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Complete Androgen Insensitivity Syndrome in a Chinese Neonate

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Abstract Complete androgen insensitivity syndrome (CAIS) is a rare X-linked disorder with a female external phenotype.[1] We report on a Chinese baby with CAIS who presented with bilateral inguinal hernias. The baby has a normal female phenotype at birth. On further evaluation, the karyotype was found to be 46, XY. Endocrine findings were compatible with androgen insensitivity syndrome. Bilateral herniotomy was performed. We would review the literature, offer an overview of the disease, and discuss the outcome with emphasis on the treatment modalities.

Key words Complete androgen insensitivity; Male pseudohermaphrodites

Introduction

In 1953, an American gynaecologist JM Morris firstly described a series of individuals with androgen insensitivity syndrome (AIS).[2] He reported that these individuals had normal female external genitalia, normal female breast development, absent or scant axillary and pubic hair, absent internal genital organs and undescended testes. AIS is the most common condition that results in male under-masculinisation.[3] It is caused by mutations in the androgen receptor (AR) gene and encompasses a wide spectrum of male pseudohermaphroditisms.[2] In complete androgen insensitivity syndrome (CAIS), the function of the AR is completely defective; while in partial androgen insensitivity syndrome (PAIS), the AR defects are incomplete.[2] The clinical manifestations range from complete external feminisation as in CAIS to a partial phenotype as in PAIS. The diagnosis of CAIS is established with a combination of clinical features, endocrine findings, and biochemical investigations which, to the best of our knowledge, has not been reported on the literature.[4] Herein we report a case of CAIS in a Chinese neonate in the local region.

Case Report

The patient was a Chinese baby born at full term by spontaneous vaginal delivery weighing 2.67 Kg. The antenatal and postnatal course was uneventful. She was the first child born to the parents. There was no consanguinity nor any significant family history, in particular there was no abnormal puberty nor infertility on the maternal side.

Physical examination during the neonatal period revealed a normal female external genitalia. She did well until day 3 of life, when her parents noted a swelling over the groin. Physical examination revealed bilateral inguinal hernias. Hormonal blood results were luteinising hormone (LH) 9.8 U/l (normal range, <1.9 U/l), follicular stimulating hormone (FSH) 3.2 U/l (normal range, <3.0 U/l), and testosterone 14.8 nmol/l (normal range, <7 nmol/l). Ultrasonography showed the presence of an infantile vagina with uterus, a structure suspected to be an ovary over the left side and the absence of fallopian tubes. The diagnosis of CAIS was suspected. Blood for karyotype was taken. While awaiting for the karyotype results, the hernia on the left side was complicated by strangulation. Emergency herniotomy was carried out. Gonads were present inside

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the hernia sacs. After recovery from the operation, laparoscopic examination was performed and showed no Müllerian structures such as uterus, fallopian tubes and there is a blind-ended vagina without cervix. The right gonad was at the level of the deep ring and the left gonad was inside the inguinal canal. Bilateral orchidectomy was then performed. Histopathological examination demonstrated normal testicular tissues on both sides. Gonadal karyotype revealed 46, XY which was the same as the blood karyotype. The diagnosis of CAIS was made. The condition was explained to the parents and the child was raised as a girl. She has been well and she would require long term follow up for both medical, psychological and sexual issues.

Discussion

Androgens are essential for male sex differentiation and the development of a normal male phenotype during embryogenesis and maintenance of the male state in the postnatal period. In the embryo, the differentiation of Wolffian duct structures and the virilisation of the external genitalia depend on the actions of testosterone and 5 alpha-dihydrotestosterone. Defective ARs are the most common aetiology that leads to a reduced or absent response to androgens[2] and the lack of development of the internal or external male genitalia.[5] The resulting phenotype is that of a female infant with a blind-ended vagina and absent uterus.[5] The AR is a member of the nuclear receptor family and the AR gene is located on the X chromosome at Xq11-12. There is a transcription factor involving high affinity androgen binding and mediates various molecular events, leading to the specific gene activation required for the development and maintenance of the male sex. Androgen binding defects cannot be demonstrated in all cases of CAIS.[3]

