Partial androgen insensitivity syndrome. Multidisciplinary approach - genetic, endocrinological, surgical, psychological, psychiatric, social, ethical and forensic

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Abstract: The partial androgen insensitivity syndrome is a particular form of sexual ambiguity. In these cases, accurately assigning the legal gender at birth has major repercussions on all aspects of the ontogenic personality development. The surgical treatment is differentiated by phenotypic appearance, sexual identity and legal gender; furthermore, the surgical therapeutic decision depends on the outcome of clinical/psychiatric and psychological assessments; thus, a multidisciplinary approach of these cases is required.

Key Words: androgen insensitivity syndrome, Reifenstein syndrome, severe hypospadias, sexual identity, passive aggression.

Androgenic hormones exert their effect on the differentiation and development of the normal male phenotype through a protein called the androgen receptor (AR) [1], located on the long arm of chromosome X (Xq11-12) [2]. The androgen insensitivity syndrome is defined by impaired sexual development in individuals with genetic male sex due to lack of response of the target organs to androgen stimulation; it is the result of inactivating mutations in the AR gene X-linked recessive transmitted, which cause varying degrees of insensitivity of the androgen receptor. Phenotypically, androgen insensitivity can be classified in: full insensitivity to androgens (CAIS - Complete androgen insensitivity syndrome); partial insensitivity to androgens (PAIS - Partial androgen insensitivity syndrome), and minimal insensitivity to androgens (MAIS - mild androgen insensitivity syndrome) [3].

The occurrence of the androgen insensitivity syndrome has been assessed based on studies of small populations [4]. Thus, the CAIS is estimated to occur in 1 out of 20,400 boys born [5], while the occurrence of PAIS has been estimated in 1 out of 130,000 boys born [6]. Within the PAIS several phenotypes have been identified: female phenotype (feminine EG, female-like pubic pilosity, with or without clitorimegaly and partially or totally merged labia), genital ambiguity, predominantly male phenotype - Reifenstein syndrome - with micropenis, perineal hypospadias and cryptorchidism [7]. The diagnosis is confirmed through laboratory hormone tests, which show elevated levels of serum testosterone, luteinizing hormone (LH), FSH, as well as through genetic testing, which show male karyotype - 46XY. The diagnosis and treatment of these patients require a multidisciplinary approach. The surgical

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treatment aims for the surgical correction of the EG in order to obtain a phenotypically male (most of the times) or female aspect. The surgical treatment is regarded as a challenge because of the technical difficulties both in correcting the scrotal hypospadias and in regards to the vaginoplasty.

Patients with intersexuality have psychological and social difficulties caused at least in part by parental attitudes and behavior, which is why long-term psychological counseling is recommended for both parents and children; it should start the moment the diagnosis was established [8]. Early diagnosis, followed by a timely start of treatment, plays a crucial role both in obtaining long-term good results and prevention through genetic counseling.

**OBJECTIVES AND METHOD**

**Case study**

*Case "M":* clinical evaluation: 17-year-old patient, legal gender as male, 155 cm waist (-3.1 DS), weight = 48 Kg, genetic target waist: 174 cm (-0.43 DS), reduced facial and body pilosity, axillary pilosity present, triangular pubic pilosity Tanner stage III, well-defined muscles, gynecomastia - mammary glands stage B III / IV Tanner - bilateral cryptorchidism (both testicles present in the inguinal canal, as observed clinically and via the ultrasound) and scrotal hypospadias with a clitoral aspect of the penis (Figs. 1 and 2). The bone age X-ray shows almost fused growth plates. Genetic determination: Barr test negative, karyotype: 46 XY.

*Case "F":* 22-year-old patient (the first time she comes for a consult), legal gender as female, reduced facial and body pilosity, axillary pilosity present, triangular pubic pilosity Tanner stage III, well-defined muscles, gynecomastia - mammary glands stage B III / IV Tanner - bilateral cryptorchidism (observed clinically and via the ultrasound), scrotal hypospadias with a clitoral penile aspect (Figs. 3 and 4). Genetic determination: test Barr negative, karyotype: 46 XY.

The hormonal investigation, performed as a collaboration between the "M.S Curie" Emergency Clinical Children's Hospital and the Parhon Institute from Bucharest, is presented in table 1 for both patients.

