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Constitutional Chromosomal Abnormalities Associated with Reproductive Disorders at Félix Houphouët-Boigny University of Abidjan (Côte d'Ivoire): Three Case Reports

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Abstract

Introduction: This article discusses female reproductive disorders, specifically primary amenorrhea and recurrent spontaneous abortions (RSA). Primary amenorrhea affects 3 to 4% of adolescent girls and can result from hormonal abnormalities, malformations, or chromosomal abnormalities, mainly involving the X chromosome. Recurrent spontaneous abortions (RSA), affecting 2% to 3% of women of childbearing age, are associated with significant psychological stress. Chromosomal abnormalities, particularly Robertsonian translocations, play a key role in RSA, with homologous translocations being particularly high-risk. The study of these genetic etiologies is limited in Côte d'Ivoire. Observations: Three clinical cases are presented. The first concerns a 16-year-old adolescent with primary amenorrhea due to a rare interstitial chromosomal duplication (Xp22.3-p11.4 and 9q11-q13). It highlights the role of chromosomal abnormalities in gonadal dysgenesis. The other two cases concern patients with RSA associated with Robertsonian translocations that disrupt meiosis. One presents with a homologous Robertsonian translocation (13;13), and the other with a heterologous translocation (13;14). The normal

karyotype of the daughter of the patient with the homologous 13 translocations demonstrates the complexity of the genetic mechanisms involved. Karyotyping was performed using G-banding and microscopic analysis. Appropriate genetic counseling was provided to the patients and their families. Conclusion: Cytogenetic analysis is essential for exploring reproductive disorders. Precise characterization of chromosomal abnormalities by PCR and sequencing is crucial for genetic counseling and understanding the underlying genetic mechanisms. These observations enhance knowledge of the links between specific chromosomal abnormalities and clinical phenotypes in Côte d'Ivoire.

Keywords

Robertsonian Translocation, Interstitial Chromosomal Duplication, Recurrent Spontaneous Abortions, Primary Amenorrhea, FÉLix Houphouët-Boigny University

1. Introduction

Primary amenorrhea is defined as the absence of menstruation in a girl of at least 15 years of age with normal growth and secondary sexual characteristics, or is considered in the absence of menarche and normal breast development by the age of 13 [1]. It is a frequent reason for consultation, affecting approximately 3 to 4% of the general adolescent population [2]. Its causes are diverse, including hormonal disorders, malformations of the reproductive system, and chromosomal abnormalities [3]. The latter are mainly represented by numerical and structural abnormalities of the X chromosome [4] [5]. Concurrently, recurrent spontaneous abortions (RSA), characterized by at least two consecutive pregnancy losses before the 22nd week of amenorrhea [6], affect 2 to 3% of women of childbearing age and are a source of considerable psychological stress [7] [8]. Although immunological factors and vitamin deficiencies are implicated [9]-[11], chromosomal abnormalities, particularly Robertsonian translocations, are frequently associated with RSA [12]. Furthermore, homologous Robertsonian translocations, while rare, are particularly correlated with a high risk of RSA [13]. In Côte d'Ivoire, the study of the genetic etiologies of reproductive disorders, whether primary amenorrhea or RSA, remains limited due to insufficient technical resources and a lack of qualified personnel. In this context, we report three distinct cases observed at the Félix Houphouët Boigny University of Abidjan: the first concerns an adolescent presenting with primary amenorrhea associated with an unusual interstitial chromosomal duplication involving regions Xp22.3-p11.4 and 9q11-q13, and two patients consulting for recurrent spontaneous abortions involving Robertsonian translocations.

2. Observations

This article presents three cases of reproductive disorders associated with chromosomal abnormalities, observed at the Félix Houphouët-Boigny University of Abidjan.

