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From mania to diagnosis: a case report of Klinefelter syndrome unmasked by a bipolar disorder

Authors: Mohd Noor Hanisah[1]; Che Mat Khairi[1]; Tuan Hadi Tuan Sharipah[2]; Nur Yusmira Mohd Yusoff[1]; Kamarulbahri Tengku Mohd Saifuddin Tengku[1,*]

Affiliations: *[1]Universiti Sultan Zainal Abidin (UniSZA), Malaysia; [2]Sultanah Nur Zahirah Hospital, Malaysia*

ABSTRACT

Klinefelter syndrome (KS), characterized by an additional X chromosome in males, remains an underdiagnosed condition despite its prevalence. This case report delves into the multidimensional impact of KS, particularly its often-overlooked association with psychiatric disorders, notably bipolar disorder. We present the case of a 36-year-old man initially diagnosed with Bipolar Disorder Type I during a manic phase. Despite apparent improvement with conventional pharmacotherapy, recurrent syncopal attacks led to an endocrine referral, revealing an underlying KS diagnosis. The patient exhibited typical clinical features, including gynecomastia and testicular abnormalities, alongside neuropsychiatric manifestations. The patient's history of sexual abuse and familial mental illness hints at complex etiological factors influencing his psychiatric presentation.

Moreover, the co-occurrence of KS and bipolar disorder raises questions about the syndrome's psychological impact, including its implications for self-image and coping mechanisms. This case emphasizes the imperative for a comprehensive multidisciplinary approach to understand and manage complex psychiatric presentations. It highlights the necessity of considering physiological and psychological factors in comprehensive psychiatric assessments and treatment plans. Furthermore, it underscores the need for specialized multidisciplinary clinics to provide comprehensive care for individuals with KS, addressing their diverse medical, psychological, and social needs. Further research is needed to elucidate the intricate connections between genetic predispositions, psychological trauma, and mood disorders, particularly in the context of rare genetic conditions such as KS.

Keywords: Bipolar Disorder, Klinefelter Syndrome, Multidisciplinary Approach, Neuropsychiatric Manifestations

INTRODUCTION

Klinefelter syndrome (KS), characterized by the presence of an additional X chromosome in males, affects approximately 1 in 650 men, making it the second-most prevalent chromosomal disorder in men [1]. However, it is often overlooked, with late diagnosis common, resulting in 50–75% of

***Corresponding author:** Tengku Mohd Saifuddin Tengku Kamarulbahri, Lecturer, Deparment of psychiatry, Faculty of Medicine, Universiti Sultan Zainal Abidin, 20400, Kuala Terengganu, Terengganu, Malaysia. Email: tgsaifuddin@unisza.edu.my, +6013-9486883; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding:** All authors: no funding was sought; **Academic Integrity.** All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable; **Originality:** All authors: this manuscript is original has not been published elsewhere; **Review:** This manuscript was peer-reviewed by three reviewers in a double-blind review process.

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undiagnosed cases [2-4]. Typically, KS is diagnosed during adulthood [2]. Besides late diagnosis, males with KS commonly experience a spectrum of comorbidities, including gynecomastia, type 2 diabetes, obesity, valve abnormalities, osteoporosis, and various neurocognitive impairments, including neuropsychiatric manifestations [5].

Affective symptoms such as anxiety, depression, low self-esteem, and social withdrawal are prevalent among KS patients, with depression being a leading cause of disability and suicide [6]. The combined physical and psychological challenges KS patients face collectively contribute to decreased quality of life [4,7]. Impaired quality of life also increases the risk of developing psychiatric disorders in KS patients [4,6]. However, associations with bipolar disorders have seldom been reported [6].

The multidimensional impact of KS affects various aspects of life, necessitating a comprehensive multidisciplinary approach to treatment [3]. Further exploration is warranted to determine the most effective psychological, pharmacological, or combination intervention to enhance coping mechanisms, alleviate psychopathological symptoms, and improve overall quality of life [6]. This case report discussed a case of a patient who was initially diagnosed with Bipolar 1 disorder during a manic phase. Notably, the patient exhibits intriguing connections between his bipolar disorder and an underlying Klinefelter Syndrome, unraveling a complex interplay of psychological and physiological factors. This case highlights the intricate interplay between psychiatric and medical conditions, emphasizing the need for a holistic approach to understanding and managing complex cases. The patient's journey underscores the importance of considering physiological and psychological factors in comprehensive psychiatric assessments and treatment plans.

CASE PRESENTATION

A 36-year-old man initially sought psychiatric evaluation at the Emergency Department due to manic symptoms. The patient's manic symptoms included talkativeness, irritability, reduced need for sleep, increased energy levels, and hyperactivity, such as engaging in extensive baking and house cleaning. He also had grandiose delusions, including claims of mind-reading and a unique ability to see and eliminate ghosts, adding further complexity to the clinical picture. He has no history of using illicit substances.

The patient reported a recent argument with his aunt, calling him mad without reason. Stressors also included caretaking responsibilities for his younger brother with Down syndrome, as well as a desire for stable employment. A familial history of mental illness, specifically in a maternal aunt, hints at potential genetic predisposition. The patient reported a history of sexual abuse by his brother-in-law, potentially influencing his mental health. Diagnosed with Bipolar Disorder Type I in the manic phase, the patient was initiated on T. Sodium Valproate 400 mg bd. He improved with the current medication.

A pivotal discovery emerged when the patient presented with recurrent syncopal attacks, leading to an endocrine referral. His family members have noticed clinical features of Klinefelter Syndrome since he was in secondary school. He was the shortest among his classmates and had no secondary sexual characteristics such as no growth of pubic hair, facial and axillary hair, or deepening of voice. He also had gynecomastia and breast tenderness during secondary school. He also complained of cramping pain in his lower abdomen radiating to his back. The patient's clinical presentation prompted a comprehensive investigation into potential underlying causes.

