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Gender dysphoria and incongruence - neurophysiological diversity and genetic factors

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Abstract

Introduction: Transgender people may experience gender dysphoria, which is defined as the distress and impairment associated with a person's perception of a marked incongruity between their gender identification and their sex assigned at birth. The aim of the study is to understand the neurophysiological diversity of people with and without dysphoria, as well as to assess the genetic, endocrine and biological basis of the development of dysphoria.

Material and methods: A review of the available literature was performed by searching the Google Scholar and PubMed databases using the keywords: dysphoria, gender incongruity, neurophysiology, neurophysiological diversity and dysphoria, gender dysphoria and genetics. This publication is based on a literature review covering the years 2015 - 2023. Works published before 2015 were excluded from the analysis. The SANRA scale was used to maintain the high quality of the narrative review.

Results: Gender dysphoria has a polygenic basis, involving interactions between various genes and their polymorphisms. Endocrine factors are also important, so the most complete picture of the neurophysiological basis of gender dysphoria can be obtained by adding brain imaging tests and measurements of sex hormone concentrations to genetic tests.

Conclusions: Determining what biological factors contribute to gender dysphoria may have a positive impact on the mental health of transgender people. Moreover, this knowledge can be used to improve the quality of diagnosis and treatment of these people. Therefore, there is a clinical need to conduct further research in this field.

Keywords: genetics, neurophysiology, gender dysphoria, gender incongruity

Streszczenie

Wstęp: Osoby transpłciowe mogą doświadczać dysforii płciowej, która jest definiowana jako niepokój związany z postrzeganiem przez osobę wyraźnej niezgodności między jej identyfikacją płciową, a płcią przypisaną jej przy urodzeniu. Celem badania jest zrozumienie neurofizjologicznej różnorodności osób z dysforią i bez dysforii, a także ocena genetycznych, endokrynologicznych i biologicznych podstaw rozwoju dysforii.

Materiał i metody: Przeprowadzono przegląd dostępnej literatury, przeszukując bazy danych Google Scholar i PubMed przy użyciu słów kluczowych: dysforia, niezgodność płciowa, neurofizjologia, różnorodność neurofizjologiczna i dysforia, dysforia płciowa i genetyka. Niniejsza publikacja opiera się na przeglądzie literatury obejmującym lata 2015–2023. Prace opublikowane przed 2015 rokiem zostały wyłączone z analizy. Wyjątek zrobiono w przypadku kilku starszych prac, ze względu na ograniczoną liczbę podobnych badań w ostatnich latach. Skala SANRA została użyta w celu utrzymania wysokiej jakości przeglądu narracyjnego.

Dyskusja: Dysforia płciowa ma podłoże poligenetyczne, obejmujące interakcje między różnymi genami i ich polimorfizmami. Ważne są również czynniki endokrynologiczne, dlatego najpełniejszy obraz neurofizjologicznych podstaw dysforii płciowej można uzyskać, dodając do testów genetycznych badania obrazowe mózgu i pomiary stężeń hormonów płciowych.

Wnioski: Określenie, jakie czynniki biologiczne przyczyniają się do dysforii płciowej, może mieć pozytywny wpływ na zdrowie psychiczne osób transpłciowych. Ponadto wiedza ta może być wykorzystana do poprawy jakości diagnozy i leczenia tych osób. Dlatego istnieje kliniczna potrzeba prowadzenia dalszych badań w tej dziedzinie.

