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Pubertal Delay Secondary to Hashimoto's Disease in the Hypothyroid Phase: About a Case in the Internal Medicine Department of the Gabriel Touré University Hospital in Bamako, Mali

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Abstract **Case Report**

Introduction: Pubertal delay is defined by the absence of development of secondary sexual characteristics beyond the age of 13 in girls or 14 years in boys. In children of puberty age, delayed puberty is common in long-standing, untreated hypothyroidism. We report a case of delayed puberty revealed by Hashimoto's disease in the hypothyroid phase diagnosed in the Internal Medicine department of the Gabriel Touré University Hospital in Bamako, Mali. ***Observation*:** This was a female patient, aged 20 years old, without any particular medico-surgical ATCD or notion of taking medication, who had consulted at the end of 2021, in the Internal Medicine department of the University Hospital Gabriel Touré from Bamako for primary amenorrhea and delayed puberty. At the end of the clinical and paraclinical examination, a hypometabolism syndrome and pubertal delay were noted. On an evolutionary level, development of secondary sexual characteristics (From T1 to T3, and appearance of menstruation) after one year of treatment. ***Conclusion*:** Delayed puberty may be the consequence of hypothyroidism. Opotherapy with L Thyroxine helps restore normal pubertal development.

Keywords: Pubertal delay, sexual characteristics, puberty age, children, children.

INTRODUCTION

Pubertal delay is defined by the absence of development of secondary sexual characteristics beyond the age of 13 in girls or 14 years in boys [1, 2]. Clinically, it is recommended to evaluate girls who do not have breast development at age 13, and boys who do not have testicular enlargement at age 14. This concerns 2.5% of adolescents [3].

We distinguish pathological pubertal delay from simple pubertal delay, that is to say followed by complete spontaneous pubertal development. Pathological pubertal delay can be of central hypothalamopituitary origin, or peripheral gonadal. It is responsible for a delay in the acceleration of the speed of stature growth. This explains why the reason for consultation is often small size [1, 2].

Pubertal development is inhibited by chronic diseases including sickle cell disease, the leading hemoglobinopathy in the world and which is a public health problem [4]. Hospital statistics for delayed puberty in adolescents living with homozygous sickle cell disease vary around the world, ranging from 8 to 50% in Europe and 15% in Latin America [5, 6]. In Africa, the reported data confirm the same trends, particularly in Egypt: 25% and Nigeria: 75% [7, 8].

Long-standing, poorly controlled type 1 diabetes is a predictive factor for delayed puberty. Delayed puberty was linked to glycemic imbalance ($p < 0.05$), duration of diabetes ($p < 0.02$) and repeated hypoglycemia ($p < 0.02$) [9].

Hypothyroidism is the set of clinicobiological manifestations related to a reduction in the secretion of thyroid hormones. It is a common condition that affects nearly 0.8 to 1% of the world population with a clear predominance of primary hypothyroidism [10]. Thyrotropic insufficiency is much rarer than peripheral hypothyroidism with an estimated prevalence of 0.005% in the population and constitutes less than 5% of hypothyroidism [11].

Thyroid hormone deficiency indirectly induces gonadotropic insufficiency, through the stimulation of hypothalamic secretion of TRH (by negative feedback), which stimulates the secretion of prolactin, resulting in disorders of sexual function in the 2 sexes. Thyroid hormone deficiency leads to an alteration in progesterone secretion in adult women, causing menstrual cycle disorders. In children of puberty age, delayed puberty is common in long-standing, untreated hypothyroidism. In addition to the functional gonadotropin deficiency secondary to hyperprolactinemia, increased expression of a hypothalamic gonadotropin-inhibiting hormone (GnIH) has been implicated in the occurrence of pubertal delay [12].

Apart from the association of pubertal delay and sickle cell disease or pubertal delay and especially type 1 diabetes, very few studies have focused on the association of pubertal delay and Hashimoto's disease. We report a case of delayed puberty revealed by Hashimoto's disease in the hypothyroid phase diagnosed in the Internal Medicine department of the Gabriel Touré University Hospital in Bamako, Mali.

