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Late Diagnosis of Turner Syndrome in Adulthood; a Case Study from the Endocrinology-Diabetology Nutrition Department of the National Hospital of Pikine Senegal

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Abstract

Introduction: Turner syndrome is a rare genetic disorder characterised by the presence of one X chromosome and the absence of part or all of an X or Y chromosome and patients may experience delayed puberty and infertility. Our study aimed to evaluate the diagnostic delay in our practice and analyze the impact of this diagnostic delay on the effectiveness of patient management. **Patients and Methods:** Turner syndrome patients were identified from the endocrinology-diabetology nutrition department Database We examined the records of patients in whom the karyotype analysis favoured Turner syndrome. **Results:** We have selected 5 patients' records of female patients with Turner syndrome. The mean age was 25, ranging from 19 to 29 years. Primary amenorrhea and characteristic dysmorphic features were observed in all patients. One married patient, who sought consultation for infertility, expressed a desire for pregnancy. Short stature was identified in 3 patients. Primary hypothyroidism and hypertension were respectively found in 1 and 2 patients. Gonadal dysgenesis was noted in 100% of cases. Karyotype analysis revealed monosomy X in 2 patients and mosaic patterns in others. All patients received estrogen-progestin treatment. Antihypertensive therapy was initiated for 2 patients. One patient is on L-thyroxine. In the short term, treatment led to the onset of menstruation after the initial months. Evaluation of treatment efficacy on internal genital organs is yet to be performed. Due to

uncertain benefits at this age, growth hormone therapy was not considered for our patients. We provided counseling on assisted reproductive options for couples desiring to conceive. In our study, all patients were placed on estrogen-progestin therapy, and the response appeared favorable. **Conclusion:** In our practice, the diagnosis of Turner syndrome occurs very late in adulthood, at an age when growth hormone treatment is nearly ineffective. Treatment typically revolves around estrogen-progestin therapy, along with managing other comorbidities such as hypertension and primary hypothyroidism.

Keywords

Turner Syndrome, Primary Amenorrhea, Adult, Pikine

1. Introduction

Turner syndrome is the most common sex chromosome abnormality in women and occurs in approximately 1 in 2500 live births that results from a total or partial absence of an X chromosome [1]. Other karyotypes also exist, including ring X chromosomes, iso chromosomes, deletions of a part of the X chromosome, and even karyotypes involving a portion of a Y chromosome [2]. Approximately one-fifth of all cases are diagnosed at birth with obvious clinical features, while another fifth is present during childhood with short stature However, 50% of cases are diagnosed later, typically when an adolescent experiences primary amenorrhea [3]. About 20% of all cases are diagnosed at birth with obvious clinical features and another 20% are present in childhood with short stature [4]. However, 50% of cases are diagnosed later, usually when an adolescent presents with primary amenorrhea [2]. Late diagnosis of turner Syndrome exposes patients to the complications of premature ovarian failure and can also compromise the management of failure to thrive with growth hormone (GH) [5]. Our objective was to highlight this diagnostic delay in our practice and to analyse its consequences on care.

2. Patients and Methods

We compiled the records of patients with turner syndrome confirmed by karyotype analysis in the database of the internal Medicine, endocrinology-diabetology department of the Teaching Hospital of Pikine. For all patients included in the study, the following data were collected:

Sociodemographic data: age at diagnosis, marital status.

Diagnostic data; clinical and paraclinical signs of hypogonadism; dysmorphic syndrome, height, karyotype, and other associated disorders including heart defects, hypothyroidism; hypertension, diabetes, or dyslipidaemia.

Treatment data

Ethical considerations: all patients monitored in the department were informed that their medical data could be used for research while respecting their

anonymity.

3. Result

We have selected 5 patients' records of female patients with Turner syndrome.

3.1. Epidemiological Data

The mean age of the patients was 25 years, ranging from 19 to 29 years. A 29-year-old patient had been married for three years; the other patients were single.

3.2. Diagnostic Data

The gynaecology department referred all patients. The main reason for consultation was primary amenorrhea, present in all patients. The married patient (patient N3) had expressed a desire to conceive. The amenorrhea was associated with a delay in the onset of secondary sexual characteristics, as evaluated by the Tanner Stage (see Table 1). Exploration of the gonadotropic axis favoured hyper gonadotrophic hypogonadism in all five patients. Dysmorphic syndrome was present and discrete in all patients, predominating at the level of the cephalic extremity with a triangular face, low implanted hair, and epicanthus eyes. Two patients had nevi and bradymetatarsia was noted in two patients. Failure to thrive was recorded in three patients. The mean height of the patients was 1.5 m (range: 1.40 m - 1.60 m). Overweight associated with abdominal obesity was noted in Patient 3. Pelvic ultrasound revealed uterine hypotrophy in all five patients and the ovaries were not visualised. The 45, X karyotype was detected in two patients; the others had a mosaic pattern. All patients underwent fasting glycemia, investigation of lipid abnormalities, liver enzyme assay, and TSH assay. Hashimoto's thyroiditis was found in one patient. Hypertension was found

