Complete androgen insensitivity syndrome caused by a novel mutation in the androgen receptor: A case report

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Introduction. Androgen receptor (AR) genes play an important role in human gonadal development. Complete androgen insensitivity syndrome (CAIS) is a disorder of sexual development caused by AR gene mutations. Children with CAIS have female external genitalia but a chromosomal karyotype of 46, XY and internal testes. Most children with CAIS are raised as females, and the current treatment is gonadectomy after puberty to ensure normal growth and development. Here, we identified a novel nonsense variant of the AR gene. The child's parents strongly requested immediate gonadectomy for the child due to psychological and oncological risks.

CASE SUMMARY

A female child, aged 1 year and 9 months, presented to the hospital with complaints of swelling in the groin on both sides for the last 9 months. Laparoscopic inguinal hernia repair was performed, and bilateral gonads with a testicular appearance and tubal umbrella structures were found without apparent uterine structures. Gonadal biopsy pathology indicated primitive testicular tissue, and the karyotype was 46, XY. Ultrasound showed testicular-like echoes near the internal inguinal ring on both sides but no detectable uterine or

ovarian echoes. Gene sequencing revealed a c.2421C>A (p.Cys807Ter, 114) mutation in the AR gene, leading to a diagnosis of CAIS. Given parental concerns regarding psychological and oncological risks, bilateral gonadectomy was performed during the inguinal hernia repair operation.

Conclusion. The discovery of this novel mutation enriches the spectrum of AR gene variants. When a female infant presents to the hospital with an inguinal hernia, clinicians should consider the possibility of CAIS. The guidelines on the timing of gonadectomy should be followed, but the psychological well-being of the child and the parents is a greater concern, and the final decision should be made in a holistic manner.

Keywords. Complete androgen insensitivity syndrome; 46 XY disorders of sex development; Androgen receptor gene; Inguinal hernia; Gonadectomy;

Core Tip: This study identified a novel mutation in the AR gene: c.2421C>A (p.Cys807Ter, 114). The discovery of this novel mutation enriches the spectrum of AR gene variants. When a female infant presents to the hospital with an inguinal hernia, clinicians should consider the possibility of CAIS. The guidelines on the timing of gonadectomy should be followed, but the psychological well-being of the child and the parents is a greater concern, and the final decision should be made in a holistic manner.

INTRODUCTION

Androgen insensitivity syndrome (AIS), first described and proposed by Morris in 1953[1], is a disorder of sexual development (DSD) and is characterized by varying degrees of androgen resistance. It is one of the most common causes of 46,XY DSD[2], with a prevalence of 1:20,000–1:100,000.[3] Depending on the degree of androgen insensitivity, there are three clinical phenotypes: complete androgen insensitivity

syndrome (CAIS), which presents with typical female external genitalia but testicular gonads; partial androgen insensitivity syndrome (PAIS), characterized by varying degrees of hypoandrogenization of the external genitalia due to partial androgen response; and mild androgen insensitivity syndrome (MAIS), which presents with typical male external genitalia but with pubertal gynecomastia and infertility in adulthood.[4] CAIS is most common and is caused by mutations in the androgen receptor (AR) gene, 70% of which are maternal mutations and 30% of which are novel mutations.[5] The clinical manifestations are the 46,XY karyotype and female external genitalia, and patients often present with infantile inguinal masses and primary amenorrhea during puberty. Most children with CAIS are raised as females, and clinical management centers on the timing of gonadectomy. Clinical guidelines recommend delaying gonadectomy until after puberty. However, inconsistency between the genetics of the individual and the gender norms of society often causes psychological disorders in children and their parents. Therefore, many parents prefer to have their children's gonads removed during infancy and childhood without their children's knowledge to alleviate the psychological burden on both the children and their parents.[6] In the present study, we report a case of CAIS caused by a novel mutation of the AR gene, analyze the clinical features of the patient and characteristics of the genetic variant, and summarize the issues related to the timing of gonadectomy, to further improve the understanding of this disease.