2. OBSERVATION

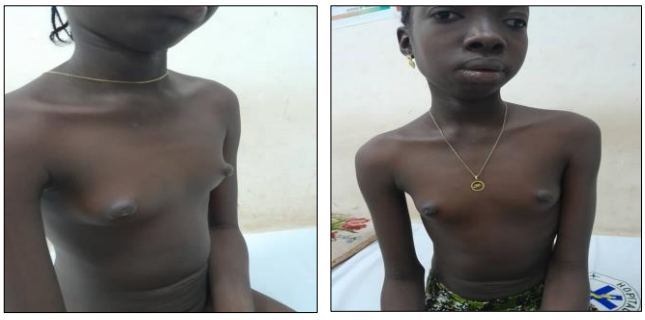
This was a 20-year-old female patient, who consulted on 12/31/2021 in the internal medicine department of the Gabriel Touré University Hospital in Bamako in Mali for absence of periods and delayed puberty. The beginning of the symptomatology dates back several years rather, through the observation by the patient herself and by her parents, of an absence of menstruation and a lack of development of the breasts without all this being able to worry them. Faced with the absence of a marriage proposal after that of his little sister, the patients decided to consult. During the clinical examination, the patient complained of physical asthenia, constipation and an absence of sweating, even in the pilosebaceous areas, such as the armpits. There was no known personal medical-surgical history or medication taken in her, but no delay in puberty was noted in her little sisters.

The parameters at entry were: weight at 55 kg for a height of 162 cm (BMI=20.95 kg/m2). Blood pressure was 130/80 mmHg.

On physical examination:

- Mucocutaneous examination: dry skin
- Breast examination: small breasts classified S1 according to Tanner (photo 1)
- Examination of the armpits: rarefaction of hair classified P1 according to Tanner (photo 3)

Photos n°1 Face and Profile: Small breasts before treatment



Photos n°2 Face and Profile: Breasts after 06 months of treatment with Levothyrox

- Examination of the external genitalia (OGE): Presence of some pubic hair, no clitoris and blind vagina (Photo 4)

Photo n°3*: *Left and right armpits before treatment

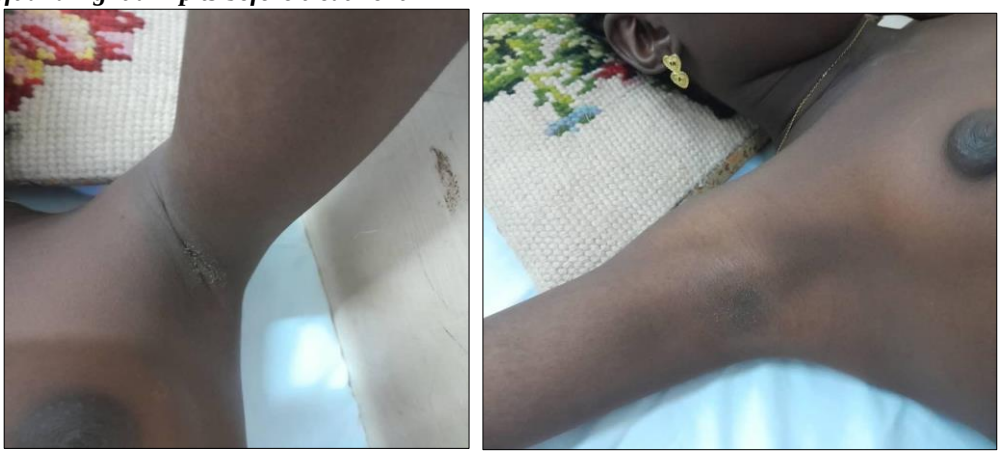
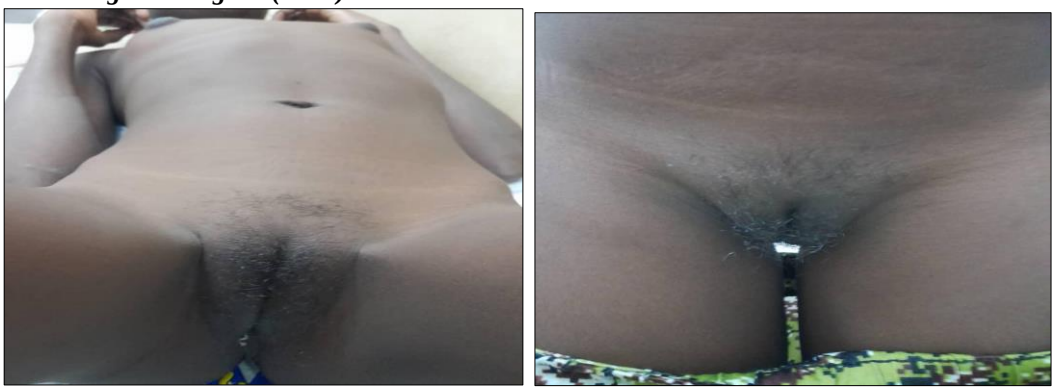