The estimated incidence of AIS is between 1:20,000-64,000 male births.[3] Searching through the literature, there has been no report of such in the Chinese children. The affected individuals are at risk for medical, psychosocial and sexual problems, early diagnosis and appropriate treatment are of paramount importance for the children and their families. The diagnosis of CAIS is established in individuals with a 46, XY karyotype who have normal female external genitalia, presence of normal testes, markedly decreased or absent postpubertal axillary and pubic hair growth, spontaneous feminisation at puberty without menses, no virilisation despite high levels of testosterone, and identification of an AR gene mutation.[4] High levels of testosterone is not universal, some cases can be normal.[6] Once CAIS is suspected, it is imperative that blood is urgently taken for karyotyping, as prompt recognition and treatment of CAIS is important in reducing the long term morbidity in this condition. In our case, if the result of the karyotype had been available earlier, our patient could have undergone one operation instead of two. In the local setting, the turn around time of karyotype is at least one to two weeks.[7] AIS is typically caused by mutations in the AR gene.[8] Because of the lack of definitive diagnostic criteria,[9] the identification of an AR gene mutation serves as a reliable handle for the diagnosis of AIS. This holds true for PAIS as other 46, XY intersex syndromes can mimic PAIS closely.[4] However, in the local setting, the molecular genetic testing of the AR gene is not routinely available. Over 300 mutations have now been described as causing various forms of androgen resistance.[3] These mutations range from a single point mutation to an entire gene deletion, which affects the functional integrity of the AR to a variable degree and results in a wide phenotypic spectrum of the AIS. There is no consistent relationship between the clinical phenotypes and the molecular defects in the AR gene.[3] Therefore the diagnosis of CAIS in our case was made on clinical findings of a normal female external genitalia, 46, XY karyotype and high testosterone and LH levels.[10]

Clinically, the CAIS is characterised by a 46, XY karyotype, normal or high serum androgen levels, normal female phenotype with breast development, complete absence of axillary and pubic hair, no uterus, undescended testes and no Müllerian duct-derived structures. Presentation in adolescence is characterised by failure of pubic and axillary hair growth and primary amenorrhoea (Table 1).[5] The affected individuals of PAIS have different degrees of virilisation, and therefore various ambiguities of the genitalia are noted.[5] They can present with minor degrees of virilisation, such as clitoromegaly or posterior labial fusion. In more severe cases, their phenotypes are mainly male but with severe defects such as perineal hypospadias.[2] They often require multiple reconstructive surgery.[3]

In our case, the initial ultrasonography showed the presence of uterus and on subsequent laparoscopy, the uterus was absent; this demonstrated the fact that ultrasonography is not a reliable tool to detect uterus in an infant.

Differential diagnosis of CAIS includes 17 beta-hydroxysteroid dehydrogenase deficiency, Leydig cell

Table 1 Clinical features of complete androgen insensitivity

Karyotype	46, XY
Inheritance	X-linked recessive; mutations in AR gene
Genitalia	Female with blind vaginal pouch
Wolffian duct derivatives	Usually absent; less commonly, rudimentary or hypoplastic
Müllerian duct derivatives	Absent or vestigial
Gonads	Testes
Habitus	Scant or absent pubic and axillary hair; breast development and female habitus at puberty; primary amenorrhoea
Hormone and metabolic profile	Increased plasma LH and testosterone concentration; increased oestradiol (for men); FSH levels often normal or slightly increased. Resistance to androgenic and metabolic effects of testosterone
Androgen receptor studies	Genetic heterogeneity; mutations can lead to low or undetectable amount of normal receptor (receptor-negative), unstable receptor (thermolabile, partial receptor deficiency), or the receptor-positive form

hypoplasia and complete XY gonadal dysgenesis. Seventeen beta-hydroxysteroid dehydrogenase deficiency can mimic CAIS clinically and be misdiagnosed as AIS. Biochemically there is a markedly elevated androstenedione at baseline or after human chorionic gonadotrophin (hCG) stimulation, with low testosterone levels. Leydig cell hypoplasia can be distinguished by their inadequate testosterone production and a feedback stimulation of LH. Complete XY gonadal dysgenesis can present in a similar way except that there is retention of Müllerian structures.[5]

To facilitate the management of this rare and complex condition, a multidisciplinary team is needed to deal with the medical, surgical and psychosocial issues.[11] While waiting for results, the team should already start explaining the procedures to the parents. As soon as the diagnosis is confirmed, the team should talk about the nature of the condition, gender assignment, medical issues and genetic counselling. CAIS individuals will be raised as a female. Therefore gender assignment is not usually an issue; whereas in the PAIS, the decisions are more complex. Classically, the gender assignment of individuals with PAIS is based on the degree of virilisation of the external genitalia at birth.[1] For the group of children with intersex, due to the inadequate information of the medical, surgical and psychosexual outcome in affected adults, controversies still exist regarding the optimal treatment, such as the gender assignment, timing and types of corrective surgery.[4] This is particularly true for those who presented with ambiguous genitalia.