Table 1. Summary of epidemiological and diagnostic data of the five patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (year)	22	26	29	29	19
Marital status	Single	Single	Married	Single	Single
Tanner Stage Pubic hair scale Breast development scale	Stage 1	Stage 3	Stage 2	Stage 3	Stage 2
	Stage 1	Stage 1	Stage 3	Stage 1	Stage 1
Size (meters)	1.59	1.45	1.46	1.40	1.60
Karyotype	(45, X (81%), 46, XX (19%)	45X	(45, X (83%), 46, XX (17%)	45, X	(45, X (80%), 46, XX (20%)
Dysmorphic syndrome	Yes	Yes	Yes	Yes	Yes
Other Signs	No	No	Strabismus	Hashimoto's thyroiditis Hypertension Abdominal obesity Pure Hypercholesterolaemia	Hypertension

in 2 patients. None of the patients had a heart defect and one patient had strabismus.

3.3. Treatment Data

All 5 patients received estrogen- and progesterone-based hormonal therapy. The first 3 months of treatment were marked by the appearance of privative bleeding. We do not have the benefit of hindsight to assess the impact of the treatment on the trophicity of the internal genital organs. Patient N3 was informed of the possibility of medically assisted procreation. Patients 3 and 4 are also on antihypertensive medication and patient 4 is on levothyroxine.

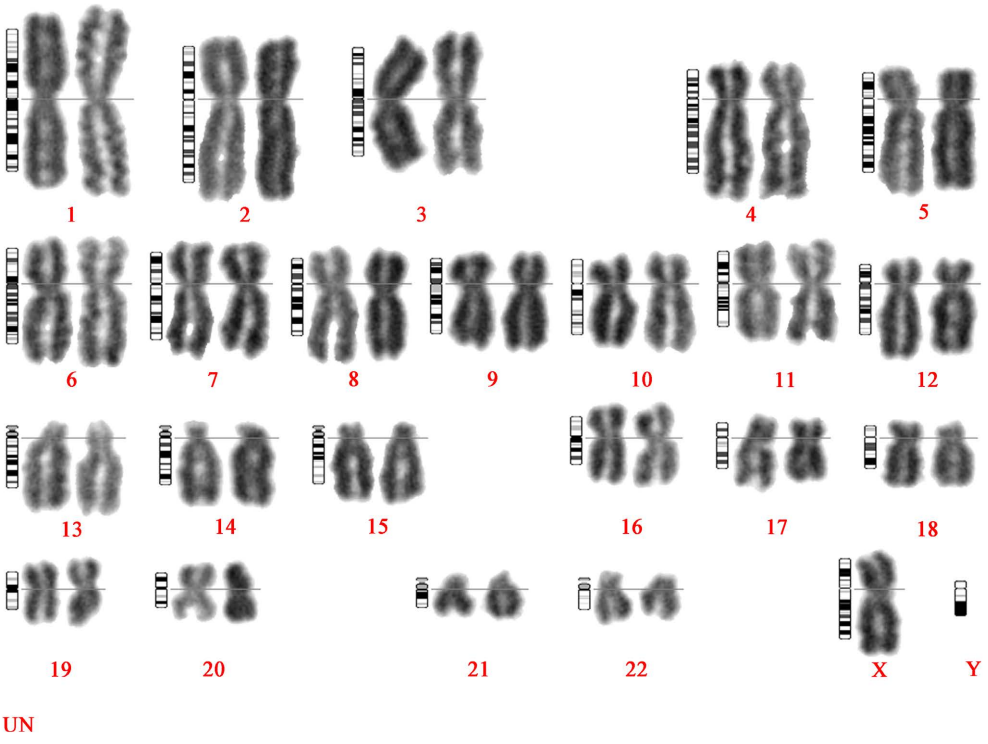
GH treatment was not considered for our patients who had delayed growth due to their age at diagnosis.

Table 1 summarises the epidemiological and diagnostic data regarding our patients.

