

Pseudo-Hermaphroditism: A Multi-Faceted Pathosis

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Abstract

Pseudo-hermaphroditism is a rare condition which has much mystique to it. It is generally due to a deficiency of the enzyme 5 α -reductase, responsible for the secretion and conversion of testosterone to dihydrotestosterone, which, in turn, defines the external genitalia during embryonic development. As a result of this, individuals present with ambiguous external genitalia, and do not have a defined idea of what their true identity is. One such example is present in Las Salinas, in the south of the Dominican Republic, where there is a growing minority of pseudo-hermaphrodites (1 in every 50 births), known as "guedoeces" which literally translates into "penis at 12". These individuals undergo a spontaneous change from female to male at puberty, which means that they are often brought up as females, but then become males at puberty. However, the issue not only lies in the physical changes that these individuals go through, rather it is a multi-faceted one that has deeply embedded psychological and psycho-social implications as well

Keywords: Pseudo-hermaphroditism; Male pseudo-hermaphrodite; Female pseudo-hermaphrodite; 5 α -reductase; Psycho social

Dominican Republic, where we have affiliations. Only pertinent data was extracted and included in the review.

Introduction

Pseudo-hermaphroditism is a rare condition which has much mystique surrounding it. It is due to a deficiency in the enzyme 5 α -reductase, which, during development, helps to define the external and internal genitalia of an individual. Individuals with a deficiency of the aforementioned enzyme present with ambiguous genitalia at birth, making it difficult to determine their true sex, until the secondary sexual characteristics develop at puberty.

These individuals possess the genotype of a male (XY) but dress and act as a female would, as they were brought up that way, and, therefore, have a different perception of themselves than what their actual genotypes dictate. These patients face many psychosocial hardships, as their perception of themselves does not agree with what society in general perceives.

Methods

A systematic review was performed from May 2014 - December 2015 employing the EMBASE and MEDLINE databases, identifying Cochrane reviews, controlled clinical trials, randomized control trials, meta-analyses and systematic reviews, discussing pseudo-hermaphroditism, and, in particular, the history of this rare condition.

The search terms used were: pseudo-hermaphrodite, male pseudo-hermaphrodite, female pseudo-hermaphrodite, 5 α -reductase, and humans. Articles that discussed pseudo-hermaphroditism were marked, and then reviewed by two reviewers for relevance and content.

Due to the lack of relevant information in the online databases, much effort went into finding information from non-catalogued sources in the libraries of Dr. Robert Reid Cabral Paediatric Hospital, and Dr. Padre Billini Teaching Hospital, in Santo Domingo,

What is Pseudo-hermaphroditism

The term "pseudo-hermaphroditism" is an expression used to describe an individual who possesses secondary sexual characteristics, also known as a phenotype, which are atypical, based on the gonadal tissue possessed (either ovary or testis) [1].

There are certain situations where the external genitalia look like an intermediate between the male penis and the female clitoris. It is due to these ambiguous genitalia that the parents of newborns born as such are confused about what the true phenotypical sex of their child is, and how to go about raising them, as a boy or a girl [1].

The term "male pseudo-hermaphrodite" is usually applied when testicular gonadal tissue is present. Despite these patients possessing the karyotype 46XY and having testis, they have secondary sexual characteristics that resemble a female or their external genitalia look like that of a female [2].

A "female pseudo-hermaphrodite" is similar to its male counterpart, in an inverted manner. Patients present with female gonadal tissue, the ovaries, and have the karyotype 46XX [1].

Conversely, the secondary sexual characteristics of these individuals resemble that of a male and they can even present with external genitalia that resembles a penis or the testes [2]. It is also important to distinguish the term pseudo-hermaphrodite from "true" hermaphrodite in order to avoid any form of confusion.

It is very rare for a Clinician to come across a true hermaphrodite, as the patient must present both forms of gonadal tissue, i.e. ovaries and testes, without any form of digenesis to either of them [1].

Both male and female pseudo-hermaphrodites can be classified as Intersex Syndromes, which are a group of different conditions where different atypical combinations of male and female physical characteristics and features are present [1].

History

In 1951, Dominican Physicians were aware about cases of hermaphroditism. However, during the early 1970s, the condition of male pseudo-hermaphroditism was found in an isolated village, known as Las Salinas in the South of the Dominican Republic [3].

