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Klinefelter Syndrome Diagnosed during the Management of Decompensated Diabetes

Mamadou Ba[1], Nafy Ndiaye[1], Ngoné Diaba Diack[1], Jean Pascal Demba Diop[2], Mouhamed Mbar Niang[1], Khadidiatou Samb[1], Sokhna Awa Balla Sall[1], Yakham Leye[1], Abdoulaye Leye[1]

[1]Department of Endocrinology-Diabetology-Nutrition, Centre Hospitalier National de Pikine, Dakar, Senegal
[2]Department of Human Genetics, Cheikh Anta Diop University, Dakar, Senegal
Email: mamadoubanews@gmail.com

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Abstract

Introduction: Klinefelter syndrome brings together all the clinical and hormonal manifestations linked to the presence of a supernumerary X chromosome, giving a classical karyotype of 47, XXY. It is a genetic disease, the leading cause of aneuploidy in humans, making it one of the most common chromosomal diseases. The association with diabetes is rare resulting from multiple pathophysiological mechanisms. **Observation:** We report the case of a 47-year-old patient with a history of familial diabetes hospitalized for initial decompensation of his diabetes in the ketoacidotic mode who also presented a clinical picture of hypogonadism with a gynoid morphotype, a micropenis, a bilateral gynecomastia, female pubic hair associated with testicular atrophy in a context of couple infertility. The picture suggested Klinefelter syndrome associated with type 2 diabetes confirmed by hormonal (hypergonadotropic hypogondism) and genetic (47XXY karyotype) explorations. **Conclusion:** Klinefelter syndrome is a common cause of hypogonadism and male infertility. It is often diagnosed late. The association with diabetes is possible under the influence of multiple physiopathological mechanisms. We must think about this syndrome in the face of any hypergonadotropic hypogonadism and have an easy karyotype in this context.

Keywords

Klinefelter Syndrome, Diabetes Mellitus, Senegal, Africa

1. Introduction

In 1942, Klinefelter published a report on 09 men with breast enlargement, sparse facial and body hair, small testes and an inability to produce sperm [1]. In 1959, it was discovered that these men with Klinefelter syndrome had an extra X chro-

mosome (genotype 47, XXY) instead of the usual male sex complement (genotype XY). The classic form of Klinefelter's syndrome, present in 80% - 90% of cases, is defined by a 47, XXY karyotype resulting from sex chromosome aneuploidy, while higher-grade aneuploidies (e.g. 48, XXXY or 48, XXYY) account for around 10% - 20% of the remaining cases. This genetic pathology is often due to this supernumerary X being associated with the onset of a metabolic syndrome [2]. In developing countries, these genetic desease are rarely described. The classic example is that of a patient with Klinefelter's syndrome diagnosed in Mali in a soldier [3]. We report the case of a 47-year-old patient diagnosed with Klinefelter's syndrome in the setting of decompensated diabetes. Klinefelter syndrome is associated with hormonal imbalances, particularly low testosterone, which increases the risk of type 2 diabetes. Cross-sectional studies have consistently reported an inverse relationship between plasma testosterone and insulin resistance in normal males. Individuals with Klinefelter syndrome have a higher risk of developing type 1 diabetes due to genetic and autoimmune factors. Obesity and insulin resistance further contribute to this increased risk [4]. Type 2 diabetes is frequent in hypogonadal patients, and vice versa, hypogonadism is also more prevalent among type 2 diabetics with presumed normal karyotype than in age-matched controls. These findings are minimized, or even absent, in some studies when correcting for body mass index (BMI) or waist to hip ratio, and question whether this association is largely mediated by adiposity rather than testosterone itself. This clinical case shows that, although rare, Klinefelter's syndrome is a reality in our countries, the association with diabetes is also a rare situation

2 Case Report

This was a 47-year-old patient with a history of first-degree diabetes in his family and a history of untreated infertility in the couple that had been evolving for 12 years. The patient is well cared for and lives with his family. He is not alocolotabagic and is well integrated into society. He is married and has unexplored couple infertility, which is common in developing countries.

He was referred to us from the Emergency Department of Pikine Hospital (Dakar/Senegal) for the management of an inaugural decompensation of diabetes.

He presented with diabetese ketoacidosis with hyperglycaemia, ketonuria, glycosuria, and Kussmaul dyspnoea.

On routine clinical examination, he also presented with a clinical picture of hypogonadism associating (**Figure 1**):

- A gynoid morphotype with a eunuchoid appearance;
- Bilateral gynecomastia, grade 3 in Simon's classification, which was the cause of persecution in her neighbourhood;
- Micropenis with a penis size of 03 cm;
- Triangular pubic hair of the female type;
- Macroskelia;
- Testicular hypotrophy with the presence of small, firm testicles on palpation.

