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Medicine

Anomalies of Sexual Differentiation in the Medicine and Endocrinology Department of the Mali Hospital - Bamako

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Abstract **Original Research Article**

Introduction: Abnormalities of sexual differentiation are conditions due to various congenital or hormonal etiologies. The aim of our study was to describe the clinical aspects of sexual differentiation abnormalities in the department of medicine and endocrinology. ***Methodology***: Our study was retro-prospective and descriptive ranging from September 2011 to July 2021 (i.e. 10 years), carried out in the Medicine and Endocrinology department of the Mali Hospital. ***Results***: Ten patients out of 8213 consultants were collected, representing a hospital frequency of 0.12%. Six (6) of them were of female phenotype, and 2 of male phenotype. The average age was 21.71 years with extremes ranging from 17 days to 46 years. Clinically, patients with a female phenotype presented an anomaly of the external genitalia (5/10), axillary and pubic hypopilosity (6/10), delayed puberty (5/10), primary amenorrhea (5/10), and the presence of a bilateral inguinal mass (2/10). For patients with a male phenotype (2/10); bilateral gynecomastia (2/10), macroskelia (1/10) with wingspan of 197cm, axillary and pubic hypopilosity (1/10), an anomaly of the external genitalia (2/10). ***Conclusion***: anomalies of sexual differentiation, although relatively rare, exist in Mali and throughout the world.

Keywords: Anomalies, Sexual differentiation, Mali Hospital, Bamako.

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1. INTRODUCTION

Disorders of sexual differentiation are rare intersex conditions characterized by a mixture of varying proportions of male and female sexual characteristics. According to the new nomenclature we no longer speak of sexual ambiguity but of anomalies of sexual differentiation (disorders of sex development), this classification is based on the karyotype.

This differentiation results from the succession in a precise chronological order of several events which take place from fertilization which determines the genetic or chromosomal sex (XX, XY), until the realization of the phenotypic sex: male or female.

During this sexual differentiation, the action of hormonal secretion of the gonads (ovaries and testes) and the sensitivity of the target tissues to these secreted hormones also intervene. Any error appearing during these different stages leads to a discordance between the internal genital organs, the external genital organs and the secondary sexual characteristics (hairiness, hoarseness of the voice, musculature). The diagnosis is generally made at birth due to abnormal external genitalia, but it can be much later at the age of puberty due to delayed puberty, amenorrhea or the appearance of sexual characteristics discordant with the assigned civil sex. During these conditions, the phenotype observed is not often the translation of the karyotype present on the one hand, and on the other hand there may be a discordance between the karyotype and the type of gonad found [1-3]. The prevalence of these conditions varies depending on the method of recruitment [4-6]. Diagnosis must be early to avoid an error in attribution of non-compliant civil status, the subsequent modification of which can have psychological and social consequences

for the patient and his family [7-9]. In Mali a few isolated cases have been reported, respectively Diallo MM found 0.23% [10] and SIDIBE AT and Col found 0.54% [11] unlike Tunisia, India, and the USA [2, 4, 5]. The aim of our study was to describe the clinical aspects of the anomalies of sexual differentiation encountered in our hospital practice, in the medicine and endocrinology department at the Mali hospital.

2. METHODOLOGY

We conducted this study in the medicine and endocrinology department of the Mali hospital. This was a retrospective and descriptive study spanning from December 2011 to July 2021 (i.e. 10 years). All patients (regardless of age and sex) hospitalized or seen as outpatients in the medicine and endocrinology department of the Mali hospital presenting one or more congenital anomalies of the genital organs were included in this study and /or secondary sexual characteristics inconsistent with the declared sex.

In the retrospective study, we used the clinical files, the other patients had a prospective clinical examination covering the morphotype, the genitals, the condition of the breasts, the axillary and pubic hair, the height, the weight, age.

The additional examinations consisted of carrying out:
Specific:

- Abdominopelvic ultrasound to look for abnormalities of the OGI, high testicles and associated urinary tract anomalies.
- Karyotype: looking for chromosomal abnormalities.
- Plasma hormonal dosages (LH, FSH, β-HCG, testosterone, prolactin, estradiol, etc.).
- Other plasma hormone measurements (17-OH progesterone, 17-OH pregnenolone, pregnenolone, ACTH, Dihydroepiandrosterone).
- Research gonadal histology search for histological abnormalities.

Non-specific:

- Blood dosage of TT4, THS us, sodium, potassium, CBC, blood sugar, creatinine,
- Wrist X-ray to determine bone age
- X-ray of the pelvis

The data were collected on an individual survey form, analyzed using SPSS 20.0 software. For comparisons, we used Fischer's exact test with a probability $p<0.05$.

Free and informed verbal consent was obtained from patients before their inclusion in the study. The patient's refusal not to participate in this study in no way prevented his treatment and follow-up in the center. The information given by each patient was completely confidential and would not have been disclosed. They were used for research purposes only. The personal information concerning each patient was coded by a number which did not allow the patient to be identified when the results of the study were published. For the retrospective collection, anonymity was used for each patient.

3. RESULTS

3.1. Medical Observations

Medical Observation 1

RCD newborn, 8 days old, resident in Bamako, referred to endocrinology for sexual ambiguity at birth.

ATCD Gyneco-Obstetrics (mother): primigravida, primiparous Absence of parental consanguinity.

Absence of androgen intake during pregnancy.

Absence of long-term corticosteroid use during pregnancy.

No digestive problems or vomiting in the child at birth.

Physical Examination: OGE: genital bud of 2.5 cm (Prader stage), Fusion of the labia majora and minora in the form of bursae, Presence of a vaginal opening, without perineal lesion or palpable testicles at the level of the lips. Absence of hyperpilosity in androgen-dependent areas.

Paraclinical Examinations: Natremia: 138mEq/l (N=136-145); Potassium: 7.22mEq/l (high) (N=3.30-7.40), Chloremia: 109 mEq/l (N=96-108), Fasting blood sugar: 0.72g/l (N=0, 70-1.10), Calcium: 105mg/l (N=90-107), Phosphoremia: 82mg/l (N=25 - 45), 8h cortisol: 29ng/ml (N = 60-285), Testosteronemia: 1.4ng/ml (high), serum LH: 10.2 IU/l (N=1.5-8), serum FSH: 21.7 IU/l (N=2.9-12), 17beta-estradiol : 16pg/ml (N=20-150), 17OH progesterone: 60ng/ml (N=0-14.13). Karyotype on day 22: 46XY.

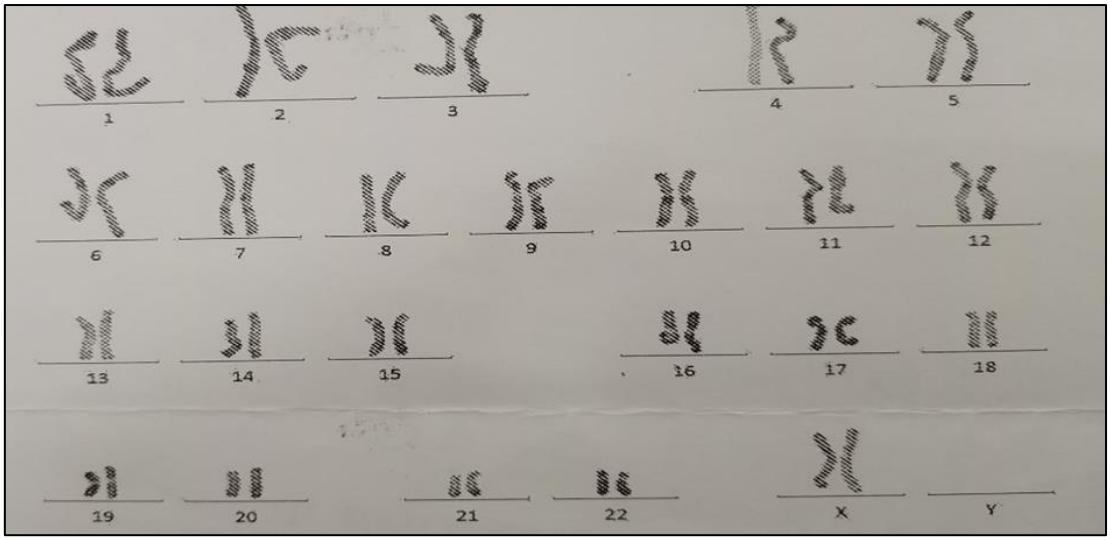


Figure 1: 46 XY karyotype

Abdominal ultrasound on day 9: Absence of biliary-hepatho-pancreatic lesions.

