Partial Androgen Insensitivity Syndrome with Type 1 Diabetes

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Abstract:

Introduction

Androgen insensitivity syndrome (AIS), also known as testicular feminization, encompasses a wide range of phenotypes that are caused by numerous different mutations in the androgen receptor gene. where there is resistance to androgen actions influencing both the morphogenesis and differentiation of androgen responsive body structures. AIS is an X-linked recessive disorder. This disorder includes a spectrum of changes ranging from male infertility to completely normal female external genitalia in a chromosomally male individual that is classified as complete, partial, or mild based on the phenotypic presentation.

Case report

An 18-year-old diabetic, phenotypic female presented to the outpatient endocrinology department with primary amenorrhea. At the age of 13, her mother noticed that our patient 's voice became deep & her body hair became more excessive and in abnormal sites (especially above upper lip & chin) with acnePhysical examinationNormal vital signs, she had low pitched voice Weight: 66 kg /Height:166 cm (US/LS : 0.9) (span:170cm) /BMI: 24kg/m2Facial acne Male distribution of body hair:Above upper lip , chin , chest , midline , back (thick , coarse , pigmented) Breast : Tanner stage 1-2 /Pubic hair : Tanner stage 5 /External genitalia : clitoromegaly (2 cm) Severe tenderness on palpation along medial side of inguinal region on both sidesHormonal profile: elevated FSH, testosterone with normal LH, Estradiol, PRL Δ4-Androstenedione 1.3 ng/ml (N: 0.4-4.5) /Testosterone 6.9 ng/ml (N: 0.1-1)FSH 90 mIU/Ml (N: 1-12) LH 2.3 mIu/Ml (N:1.9-12.5)/prolactin 10ng/ml (N:2-29ng/ml) Trans-rectal US: uterus and ovaries are not visualized /MRI pelvis : Non visualized uterus & ovaries

.Bilateral inguinal ovoid structures are seen representing undescended testes (Rt 2.5 X 2 cm) (LT 2 X 2 cm). karyotyping: The case showing male genotype 100 % (46XY).

Conclusion

Androgen insensitivity syndrome is distressing to the patient as well as to the family. Systemic disclosure of the diagnosis in an empathic environment with both professional and family support is encouraged. Patient will be benefited by a multidisciplinary approach including gonadectomy, detailed and repeated psychological counseling along with estrogen replacement. The medical and psychological prognosis for a woman with androgen insensitivity syndrome is excellent if she has appropriate support and counseling.

Introduction

Sex differentiation is a process that starts early during embryogenesis. In males, the SRY gene, located in the short arm of chromosome Y, encodes for the testis-determining factor, which causes the gonad to differentiate into testis[1].
AIS is one of the most commonly diagnosed XY DSD (disorder of sex differentiation), with an estimated prevalence of 2:100.000 to 5:100.00013 and an incidence of 1:20.00014 to 1:99.00015[2].
It is also known as testicular feminization, encompasses a wide range of phenotypes that are caused by numerous different mutations in the androgen receptor gene, where there is resistance to androgen actions influencing both the morphogenesis and differentiation of androgen responsive body structures. AIS is an X-linked recessive disorder. This disorder includes a spectrum of changes ranging from male infertility to completely normal female external genitalia in a chromosomally male individual that is classified as complete, partial, or mild based on the phenotypic presentation[3].In case of minimal androgen insensitivity (MAIS), the individual is a phenotypically male with male sterility, azoospermia, and gynaecomastia. The other end of the spectrum includes XY individuals who have complete androgen insensitivity and they present as tall phenotypically females with well-developed breasts, blind vagina, and absent or scanty pubic and axillary hair[4].
PAIS results in a varied phenotype from the residual

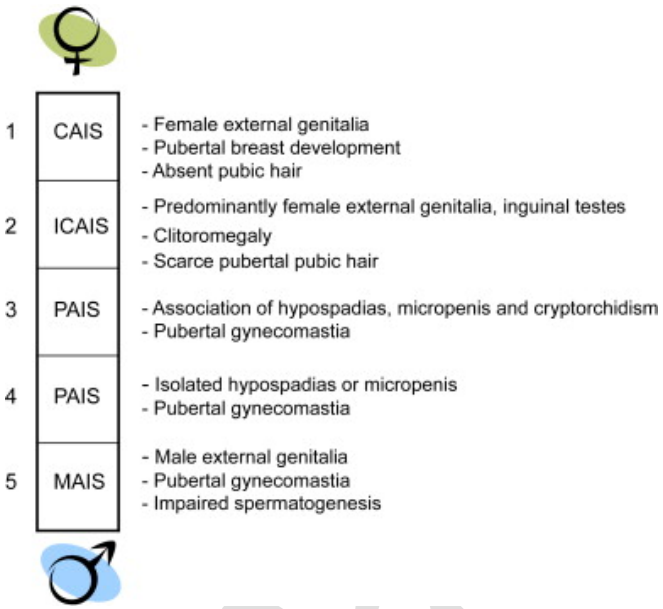
androgen receptor function. Symptoms vary from severe under-masculinization with female genitalia to male genitalia[5].

