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### RESEARCH ARTICLE

#### KLINFELTER'S SYNDROME AND THALASSEMIA MAJOR-A RARE ASSOCIATION

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#### Abstract

**Introduction:** Klinefelter's syndrome (KS) is the most common cause of male hypogonadism. It is also the most common sex chromosome disorder among men. Key clinical features of KS are small testes, gynaecomastia and long legs. It is known to be associated with other conditions like mitral valve prolapse, varicose veins, breast cancer and autoimmune diseases<sup>1</sup>. Rarely it can be associated with thalassemia<sup>2</sup>. Here we are reporting a similar rare association of KS with thalassemia major.

**Case report:** A18 years old boy presented with poor development of secondary sexual characteristics. He was born out of non-consanguineous marriage with no significant perinatal events. At 4years of his age, he was evaluated for easy fatigability, tiredness and weakness and found to have anemia. On further work-up, it turned out to be thalassemia major and both parents were found to have thalassemia trait. Since then, he is on regular blood transfusion and iron chelating therapy. However he stopped iron chelating therapy recently. From last three years he noticed bilateral enlargement of breast. On examination he had small testes, under developed pubic hair, bilateral gynaecomastia, long legs and hepatic enlargement. Laboratory evaluation showed low testosterone (237ng/dL), elevated follicular stimulating hormone (FSH -68mIU/mL), luteinizing hormone (LH-62mIU/mL), which is indicative of primary gonadal failure. His karyotype was 47,XXY. Diagnosis of Klinefelter's syndrome was made based upon clinical and laboratory findings. Other laboratory tests showed: hemoglobin - 11.7g%, fasting blood sugar (FBS)- 92mg/dL, serum calcium- 9mg/dL, and normal renal and liver function tests. Other hormonal tests such as thyroid profile, prolactin, serum estradiol and serum cortisol were normal. His serum ferritin was high (5671ng/mL) as he had stopped iron chelating therapy. In our patient, cause of hypogonadism was primary testicular failure due to KS. Our patient has KS associated with thalassemia major, which is a rare association. In thalassemia, hypogonadism results from iron overload and hypogonadotropic hypogonadism often responsible for this. Even though serum ferritin elevated it has not resulted in any impact on

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gonadotropic hormones and this might be due to short time interruption of iron chelating therapy.

**Conclusion:** In our patient delayed puberty was due to KS. Association of KS with thalassemia major is very rare. To our knowledge this is the first case report on KS associated with thalassemia major.

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## Introduction:-

Klinefelter's Syndrome (KS) is a common cause of hypogonadism among men. These individuals have small testes, reduced penile length along with other phenotypic features. The principal karyotype in majority of cases with KS is 47,XXY. KS is known to be associated with other comorbidities like mitral valve prolapse, varicose veins and autoimmune diseases. Rarely associates with thalassemia. This case report is going to reveal about a rare combination of KS with thalassemia major.

## Case details:

A 18-year-old boy presented with poor development of secondary sexual characteristics. He was born out of non-consanguineous marriage, full term of normal vaginal delivery and without significant perinatal adverse events. At birth, both testes were in scrotal region, penis was of normal length and no genital ambiguity was present. Milestones were as per chronological age.

At 4 years of his age, while evaluating for easy fatigability, weakness and tiredness, he was found to have anemia. On further evaluation he was diagnosed as thalassemia major.

Diagnosis of Beta thalassemia major was made after hemoglobin electrophoresis (HbA2-1.2%, HbF-20.8%) and DNA analyzed by sequencing for beta globulin gene which revealed compound heterozygous for IVS1-5(G-C) and poly A (T-C) mutations.

Parents were evaluated and both were found to have thalassemia trait.

He was requiring blood transfusion since then and presently he is on blood transfusion once in 2 weeks. He underwent splenectomy 4 years back. From last three years he has noticed the enlargement of both breast, which are not painful, and not having any discharge.

On examination, his weight was 47kg, height-158cm, body mass index (BMI)-18.8kg/m<sup>2</sup>, arm span-159cm, upper segment (US)- 73.5cm, lower segment (LS)- 84.5cm. His anthropometry is suggestive of long legs, which is typical of KS. On further examination, he was found to have bilateral gynaecomastia, short stretched penile length (SPL) (8cm), small testes and firm in nature (3ml volume on Prader's orchidometer), Tanner staging of pubic hair - P3 (curly hair distributed in inverted triangle) and axillary hair A1 (axillary hair absent). Skin complexion was normal and brown in color. On systemic examination, he only had hepatomegaly and other systems were normal.

Investigations are shown in table no: 1. Hormonal profile revealed low testosterone, elevated gonadotropic hormones suggestive of primary hypogonadism. Other hormonal evaluation (serum prolactin, thyroid profile, serum estradiol and serum cortisol) was normal. On further testing, his karyotype was 47,XXY, and Klinefelter syndrome was confirmed. Biochemical investigations revealed iron overload as he had stopped iron chelating therapy few months prior to testing. Other laboratory tests showed Hb-11.7g%, and renal and liver function tests were normal.