Observation 1: This case involves a 16-year-old female student, nulliparous, with no significant genetic or pathological history, and born from a non-consanguineous marriage. She reports no consumption of alcohol or tobacco, and does not use any estrogen-progestin contraception. Her parents have no known history of genetic pathologies. She consulted the histology, embryology, and cytogenetics department of the Cocody University Hospital Center (CHU) for the management of primary amenorrhea. The medical history reveals no chronic headaches or visual disturbances. The clinical examination reveals a female phenotype; however, the development of secondary sexual characteristics is insufficient, notably breast development (Tanner stage S1) and pubic and axillary hair growth (Tanner stage P2), suggesting hormonal dysfunction. Laboratory tests confirm severe hypogonadotropic hypogonadism, with estradiol (< 9 pg/mL), LH (0.17 mIU/mL), and FSH (0.94 mIU/mL) levels below normal. Pelvic magnetic resonance imaging (MRI) confirms uterine hypoplasia and the absence of visible ovaries, consistent with the ultrasound findings.

Observation 2: This case concerns a 37-year-old patient, gravida 8, parity 2, who does not consume alcohol or tobacco. Her obstetric history includes a miscarriage at 12 weeks in her first pregnancy, followed by the term birth of a daughter with autism (now 7 years old), then a premature birth at 7 months with a stillbirth, and finally 5 successive spontaneous miscarriages before 12 weeks. The physical examination is generally normal, except for being overweight, with a body mass index (BMI) of 28. Imaging examinations (ultrasound and pelvic MRI) are unremarkable. Similarly, the hormone levels (FSH, TSH, testosterone, AMH) are within the normal range.

Observation 3: The last observation concerns a 36-year-old patient, gravida 7, parity 1, who does not consume alcohol or tobacco. Her obstetric history includes two miscarriages at 12 weeks in her first two pregnancies, followed by the term birth of a son (now 11 years old), and finally 4 successive spontaneous miscarriages before 12 weeks. The physical examination is generally normal, except for obesity, with a body mass index (BMI) of 35. Imaging examinations (ultrasound and pelvic MRI) and hormone levels (FSH, TSH, testosterone, AMH) are normal.

For each patient, a constitutional karyotype was performed. This procedure began with the collection of a venous blood sample into a tube containing sodium heparin. Subsequently, the lymphocytes were cultured to stimulate their division. Once the cells were blocked in metaphase, they underwent hypotonic shock, then were fixed and washed to allow for chromosome spreading on slides. G-banding was then applied, allowing for the identification of chromosomes based on their specific patterns of light and dark bands. Microscopic analysis of the metaphases and their interpretation were carried out in accordance with the international recommendations of the International System for Human Cytogenetic Nomenclature (ISCN).

This analysis involved a minimum of 30 cells with a resolution of 550 bands, ensuring precise detection of any chromosomal abnormalities. It is important to note that the products of the miscarriages could not be karyotyped.

The karyotype results revealed the following abnormalities: For patient 1, an interstitial duplication was observed, affecting both chromosomes X (Xp22.3-p11.4) and 9 (9q11-q13) (Figure 1). The nature of the chromosomal duplication was explained to the patient and her family in detail, emphasizing that it is a rare anomaly where portions of chromosomes X and 9 are present in excess. Her potential implications for pubertal development, ovarian function, and fertility were detailed.

Regular endocrine follow-up was also recommended for the patient, and karyotyping for the parents to assess the risk of recurrence. Informing about the need for regular endocrine follow-up and a multidisciplinary approach.

For patient 2, the analysis revealed a homologous Robertsonian translocation involving both chromosomes 13, with a karyotype described as 45, XX, rob (13;13) (q11.2;q11.2) (Figure 2). Furthermore, the daughter of this patient has a normal karyotype. Finally, in patient 3, a heterologous Robertsonian translocation was identified, involving chromosomes 13 and 14, with a chromosomal formula 45, XX, rob (13;14) (q11.2;q11.2) (Figure 3). Similarly, the son of this patient has a normal karyotype. The patients were informed about the role of Robertsonian translocations in RSA, the high risk of recurrent miscarriages or trisomy in the child, and assisted reproductive options such as preimplantation genetic diagnosis (PGD) and prenatal diagnosis, and gamete donation.

3. Discussion

These three case reports, originating from the cytogenetics laboratory at Félix Houphouët Boigny University in Abidjan, illustrate the diversity of chromosomal abnormalities associated with reproductive disorders in women. The first case highlights the etiological complexity of primary amenorrhea, while the latter two underscore the role of chromosomal abnormalities in recurrent spontaneous abortions (RSA).

