

**PRIMARY AMENORRHEA REVEALING AN ISOCHROMOSOME OF THE LONG ARM OF THE X CHROMOSOME: A CASE REPORT**

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**ABSTRACT**

An iso chromosome is an abnormal chromosome consisting of two long arms or two short arms of the same chromosome with loss of the other arm. The long arm iso chromosome of the X chromosome is a variant of Turner syndrome. We report the case of an 18 year old female patient, without any notable pathological history, who consulted us for primary amenorrhea with a delay in height and weight, in whom the clinical examination showed a female morphotype, with no disorders of sexual differentiation, and no signs of virilization. The karyotype showed a 46XX with isochromosome of the long arm of the X chromosome. The hormonal assessment showed a very high level of pituitary gonadotropins.

**KEYWORDS:** Turner syndrome, Isochromosome X, Primary Amenorrhea, Gonads.

**INTRODUCTION**

Primary amenorrhoea is defined as the absence of a menstrual cycle in girls after the age of 16 with or without pubertal development.

There are multiple etiologies. X chromosome abnormalities are a frequent cause of primary amenorrhoea, dominated mainly by Turner syndrome and its variants. The isochromosome of the long arm of the X chromosome is an infrequent chromosomal abnormality, most often revealed by primary amenorrhoea. Hormone replacement therapy is prescribed to combat the deleterious effects of hypo-estrogenism and allows these patients to have psychologically reassuring withdrawal bleeding.

**Clinical observation**

This is an 18 year old female patient, with no particular personal or family history, who presented with primary amenorrhea.

In the siblings, the patient has a sister who is normally regulated, with a normal statural-ponderal development.

The clinical examination found a weight of 58 kg, with a height of 148 cm, below the 3rd percentile.

Breast examination showed mammary buds corresponding to stage 2 of Tanner.

Examination of the external genitalia shows no sexual ambiguity, with a feminine appearance, the presence of an infantile appearance of the labia majora, 2 orifices, no palpable mass in the labia majora or inguinal regions, the rest of the examination is without abnormality, notably no clinical signs of hyper androgenism, no olfactory disturbances, and no abnormalities of vision or headaches.

The clinical picture is one of primary amenorrhoea with poorly developed secondary sexual characteristics.

A biological assessment was requested, including a very high FSH level of 95.22 IU/l, a low oestradiol level, with a collapsed AMH level.

A radiological work-up was also ordered, including a pelvic ultrasound, which showed a hypoplastic uterus 27 mm long and 17 mm thick, with no visible ovaries.

A wrist X-ray showed a bone age of 18 years according to the Greulich and Pyle atlas (Figure 1).

In view of this clinical picture, in particular the short stature in relation to the siblings, gonadal dysgenesis was suspected, which led to the prescription of a karyotype which was of the female 46XX type, and the diagnosis of a pseudodicentric X iso chromosome was retained (figure 2).

The patient was put on low estrogen hormone replacement therapy. The evolution was marked by the

occurrence of a withdrawal haemorrhage after 3 months of treatment.



Figure 1: X-ray of the left wrist showing a bone age of 18 years.

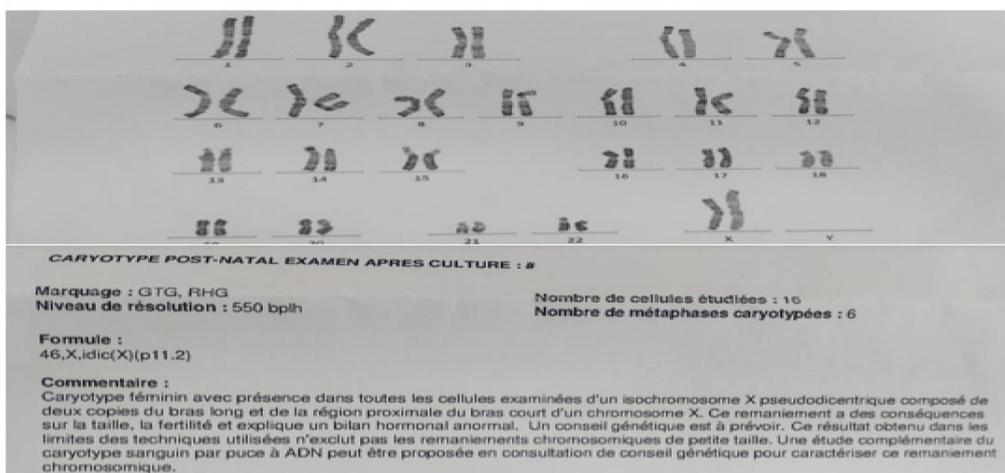


Figure 2: Female karyotype with isochromosome of the long arm of the X chromosome.