**Table-1:-** Laboratory investigations.

Parameter	Patient's values	Normal values
Hb (g%)	11.7	13-16
Serum creatinine (mg/dL)	0.9	0.5-1.4
FBS (mg/dL)	92	70-99
Serum Calcium (mg/dL)	9	8-10
Total bilirubin (mg/dL)	1.0	0.2-1.3
SGOT (IU/L)	36	<40

SGPT (IU/L)	36	<40
Serum Testosterone (ng/dL)	237	300-800
FSH (mIU/mL)	68	1.5-12
LH (mIU/mL)	62	1.2-8
Serum estradiol (pg/mL)	19	10-40
T3 (ng/mL)	1.1	0.8-1.8
T4 (mcg/dL)	6.3	5.5-12
TSH ( $\mu$ IU/mL)	1.9	0.5-5
Serum prolactin (ng/mL)	14	4-16
Serum cortisol (8AM) (mcg/dL)	12	5-20
Serum ferritin (ng/mL)	5671	25-340

### Discussion:-

Klinefelter's syndrome (KS) often presents with poor development of secondary sexual characteristics like facial hair, pubic and axillary hair, small testes and penis. It is the most common cause of hypogonadism and sex chromosomal disorder among men<sup>1</sup>.

Initially, Harry F. Klinefelter Jr. observed a group of patient under specific syndrome with features like bilateral gynaecomastia, small testes, aspermatogenesis and increased follicular stimulating hormone (FSH)<sup>3</sup>. Later, this syndrome was named after him. Later on, it was recognised that there were several conditions that were found in association with KS.

KS is characterized by very small and firm testes, azoospermia, infertility, long legs and significantly elevated gonadotropin levels. Small testes is uniform finding in KS<sup>1</sup>.

The reported prevalence of this syndrome was 1 in 500- 1000 men<sup>4</sup>. It is the most common sex chromosome abnormality. The basic chromosomal abnormality in Klinefelter syndrome is the presence of one or more extra X chromosomes. The principal karyotype in majority (90%) of KS is 47,XXY. The remaining proportion will have mosaic KS (47,XXY/46,XY). Rarely, KS individuals may have more than one extra X chromosomes (48,XXXY, 49,XXXXY), which is prone to have severe clinical features. While mosaic KS individuals have less severe clinical features<sup>1</sup>.

Diagnosis of KS should be considered in a person who presents with delayed puberty having small testes, gynaecomastia and long legs.

KS is known to be associated with other conditions such as mitral valve prolapse, varicose veins, non-Hodgkin's lymphoma, breast cancer, mediastinal cancers, abdominal obesity, type 2 diabetes and autoimmune diseases like Sjogren's syndrome, systemic lupus erythematosus and rheumatoid arthritis<sup>1</sup> etc.

It is very rare to have association with Thalassemia. To our knowledge there is only one case report in this regard. That too it was Thalassemia intermedia<sup>2</sup>. This would be the first case report to reveal association with  $\beta$ -thalassemia major.

Thalassemia is known to be associated with several endocrinopathies. These include hypogonadism, diabetes, hypoparathyroidism, hypothyroidism, adrenal insufficiency and growth hormone deficiency. Among these hypogonadism is the most common endocrine disorder. Hypogonadotrophic hypogonadism occurs more often than primary hypogonadism<sup>5</sup>. Gonadotrophic cells show more affinity towards iron that make them more susceptible than other pituitary cells.

A recent study from UK showed that 75% of patients had at least one endocrine disorder. Hypogonadism was found in 67%, diabetes in 41%, hypoparathyroidism in 17%, and hypothyroidism was seen in 14% of the subjects<sup>6</sup>. Any individual with thalassemia who presents with features of delayed puberty, central hypogonadism is likely the possibility.

However, our patient had primary hypogonadism due to KS. His testes size was small and firm in nature and also his

lab tests were showing elevated FSH and low testosterone. This pattern suggests primary hypogonadism. And it was further supported with his karyotype, 47,XXY (KS) that primarily causes testicular failure.

Lab results were showing iron overload as he had stopped iron chelating treatment recently. Because of the short duration of interruption of therapy, iron overload might have not shown the impact on gonadotropic cells, yet.

Klinefelter syndrome associating with thalassemia is rare. That too associating with thalassemia major is not reported so far. Early recognition and treatment of hypogonadism will help in induction of secondary sexual characters and also improve the quality of life. In Klinefelter syndrome apart from giving treatment for hypogonadism, we have to look for the detection and management of associated conditions, which is very important.

In thalassemia patients also, we have to look for the development of endocrine abnormalities secondary to iron overload. Special focus has to be given to children as these endocrine disorders are going to affect their growth and development significantly.

### **Conclusion:-**

In our patient, delayed puberty was due to KS. Association of KS with thalassemia major is very rare. To our knowledge this is the first case report on KS associating with thalassemia major.

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