Diagnosis Retained: Congenital adrenal hyperplasia due to 21 Hydroxylase deficiency

Treatment: She received hydrocortisone tablets at a rate of 12 mg/m2/day or 49.18 mg/day divided into 3 doses per day: 30 mg in the morning, 15 mg at midday and 5 mg at 4 p.m.; which tablets are administered dissolved in a teaspoon of water for 5 days and Fludrocortisone at a rate of 150µg/day in one dose then strict monitoring of signs of dehydration which could lead to a syndrome of loss of stools has been done.

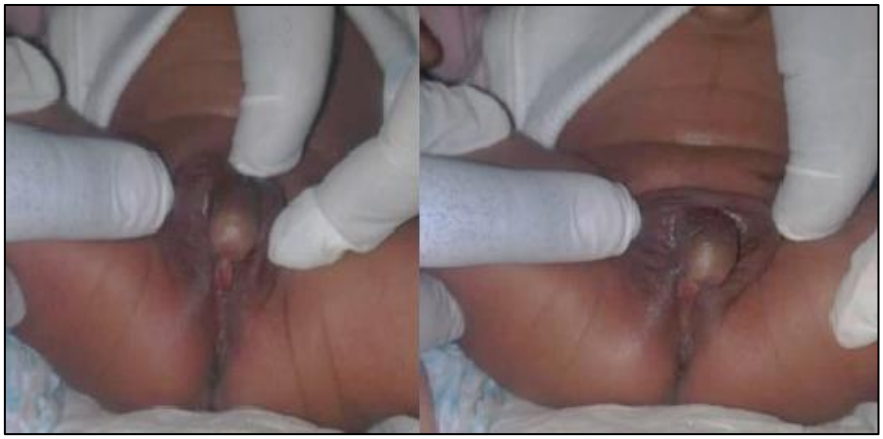


Figure 2: Absence of palpable gonads **Figure 3: Presence of a small vaginal opening**

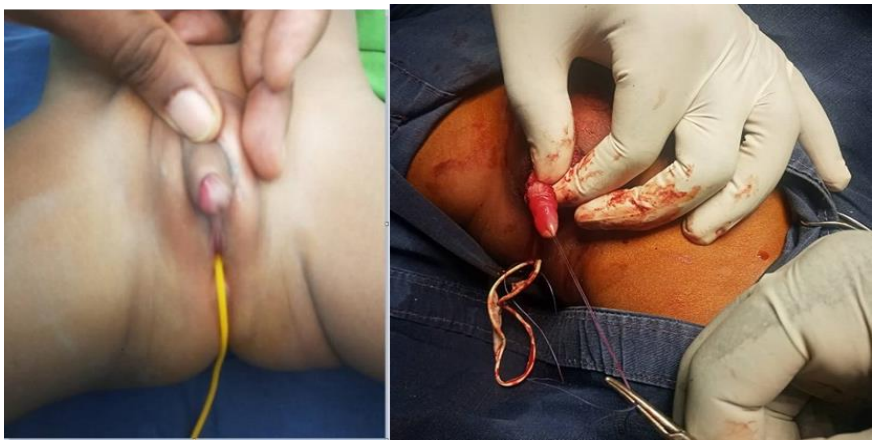


Figure 4: Clitoridoplasty images

Medical Observation 2:
Ms. RD, housewife, F/M, 23 years old, lives in Kayes.

Reason for consultation: primary amenorrhea.

History of the disease: onset dates back to 11 years, marked by the presence of two small lumps under the pubic bone on either side. The current episode dates back 12 months, punctuated by the difficulty of having a satisfactory sexual relationship (married 1 year ago). It signals an absence of menstruation, hoarseness of the voice.

Medical and personal history: unknown Medical and family history: unknown.
Gyneco-obstetric history: nulligest (primary amenorrhea), pubarche: 14 years-15 years.

General examination: weight: 52kg, height: 1m67, BMI: 18.70kg/m² Male morphotype with breasts: S2, pubic hair: P2
Urogenital system: Two large testicles (20ml according to Prader), blind vagina 1.5cm deep.
Skin examination: diffuse hairs on normally hairless areas in women.

The rest of the examination is unremarkable.

Paraclinical examinations:
Serum LH: 37.5IU/ml, FSH: 52.2IU/l, Testosteronemia: 2.1ng/ml (0.10-O.90);
Karyotype: 46XY; 17OH progesterone: 1.67ng/ml; Pelvic ultrasound: absence of internal genital organs.

Diagnosis: Morris syndrome or androgen insensitivity
Treatment: removal of testicles and androgens

Figure 5: Female morphotype front view rear view

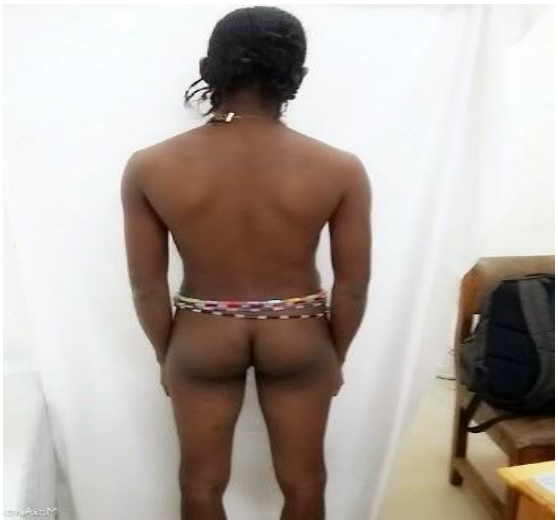


Figure 6: Female morphotype

Figure 7: Axillary hair

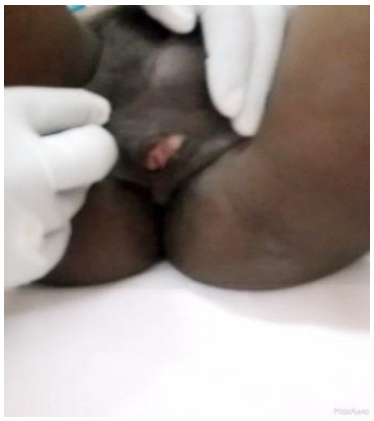


Figure 8: Blind Vagina

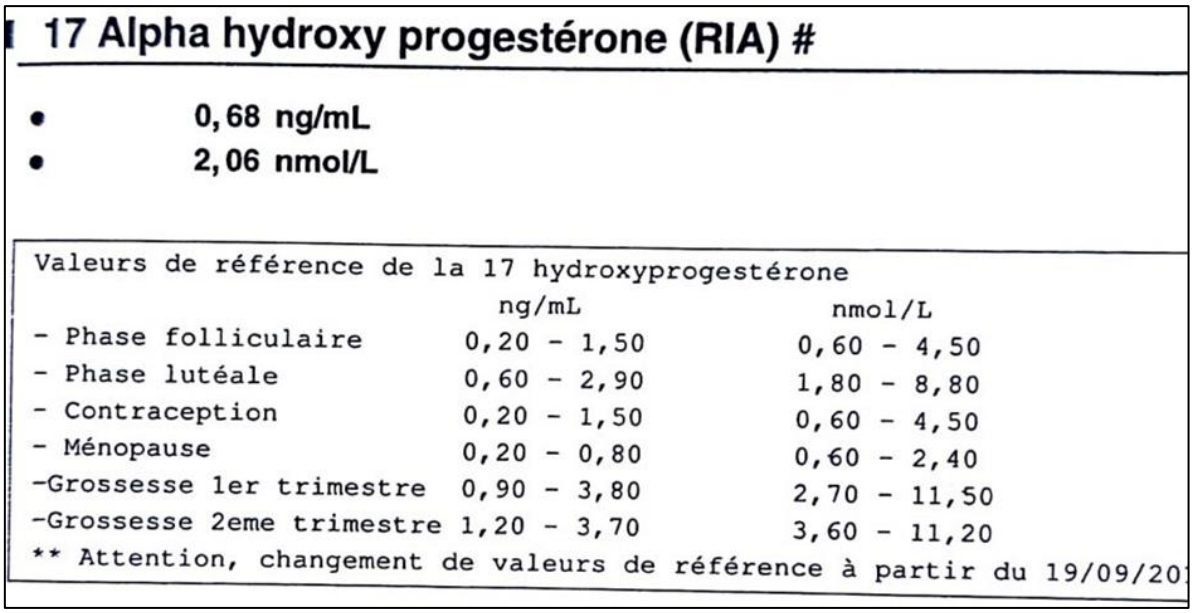
Figure 9: Bilateral inguinal mass

Medical Observations 3:
Ms. MZ, student, F/M, 18 years old, lives in Bamako.
Reason for consultation: primary amenorrhea.

