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CLINICAL CASE REPORT SERIES

Neural Correlates of Psychosis and Gender Dysphoria in an Adult Male

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Abstract Gender dysphoria (GD) (DSM-5) or transsexualism (ICD-10) refers to the marked incongruity between the experience of one's gender and the sex at birth. In this case report, we describe the use of LSD as a triggering factor of confusion in the gender identity of a 39-year-old male patient, with symptoms of psychosis and 25 years of substance abuse, who sought psychiatric care with the desire to undergo sex reassignment surgery. The symptoms of GD/psychosis were resolved by two therapeutic measures: withdrawal of psychoactive substances and use of a low-dose antipsychotic. We discuss the hypothesis that the superior parietal cortical area may be an important locus for body image and that symptoms of GD may be related to variations underlying this brain region. Finally, this case report shows that some presentations of GD can be created by life experience in individuals who have underlying mental or, synonymously, neurophysiological abnormalities.

Keywords Gender identity · Transsexualism · Lysergic acid diethylamide · Parietal lobe · Psychotic disorders · DSM-5

Introduction

Individuals diagnosed with gender dysphoria (GD) feel discomfort or inadequacy with their anatomical sex and may undergo surgical and/or hormonal treatment interventions in order to make their bodies consistent with the sense of gender. As the unifying common factors predisposing to GD remain elusive, the diagnosis can be a challenge for multidisciplinary team and patients involved (Hoekzema et al., 2015; Kórász & Simon, 2008; Simon et al., 2013).

Delusions about one's physical appearance and the desire to change the body can be observed in patients with schizophrenia or other psychotic disorders. Therefore, the differential diagnosis between psychotic disorders and GD is crucial for therapeutic planning (Baltieri & De Andrade, 2009). We describe a case of an individual, with symptoms of psychosis and 25 years of substance abuse, who sought psychiatric care in the Gender Identity Program (PROTIG) of the Hospital de Clínicas de Porto Alegre, Brazil, with the desire to undergo sex reassignment surgery (SRS).

Case Report

CFB, an unemployed 39-year-old male, with a partial college education, sought psychiatric treatment for the first time in October 2010 aiming to accomplish a transformation of his gender identity. He attended the clinic accompanied by his mother, unshaven, and wearing female apparel, including earrings, false nails, and a scarf covering his sparse hair. The patient spoke quickly, quietly, and showed notes relating to his biography, which contained drawings, excerpts of palmistry interpretations, and the Chinese divination manual I Ching. He exposed the biographic notes which revealed his female identity, although no female name was reported.

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The patient had no critical judgment and kept little eye contact with the interviewer. CFB reported always having had few friends or girlfriends, although he felt attracted to women. He stated that he did not know whether he was a transvestite or not, defining himself as an inactive bisexual who had had two homosexual experiences. He had never noticed any incongruent gender behavior or doubts about his sexuality in childhood, adolescence, or adulthood.

The mother reported that CFB was the first child of two (his brother is 36 years old). He had a natural birth with his mother experiencing no problems during pregnancy. He had no psychomotor developmental delay or seizures during infancy. He presented only one school failure.

Regarding occupation, CFB attended a semester of college majoring in advertising and marketing, but interrupted the course due to financial difficulties. He achieved the qualification as a driver and then set to work, but he was "nervous" when driving busses, preferring taxis because this function was not routine. Five years ago, he began working the night shift, going by places where he watched the prostitution of transvestites and became interested in their lifestyle. However, he stopped working a year ago, remaining isolated in his room, and spent hours on the internet.

CFB reported that he sniffed glue from 17 to 22 years to "open" his mind. In addition, he used marijuana and cocaine in a dependent way since he was 12 and currently smoked about 40 cigarettes a day (for the last 20 years). He considers the use of these drugs to have undermined his studies and romantic relationships.

Under the influence of marijuana, he used to masturbate watching pornographic videos of various themes. He was socially isolated, with limited outside sexual activity for years. A year ago, he made use of LSD and on the "trip" he had the revelation he would have a female identity and began living as a woman. CFB reported the use of LSD only once, in the woods of the condominium where he lived.

After the initial interview, psychiatric hospitalization was recommended for better evaluation of his clinical state. The hospitalization lasted 15 days, and during this period CFB was interviewed by several professionals from the Psychiatric Services and by the PROTIG of the Hospital de Clínicas de Porto Alegre, Brazil.