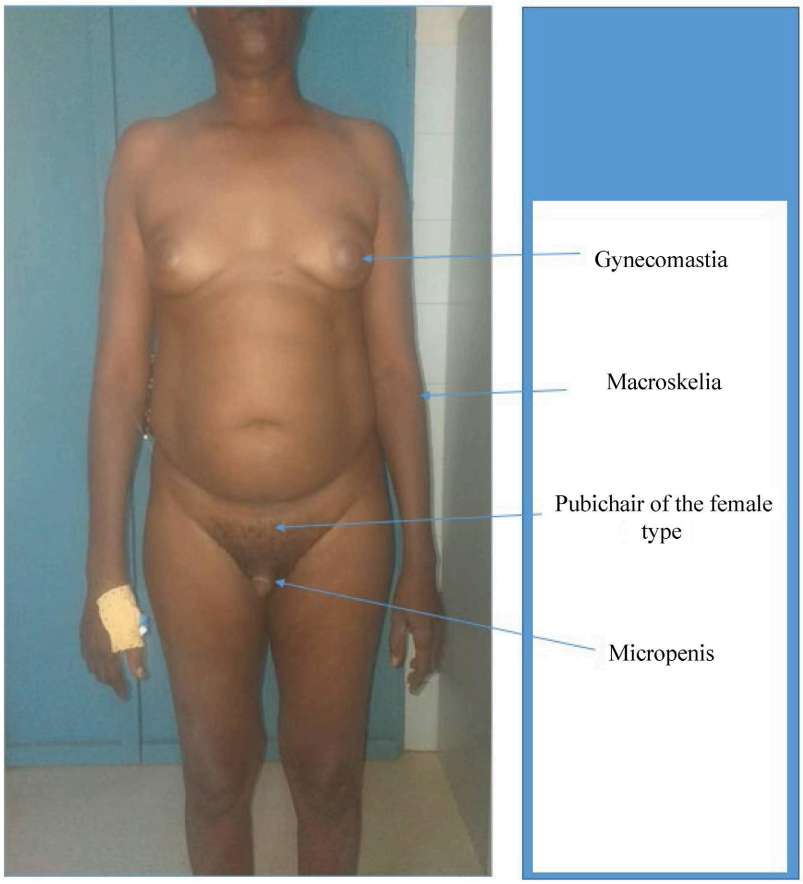

Figure 1. Eunuchoid appearancein a 47-year-old patient with Klinefelter syndrome.

In the face of this clinical picture of clinical hypogonadism, hormonal investigations showed a decrease in testosterone levels with low testosteronemia: 1.31 nmol/L (norm: 9.90 - 27.80) and high FSH: 13.49 mUI/ml (norm: 0.95 - 11.95) confirming the gonadal origin (hypergonadotropic hypogonadism). The spermogram revealed azoospermia. Testicular ultrasound revealed small testicles. The main diagnostic hypothesis was Klinefelter's syndrome. Genetic analysis confirmed this hypothesis by finding a 47, XXY karyotype.

The measurement of total testosterone levels helps confirm the diagnosis of hypogonadism. Once this diagnosis is made, the origin, whether central or peripheral, should be determined by measuring FSH/LH levels. When a testicular cause is confirmed, the most common etiology is Klinefelter syndrome. In adult KS patients, levels of testosterone are decreased, whereas FSH and LH are elevated. We were in the presence of a combination of Klinefelter's syndrome and diabetes.

This diabetes was close to type 2 in view of the presence of a metabolic syndrome, his advanced age, a history of family diabetes, and the negativity of anti-GAD and anti-AI2 antibodies.

From a therapeutic point of view, the patient was put on testosterone enanthate (Androtardyl*) at the rate of 250 mg per fortnight by intramuscular injection, on insulin and then on metformin at an optimal dose, in addition to the hygienic and

dietary measures and psychological support inherent in these treatments. The patient's diabetes was well controlled. The clinical picture of hypogonadism persisted. A proposed operation for gynaecomastia could not be carried out for financial reasons.

3. Discussion

- **Epidemiology**

Klinefelter's syndrome is the leading cause of aneuploidy in humans. With an estimated prevalence of 1/600[4], it is one of the most common chromosomal disorders. Worldwide prevalence is currently estimated at around 150 per 100,000 population, making it a not uncommon disease, which means that every doctor in the course of his or her practice will be confronted with this condition, whether knowingly or unknowingly. It is a major genetic cause of infertility, affecting almost 11% of men with azoospermia [5], and a major cause of hypogonadism. It is thought to be more common in Asian populations, where a recent series found an incidence of around 335 cases per 100,000 inhabitants.

- **Diagnosis**

The clinical picture of Klinefelter syndrome is classically one of eunuchoidism resulting from this male hormone deficiency. This clinical presentation is similar to that of the Malian military patient who had Klinefelter syndrome [3]. Both patients had bilateral gynecomastia, hypergonadotropic hypogonadism, testicular atrophy, and a karyotype of 47, XXY.