History of the disease: it began when he was 13, marked by the presence of two small lumps under the pubic bone on either side.

The current episode dates back 3 months, marked by the occurrence of an incident between the patient's parents regarding her sexual orientation.

Medical and personal history: unknown Medical and family history: unknown.
Gyneco-obstetric history: nulligest (primary amenorrhea); Pubarche: 15 years.
General examination: weight: 58 kg, height: 1.77 m, BMI: 19.39 kg/m²; Male morphotype with breasts: S0 Hair: P2
Urogenital system: Two large testicles (20ml according to Prader), blind vagina with 1.3 cm deep.
Skin examination: diffuse hairs on normally hairless areas in women. The rest of the examination is unremarkable
Paraclinical examinations:
Serum LH: 5, 8.5 IU/ml, FSH: 13.2 IU/l, serum testosterone: 10.2 ng/ml (0.10-O, 90 ng/ml)



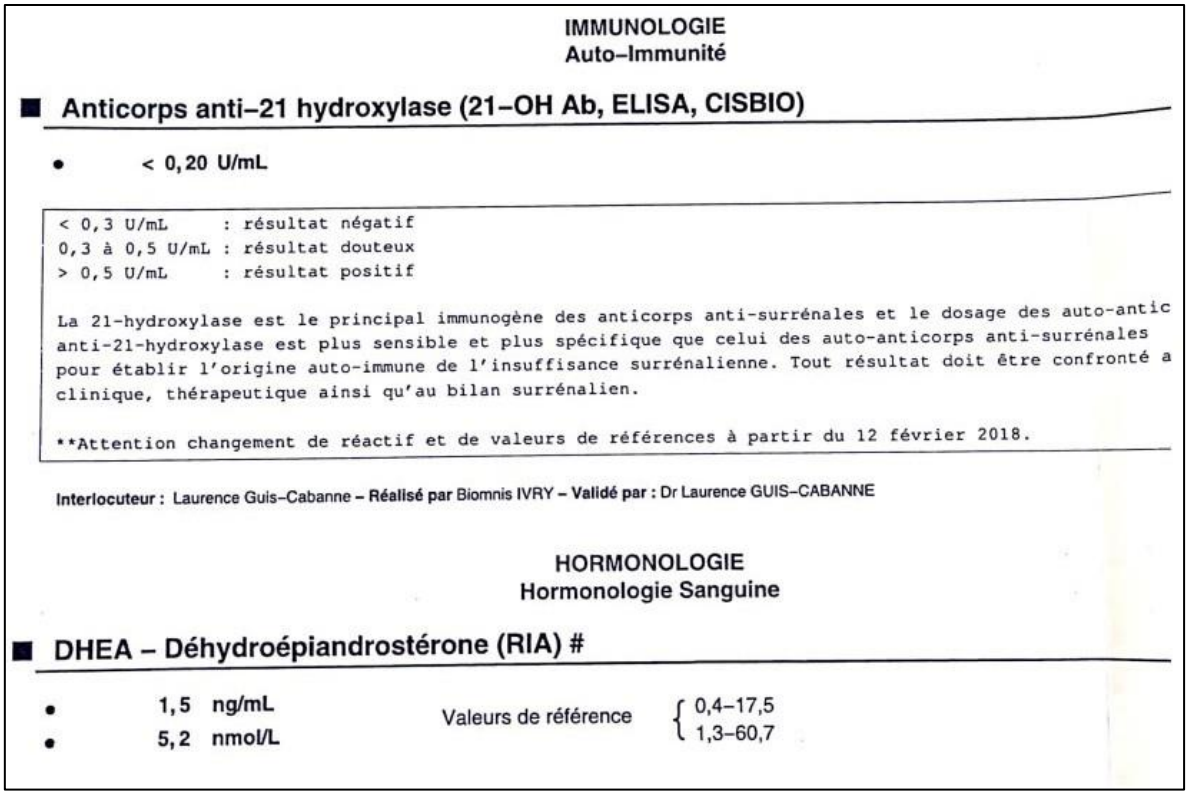
17 Alpha hydroxy progestérone (RIA) #

- **0,68 ng/mL**
- **2,06 nmol/L**

Valeurs de référence de la 17 hydroxyprogestérone

	ng/mL	nmol/L
- Phase folliculaire	0,20 - 1,50	0,60 - 4,50
- Phase lutéale	0,60 - 2,90	1,80 - 8,80
- Contraception	0,20 - 1,50	0,60 - 4,50
- Ménopause	0,20 - 0,80	0,60 - 2,40
-Grossesse 1er trimestre	0,90 - 3,80	2,70 - 11,50
-Grossesse 2eme trimestre	1,20 - 3,70	3,60 - 11,20

** Attention, changement de valeurs de référence à partir du 19/09/20



IMMUNOLOGIE
Auto–Immunité

Anticorps anti–21 hydroxylase (21–OH Ab, ELISA, CISBIO)

- **< 0,20 U/mL**

< 0,3 U/mL : résultat négatif
0,3 à 0,5 U/mL : résultat douteux
> 0,5 U/mL : résultat positif

La 21-hydroxylase est le principal immunogène des anticorps anti-surrénales et le dosage des auto-antic anti-21-hydroxylase est plus sensible et plus spécifique que celui des auto-anticorps anti-surrénales pour établir l'origine auto-immune de l'insuffisance surrénalienne. Tout résultat doit être confronté a clinique, thérapeutique ainsi qu'au bilan surrénalien.

**Attention changement de réactif et de valeurs de références à partir du 12 février 2018.

Interlocuteur : Laurence Guis–Cabanne – **Réalisé par** Biomnis IVRY – **Validé par :** Dr Laurence GUIS–CABANNE

HORMONOLOGIE
Hormonologie Sanguine

DHEA – Déhydroépiandrostérone (RIA) #

- **1,5 ng/mL**
- **5,2 nmol/L**

Valeurs de référence { 0,4–17,5 / 1,3–60,7

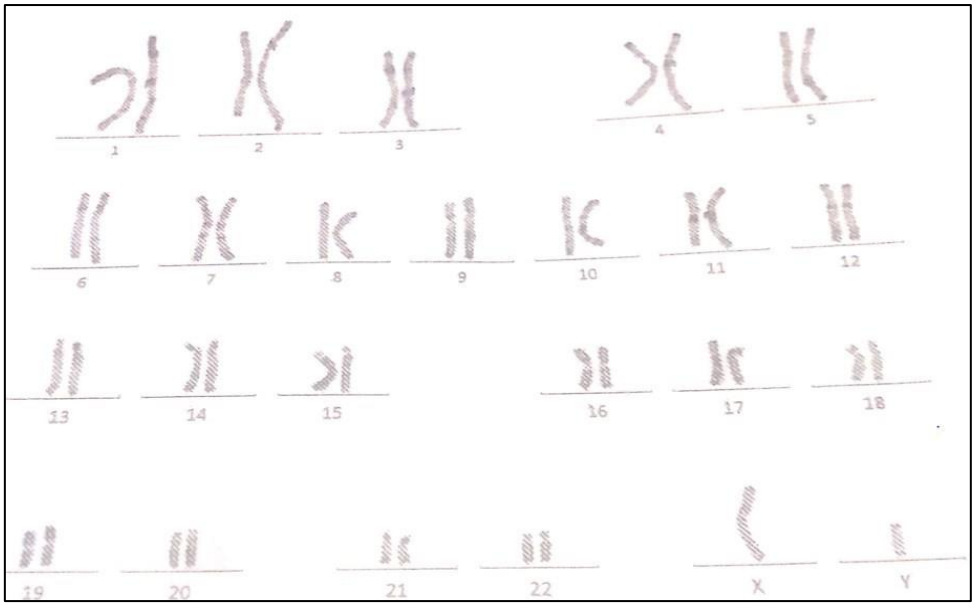


Figure 10: Karyotype: 46XY

17OH progesterone: 0.8 ng /ml
Pelvic ultrasound: the prostate is of normal dimensions.
The right testicle is in anatomical position, the left in the left iliac fossa. They are of normal dimensions.
TD: 3.20 x 2.31