Słowa kluczowe: genetyka, neurofizjologia, dysforia płciowa, niezgodność płci

Introduction

Gender identity is defined as a deeply felt, internal, inextricable sense of being male, female or another gender. It may not correspond to the sex assigned at birth or to the sexual characteristics a person has [1]. This term is of key importance in understanding the concept of transgender, understood as a collective term for people whose gender identity or gender roles differ from those typical of the sex assigned to them at birth [2]. Transgender people may experience gender dysphoria (GD), which is defined as the distress and impairment associated with a person's perception of a marked incongruence between their gender identification and their sex assigned at birth [3]. Some of them report the need to undergo transition, i.e. medical procedures that confirm gender, such as hormone therapy or surgical interventions. In order to provide them with access to such resources, diagnostic entities related to transgenderism are included in the ICD and DSM diagnostic classifications. For a long time, they stigmatized transgender phenomena and were harmful to transgender people. When preparing new editions of the above-mentioned diagnostic classifications, efforts were made to destigmatize phenomena in the area of transgenderism, while ensuring access to the desired medical care for trans people [4,5]. Therefore, both the DSM-5, released on May 18, 2013, and the ICD-11, released on May 25, 2019, introduced significant changes in the discussed diagnostic units compared to their previous editions. It is also worth mentioning that it is possible to correct personal data without medical intervention. The new approach assumes great flexibility, but the patient's informed consent to any interventions is crucial.

The basic change introduced in DSM-5 was the change of the name from gender identity disorder, present in DSM-IVR, to a less stigmatizing and better reflecting the nature of the problem - i.e. suffering caused by inconsistency between the perceived and assigned gender at birth - gender dysphoria. Moreover, it was placed in a chapter separate from paraphilias and sexual dysfunctions. The previously separately listed criteria A (identification with the opposite sex) and B (discomfort with gender assigned at birth) were combined. It also used less binary language and replaced the term "sex" with the term "gender" – emphasizing the socio-cultural importance of gender identification. In order to determine the permanence of gender dysphoria, a criterion of duration of at least 6 months was introduced. Diagnosis for intersex people has been made possible - therefore, the designations "with DSD" and "without DSD" (disorders/differences of sex development) were introduced. A designation was also introduced for transgender people who have undergone at least one somatic intervention or treatment that affirms their gender. This allows people who previously received the diagnosis to lose their diagnosis while still allowing them to continue to access medical care. However, sexual orientation was not taken into account in the process of diagnosing gender dysphoria, because gender identity and sexual orientation are two separate concepts. In

the case of the diagnostic unit devoted to children, the changes introduced included: changing the nomenclature of some diagnostic criteria and establishing criterion A (a strong need to be of a different gender or insistence that one is of a different gender) as necessary to make a diagnosis [6]. The changes introduced in ICD-11 seem to destigmatize transgender phenomena more than in DSM-5. The previously used term "gender identity disorder" was replaced by "gender incongruity", defined in adults and adolescents as a significant and persistent inconsistency between an individual's perceived gender and his or her assigned gender. To confirm it, at least 2 of the following symptoms must be present: 1) strong reluctance or discomfort related to the individual's having primary or secondary sexual characteristics caused by inconsistency with the experienced gender; 2) a strong need to get rid of some or all primary or secondary sexual characteristics (expected sexual characteristics in adolescents) caused by inconsistency with the experienced gender; 3) a strong need to have primary or secondary sexual characteristics consistent with one's experienced gender. A person with gender nonconformity feels a strong need to be treated in accordance with their gender identity. This diagnosis cannot be made before the onset of puberty or on the basis of gender-atypical behavior alone. In addition, gender nonconformity has been moved from the division devoted to mental and behavioral disorders to the category of conditions related to sexual health [7]. The criterion for the duration of the above-mentioned symptoms has been shortened to several months compared to 2 years in ICD-10. The "real life test" was also abandoned, which required a person to function in a role consistent with their perceived gender for a set amount of time in order to verify whether gender correction was a person's actual desire. It is now considered harmful. In ICD-11, the terms "opposite sex" and "anatomical sex" have been replaced by the more contemporary and less binary "lived gender" and "felt gender". This is related to the rejection of the assumption that all people desiring transition want to fit in with the "opposite sex". A change from ICD-10 is also the emphasis on the importance of expected sexual characteristics in young adolescents before the last stages of puberty [8]. A diagnostic unit intended for children before puberty was also presented – gender nonconformity in children. Defined as a significant discrepancy between an individual's experienced or expressed gender and assigned gender in pre-pubescent children. It is characterized by a strong need to be a gender other than the assigned gender, a strong aversion to anatomical features associated with the assigned gender or expected gender characteristics as well as taking part in games, using toys, games, engaging in activities and choosing playmates typical of the child's perceived gender rather than the assigned gender. According to some clinicians, there is a shift away from assessing the selection of "typical" games and activities because these differences seem to be blurring currently. The symptoms listed should last continuously for at least 2 years [7]. The most pronounced difference between the above-mentioned modifications in the perception of transgenderism in diagnostic classifications seems to be the maintenance of the diagnosis of gender dysphoria in the chapter on mental disorders in DSM-5 compared to ICD-11, in which gender non-conformity was placed in the category of conditions related to sexual health. Unlike DSM-5, ICD-11 recognizes that distress and impaired functioning may occur together with gender dysphoria, but are not required criteria for diagnosis. The creators of ICD-11 thus emphasized that people who experience gender nonconformity but do not suffer from it and do not experience functional disorders may also feel the need to use gender-affirming medical treatments [8,9].