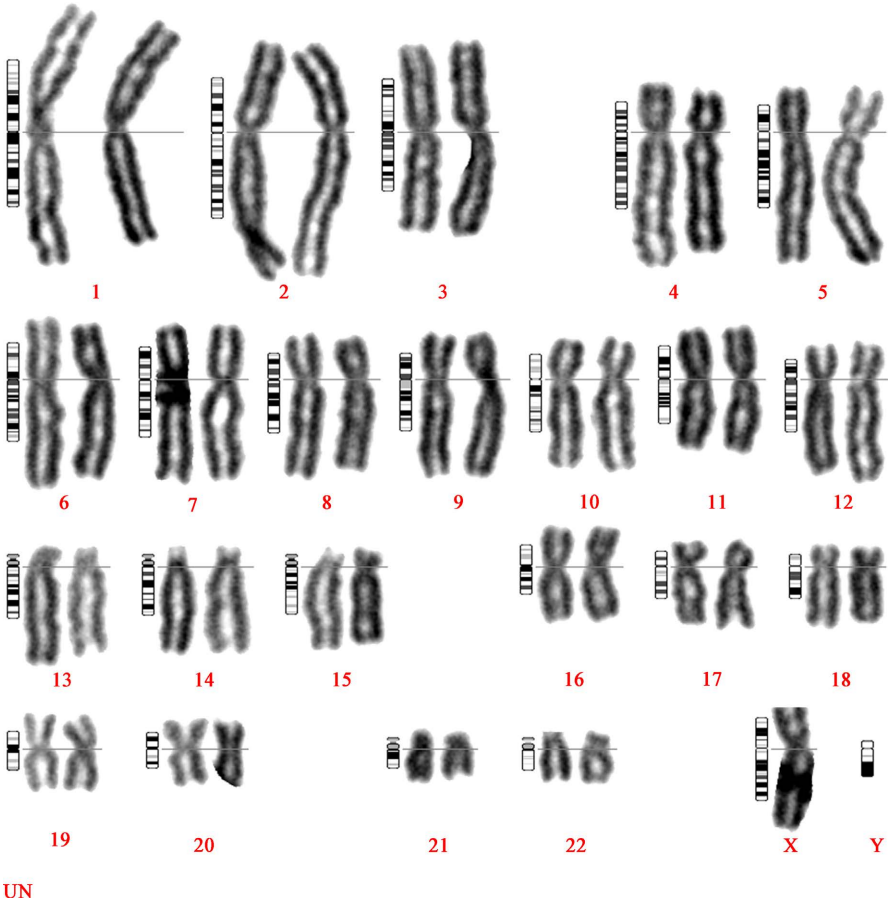
Figure 1 illustrates Karyotype of patient's number 4.

4. Discussion

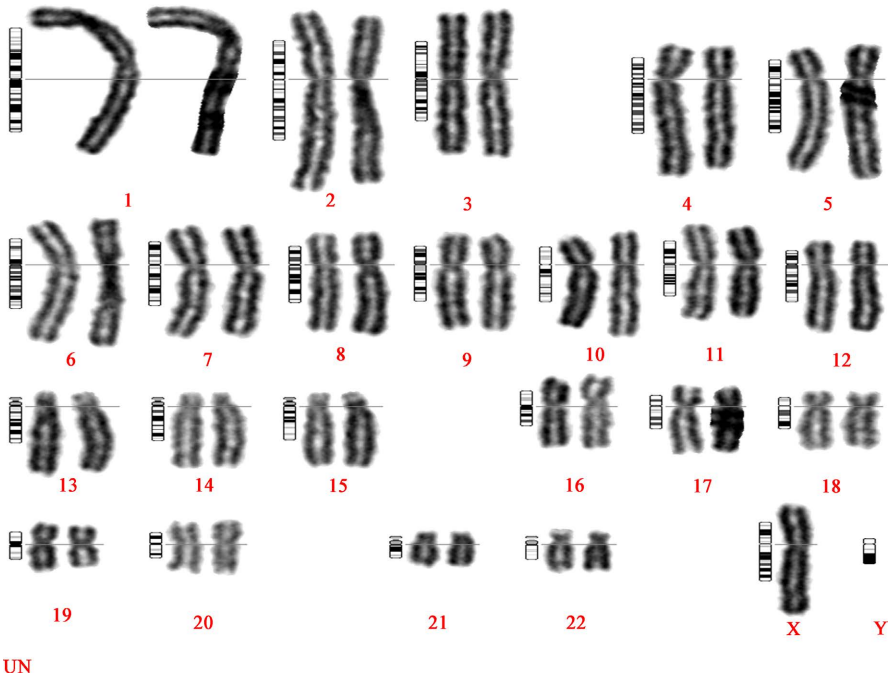
Turner syndrome is a congenital syndrome, presenting in approximately 1 in 2000 live-born girls [1] [3]. Only 30% to 66% of all people with Turner syndrome are diagnosed, with a wide range of ages at the time of diagnosis, from the prenatal period to postmenopausal. The median age at diagnosis is generally 15 years [2]; however, in our series, the average age at diagnosis was 25 years. This diagnostic delay is reported in the literature; almost 50% of patients are diagnosed in adolescence or adulthood [2]. During adolescence, the diagnosis often