Taking into consideration the karyotype, the hormonal investigation results and the clinical examination, both patients were diagnosed with the syndrome of partial insensitivity to androgen action - the Reifenstein syndrome. The surgical procedures in patient "M" consisted of: bilateral orchiopexy; mammary gland ablation; multistage treatment of the scrotal hypospadias (Stage I of flexing and transforming the scrotal hypospadias in proximal penile hypospadias, stage II: urethroplasty with bringing the urethral meatus at the glandular level)(Figs. 5-7).

In the "F" case study, due to the fact that the patient came to the doctor late (22-year-old), there was a mismatch between genetic sex (male) and legal sex (female), and the patient had expressed her wish to do so, the surgery consisted initially of gonads removal, later to be followed-up with a reduction plasty of the clitoris and vaginoplasty. The anatomical and pathological investigation of the surgically removed gonads revealed no malignant transformation.

The psychiatric examination was carried out within the Forensic Psychiatry Department of the "Mina Minovici" National Forensic Institute in Bucharest (semi-structured interviews with semi-open and open ended questions were used):

1. The heredo-collateral history is presented in Figure 8.
2. Personal history: The first sibling was declared a girl at birth; the second born was declared a boy. The two patients denied a pathologically relevant personal history.
3. Premorbid personality: Patients come from rural areas. The family presents with genetic pathology, has low social, economic and educational levels, adheres...
to ancestral values which are inconsistent with the macro environment it is part of; it is marginalized without being ostracized. The family has shown indifference towards the children's pathology so far. Parental attitude towards children's school education is negative. ("M" - 4 years of primary school, "F" - 3 years). The educational model shows a clear ancestral delineation between the different social roles of men and women - a model the patients have acquired as well. They admit sporadic conflicts with the parents related to their pathology. Each patient presents with a sexual orientation toward the opposite sex of their legal gender.

4. Current psychiatric status. Both patients have a common psychiatric chart with different characteristics. The differences are shown in table 2 (with reference to the results of hormonal tests). What they have in common can be summarized as follows: lack of psychiatric symptoms of intensity/ clinical relevance; cognitive level in the lower intelligence spectrum; mismatch between logical and reasoning ability performance, the ability to associate, compare and grasp the absurd, above the presumed level; low level of acquired abstract concepts; grammatical discourse above the presumed level; slightly impaired verbal fluency; acquisition of practical information and skills related to mechanical mechanisms, modern ones included, "F" being more adept in this regard; affective deprivation; compensation mechanisms by avoiding the home; harsh analysis of their circumstances; life plans are unrealistic; expectations about their future are linked with the success of the surgeries; they identify with their legal gender. A psychiatric diagnostic cannot be delimited based on the ICD - 10 criteria; clinically, it is estimated that "M" presents with a risk of personality structuring on the "borderline" model, while with "F" one can raise the issue of reactive, primitive behaviors, based on the noted structure.

5. Psychological examination (psychological interview, projective tests). In both patients the results were interpreted as expressing the primitive I, a projection of "monstrosity" awareness, hidden aggression, repressed depression, anxiety, efforts to adapt, shallow and ineffective real adjustment, severe risk of violent, explosive behavior; with "M" typical borderline traits stand out, while with "F", paranoid type ones.

Table 1. Hormonal investigations

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Patient &quot;M&quot;</th>
<th>Patient &quot;F&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteinizing Hormone (LH)</td>
<td>13.94 mIU/mL</td>
<td>24.3 mIU/mL</td>
</tr>
<tr>
<td>FSH</td>
<td>17.46 mIU/mL</td>
<td>35.4 mIU/mL</td>
</tr>
<tr>
<td>Serum Testosterone</td>
<td>13.75 ng/mL</td>
<td>51.63 nmol/L</td>
</tr>
<tr>
<td>Serum Estradiol</td>
<td>44.44 pg/mL</td>
<td>201.8 pmol/L</td>
</tr>
<tr>
<td>Sex hormone binding globulin (SHBG)</td>
<td>80.69 nmol/L</td>
<td>76.32 nmol/L</td>
</tr>
<tr>
<td>Anti-Müllerian hormone (AMH)</td>
<td>4.44 ng/mL</td>
<td>-</td>
</tr>
<tr>
<td>Serum Dihydrotestosterone</td>
<td>0.753 ng/mL</td>
<td>958 pg/mL</td>
</tr>
<tr>
<td>17 oh progesterone</td>
<td>2.4 ng/mL</td>
<td>-</td>
</tr>
<tr>
<td>Serum Androstenedione</td>
<td>2.81 ng/mL</td>
<td>4.27 ng/mL</td>
</tr>
<tr>
<td>DHEAS</td>
<td>297.1 mcg/dL</td>
<td>-</td>
</tr>
<tr>
<td>Total HCG</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 5. Urethroplasty stage I – immediate post-operative status. (transforming the scrotal hypospadias in proximal penile hypospadias and penile deflection).