Although the changes introduced are generally perceived as positive, the very existence of transgender diagnoses is controversial. It is argued that human rights to health and non-discrimination support the depathologization and thus the removal of the above-mentioned diagnoses from diagnostic classifications. It is assumed that the very fact of giving a transgender person a diagnosis exposes him/her to stigmatization, and the necessity of giving it in order to obtain the desired medical services and legal regulation of personal data is a debatable element [10]. Leaving diagnoses for children in diagnostic classifications is particularly controversial. It is argued that prepubescent children do not need to use gender-affirming medical treatments, therefore issuing a diagnosis seems pointless and only pathologizes the child's exploration of gender identity [11].

Material and methods

The following review aims to present the neurophysiological diversity of people with and without dysphoria, as well as to assess the genetic, endocrine and biological basis of the development of dysphoria.

A review of the available literature was performed by searching the Google Scholar (GS) and PubMed (PM) databases using the following keywords: dysphoria, gender nonconformity, neurophysiology, neurophysiological diversity and dysphoria, gender dysphoria and genetics. This publication is based on a literature review covering the years 2015 - 2023. Works published before 2015 were excluded from the analysis. An exception was made in the case of several older works due to the limited number of similar studies in recent years. The SANRA scale was used to maintain the high quality of the narrative review.

Results

a.i.1. The influence of genetic, endocrine and biological factors on the development of gender dysphoria.