CASE PRESENTATION

Chief complaints

The patient was admitted to the hospital with complaints of swelling in the groin on both sides for the past 9 months.

History of present illness

The female patient was aged 1 year and 9 months, and her main symptom was swelling in the groin on both sides.

History of past illness

The patient presented to the hospital 9 months ago with complaints of swelling in the groin on both sides. Ultrasound scan revealed "bilateral inguinal hernias". Laparoscopic inguinal hernia repair was performed, and the internal inguinal ring on either side was found to be unenclosed. The bilateral gonads were located at the level of the internal inguinal ring, and the gonads were porcelain-white in color, resembling testicles (Figure 1), with tubal umbrella structures; moreover, no uterine structures were detected on examination, was an indicator of a DSD. Bilateral gonad tissue biopsy was performed, and postoperative pathology revealed that the gonads were primitive testicular tissue, with visible seminiferous tubules and thickened fibrous peritoneum (Figure 2).

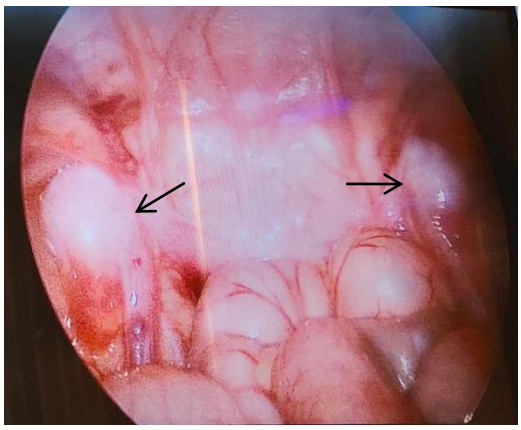

Figure 1 Bilateral cryptorchidism images under laparoscopy (indicated by ↑)

Note: During surgery, the female child was found to have "bilateral gonads" resembling testicles.

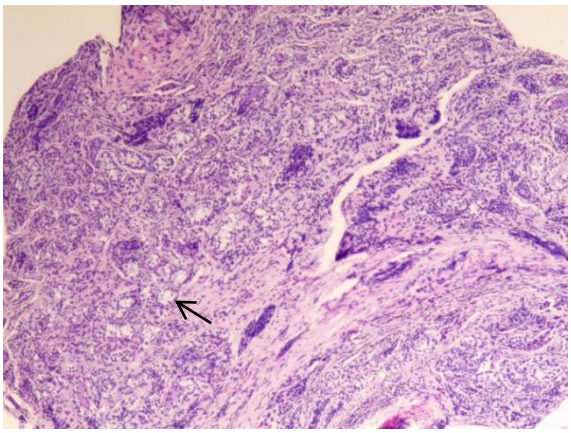

Figure 2 Pathology of gonadal tissue of the patient by hematoxylin-eosin staining (40×)

Note: visible seminiferous tubule (indicated by ↑) indicates that the gonad is primitive testicular tissue

Personal and family history

The parents of the patient were nonconsanguineous, and both parents and the patient's 7-year-old sister had a normal phenotype. The maternal aunt of the patient presented to the hospital at the age of 1 for inguinal hernia, with a chromosome karyotype of 46,XY, and was subsequently diagnosed with DSD. Bilateral inguinal hernia repair surgery was performed simultaneously with bilateral gonadectomy. No estrogen replacement therapy was given during puberty. The aunt of the patient is now 27 years old, 170 cm in height, with a female appearance, and B3 stage bilateral breast development. She had no pubic hair or armpit hair and no menstrual flow.

Physical examination

The patient's height was 88 cm and weight was 11 kg. Her vulva was normal, and the urethra and vagina had a separate opening. Significant tumors could be palpated in the bilateral inguinal area; these tumors were approximately 3 cm * 2 cm * 2 cm in size, had a tough texture, were not tender, and could be retracted by compression. The transillumination test was negative.

