

Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up

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Objective: To demonstrate that adequate pubertal history, physical examination, and a basal hormone profile is sufficient to exclude disorders of sexual development (DSD) in adult transsexuals and that chromosomal analysis could be omitted in cases of unremarkable hormonal profile and pubertal history.

Design: Retrospective chart analysis.

Setting: Endocrine outpatient clinic of a psychiatric research institute.

Patient(s): A total of 475 subjects (302 male-to-female transsexuals [MtF], 173 female-to-male transsexuals [FtM]). Data from 323 (192 MtF/131 FtM) were collected for hormonal and pubertal abnormalities. Information regarding chromosomal analysis was available for 270 patients (165 MtF/105 FtM).

Intervention(s): None.

Main Outcome Measure(s): Pubertal abnormalities, menstrual cycle, and hormonal irregularities in relation to chromosomal analysis conducted by karyotype or hair root analysis.

Result(s): In the MtF group, 5.2% of the patients reported pubertal irregularities and 5.7% hormonal abnormalities, and in the FtM group 3.8% and 19.1%, respectively. Overall chromosomal abnormality in both groups was 1.5% (2.9% in the FtM and 0.6% in the MtF group). The aneuploidies found included one gonosomal aneuploidy (45,X[10]/47,XXX[6]/46,XX[98]), two Robertsonian translocations (45,XXder(14;22)(q10;q10)), and one Klinefelter syndrome (47,XXY) that had already been diagnosed in puberty.

Conclusion(s): Our data show a low incidence of chromosomal abnormalities and thus question routine chromosomal analysis at the baseline evaluation of transsexualism, and suggest that it be considered only in cases of abnormal history or hormonal examination. (Fertil Steril® 2013; ■ : ■ – ■ . ©2013 by American Society for Reproductive Medicine.)

Key Words: Transsexualism, karyotype, hormones, puberty, menstrual cycle

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The role of the adult endocrinologist in the treatment process of transsexuals is essential, but the exact diagnostic work-up at first pa-

tient presentation remains rather vague, mainly due to the paucity of controlled studies. Endocrinologists primarily focus on the determination

of contraindications for cross-sex hormone treatment (1, 2). A common practice in many centers is to exclude chromosomal abnormalities and disorders of sexual development (DSD) at baseline evaluation by performing a karyotype analysis, although the underlying rationale is questionable (3). Both disorders are extremely rare. For transsexualism, there is a high variety in reported prevalence rates from 1:11,900 to 1:45,000 for

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male-to-female individuals (MtF) and 1:30,400 to 1:200,000 for female-to-male (FtM) individuals (4). The overall prevalence of DSD has been estimated at a rate of one person in 5,500 (0.018%) (5), and by including Klinefelter, Turner, and late-onset adrenal hyperplasia, the prevalence might rise to 1.7% (6). Because, according to these numbers, gender identity disorder is less common than DSD, routine karyotype analysis accounts for the concern to overlook a “biologic” reason for gender dysphoria, resulting in an instable gender identity and therefore premature initiation of treatment (7). However, a recent publication has challenged this approach even more, because the authors reported only a marginally increased incidence of gonosomal karyotype abnormalities in a large sample of transsexual patients (8). The policy may be driven by concern regarding irreversible surgical procedures in individuals suffering from DSD accompanied by transient gender dysphoria that might eventually resolve over time, and individuals would then regret their initial decision. DSD are classified as sex-chromosome DSD, such as Klinefelter and 46,XY or 46,XX DSD (9). Although 46,XY or 46,XX DSD may be associated with gender identity issues, there are only some anecdotal reports on 47,XXY- and XXX-karyotype findings in transsexual subjects (10, 11). The exclusion of any chromosomal abnormality has therefore been incorporated by the 10th Edition of the International Classification of Diseases (ICD-10) as one of the diagnostic criteria for gender identity disorder (“The disorder is not a symptom of another mental disorder or a karyotype abnormality”) (12). This has been interpreted by health providers in Germany and many other European countries in such a way that karyotype analysis is a mandatory precondition for reimbursement of gender reassignment surgery costs (8).

