From the Mayo Clinic

A Man's Brain in an Ambiguous Body: A Case of Mistaken Gender Identity

J. Michael Bostwick, M.D.

Kari A. Martin, M.D.

Case Presentation

Chief complaint: "I feel like I have the brain of a man. Am I crazy?"

On her first visit to a psychiatrist (J.M.B.), "Ms. C," a 48-year-old woman, asked this question about her confused gender identity. Having also discovered a primary sexual attraction to women, Ms. C was having difficulty reconciling her church's injunctions against sinful homosexual activities with her sense of herself as fundamentally male. She was dressed in a subtly frilly blouse and leather jacket she called "my leather-and-lace look." Encircling each wrist were tattooed bracelets, traceries of curlicues and rosebuds that gently contradicted pearl earrings and a delicate gold locket.

Born in the early 1950s and raised resolutely as a girl, Ms. C did not learn until she was 23 and married the unusual circumstances of her birth. Her mother finally divulged that she had entered the world with strange-looking genitals—neither male nor female. Doctors told her parents it was best to remove the odd tissue, fashion what remained to look female, and raise her as if nothing unusual had happened. At 6 months, surgeons removed both external tissue and presumed intra-abdominal testicular tissue and fashioned labia around the vaginal entrance she had always had. In grade school, she was told her large abdominal scar resulted from herniorrhaphy. At 12, after starting daily estrogen pills to induce puberty, she developed breasts and feminine curves, although without menarche or an increase in height beyond 5 feet. Her mother said she could not have children but did not explain why.

She recalls being a tomboy who preferred boys for playmates. Because of her small stature and feminine appearance, however, boys were not particularly comfortable hanging out with her. Then, as now, she identified with the way males think rather than a sense of being physically male. She dated boys in high school, had a sexual experience with a woman during college, and married a man with whom she enjoyed satisfying marital relations for nearly two decades until they experienced a ménage à trois. Her husband fell in love with the other woman, and she kindled awareness of her greater attraction to women than men. The marriage ended, and she embarked upon two long-term lesbian relationships and a struggle with alcoholism.

Ms. C found sobriety and her church while that second relationship was unraveling. Welcomed and spiritually nurtured by church members, she felt happy except for increasing discontent with her pastor's insistence that homosexual desires were her "cross to bear" and her options were either heterosexual marriage or celibacy. On one hand, her personal theology concurred that homosexuality was against God's plan. On the other, she struggled with identifying herself as either man or woman, a dilemma her pastor could not solve.

Ms. C's childhood medical records had been lost. The psychiatrist asked if she had been karyotyped, given her unusual birth. She did not know. When she was born, chromosome testing was not routinely available. Given medical advice to raise her unquestioningly as a girl, the issue had not resurfaced. The psychiatrist suggested the test, and when results revealed 45,X/46,XY chromosomes, 75% the latter, the fragments—the childhood operation, hormones, her short stature, "brain of a man"—fell into place. She immediately reported feeling "less of a freak" now that she had a name—"intersexual"—for her condition.

"Understanding constituents defining gender identity and sexual orientation is a work in progress, with intricacies and subtleties not yet fully appreciated….[One thing is clear:] Neither external genitals nor environment solely determines gender identity."

Discussion

Ms. C asked a question for which the differential of psychiatric conditions that include gender dysphoria is broad. Potential diagnoses include psychosis, somatic or religious delusions, body dysmorphic disorder, such personality disorders as borderline or schizotypal, and neurotic conflicts over sexual orientation (1). Without other psychopathology and knowledge of her intersexuality, Ms. C's presentation was consistent with gender identity disorder. In DSM-IV-TR terms, she had "strong and persistent cross-gender identification," "persistent discomfort with [her] sex or sense of appropriateness in the gender role of that sex," and "clinically significant distress or impairment in social, occupational, or other important areas of functioning" (2).