Hospital de Clínicas de Porto Alegre cares for individuals diagnosed with GD since 1998, with a multidisciplinary team consisting of medical specialties (gynecology, urology, endocrinology, mastology, and psychiatry), speech therapist, bioethics committee, social worker, and psychology. The program offers psychosocial support, medical care, and family counseling, and recommends SRS when indicated. Approximately 70 individuals are assisted monthly at PROTIG, which accounts for more than 400 patients (diagnosed with GD) attended or in attendance, and about 200 underwent SRS since 2000.

Assessment

Psychological Testing

During the hospitalization period, psychological evaluation was conducted by a clinical psychologist with experience at the Gender Identity Disorder Program. Psychological tests were selected to provide information about the patient's cognitive and subjective mental processes: Wechsler Adult Intelligence Scale (WAIS-III), Rorschach Projective Test, Bender Visual Motor Gestalt Test, and the Mini International Neuropsychiatric Interview (Portuguese version 5.0).

The WAIS-III results showed an overall lower average intellectual functioning (IQ Verbal: 93-Average; IQ Executive: 84-Low Average; IQ Average Total: 89-Low Average).

The Rorschach Projective Test was applied using the Exner Comprehensive System (Exner, 1999), and a semi-directive interview was also performed for further exploration. CFB provided 15 percepts. The predominance of answers at (Wv) vague responses, (DQv/+), and the small number of formal and good-quality answers (F+ %) indicated a superficial and immature form of reality testing, poor analytic capacity, and poor ability to synthesize, tending to a concrete and impressionist formal thought conclusions. Low answers at affective control module (FC < CF + C), at subject module (H), and higher answers at human and animal module details (Hd and Ad) indicated high levels of immature personality traits showing that CFB has difficulty to differentiate himself from others, inducing fragmented, distorted, and uncompleted reality conclusions. Finally, higher answers at color projections (Cp), morbid content (MOR > 2), fabulized combination (FABCOM), and perseveration (PSV) indicated cognitive immaturity and attention and symbolization difficulties.

The Bender Visual Motor Gestalt Test showed organic signs that might be related to the chronic substance use. He presented distortion of drawn shapes, spatial confusion, difficulty in rotation, and integration (replacement of elements). Furthermore, it was observed motor symptoms characterized by tremors.

CFB met criteria for Substance Abuse and Dependency by the Mini International Neuropsychiatric Interview (Portuguese version 5.0).

Neurological and Laboratory Investigations

Single-photon Emission Computed Tomography (SPECT) was performed in GE Infinia equipment, using technetium-99 m radiopharmaceuticals, revealing images compatible with reduced perfusion and/or function in bilateral hemisphere superior parietal and frontal paramedian regions. Brain SPECT is a method of functional imaging capable of detecting localized changes in regional cerebral blood flow through the intravenous administra-

tion of radioactive substances to the patient, followed by three-dimensional mapping of the distribution of the substance in the brain. The exam has the ability to detect changes early on in the course of disease, even before structural changes are noted in anatomical imaging modalities as magnetic resonance imaging (MRI). Furthermore, changes in brain metabolism observed with glucose reflect changes in perfusion, and this may be used to evaluate alterations due to drug dependence. Cannabis sativa (marijuana) neuroimaging studies, for example, have demonstrated hypoperfusion in the temporal lobes and severe abnormalities among those that begin abusing the drug earlier (Etchebehere, Oliveira, Amorim, Serrat, & Camargo, 2010). The patient also underwent a CT scan of the brain, with a normal result. Laboratory tests (blood count, glucose levels, liver function, blood urea nitrogen, creatinine blood test, and serological tests) also gave normal results.

Diagnostic Hypothesis

CFB presented with a strong and persistent cross-gender identification and a persistent discomfort with his sex or sense of inappropriateness in the gender role of that sex. His disturbance was not concurrent with a physical intersex condition and caused distress and impairment in social or occupational functioning (he felt anxious because of gender identity conflict, showing irritability at home and avoiding going out in social situations), such that he sought evaluation for sex reassignment surgery, according to the DSM-IV-TR diagnostic criteria for gender identity disorder. However, when we performed the differential diagnosis, he showed symptoms of psychotic disorder due to psychoactive substance use.