The adult endocrinologist is additionally expected to assess hormonal irregularities, such as polycystic ovary syndrome (PCOS), at baseline evaluation before initiation of cross-sex hormone treatment (13) and to assess possible contraindications for the therapy, such as severe liver damage, history of recurred thromboembolism, or hormone-sensitive cancer (1). Another aspect in this context may be that disorders of sexual development or gonosomal aneuploidies are frequently accompanied by abnormalities in sex hormone levels, such as hypogonadism and hyperandrogenemia (14–16). Additional useful information is provided by evaluation of pubertal history and physical examination. In phenotypically female patients for example, presence of 46,XY DSD can be ruled out in most cases by detailed evaluation of menstrual history and physical examination (15).

Although milestones of pubertal development in male patients are harder to define than in female patients, there are conditions known as “XX male syndrome” in which a genotypic female, primarily due to chromosomal translocation processes, would present with a male phenotype. A much more common gonosomal abnormality is represented by Klinefelter syndrome. This condition may be accompanied by hypogonadism or pubertal irregularities (17). Although there is a large variety in terms of phenotypic appearance, especially in those exhibiting chromosomal mosaicism, there is as yet no evidence for an increased risk of gender dysphoria in these patients.

In the present study we tried to provide a critical evaluation of the role of chromosomal analysis in transsexualism based on more than 20 years of experience in the treatment of adult transsexual patients. We retrospectively analyzed the charts of each transsexual patient who had ever visited our department during this time and hypothesized that karyotyping in adult transsexuals would be in the vast majority of cases dispensable, especially when additional information such as pubertal development or hormonal profiling was incorporated in the diagnostic procedure.

MATERIAL AND METHODS

Patient Population

We retrospectively evaluated the patient charts of all patients with the diagnosis of gender identity disorder who had been treated in the endocrine outpatient department of the Max Planck Institute of Psychiatry in the period from January 1992 to December 2012. All patients were included, regardless of whether they had ever been seen by an endocrinologist before, received cross-sex hormone treatment, or had even undergone sex reassignment surgery. The whole study population consisted of 475 subjects (302 MtF, 173 FtM). At first visit 110 patients (81 MtF, 29 FtM) had already gone through the endocrine evaluation process and were receiving cross-sex hormone treatment or had even undergone sex reassignment surgery. These were examined only for reported karyotypes/hair root analysis. Twenty-nine MtF and 13 FtM were excluded because of insufficient information on pubertal development. Therefore, the final sample for hormonal and pubertal evaluation consisted of 323 subjects (192 MtF, 131 FtM). Information regarding chromosomal analysis was available for 270 patients (165 MtF patients: 83 karyotype analyses and 83 hair root analyses with one patient being examined with both methods; 105 FtM patients: 56 karyotype analyses and 49 hair root analyses). The study was approved by the Institutional Review Board of the Ludwig Maximilian University in Munich.

Clinical Information

We collected information on pubertal development and extracted any documented irregularity during that period. In our outpatient clinic, a standardized form is used for anamnestic information to assess cycle length at day of presentation (female), date of last menstrual bleeding (female), libido abnormalities (male and female), and a separate category and free text form to enter pubertal abnormalities (male and female) and estimated date of first menstrual bleeding (female). A further check-up section in the anamnestic form for “unremarkable pubertal development” as well as a free text field to enter suspicious pubertal development are available.

In female patients, pubertal irregularities were categorized as follows: self-reported premature menarche (menarche <10 years of age), delayed menarche (menarche >18 years of age), and primary amenorrhea (18). Patients’ files with missing information regarding menarche were excluded from further analysis. In addition, menstrual abnormalities

at baseline evaluation were recorded in those who had never received any cross-sex hormone treatment before and had not taken any oral contraceptive pills ≥ 6 months before the first visit. These were categorized as oligomenorrhea (menstrual cycle >35 days), polymenorrhea (menstrual cycle <21 days), oligo/polymenorrhea (alternation in both), or secondary amenorrhea, defined by the absence of menstrual bleeding for at least three usual cycle lengths (19).