Gender dysphoria in terms of genetics has so far been studied mainly in terms of specific mutations or polymorphisms in genes related to sex hormones. Most studies have been conducted on twins and fewer have been based on family studies [12]. Researchers are trying to determine to what extent a genetic factor may influence the occurrence of GD, and to what extent it is related to environmental factors [13]. Already in 2000, a study was published in which the authors suggested a possible genetic basis for the occurrence of GD [14]. This is a series of ten cases where siblings or both children and parents had a different psychological sex than assigned at birth. The authors suggest that the development of new genetic technologies will make comparisons of such families an essential source of knowledge on gender incongruence. Another study on the familial occurrence of GD in non-twin siblings found that siblings of a transgender person, in turn, have a very low probability of developing GD [15]. Dutch and Belgian researchers aimed to investigate the concordance rate for GD in identical and dizygotic twins. For fraternal twins, this coefficient was much higher, which further confirmed the role of genetic factors in the development of GD [16,17]. Heritability is measured on a scale of 0 to 1, where 0 means no genetic link and 1 means full genetic determination. In a GD study of 1,891 twins, heritability was 0.50–0.57 in men and 0.30–0.37 in women [18]. Based on their research on a group of 315 twins, Coolidge et al. found that genetics is responsible for 62% of dysphoria [19]. Knafo et al. reported an inheritance pattern of 0.21 in boys and 0.74 in girls, and Burri et al. – 0.11 in girls [20, 21]. Although these authors conducted research on the relationship between genetics and GD, they did not examine individual genes. Discrepancies in study results are probably caused by different sizes of the study group and population variability. In 2018 cytogenetic analysis of karyotypes in 444 transgender women and 273 transgender men showed a five-fold higher incidence of cytogenetic changes in people with GD compared to the general population. The authors found a significantly higher incidence of Klinefelter syndrome and the 572 Kb 17q21.31 microduplication, which included the KANSL1 gene [22]. It should also be noted that most of the research to date questions the clinical utility of molecular karyotype in the examination of dysphoria in children and adolescents [23–25]. Henningsson et al. report that GD may be the result of various factors at the early stage of brain development [26]. Studies in an animal model have shown an effect of testosterone on sex dimorphism in brain development, leading researchers to conclude that it may be related to the androgen receptor (AR) or estrogen receptor (ER) [27]. Hare et al. examined the association between the development of GD in transgender women and gene polymorphisms known to be associated with under-masculinization or feminization. The length of the CAG repeat in the AR gene, the length of the CA repeat in the ERβ gene, and the length of the TTTA repeat in the aromatase gene (CYP19) were examined in 112 transgender women and 258 cisgender men from the control group. In the transgender group, the length of CAG repeats in the AR gene was greater than in the control group [28]. However, other studies have confirmed that the length of these repeats is related to the weaker affinity of AR for testosterone [29,30]. Researchers concluded that the AR gene may be associated with the occurrence of GD [28]. However, further studies aimed at finding polymorphisms in potential genes related to sex hormones, coding AR, ERα and ERβ, CYP19 and progesterone receptor (PR), did not reveal any genetic association with susceptibility to dysphoria [31]. In 2013, a study in a group of transgender men with dysphoria showed a greater length of the ERβ gene compared to the control group. The authors suggested that a possible mechanism leading to GD may be related to the fact that greater gene length leads to increased receptor transcription and, consequently, higher ERβ activation may result in less feminization of the brain [32]. A 2015 study found that the mutant A1 allele of the cytochrome P450 17A1 (CYP17) gene, which controls the level of sex hormones produced, is more common in transgender men [33]. At the moment, research shows conflicting conclusions regarding the role of sex hormone genes in the occurrence of dysphoria. This may be related to the heterogeneity of the group of people studied and too small research groups [34]. In order to examine a more homogeneous group in the study by Fernández et al. tested the AR, ERα, ERβ, and CYP19A1 genes in 549 transgender women compared to 728 cisgender men and 425 transgender men compared to 599 cisgender women in the control group [34]. In the group of transgender women, there was an interaction between ERβ and AR when one of the genes of these receptors was short and the other long. In transgender men, there was an association between ERβ and ERα, but no interaction between the polymorphisms. There is also evidence of a link between GD and genes involved in sex hormone signaling, but the authors emphasize that it may be oligogenic [35]. Yang et al. used whole-genome and whole-exome sequencing in four transgender women and nine transgender men. Three heterozygous mutations in the RYR3 gene were found in unrelated transgender men, and none in the control group [36]. This gene encodes the ryanodine receptor, which releases calcium ions from the sarcoplasmic reticulum in muscle cells or the endoplasmic reticulum in other cells [37]. Protein structure modeling

of the RYR3 mutation showed that the R1518H mutation caused a large structural change in the RYR3 protein. The authors concluded that these results provide information about the genetic basis of GD [36].

Among the various factors that influence brain development, sexual identity and sexual orientation throughout the lifespan, the evidence clearly shows that endocrine factors also play a key role [38]. Increased prenatal exposure to androgens is of great importance [39]. In humans, research on the effects of prenatal hormones on gender identity and gender dysphoria has most often been conducted in people with disorders of sex development (DSD). DSDs are congenital factors affecting the reproductive system and contributing to the development of atypical anatomical, gonadal and chromosomal sex [40]. Such disorders can be observed in people with congenital adrenal hyperplasia (CAH), complete and partial androgen insensitivity syndrome (CAIS - partial androgen insensitivity syndrome, PAIS - partial androgen insensitivity syndrome), micropenis, mixed gonadal dysgenesis, as well as in as a result of 5α-reductase-2 and 17β-hydroxysteroid dehydrogenase-3 in people whose karyotype is 46, XY. [39]. When considering the impact of androgen exposure on gender identity development, the relationship with other factors, such as sexual orientation or the level of parental care during childhood, should also be taken into account [41].

a.i.2. Neurophysiological diversity between people with and without gender dysphoria.