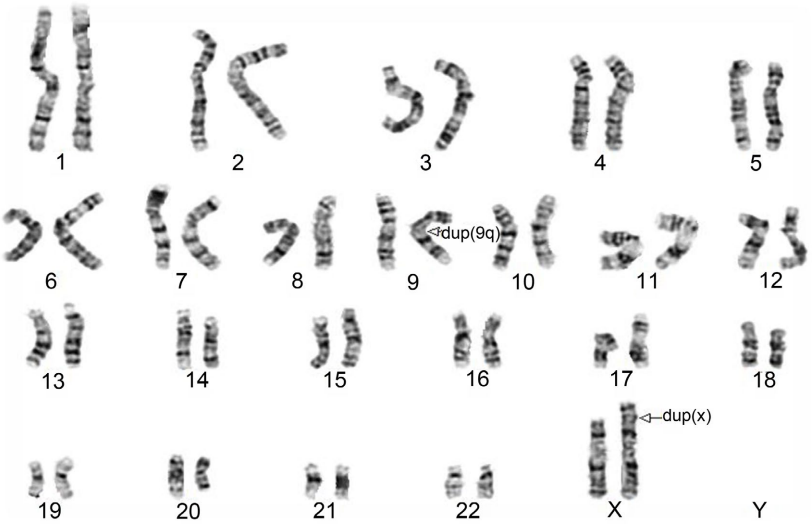

Figure 1. Female karyotype exhibiting interstitial duplications of one X chromosome and chromosome 9: 46, XX, dup(9) (q11q13), dup(X) (p22.3p11.4).

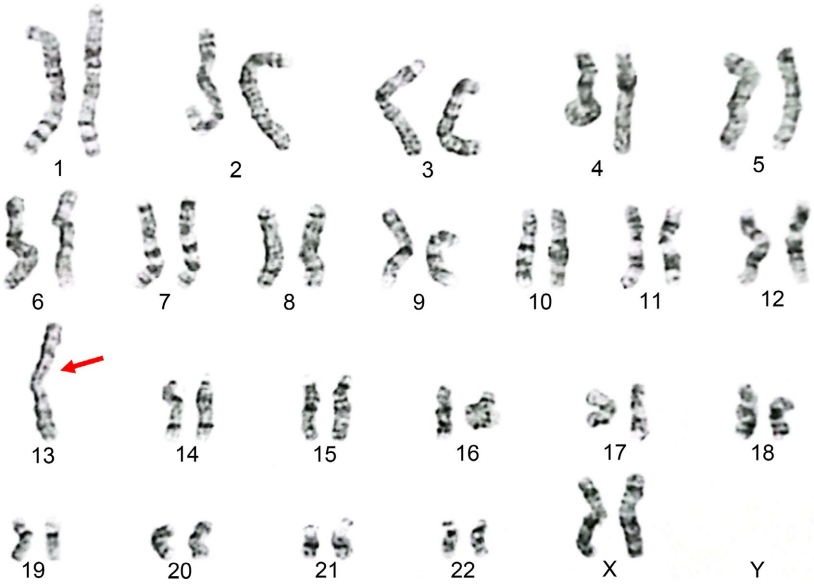

Figure 2. Female karyotype with a homologous robertsonian translocation 45, XX, der(13;13) (q11.2;q11.2).

