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DIAGNOSTIC AND MANAGEMENT CHALLENGES IN AR-NEGATIVE AIS-LIKE PHENOTYPES: A CASE SERIES

Jafarli I.^{1*}, Huseynova I.²

Abstract

We report on three pediatric patients (18-35 months) presenting with features of a 46, XY disorder of sex development (DSD) with an androgen insensitivity syndrome (AIS)-like phenotype, including variable presentations of chordee, penoscrotal transposition, hypospadias-associated anomalies, and undescended testes. These cases were initially suspected of having Partial Androgen Insensitivity Syndrome (PAIS) based on clinical presentation; however, no structural Müllerian, renal, or anorectal anomalies were identified.

Genetic evaluation included targeted AR gene sequencing and broader DSD panels. Endocrine evaluation included basal and stimulated testosterone, gonadotropins, and testicular function markers (AMH, inhibin B). Immunohistochemistry (IHC) was performed on gonadal and scrotal tissue biopsies to assess androgen receptor (AR) expression patterns. Clinical management followed a multidisciplinary team approach, emphasizing conservative surveillance, longitudinal endocrine monitoring, and individualized developmental support, consistent with frameworks established in recent pediatric surgical literature [1]. All three patients tested negative for pathogenic variants in AR and standard DSD panel genes, with baseline hormonal profiles showing normal-to-low-normal responses to hCG stimulation. IHC analysis in Case 1 revealed atypical AR expression, characterized by weak, variable positivity in preputial and scrotal epithelial cells, with significant AR-negative regions. Management remained conservative; early gonadectomy was strictly avoided, and elective reconstructive surgeries (such as chordee correction and orchidopexy) were deferred to allow for spontaneous pubertal progression and further phenotypic assessment.

These cases illustrate the diagnostic challenges of "AR-negative" DSD, where an AIS-like phenotype persists despite the absence of identifiable genetic mutations. The presence of atypical AR expression patterns suggests potential receptor dysfunction or undiscovered regulatory mechanisms. A flexible, multidisciplinary management strategy is incorporating psychological support, genetic counselling, parental informed consent, and the deferral of non-urgent irreversible surgeries is essential to provide comprehensive, patient-centered care [2].

Key words: disorders of sex development, Partial Androgen Insensitivity Syndrome, AR gene, immunohistochemistry, whole-exome sequencing

INTRODUCTION

Disorders of Sex Development (DSD) represent a heterogeneous group of

congenital conditions where chromosomal, gonadal, or anatomical sex development is atypical. Among these, 46,XY DSD caused



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by androgen resistance clinically termed Partial Androgen Insensitivity Syndrome (PAIS) is a major diagnostic consideration for infants presenting with ambiguous genitalia and external virilization defects [3]. Classically, the suspicion of PAIS triggers genetic sequencing of the AR gene. However, clinical literature indicates that less than 30% of boys with phenotypes suggestive of PAIS harbor a detectable AR mutation [4]. This diagnostic gap leaves clinicians with "AR-negative" cases where the clinical and hormonal profile suggests androgen resistance, yet the molecular etiology remains elusive. Furthermore, ethical standards in paediatric surgery require strict adherence to institutional review board (IRB) oversight and explicit parental informed consent, particularly when evaluating delicate congenital variations.

MATERIALS AND METHODS

Clinical Presentation and Diagnostic Findings

The three patients presented between 18 and 35 months of age. Clinical features varied per individual case, encompassing localized genital anomalies without structural Müllerian, renal, or anorectal involvement. Maternal androgen exposure was ruled out in all instances.

Baseline and Stimulated Hormonal Profile:

To assess testicular function and clarify the biochemical basis of suspected androgen resistance, baseline and human chorionic gonadotropin (hCG)-stimulated hormone levels were evaluated. Basal luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone fell within age-appropriate prepubertal ranges. Post-hCG stimulation testing demonstrated appropriate testosterone increments alongside preserved serum Anti-Müllerian Hormone (AMH) and inhibin B levels, confirming functional testicular tissue without evidence of gonadal dysgenesis.

Genetic Analysis: Sequencing of the AR gene and extended panel testing for DSD-related genes were negative for pathogenic variants across all three patients.

Immunohistochemistry: Analysis of Case 1 revealed atypical AR expression, with variable, weak positivity in the prepuce and scrotal samples, and significant regions of AR-negativity.

The presence of a clinical AIS-like phenotype without an identified genetic cause highlights the limitations of current targeted gene sequencing and the potential role of undiscovered molecular pathways or regulatory region abnormalities [4].