In male patients, regular pubertal development was assumed if “unremarkable pubertal development” or “no pubertal abnormality” in the check-up section was documented. In case of missing definite statement on pubertal development, the patients were excluded from further analysis. Therefore, the final sample for hormonal and pubertal irregularities consisted of 192 subjects. If pubertal abnormalities were documented, they were categorized as follows: Precocious or delayed puberty was assumed only if onset of recalled first conscious ejaculation (oigarche) before the age of 12 years or after the age of 16 years, respectively, was documented (20). Developmental abnormalities were also noted if any history of cryptorchidism or absence of pubertal voice change was reported by the patients. Genital examination and ultrasound examination of the testicles was not performed on a routine basis, but only in cases in which male transsexual patients reported pubertal irregularities or in those representing with biochemical abnormalities in terms of hypogonadism. This approach was chosen because many transsexuals avoid genital examinations because they are uncomfortable with their primary sexual characteristics, and the necessity for conduction of this examination remains controversial (21).

Laboratory Analysis

Standard commercial manual radioimmunoassays were used before 1996 for sex-steroid and gonadotropin measurement, which were routinely controlled in our laboratory for batch-to-batch variability and precision criteria. From 1997 on, the automated electrochemiluminescence immunoassay Elecsys 2010 (Roche-Boehringer) was used. The maximum intra- and interassay coefficients of variation at different hormone concentrations were, respectively, luteinizing hormone (LH) 2% and 5%, follicle-stimulating hormone (FSH) 2% and 5%, estradiol (E_2) 6% and 6%, and testosterone (T) 5% and 7%. From the year 2006 on, hormone concentrations were measured with electrochemiluminescence immunoassay on a Cobas 6000 system E601 (Elecsys module) immunoassay analyzer (Roche Diagnostics) with the same batch of reagents.

Information on sex steroids, such as T and E_2 , and on gonadotropin levels, such as LH and FSH, were collected from cross-hormone naïve patients that had not undergone any hormonal or surgical treatment at first presentation.

In women, due to the high variability within the menstrual cycle, we only assessed hyperandrogenemia defined as T above the female normal range or T and androstenedione above the female reference range (>2 SD) and if these findings were at least confirmed once by repeated measurement within the follicular phase (day 3–9 after the first day of menstrual bleeding) of those having a regular cycle. If the cycle phase was not exactly determinable or absent

because of menstrual irregularities, hormones were measured at time of presentation. In case of elevated T levels, ACTH stimulation test (250 μg Synacthen) was performed within the follicular phase. Congenital adrenal hyperplasia (CAH) was then biochemically diagnosed by elevation in 17OH-P levels 60 minutes after the ACTH challenge test (22). Presence of PCOS was recorded after verification of being in accordance with the Androgen Excess Society Guideline from 2006 (23).

In men, hormonal irregularities were categorized according to the given reference ranges (hormonal value within the 2.5th and 97.5th percentiles) as follows. Primary hypogonadism was defined as T below the reference ranges and elevated levels of LH and FSH. Secondary hypogonadism was defined as low T and LH combined with low FSH or T and LH and FSH within the normal ranges. We also documented any isolated increase in FSH or LH. Because different hormone assays had been used in the course of the past 20 years, we decided not to report definite hormone values owing to limited comparability, but instead only qualitative deviations according to the given reference ranges provided by the corresponding manufacturer.

Karyotyping/Hair Root Analysis

The majority of karyotypes were examined in the Synlab Laboratory in Munich. Standard chromosome analysis was performed on cultured lymphocytes with G banding techniques at a resolution of 400–500 bands per haploid genome. Ten to 14 mitotic cells per patient were examined.