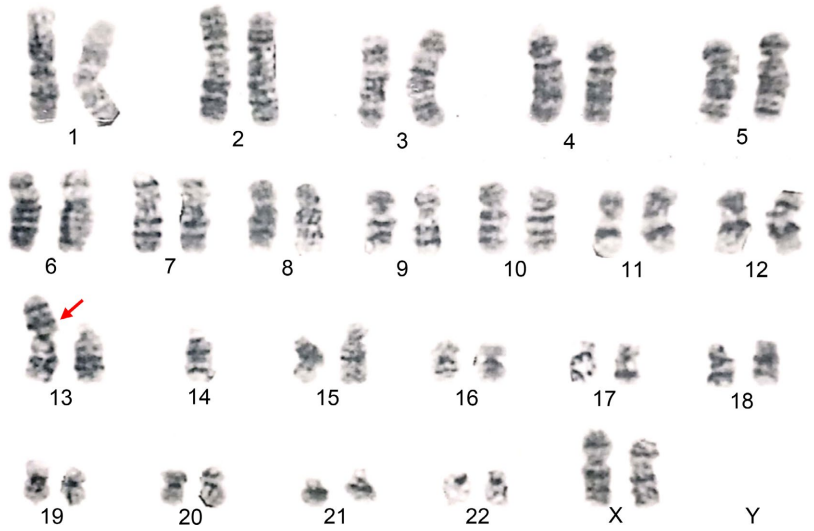

Figure 3. Female karyotype with a heterologous robertsonian translocation 45, XX, rob (13;14) (q11.2;q11.2).

The case of primary amenorrhea associated with interstitial duplications of chromosomes 9 (9q11q13) and X (Xp22.3p11.4) emphasizes the significant contribution of structural chromosomal abnormalities to gonadal dysgenesis, a common cause of primary amenorrhea [3]. The duplication in Xp22.3p11.4 is particularly relevant given the presence of key genes for ovarian function such as NR0B1/DAX1 and EIF1AX [14] [15]. The overexpression of the EIF1AX gene, which escapes X chromosome inactivation and is highly expressed in the ovary, has also been implicated in primary ovarian insufficiency [15]. A 2015 study reporting an atypical case of Turner syndrome with a complex X chromosome rearrangement [46, X,der(X)(pter->q21.2-p11.23->pter)] also illustrates how abnormalities affecting

the short arm of the X chromosome can impact the gonadal phenotype [16]. The presence of the SHOX gene in Xp22.33, involved in bone growth, and the concentration of genes related to ovarian function on the long arm of the X chromosome (Xq) partly explain the observed phenotypic variability [16]. Furthermore, the Xp22.3p11.4 region harbors genes involved in neurological and cardiovascular functions, such as NLGN4X and TSPAN7, whose mutations are associated with neurodevelopmental disorders [17] [18]. The interstitial duplication in 9q11q13, although less frequently associated with primary amenorrhea, could potentially disrupt the expression of metabolic genes like GALT [19], highlighting the complexity of the phenotypic consequences of chromosomal abnormalities. This first case highlights the diagnostic challenge posed by these duplications and the necessity of molecular cytogenetics for precise characterization and adapted genetic counseling. Additionally, regular neuropsychological monitoring is recommended for the early detection and management of potential cognitive disorders.

The last two observations demonstrated two distinct presentations of recurrent spontaneous abortions (RSA) associated with Robertsonian translocations. The first concerns the identification of a derived translocation involving chromosomes 13 and 14 (45, XX, rob (13;14) (q11.2;q11.2)). The second reports a homologous Robertsonian translocation involving chromosome 13 (45, XX, rob (13;13) (q11.2;q11.2)). These observations align with the literature that clearly establishes the role of chromosomal abnormalities, both numerical and structural, including Robertsonian translocations, in the etiology of recurrent miscarriages [20] [21]. Homologous Robertsonian translocations, although rare for chromosome 13, disrupt chromosomal segregation during meiosis, leading to the formation of unbalanced gametes that are often incompatible with embryonic development [22]-[25]. However, the normal karyotype of the daughter of this patient presenting the homologous Robertsonian translocation involving chromosome 13 highlights the complexity of the genetic mechanisms governing embryonic development. Phenomena such as uniparental disomy or mosaicism could potentially allow for the normal development of embryos in carriers of chromosomal abnormalities [26], although this is not directly demonstrated in this specific case.

4. Conclusion

These three case reports underscore the crucial importance of cytogenetic analysis in the investigation of reproductive disorders. They illustrate the diversity of chromosomal abnormalities encountered and the complexity of their phenotypic consequences. Genetic counseling was provided to the patients and their families. However, the precise characterization of these abnormalities through PCR and sequencing is essential for tailored genetic counseling for affected families and a better understanding of the genetic mechanisms underlying reproductive disorders. These observations contribute to expanding our knowledge of the associations between specific chromosomal abnormalities and clinical phenotypes in the Ivorian population.

Conflicts of Interest

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

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