

Gender dysphoria in an adolescent diagnosed with Klinefelter syndrome over a follow-up period

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ABSTRACT

Although genetic factors have been thought to be main cause for gender dysphoria, its etiology is still not clearly understood. Klinefelter syndrome is the most seen sex chromosomal disorder. In the literature, there are fewer case reports in connection with Klinefelter syndrome and gender dysphoria. Herein, we report a 16-year-old adolescent patient displaying gender dysphoria features, who has revealed Klinefelter syndrome after genetic examination, and has been treated with testosterone hormone, and his gender dysphoria symptoms have disappeared. In our case, chromosomal anomaly and lower levels of androgen could play a role in the etiopathogenesis of gender dysphoria. Bringing Klinefelter syndrome disorder to mind in gender dysphoria cases, even it is a rare disorder, could positively affect the course of the treatment as was in our case. The relation between psychiatric symptoms, which can be seen in gender dysphoria, and testosterone is not known exactly. Further studies, which are randomized-controlled ones, can help to better understand the subject.

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Introduction

It is assumed that the development of the sexual identity is completed at the end of the adolescence period with a prominent appearing the secondary sex features. Some children would experience in some degree of trouble to identify and build their gender identity by virtue of their biological features, family dynamics and environmental features. Children having trouble with their gender identity would experience some degree of discomfort regarding their biological

gender, feeling themselves as having actually an opposite sex, liking with opposite sex's activities and features [1].

Gender dysphoria is generally used as a term and a clinical entity although is not yet located in Diagnostic and Statistical Mental Disorder (DSM) classification system as a diagnosis having with criteria. Its etiology is still not clearly understood yet there are studies pointing out an importance of genetic factors playing crucial role in the etiology of gender

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dysphoria based on studies carried with twins (as concordance studies) and affected family members [2, 3]. In addition, with some chromosomal anomalies reported in the cases with gender dysphoria in the literature is also presented as the possible salient facts of the underlying mechanisms of gender dysphoria [4-11].

Klinefelter's syndrome is by far the most seen sex chromosomal disorder and second frequent disorder in terms of presence an extra-chromosome. Its prevalence is 1.09 to 1.72/1000 in male sex and characterized by a 47,XXY karyotype chromosomal anomaly [12]. In the literature, still there are fewer cases reporting association of gender dysphoria and Klinefelter syndrome [10, 11].

In this report, an adolescent admitted to our department because of his complaints of sexual interest towards his own sex and feeling bothered by it. He was evaluated as having possible traits of gender dysphoria. He was diagnosed with Klinefelter syndrome over his follow-up period and his psychiatric complaints improved after treating with endocrinological approach. Therefore, the association of gender dysphoria and Klinefelter syndrome was discussed in this case report using with literature knowledge.

Case Presentation

The patient is a 16-year-old male, third grade student in a high school, living with his older brother. He admitted to our clinic by virtue of his thoughts related to their sexual identity as he is a homosexual and he wanted to us the elimination of these thoughts. He referred himself as a comfortable person except these thoughts, however, his older brother described him as aggressive and indisposed and according to older brother, he prefers being alone. He was born in a small village, he lived there with his mother, father, older brother and younger brother until he was 14. When he won a high school scholarship, he moved to the metropolis and stayed in a male hostel where located near to his high school. He has always been criticized with "talking, acting and dressing like a girl" by both his family and his relatives because of his thin voice, polite conversation attitudes, gestures and mimics that he uses when he is talking and his clothing style. Six months later when he set the hostel, some troubles emerged between him and his roommates and he moved in with his older brother since he began to

work in a job and could be able to afford a flat to live in. Questioning of his sexual life, he revealed that he remembered when he was in 7-8, once he played with his male friends from his classroom as looking at their sexual organs of each other. When he was in high school, he went with it especially one male friend of him, spending lots of time together with him, he had fantasy related to him and dreamed with sexual content about him. When he told to him he was liking of him, he exposed much of opposition from his hostel friends and he had to leave from the hostel. He began to think himself about that he might be a homosexual person at that time. Then some symptoms have become to emerge which diagnosed by major depressive disorder like malaise, not to be able to enjoy from living, decrease in food intake, difficulty in falling asleep. He has always been a fine and successful student throughout the entire of educational life in school. He was excluded by his male friends because of his polite speaking style and he began to spend his time with girl friends but he couldn't be able to close to them very well and could not made close friendship.

History

He was born after a planned pregnancy. There had no expectation by his parents regarding the sex of the baby. According to older brother's report, the pregnancy was normal and his mother did not use any medication. The delivery was uneventful at full term. The neonatal period was uneventful. His developmental stages were normal.

Family history

Information reported about family history was limited because his parents who lived outside of the metropolis could not be interviewed by the clinician. There were no gender dysphoria and Klinefelter syndrome cases in his family members or relatives. According to older brother's report, when he was a toddler, his mother had a major depression and behaved him hostilely. His father also did not care about him. There were his father's humiliating and overwhelming attitudes toward his mother and him.