The most extreme manifestation of gender identity disorder is transsexualism, defined as "the inconsistency between perceived gender identity and phenotypic sex" (3). Most such patients have no discernible neuroendocrinological abnormality. If they do, they by definition cannot have gender identity disorder because DSM-IV specifically excludes concurrent physical intersex disorders. Their diagnosis falls instead within intersexuality, conditions in which patients have features of both sexes. Intersex subcategories include male pseudohermaphroditism, female pseudohermaphroditism, true hermaphroditism, and gonadal dysgenesis. Any of these diagnoses can raise issues of gender identity or sexual orientation.

This review focuses on the differential diagnosis and biological underpinnings of intersex conditions manifesting in gender dysphoria. Additionally, it addresses evidence for brain masculinization's influence on sexual orientation. At first our patient was unaware that she was intersexed. Given her history, her ignorance proved understandable. Paradoxically, once the psychiatrist helped establish her intersexed status and the likelihood of a masculinized brain, her "clinically significant distress" dissipated. Understanding this patient required consideration of an emerging literature supporting brain masculinization in utero, as well as several conditions in which abnormal brain masculinization figures prominently.

During early fetal development, all embryos contain bipotential gonads able to develop as male or female in response to triggering hormones. This bipotentiality is short-lived; by the 12th gestational week, internal and external genitalia have formed (4). Absent a Y chromosome, embryos default to female. With a Y chromosome present, however, a carefully choreographed hormonal sequence governs male development. First the Y chromosome's sex-determining region Y gene directs production of testis-determining factor. Testis-determining factor then causes the bipotential gonad to differentiate into testis-producing testosterone and Müllerian-inhibiting substance. Müllerian-inhibiting substance facilitates involution of female internal genitalia, including *anlage* for uterus, fallopian tubes, and vagina. After exposure to Müllerian-inhibiting substance, XX embryos retain only ovaries and primitive urogenital sinuses (4).

In XY embryos, three hormones—testosterone and two of its metabolites—induce genital differentiation and brain masculinization. Between the sixth and 12th weeks, testosterone directly stimulates Wolffian duct evolution into internal genitalia, including epididymides, vasa deferentia, seminal vesicles, and ejaculatory ducts. External genitalia development depends on dihydrotestosterone, hydroxylated from testosterone by 5-alpha reductase. By 12 weeks, the penis and scrotum have formed from structures analogous to the female clitoris and labia. Likewise, brain masculinization occurs only after testosterone aromatizes to estradiol, a process likely continuing through late gestation (5).

Paradoxically, the hormone-inducing feminization at menarche is the same one causing fetal brain masculinization. Normally, calibrated sexual differentiation cues yield synchronized soma and psyche. If the balance is skewed, intersexed fetuses with ambiguous brains, bodies, or both may result.

Sexual differentiation disorders comprise two broad pathological categories: disorders of genital embryogenesis and intersex conditions. Examples of the former include isolated aphallia and cloacal extrophy in XY newborns. Despite compromised external genitalia, these fetuses develop in a normal intrauterine endocrine environment, with undescended but functioning testes producing testosterone for brain masculinization.

Intersex conditions subsume diverse neuroendocrinopathies ranging from end-organ full or partial androgen insensitivity to chromosomal mosaicism. Despite ambiguous genitals or genitals opposite from the karyotype, pseudohermaphrodites have exclusively male or female chromosomal lines. Individuals with mixed gonadal dysgenesis may manifest features of both sexes, emanating from carrying cell lines of both sexes (4). Rarely, true hermaphrodites occur, with ovotestes containing both ovarian and testicular tissue or one each of a testis and an ovary.

Female Pseudohermaphroditism

In genetic XX females, an excess of any of three hormones usually present only in trace amounts can cause ambiguities. Congenital adrenal hyperplasia accounts for most female pseudohermaphroditism cases. All six congenital adrenal hyperplasia types involve enzymatic defects in the cortisol-synthesizing pathway. Cortisol provides negative feedback to ACTH in the hypothalamic-pituitary-adrenal axis. When cortisol is low, ACTH rises, stimulating increased adrenal androgen output. All six types share hypertrophied adrenal glands and excess production of cortisol precursors, all acting androgenically on developing fetuses.