Regarding the DSM-5 criteria for GD, CFB would meet criteria A and B. In relation to the differential diagnosis, the patient had no body dysmorphic disorder, cross-dressing disorder, or non-compliance with the gender role; nonetheless he had psychotic symptoms. CFB did not manifest the symptoms of gender dysphoria during childhood or lived as a woman for a longer period than a year. According to ICD-10, since the diagnosis is made, the new gender identity must have been present persistently for at least 2 years and to be not considered as a symptom of another mental disorder.

Besides the GD symptoms, CFB met criteria for mental and behavioral disorders due to psychoactive substance use (ICD-10, F 19): residual and late-onset psychotic disorder.

Course

In the course of the inpatient treatment, CFB developed better personal and speech organization and gradually ceased to wear female clothing. He was discharged with the recommendation to refrain from using any psychoactive substances and maintain taking Thioridazine indefinitely. After discharge, CFB attended fortnightly consultations with a masculine aspect, modulated emotions, making reference to his non-use of drugs. He remained isolated, without work, but with a good relationship with the mother.

In December 2010, 2 months after discharge, CFB began to show symptoms of panic. He tried to work as a bus driver again, but failed due to panic attacks. He was then treated with Fluoxetine 20 mg/day. Two years later, in December 2012, the patient was still very well, presenting modulated emotion and with a masculine appearance. He continued not to work but with good family relationships. He reported not to use marijuana anymore and that he would like to suspend Fluoxetine. It was agreed that he should keep using 100 mg/day of Thioridazine and suspend Fluoxetine. In October 2013, the patient appeared with a remission of phobic symptoms, friendly, and with a masculine aspect. He has been working for a year as a van driver and reported good family relationships.

Discussion

Gender dysphoria (DSM-5) refers to the marked incongruity between the experience of gender and the sex at birth. Adults with gender dysphoria experience discomfort or inadequacy with their anatomic sex and may undergo hormonal and/or surgical treatment in order to make their bodies congruent with their sense of gender.

This case is an example of atypical onset of GD that occurred in a profoundly impaired adult, which resolved with withdrawal of brain toxins and treatment with a low-dose antipsychotic agent. The treatment possibly altered our patient's sensory input from the body and his transitional GD, so that the patient returned to feeling comfortable about his gender in relation to his biological sex. The mystical readings, his loneliness, isolation, vocational failures, marginalization, thoughts about transvestite prostitutes, and lower IQ related to drug abuse may have influenced reality and hallucination discernment (psychotic characteristics).

In the scientific literature, there are some descriptions of a diagnosis of psychotic disorders in persons diagnosed and treated as transsexuals, in whom the transsexual thinking disappears after using antipsychotic drugs (Urban, 2009). Moreover, delusions about the physical appearance and the desire to change the body can be observed in patients with schizophrenia (Baltieri & De Andrade, 2009). Therefore, in these cases, the differential diagnosis between psychotic disorders and GD is crucial, as in the case of our patient. He was not considered a candidate for SRS.

The brain effects of hallucinogens that the patient ingested generated many questions. Behavioral and neuroimaging studies have shown that these drugs modulate neural circuits involved in mood and affective disorders (Gonzalez-Maeso et al., 2007; Vollenweider & Kometer, 2010). In one such study (Guedes, 1961), it was reported, among other symptoms, that some patients had changes in the body scheme. The denial of body parts (like arms

and hands) or the whole body ("I do not exist") was identified a few times as well as the feeling of decreasing in size or becoming very small, as a child. One patient, for example, had lost the spatial positioning of the body for a while, complaining of not knowing where his head was or which way his body turned. In the same study, LSD produced anxiety in two subjects, which was resolved by the verbal support of researchers. The anxiety was related to the fear of losing control of thought, disembodiment, and loss of the self.

Dutt et al. (2015) showed that individuals with high clinical risk of developing psychosis have generalized functional abnormalities in the brain. This systematic review of functional magnetic resonance imaging (fMRI) studies aimed to determine which regions of the brain and cognitive systems are dysfunctional in affected individuals. In general cognitive function tasks, these subjects seem to have abnormal activation patterns in the frontal regions bilaterally and in the lower right parietal lobe, who can also present some shifts in working memory tasks. In social cognition functions, the left temporal region would be compromised.