Yazışma üçün əlaqə:

Jafarli İ.^{1*}, Huseynova İ.²

¹Chelsea and Westminster Hospital, UK

²Institute of Molecular Biology and Biotechnologies, Azerbaijan

*For correspondence E-mail: ilhama.jafarli@nhs.net

Table 1. AR-Negative Inconclusive Cases

Cases	Age (months)	Clinical Presentation	Hormonal Profile (Basal hCG Stimulated)	Gene Sequencing	Immunohistochemistry	Management
1	18	Abnormal scrotal skin attachment, chordee, widened penoscrotal distance	LH: normal; FSH: normal; T: normal prepubertal rise post-hCG; AMH/Inhibin B: normal	No mutations in AR or extended DSD panel genes	Atypical AR expression: 30% of epithelial cells in prepuce/scrotal skin showed weak, variable positivity. ~2% of epidermal cells showed strong nuclear positivity. Scrotal samples were AR-negative except for an isolated sebaceous gland.	Deferred early reconstructive surgery Planned future chordee correction/penile degloving if indicated Genetic counseling and formal parental consent Longitudinal MDT endocrine surveillance
2	24	Meatal stenosis, webbed penis, scrotal transposition	LH: normal; FSH: normal; T: adequate response post-hCG; AMH/Inhibin B: normal	Negative for AR mutations	Not performed (insufficient tissue biopsy)	Deferred non-urgent surgery Serial growth and endocrine monitoring Enrolled in longitudinal MDT review

Management and Therapeutic Strategy

A conservative management approach was adopted, with emphasis on careful longitudinal follow-up under institutional ethical guidelines and parental informed consent. The patients underwent regular endocrine monitoring, including serial hormonal evaluations to measure hypothalamic-pituitary-gonadal axis function. Growth velocity and pubertal development were monitored through periodic clinical assessments to evaluate ongoing physical maturation.

Surgical strategy explicitly avoided early gonadectomy, as histological evaluation

and hormonal markers confirmed functional, non-dysgenetic testes with no elevated malignancy risk. Elective reconstructive procedures (such as chordee correction, penoscrotal transposition repair, and orchidopexy) were intentionally postponed to allow for spontaneous physical development and to support shared decision-making as the child matures [5]. In addition, comprehensive psychosocial support was provided to the families to facilitate coping, address concerns related to the diagnosis, and prepare for future discussions

regarding gender identity and long-term well-being.

DISCUSSION

The challenge of managing AR-negative DSD lies in the unpredictability of long-term outcomes. While patients with genetically confirmed PAIS may show higher rates of complications like gynecomastia, the prognosis for those without identified mutations is less clear [4].

The use of immunohistochemistry (IHC) for AR remains a useful but supplementary tool. As seen in Case 1, patchy or weak nuclear expression does not necessarily confirm a functional defect but suggests potential receptor dysregulation. Future diagnostics may increasingly rely on Whole-Exome Sequencing (WES) to uncover novel genetic factors, as recent studies have identified causal variants in previously "idiopathic" cases through expanded research-based sequencing [6]. Recent advances in next-generation sequencing (NGS), particularly whole-exome sequencing (WES), have substantially expanded the spectrum of genes implicated in AIS-like phenotypes, facilitating the identification of pathogenic variants in genes involved in androgen biosynthesis, androgen signaling pathways, gonadal development, and other molecular mechanisms that may mimic classical AIS [7].

Some studies demonstrated that incorporating NGS into the diagnostic evaluation of patients with DSD significantly improves molecular diagnostic yield compared with conventional sequential testing [7]. Their findings emphasize that patients with an AIS-like presentation but negative AR testing frequently receive alternative molecular diagnoses through broader gene panel or exome sequencing, allowing for more accurate disease classification and personalized clinical

management. Similar research highlighted the evolving role of WES as an important diagnostic tool in unresolved DSD cases, particularly when the phenotype does not clearly correspond to a single genetic disorder [6]. The authors emphasized that identifying the underlying molecular defect not only refines diagnosis but also improves genetic counseling, recurrence risk assessment, and multidisciplinary clinical decision-making.

CONCLUSION

The recognition of AR-negative AIS-like phenotypes has important implications for patient management beyond establishing a molecular diagnosis. Accurate genetic and hormonal characterization contributes to individualized decisions regarding gonadal surveillance, endocrine treatment, fertility counselling, and psychosocial support. Furthermore, long-term outcome studies have reinforced the importance of integrating genetic diagnosis with careful multidisciplinary evaluation when making decisions regarding sex assignment and lifelong management. Another study emphasized that gender-related outcomes in individuals with DSD depend on multiple factors, including the underlying diagnosis, hormonal function, psychosocial environment, and ongoing clinical support [8]. Consequently, establishing a precise molecular diagnosis through comprehensive genomic testing provides a stronger foundation for patient-centered counselling and shared decision-making. Collectively, these findings support the routine integration of comprehensive genomic approaches, including WES, into the evaluation of patients with AR-negative AIS-like phenotypes to improve diagnostic accuracy, optimize long-term management, and advance understanding of the complex genetic architecture of DSD.

