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Complete Androgen Insensitivity Syndrome and Literature Review

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Abstract

Backgroung: Complete Androgen Insensitivity Syndrome (CAIS) has been reported since 1923, but in 1953 it became known as "testicular feminization". It is a rare recessive genetic disorder linked to the X chromosome that results in different mutations in the androgen receptor. The main clinical presentation in childhood is the presence of bilateral inguinal hernia in phenotypically female subjects. Incidence of androgen insensitivity syndrome in phenotypically females with inguinal hernia is estimated in 0.8% to 2.4%. This is a case report of complete androgen insensitivity syndrome and literature review of preoperative diagnostic methods.

Case Summary: We present a 3 years and 6 months old child with female phenotype, born in São Paulo, Brazil which was diagnosed intraoperatively with complete androgen insensitivity syndrome, during inguinal hernia repair and present potential diagnostic alternatives that we consider viable options in order to avoid this kind of surprise during surgery.

Conclusion: Investigation of CAIS should be standard in pre-pubertal girls with bilateral inguinal hernia, genetic techniques involving X chromatin or Y chromosome tests present the best choices.

Keywords: androgen-insensitivity syndrome, dihydrotestosterone receptor deficiency, sex differentiation disorders, hernia, child.

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Authors summary

Why was this study done?
To report a case of Complete Androgen Insensitivity Syndrome (CAIS).

What did the researchers do and find?
This is a case report and literature review of preoperative diagnostic methods.

What do these findings mean?
This is a case report and literature review of preoperative diagnostic methods.

INTRODUCTION

Repair of inguinal hernia is one of the most common operations in general surgery[1]. The main clinical presentation of complete androgen insensitivity syndrome (CAIS) in childhood is the presence of bilateral inguinal hernia. The incidence of CAIS in girls with inguinal hernia varies from 0.8% to 2.4%[2,3].

CAIS is a rare recessive X-linked genetic disease with an estimated prevalence of between 1: 20,000 and 64,000 births[4,5]. CAIS is caused by several mutations in the androgen receptor (AR) that result in a suppressed response of target cells to testosterone and *dihydrotestosterone* (DHT)[6].

Diagnosis of CAIS is usually made at puberty. The most frequent complaint is primary amenorrhea, accompanied by the absence or reduction of pubic and axillary hairiness, dyspareunia, no acne and no voice change at puberty[6]. The breasts are usually well developed and the female body contours are present due to the aromatization of peripheral testosterone to estradiol[7]. Serum testosterone levels are generally above the normal range for women, while serum estradiol levels are normal or high and serum LH and FSH levels are also high[7].

Treatment for patients with CAIS involves prophylactic gonadectomy, hormone replacement therapy, calcium and vitamin D supplementation and vaginoplasty[8].

Here we describe the case of a pre-pubescent patient with a female phenotype who was diagnosed with CAIS after the unexpected identification of testicles in the hernia sac during bilateral inguinal hernia repair surgery and present a literature review of potential diagnostic alternatives in order to avoid this.

CASE REPORT

The patient 3 years and 6 months old with female phenotype, born in São Paulo, Brazil, attended a specialty clinic due to bilateral inguinal hernia and umbilical hernia. Elective surgery for bilateral inguinal and umbilical hernia repair was performed. During inguinal hernia repair, unexpected content in bilateral hernia sac was identified. The sac was opened surgically and the bilateral presence of testicles was confirmed. On the left side, the testicle size, shape and consistency were normal (Figure 1A). On the right side, the shape and size were smaller and more rigid compared to the contralateral side (Figure 1B). The left gonad was positioned in the left inguinal canal, since the diagnosis of CAIS was made intraoperatively and the family had not previously consented to a surgical sterilization. We opted to perform a right orchidectomy and the material was sent for anatomopathology (AP) analysis. No fallopian tubes or ovaries were present. The AP test confirmed the presence of a pre-pubertal testicle without histological alterations in the epididymis (Figures 1 C and D). No morphological signs of malignancy were present. A later karyotype examination confirmed a 46 XY genotype.

