University Journal of Medicine and Medical Specialities

ISSN 2455- 2852 2019, Vol. 5(7)

# Attention Deficit Hyperactivity Disorder in a girl with Androgen Insensitivity Syndrome

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**Abstract :** Objective- To describe the occurrence of Attention Deficit Hyperactivity Disorder(ADHD) in a girl with Androgen Insensitivity Syndrome(AIS).Clinical features- This girl presented with excessive activity, being intrusive in others conversations and being inattentive. She had already been diagnosed with AIS and had underwent bilateral orchidectomy previously. Examination of her external genitalia revealed mildly enlarged clitoris and no vagina. Intervention and outcome- For her AIS, she had already underwent bilateral orchidectomy and feminizing genitoplasty has been planned to be done once she reaches adolescence. For her ADHD, she was started on atomoxetine, and she improved with the medication.

**Conclusion**- The finding of ADHD occurring in a girl with AIS raises a question that there could be an association between the two conditions. This question needs to be addressed by future research.

**Keyword :**attention deficit, hyperactivity, androgen insensitivity, testicular feminization

## Introduction

*About AIS*

Androgen Insensitivity Syndrome(AIS) was previously known as Testicular Feminization Syndrome(TFS). It is an X-linked recessive condition. Though the individuals will be genotypically (chromosomally) male (karyotype: 46 XY), they will be phenotypically female. This is because there will be failure of normal masculinization of the external genitalia. There are two subtypes based on the extent of virilization- 1. cAIS (complete AIS)- presence of female external genitalia with normal labia, clitoris, and vaginal introitus. 2. pAIS (partial AIS)- presentation may range from mildly virilized female external genitalia (clitoromegaly without other external anomalies) to mildly undervirilized male external genitalia (hypospadias and/or diminished penile size). Testes will be normal, with normal production of testosterone and its normal conversion to dihydrotestosterone (DHT). Because the testes produce normal amounts of müllerian-inhibiting substance (MIS), affected individuals do not have fallopian tubes, a uterus, or a proximal (upper) vagina.

*Pathophysiology of AIS* The basic etiology of AIS is a loss-of-function mutation in the androgen receptor (*AR*) gene, located on the long arm of the X chromosome (ie, Xq11-13). Loss of AR function means that, despite normal levels of androgen synthesis, the typical postreceptor events that mediate the effects of hormones on tissues do not occur. This results in the phenotype of prenatal undervirilization of external genitalia, absence of pubic and axillary hair, lack of acne, and absence of voice changes at puberty. *Incidence of AIS*

It is approximately 1 case per 20,400 liveborn males. cAIS appears to be more common than pAIS, although exact figures are unavailable. *Comorbidity with AIS* In contrast to medical morbidity, psychological morbidity is common. Their psychosocial problems range from identity issues to problems dealing with the gender perceptions of the outside world and the style and sensitivity (or lack thereof) they encounter within the medical system. Many of these patients have been told that they really are not women but actually are men because of the presence of a Y chromosome and testes. These difficulties and doubts often cause shame and self-doubt as well as anger and frustration with a medical system they had expected to take care of them. Separating the concepts of sex and gender is crucial with these patients. The term *sex* is usually based on physical attributes, whereas the concept of *gender* is based on an individual's self-concept and self-identification as well as the role an individual assumes in society. Most patients with cAIS have a female gender. This is due to the patient's role assignment and upbringing before the diagnosis. Partial androgen insensitivity syndrome is a more complicated problem for gender identity. Just as the genitalia may be highly varied in the degree of virilization, gender identity may be either female or male.

Most cases of androgen insensitivity syndrome (AIS) are identified in the newborn period by the presence of inguinal masses, which later are identified as testes during surgery. Some patients are first seen in the teenage years for evaluation of primary amenorrhea.1

*About ADHD*

Attention Deficit Hyperactivity Disorder (ADHD) is a condition characterized by impairment of sustained attention and higher levels of impulsivity in a child or adolescent than expected for someone of that age and developmental level. To confirm a diagnosis of ADHD, impairment from inattention and/or hyperactivity-impulsivity must be observable in at least two settings. Incidence is about 3 to 7 percent. It is more prevalent in boys than girls (ratio ranges from 2:1 to 9:1).2 *Etiology of ADHD*

Most children with ADHD have no evidence of gross structural damage in the central nervous system (CNS). Despite the lack of a specific neurophysiological or neurochemical basis for the disorder, it is predictably associated with a variety of other disorders that affect brain function, such as learning disorders. Evidence for a genetic contribution to the emergence of ADHD

includes greater concordance in monozygotic than in dizygotic twins. The most widely studied drugs in the treatment of ADHD, the stimulants, affect both dopamine and norepinephrine, leading to neurotransmitter hypotheses that include possible dysfunction in both the adrenergic and the dopaminergic systems. The locus ceruleus, consisting of mainly noradrenergic neurons, has been shown to play a major role in attention. Studies using positron emission tomography (PET) have found lower cerebral blood flow and metabolic rates in the frontal lobe areas of children with ADHD than in controls. This probably means that the frontal lobes in children with ADHD are not adequately performing their inhibitory mechanism on lower structures, leading to disinhibition. Stressful psychic events, disruption of family equilibrium, and other anxiety-inducing factors contribute to the initiation or perpetuation of ADHD. *Clinical features of ADHD* Inattention- making careless mistakes in schoolwork, not following instructions, difficulty organizing activities, losing things often, being easily distracted by external stimuli, being forgetful. Hyperactivity- being fidgety, leaving seat when being seated is expected, often "on the go" as if "driven by a motor", talking excessively Impulsivity- blurting out answers before question is completed, difficulty awaiting turn, intruding on others.