Case presentation:

Our case is an 18 years old student presented with DM for 5 years with frequent attacks of DKA due to noncompliance to treatment.
The patient gave history of primary amenorrhea. She developed axillary and pubic hair, but no history of breast development.
At the age of 13, her mother noticed that the patient 's voice became deep & her body hair became excessive and started appearing in abnormal sites (specially above her lip & on her chin) with the appearance of acne. The patient was born with normal vaginal delivery with no peri-partum complications with normal mental and developmental milestones.She gave past history of circumcision, appendicectomy 3 years ago.
Upon examination, the patient has low pitched voice with acne, temporal recession of her hairline & male distribution of body hair. Tanner scale was B1-2 P5. External genitalia: Clitoromegaly (2 cm), Small vaginal pouch & severe tenderness on palpation along medial side of inguinal region on both sides .
Investigations showed HbA1C: 13.6%, hormonal profile: with normal FSH, LH, Estradiol, PRL, thyroid profile. Testosterone was 6.9 ng/ml (0.1-1) & DHT was 10.5 ng/ml (4-22). Xray LT wrist: bone age matched with chronological age. Trans-rectal US: uterus and ovaries are not visualized. MRI pelvis: Non visualized uterus & ovaries, bilateral inguinal ovoid structures are seen representing undescended testes (Rt 2.5 X 2 cm) (LT 2 X 2 cm).
Karyotyping: male genotype 100 % (46XY).

Discussion:

Our case was a case of partial androgen insensitivity syndrome which presented as a female with clinical presentation of primary amenorrhea and severe virilization at the time of puberty as has been shown in the clinical examination & the high testosterone level & the normal dihydrotestoserone level. The high testosterone indicates the partial form with some activity of the receptors at the time of puberty. The normal DHT excludes deficiency of 5 alpha reductase syndrome. The following image describes the different types of the syndrome including complete, partial & mild forms[6].



According to the different grades described in the above image, our case definitely lies in the spectrum of the partial subtype.
Our patient was diabetic presented with several attacks of DKA. She was diagnosed as type 1 & was given insulin treatment.
By reviewing the literature & the different case presentations of AIS associated with DM, there was a case study describing DM, insulin resistance & dyslipidemia in association with complete AIS[7]. The case was diagnosed as having DM at the age of 21 with no ketoacidosis & negative antibodies for IAA, ICA, and GADA [7].Both epidemiological studies and experiment have demonstrated that AR signaling plays a role in glucose homeostasis and lipid metabolism. It was reported that male AR knockout mice showed a risk factor for the development of obesity and metabolic abnormalities. In addition, androgen deficiency in men was associated with increased body fat and impaired insulin sensitivity. Recently, some disorders of sex development are reported to be associated with increased risks of diabetes and metabolic syndrome as well[7]Evidence presented in this review suggests that androgen deficiency in males and androgen excess in females produce metabolic dysfunction via deficient or excessive AR action, respectively, in multiple tissues including the central nervous system, liver, skeletal muscle, adipose and β-cells[8].Our case preferred to continue her life as a female & bilateral oophorectomy was planned.

Conclusion

Androgen insensitivity syndrome is distressing to the

patient as well as to the family. Systemic disclosure of the diagnosis in an empathic environment with both professional and family support is encouraged. Patient will be benefited by a multidisciplinary approach including gonadectomy, detailed and repeated psychological counseling along with estrogen replacement. The medical and psychological prognosis for a woman with androgen insensitivity syndrome is excellent if she has appropriate support and counseling.

References

Grob F, et al. Síndrome de insensibilidad completa a andrógenos con persistencia de restos mullerianos. Descripción de un caso. Endocrinol Nutr. 2013; 60:216---8.

C. Gulía, S. Baldassare, A. Zangari, V. Briganti, S. Gigli, M. Gaffi, et al., European Review for Medical and Pharmacological Sciences 2018; 22: 3873-3887

Galani A, Kitsiou-Tzeli S, Sofokleous C, Kanavakis E, Kalpini-Mavrou A (2008). "Androgen insensitivity syndrome: clinical features and molecular defects". Hormones (Athens). 7 (3): 217–29.

Hughes IA, Deeb A. Androgen resistance. Best Pract Res Clin Endocrinol Metab. 2006; 20:577–598. Priya Vaidyanathan and Paul Kaplowitz. Endocrinology, Diabetes & Metabolism Case Reports. Volume 2018: Issue 1. DOI: https://doi.org/10.1530/EDM-18-0128

CharlesSultan, PascalPhilibert†LauraGaspari, rancoiseAudran,LaurentMaimoun,NicolasKalfa§FrançoiseParis, Genetic Steroid Disorders, 2014, Pages 225-237. https://doi.org/10.1016/B978-0-12-416006-4.00016-8

Peng Yang, Xiang Liu, Jingyang Gao, BS, Shen Qu, and Manna Zhang. Medicine (Baltimore). 2018 Aug; 97(33): e11353. Published online 2018 Aug 17. doi: 10.1097/MD.0000000000001135

Navarro G, Allard C, Xu W, Mauvais-Jarvis F. The role of androgens in metabolism, obesity, and diabetes in males and females. Obesity (Silver Spring). 2015 Apr;23(4):713-9. doi: 10.1002/oby.21033. Epub 2015 Mar 6. PMID: 25755205; PMCID: PMC4380643.