The unifying common factors predisposing to GD remain elusive, although some research has pointed to anatomic brain factors in its development. Luders et al. (2009) analyzed fMRI data of 24 male-to-female (MtF) transsexuals not yet treated and found a significantly larger volume of gray matter (GM) in the right putamen of transsexuals in relation to both female and male controls. In contrast, Savic and Arver (2011) reported a difference in regional GM volume of the right putamen when comparing individuals with GD and controls (men and women). Simon et al. (2013) also found differences in the GM structure of transsexual compared with control subjects, independent from their biological gender, in the cerebellum, the left angular gyrus, and in the left inferior parietal lobule. Hoekzema et al. (2015) noted less GM volume in the right cerebellum and more volume in the medial frontal cortex in female-to-males in comparison to females without GD, while male-to-females had less volume in the bilateral cerebellum and hypothalamus than control males. Other research has shown changes in the microstructure of white matter in female-to-male (FtM) transsexuals (Rametti et al., 2011, 2012) and cortical thickness in FtM and MtF patients (Zubiaurre-Elorza, Junque, Gomez-Gil, & Guillamon, 2014) after hormonal treatment. Although these studies were not replicated, the regions pointed as presenting structural differences in some studies are mainly involved in neural networks that play a role in body perception, including memory retrieval, self-awareness, visual processing, body and face recognition, and sensory motor functions (Hodzic, Kaas, Muckli, Stirn, & Singer, 2009; Simon et al., 2013).

The inconclusive findings are probably due to methodological differences in brain imaging acquisition, small sample sizes, and different hormone treatment phases; however, significant structural differences were found between transgender patients and controls and, in some cases, in overlapping brain areas (Hoekzema et al., 2015; Simon et al., 2013). Therefore, this kind of research is crucial for the advance of the physiopathology knowledge of atypical gender behavior.

A pathophysiological hypothesis for GD proposed by Ramachandran (2014) and Jalal and Ramachandran (2014) is based on the premise that the human brain has a partially innate body image. When this image does not match the sensory input from the body, whether visual or somatic, as occurring in GD, the resulting disharmony could affect the self-sense of unity.

The neural mechanisms underpinning the body image processing in transsexuals have not yet been explored (Lin et al., 2014). It has been suggested that the somatosensory information is sent to the superior parietal lobe (SLP), where it is combined with information coming from the inner ear and visual feedback regarding the position of the limbs (Caminiti et al., 2010; Ramachandran, 2014). These inputs would build our self-image: a unified representation in real time of our physical self (Case & Ramachandran, 2012). These would be the same circuits which dictate the esthetic preference and sexual body morphology (Ramachandran, Brang, McGeoch, & Rosar, 2009). Thus, unusual patterns of activation of the SPL could explain the symptoms of GD, apotemnophilia (a disorder characterized by the desire to amputate one or more healthy limbs), and somatoparaphrenia (in which the patient believes one of the body parts is not part of the body) (Jalal & Ramachandran, 2014; McGeoch et al., 2011; Ramachandran, 2014).

Case and Ramachandran (2012) have also hypothesized that a case of alternating gender incongruity may be related to an unusual degree or depth of hemispheric switching and corresponding callosal suppression of sex appropriate body maps in parietal cortex—possibly the superior parietal lobule—and its reciprocal connections with the insula and hypothalamus. Lin et al. (2014) suggest that neural network of body representation differs between transsexuals and cissexuals, and the changes in the functional connectome (a comprehensive map of neural connections in the brain) may consist in representational markers for the dysphoric bodily self of transsexuals. This hypothesis partially agrees with the findings of the SPECT examination of our patient. Although the findings could not be compared with other imaging studies and not knowing if it was congenital or acquired, they suggest that the parietal lobe is an area to be investigated.

We plan to test this hypothesis through brain imaging investigation, identifying regions possibly involved in the construction of body image, as the superior parietal lobe, and comparing individuals diagnosed with GD and controls.

Finally, the interesting point of this report is that the GD/psychosis symptoms resolved by two therapeutic measures: withdrawal of psychoactive substances and use of low-dose antipsychotic (Thioridazine 100 mg/day). Therefore, we might think that, in this case of a profoundly impaired adult, the atypical gender identity disorder was pathophysiologically related to this chronic substance use and triggered by LSD.

Conclusion

We described a case in which the use of LSD caused symptoms of GD in a male person. This atypical late GD occurred in a profoundly impaired adult and has resolved with withdrawal of brain toxins and treatment with a low-dose antipsychotic agent. This case describes the importance of differential diagnosis between GD and psychotic disorders and suggests that changes in gender identity can be created by life experiences. We postulate that functioning changes of the parietal lobe may be involved in the distortion of the body image.

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