The patient later underwent further surgery at another health service, where both vaginal length measurement and left gonadectomy were performed. The material was also sent for AP. The vaginal length was 5 cm and the AP confirmed the presence of a pre-pubescent testicle showing stromal and capsular fibrosis, immature epididymis and vas deferens without histological abnormalities.

Figure1: A: Left testicle (arrow) B: Right testicle (arrow) C: Right testicle microscopy in low magnification; D: Right testicle microscopy in high magnification.

DISCUSSION

Complete androgen insensitivity syndrome (CAIS) is one of the most common causes of sex development disorders, it's presented in a patient with a complete external female phenotype, despite a 46, XY karyotype and unrestricted testicular development. The underlying condition is a peripheral resistance towards all androgenic steroids due to a mutation of the androgen receptor gene (AR), mapping in region q11-12 on the X chromosome, with 8 exons and encoding a protein of 919 amino acids, detected in more than 95% of women with CAIS[9-11].

The AR is an intracellular transcription factor belonging to the nuclear receptor superfamily, it's necessary to regulate the transcription of target genes in order to initiate a series of molecular events required for male sex differentiation[11]. It's consist of three major functional domains, an N-terminal transactivational domain, involved in the transcriptional activation of target genes; an DNA-binding domain; and the C-terminal ligand binding domain, which is involved in dimerization and transcriptional activation[12].

Patient characteristic features include, normal breast development, an absence of or sparse pubic and axillary hair, normal external genital appearance, but the vagina length is shorter than average with a blind end, and also, there is not a uterus, fallopian tubes or ovaries. Gonads, in the form of testicles, are usually located in the path of testicular descent and could be localized intra-abdominally, in the internal inguinal ring, or in the large labia. Androgens such as testosterone are normally produced by these gonads. In addition, preserved estrogen and aromatase activity are responsible for breast development in these patients[4-6,9,13].

CAIS is diagnosed in approximately 0.8% to 2.4% of cases of bilateral inguinal hernia in phenotypically female individuals[2,3]. In light of this association, a study in Ireland and the United Kingdom was conducted in 1999, with the participation of 110 pediatric surgeons, who were asked whether they excluded CAIS in cases of inguinal hernia in girls. Forty one percent of doctors did not exclude CAIS because they believed that the incidence was very low; the other 59% excluded CAIS during surgery by examining the ovary or fallopian tube[14]. Thus, the second most common way to diagnose CAIS is through hernia repair surgery, since the most prevalent diagnosis is made at puberty based on primary amenorrhea[4,6,7]. A similar situation occurs in Brazil, where most surgeons do not screen for CAIS because of its low incidence. For this reason, the diagnosis can occur unexpectedly during the course of bilateral inguinal hernia repair, as reported here.

Viner *et al.*[15] studied patients with CAIS and found that about 80% had inguinal hernia, with 31% unilateral and 59% bilateral. Testicles were palpable in about 80% of cases. Thus, the presence of bilateral inguinal hernia in girls should raise suspicion about the child's genotype. It has been suggested that screening methods such as ultrasound[1], measurement of vaginal length[3] and investigation on X chromatin[2], Y chromosome[16] or karyotype[15] should be used to rule out CAIS all pre-pubescent girls with bilateral inguinal hernia.

Rahman *et al.*[16] recently reported a method of diagnosis that is considered fast, inexpensive, easy to perform and of wide acceptance. It was conducted through an oral mucosa smear, which was well tolerated by children and acceptable to parents and involved the novel technique of extraction of Y chromosome–specific DNA. The results of this examination took on average 4.9 days to completed, as compared with a minimum of 10 days for a standard karyotype. As a disadvantage, in this study only 25 samples were suitable for DNA extraction in a total of 29 samples. A prospective study by German *et al.*[2] also used oral mucosa smear to investigate the presence of X chromatin, which was found in 32 of 35 patients. In 32 patients, X chromatin was present in 15 – 55% of the cells, however, it was done in a small number of patients.