## DISCUSSION

The age of menarche (onset of the first menstrual period) in France is 12.8 years. With the variations inherent in all biological data ( $\pm 2$  SD), we speak of primary amenorrhoea if menarche has not occurred by the age of 16.

The diagnostic approach is based on careful questioning and careful clinical examination, leading to an etiological diagnosis.

X chromosome anomalies are known to cause gonadal dysgenesis, notably Turner syndrome, and the long arm isochromosome of the X chromosome, which is a variant of Turner syndrome.

Turner syndrome is a common cause, defined by the total or partial loss of one of the two X chromosomes. Its incidence is one in 2500 girls.<sup>[1]</sup>

It is characterised by ovarian dysgenesis, associated with a variable number of extragenital anomalies. It is the consequence of an absence or abnormality of one of the two X gonosomes, resulting in a haploinsufficiency of genes involved in the development and maintenance of

the ovarian follicular pool. In ST, the initial follicular pool is normal at 17 weeks of amenorrhoea.<sup>[2]</sup> and then its deterioration in utero will be accelerated, leading later to variable histological pictures and gonadal functioning.

In 50% of cases, the karyotype shows an X monosomy (45,X), in 5 to 10% of cases a duplication of the long arm of an X chromosome (46, X, i[Xq]). The other karyotypes are mainly mosaic forms (45X, 46XX). In the vast majority of cases, amenorrhoea is primary.<sup>[3]</sup> Clinically, short stature, low hairline, pterygium colli, ulna valgus may point to the diagnosis of Turner syndrome, but none of these signs are consistent. The essential examination to perform is a karyotype.

Although rare spontaneous pregnancies have been described, gonadal dysgenesis is most often responsible for impuberty and infertility, the prognosis of which has been radically changed by the practice of donor assisted reproduction (DAR).

An iso chromosome is an abnormal chromosome formed by two long arms or two short arms of the same chromosome. This chromosome consists of two identical parts with a duplicate region and a deleted region. An

isochromosome may be monocentric or dicentric depending on the mechanism of formation (Figure 3). The most common isochromosome encountered is the isochromosome for the long arm of the X chromosome which is a cytogenetic variant of Turner syndrome, and this is the case in our patient. Structural abnormalities of the X chromosome such as isochromosome Xq represent more than 15% of Turner Syndromes. Their origin can be maternal or paternal.<sup>[4]</sup>

The clinical signs of this chromosomal anomaly are similar to the clinical signs of Turner syndrome, in our patient's case, she only had a delay in growth with impuberty.

All structural abnormalities of chromosomes are likely to be inherited.

It is therefore necessary to make a family tree as complete as possible, with the collection of history, particularly gynaecological. The aim is to manage patients who are potentially at risk of being inherited. A karyotype should be performed in the first-degree relatives and in the rest of the family depending on the status of the common first-degree relative.

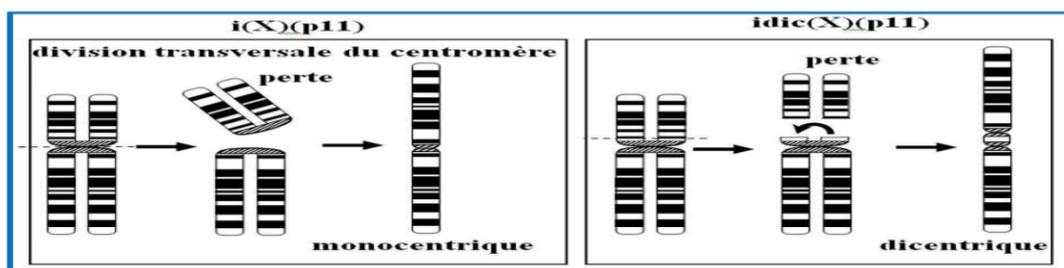


Figure 3: Mechanism of isochromosome formation.

Multidisciplinary management, with increased gynaecological, endocrine and cardiological follow-up, should be implemented. The rest of the management will depend on the clinical signs present in the patient,<sup>[5]</sup> in our patient's case, an oestrogenic hormone replacement therapy was started, to prevent the complications of hypo-oestrogenism, notably cardiovascular and metabolic.

## CONCLUSION

Turner syndrome and its variants are a frequent cause of primary amenorrhoea, and the diagnosis should always be made in the presence of hypergonadotropic hypogonadism, especially if there is associated statural delay, diagnosis is based on karyotyping, hormone replacement therapy is necessary, and screening of first-degree relatives and the rest of the family is necessary.

## Patient consent

Informed consent was obtained from the patient for publication.

## Conflict of interest

The authors declare no conflict of interest.

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