The management of CAIS should include the following key elements. Gender assignment is of paramount importance and should be resolved as early as feasible. The surgical management of children with CAIS remains controversial.[11] There are at least two schools of thoughts recommending different timings for gonadectomy:the former is early gonadectomy and the latter is gonadectomy in late puberty . It has been argued that in these individuals, there is an increased incidence of gonadal malignancies, namely the germ cell tumours. Another argument for early gonadectomy is that both the physician and the parents think the child will suffer less if the surgery is done earlier.[3] Furthermore, it is possible that bone mineralisation and body development in puberty may be benefited by the gradual and early emergence of endogenous sex steroids.[11] However, there is a lack of evidence to recommend it on that ground alone.[3] Despite the difference in opinion regarding the timing for gonadectomy, oestrogen treatment is required after gonadectomy.[5] In our patient, gonadectomy was performed in the neonatal period as she presented early with hernias. Late gonadectomy during puberty, after full discussion and informed consent, allows the spontaneous development of puberty in the individual, hence enhancing the self esteem. Vaginal length is functional in most CAIS individuals. Therefore no surgical elongation is needed in the majority.[1] Self vaginal dilatation is the preferred option and success rates of 85-90% have been reported. If total vaginal replacement is needed, use of the sigmoid colon or ileum is the best choice.[11]

Psychological support is crucial for the individual and the family. Counselling should be an ongoing process for

the affected individual and the family, especially around times of schooling, puberty and sexually active age.[12] The contents of the counselling sessions should include medical, surgical and psychosexual issues. Details of puberty, menstruation, fertility, contraception and safe-sex are discussed. As the individual with CAIS is infertile, the possibility of adoption can be introduced. It is suggested that early discussion is useful to empower these individuals, so that they can organise their future in a more structural way. Last but not least is a support group to share their feelings and experiences.[12]

As CAIS is a genetic disorder with an X-linked inheritance, genetic counselling should be offered to the families of the affected individual. Ideally, the family members should be investigated to clarify their genetic status, and have the genetic risk explained to them, in particular the carrier female members.[1] As the gene probe is not available locally, the genetic status of the family members of our patient was not checked.

In this rare heritable disorder, the long term outcome will unveil to us the short comings of the present management. Hopefully this would improve our understanding of the condition and help us formulate a better management protocol. Wisniewski[4] conducted a study on the long term outcome of individuals with CAIS including the physical measurements in adulthood, psychosexual outcome and issues related to the treatment. These affected individuals appeared to be tall with normal secondary female sexual characteristics, except that they did not have axillary and pubic hair. The majority of them were satisfied with their physical appearance, sexual functioning and they had no problems with libido and experiencing orgasms. The affected CAIS individuals perceived themselves as being feminine throughout their development. A large majority of them reported female heterosexual preference in terms of sexual attraction, fantasies and experience. All of them were satisfied with being raised as female and no gender reassignment was requested. The majority of women did not agree with rearing children with intersex according to a third gender.

There were a few long term medical issues requiring attention in these individuals with CAIS. Osteoporosis is one of the most reported medical condition in this group of individuals, so follow up is essential. It is not clear whether the osteoporosis is due to androgen insensitivity or resulted from inadequate oestrogen replacement.[4] Another issue is the compliance with the oestrogen replacement as this is required life long. Therefore, the parents and the individual have to be informed.

Conclusion

In summary, we present a case of CAIS in an infant with normal female phenotype who presented with bilateral inguinal hernias. The diagnosis requires a high index of suspicion in an otherwise normal female with inguinal hernias. This case illustrates the importance of including CAIS on the list of differential diagnoses and checking the karyotype in these patients. Early diagnosis is essential in preparing both the parents and the individual psychologically, so that they can plan for an organised future. When the parents are fully equipped, they can help the affected child by counselling her as she grows. In view of the vast numbers of mutations, the variability of the androgen binding and the poor correlation of the genetic studies to the phenotype, the diagnosis still rests on the clinical features and the karyotype in CAIS. This is demonstrated in our case. After the diagnosis is reached, there is a need to deal with a series of problems. A multidisciplinary team is needed from disclosure of the diagnosis, gender assignment, surgical management, hormonal replacement therapy, to counselling and support.

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