Pituitary Macroadenoma in a Girl with Male Karyotype: A Rare Case Study

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ABSTRACT

Macroadenoma is a tumor that typically develops in the epithelial cells of the pituitary gland. Patients suffering from the condition are often asymptomatic with complaints that are caused by hormonal imbalance. Therefore, chromosome analysis needs to be done to females aged >16 years presenting with amenorrhea. Karyotype 46,XY is a disorder of sex development (DSD) that is caused by the complex process of gene interactions, androgen synthesis, and hormone regulation.

The patient initially came to the hospital for a scheduled transsphenoidal surgery due to pituitary macroadenoma, and later complained of primary amenorrhea and atypical external genital. Furthermore, physical examination of genitalia revealed mild clitoromegaly without obvious introitus vagina. Laboratory testing showed elevated prolactin and testosterone level, while ultrasonography imaging revealed the absence of the uterus and ovaries. The brain magnetic resonance imaging (MRI) demonstrated a pituitary adenoma, and cytogenetic analysis showed 46,XY karyotype. Subsequently, hyperprolactinemia, imaging, and histopathology examination were used to confirm pituitary macroadenoma in the patient. It was assumed that the undermasculinized genitalia was caused by hormonal disorders including the deficiency of androgen action or 5-alpha-reductase enzyme. 46,XY DSD has many different symptoms, hence, clinicians need to be aware of potential multifactorial aetiologies. Imaging of internal genitalia, hormonal and chromosomal analysis should be carried out to assess patients with unknown causes of the disorder. Molecular analysis needs to be carried to exclude the possible gene mutation.

Keywords: *Disorder of sex development (DSD), primary amenorrhea, pituitary macroadenoma.*

INTRODUCTION

Disorder of sex development (DSD) is a condition that is characterized by atypical development of chromosomal and gonadal/ anatomical sex organs,[1-6] and it occurs in the ratio of 1: 2500-5000 live births.[6,7] Furthermore, it appears in various forms at different ages,[8,9] and is classified into three main categories, namely 46,XYDSD; 46,XX; and sex chromosome DSD.[1,7,10] Phenotypes of patients with 46,XY DSD range from female external genitalia to atypical male phenotype with testicular regression.[4,5,11,12] The victims generally seek medical attention, which is often delayed until puberty or a later time due to the lack of breast development and/or primary amenorrhea.[13] Meanwhile, the underlying cause of the disorder can be attributed to gene mutations complex process, androgen synthesis disorders as well as hormone regulation. Further tests, such as hormonal, imaging, and cytogenetic analysis, which complement physical examination are necessary to establish a diagnosis of the condition.[2,7,14] The genetic aetiology of most cases of the disorder is heterogeneous, hence, it remains debatable whether every patient with 46,XY DSD needs to experience parallel sequencing of a wide range of genes.[15]

A complete family history, including pedigree and history of consanguinity, is important and need to be carefully reviewed in cases of DSD.[2,7] Furthermore, physical examination of secondary sex characteristics by Tanner staging and a detailed assessment of external genitalia anatomy by Quigley staging are the first steps for its diagnosis. Laboratory evaluation for FSH and LH are needed to observe the pituitary function. Loss of LH and FSH causes amenorrhea, which is characterized by hypogonadotropic hypogonadism. Prolactin and testosterone level tests are also needed to confirm the diagnosis of the disease. Meanwhile, elevated prolactin level is a symptom of pituitary tumor.[2] Laboratory testing for FSH, LH and prolactin levels help to determine the endocrine system's role in the pathogenesis of primary amenorrhea symptoms. Ultrasonography of the pelvic region is used to confirm the presence or absence of female reproductive organs as well as to locate the gonads.[16]

Pituitary adenoma is the third most common brain neoplasm, and it accounts for approximately 15% of all primary brain tumors.[17,18] Furthermore, the increased tumor size produces many symptoms, such as headache, visual defect, olfactory dysfunctions, and various hypopituitarism manifestations. Headache and visual defects are the most common symptoms that occur in 40-70% of patients. Brain MRI (Magnetic Resonance Imaging), ophthalmologic monitoring, and hormone tests are needed to evaluate a pituitary tumor. However, brain MRI is the most sensitive tool to assess the pituitary gland.[18]

Primary amenorrhea has several causes, and chromosomal abnormalities are the most common cause, which account for 40% of cases.[16] Therefore, cytogenetic analysis needs to be performed to evaluate chromosome aberration. This is a case study of a patient who was diagnosed with primary amenorrhea and atypical external genitalia after experiencing transsphenoidal surgery to treat pituitary macroadenoma.