*ADHD subtypes*-

1. ADHD, predominantly hyperactive-impulsive type
2. ADHD, predominantly inattentive type
3. ADHD, combined type

In the current paper, we report the rare co-occurrence of ADHD in a child with AIS.

**Case report (Methods)**

This 5 ½ year old girl, Ms B, studying in 1st std, was brought to the clinic by her mother with the following complaints. Since a very early age, she had been found to be much more active compared with peers. She was found to be inattentive both at home as well as in school. She could not sit in a place for more than ten minutes. On many occasions, she was found to not listen while being talked to. However, she used to complete her homework daily. Her scholastic performance was average except for maths in which she scored poorly. She frequently lost her pencils, erasers and other things at school. At school, she beat her classmates frequently. According to her teachers, she was excessively talkative in class, and would often blurt out answers before the teacher completed the question. She also interfered in others' conversations. She used to go to bed late at night and would wake up very early in the morning. She also ate very less compared to other children of her age. Her mother reported that she had started telling a lot of lies recently. About two years before she had been diagnosed with AIS, and she had undergone bilateral orchidectomy. She was born out of a second degree consanguinous marriage. Her younger sister also had been diagnosed with AIS. Birth and developmental milestones were normal.

*Physical examination*- Child was alert, afebrile, moderately built and nourished. Her general condition was fair and vitals were stable.

*Systemic examination*- Cardiovascular, respiratory, alimentary and central nervous system examination was normal. *Genital examination*- Mild clitoromegaly, small urethral orifice, no vagina *Mental status examination*- Child was alert, ambulant, restless, fidgety, running around in the interview room, falling repeatedly from chair, spitting at times, scolding her mother and beating her sister at times during the interview. Psychomotor activity was increased. Quantum and rate of her speech was slightly increased, reaction time was decreased, and was relevant and coherent. She was cheerful and there were no other thought or perceptual disturbances.

***Investigations-***

Abdominal ultrasound (dated 20/11/09)- No mullerian derivatives. Both gonads seen in inguinal canal. Blood levels of total and free testosterone, sex hormone binding globulin(SHBG) and 17-hydroxy progesterone- normal. Karyotype- 46 XY Histopathological examination of orchidectomy specimen (dated 13/07/10)- Right and left gonads: seminiferous tubules with epididymis, minimal stroma and .focal congestion. *Management*- Child's mother was educated about her condition. She was started on Tab. Atomoxetine 10mg 1-0-0. At review, 2 weeks later, child had improved and her hyperactivity and inattention had decreased significantly. Feminizing genitoplasty has been planned for her once she attains puberty

**Discussion**

AIS has been found to be usually associated with psychiatric comorbidity. A diagnosis of CAIS often leads to psychological distress in the teen and her family and counselling should be strongly encouraged. Disorders of Sexual Development (DSD) counseling should be made part of the treatment plan as soon as possible. Genetic counselling for the family is also recommended.3 One case report described AIS in two sisters. One sister was hospitalized for a polymorphous neurotic reaction; the other was apparently healthy, with certain masculinoid traits in her behavior.4 High concentrations of pre- and postnatal androgens contribute to male-typical behavior development, whereas female-typical behavior develops in the absence of high androgen levels.5 The male predominance of externalizing behaviors suggests that the X-linked androgen gene might be involved. One study found a significant association between the *AR* haplotypes and ADHD, conduct disorder, and oppositional defiant disorder. These results suggest that genetic variation at the human *AR* gene plays a role in human externalizing disorders.6 A significant association of the short alleles of the GGC repeat polymorphism of the AR gene with a range of measures of aggression and impulsivity has been documented.7 The discovery of the wide distrib ution of steroid hormone receptors, as well as that of the possibility of metabolizing or synthesizing steroids by neural cells (neuroactive steroids), suggest, on the contrary, that interactions among steroids and nervous system are key points of the regulatory processes in the central and peripheral nervous system in normal conditions as well as in pathological conditions.8 ADHD-like symptoms have been seen in children exposed in utero to repeated courses of synthetic glucocorticoids.9

**Conclusion**

There have been no case reports of ADHD occurring in individuals with AIS. Hence we have presented this rare occurrence. As we can see from the existing sparse literature on this subject, the association between AIS and ADHD appears to be more than due to chance. Further research is required to throw more light on this association.

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