Within this village, children who appeared to be girls turned into men, upon reaching puberty [4]. By age 12, these children were referred to as “guevodoces”, which literally translates as: “penis at 12”. Locally, they are also known as “machihembras”, which means, “part men part female” [4].

In the year 1971, investigation into the underlying etiology of pseudo-hermaphroditism began with Dr. Teófilo Gautier Abréu, and Dr. Luis A. Guerrero, Endocrinologists from the Division of Endocrinology at Cornell University, New York, United States. Dr. Guerrero mentioned the existence of pseudo-hermaphrodites in Las Salinas, Barahona, Dominican Republic to his director, Dr. Ralph E. Peterson, and Dr. Julianne Imperato-McGinley [3].

Dr. Peterson obtained approval from Cornell University to commence the study, but the consent from the Dominican authorities was still pending [5]. After much waiting, multiple correspondences, and a lot of red tape, Dr. Humberto Sangiovanni, Director of the School of Medicine and Dr. Manuel F. Pimentel Imbert, Dean of the Health and Science Faculty of Pedro Henríquez Ureña National University (UNPHU) agreed to approve the commencement of the study.

Later, they also successfully obtained the permission of the Secretary of State of Public Health and Social Assistance (SESPAS) to carry out the study. The investigation began in the year 1972 [5].

The first patients were studied in Robert Reid Cabral Paediatric Hospital, and in the same year at the Annual Reunion of Clinical Investigation in the United States in Atlanta, Dr. Teófilo Gautier Abréu and his group presented their first work, “Male Pseudohermaphroditism Secondary to 5 α -Reductase Deficiency” [2].

It was Dr. Julianne Imperato-McGinley who was the first in the group to think of the impact of the enzyme 5 α -reductase [2]. Later in the same year, they made their first publication in *Science* magazine (Vol. 186 p 11n, 1974) which marked the beginning of a series of investigations involving every type of patient who presented with genital ambiguity [4].

They learned that there was a hereditary component to 5 α -Reductase deficiencies, which explained why communities of pseudo-hermaphrodites exist in small clusters, such as in Las Salinas (1 in every 50 births) [4].

Furthermore, they were able to see the long-term effects of decreased 5 α -reductase production in these patients, which resulted in prostates which were smaller than average [2]. It was this finding that was picked up by pharmaceutical giant Merck, which allowed them to go on to develop Finasteride, a world-renowned drug which inhibits 5 α -reductase production, and is used to reduce symptoms felt by patients suffering from Benign Prostatic Hyperplasia [6].

In 1976, Dr. Teófilo Gautier Abréu decided to open a Clinic in the Dominican Republic for patients with ambiguous genitalia. The goal was to provide all patients with the condition access to Endocrinology service at Robert Reid Cabral Hospital, along with a number of sophisticated tests which would be analyzed in University laboratories in the United States [5].

Associated Etiological Factors

Genetic perspective

A study was conducted by The University of Texas South western School pertaining to the underlying causes of pseudo-hermaphroditism. Their study compared the properties of 5 α -reductase from the genital skin fibroblasts of 5 different patients [7]. Their study revealed that hereditary male pseudo-hermaphroditism results from deficient conversion of testosterone to dihydrotestosterone. Two specific mutations, that can cause male pseudo-hermaphroditism, were uncovered by the study [7].

Within the first noted mutation, the 5 α -reductase was immeasurable from a homogenate of epididymis removed from one of the patients, but it was found that the 5 α -reductase activity was normal, within intact fibroblasts and fibroblast extracts [7]. The k_m for testosterone appeared to be near normal levels, however, the k_m for NADPH was elevated approximately 40-folds above the normal ranges within these mutated cells. The enzyme is not protected against denaturation by increased concentrations of NADPH at 450°C that stabilize the normal 5 α -reductase, and enzymatic activity drops as protein synthesis is inhibited. Therefore, the first mutation can be attributed to an unstable enzyme [7].

The second mutant strain notes low levels of 5 α -reductase activity at the optimal pH and conditions for enzymatic activity and reactions [7]. It was also noted that the apparent k_m for testosterone was 20-fold higher than those which are normally found within controls. Therefore, this mutation arises as a result of lower enzymatic activity related to the decreased affinity of testosterone [7].