Photo n°4: External genital organs (OGE)



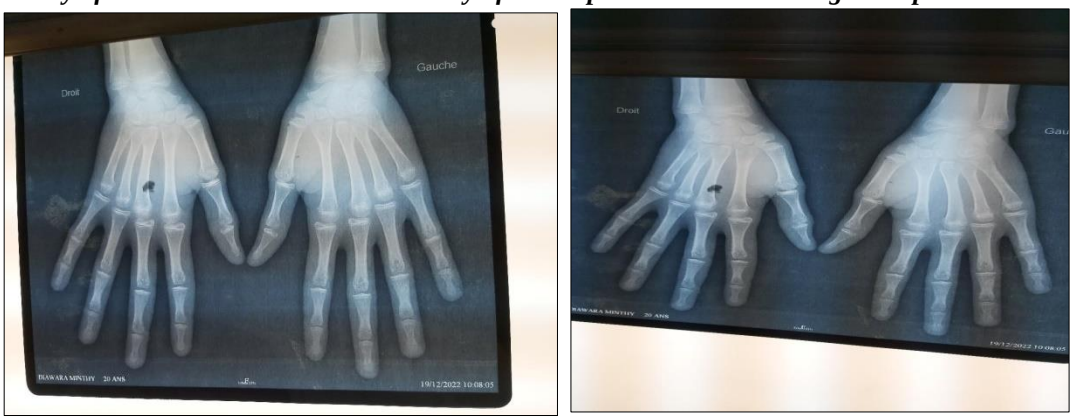
The biological assessment is summarized in the following table:

Assessment/ Dates	**Patient value**			**Normal values**
	12/19/2022	06/20/2023	10/17/2023	
TSH (us)	**89, 65**	**27, 6768**	**3, 8529**	0, 3-4,5 µUI/ml
FT4	6,202	**20, 11**	**10, 31**	08, 9-17, 2 Pg/ml
FT3	1,073			2,0-4,2 Pg/ml
Anti-thyroperoxidase (TPO) antibodies	**512,92**			< 5,61 UI/l
TSH Ab receptor	2, 94			< 3, 10
Estradiol	32,68	35,00		Follicular phase= 15-112 Pre-ovulatory phase= 93-409 Luteal phase= 29-318 Menopause < 58)
Prolactinemia	**543,1**	16,03		66-490 µUI/ml
Serum LH	**5,079**	**3,98**		Follicular phase=1.5-8.0 Ovulation=9.6-80µIU/ml Luteal phase=0.2-6.5 µIU/ml Menopause=08-33 µIU/ml)
Serum FSH	**8,766**	**5,1**		Follicular phase=3.03-08.8 µIU/ml Ovulation=2.5-16.69 µIU/ml Luteal phase= 1.38-5.47 µIU/ml Postmenopause= 26.72-133.41 µIU/ml)

An x-ray of the hands and wrists carried out on 12/19/2022 found a satisfactory calcium load. The sesamoids of the thumbs and the radial styloids have not yet appeared. All the ossification nuclei of the carpus are present except that of the pisiform. These carpal bones present are immature. The radial and ulnar epiphyses are immature with clearly visible growth plates.

CONCLUSION: According to the GREULICH and PYLE Atlas, this x-ray of the hands and wrists corresponds to a **bone age of 10-11 years**. (***Photo No. 5***)

Photo n°5: X-ray of the hands and wrists: Immaturity of the carpal bones with visible growth plates



The abdominopelvic ultrasound carried out on **12/19/2021** describes:

Uterus:

Normally flexed, it is small, measuring 54mm in height, 28mm in width and 17mm in thickness. Its contours are regular, its echo-structure homogeneous and its contents empty (fine and regular cavitary line). The endometrium is measured at 05 mm thick.