CASE ILLUSTRATION

A 43 years old woman [II.9] was referred to Dr. Kariadi province referral hospital for evaluation of primary amenorrhea. The patient's weight and height were 50 Kg and 157 cm, respectively, with a body mass index of 20,28 kg/ m^2. Furthermore, there was no family history of the condition, as shown in **Figure 1**. The patient also experienced visual disturbances on the right eye since the previous year, which slowly got worse. Visual acuity test using Snellen Chart was on the right eye showed a value of 2/60 and left eye >3/60. Patient also did not complain of headache.

On physical examination, the patient had no female breast development, as seen in Tanner stage 1, while pubic and axilla hair growth was normal, as seen in Tanner stage 5. Inspection of the external genitalia showed normal labia majora and minora. However, mild clitoromegaly and a small perineal opening without obvious introitus vagina were detected. There was also a 2 cm palpable mass that is similar to testes in the left side of labia majora, as shown in **Figure**

2. Based on an interview with the patient and family, the genital ambiguity occurred right from birth.

Laboratory testing revealed an elevated prolactin level of 686.83 ng/mL as well as an increased testosterone level of 85.03 ng/ml. Furthermore, the patient had a normal FSH, LH, and thyroid profile with values of 16.6 mIU/ml, 4.01 mIU/ml, and 15,52 ρmol/L, respectively. **Table 1** shows the result of the hormonal assay.

The pelvis ultrasound imaging showed the complete absence of internal genital organs, namely uterus and ovaries. The initial brain MRI demonstrated a pituitary macroadenoma, which extends to the right parasellar (AP 2.71 cm x CC 2.81 cm x LL 2.72 cm), thereby causing an encasement on the right internal carotid artery and compression in the intracranial part of the right optic nerve and optic chiasm. However, there was no bleeding or sign of elevated intracranial pressure, as shown in **Figure 3**.

Transsphenoidal surgery was performed, which revealed that the tumor was a pituitary macroadenoma. The histopathological microscopic examination of the excised tumor also showed that the hypercellular mass contains medium cells that formed a solid structure bonded by connective tissue and blood vessels. Furthermore, the pseudorossette structure contains polarized cells with elongated cell processes as well as a round or oval nucleus, mild pleomorphic, and stippled chromatin with sparsely granulated cytoplasm. The mitotic structures were difficult to locate, and there were also tumor areas with fibrosis as well as inflammation of lymphocytes, histiocytes, macrophage, cellular organization, prolonged bleeding, and cystic degeneration. However, there were no visible areas of necrosis and no sign of malignancy on the preparation. The histopathological features were consistent with pituitary macroadenoma accompanied by chronic degeneration and inflammation.

Table 1. Hormonal profile of the patient with primary amenorrhea

Hormone	Result	References range
Testosterone in ng/ml	85.03	10.83-56.94
FSH in mIU/ml	16.6	Follicular phase : 3.03-8.08 Mid-cycle peak : 2.55-16.69 Luteal phase : 1.38-5.47 post menopause females without HRT : 26.72-133.41
LH in mIU/ml	4.01	Follicular phase :1.80-11.78 Mid-cycle peak : 7.59-89.08 Luteal phase : 0.58-14.00 Post menopause females without HRT*: 5.16-61.99
Prolactin in ngmL	686.83	5.18-26.53
TSHs in μIU/mL	3.41	0.51-4.94
free T4 in ρmol/L	15.52	10.6-19.4

*HRT: hormone replacement therapy

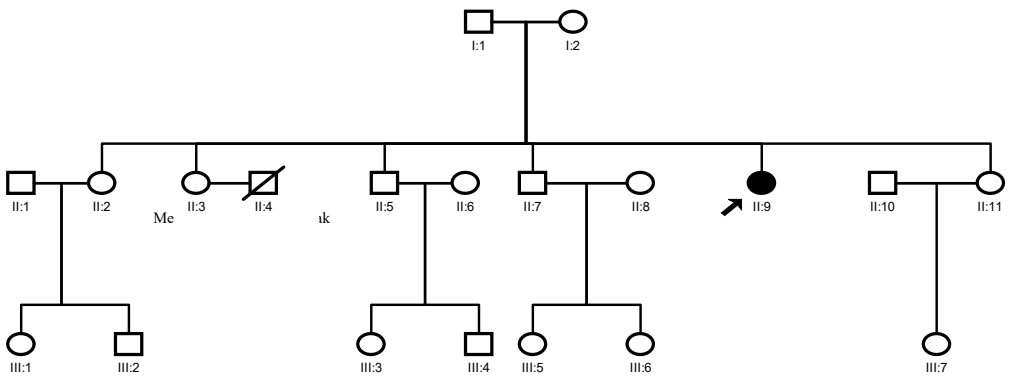

Figure 1. Pedigree of the family showing no family history of the same condition. Circles represent females and squares represent male gender. A slash through the symbol indicates that the family member is deceased. Open symbols are unaffected, while the filled circle denoted by an arrow represents the affected patient [II.9].