The earlier the androgen exposure, the more masculinized XX fetuses become, with more extensive labioscrotal fusion, more penis-like clitorises, and a higher likelihood of urogenital sinus retention (4). XX fetuses not exposed until the second trimester sustain only clitoromegaly, although brain organization may be affected. They are more likely to have homosexual fantasies and exhibit masculine characteristics of enhanced aggression and visuospatial ability, even while typically retaining core female gender identity (6). In sum, internal genitalia are normal female; external genitalia and the brain have androgen-induced virilization (7).

Male Pseudohermaphroditism

Whereas too much of any of three hormones—testosterone, dihydrotestosterone, or estrogen—can cause problems for females, the opposite is true for males. Insufficient androgen supplies yield ambiguous or frankly female bodies or brains (4). Male pseudohermaphrodites have testes, but genitalia may be underdeveloped. Brains may masculinize incompletely, if at all. Causes include inadequate testosterone secretion with testicular dysgenesis, target tissue unresponsiveness to testosterone, or 5-al-

pha reductase deficiency, an enzyme defect yielding female-appearing fetuses with XY karyotypes.

Although CNS responsiveness to aromatized testosterone is intact and internal genitalia develop normally, the absence of 5-alpha reductase converting testosterone to dihydrotestosterone prevents external virilization (4, 7). Born with clitoris-like micropenises, these children are often reared as girls until pubertal testosterone surges prompt penile growth. Male gender behaviors and sexual attraction to females may emerge at puberty. Transition from female child to male adolescent goes well in populations familiar with the condition, principally genetic isolates in the Dominican Republic, Turkey, and New Guinea (7). The protagonist of *Middlesex*, Jeffrey Eugenides's best-selling novel, likely had this condition.

Another male pseudohermaphrodite condition illustrates what happens when neither brain nor Müllerian tissue responds to testosterone. In complete androgen insensitivity syndrome, a testosterone-receptor gene defect underlies testosterone unresponsiveness in both brain and peripheral tissue. Externally, these individuals resemble normal females. Internally, their normal testes produce both Müllerian-inhibiting substance and testosterone, but they have neither male nor female structures otherwise. Müllerian-inhibiting substance facilitates resorption of Müllerian derivatives, but the testosterone-receptor defect prevents Wolffian structure formation. A primitive urogenital sinus replacing a vaginal pouch is usually insufficient for sexual penetration (4).

Unless kindreds know they carry this X-linked condition, complete androgen insensitivity syndrome is not usually diagnosed until abdominal testes herniate or menarche fails to occur. A variant, partial androgen insensitivity syndrome, manifests in incomplete brain and body masculinization (4).

Gonadal Dysgenesis Versus True Hermaphroditism

Ambiguous genitals and masculine gender sensibility notwithstanding, our patient did not fall into the above pseudohermaphrodite categories. Her karyotype revealed another recognizable syndrome: gonadal dysgenesis (4).

Occurring in complete and incomplete forms, gonadal dysgenesis anomalies range from completely undifferentiated streak gonads through varying degrees of dysgenesis (7). Incomplete gonadal dysgenesis, also known as partial or mixed gonadal dysgenesis, includes either paired dysgenetic testes or a dysgenetic testis coupled with a streak gonad or a functional testis. Most common with mosaic 45,X/46,XY karyotypes, in which an individual has cells of both genotypes, mixed gonadal dysgenesis phenotypes extend from normal male to Turner female (4, 7).

Gonadal histology, not chromosomes or external anatomy, distinguishes true hermaphrodites from pseudohermaphrodites. Unlike the latter, the former possess both ovarian and testicular tissue, either intermixed within gonads or as independent testis and ovary. Seminiferous tubules are typically atrophic, but well-developed ovarian follicles may retain reproductive potential (8).

The rarest form of human intersexuality, true hermaphrodites, result from events as diverse as chromosomal nondisjunction, double fertilization, or Y-chromosome translocation (7). Neither phenotypes nor karyotypes are predictable. Some appear male, others female, but most are ambiguous (4). Sixty percent have 46,XX karyotypes; 20% are 46,XY. The remainder show mosaicism, typically of 45,X and 46,XY cell lines.

