Case Report:

Mild Androgen Insensitivity Syndrome presenting in male with infertility and sexual difficulties

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Abstract:

Androgen insensitivity syndrome has a wide spectrum of presentations. It results from a mutation in androgen receptor (AR) gene. It ranges from mild androgen insensitivity syndrome (MAIS) which is the mildest form to complete androgen insensitivity syndrome (CAIS). In case of MAIS, the abnormality that can be observed appears to be male infertility and sexual difficulties including premature ejaculation and erectile dysfunction. In this case report, we discuss a case of MAIS in a 37-year-old male who presented with infertility, premature ejaculation, and secondary erectile dysfunction.

Keywords: Mild androgen insensitivity syndrome; Infertility; Oligospermia; Premature ejaculation

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Introduction:

Androgen insensitivity syndrome (AIS) is defined as under-masculinization of the external genitalia at birth, as well as aberrant secondary sexual development during puberty and/or infertility in people with a 46 XY karyotype [1]. Complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS) are the three phenotypes of androgen insensitivity syndrome (MAIS). Androgen Receptor (AR) gene mutations result in AR dysfunction, including loss of function. The incidence is predicted to be 1:20000-1:64000 male births[2]. MAIS is the most infrequent type, and it is possible that a diagnosis will be delayed or overlooked. Gender identity, reproductive concerns, and how the outside world perceives them all necessitate attentive support. As a result, emphasis the need of addressing emotional, psychological, and mental vulnerabilities in matters of relationships, infertility, and conception[3]. Another study also shows that male infertility is not affected by age[4]. We present a case of MAIS in a 37-year-old man who had significant oligospermia, infertility, premature ejaculation, and erectile dysfunction as a result of his condition.

Case report:

A 37-year-old married man visits our outpatient Men's Health Clinic in 2015 for premature ejaculation and infertility. He was married with two wives. He first marriage was in 2009, but they were having trouble conceiving. His wife was treated by a gynaecologist for infertility. Her menses were regular, and she had no previous medical history that could have harmed

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her fertility. The wife underwent in vitro fertilisation (IVF) twice. They had one child after a successful IVF procedure. The second IVF was completed in early 2021 and his wife is now expecting their second child. He was distressed with his short ejaculatory time causing marital instability. He subsequently sought medical help. During first visit to our clinic, he complained of early ejaculation during sexual intercourse of less than one minute. There were no abnormalities found in the physical examination. He was started on Tab. Sertraline 50mg PRN. His seminal fluid analysis (SFA) at that time showed the sperm count was 1.5 million/ml (severe oligospermia). The symptom of premature ejaculation did not improve during the next review. Tab. Sertraline was increased from 50mg PRN to 50mg OD. He was told to employ the start-stop approach and the double condom method.

He defaulted follow up until December 2020. The patient also revealed that he was having marital problems with his first wife and is experiencing financial problems because of the COVID-19 pandemic. These issues made him ponder a lot, but he denied any depressive symptoms but claimed to develop erectile dysfunction. Tab. Dapoxetine 30mg and Tab. Sildanefil 50mg were prescribed during this visit. A blood sample was taken and SFA was scheduled for the following visit. On subsequent visit, the patient informed us that the use of Tab. Dapoxetine does not improve his ejaculatory time. The results of blood tests were all normal. Tab. Sildenafil and Tab. Dapoxetine were prescribed along with Lignocaine spray 4%. A genetic study was planned. Several analyses of the sperm revealed severe oligospermia and very low volume ejaculate. Hormones studies including Follicle-stimulating hormone (FSH) and prolactin levels were normal. However, luteinizing hormone (LH) levels were high and testosterone levels were within normal range (Table 1). His Y chromosome genetic analysis revealed no complete microdeletions, and his karyotyping was 46XY.

Table 1: Hormone results of the patient on 7 April 2021.

Tests	Results	Normal range
Testosterone	29.03 nmol/L	8.64 – 29.0 nmol/L
FSH	10.97 IU/L	1.5 – 12.4 IU/L
LH	11.07 IU/L	1.7 – 8.6 IU/L
Prolactin	105.5 mIU/L	86.0 – 324 mIU/L
TSH	1.67 mIU/L	0.27 – 4.2 mIU/L
FreeT4	17.35 mIU/L	12.0 – 22.0 mIU/L

FSH– follicular stimulating hormone; LH – luteinizing hormone; TSH – thyroid stimulating hormone

Discussion:

An American gynaecologist originally described androgen insensitivity syndrome (AIS) in 1953[5]. The main cause is a loss of function caused by a mutation in the androgen receptor (AR) gene on the X chromosome's long arm. There have been over 1000 mutations documented, including gene deletions, point mutations, and small deletions[6]. Complete androgen insensitivity syndrome (CAIS) with typical female genitalia, partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male, or ambiguous genitalia, and mild androgen insensitivity syndrome (MAIS) with typical male genitalia are the three phenotypes of androgen insensitivity syndrome.Because of the wide range of biochemical, molecular, and morphologic variations, no official diagnostic criteria available. Under-masculinization of the external genitalia, normal testes with reduced spermatogenesis, normal or enhanced testosterone synthesis, normal or increased luteinizing hormone, and/or the detection of a hemizygous pathogenic variant in androgen receptor (AR) are all signs of AIS[1]. Males with normal external genitalia may present with MAIS. Spermatogenesis maybe impaired and erectile dysfunction may present. In certain condition, male infertility maybe the only presenting complain. Thus, MAIS could explain some cases of idiopathic male infertility [1]. MAIS caused by single-nucleotide variations of AR [7]and MAIS induced by enlargement of the polymorphic CAG repeat in AR[8] may be clinically indistinguishable. Because the clinical presentation and hormonal profiles are compatible, this patient is classified as MAIS. The ability of the cell to respond to androgens is mildly impaired as a result of MAIS. The degree of impairment is sufficient to impact sexual function (erectile dysfunction) and affect spermatogenesis[9]. Our patient had normal features of male and he only seek medical attention when having difficulties to conceive. Subsequently investigated to have severe oligospermia and premature ejaculation. It is already known that methods of mental distraction used to gain control on ejaculation may result in erectile dysfunction later, and same may happened to the case and he developed erectile dysfunction. The only treatment for MAIS is symptomatic relief. Patients can be treated with testosterone, however exogenous

androgens have a negative feedback effect on the axis, resulting in the end of spermatogenesis. However, there have been examples of high-dose testosterone reversing infertility caused by low sperm count[10]. In this case, patient proceeded with assisted reproduction, phosphodiasterase-5-inhibitor (Sildenefil), Dapoxetine and Lignocaine spray were prescribed for the treatment of erectile dysfunction and premature ejaculation, respectively together with psychological intervention.

Conclusion:

Detection of MAIS may be delayed due to its mild presentation. This case emphasizes the need for screening for mild androgen insensitivity when a patient presents with infertility and sexual difficulties including erectile dysfunction.

Declarations:

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