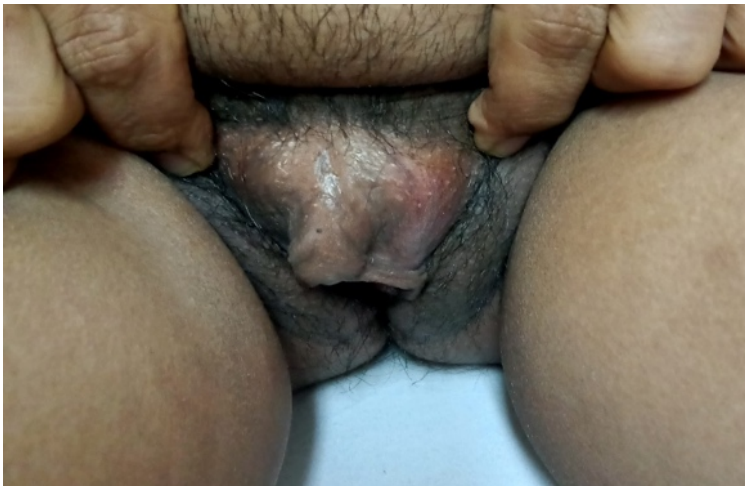

Figure 2. Physical examination of the external genitalia showed normal labia majora and minora. Mild clitoromegaly was detected with a small vaginal-introital opening without obvious bulging of the hymen. A 2 cm palpable mass that is similar to testes was found in the left side of labia majora, while the pubic hair had normal growth, as seen in Tanner stage 5.