Laboratory examinations

The chromosome karyotype was 46, XY. The hormone levels were as follows: luteinizing hormone 3.82 mIU/mL, follicle-stimulating hormone 4.83 mIU/mL, estradiol <18.35 pmol/L, progesterone 0.769 ng/mL, testosterone 2.28 nmol/L, prolactin 319 μIU/mL, adrenocorticotropic hormone 20.20 pg/mL, cortisol (8:00) 12.2 μg/dL, (16:00) 4.09 μg/dL, (24:00) 1.27 μg/dL, anti-Müllerian hormone 71 ng/mL, 17 α hydroxyprogesterone 1.40 ng/mL, estrone 1.75 nmol/L, dehydroepiandrosterone sulfate 25.21 μg/dL.

Imaging examinations

In the ultrasound scan of the bilateral inguinal region, there was no echogenic area in the bilateral inguinal region, and testicular-like echoes appeared near the internal inguinal ring on either side. In the gynecological ultrasound scan, uterine and ovarian echoes were not detected around the bladder, and the vagina was approximately 4.1 cm in length.

Gene detection

After informed consent was obtained from the parents of the patient, 2 mL peripheral venous blood samples were collected from the patient and the parents, anticoagulated with EDTA, preserved at 4 °C, and sent to the Beijing ZhiYin DongFang Translational Medicine Research Center for whole-exome sequencing. Sanger sequencing was used to validate the mutation loci of the patient and the parents. Sequencing revealed a nonsense variant, c.2421C>A (p.Cys807Ter, 114), in exon 6 of the AR gene of the patient that was inherited from the mother (Figure 3). The mutation of base C to A at position 2421 in the coding region results in a change of the cysteine at position 807 to a termination codon and a truncation of the AR protein by 114 amino acids.

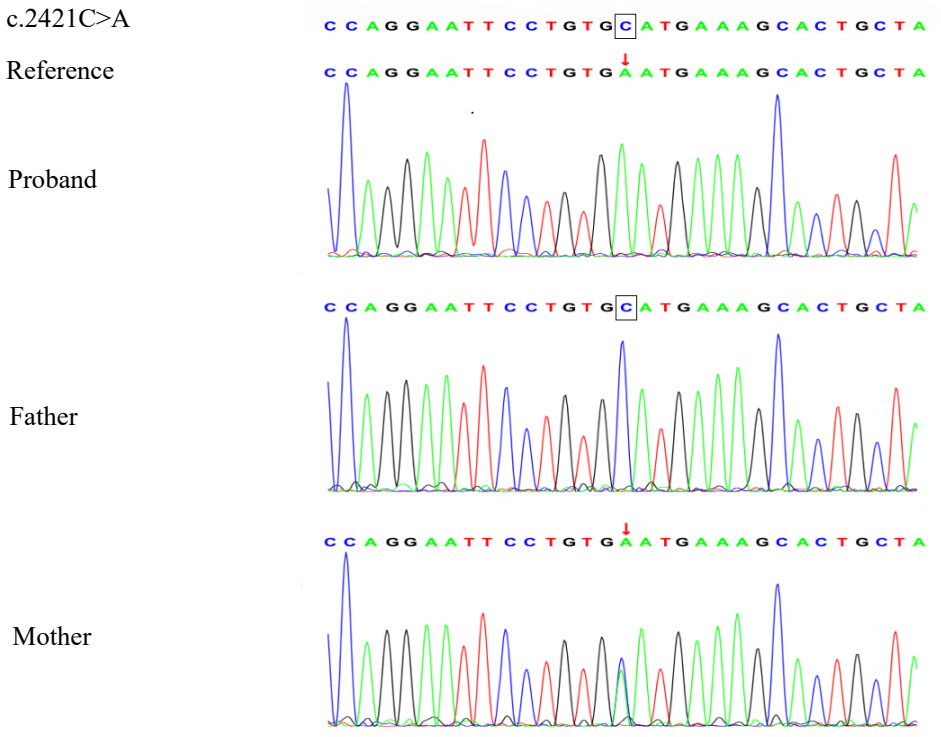

Figure 3 AR gene sequencing map of the patient and her parents

Note: Boxes indicate normal loci, while arrows indicate mutant loci.