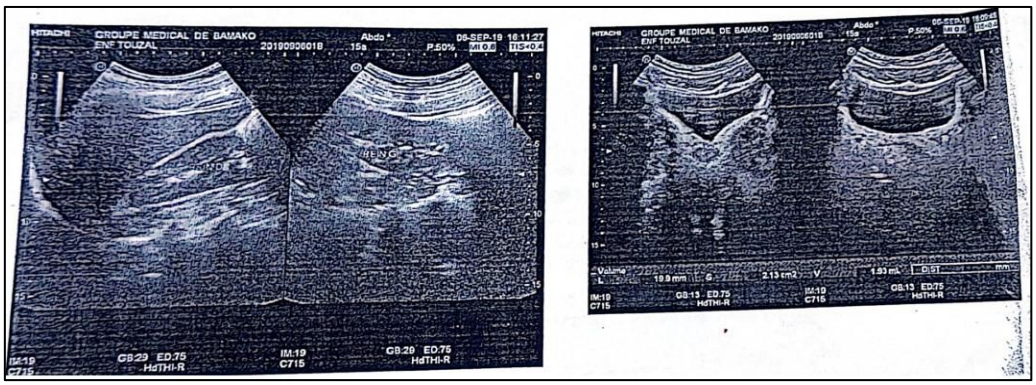


Figure 11: Echo

Diagnosis: Morris syndrome or androgen insensitivity.
Treatment: removal of the testicles, because of the risk of cancer.

Figure 12: Female morphotype

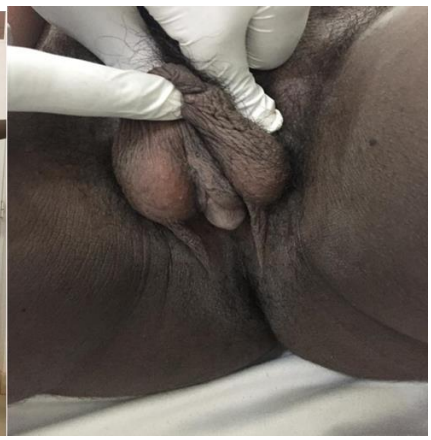


Figure 13: Presence of the right testicle the right bursa

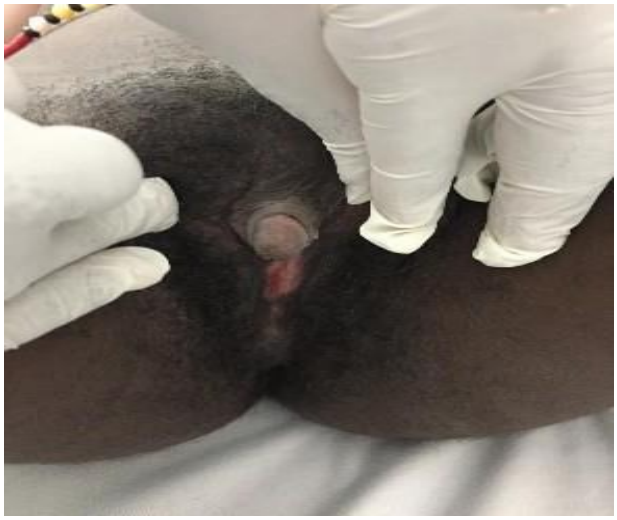


Figure 14: Presence of blind vagina of 1.3 cm

Medical Observation 4:

Ms. DL, student, F/M, 22 years old, resident in Bamako.
Reason for consultation: primary amenorrhea
History of the disease: onset dates back to the age of 14, marked by the presence of two small rounded para-inguinal masses.
The current episode dates back 15 months, marked by the absence of breast growth.
Medical and personal history: unknown medical and family history: unknown
Gyneco-obstetric history: nulligest (primary amenorrhea); Pubarche: 16 years old
General examination: weight: 66 kg, height: 179 cm, BMI: 20.62 kg/m²; Male morphotype with breasts: S0, Hair: P3
Urogenital system: Two large testicles (20ml according to Prader); blind vagina 1.16 cm deep
Skin examination: diffuse hairs on normally hairless areas in women the rest of the examination is unremarkable
Paraclinical examinations:
Serum LH: 7.8 IU/ml, FSH: 12.3 IU/l, serum testosterone: 7.30, ng/ml (0.10-0.90 ng/ml)
17OH progesterone: 1.8 ng/ml
Karyotype: 46XY
Pelvic ultrasound: the prostate is of normal dimensions. Presence of two testicles below the pubis. Right testicle dimension: 3.6 x 2.12
Diagnosis: Morris syndrome or androgen insensitivity.

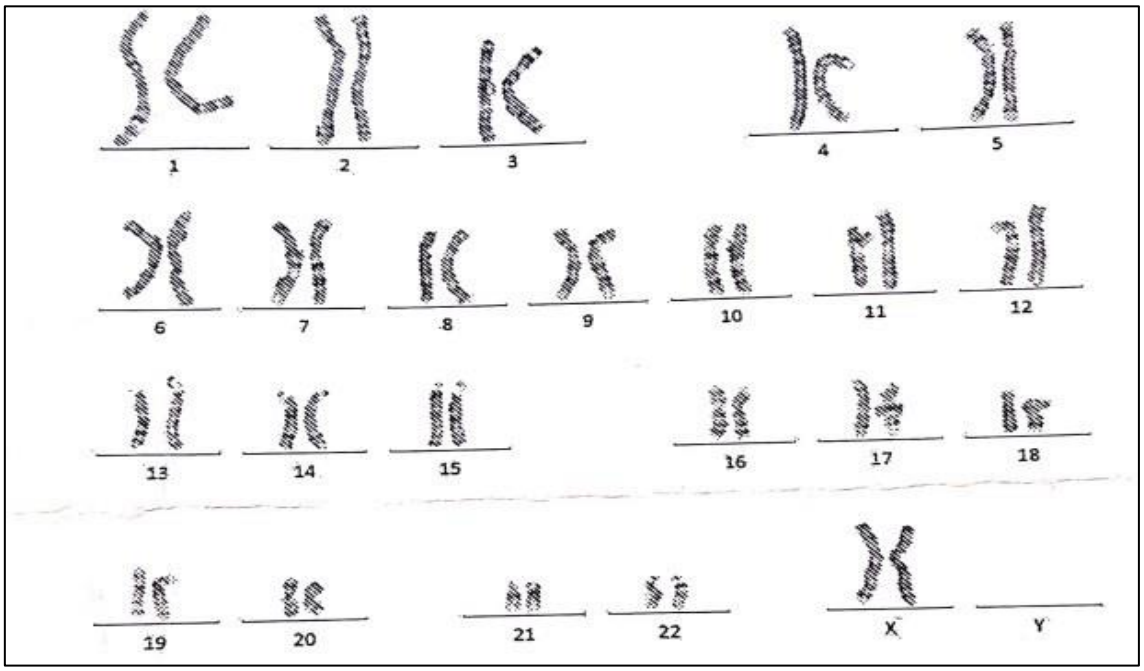


Figure 15: Karyotype: 46XY

Treatment: removal of the testicles, because of the risk of cancer.