Ovary:

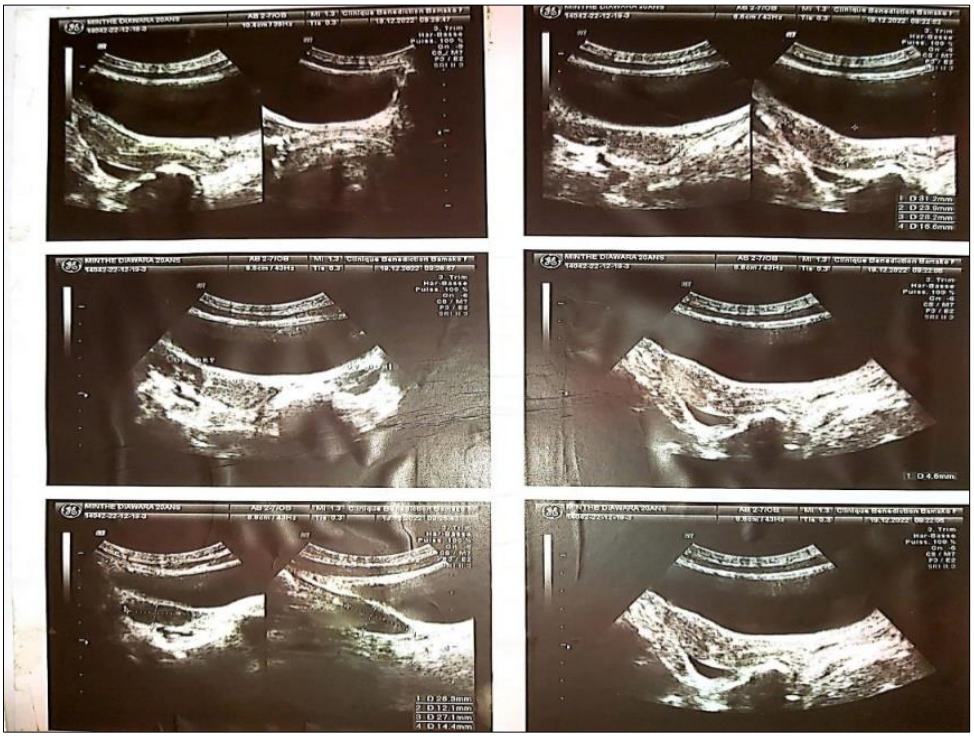
They are of echo-structure and of normal size measuring on the right 28 x12mm and on the left 27x14mm. Note the presence of a low abundance of liquid effusion in the Douglass.

Bladder: It Is Transacoustic and Thin-Walled.

CONCLUSION

Small uterus with a juvenile appearance, homogeneous and empty with an endometrium of 05mm. Normal-sized ovary containing follicles of variable size. Fluid effusion in the Douglass. NB: vaginal light exists.

Photo n°7: Pelvic ultrasound showing a small uterus



Treatment:

Pubertal induction… When pubertal delay is secondary to a hypothalamic-pituitary or gonadal pathology, pubertal development must be induced by hormonal replacement treatment, at the normal age of onset of puberty when the diagnosis has been made sufficiently early. The objectives of treatment are to induce a satisfactory pubertal growth peak, the development of secondary sexual characteristics, then normal adult sexual activity and, if possible, fertility. It

begins with the administration of small doses of sex steroids, the dosage of which is gradually increased every 6 months, so as to mimic normal pubertal development. After 2-3 years in girls, when breast and uterine development are considered satisfactory, estrogen treatment is combined with progesterone cyclically to induce menstruation [1, 2].

Our patient was put on L Thyroxine at a progressive dose.

- **Evolution:**

After a 06-month treatment, we witnessed on the clinical level:

- ✓ the development of secondary sexual characteristics with increase in breast volume from S1 to S4 (***photos No. 2*** compared to ***photos No. 1***),
- ✓ development of the external genitalia with the onset of menstruation
- ✓ Paraclinically, there was a decrease in TSH (us) which went from 89.65- to 3.8529 µIU/ml after approximately 10 months of treatment (***see table above***).

3. DISCUSSION

- **Clinical Signs:**

The examination must be general: blood pressure, wingspan, sitting height, weight, height, BMI. In boys, as in girls, the different stages of pubertal development are rated from 1 (absence of pubertal development) to 5 (complete adult development) according to the classification of Marschall and Tanner [13, 14].

In girls [15]. The first pubertal manifestation is the development of the mammary glands, beginning on average from 10.5/11 years of age (between 8 and 13 years for 95% of girls) and which is complete 4 years later. Examination of our patient's breasts before treatment revealed less developed breasts classified as Tanner S1. (***See photo 1***)

Hair growth in the pubic region most often begins 6 months after the mammary gland, and takes on an adult appearance in 2-3 years in a triangle with a horizontal upper base [15]. In our patient, we noted some pubic hair, classified Tanner P1 (***photo 4***)

Axillary hair appears on average 12 to 18 months later. It evolves over 2-3 years [15]. Our patient noted an absence of axillary hair on the right and a few rare hairs on the left (***photo 3)***.