In most patients who had their first appointment at our department before the year 2000, chromosomal abnormalities were evaluated by means of hair root analysis (24, 25). Subsequent karyotype analysis was performed only for confirmation purposes in case of pathologic findings. Briefly, the root sheath was stained with a stain-fixative, such as aceto-orcein, and then put under a coverslip. In a suitable area, the presence of Barr bodies indicated an inactivated X-chromosome as in regular 46,XX karyotypes but also as in disorders such as 47,XXY, where, e.g., two Barr bodies would be visible. In men (46,XY) no Barr body should be detected. Thus the method allows chromosomal sex assignment. The sensitivity of this method to detect gonosomal aneuploidy, such as Klinefelter syndrome, is reported to be up to 82% and the specificity up to 92% (26).

Statistics

All statistical analyses were performed with the use of SPSS v.18.0 (IBM). A two-tailed *P* value of .05 was considered to be statistically significant with a 95% confidence interval (CI). The chi-squared (χ^2) test was used to evaluate the influence of the different categoric hormonal abnormalities and the presence of disturbances in menstrual cycle and time of menarche in women or developmental abnormalities in men. It was performed only in subjects that had never been on treatment before and in whom clear anamnestic information was available in the files.

RESULTS

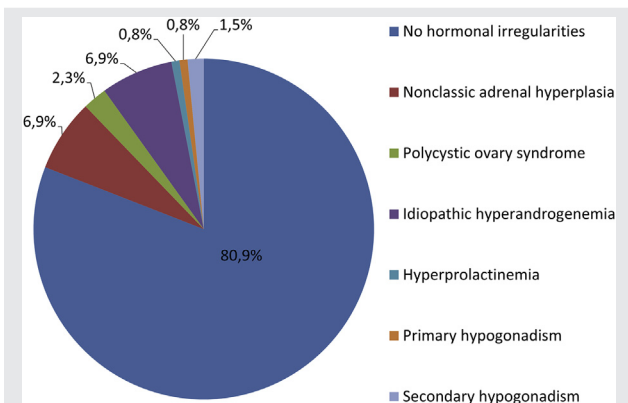
Female-to-Male Transsexual Patients

After exclusion of the patients already treated at first presentation and to avoid interference of previous treatment strategies with menstrual history or hormonal analysis as previously described, we focused our further analysis on the group of cross-sex hormone-naïve patients ($n = 131$; mean age at first presentation 33.2 ± 11.6 years). At first presentation all patients were premenopausal. Five (3.8%) reported pubertal irregularities in terms of premature menarche ($n = 2$; 1.5%) or late menarche ($n = 3$; 2.3%). No patient reported primary amenorrhea. Menstrual irregularities after menarche were detected in 14 subjects (10.7%), of which the majority were accounted for by oligomenorrhea and secondary amenorrhea (Table 1). No patient reported oligo/polymenorrhea.

Information on basal sex steroid hormone levels and gonadotropins was available in all 131 cross-sex hormone-naïve FtM patients. According to our definition, hormonal disturbances at first presentation could be recorded in 25 subjects of the FtM group (19.1%). Hyperandrogenemia was the most common diagnosis, owing to a high prevalence of biochemically confirmed nonclassic adrenal hyperplasia (NCAH) that accounted for almost one-half of those representing with hyperandrogenemia. One patient not included in the analysis had already been diagnosed with classic CAH due to a homozygote mutation in the *CYP21A2* gene. Another was subsequently diagnosed with a mutation in the *3 β -HSD* gene. PCOS was less common (2.3%), and in nine patients no definite cause for hyperandrogenemia according to our criteria could be identified and was therefore referred to as idiopathic. Secondary hypogonadism was seen in two patients, one of whom was suffering from anorexia nervosa and the other from hyperprolactinemia (Fig. 1).

Of 21 patients with hyperandrogenemia, five (23.8%) presented with concomitant menstrual cycle abnormalities. Two were suffering from oligomenorrhea and three from secondary amenorrhea. However, there was no significant association between hyperandrogenemia and any menstrual irregularity. There was also no significant difference regarding

FIGURE 1



Hormonal irregularities in female-to-male individuals (FtM) at first presentation. Hormonal disturbances were present in 25 subjects (19.1%) of the FtM group. Hyperandrogenemia was the most common diagnosis (16%), owing to a high prevalence of biochemically confirmed nonclassic adrenal hyperplasia (NCAH) in nine subjects (6.9%). PCOS was less common, with three cases (2.3%), and in nine patients (6.9%) no definite cause for hyperandrogenemia according to our criteria could be identified, and it was therefore referred to as idiopathic. Secondary hypogonadism was seen in two patients (1.5%) one of whom was suffering from anorexia nervosa (0.7%) and the other from hyperprolactinemia (0.7%).