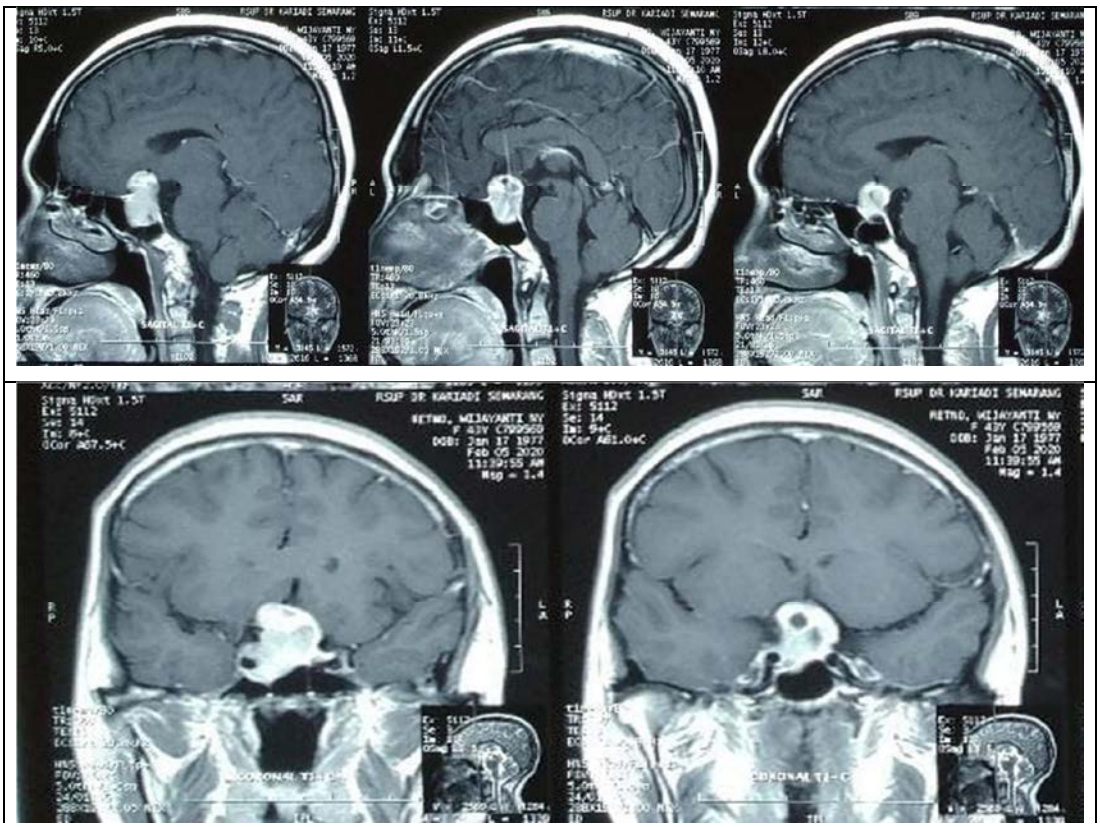

Figure 3. Brain MRI on the first admission. Preoperative MRI revealed a pituitary adenoma, which extends to the right parasella (AP 2.71 cm x CC 2.81 cm x LL 2.72 cm) causing an encasement of the right internal carotid artery as well as compression in the intracranial part of the right optic nerve and optic chiasm. There was no bleeding or sign of elevated intracranial pressure.

Cytogenetic examination was carried out, which indicated a male karyotype 46,XY without structural and numerical abnormalities. Meanwhile, during hospitalization, the patient was monitored daily and Diabetes Insipidus (DI) occurred 3 days after the surgery with polyuria >3 L a day. The DI was transient and recovered in the first postoperative week.

We followed up the patient for three months after the surgery and there was no recurrence of tumor, as shown on the MRI.

Ophthalmological examination showed right-sided visual impairment and bitemporal visual field defect. The neurological examination was normal as well as the muscle power of extremities for both sides (grade 5/5).

DISCUSSION

Aetiology of patients with 46,XY DSD undermasculinized male is associated with enzyme disturbances that occur during testosterone synthesis as well as androgen insensitivity syndrome, deficit of 5-alpha-reductase enzyme, gonadal dysgenesis, and ovotesticular DSD. Meanwhile, some of the 5α-reductase deficiencies are often misdiagnosed as androgen insensitivity syndrome because they have a similar clinical phenotype, while others escape recognition completely.[19,20]

Diagnosis of the disorder is established by assessing the patient's family history, physical examination, hormonal analysis, imaging, and cytogenetic analysis.[2,21] In this case, the diagnosis was made based on the clinical manifestations and available laboratory investigations.

The symptoms of the patient include primary amenorrhea, phenotypic female external genitalia, lack of breast development, and mild clitoromegaly. Meanwhile, mild clitoromegaly was found at birth but the primary amenorrhea was diagnosed late. 7% labial and/or clitoral anomalies were also observed in the patient.[22] There was a small mass in the left side of the labia majora, which was similar to the shape of a testis, while on the right side, there was no palpable mass. Consequently, it was assumed that the right testis was located in the inguinal or intra-abdominal region. Male gonads are palpable in the majority of 46,XY DSD cases depending on the location of the external genitalia.[11] Some of the clues used for the diagnosis of DSD in older patients include unrecognized genital ambiguity, delayed or incomplete puberty, and primary amenorrhea.[16,22,23]

Ultrasonography imaging is an effective diagnostic tool used to identify the presence/absence of uterus and ovaries in 46,XY DSD cases. Furthermore, females with only primary amenorrhea caused by pituitary dysfunction often have a normal uterus. Detailed study on the patient revealed that there was no sign of uterus and ovaries, which indicates the absence of female internal reproductive organs. LH, FSH, and TSH levels were then evaluated to assess the pituitary function, and the result showed that the patient had normal pituitary hormone levels.

The 5-Alpha-Reductase Deficiency (5-ARD) is a rare autosomal recessive symptom of 46,XY DSD caused by mutations in steroid 5α-reductase 2 (SRD5A2).[24] The deficiency was suspected in this case because of the characteristic phenotype and increased testosterone level. Furthermore, testosterone cannot be converted to dihydrotestosterone (DHT) at the external genitalia target cells of a patient with the condition. DHT is required for normal masculinization of the external genitalia, and the patient had an elevated testosterone level of 85.03 ng/ml. Meanwhile, the testosterone level ranged from 35 to 84 in other studies. Diagnosis of mutation in 5α-reductase enzyme can be made by DNA analysis, but it was not performed in this case. The diagnosis of 5α-reductase deficiency was assumed to be based on the patient's clinical presentation and hormonal assay, which revealed an elevated testosterone level. Furthermore, the 3 generation pedigree shows that there was no consanguinity and no other member was affected, hence, the ARD was bearable. Gonadal dysgenesis is characterized by a low testosterone level,[19] but this current case was different.