Psychiatric examination

Looking with little hairy face and his behaviors and talking style demonstrates childish and feminine features, his outfit is appropriate with his socioeconomic level, a male adolescent with showing truly his own age. His mood examination revealed as

depressive, his affect was anxious, his speech was clear, understandable with proper response to the questions and seen as cooperative. His perception, consciousness, orientation, attention and memory examination were normal. His thought processing was normal, accompanying with worthlessness of thought content and guilt as well as alongside with dominancy of concern for the future. There was no delusion. His intelligent quotient was normal. Clinical interview based on DSM-5 criteria [13] revealed major depressive disorder and gender dysphoria. Weekly sessions of the therapy aiming to obtain insight to him was planned. These sessions were structured with his traumatic experiences, family relations and relationship with members of it to be increased the awareness of him, ensuring separation of his individuality and make him to be realized his strength points. Daily 50 mg of sertraline, the selective serotonin re-uptake inhibitor (SSRI) was ordered. Over the follow-up period, he was referred to the endocrinology department because of his phenotypical features mentioned before. He was diagnosed with Klinefelter syndrome after evaluating and examining by the endocrinology department. Testosterone treatment began to him. After treating with testosterone, he experienced more hair on his face and his facial appearance has become masculine features with voice thickened. Diagnosed with Klinefelter syndrome during follow-up, and interpreted his gender dysphoria symptoms as having an organic and solid-based disorder by himself, had a positive effect regarding his position. At the end of the follow-up period, he has become less interested in with the same sex, with lesser extend of feminine appearance, mimic and gestures, and he became make friends with girls in sexual and emotional context and enjoyed from it with improved depressive symptoms.

Discussion

Gender dysphoria is highly complex issue for evaluating in a context of biological, psychological and social variables and needed to be evaluated by multidisciplinary attitude with many areas of professionals. Genetic factors and prenatal exposure of sex hormones are thought to be responsible for underlying mechanisms of gender dysphoria. Throughout pregnancy, fetal brain develops as a male brain with under effect of androgen hormones. If there are no androgen hormones, fetal brain switches to the

female characteristics. Gender identification of the brain appears later than the development of genital organs [14]. Gender dysphoria could emerge if there is a conflict between gender development of the brain and genital differentiation [1].

Klinefelter syndrome is characterized by, as in our case, longer arms and legs, feminine hip and muscle development, gynecomastia and hypergonadotropic hypogonadism. In general, their voices are thin with feminine type body hairs, very limited beard and mustache growth and their testicles are smaller with lower testosterone hormone levels [15]. Testosterone displays its biological effects via binding to the androgen receptors [16]. In Klinefelter syndrome, there have been reported a relation between some mechanisms including the androgen receptor polymorphism (longer CAG repeated), X chromosome inactivation and parental origin of extra-X chromosome and an increased prevalence of psychiatric symptoms and disorders such as depression, anxiety, autism, schizophrenia, attention deficit, hyperactivity, learning difficulties and cognitive inabilities [17]. Related to the brain volumes of Klinefelter syndrome cases, it was argued that inactivation of X chromosome might associated with an effect on gray matter of whole brain as well as left insula volume which is smaller. It is also suggested that X-linked genes would have a potential impact on the development of these volumes [17].

Yet, these hypotheses could not be clearly showed. Some studies reported longer repeated androgen receptor genes in gender dysphoria cases and Klinefelter syndrome alike compared to the healthy controls [18].

Neuroimaging studies revealed a difference between volumes of white and gray matters of the brain in affected peoples compared to the controls but it could not be enough to be used as diagnostic tool for these patients [1].

Although its prevalence is rare in etiology of gender dysphoria, chromosomal anomalies including Klinefelter syndrome should come to mind during the evaluation of patients having gender dysphoria symptoms. Like in our case, doing so might be beneficial for determining of accompanying disorder, if any, and treating to it. Testosterone treatment of Klinefelter syndrome has been shown as positively effective on symptoms of patients affected, although its mechanisms not clearly proved [19]. Testosterone treatment has been reported that it developed and improved the functions of neuromotor, speech,

cognitive and reading skills [20]. Testosterone treatment has a positive effect on some features including sleep pattern, mood and irritability symptoms [21]. In 1979, Rinieris et al. [22] reported in two cases with Klinefelter syndrome that with testosterone treatment, depressive symptoms of two cases did not recur. In 2015, Kawahara et al. [12] showed in a case with Klinefelter syndrome and bipolar disorder that testosterone hormone treatment ended with a cease in manic attacks.

In our case, testosterone might have an effect to improve depressive symptoms accompanying with sertraline treatment. In addition, interpreting of gender dysphoria as a consequence of an organic disorder, he began to grow beard with masculine appearance of his facial contours and thickening his sound after treating with testosterone, all these developments could very well ease to establish identification of male sex and thus, it might indirectly ameliorate the depressive symptoms of him. Psychiatric symptoms improved with testosterone hormone treatment in Klinefelter syndrome is not fully proven and its mechanism of action is not yet clearly certain. Further randomized studies would be beneficial to fully understand of testosterone effects on psychiatric symptoms.

Conclusion

In our case, chromosomal anomaly and lower androgen hormone levels might play a role in the ethiopathogenesis of gender dysphoria. Nonetheless, the possible causative relation between gender dysphoria and 47-XXY is still not clearly understood. Genetic factors and hormones could very well be included to the topics for the future researches in this area. Gender dysphoria cases having different symptoms and features, as in our case, would add a valuable outlook to build new hypothesis in connection with scientific studies. Screening for the frequency of gender dysphoria in cases with Klinefelter syndrome would might contribute to better understanding the etiology of gender dysphoria.

Informed consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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