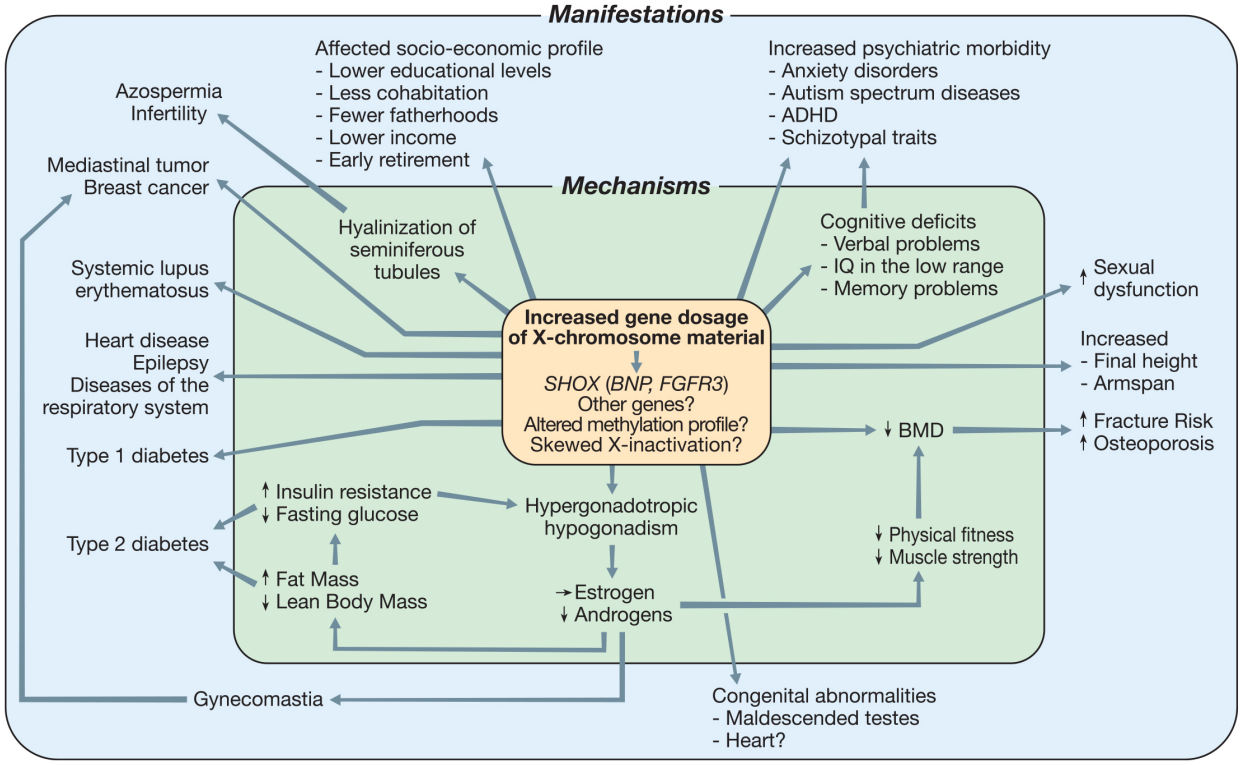

Figure 2. Relation between diabetes and Klinfelter syndrom [6].

The association of Klinefelter syndrome with diabetes is described at the pathophysiological level in relation to the expression of supernumerary X. Our patient presented with diabetes close to type 2 in view of his family history of diabetes, his metabolic syndrome and the negativity of anti-GAD and anti-AI2 antibodies (**Figure 2**). Over the past 50 years, numerous studies have examined the prevalence of diabetes in men with Klinefelter syndrome. Most of the literature implicates type 2 diabetes, which is significantly more common than type 1 diabetes in this patient population, as in the general population [7]. Estimates of the prevalence of type 2 diabetes vary, ranging from 10 to 39% depending on the population studied [8]. A small study of 31 men with Klinefelter's syndrome found that 17% of those under 50 and 62% of those over 50 had an abnormality on the oral glucose tolerance test, compared with 1.6% and 16% respectively in the general population. This frequent association is linked to the expression of the supernumerary X chromosome, the expression of which leads to a metabolic syndrome [9].

- **Therapeutics**

Our patient was put on hormone therapy based on testosterone enanthate making it possible to palliate his deficit to his hypogonadism. In relation to his diabetes at the time of decompensation insulin therapy with hydroelectrolyte rebalancing. The clinical picture, which suggested type 2 diabetes, led to oral antidiabetic treatment (metformin), which resulted in good glycaemic control.

4. Conclusion

Klinefelter's syndrome is a rare condition that is certainly under-diagnosed in our regions. Its association with diabetes and metabolic syndrome is not uncommon and requires regular monitoring of blood glucose levels in these patients. Its management in our countries is difficult because of the low socio-economic level of our populations. In order to improve monitoring, these rare diseases need to be listed, and programmes need to be set up to manage them.

Conflicts of Interest

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

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