Figure 16: Front view

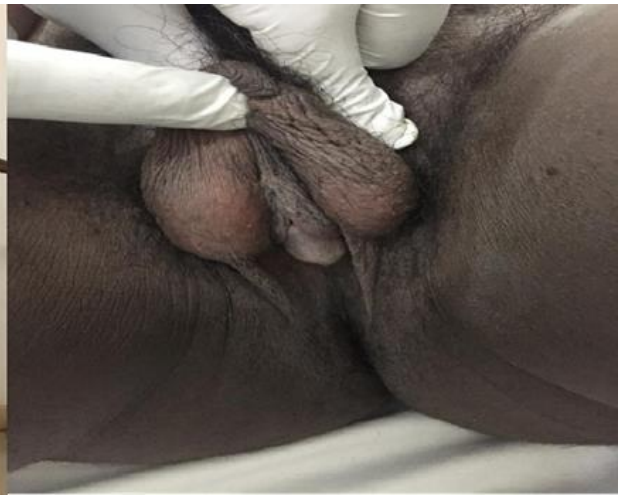


Figure 17: Presence of the right testicle the right bursa

Medical Observation 5:

Mr. BS, 46 years old, telecoms controller, resident in Bamako, consulted for asthenia and vomiting. He also complains of diffuse bone pain associated with bilateral knee pain, especially marked on the left.

Personal ATCD: HTA since 2002 and regularly monitored; asthma since childhood and follow-up. He is single with no children.
Family ATCD: father is hypertensive and asthmatic
Physical examination: T°: 36.1°C; Weight: 106 Kg, T: 1.68 m, BMI: 37.55 Kg/m2, TAC: 160/100 mm Hg, TAD: 120/90 mm Hg, HR: 108 beat/min, TT: 126 cm Rounded face, large stretch marks located on the abdomen and lower back.
OMI bilateral, soft, cupping, painless.
Its wingspan: 197 cm, amyotrophy of the upper limbs; bilateral gynecomastia, without galactorrhea since 1994-95.
Non-palpable micropenis and testicles (fairly developed and palpable before 1994), absence of beard, P3.

Paraclinical examinations:
Cortisolemia; 13.59nmol/l; Testosteronemia; 0.025ng/ml, FSH; 1.17mIU/ml, LH: 0.628,
Prolactinemia: 131.7µIU/ml,
Fasting blood sugar: 5.47mmol/Serum creatinine: 35µmol/l, Serum creatinine clearance: 301.38ml/min
Karyotype: 47, XXY [2d/46, XY {48|

Abdominal and pelvic echography:
Homogeneous steatotic hepatomegaly without focal lesion.
Absence of retro-vesical uterine structure or ovary on examination today. Presence of a small prostate with small calcifications.
We also find a short penis with corpora cavernosa of normal appearance and small testicles at the base of each inguinal canal.

Brain CT: normal
Diagnosis retained: Klinefelter Mosaic

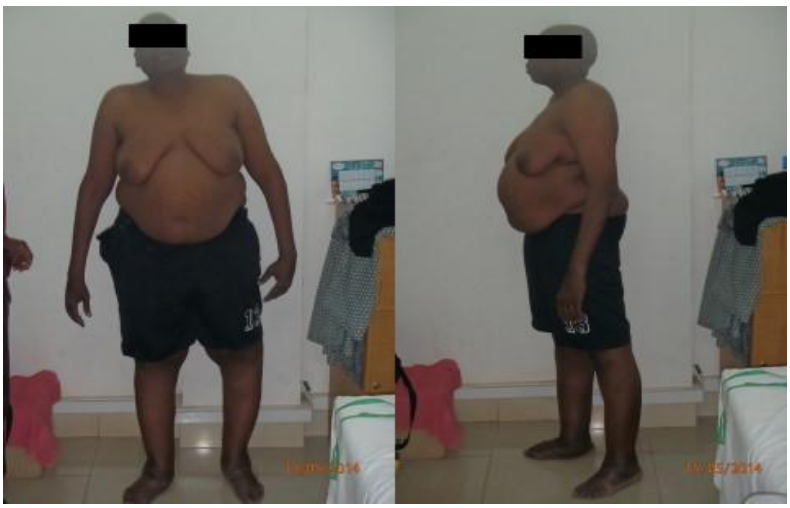


Figure 18: Gynoid morphotype face and profile

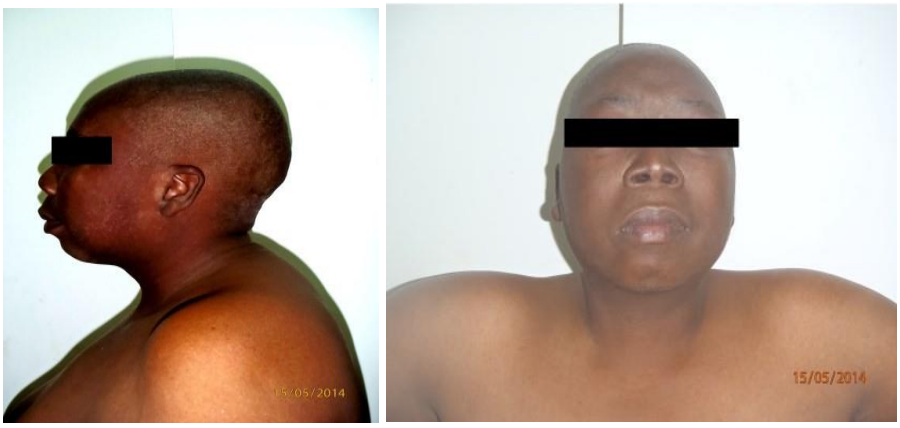


Figure 19: **Absence of beard / mustache seen from the front and profile**

Figure 20: Female pubic hair, presence of two scrotums and a micro penis

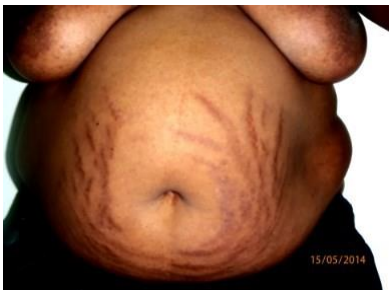


Figure 21: Tanner stage III breasts (Gynecomastia), android obesity with stretch marks seen from the front

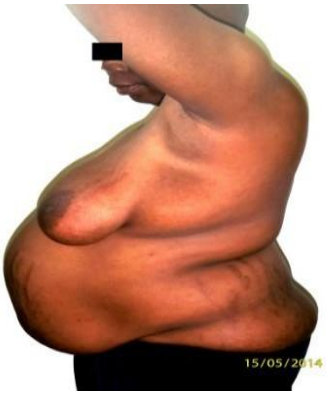


Figure 22: Tanner stage III breasts (Gynecomastia), android obesity with stretch marks seen in profile

Medical Observation 6:

A 14-year-old girl, the third child of a family of five, who consulted for treatment of delayed growth and puberty. There is a family history of undocumented heart disease in the grandfather. She clinically presents with a dysmorphic syndrome (nevi on the posterior side of the trunk and left arm, enlargement of the base of the neck, curled fingers, anteriorly convex thorax). She presents with delayed puberty (secondary sexual characteristics are at TANNER stage 1) with growth retardation (weight and height at -3 SD, bone age estimated at 9 and a half years).

Biology found: IGF1: 14 nmol/ (n=14-76); estradiol: less than 5pg/ml (n=5-27); FSH: 117.6mIU/ml (n=3.5-12.5) LH: 28mIU/l (n=2.4-12.6)
8-hour serum cortisol: 442nmol/l (n=171-536), TSHus : 2.8uIU/ml (n=0.53-3.5); FT4: 14.89pmol/l (n=12-20), Fasting blood sugar: 0.79g/l

The genetic study reveals an unbalanced female karyotype with the presence in all cells examined of a normal X chromosome and an iso chromosome Xq, consisting of twice the mirror-duplicated long arm. FISH techniques with wcpX and telomere Xq paint probes would be desirable to characterize this structural anomaly.