Male pseudo-hermaphrodites

Due to the disturbances or alternations in the enzymatic activity and affinity for testosterone, male pseudo-hermaphrodites undergo a number of developmental anomalies. As the enzyme androgen receptor is affected, a deficiency of the testicular substance responsible for the involution of the Mullerian duct is present [2]. This results in well-developed Mullerian structures, such as the fallopian tubes and uterus, to develop in conjunction with the normal male gonadal structures, such as the epididymis, vas deferens and the seminal vesicles which are derived from the Wolffian duct [2]. Associated conditions resulting from the conjunction of Mullerian and Wolffian components are bilateral cryptorchidism and inguinal herniation of the Mullerian components. Generally, the size of the penis in these patients can vary, but are usually very small [2].

Female pseudo-hermaphrodites

Female pseudo-hermaphroditism, similar to male pseudo-hermaphroditism results due to exposure of intrauterine androgens, both endogenous and exogenous, that leads to a marked masculinization of the secondary sexual characteristics of the female [2]. These characteristics usually begin to appear at puberty, where these females begin to develop muscular architecture similar to males and their voices deepen [8].

Clinical Case

A 38-year-old patient, originally from Samaná, Dominican Republic, arrived at Padre Billini Teaching Hospital, presenting with a right inguinal hernia and bilateral hydrocele. He reported that he had

noticed the swelling for the past ten years, and had discomfort in the right inguinal region of the genitalia [8]. The patient reported no past medical illness, and the family history was negative for any significant illnesses. However, the patient does remember being referred to Robert Reid Cabral Paediatric Hospital, at age 10, when he started to notice changes occurring in his external genitalia [8].

Upon physical examination, the patient presented outwardly with the characteristics of a male, which included a deep manly voice and a masculine physique, but had the clothing and certain mannerisms of those found in a woman [8]. Upon further examination, it was revealed that the patient had an absence of breast tissue growth and presented with ambiguous genitalia, which included: a micro penis, a hypertrophied clitoris, and a bifid scrotum that simulated the labia major. The presence of a hernia protruding in the right inguinal region of the patient was also observed [8].

The rest of the examination was insignificant, and a sonography, to assess the presence of internal genitalia was completed, and found the presence of testicular tissue in both inguinal regions. After completing the additional studies, the patient was admitted to surgery and, under local anesthetic, dissection of the right inguinal region was carried out.

The main highlights of the procedure included the discovery of a herniated sac, and undescended testicles with concomitant hydrocele. Utilizing the Bassini technique, an orquihydrocelectomy was performed along with a herniography [8]. The procedure was completed without any complications and the patient was discharged the same day, without any significant complications.

It was only two years later that the patient would return and wanted to become a “normal” part of society. Despite having the physical characteristics of a male, the patient felt as though he was a female.

The patient became quite happy when certain doctors came to the country and performed hormone therapy on him, allowing him to grow mammary tissue and the partial presence of a vagina. A pelvic ultrasound was administered on the patient to check for the possibility of internal female organs, but it came out negative. Rather, the studies showed that the patient had a hyperplastic prostate [8].

The patient then sought medical treatment in the United States, in hope that he could undergo an operation for a sex change to a female. However, the doctors had limited knowledge of this syndrome and the patient lacked any internal female organs. They recommended that the patient get a male sex change performed on his genitalia [8]. However, the patient refused and returned to the Dominican Republic.

Psychosocial Implications

Individuals suffering from pseudo-hermaphroditism do not have a defined idea of what their true identity is, and, therefore, they face a large number of different psychological and psychosocial implications.

When looking at the patient previously mentioned, one can see that he sees himself as a woman, despite having the genotype XY, and the characteristics of a male. He was born from a family that did not suffer from this genetic disorder, and they brought him up as though he was a girl. When his sexual desires awakened at the age of nine, he attempted to have sexual intercourse [8].

However, penetration was impossible, and when his partner wanted to retry penetration, the patient feared that his partner would be knowledgeable of his condition, so he declined the offer. Shameful of his difference and with a newly-lowered self-esteem, he became very

insecure. When he was ten years old, his body started to present a more masculine physique, which did not go in line with his psycho-emotional state [8]. This further led him to develop a severe state of depression, as he faced much ridicule and lost many friends due to the ignorance society presented, in understanding his true condition. Also, due to the rareness of the disorder, and lack of support present, the patient believed that he was the only one suffering from this condition, which made him feel as though no one would be able to truly understand him or be able to help him live out his true desires [8].