Further investigation revealed Klinefelter Syndrome, evidenced by a karyotyping study (47XXY), gynaecomastia, and testicular abnormalities. The patient exhibited hypergonadotropic hypogonadism, leading to delayed puberty and gynecomastia. Hormone levels confirmed hypergonadotropic hypogonadism. Subsequently, he underwent puberty induction with testosterone by the endocrine team. While on puberty induction, the patient has shown Tanner Stage progression. However, after eight months of puberty induction, the patient developed haemoconcentration, which is a known potential adverse effect of testosterone therapy. The dose of monthly testosterone injection was then reduced. After the reduction of the monthly testosterone injection dose, the patient no longer exhibited haemoconcentration. Furthermore, the patient continued to show Tanner Stage progression and no longer experienced manic symptoms.

DISCUSSION

Klinefelter syndrome (KS), with a prevalence ranging from 1 to 1.5 in 1000 newborns, represents the most common sex chromosome aneuploidy, characterized by hypogonadotropic hypogonadism, testosterone deficiency, and infertility [5,8]. Despite its high impact, KS remains inadequately understood as a genetic risk factor for neuropsychiatric impairment [9]. Clinical studies have consistently reported an elevated prevalence of mental illness in individuals with sex chromosome aneuploidies, notably KS, with a hazard ratio of 2.20 (95% CI 1.42–3.39) [8]. Furthermore, research on KS individuals, irrespective of psychiatric diagnosis, indicate a heightened prevalence of various conditions, including schizotypal traits, symptoms of schizophrenia, and disorders encompassing psychosis, depression, anxiety, autism spectrum, and attention-deficit/hyperactivity (ADHD). Nevertheless, associations with bipolar disorders have seldom been reported [6].

The neurobiological mechanisms underlying neuropsychological profile remain elusive [7]. The 47, XXY karyotype arises from paternal or maternal meiotic nondisjunction during gametogenesis. Pathogenesis in KS is likely driven by gene overdosage effects from supernumerary X-chromosomal genes and testosterone deficiency [2]. In people with KS, distinct patterns of global and regional brain volumetric differences have been identified, alongside initial indications of functional brain alterations related to auditory, motor, language, and social processing [7].

Studies indicate that men with KS exhibit poorer mental health outcomes compared to controls, with pronounced difficulties in social adjustment and coping with social situations [6,10]. Reports of social anxiety, withdrawal, and shyness coincide with high levels of distress during social interactions [6]. Moreover, KS males are predisposed to impairments in social cognition, displaying decreased accuracy in perceiving social-emotional cues, heightened emotional arousal, and reduced ability to articulate emotions [11]. Individuals with Klinefelter syndrome often utilize atypical emotion regulation strategies, such as increased emotional expression, avoidance, distraction seeking, and passive coping. These difficulties in emotion regulation are associated with symptoms of anxiety, depression, thought problems, and hostility, emphasizing the complex interplay between cognitive and emotional processes in KS [1].

Management of psychiatric conditions in patients with rare diseases, such as KS, poses challenges for psychiatrists due to the lack of clear guidelines. A multidisciplinary team approach is likely optimal for addressing these patients' diverse medical, psychological, and social needs [12]. Establishing specialized multidisciplinary clinics is imperative to provide comprehensive care for people with KS [3]. All KS patients should undergo comprehensive psychological or psychiatric assessments to address the heightened risk of anxiety, depression, psychosis, or behavioral disorders [6]. Healthcare professionals should routinely screen for mood symptoms such as mania and depression, with early involvement of psychiatrists in multidisciplinary teams due to the complexities involved in managing these patients [12].

Psychological support is crucial in promoting lifelong health and well-being and facilitating discussions on endocrine and fertility concerns. Psychological support can aid in developing strategies to recognize, process, and express feelings and thoughts, thereby reducing stress and anxiety and enhancing comprehension of clinical discussions and treatment decisions [11]. Emotion regulation emerges as a potential target for treatment, mainly focusing on executive functions in managing emotions in individuals with 47, XXY [1]. Additionally, psychological interventions may improve pharmacological compliance among KS individuals [6].

The gonadal dysfunctions in patients with KF underscores the importance of considering both physiological and psychological factors in comprehensive psychiatric assessments and treatment plans. Marked gonadal dysfunctions, characterized by severely attenuated spermatogenesis and hypergonadotropic hypogonadism, are prevalent in KS individuals, often accompanied by neurocognitive, and psychosocial, which contribute to increased morbidity and mortality [2]. The gonadal dysfunctions among adult males with KF necessitate specialized attention to testosterone treatment in their care. However, current data indicates that a significant number of patients may not receive appropriate treatment [2,3]. Evidence from predominantly cross-sectional studies suggests beneficial effects on factors contributing to the elevated morbidity and mortality observed in adult KS. Encouragingly,

existing studies have not identified severe adverse events associated with properly managed testosterone treatment in adult KS, implying its safety [3].

CONCLUSION

This case emphasizes the need for a comprehensive understanding of the interrelation between psychiatric disorders and genetic conditions. The correlation between bipolar disorder and Klinefelter Syndrome raises questions about the potential psychological impact of the syndrome, including the patient's self-image and experiences of abuse. This case underscores the importance of a multidisciplinary approach in addressing complex psychiatric presentations, especially when comorbidities such as Klinefelter Syndrome are involved. Further research is warranted to elucidate the intricate connections between genetic predispositions, psychological trauma, and mood disorders.

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