Complete Androgen Insensitivity Syndrome (CAIS) cases often have a history of primary amenorrhea,[2] and female patients usually have a normal-looking clitoris, vaginal introitus, labia minora, and labia majora. Depending on the severity of androgen resistance, the clinical features also vary with unilateral or bilateral gonads that can be located anywhere along the path of embryonic testicular descent. However, patients with CAIS can be distinguished by adequate breast development and X-linked pattern of inheritance.[7,12,14] Breast development and pubertal growth spurt are normal because testosterone was aromatized to estrogen in the circulation.[2] CAIS causes the production of

testosterone, but androgen action is deficient because of mutations in the androgen receptor (AR) gene. Therefore, molecular sequencing of AR gene is needed to identify mutations in 90-95% cases.[2,15,22,25]

DSD was suspected in the patient due to the presence of clitoromegaly, tanner stage 1 no breast development, and palpated gonad in the left side of labia majora, hence, clinicians are advised to perform a cytogenetic examination to determine the karyotype and gender assignment when needed. CAIS and gonadal dysgenesis are characterized by the presence of female external genitalia.[5] Meanwhile, the absence of virilization results in female–typical genitalia was strictly linked to the androgen action and AR function. Both adrenal and ovarian androgens facilitate the growth of axillary and pubic hair in girls. Therefore, any type of alteration along the androgen pathway can lead to impaired virilization. Patients with the syndrome normally develop testes due to the presence of the SRY region and they also produce testosterone whose action is not effective because of the AR gene mutation. Therefore, they lack male genitalia, except for testes. The hormonal profile of CAIS patients is characterized by high LH and normal FSH levels, while testosterone results are typically within the normal male range but increase relatively to the female range.[25]

There was an elevated prolactin level in the patient due to prolactin-secreting pituitary macroadenoma. Meanwhile, the adenoma accounts for 85% of tumors in the pituitary gland,[26] and it affects approximately 20% of the general population.[17] In this present case, brain tumor is a pituitary adenoma that was caused by hyperprolactinemia. A pituitary macroadenoma was revealed after transsphenoidal surgery, and there was a positive relationship between hyperprolactinemia and visual changes. Several etiopathogenetic hypotheses have been proposed to explain brain tumors and primary amenorrhea. One of the pathological causes of hyperprolactinemia is pituitary adenoma.[27]

At the time of diagnosis, the patient complained of visual disturbance, which was in the form of decreased visual acuity in the right eye due to a pituitary macroadenoma that compressed the intracranial part of the right optic nerve and optic chiasm. Furthermore, compression of the visual pathways causes a disturbance in the visual functions, such as a slow progressive visual loss.[17]

The patient developed DI with polyuria >3 L a day, which was transient 72 hours after surgery, and recovered over the next couple of days. Meanwhile, DI, which can either be transient or permanent is a common complication that occurs after neurosurgery of the pituitary gland, specifically with the transsphenoidal approach.[28,29] Most cases of the disease were transient and the patient recovered within 2 weeks of post-operative.[28] It is usually caused by mild-reversible injury to the pituitary stalk.[29]

After 3 months follow-up, MRI showed that there was no recurrence of the tumor. Meanwhile, the recurrence rate in patients with pituitary adenoma 4 years after surgery was 22%.[17] The recovery of visual function usually correlate with time, but there was a slow improvement of the right eye in this case.[17]

The clinical management of 46, XY DSD patients includes prophylactic gonadectomy, which needs to be carried out due to an increased risk of gonadal malignancy.[11,21] Furthermore, patients with abdominal gonads have a high risk of germ-cell tumors development[30] with an incidence rate of approximately 25-33%.[23]

Another appropriate management of XY female with the disorder includes hormonal therapy and psychological counseling.[14] Optimal care of the condition also requires a multidisciplinary approach.[4,5,23] Psychological counseling for the patient is important, specifically when they experience gender dysphoria after being diagnosed with DSD.[8,12,23]

The presence of female external genitalia and mild clitoromegaly since birth as well as visual disturbance that was observed lately in a single patient is a rare combination, and it indicates the possibility of a dual diagnosis. Therefore, further examination is needed to determine whether the atypical genitalia and pituitary macroadenoma contributed to the disease condition. This rare coexistence of 46,XY DSD with pituitary macroadenoma was assumed to be a coincidence, hence, a case study was carried out. However,

there were some limitations because molecular observation was not carried out.

CONCLUSION

Based on the results, 46, XY DSD has many different symptoms, and this case highlighted the atypical genital and primary amenorrhea, which were caused by various factors, hence, a multidisciplinary approach was carried out. Furthermore, chromosomal analysis is important to assess the genetic factor and sex assignment of patients with the disorder. Hormonal problems in the central pituitary gland can also be considered in some cases.

Although the precise mechanism was not determined with advanced molecular analysis of 46,XY DSD in the patient, a dual diagnosis is still impossible. This case study is expected to provide valuable insight on the approach that can be used to manage the disorder.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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