Figure 6. Urethroplasty stage II using surrounding ventral penile skin, preoperative status.

Figure 7. Urethroplasty stage II using surrounding ventral penile skin. Post-operative status.
DISCUSSIONS AND CONCLUSIONS

Given the observed phenotypic traits, we consider both patients fall under the PAIS severity level number 3 according to the androgen insensitivity severity scale (Fig. 9) [after 9].

1. From the medical point of view, the only therapeutical solution is the surgical one, which consists in correcting the EG towards either the male or the female sex, depending on the severity of androgen insensitivity.

   In the "M" case study, it was intended to treat the gynecomastia, the orchiopexy and the hypospadias. The correction of the severe scrotal hypospadias requires a multistage approach. The penile deflection requires the use of penile foreskin to cover the ventral penile skin defect. On the other hand, the neourethra can be obtained from surrounding skin. If this is insufficient, one can use either dorsal foreskin flap or oral cavity (Bracka procedure) [10, 11]. For "M", the urethroplasty was performed in 2 surgical stages, using the urethral plate (stage 1) and ventral penile skin (stage two) with good results. Given the known risk of developing testicular germ tumors - 15% - if the gonad is positioned nonscrotally [12], it was recommended a periodic ultrasound monitoring once the testicles descended into the scrotum. Beta HCG and alpha-fetoprotein will also be checked regularly.

   Patient "F" (which came to the doctor for the first time at the age of 22) has expressed her desire to maintain her legal gender. The gonad ablation was performed, later to be followed-up with a reduction plasty of the clitoris and vaginoplasty.

   All types of androgen insensitivity are associated with infertility, with some exceptions for partial or moderate forms [13], as well as sexual dysfunction (impotence and lack of ejaculation)[14].

   1. From a multidisciplinary/interdisciplinary perspective, PAIS was approached through a trivalent
Table 3. Integrated / interdisciplinary medical synthesis (trivalent cybernetic model)

<table>
<thead>
<tr>
<th>ARGUMENTATION BY CLINICAL REASONING</th>
</tr>
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<tbody>
<tr>
<td>TRUE</td>
</tr>
<tr>
<td>✓ Genetic defect and incorrectable hormonal disorders; infertility;</td>
</tr>
<tr>
<td>✓ Unsupportive family, severe instructive – educational deficit, inadequate parental model, poor social, economic and cultural status;</td>
</tr>
<tr>
<td>✓ Sublimation with poor coping mechanisms, social marginalization;</td>
</tr>
<tr>
<td>✓ Passive/ dormant aggressiveness;</td>
</tr>
<tr>
<td>✓ Biological, psychological and social vulnerability;</td>
</tr>
<tr>
<td>✓ Successful surgical corrections – the only beneficial somatic, psychological and social factor</td>
</tr>
<tr>
<td>POSSIBLE</td>
</tr>
<tr>
<td>✓ Manifest aggressive behaviour, addictions, suicide, forensic implications;</td>
</tr>
<tr>
<td>✓ Failure of complex medical monitoring, due to lack of compliance;</td>
</tr>
<tr>
<td>✓ Malign transformation – testicular germ tumors</td>
</tr>
</tbody>
</table>