The c.2421C>A variant has not been reported previously. The allele frequency of this variant was not recorded in the dbSNP, 1000 Genomes or gnomAD databases. The variant is predicted to be deleterious by protein function prediction software. The pathogenicity of the genetic variant was assessed according to the standards and guidelines for the classification of genetic variations established by the American College of Medical Genetics and Genomics (ACMG).[7] The variant was determined to be a pathogenic variant (PVS1+PM1+PM2), with specific evidence as follows: strong pathogenic evidence (PVS1), the LOF variant results in a probable loss of gene function; moderate pathogenic evidence (PM1), the variant is located in the hotspot

region of pathogenicity; and supportive pathogenic evidence (PM2), the minor allele frequency is less than 0.0005, indicating a low-frequency variant.

FINAL DIAGNOSIS

The final diagnosis of the patient was CAIS.

TREATMENT

The patient was subsequently admitted for laparoscopic inguinal hernia repair and bilateral gonadectomy. The intraoperative specimen showed that the right testis was approximately 1.5 cm*1.2 cm*0.8 cm and that the left testis was approximately 1.0 cm*0.8 cm*0.6 cm. The color was normal. Both testes were joined with some spermatic vessels and vas deferens. Postoperative pathology results indicated that the gonads were testicular tissue.

OUTCOME AND FOLLOW-UP

The patient recovered well after surgery. We intend to follow up with the patient for a long period of time and closely monitor her growth and development.

DISCUSSION

In this study, the nonsense variant c.2421C>A (p.Cys807Ter, 114) in the LBD of the AR gene was found to be causative of the CAIS phenotype in the patient. The AR gene is located on chromosome Xq11-12 and consists of eight exons, encoding a protein of 920 amino acids. It is highly expressed in the prostate, testes, mammary glands, and skin.[8] Currently, more than 1000 different mutations in the AR gene have been described in patients with AIS[9], the most common of which are missense

mutations, followed by shifted code mutations due to insertions and deletions.[4, 10] The AR gene consists of four major functional domains: the N-terminal transcription domain (NTD) encoded by exon 1, the DNA binding domain (DBD) encoded by exons 2 and 3, the ligand binding domain (LBD) encoded by exons 4-8, and the hinge region connecting the LBD and DBD.[11] More than 50% of AR gene mutations occur in the LBD region[10], which is critical for androgen binding. ARs are typically located in the cytoplasm and form multimeric complexes with heat shock proteins. Once the AR binds to its ligand, it translocates to the nucleus and homodimerizes, inducing transcription of androgen-responsive genes through binding to androgen-responsive elements.[12, 13] Mutations in the LBD region interfere with ligand binding and disrupt dimer formation[4, 12], which impairs AR protein function more severely, resulting in more pronounced androgen resistance and a more feminized phenotype.[14] Therefore, these mutations are more likely to lead to CAIS. In the pediatric case in our study, an unreported nonsense mutation, c.2421C>A (p.Cys807Ter, 114), in exon 6 of the LBD region of the AR gene caused a premature termination codon, resulting in the synthesis of a truncated protein that has only partial function. This further leads to a significant reduction in the ability of androgens to bind to the AR protein, ultimately resulting in CAIS. The discovery of this mutation enriches the AR gene mutation spectrum.

Infants with CAIS tend to present with inguinal masses. Bilateral inguinal hernias have been reported in 80-90% of infants with CAIS.[15] Androgens play a key role in the descent of the testes, which generally descend into the scrotum before birth, and the peritoneum of the processus vaginalis is closed to prevent the occurrence of inguinal hernia.[16] For pediatric patients with CAIS, due to androgen insensitivity, the testes do not complete their descent and are usually located in the abdomen (35.7%),

inguinal canal (48.2%), and labia majora (16.1%), presenting as inguinal hernias or labial swelling.[16, 17] The incidence of inguinal hernia in children has been reported to be approximately 1% to 4%, with a male to female ratio of 10:1.[17] The incidence of CAIS in female infants with inguinal hernias ranges from 0.8% to 2.4%.[18] Therefore, female infants presenting with unilateral or bilateral inguinal hernias should be alerted to the possibility of this condition. In this case, the patient and her maternal aunt both presented with inguinal hernias at the age of 1 year, and the presence of testes was not noted on ultrasound; the testes were found only during laparoscopic inguinal hernia repair. This case suggests that when a female infant presents to the hospital with an inguinal hernia, clinicians should consider the possibility of CAIS and look for testes on examination by color Doppler ultrasound.