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AR-MƏNFI ANDROGENLƏRƏ QISMƏN HƏSSASLIQ SİNDROMUNA BƏNZƏR FENOTİPLƏRDƏ DIAQNOSTIKA VƏ MÜALİCƏ PROBLEMLƏRİ: KLİNİK HALLAR SERİYASI

Cəfərli İ.^{1*}, Hüseynova İ.^{2*}¹ Çelsi və Vestminster Xəstəxanası, Böyük Britaniya² Molekulyar Biologiya və Biotexnologiyalar İnstitutu, Bakı, Azərbaycan* Yazışma üçün E-mail: ilhama.jafarli@nhs.net

Xülasə

Biz 46,XY cinsiyyət inkişafı pozğunluğunun xüsusiyyətlərini nümayiş etdirən, 18–35 aylıq üç pediatrik pasiyent haqqında məlumat veririk. Pasiyentlərdə androgenlərə qismən həssaslıq sindromuna bənzər fenotip müşahidə olunmuşdur. Klinik təzahürlərə müxtəlif dərəcələrdə xordeya, penoskrotal transpozisiya, hipospadiya ilə əlaqəli anomaliyalar və kriptorxizm daxil olmuşdur. Bu hallar ilkin olaraq klinik təzahürlərə əsasən *Androgenlərə Qismən Həssaslıq Sindromu* kimi qiymətləndirilmişdir. Lakin Müllərian strukturlarında, böyrəklərdə və anorektal nahiyədə heç bir struktur anomaliya aşkar edilməmişdir.

Bu hallar “AR-mənfi” cinsiyyət inkişafı pozğunluğunun diaqnostik çətinliklərini nümayiş etdirir. Belə hallarda müəyyən edilə bilən genetik mutasiyalar olmadığı halda androgenlərə qismən həssaslıq sindromuna bənzər fenotipin davam etməsi müşahidə olunur. AR ekspressiyasının atipik nümunələrinin mövcudluğu reseptor disfunksiyasının və ya aşkar edilməmiş tənzimləyici mexanizmlərin mümkünlüyünü göstərir. Kompleks və pasiyentyönlü tibbi yardımın təmin edilməsi üçün psixoloji dəstək, genetik məsləhətləşmə, valideynlərin məlumatlandırılmış razılığı və təcili olmayan, geri dönməz cərrahi müdaxilələrin təxirə salınmasını əhatə edən çevik, multidissiplinar yanaşma vacibdir.

Açar sözlər: cinsi inkişaf pozğunluqları; androgenlərə qismən həssaslıq sindromu; AR geni; immunohistokimya; tam ekzom sekvenslənməsi.

ДИАГНОСТИЧЕСКИЕ И ТЕРАПЕВТИЧЕСКИЕ ПРОБЛЕМЫ ПРИ AR-НЕГАТИВНЫХ ФЕНОТИПАХ, СХОДНЫХ С СИНДРОМОМ НЕЧУВСТВИТЕЛЬНОСТИ К АНДРОГЕНАМ: СЕРИЯ КЛИНИЧЕСКИХ СЛУЧАЕВ

Джафарли И.^{1*}, Гусейнова И.²

¹ Больница Челси и Вестминстера, Великобритания

² Институт молекулярной биологии и биотехнологий, Азербайджан

* Для корреспонденции E-mail: ilhama.jafarli@nhs.net

Резюме

Мы представляем три клинических случая у детей в возрасте от 18 до 35 месяцев с признаками нарушения полового развития 46, XY и фенотипом, сходным с синдромом нечувствительности к андрогенам. Клинические проявления включали различные варианты хордэ, пеноскротальной транспозиции, аномалий, ассоциированных с гипоспадией, а также крипторхизмом. Первоначально на основании клинической картины у этих пациентов предполагался синдром частичной нечувствительности к андрогенам (СЧНА). Однако структурных аномалий мюллеровых структур, почек или аноректальной области выявлено не было.

Эти случаи демонстрируют сложности диагностики нарушений полового развития с «отрицательным AR»-статусом, при котором фенотип, напоминающий синдром нечувствительности к андрогенам, сохраняется несмотря на отсутствие выявляемых генетических мутаций. Наличие атипичных паттернов экспрессии AR указывает на возможную дисфункцию рецептора или существование ещё не выявленных регуляторных механизмов. Для обеспечения комплексной, ориентированной на пациента медицинской помощи необходим гибкий мультидисциплинарный подход, включающий психологическую поддержку, генетическое консультирование, информированное согласие родителей и отсрочку проведения необязательных необратимых хирургических вмешательств.

Ключевые слова: нарушения полового развития; синдром частичной нечувствительности к андрогенам; ген AR; иммуногистохимия; полное экзомное секвенирование.