Mixed gonadal dysgenesis, likewise, expresses itself in a range of different phenotypes. The dysgenetic testes' capacity for testosterone secretion defines the extent of fetal masculinization (4, 7). Until 20 years ago, few reports existed of phenotypically normal males with mixed gonadal dysgenesis (9). Subsequent investigators demonstrated dramatic ascertainment bias, hinging on defects obvious at birth. In a mixed gonadal dysgenesis case series diagnosed by amniocentesis, 75 of 76 newborns had male phenotypes, and 72 of 75 (95%) appeared completely normal (10). Without amniocentesis, mixed gonadal dysgenesis would have gone undetected in most of these newborns.

Historical Management

Historically, infants with ambiguous genitalia have been at the mercy of medical fashion and societal demands for labeling sex at birth. Before the 1950s, chromosomes could not be factored into decision making. Technical limitations caused most children to be "made" into girls, given the purported surgical challenge of creating realistic—let alone functional—male organ facsimiles (11).

Failure to impose a definitive gender in infancy was considered unethical and irresponsible, as was letting the growing child assert its own gender identity. Largely through the preeminence of John Money, the doctrine that nurture always trumps nature drove gender assignment in infants with ambiguous genitalia or genital trauma (11). Clinical decision making within this "optimal gender" paradigm sought to balance 1) genital verisimilitude, 2) fertility potential, and 3) sexual function, emphasizing capacity for adequate penile-vaginal intercourse over neurovascular responsiveness or satisfaction. As long as caregivers enforced feminine accoutrements and expectations, "she" should not doubt "her" femaleness (12). Ms. C was raised according to Money's "optimal gender approach."

Money held that a newborn assumed the parentally assigned gender through postnatal imprinting "by words, attitudes, and comparison of one's body to that of others" (4). He defined a "critical period for psychosexual differentiation and the imprinting of a gender role and psychosexual identification as male or female," placing it between 18 months and 5 years, beyond which "a fixed and irreversible psychosexual identity [has] already [been] established" (13). Before 18 months was "a period of unlimited freedom of choice," with development unfolding normally in the assigned sex as long as surgery happened before core gender identity establishment (13).

Identical male twins, individuals as similar as two humans can be, gave Money the ultimate opportunity to prove his nurture trumps nature theory. When a circumcision accident burned one of the 6-month-old's penises irretrievably, Money advised castrating him and raising "her" as a girl alongside "her" identical brother. Known as "the Joan/John case," this experiment had disastrous repercussions, with "Joan" exhibiting depression, oppositionality, male behaviors, and social maladjustment. As early as preschool, "she" would rip off "her" dresses or flatly refuse to wear them. In grade school, "her" anger at being treated like a girl fueled constant insubordinacy and fights with fellow students. Home life was no better, with parents torn over raising their disfigured, combative son relentlessly as a girl. In adolescence, "she" refused follow-up visits with Money, experiences "she" had always considered humiliating and degrading (14).

At age 14, at the urging of "her" psychiatrist, Keith Sigmundson, "her" parents finally informed "her" of the botched circumcision and sex reassignment but not before "she" had undergone estrogen-induced puberty. Shortly afterward, "she" rejected whatever female vestiges remained and declared "herself" male. Adopting the name David, he embarked upon painful reconstruction of his maleness. Estrogen was discontinued, and testosterone prescribed, a necessity stemming from his orchiectomies in infancy. Years of surgeries, including mastectomies and numerous marginally successful phalloplasties, followed. He eventually married a woman and worked as a tradesman (14).

Reporting that "Joan" had accepted female gender identity and was living contentedly as a girl, Money cited these results to justify gender reassignment in other genitally ambiguous infants. In the *Archives of Pediatric and Adolescent Medicine*, Diamond and Sigmundson (15) eventually described what had actually happened with "Joan," underscoring the failure of the vigorously applied "optimal gender approach" and noting that even "Money no longer holds such extreme views." The story did not end happily. Two years after his twin killed himself, David did also, dying in 2004 at age 38.