Trying to change his fate, and live the life he desired to have, as a female who could get married and bear children, he went to the United States for help. However, according to science, he was a man and they actually recommended that he undergo the surgery to be modified as a man [8]. Due to the fact that he was being regarded by the genotype that he presented, and not by his mental perception of himself, he refused to get the procedure done.

Instead, he decided to return to the Dominican Republic, where he got a sex change operation completed on himself, giving himself a more female physique [8]. Afterwards, foreign doctors helped him through hormonal treatment to develop mammary tissue and a partial presence of a vagina. Through these modifications, he felt more feminine and this motivated him to modify his actions to be more feminine, including the way that he combed her hair, etc. [8].

Looking at another case, one can see clearly how ignorance and negligence by the parents of these patients can lead to extreme psychological implications. A mother of three pseudo-hermaphrodite sons in Las Salinas, Dominican Republic stated how she never really classified her children as one gender or the other and would often dress them in clothing of both sexes, believing that they would assimilate into whatever gender they felt was better [3].

One child of hers, who suffers from the condition, mentally believes that “she” is a female, despite her clearly masculine physique. Despite dressing as a female and acting in a similar fashion, she is allowed to work in a moving company, doing strong manual labour, work which is considered to be done solely by male workers in the Dominican Republic. This shows that her poor upbringing has not allowed her to truly define her gender and she is comfortable playing a dual role in society, as both a male and a female [3].

Several blocks down the road from their house lives the oldest of the pseudo-hermaphrodites in the Dominican Republic. At the age of 70, he remains indifferent of his sexual condition, and says, “even if the people speak a lot about me behind my back, I never questioned anything, as they are things pertaining to God” [3]. Nevertheless, at the age of 40, to the shock of many, he got married and adopted his wife’s children from her first marriage [3]. His wife assures that there are no problems in performing intercourse, though she does note that her husband does have the regret and a form of incompleteness inside himself because he was not able to conceive children of his own.

Other patients know that something is wrong with them and they want to make things normal. In the case of a young woman of 23 years, she really faced reality when she decided to break her marriage of 3 years [3]. Her mother, out of ignorance, never took her to a gynaecologist and, she was thus, unaware of her situation. Conscious that something must be out of the ordinary, she sought out a specialist, which confirmed her disorder at the age of 20. According to her sister, “she left her husband, cut her hair, and now dresses as a man, and it has been 2 years since she opted for operation” [3].

Discussion

Evidenced above, one can see that the Intersex Syndromes, Male Pseudo-hermaphroditism and Female Pseudo-hermaphroditism, are multi-dimensional disorders that subject the patient to a number of different stresses within their lives, such as finding their own true identity and being able to integrate into society without being ridiculed or belittled by their colleagues or friends.

While there is an increasing presence of Intersex Support groups, and related entities, both privately and governmentally funded, present in advanced first world countries such as the United States, Canada, the UK, and Australia, the vast majority of the world still lacks those facilities, leading to many repeated cases similar to those mentioned above. Despite having support groups present, their scope is still limited, and many patients shy away from these groups, and do not receive the help and support that they desperately yearn for [9].

Clearly, the upbringing of a patient plays a large factor in how they perceive themselves, along with their socioeconomic background, as the patient may not have the financial means to get medical advice or diagnosis for their condition until later on in their lives when the psychological damage is already done.

In the year 2001, a meeting took place in Houston, Texas, where a psychologist, urologist, geneticist, endocrinologist, and a specialist in bioethics had the mission to advise parents, who give birth to children with this disorder, to let their children live with an “undefined” sex [9]. They believe that the children will then decide for themselves, which gender best suits them. According to the psychologist Mónica Intraub, “the manner that we acquire a gender identity is enormously complex”, and parents should not interfere in this complex processing, as they are not aware of the true desires of the child, and what they are truly inclined to be [9]. This signifies that the baby can be seen as a “subject” and has the opportunity to choose, when it can understand the situation. This is an innovating vision that differs from the vision in which people are “fixed” under a gender since early stages, and

hopefully, it helps these individuals to be at peace, both internally and in society.

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Disclosure

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