following a forensic and forensic psychiatry expertise at the request of the court (which has been required to act as such by the adult patient) in cases of hemraphroditism and transsexuality (except in cases of pseudohemaphroditism) as the legal gender must be changed as well. In this case, "F" requires changing/ correcting the anatomical sex so as to be aligned with the legal one, so a court order is not necessary. If hypothetically "F" required the legal gender to match the genetic gender, considering the above characteristics, major problems would arise that would require a different forensic and legal approach which is not yet provided for in the methodology for sex reassignment surgery (medical management of a PAIS patient consists in diagnosis as well as surgical correction as early as possible (before the age of 18). Theoretically, the two patients are at risk of violent behavior with possible future forensic consequences (more severe in "F"). The complex prevention possibilities are limited because they depend on factors that cannot be legally imposed. Moreover, in the event of criminally sanctioned behaviors (possible complication of the pathology), the defense usually requires a psychiatric forensic expertise to assess mental competency at the time the offense was committed. The genetic implications together with the psychological and social effects of the pathology will lead to disagreements regardless of the nature/ motivation/ cause of the crime scene.

6. Ethical aspects. The data presented lead to the conclusion that patients should be monitored from a multidisciplinary point of view. If the somatic field shows no ethical implications, these may occur for preventive psychiatric monitoring as there are no legal provisions in this regard. Analyzing the premorbid history and the social and economic level of patients, it results a low compliance of the family with the expert advice. Thus both patients represent cases of undertaken social risk for possible antisocial behaviors with criminal implications. Assigning the female gender to "F" cannot be considered a medical error, as the external genitalia at birth were ambiguous. The inconsistency between legal gender assigned at birth and genetic gender involve the well-known long-term health risks (risks of malignancy, infertility, etc.) as well as the assumed social risk of inappropriate, possibly criminal, behavior.

cybernetic model (true - false - possible), specifying vulnerabilities at all levels of personality structure (biological, psychological, sociological).

2. The biological dimension of personality in PAIS targets both sexual activity and the biological sub layer of aggression [15-17].

3. The psychological dimension research is more controversial (due to the limits in applying different scales and standards). Most studies have shown in criminal subjects (serious offenses of violence and assault) with no sexual endocrine pathology, a positive correlation between high testosterone and LH levels and psychological variables that would express manifest violent behavior [18]. Basal violent tendencies have not been analyzed and standardized, and studies which eliminate the differences of opinions are not enough in order to assess the passive/ dormant aggressiveness.

4. The sociological dimension is marked by the biological sub layer through a double mechanism of feed-before and feed-back. Vasopressin plays a key part in regulating complex social behaviors such as social recognition and constructive aggression. Major stress is discussed both from the perspective of maximum severity (individual preservation by life or health threat and species preservation by reproduction threat), and from the perspective of response to cumulative stress factors, based on the "untergrunt" - "hintergrunt" relationship model - trigger stress factor/ key experience and reactive effect through impulsive/ aggressive behavior. Stress affects personality, behavior and health, and has cognitive, physiological and social functioning consequences. Exposure to severe stress may lead to damage of the amygdala with secondary dysfunctionality [19,20]. The social and cultural dimension relates both to a "country" [21] pattern and to the concrete conditions of the PAIS children's development (educational level and parental support) [22-24].

The medical status of the two patients is summarized by a trivalent model approach in table 3.

5. The forensic aspects regarding legal gender identity. "F" genetically belongs to the male sex, but she was declared as female and was educated as such. Legally, in Romania, the sex reassignment surgery is performed
Summarizing, we emphasize that from a surgical standpoint, the prognosis is good; the success of the surgical interventions represent the only beneficial somatic, psychological and social factor. The earlier the diagnosis and the surgery take place (initiating surgical treatment in the first 2-3 years of life and continuing specifically into adolescence), the greater the benefit of surgery is. In the two cases presented, the psychiatric/ psychological/ sociological prognosis is cautious. Given the controversies in the reference literature on the forecast correlations between testosterone/ aggression, the fact that in this case the Department of Forensic Psychiatry of the INML (The National Forensic Institute) Bucharest carried out clinical and projective psychological examinations proved to be a beneficial solution in order to capture the elements of latent (masked / passive) aggression.

**Conflict of interest**

We declare that there are no ethical conflict of interest.

**Abbreviations.** AR = androgen receptor; PAIS = partial androgen insensitivity syndrome; "M" = patient with legal gender as male; "F" = patient with legal gender as female; 5-HT = serotonin; NA = noradrenaline; 5-HT1A = serotonin receptor; LH = luteinizing hormone; FSH = follicle stimulating hormone; EG = external genitalia.

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**References**