Modern Management

During the last decade, the approach to genitally ambiguous infants has dramatically changed. Reiner and Gearhart (16) further discredited the optimal gender approach as simplistic and reductionistic, given the complexity of neurobiological and psychosexual developmental (15). With a catastrophic medical condition—cloacal extrophy—they showed that a high proportion of children with androgenized brains assert male core gender identity, regardless of absent male genitalia (16). Endowed with XY chromosomes and normally functioning abdominal testes, these boys have severe congenital pelvic defects, including gastrointestinal and genitourinary malformations and absent genitals. Under Money's theory, they were routinely orchiectomized and raised as girls. As with David, the Canadian twin, however, many rebelled against the female role and exhibited male-typical behaviors (16).

Reiner and Gearhart followed 16 genetic males with cloacal exstrophy, all but two neonatally reassigned as girls. All 16 exhibited stereotypic male behaviors. By the study's end, eight of the 14 "females" declared themselves male, some as early as age 5. Six of eight were transitioning to life as males. Although self-identified as males, two continued living as females in deference to their parents demanding that they not change. Five considered themselves females. One refused to discuss gender. Given these widely discrepant outcomes, Reiner and Gearhart advocated postponing definitive reassignment surgery until a child is old enough to declare a gender (16).

Implications of a Masculinized Brain

Except in the broadest strokes, determinants of gender identity and sexual orientation remain largely unknown. Evidence continues to mount, however, from neuroimaging and neuroanatomical correlations that male and female brains differ. Whereas most humans have genitals agreeing with their self-identifications as male or female, myriad variations do occur. By age 2, most children can clearly name their core gender identity, which usually—regardless of eventual sexual orientation—agrees with chromosomal and phenotypic sex. Moreover, it is a sociocultural truism that most toddlers behave in ways recognizably masculine or feminine.

The "masculinized brain" construct encompasses the postulated effects of in utero testosterone and its estradiol metabolite (17). Panksepp (5) described implications of mismatched soma and psyche for intersexed children: "If brain and body organization do not match up, the individual will have to discover through painful experience which gender was predominantly imprinted within his or her brain, and to what extent." Distress intensifies if physicians and family favor visible anatomy over evidence of brain imprinting.

Critical periods for hormonal effects remain largely unknown, although brain differentiation continues throughout fetal life. Sex hormones have "organizational" effects on fetal brains, and "activational" effects are most prominent during pubertal hormonal surges (5). The hypothalamic sexually dimorphic nucleus exemplifies differential neuroanatomic organization correlating with gender identity and sexual orientation. Males have larger, more cell-dense sexual dimorphic nuclei than females, and homosexual males have sexual dimorphic nuclei intermediate in size between males and females (18). An activational example involves the anterior hypothalamus, which, measured by positron emission tomography, responds to male sweat pheromone similarly in heterosexual females and homosexual males. The hypothalamic response of heterosexual males and homosexual females to female urine pheromone is parallel (19).

Correlations between hormonal influences, differences in male and female neuroanatomy and neurofunction, and variations in gender expression and sexual orienta-

tion continue to amass. Contemporary formulations acknowledge in utero organizational effects of sex hormones on sex-steroid responsive brain tissue, as well as pubertal activational influences on gender behavior and sexual object choice (3, 5). In human psychosexual differentiation, however, nothing is absolute. Prenatal androgen exposure facilitates—but does not absolutely determine—male gender identity (4). Although strongly supporting both organizational and activational influences of prenatal androgens on male gender development, the cloacal extrophy series of Reiner and Gearhart (16) includes self-identified males and females. The extent of atypical behavior does not reliably correlate with degree of virilization, however, thereby illustrating the lack of absolute outcomes for these children (6).

Degree of brain masculinization appears to affect both sexual orientation and gender identity in individuals with partial androgen insensitivity syndrome, congenital adrenal hyperplasia, 5-alpha-reductase deficiency, and congenitally absent or traumatically lost penises. Failed brain masculinization sheds light on these issues in patients with complete androgen insensitivity syndrome. Given complete testosterone insusceptibility, the situation is straightforward. They show core female gender identity, typical female behaviors, and predominant sexual attraction to males.