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type of menstrual irregularities between hyperandrogenemia due to NCAH or due to other causes. In contrast, menstrual cycle abnormalities at first visit were significantly associated with the presence of conspicuous findings in the hormone profile ($P < .05$). Delayed menarche was significantly associated with the presence of oligomenorrhea at first presentation ($P < .01$). Age according to different quartiles (≤ 25 , 26–33, 34–41, and > 41 years) had no significant influence on frequency or kind of hormonal, pubertal, or menstrual irregularity (data not shown).

Male-to-Female Transsexual Patients

We assessed the pubertal history and hormone levels in the group of 192 cross-sex hormone-naïve patients (mean age at first presentation 34.4 ± 10.9 years), after excluding patients who had already undergone any hormonal or surgical treatment. Pubertal irregularities could be recalled in the history of ten patients (5.2%), of which five accounted for delayed puberty in terms of oigarche and three recalled that they had suffered from maldescensus testis. Two patients reported that there had been no pubertal voice change (Table 1).

Regarding hormonal abnormalities at first presentation, 25 were found to have any abnormality in their hormone profile according to our definition. After deeper investigation of the medical history, six subjects admitted use of unprescribed sex steroids before, whereas further reasons for exclusion were GnRH analogue treatment because of prostate cancer, severe testicular damage due to persistent cryptorchidism, or intermittent treatment with the steroid danazole because

TABLE 1

Pubertal and menstrual cycle irregularities in treatment-naïve patients.

	n	%
Female-to-male		
Pubertal irregularities present	5	3.8
Premature menarche	2	1.5
Delayed menarche	3	2.3
Menstrual irregularities after menarche present	14	10.7
Oligomenorrhea	8	6.1
Polymenorrhea	1	0.8
Secondary amenorrhea	5	3.8
Male-to-female		
Pubertal irregularities present	10	5.2
Delayed oigarche	5	2.6
Cryptorchidism	3	1.6
No pubertal voice change	2	1

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of hereditary angioedema. Finally, in two additional patients with hypogonadism, repeated hormonal evaluation could not reconfirm the initial diagnosis (data not shown).

After exclusion of cases in which hormonal abnormalities either could not be reconfirmed or could not be attributed to or explained by any additional information acquired by a more detailed anamnestic work-up, only 11 patients remained. Thus in the final sample, two patients presented hyperandrogenemia (1%), one primary hypogonadism (0.5%), and three secondary hypogonadism (1.6%), two presented with elevation in E₂ levels (1%), and three with isolated high FSH (1.6%). No patient presented with isolated LH elevation. In these patients, hormonal irregularity was not significantly associated with any developmental suspicious finding or with any of the particular hormonal diagnosis (Fig. 2).

Chromosomal Analysis

Data regarding chromosomal analysis were collected from the initial group of transsexual patients. In the FtM group, data regarding chromosomal status—in the form of karyotypes or hair root analyses—were available in 105 subjects (60.7%). Fifty-six karyotypes were available, whereas in 49 patients female nuclear sex was diagnosed by single Barr body positivity. Chromosomal aneuploidies were found in three of these patients. Two of them had autosomal aneuploidies due to the same robertsonian translocation (45,XX der(14;22)(q10;q10)). The other patient was diagnosed with Turner syndrome with mosaicism (45,X[10]/47,XXX[6]/46,XX[98]; Table 2). However, the latter patient showed no irregularities in terms of pubertal development or hormonal disturbances.