Sarpel *et al.*[3] studied and identified patterns of vaginal length in girls with bilateral inguinal hernia. The advantage of this method is to create an inexpensive and easy to perform screening tool to aid the early recognition of the disease. In addition, it can assist surgeons during intraoperative diagnosis in cases where the fallopian tube and ovaries are difficult to examine. As a disadvantage, this screening method had high rates of false positive and false negative; therefore, a multicenter randomized study is necessary in order to evaluate the statistical value of this measure.

Surgeons can repair inguinal hernias without identifying the underlying pathology; therefore, we are confident of the benefits of pre-operative diagnosis on CAIS[1]. Performance of a pre-surgical ultrasound can assist in the early identification of the presence of gonads and more precisely dictate the surgical plan[1]. The presence of an inguinal hernia during childhood should not be taken as an indication for early gonadectomy. After hernia repair, the gonad must be fixed in the internal inguinal ring or repositioned into the abdomen[9]. Furthermore, this approach also provides more time for patients and families to accept and understand the disease and its repercussions. It helps during important decisions regarding the treatment and the better moment to performing orchidectomy, as gonadal malignancy in patients with CAIS increases with age, ranging from 3% in the age of 20 years to 30% in the age of 50 years old[4]. Still, the global variation of gonadal malignancy in patients with CAIS is approximately 50% [5].

If gonadectomy is considered, it's the responsibility of the surgeons to assess the individual balance of risks and benefits and to inform that to the patient[9]. Orchidectomy performed before puberty decreases the chance of malignancy[5], but the use of hormone replacement therapy is required to achieve induction of puberty and maintenance of sexual function, psychosocial well-being, and bone health[9]. The postponement of eventual gonadectomy into adult age, allow not only spontaneous puberty occurs, but permits informed and authoritative decision-making by the patient , also if orchidectomy is performed after puberty, proper bone density is preserved, secondary sexual characteristics develop due to the aromatization of testosterone to estradiol; therefore hormone replacement therapy is not required[5,9]. However, the difficulty of following this approach in a country with a failing health system, increases greatly the likelihood of occurring a malignant change in the testicles.

FINAL CONSIDERATIONS

We believe that investigation of CAIS should be standard in pre-pubertal girls with bilateral inguinal hernia, and that this diagnosis can be carried out through any one of many available methodologies. In our view, genetic techniques involving X chromatin or Y chromosome tests present the greatest promise as they are minimally invasive, well tolerated by patients and their families, are easy to perform and have low costs compared to other methods. The adoption of these approaches would provide a more precise surgical indication for cases of inguinal hernia and avoid surprises during surgery, providing more time for patients and their families to understand this disorder and its repercussions.

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The authors have disclosed that they have no relationship with, or financial interest in, any commercial companies pertaining to this article.

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Resumo

Introdução: A síndrome da insensibilidade androgênica completa (SIAC) é relatada desde 1923, mas foi em 1953 que ficou conhecida como “feminilização testicular”. É uma doença genética recessiva rara, ligada ao cromossomo X, causando diversas mutações no receptor de androgênio. A principal apresentação clínica na infância é a presença de hérnia inguinal bilateral em indivíduos fenotipicamente femininos com uma incidência estimada de 0,8% a 2,4%. Apresentamos um caso de insensibilidade androgênica completa, com revisão de literatura dos métodos diagnósticos pré operatórios.

Relato do Caso: Apresentamos uma criança de 3 anos e 6 meses de idade com fenótipo feminino, nascida em São Paulo, Brasil diagnosticada com síndrome da insensibilidade androgênica completa, durante a cirurgia de herniorrafia inguinal bilateral e apresentamos potenciais alternativas diagnósticas a fim de evitar esse tipo de surpresa durante a cirurgia.

Conclusão: Em meninas pré-puberes, portadoras de hérnia inguinal bilateral, a pesquisa de SIAC se faz necessária, técnicas genéticas que utilizam a pesquisa da cromatina X ou do cromossomo Y seriam as melhores escolhas.

Palavras-chave: síndrome de resistência a andrógenos, receptores androgênicos, transtornos do desenvolvimento sexual, Hérnia, criança.