Diagnostic Investigation of Newborns With Ambiguous Genitalia

For newborns with obviously ambiguous genitalia, a team approach to the workup "to minimize medical, psychological, and social complications" is recommended, with representatives potentially from genetics, endocrinology, urology, gynecology, psychiatry, and social services (20). Endocrinological screening, karyotype, fertility potential, and external appearance may all factor into initial diagnosis and management. With congenital adrenal hyperplasia the most common cause of ambiguous genitalia, the American Academy of Pediatrics recommends endocrine screening for this disorder in infants with symmetrical external masculinization and nonpalpable gonads (20).

Without palpable gonads, all four intersex subcategories—female pseudohermaphroditism, male pseudohermaphroditism, gonadal dysgenesis, and true hermaphroditism—are possible, although female pseudohermaphroditism is most common. With two palpable gonads, male pseudohermaphroditism is likely. One palpable gonad rules out female pseudohermaphroditism and pure gonadal dysgenesis and suggests a testis (male pseudohermaphroditism, mixed gonadal dysgenesis) or ovotestis (true hermaphroditism) because ovaries and streak gonads do not descend (7).

Palpable gonads or a negative congenital adrenal hyperplasia screen mandates further exploration, including pelvic ultrasound seeking a muscular uterine body and a genitogram clarifying whether a vagina, a uterine canal, fallopian tubes, or vasa deferentia are present. Additional laboratory testing may identify testosterone biosynthesis blocks, decreased 5-reductase activity, or androgen insensitivity. Elevated luteinizing hormone and follicle-stimulating hormone levels accompanying nonresponse to human chorionic gonadotropin stimulation suggest the gonadal absence of pure gonadal dysgenesis. Gonadal biopsy reveals mixed gonadal dysgenesis, if present (7).

Until recently, gonadectomy was immediate, particularly when children with ambiguous genitalia were routinely raised as girls. Although the potential for cancer remains concerning, surgery is no longer automatic. In recommending waiting as long as safely possible before definitive surgeries, ideally until the child can participate in decision making, Diamond and Sigmundson (15) advise "perform[ing] no major surgery for cosmetic reasons alone; only for conditions related to physical or medical health." They also propose assigning sex "on the nature of the diagnosis rather than only considering the size of functionality of the phallus, respect[ing] the idea that the nervous system involved in adult sexuality has been influenced by genetic and endocrine events" (15).

Protocol-driven approaches to gender assignment are increasingly eschewed because of limited or inconsistent outcome data about approaches tried for rare disorders (16). Citing poor predictive power for adult gender identity in newborns with ambiguous genitalia, Houk and Lee (3) advocated doing as little as possible in early childhood, asserting that "the primary problem for transsexual and intersexed children seems to arise from society's expectations and insistence that gender role and identity align with anatomic sex."

Houk and Lee advocated individualized approaches as alternatives to optimal gender (3). Prenatal hormone effects trump chromosomal analysis, which can serve only as a guide. Sexual pleasure is at least as important as genital morphology, and neurovascular supplies to sex organs making sexual responsiveness possible should not be sacrificed to early cosmetic procedures.

Situations nonetheless remain in which early gonadectomy remains the treatment of choice. In mixed gonadal dysgenesis, rudimentary gonads should be excised within the first year because Y-containing gonads most at risk of malignant degeneration are both dysgenetic and intra-abdominal, with more than 30% developing cancers, some as early as prenatally (8). Histologically normal undescended testes become malignant at a lower rate and later age. Ideally, they should be relocated to the scrotum, with frequent ultrasounds for gonads left within the abdomen. In true hermaphrodites, ovarian tissue is more likely than testicular tissue to be normal. Dysgenetic testicular tissue can be removed, preserving mature female tissue and potential fertility when other reproductive organs are intact. Scrotal testes accompanying a large enough phallus support rearing as a male (8). Gonads should not be excised before a clear diagnosis and malignant risk are ascertained.

Given the normal testes in complete androgen insensitivity syndrome, they may wait until puberty to permit testosterone conversion to the estradiol-facilitating spontaneous secondary sexual characteristic development.