Total nuclear sex analysis was available in 165 MtF (83 karyotypes and 83 hair root analyses, with one patient evaluated with both karyotype and hair root analysis; Table 2). The only patient with an abnormal 47,XXY karyotype

TABLE 2

Chromosomal profile of the patient group.

	n	%
Female-to-male (FtM)		
Karyotype available	56	53.3
Unremarkable karyotype 46,XX	53	94.6
Abnormal karyotype	3	5.4
45,X[10]/47,XXX[6]/46,XX[98]	1	1.8
45,XXder(14;22)(q10;q10)	2	3.6
Hair root analysis available	49	46.7
Barr body positive	49	100
Barr body negative	0	0
Overall chromosomal abnormality in the FtM group	3	2.9
Male-to-female (MtF)		
Karyotype available	83	30.4
Unremarkable karyotype 46, XY	82	98.8
Abnormal karyotype	1	1.2
47,XXY ^a	1	1.2
Hair root analysis available	83	30.4
Barr body positive ^a	1	1.2
Barr body negative	82	98.8
Overall chromosomal abnormality in the MtF group	1	0.6

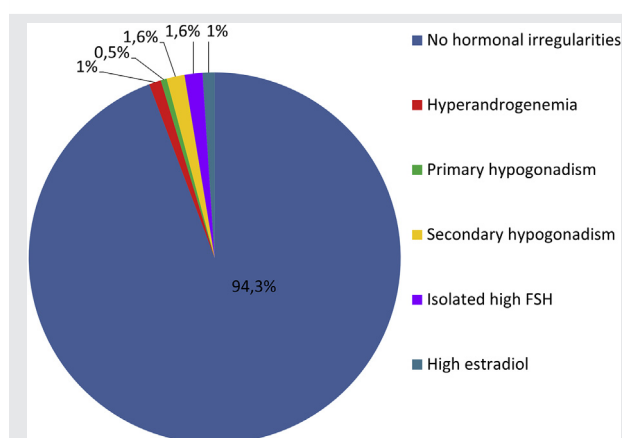
^a Same patient.

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confirmed also by Barr body positivity root analysis had already been diagnosed with a Klinefelter syndrome during pubertal development due to a suspicious phenotype (small testicles and genitalia, gynecomastia). In nine patients with abnormal hormone laboratory findings, chromosomal information was available (three karyotypes and six hair root analyses), of which none was suspicious for DSD. Patients presenting with primary or secondary hypogonadism had a normal male karyotype.

Overall chromosomal abnormality was 2.9% in the FtM group and 0.6% in the MtF group, whereas 1.5% of all transsexual patients presented with any type of chromosome abnormality.

FIGURE 2



Hormonal irregularities in male-to-female individuals (MtF) at first presentation. Two patients presented with hyperandrogenemia (1%), one with primary hypogonadism (0.5%), and three from secondary hypogonadism (1.6%). Two patients (1%) presented with elevation in E₂ levels and three with isolated high FSH (1.6%).

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DISCUSSION

In the present study we could show that chromosomal abnormalities in transsexuals are rare and do not seem to be associated with the gender identity disorder. Our study showed a low prevalence of 1.5% of overall chromosomal aberration in the initial group of transsexual patients. Only one MtF patient (0.6%) presented with an abnormal 47,XXY karyotype, and this patient had already been diagnosed with Klinefelter syndrome owing to pubertal abnormalities. In the group of FtM patients, three cases (2.9%) presented with chromosomal aneuploidies, including a single case of Turner syndrome with mosaicism (45,X[10]/47 XXX[6]/46,XX[98]) and two additional patients with autosomal aneuploidy, both due to the same robertsonian translocation (45,XXder(14;22)(q10;q10)).

Our results are in accordance with those presented by Inoubli et al. (8), who reported a similar karyotype abnormality frequency of 2.45% in an equally large sample of transsexuals. The prevalence of any karyotype aberration in the general population has been reported as 0.53% (27). Regarding MtF individuals, a low prevalence of Klinefelter

syndrome could be detected, as also shown by Inoubli et al. (8). This may be higher than the expected frequency in the general population, which is reported to be 0.12%, but the significance of the finding is debatable owing to the low overall incidence (27). Regardless of basing only on karyotype results or overall chromosomal information, aberrant karyotypes in our study population were more frequent in FtM than in MtF (5.4% vs. 1.2% and 2.9% vs. 0.6%, respectively) although this difference was not statistically significant.

