cell neoplasia unclassified' (IGCNU), used in the reports, were considered to be equivalent to the new term 'germ cell neoplasia in situ' (GCNIS) used in this analysis.

Ethics approval for the study was obtained from the local research committee, and institutional approval was obtained from the Research and Development Committee of the Cambridge University Hospitals NHS Foundation Trust.

Results

A total of 225 patients with CAIS (age range 3–88 years at the time of analysis) were identified in the database, of which 141 had undergone gonadectomy. The following were excluded: no information on gonadal histology available ($n = 6$); *AR* gene screening was not performed ($n = 1$); mutation was not identified by single-strand conformation polymorphism (SSCP) and no sequence analysis performed ($n = 1$). Six cases that were not screened for an AR mutation, but one had been identified in another affected family member, were included. A total of 133 cases were included in this study. The median age at gonadectomy was 14.0 years (range: 18 days–63 years). There were two peaks in the age of gonadectomy: during infancy to early childhood, and after puberty (Fig. 1). An equal number of patients had gonadectomy performed before and after puberty (62 and 68 patients, respectively). Timing of gonadectomy in relation to pubertal status was unknown in three cases. In cases that had gonadectomy before the age of 13 years, approximately 60% of gonads were located in the inguinal region. In contrast, in cases that had gonadectomy after age 13 years, 60% of the gonads were intra-abdominal or non-palpable (Fig. 2).

Histology in relation to age of gonadectomy is shown in Fig. 1. Abnormalities were reported in 27 cases (20.3%). In 18 cases (13.5%) the histology was considered benign. This subset comprised cases of Sertoli cell adenoma (SCA, $n = 6$), testicular hamartoma (TH, $n = 8$), mixed SCA/TH ($n = 2$) and sex cord tumour 'with annular tubules' ($n = 2$). Immunohistochemistry was negative for PLAP in four cases.

The local pathologist reported five cases of premalignant changes (GCNIS). GCNIS was identified in two additional cases on further review; from the original histology reports it was unclear if and what immunohistochemical studies had been performed in these cases (Table 1). Two cases also had concomitant benign changes (SCA + GCNIS; hamartoma + GCNIS). In Case 1, premalignancy was reported at an early age, based on areas in the gonad with increased germ cell numbers and cell atypia with some

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