The first periods (menarche) appear around the age of 13 (between 10 and 16 years), 2-2.5 years after the appearance of the first puberty signs (maximum 4 years later). The hemorrhages are not cyclical from the outset, becoming so after 18-24 months, when the cycles have become ovulatory [15]. At 20 years old, our patient had never seen her period (primary amenorrhea).

Hypothyroidism:

Hypothyroidism acquired during childhood or adolescence is most often peripheral or primary, linked to autoimmune thyroiditis (Hashimoto). Slow growth rate is most often associated with excessive weight gain and other clinical signs of hypothyroidism, and sometimes goiter. Bone age is often much lower than chronological age (> 2 years) [16]. In our patient we noted constipation, physical asthenia and an absence of sweating, even in the pilosebaceous areas such as the armpits.

- **Paraclinical Signs:**

In case of delayed puberty, measurement of baseline pituitary gonadotropins and under stimulation, measurement of inhibin B and anti-Müllerian hormone (AMH), performance of a pelvic ultrasound and standard karyotype in girls will be informative.

Determination of Bone Age:

Carrying out a bone age must be systematic, making it possible to assess the overall maturation of the body. It uses a frontal X-ray of the left hand and wrist, read by a trained radiologist using the Greulich and Pyle atlas [17]. The start of puberty occurs at a bone age close to 11 years in girls, 13 years in boys, corresponding to the appearance of the sesamoid of the thumb.

In the case of delayed puberty, the bone age is often related to the delay in physical maturation, and therefore less than 11 years in girls, less than 13 years in boys, without prejudging the cause. Conversely, a bone age greater than 11 years in girls, or greater than 13 years in boys, while the patient is pre-pubertal, is abnormal and primarily indicates hypogonadism [17].

In the fetus, thyroid hormones are not essential for growth, but they are essential for differentiation and bone maturation. Their absence is accompanied by a delay in the appearance of epiphyseal ossification points [2]. On the x-ray images of our patient, we see that the carpal bones present are immature. The radial and ulnar epiphyses are immature with clearly visible growth plates, suggesting a bone age of 10-11 years (photo 5). During the postnatal period, thyroid hormones become essential for growth and continue to control bone maturation and differentiation. They act in synergy with growth hormone (GH). The latter promotes chondrogenesis and the growth of cartilage, while thyroid hormones allow the maturation and ossification of cartilage. In addition, they promote GH secretion and potentiate the effects of IGF-1. In children, congenital hypothyroidism can be responsible for disharmonious dwarfism. [2].

The positive diagnosis of hypothyroidism is based on basic hormonal measurements (TSH and FT4) [12].

- ✓ The ultrasensitive (us) determination of TSH by the immunoradiometric method (IRMA) is the reference examination. It is achieved from first

intention. Venous samples can be taken at any time of the day, as nycthemeral variations have no repercussions in the clinic. In primary hypothyroidism, TSHus is generally > 10 mU/l.

- ✓ Free thyroxine (FT4) assay: The discovery of an elevation in TSH must be monitored by a FT4 assay by radioimmunological method (RIA).

In our patient, TSH (us) was elevated at **89.65**µIU/ml (VN: 0.3-4.5) on 12/19/2022 before the start of hormonal treatment.

The diagnosis of thyroiditis is based on the existence of antithyroid antibodies at increased levels. In our patient, anti-thyroperoxidase (TPO) antibodies were 512.92 IU/l (VN < 5.61).

Hypothyroidism is less frequently of central, hypothalamic-pituitary origin. In general, in this case, it is accompanied by other accompanying signs and is most often of tumor origin. Here we find a low T4l and an abnormally normal (inappropriate) TSH [16].

Pubertal development is inhibited by chronic diseases including sickle cell disease, the leading hemoglobinopathy in the world and which is a public health problem [4]. Several studies report that sickle cell disease is responsible for endocrine complications in adolescence, including growth retardation and pubertal delay [5-18]. In our patient, hemoglobin electrophoresis was normal (AA profile).

CONCLUSION

Pubertal delay following Hashimoto's disease is rarely described in African publications. This clinical case constitutes a significant advance in endocrinology in Africa.

Declaration of Link of Interest: The authors declare no conflict of interest.

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