This result falls within the framework of a Turner syndrome with iso chromosome Xq.

Diagnosis: Turner syndrome
The frontal X-ray of the left hand and wrist shows a bone age estimated at 9 and a half years according to the Greulich and Pyle method.
Pelvic ultrasound was normal.

Treatment must be done with growth hormones and estrogen progestins but out of reach of the patient.

Medical Observation 7:
Ms. DC, Student, 17 years old, resident in Bamako
Reason: Failure to thrive
History: It was after obtaining her baccalaureate in 2017 (16 years old) that her parents decided to take her for consultation for the absence of appearance of secondary sexual characteristics and primary amenorrhea.
Elsewhere an intermittent headache with no notion of visual blur Medical and personal history: none
Medical and family history: Unknown Surgical history; none
Gyneco-obstetric history: primary amenorrhea. General examination: good general condition.
Height: 1m32, pulse: 80beat/min, wingspan: 128cm, BP: 120/80mmhg,
Examination of external genitalia:
-Puberty: Tanner: S0, P3
Presence of urethral meatus and a small vaginal opening
Absence of carrying out paraclinical assessments (abdominal ultrasound, LH, FSH, testosterone, prolactin, estradiolemia, karyotype).
Suspected diagnosis: Turner syndrome

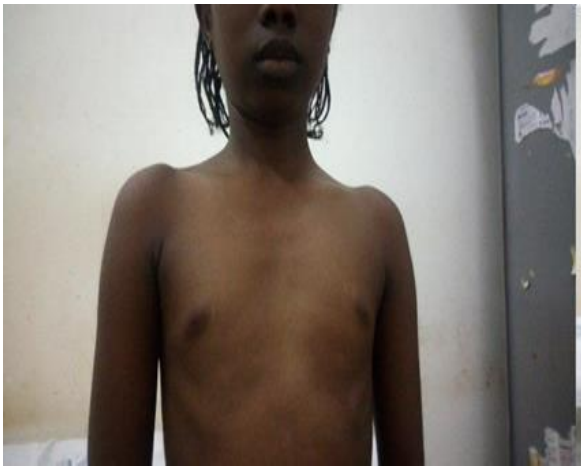


Figure 23: Breasts

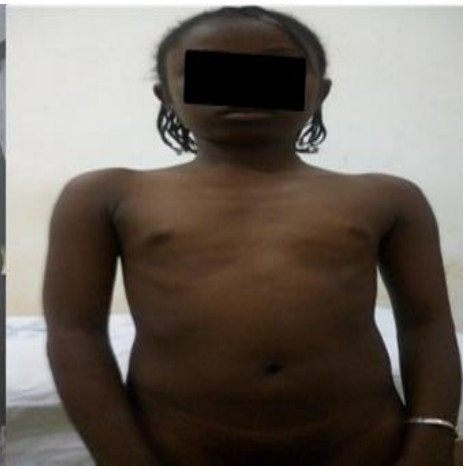


Figure 24: Female morphotype, front view

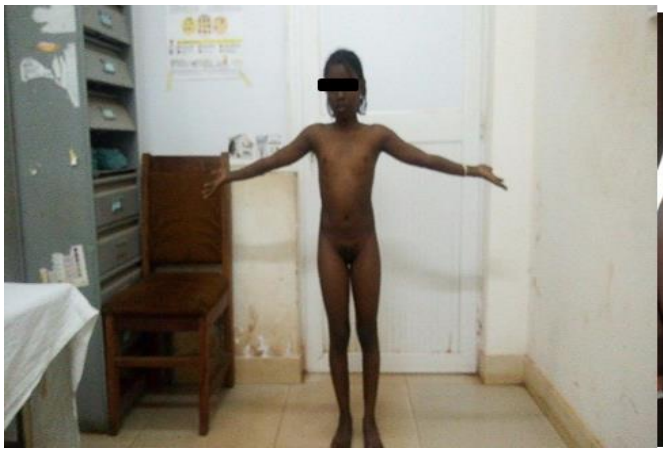


Figure 25: Morphotype with female wingspan, front view

Figure 26: Pubic hair

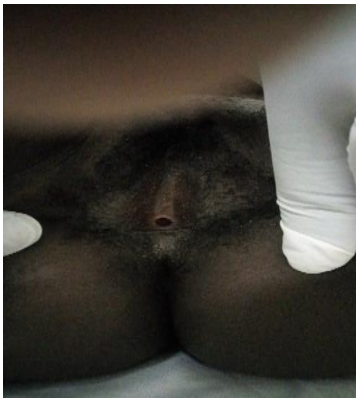


Figure 27: Small vaginal opening and pubic hair

Medical Observation 8:

Ms. FB: housewife, 20 years old, resident in Kayes Reason for consultation: primary amenorrhea Medical and personal history: none Medical and family history: unknown

General examination: weight: 36kg, Height: 1m43, Blood pressure: 130/90mmhg. Examination of external genitalia:

-Puberty: Tanner S1, P2

-Presence of the labia majora and minora with the presence of a narrowed vaginal opening.

-Absence of external gonads. Skin examination: alopecia

Paraclinical assessment:

FSH: 91.02mIU/ml, LH: 9.51mIU/ml, estradiol: 9.00pg/ml.

17OH progesterone, testosterone, prolactinemia, karyotype: not done.

Diagnosis mentioned: Turner syndrome

Abdominopelvic ultrasound: Ultrasound appearance favoring the internal genital organs of the infantile type.