Data regarding karyotype aberrations, such as aneuploidy, in earlier studies of FtM transsexuals are lacking (28–30), and a lower prevalence was reported by Inoubli et al. (8). The detected autosomal aneuploidy (45,XXder(14;22)(q10;q10)) is reported with a frequency of 1.2% in the general population (31). The physiologic consequences of this aneuploidy, however, are not understood. A possible association with reduced reproductive capacity was suggested in men (32).

There is so far no pathophysiologic concept in the literature linking autosomal or gonosomal translocation with transsexualism or gender dysphoria. Although there is evidence that Klinefelter syndrome is markedly underdiagnosed in the general male population (33), we do not support the idea of placing a specific focus in diagnosing Klinefelter in the transsexual population. Men with Klinefelter syndrome usually present with a male gender identity. Although increasing the detection rate of this syndrome in the general population would be desirable, this does not provide us with any extra information in transgender individuals, regarding neither therapeutic options nor treatment outcome.

The same seems to be true for patients with Turner syndrome with mosaicism. There is another case in the literature that describes a case of Turner syndrome with a mosaic karyotype in the context of gender dysphoria suffering from primary amenorrhea (34). Our patient presented with only a mild XO-mosaic, which may also account for the unsuspecting phenotype. It needs to be elucidated if we should treat individuals with Turner syndrome and gender dysphoria differently. So far, only a study by Zuckerman-Levin et al. (35) has investigated effects of low-dose androgen replacement in Turner syndrome on metabolic and mental outcome variables. It is not known if they would have a higher risk for adverse events by receiving high-dose T as in cross-sex hormone treatment, because these patients are predisposed to suffer from cardiovascular comorbidities (36).

Regarding hormonal irregularities, we could show a prevalence of 19.1% and 5.7% in cross-sex hormone-naïve FtM and MtF patients, respectively. Six MtF denied having administered hormones at first presentation and admitted later intermittent self-administration of nonprescribed hormones. This underscores the importance of considering hormone self-administration in this population before interpreting basal hormone profiles (37). In two additional MtF, initial findings could not be confirmed in repeated laboratory measurements, and in one individual hypogonadism was probably due to medication-induced hyperprolactinemia.

Furthermore, we could show that secondary amenorrhoea was associated with secondary/combined hypogonadism in our FtM population and that delayed menarche was significantly associated with the presence of oligomenorrhoea at first presentation. Prevalence rates for secondary amenorrhoea

were not different from those reported in the literature for the general female population (38, 39). Despite the fact that the prevalence of PCOS in FtM has been reported to be higher than in the general female population (13), we could not confirm this finding in our study. One reason that could account for this is that there are different diagnostic criteria for PCOS which are used in parallel and may therefore make comparability between different studies more difficult (40). However, there are also studies not supporting the idea of higher prevalence rates of PCOS in FtM (41). Selection bias may account for the finding that prevalence of PCOS in our cohort is lower than that usually reported for the general population (42). First, our patients were not screened for PCOS, and second, FtM often deny gynecologic examination for assessment of polycystic ovaries.

In our patient sample we found a high prevalence of 6.9% in biochemically diagnosed NCAH. Genetic testing was available in only one of these patients, which is in accordance with the guidelines of the endocrine society on CA, implying that the ACTH challenge test is sufficient to confirm the most common cause for NCAH, i.e., 21-alpha-hydroxylase deficiency (43). In those presenting with clinical signs of hyperandrogenemia, prevalence is reported to be ~2% (44). Keeping in mind that we tested only those with hyperandrogenemia, our rates may be much higher than in the general population, but we could not confirm the extreme high frequencies of CAH (50%) reported in a small sample of unselected FtM (45).