Most children with CAIS are raised as females, and the timing of gonadectomy remains a hot topic of discussion. Physiologically, clinical guidelines recommend delaying gonadectomy until after puberty to ensure normal breast development and a normal growth spurt during puberty and to avoid the need for hormone replacement therapy to induce puberty. However, the psychological aspect should not be neglected when determining the timing of surgery. Inconsistency between the genetics of the individual and the gender norms of a society often causes anxiety in parents and psychological disorders in the children themselves, affecting their subsequent development.[4] This concern has led to a change in clinical practice. When children with CAIS present with an inguinal hernia in infancy, parents have the option of requesting early gonadectomy at the same time as inguinal hernia repair, followed by induction of puberty.[19] Removal of the gonads without the child's knowledge can prevent further psychosocial problems and improve their well-being in adulthood.[6] The risk of gonadal tumors should also be considered as a factor in the timing of

surgery. The risk of gonadal development of malignant tumors in children with CAIS is very low, especially before puberty, at approximately 0.8%-2%[20], but it has still been reported. Handa et al. reported a case of a 17-month-old girl with CAIS presenting with a metastatic yolk sac tumor of the abdominal testis.[21] In this case, the parents were severely anxious and had a strong preference for immediate bilateral gonadectomy, requesting it based on its success in the child's maternal aunt and tumor risk considerations; however, the clinical guidelines suggest that the optimal time for gonadectomy is 16-18 years of age, so there was an obvious conflict between the preference and the guideline. After being fully informed of the long-term risks of gonadectomy and repeated communication, the parents still insisted on gonadectomy, so bilateral gonadectomy were performed at the time of inguinal hernia repair on the second admission. In summary, the guidelines on the timing of gonadectomy should be followed, but the psychological well-being of the child and the parents is a greater concern.

CAIS is an X-linked recessive genetic disease, and thus, there is often a maternal family history of the disease. In this case, the maternal aunt of the patient had a similar medical history, and she is now growing and developing well. The child's parents believed that the child's future growth and development will be similar to that of her maternal aunt. However, studies have shown that there is not a strong correlation between the genotype and phenotype of AIS[4], and the clinical manifestations may differ even in family members with the same mutation. Liu et al. reported a family in which both the proband and her brother carried the c.2290T>C (p.Tyr764His) mutation in the AR gene, but each of them presented with CAIS and PAIS phenotypes, respectively.[22] This difference may have been related to the extent of secondary 5-α reductase deficiency. Jukier et al. reported that mutations in the AR

gene cause secondary 5-α reductase deficiency, which modulates the expression of primary androgen receptor defects, and that the greater the extent of 5-α reductase deficiency is, the greater the degree of androgen resistance.[23] Therefore, in this case, the future growth and development of the child may not necessarily be similar to that of her aunt, and we still need to follow up with her for a long time.

CONCLUSION

The discovery of this novel mutation enriches the spectrum of AR gene variants. When a female infant presents to the hospital with an inguinal hernia, clinicians should consider the possibility of CAIS, look for testes on examination by color Doppler ultrasound, and perform chromosome karyotype analysis and genetic testing, if necessary, to confirm the diagnosis. The guidelines on the timing of gonadectomy should be followed, but the psychological well-being of the child and the parents is a greater concern, and the final decision should be made in a holistic manner.

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AUTHOR CONTRIBUTIONS

Ji KJ, Zhang GX and Chen BF contributed to manuscript writing and editing, and data collection; Zhu T, Zhao RH, Wang ZW and Wang NN contributed to data analysis; all authors have read and approved the final manuscript.

Study participant and her legal guardian had provided informed written consent prior.

The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016)

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