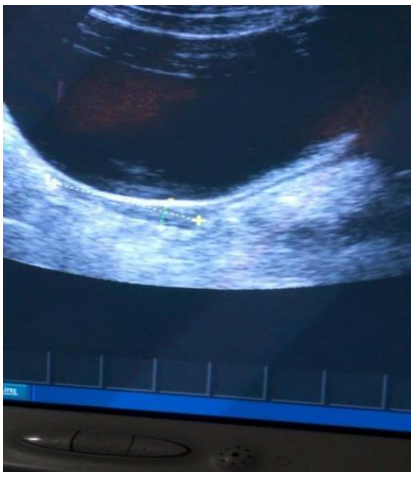


Figure 28: Internal genitalia

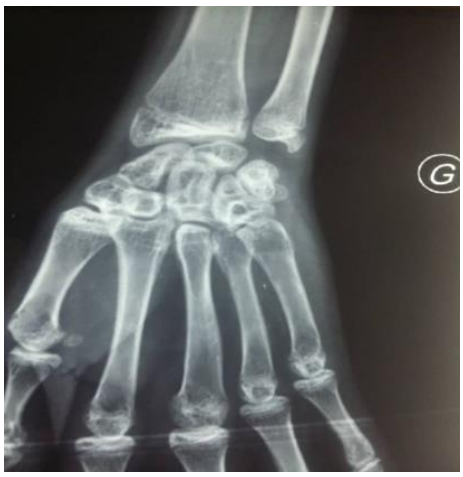


Figure 29: X-ray of the left wrist: presence of the sesamoid and fusiform bone

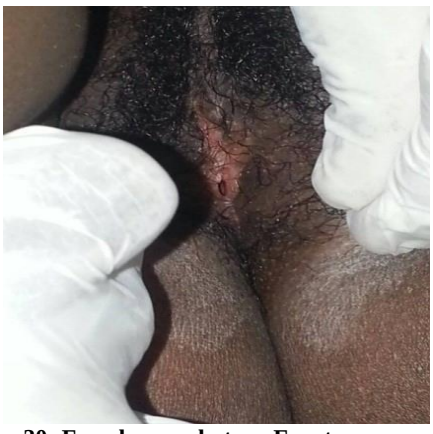


Figure 30: Female morphotype Front

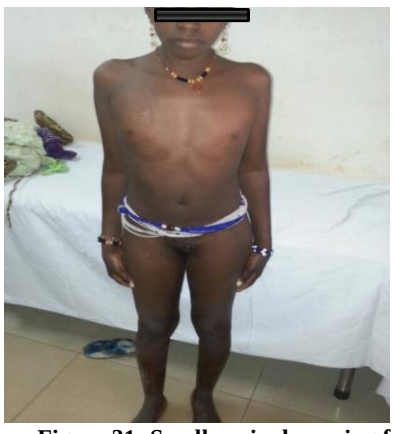


Figure 31: Small vaginal opening from the front

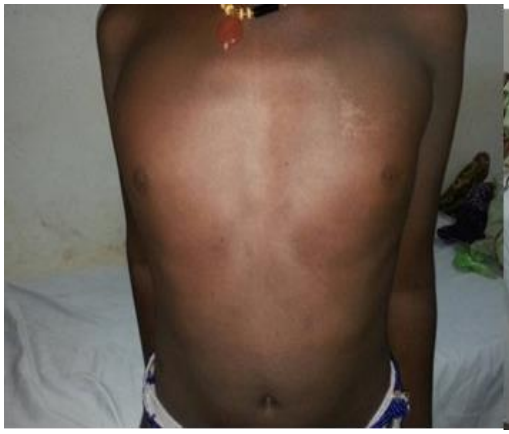


Figure 32: Breasts

Figure 33: Pubic hair

Figure 34: Alopecia

Medical Observation 9:

15-year-old adolescent, student, of Malian origin, resident in the Ségou region who consulted for bilateral gynecomastia on 08/27/2015. The onset dates back to March 2013 with bilateral breast development at the age of 12, painless without nipple discharge. Faced with the significant increase in breast volume, the parents decided to take her for a consultation. Furthermore, concept of morning erection.

- In these antecedents:
No known illness, A deaf-mute brother; No consanguinity, no tobacco or alcohol intoxication, does not take drugs.

- At the exam:
Weight 55 kg; Height: 169cm; BMI: 19.26 Kg/m2, Target size indeterminate Blood pressure: 120/65mmHg -Pulse: 86 beats/minute.

Bilateral increase in breast volume, supple, painless, without mass or spontaneous or induced galactorrhea.

On the urogenital level, well pleated scrotum with the presence of two testicles, reduced in volume, measuring 3 ml on the left and 2 ml on the right on the PRADER Orchidometer of a firm, painless consistency. We note a micropenis, measuring 6.3 cm at rest, presence of a post-circumcision healing rim. The urinary meatus is hypospadias on the ventral surface of the penis (hypospadias-Peno-Scrotal) according to the DUCKETT classification, measuring 4 by 1 cm; Pubic and axillary hair P4.

- The remainder of the physical examination is normal.
- Hormonal exploration revealed a profile of hypergonadotropic hypogonadism
- Testicular ultrasound shows bilateral testicular hypotrophy: right testicle of reduced size 22 x 15 x 11 mm carrying a centrotesticular cyst of 0.2 ml and left testicle measuring 17 x 11 x 10 mm.

Hormonal Checkups	Results	Normal Values	Units
L.H.	16.4		IU/l
FSH	22.2		IU/l
Testosterone T	0.4		ng/ml
Te bioavailable	0.1		ng/ml
Free Te	5		ng/ml
17 β Estradiol	25		Pg/ml
Prolactin	11.1	4.0 - 15.2	µg/l
AMH	1.3	4.2-84	ng/ml

- Abdominopelvic ultrasound performed revealed a prostate gland and the presence of the two seminal vesicles in place with the presence of a tissue flap in the detrusor measuring 19 x 10 mm, probably in favor of a uterine remnant.
- Breast ultrasound: Bilateral gynecomastia without other associated anomalies.
- Faced with hypergonadotropic hypogonadism associated with bilateral testicular atrophy, the patient underwent cytogenetic analysis on two occasions which concluded that akaryotype 46, XX with negative SRY.
- Diagnosis mentioned: Anomaly of Sexual Differentiation at caryotype XX (enzymatic defect).

Furthermore, the spermocytogram could not be carried out given the age of the patient and the state of modesty required by the parents.

Medical Observation 10:

Ms. RA, 17 years old, student, resident in Bamako (Fadjiguila) Reason for consultation: absence of periods and breasts Medical and personal history: married for 2 years Medical and family history: unknown.

General examination: weight: 54kg, Height: 1m75, BMI: 17.53kg/m², Blood pressure: 130/70mmhg.

Examination of external genitalia: absent labia minora, short vagina, presence of two masses in the pelvis, breasts: S0, hair: P3 Exploration: FSH: 69.62 mIU/ml, LH: 67.97mIU/ml, estradiol: 26 .39pg/ml, testosterone: 7.79ng/ml

Abdominopelvic ultrasound: uterus and ovaries not seen, testicles visualized and located at the right inguinal level measuring 33x23x11mm (4.75cc) and left measuring 30x22x13mm (4.34cc), no prostate seen, all suggestive of an anomaly of sexual differentiation: 46XY lack of virilization in a boy. Karyotype not done (androgen resistance).

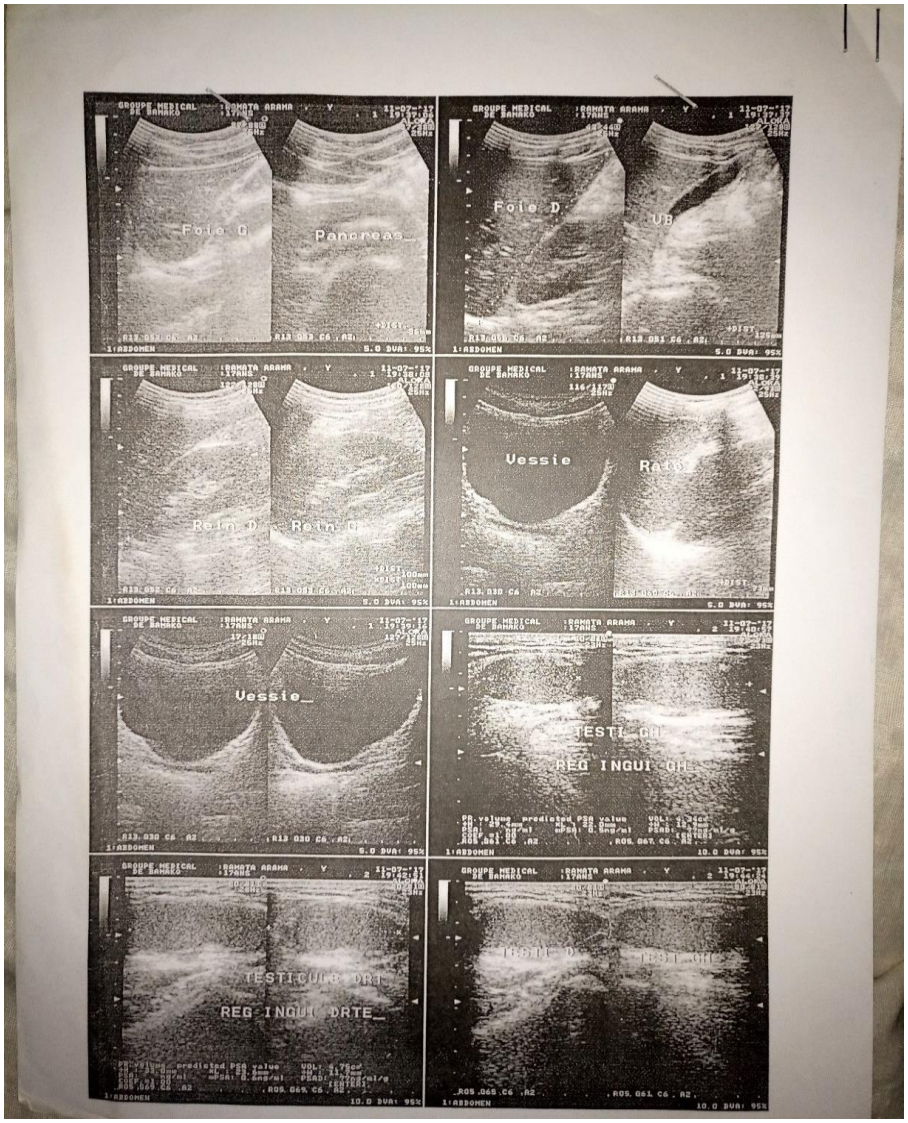


Figure 35: Testicles visualized and located at the right inguinal level

3.2. Overall Results:

Out of 8213 consultants, 10 patients presented anomalies of sexual differentiation, giving a hospital prevalence of 0.12%.