Research conducted so far has shown that there are significant differences in the structure of the brain depending on gender. Anatomical differences concern in particular the nucleus of the preoptic area, the interstitial nucleus, the nucleus intermedius, and the total volume of the brain. It has been shown that the total brain volume is larger in men than in women, but women have a larger share of gray matter and men have a greater share of white matter [42–46]. These results prompted researchers to look for an answer to the question whether psychological identification with a gender other than the one assigned at birth could also be reflected in the anatomy of the brain. Both postmortem anatomical analyzes and in vivo neuroimaging studies have revealed structural differences in various brain regions when comparing transgender individuals and control subjects [47].

Cerebral cortex thickness was measured in both transgender women and transgender men. Cortical thickness in transgender women showed signs of feminization, being thicker than cortex in cisgender male controls, particularly in areas such as the fronto-orbital, occipital, insular, and medial regions. However, transgender men showed no signs of masculinization in cortical structure, but compared to cisgender women in the control group, they had greater thickness in the parietal and temporal regions [48]. Similarly, a study by Luders et al. confirms the findings of feminized cortical thickness in transgender women, and cisgender male controls did not exhibit these characteristics. The transgender women's cortical thickness more closely resembled that of people with whom they shared their gender identity [49].

Gray matter volume was also analyzed in both transgender women and men and cisgender women and men in the control groups. Both categories of transgender people showed a reduction in gray matter volume in some areas of the cerebellum (including the anterior lobe, left posterior lobe, dentate nucleus), as well as in the left angular gyrus and the left inferior parietal lobe. In the inferior and central right occipital ganglia, the lingual and fusiform ganglia, and the inferior right temporal gyrus, gray matter volume was high in individuals with a female gender identity. In turn, in people with male gender identity, the volume of gray matter was large in the left central ganglia, left posterior cingulate gyrus, and the carinae sulcus [50].

A new theory has been created regarding the occurrence of gender dysphoria, which is defined as "multi-sensory", focusing on the function of networks connecting various brain regions. It is, as it were, an altered state of perception and a change in the sense of gender, which is influenced by related reflex behavioral responses and changed activity in three specific networks: stress or negative stress, social behavior and sense of belonging to the body [47].

Conclusions

The collected literature review shows that gender dysphoria has a polygenic basis, including interactions between various genes and their polymorphisms. It should be noted, however, that although there is a correlation between genetic factors and the development of GD, it is not the only determinant of gender identity. Genome-wide association studies should be conducted to better understand how genetic variants contribute to gender dysphoria. Endocrine factors are also important, so the most complete picture of the neurophysiological basis of GD will be obtained by adding brain imaging tests and measurements of sex hormone concentrations to genetic tests [35,38,51]. Future research into the genetic basis of gender dysphoria may become increasingly more precise as new genetic techniques become available [35]. Additionally, epigenetic studies may provide another perspective on the link between genetics and GD [51].

In the context of diagnostics and gender-affirming activities, it is worth raising the topic of gatekeeping, a practice that requires transgender people to go through

certain stages – numerous tests and visits to specialists – before receiving a diagnosis and accessing hormone replacement therapy, which has been criticized for creating unnecessary barriers, incurring expenses, and delaying the entire process. Moreover, transgender people continue to face high levels of gender discrimination in the healthcare system, when looking for work and in educational institutions [10,12]. Determining what biological factors contribute to gender dysphoria may influence public opinion associated with this community. Moreover, such knowledge can be used to improve the diagnosis and treatment of transgender people. Therefore, there is a clinical need to conduct further research in this field.

Conflict of interest

The authors have declared no conflict of interest.

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