Because the cancer risk for normal abdominal testes rises from the second decade, however, orchiectomy should occur soon after puberty (8). Children with complete androgen insensitivity syndrome may also require surgery to create a neovagina from the colon, although little is yet known about adult sexual function and satisfaction (21).

Ultimate gender assignment decisions thus depend upon a constellation of factors: sexual and reproductive capacity, malignant potential, testosterone imprinting, and parental sensibilities. It also depends upon creating room for the growing child to assert gender identity. Early caregiver decisions on the infant's behalf do not guarantee adult acceptance of assigned gender, as patients such as Ms. C demonstrate. When adults present with gender dysphoria, limitations of current knowledge make the extent of brain masculinization difficult to ascertain. If medical histories are unavailable, tests performed in infancy may need revisiting. Now readily available, karyotyping may offer dramatic explanations, as it did for Ms. C.

Some adult patients with severe dysphoria—transsexuals—have neither history nor objective findings supporting a known biological cause of brain-body disjunction. They require 1) a thorough medical history and physical examination, 2) potential karyotyping, 3) consideration of the degree of brain masculinization, and 4) a thorough psychiatric examination. Absent psychosis or severe character pathology, patients' subjective assertions are presently the most reliable standards for delineating core gender identity.

Our Patient

Adults presenting today with gender dysphoria may not know the specifics of their medical histories. They may struggle—as our patient did—with an unassembled and incomplete puzzle of surgical scars and medical treatments hinting at something gone terribly awry. Psychiatrists must bring to bear all dimensions of the biopsychosocial model in making sense of the patient's gender and sexuality.

Our case of mixed gonadal dysgenesis illustrates the value of a careful history and a thorough medical workup, even in midlife, in patients with gender and sexuality concerns. The diagnosis best fitting our patient was mixed gonadal dysgenesis with 45,X/46,XY mosaicism, brain masculinization, and phenotypic elements of Turner's syndrome, including short stature and diabetes mellitus. Without pathological findings from tissue removed in infancy, it is impossible to know whether Ms. C was born a true hermaphrodite or a pseudohermaphrodite. Regardless, her history of ambiguous genitalia, coupled with aberrant chromosomes, contextualizes her masculine gender sensibility and sexual attraction to females.

Despite Ms. C's sense of brain and body not matching, she did not want to alter her gender presentation. Knowing she had XY chromosomes, however, helped her to better accept her atypical gender behaviors and sexual attraction to women. The chromosomal findings also changed her diagnosis from gender identity disorder to gender identity disorder not otherwise specified, the classification applied to gender dysphoria in intersex conditions (2).

Afflicted with a confluence of chromosomes, anatomy, and desires not addressed in scripture, Ms. C's religious beliefs undermined her comfort with her sexual and gender fluidity until she embraced an intersexual identity. She accepted her iatrogenically modified body, but not without lingering questions.

Conclusions

Phenotypically, intersexed individuals range from overt masculinization in XX females with congenital adrenal hyperplasia to flawless female physiognomies in XY males with complete androgen insensitivity syndrome. Psychologically, they are equally diverse. Questions of gender identity and sexual orientation may dominate a life or be of no psychological consequence. Neither external genitals nor environment solely determines gender identity. The penis neither makes the man nor negates the woman. Aphallic boys with cloacal exstrophy raised as girls spontaneously declare themselves male. Girls with congenital adrenal hyperplasia with micro phalluses and scrota exhibit firm female identity.

A 45,X/46,XY mosaic, with sexual and gender fluidity, Ms. C felt compelled to settle somewhere, even if it was not strictly male or female. After karyotyping, Ms. C's experience of having a male brain seemed logical. She appreciated the serenity a rational explanation bestowed.

Understanding the constituents defining gender identity and sexual orientation is a work in progress, with intricacies and subtleties not yet fully appreciated. Initial evaluation of gender dysphoria should focus on organic rather than psychological explanations. Only after ruling out intersexed conditions should primary psychiatric diagnoses be entertained.

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