The average age was 17.13 years with extremes of 8 days and 46 years (See table I).

Six out of ten patients had a female morphotype with a sex ratio of 1.5.

10 out of 10 patients had an abnormality of the external genitalia (See table II).

07 out of 10 patients had done the karyotype (See table III).

More than half of our patients had a precise diagnosis. (See Table IV).

Table I: Age distribution

Age (year)	Effective
0-4	1
5-9	0
10-14	1
15-19	4
20-24	3
25-30	0
30	1
Total	**10**

Table II: Distribution According to Clinical Signs

Clinical Signs	Effective
Hypo pubic and axillary hair	8
Primary amenorrhea	7
Delayed Pubertal	7
External genitalia abnormality	10
Bilateral inguinal mass	4
Bilateral gynecomastia	2
Early Pubic Hair	0
Macroskele	1

Table III: Distribution according to the nature of the karyotype

Nature of the Karyotype	Effective
47XXY /46XY	1
45XXq	1
46XY	3
46XXa	2

Table IV: Distribution according to the diagnostic evolution

Diagnosis mentioned	Workforce
Turner syndrome verified	1
Suspected Turner syndrome	2
Klinefelter syndrome	1
Androgen insensitivity	3
Unspecified	2
Block in 21 hydroxylase	1
Total	**10**

4. COMMENTS AND DISCUSSION

We conducted a retrospective, prospective and descriptive study spanning from September 2011 to July 2021 (i.e. 10 years). It took place in the medicine and endocrinology department at Mali hospital. Ten patients out of 8213 consultants presented a discordance between OGE, OGI or secondary sexual characteristics confirmed, either by an abdominopelvic ultrasound and sometimes associated with hormonal disorders. Hence a hospital prevalence of 0.12%. SIDIBE AT and Col [11], found 0.54%, Diallo MM found 0.23% in Mali, Sridcha R Gumpey [4] found between 2.5% to 12% in an endocrinology center in India, in the USA, the prevalence was estimated at 1 per 2,000 births according to the inter sex Society of North America (ISNA) [4, 5].

The figures vary depending on the method of recruitment.

In our series the female phenotype represented 6 out of 10, unlike that of SIDIBE AT and Col [11], in Mali who found 10 out of 12; CHAABOUNI and Col in Tunisia [2] who found 39 out of 41.

Analysis of socio-demographic data showed a relatively high frequency of anomalies of sexual differentiation in large cities: 6 out of 10 patients for the city of Bamako. This proportion could also be explained by the fact that for reasons of accessibility and awareness, urban residents consult more frequently than rural residents.

The female phenotype represented the most affected with a sex ratio of 1.5. This is explained by the fact that in anomalies of sexual differentiation, any anomaly preventing the expression of male gonads in the fetus would result in the constitution of a female phenotype. Only the karyotype would have made it possible to establish the real sex ratio.

The average age of our patients was 17.13 years with extremes of 08 days and 46 years. This result differs from that of SIDIBE AT and Col [11] who were 14 years old. This means that the average age of diagnosis of anomalies of sexual differentiation was around adolescence and adulthood while the diagnosis must be posed during childhood according to, Joel Hutcheson and Howard M Snyder III [6]. The proportion of cases of pure gonadal dysgenesis could explain this situation because in general, this diagnosis is only mentioned in cases of puberty disorders [2].

Clinically, among the reasons for consultation, OGE abnormalities constituted the most observed reason among patients. In childhood, the clinical aspect of OGE can worry parents and push them to consult a doctor. Older patients had normal OGE and only came for consultation when problems with height and weight development or puberty arise. Joel Hutcheson and Howard M Snyder III have reported the same situation in the literature [6].

Six out of seven patients had a hair disorder. These results can be explained by the fact that the gonads and adrenals are involved in the production of androgens (stimulators of the development of axillary and pubic hair). Their anomaly would therefore have direct repercussions on hair growth, as pointed out by F KUTTENN [3].

Five out of seven adolescent and adult patients have a breast development disorder. These disorders could be explained by the disruption of testosterone and estrogen secretion, which itself would be due to gonadal anomalies presented by our patients. Because, as F KUTTENN [3] pointed out, these hormones are involved in stopping breast growth.

On a biological level, out of 6 female phenotypes who were able to perform the FSH assay, 4 had a high level and these 4 female phenotypes had no ovaries or only had remnants. The absence of negative feedback from estradiol which is normally produced by the ovaries would explain these high levels and the reasons for failure to thrive which had brought some of them to consultation. Indeed, estrogens stimulate the general development of the body during puberty, according to F KUTTENN [3].

Two women who did not have ovaries were able to measure estradiol in their blood and all had low levels. This would be due precisely to the absence of ovaries which are the main glands producing estradiol, according to F KUTTEN [3], R BRAUNER [8].

Only one of our patients was able to measure progesteronemia and had a high level even though she was already on progestin.

Both male phenotypes were able to perform the testosterone assay and had low levels. This low rate had repercussions on the development of these patients because their OGEs were not virilized as required. This low level would also explain their physical appearance (infantile penis, gynecomastia, large size) because, normally, testosterone is responsible in boys for the virilization of the OGE, the cessation of breast growth and the fusion of the growth plates, according to F KUTTENN [3], M. Pholsena and G. Schaison [7].

Considering the imaging results, all male phenotypes had at least one testicle in the bursa (4/4), while only 1 in 6 female phenotypes had normal ovaries. The others are characterized either by a total absence of gonads, or by remnants of gonads. These results would be due to the fact that in men, the presence of functional male gonads is essential for the expression of this phenotype while the mere absence or non-functionality of male gonads is sufficient to express the female phenotype, according to Hutcheson J and Snyder. III HM [6], SHIMADA K *et al.*, [9]. Each time we found normal ovaries or remnants, they were always in a normal position. Joel Hutcheson reports the same situation in his work [6].

On the etiological level, we had difficulty establishing a very precise diagnosis either because of financial constraints in carrying out the necessary investigations, or because of an insufficient technical platform (especially the impossibility of carrying out the karyotype).

Pure gonadal dysgenesis was retained 4 times out of 7 and seems the most frequent while Hutcheson J [6] reports in his article that HCS is the most common with a frequency of 60% of all intersex cases. The aforementioned difficulties did not allow us to carry out all the necessary investigations in order to establish more precise diagnoses.

On the therapeutic level, treatment began with the definitive assignment of the rearing sex although our patients all came with a sex declared at birth. This assignment took into account the type of OGE and their appearance, the possibility of subsequent normal genital activity, the presence and type of gonads, levels of sex hormones and the age of the patient. But this definitive assignment of sex and the rest of the care was not done within a multidisciplinary team (endocrinologist, pediatrician, surgeon, psychologist, cytogeneticist, molecular biologist, hormonal biochemist, obstetrician and urologist), as the reported Hutcheson J and Howard M Snyder III [6] and SIROL F [7]. Even though the files were not managed in a collegial manner, in 1 out of 7 patients the opinion of another specialist was requested as part of the treatment and, each time, the doctor did so. effort to explain and reassure patients and parents. Many exogenous factors made this collegial care difficult: the dispersion of specialists and specialized services in the

city of Bamako, the absence of a culture of feedback between doctors and the non-existence of certain specialties.

Our relevant study was unable to benefit from the necessary financial resources and technical support to establish definitive diagnoses for 3 of them. The problem of abnormal sexual differentiation exists in our center and deserves a better multidisciplinary approach.

CONCLUSION

Abnormalities of sexual differentiation, although relatively rare, exist in Mali and throughout the world. Their diagnosis in Mali, given the insufficiency of the technical platform, is based on interrogation, examination physical, abdominopelvic ultrasound, blood level of sex hormones and, possibly, karyotype.

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