In our cohort we did not find any association between chromosomal aneuploidies and gender identity disorders, which is in accordance with earlier reports (8, 29). In our sample, we did not identify a single case of 46,XY DSD. Usually DSD and gender dysphoria are two distinct phenomena which only in the minority of cases overlap (46). The most common virilizing condition (CAH) in girls is only exceptionally associated with a male gender identity (47). The most common feminizing disorder of sexual development is complete androgen insensitivity syndrome. Almost 100% of affected subjects have a regular female gender identity which is stable throughout adolescence and adulthood (48). Only those with partial androgen insensitivity syndrome may present with incongruent gender identity, but in the majority of cases they can be noticed by distinct discriminating phenotypic characteristics (49).

A special case is 5-alpha-reductase deficiency, in which gender identity may change in the course of pubertal development from female to male as a consequence of the testosterone surge during that period (50). Although a significant number of such subjects report change in gender identity for the first time in early adulthood, they would not present with menarche or even regular menses. For the exclusion of this extremely rare disorder, with estimated prevalence rates of 0.1%–2% according to different definitions (51), karyotyping in children and adolescents may be helpful (52). Additionally a significant number of DSD are nowadays routinely diagnosed during new-born screening, particularly CAH, which exhibits elevated levels of 17OH-P in infants (7). Therefore, from the perspective of an adult endocrinologist, all worries regarding premature treatment initiation and harm the patient are basically unfounded. Another picture may be

given for the diagnostic procedure of gender identity disorder in childhood or adolescence. Growing efforts are made to shift time of diagnosis regarding potential hormonal pubertal suppression to these early years. Consequently, a variety of clinical and biochemical information regarding course of pubertal development are lost (53). In these cases we further support the routine screening for DSD by karyogram analysis.

Study Limitations

As in the case of every study, our investigation has limitations and strengths. This study is, to our knowledge, the first systematically assessing the prevalence of chromosomal analysis in combination with hormonal and developmental evaluation. Regarding the limitations, as in every retrospective analysis, the present study includes an information bias. We cannot realistically assume that every doctor who has worked in our outpatient clinic within the past 20 years has followed the exact same clinical and anamnestic evaluation process, although an unchanged standardized form was used during that period. Whereas time of menarche, menstrual cycle length, and date of last menstruation are mostly easy to determine, pubertal development in boys is hard to assess when clear information on, e.g., Tanner stages is missing. Because this information is commonly not available retrospectively, we chose oigarche as a surrogate for pubertal development, being aware that it a relatively weak indicator (54). However, this is a general problem in adult endocrinology, and from a practical point of view corresponds to daily routine management. Although this could further be affected by recall bias, it is interesting to note that those within the highest age group reported significantly higher prevalences of pubertal irregularities. We also stress that because we excluded patients if we did not find a clear statement on pubertal development, we cannot completely rule out that in these cases pubertal development was always unremarkable, leading to an underestimation of the true prevalence of irregularities in pubertal development.

CONCLUSION

Though there is evidence that chromosomal abnormalities may have a slightly higher prevalence in transsexualism, the routine screening for these disorders is highly questionable, because so far there is no evidence for any functional relationship with gender dysphoria, therefore limiting the consequences of any suspicious findings in this context. There is also no support for the idea that even if transsexual individuals are diagnosed with chromosomal aneuploidy, they should be treated differently or that gender dysphoria could be revoked. Apart from this, most DSD can be excluded by adequate anamnesis covering menstrual irregularities and pubertal development, although we could not demonstrate this by our own data owing to the fact that none of our investigated patients was diagnosed with DSD. On the other hand, this underscores that these disorders are extremely rare and nowadays they commonly arise before the patient's first presentation to the adult endocrinologist. We confirmed earlier reports that there is a higher prevalence of androgen excess in FtM mainly due to NCAH, an observation that remains without therapeutic consequence once the psychiatric diag-

nosis of transsexualism is established. We therefore recommend that exclusion of chromosomal abnormality by karyotype analysis should no longer be included as a mandatory step for the diagnosis of gender identity disorders in adults in the upcoming ICD Revision, although there might still be a rationale for the diagnostic management in adolescents.

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