(a)



(b)



(c)

Figure 1. Karyotype of Patient number 4: number of mitoses count 15; number of mitoses classsified 3.conclusion 45X.

derives from the presence of partial or total pubertal delay or, more frequently, from the presence of primary amenorrhea and/or delayed growth. Similarly, in young adults, the diagnosis is often made when exploring infertility. Generally, a mosaic karyotype, which would be associated with a more discrete phenotype, is found in patients with a late diagnosis of turner syndrome [6]. This mosaicism occurs in 60% of our patients and the correlation between phenotype and karyotype is questioned by some authors [7]. In our series, this diagnostic delay could be partly related to the presentation of discrete dysmorphic syndrome in all our patients.

The severity of turner syndrome is attributable to cardiovascular disease, which is the leading cause of death [8]. Nearly 50% of individuals with turner syndrome are born with a congenital heart defect, such as bicuspid aortic valve, coarctation of the aorta, and lengthening of the transverse aorta [9]. Patients with turner syndrome have a three-fold higher risk of hypertension than the general population, and it is estimated that up to 40% of children and around 60% of adults with turner syndrome have hypertension [4] [8]. Patients with turner syndrome have a higher incidence of cardiovascular events that manifest early and with high mortality [8] [10]. In our cohort, two of the five patients had hypertension, however, none had a heart defect.

With a late turner syndrome diagnosis, the physician faces two dilemmas, the appropriateness of Growth Hormone (GH) treatment and the management of already delayed puberty to optimise the overall results [4]. The latest international guidelines from 2016 recommended initiating GH treatment early (around four to six years of age, and preferably before the age of 12 to 13 years) if the child already shows signs of growth delay [11]. The most important factors associated with good response and better height gain are age at treatment initiation (negative correlation) and duration of treatment (positive correlation) [12]. The greatest height gain during GH treatment for turner syndrome occurs in the prepubertal period. Oestrogen is involved in epiphyseal fusion and may represent a limiting factor for longitudinal bone growth, resulting in decreased height gain with reduced stature growth. However, the common practice of delaying the onset of puberty to allow GH to work during an oestrogen-free period should now be considered obsolete. This is particularly important in patients with a late diagnosis, in whom both treatments should be started simultaneously [5]. In our series, the three patients with short stature were between 22 and 29 years old. In these patients, GH treatment was not considered after cost-benefit assessment. Growth hormone was not available in Senegal, so it had to be purchased in Europe, which increased the treatment cost. Furthermore, GH treatment is not justified in adulthood [5] [12].

Hormone replacement therapy (HRT) is necessary to induce puberty, maintain secondary sex characteristics, and achieve peak bone mass. HRT is known to reduce the risk of fractures and osteoporosis, ischemic heart disease, hypertension, stroke, and diabetes mellitus [3] [5]. HRT can also reduce aortic rigidity, decrease intima-media thickness, and improve endothelial function [13]. Oes-

trogen therapy is necessary to ensure uterine growth and improve the chances of implantation if pregnancy is contemplated [5] [14]. This emphasises the importance of adequate HRT, initiated during puberty, well before the demand for fertility [14]. All our patients received HRT.

Oocyte donation is the most common option for patients seeking to conceive as it leads to fewer miscarriages compared with using one's own oocytes. The clinical pregnancy rate is 30% - 46% depending on the method (fresh/frozen) and, therefore, similar to the corresponding rates in eukaryotic oocyte recipients [15]. Pregnancies achieved through oocyte donation are associated with a higher incidence of gestational hypertension and pre-eclampsia compared with conventional *in vitro* fertilization (IVF), and up to 35% of TS women receiving an oocyte donation develop complications related to hypertension [15].

Contraindications relating to an increased risk of aortic dissection should be respected, such as bicuspid aortic valve, transverse aortic elongation, coarctation of the aorta, and hypertension [3] [15].

The 29-year-old patient who wished to conceive had hypertension as a contraindication, along with other comorbidities, such as dyslipidaemia and abdominal obesity, which increased the risk of cardiovascular complications. In any case, it would be necessary to control all these risk factors and ensure good uterine growth with regular ultrasounds to assess the thickness of the endometrium before considering Assisted Reproductive Technology (ART).

5. Conclusion

Turner syndrome, in our practice, is diagnosed in adulthood, when presenting with delayed puberty or an infertility assessment. This delay in diagnosis may be due to the discrete nature of the dysmorphic syndrome. This is a limiting factor in the management of failure to thrive; furthermore, it reduces the chances of childbearing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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