Adverse orthopedic effect of exogenous estrogens on men undergoing cross-gender hormonal therapy

Muhammad Adil Abbas Khan, Zain A. Sobani and Mark Gorman

Ther Adv Endocrinol Metab

(2011) 2(4) 165–167

DOI: 10.1177/
2042018811414454

© The Author(s), 2011.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Introduction

Transsexualism is a condition in which a person with apparently normal somatic sexual differentiation is convinced that he or she is actually a member of the other sex. The attainment of the sexual characteristics of the desired gender is contingent on the use of sex steroids. The adverse effects of sex steroid therapy are real and apparent, with numerous contraindications. In this report we describe the development of spontaneous septic arthritis and other biochemical changes in a patient who had been on sex steroids (estrogen and progesterone) for a few months.

Case report

A 31-year-old male nurse presented with pain in his left ankle joint. He denied any trauma to the joint. On physical examination he was febrile at 37.9°C and had a flushed appearance. The ankle was mild to moderately tender globally and mild to moderately swollen (3 cm greater in circumference than the right ankle at the midmalleolar level). The overlying skin was warm, but there was no erythema. Passive range of movement (ROM) was on average 20° better than the active ROM for all joints. He had flat feet, and on a focused examination of the left ankle joint the active ROM was limited to 20° of dorsiflexion and 20° of plantarflexion. The active ROM of the subtalar joint was also limited to 10° of eversion and 20° of inversion. There was no evidence to suggest the presence of a joint effusion.

Systemic examination did not reveal any foci of possible infection. The hair on both his legs had been waxed off, as had the hair on both his arms and his chest. Moderate bilateral gynecomastia and severe scarring with erythema on the face along the distribution of where his beard might have been were observed. Very few hair follicles were visible on the skin overlying the mandible.

On further questioning he reluctantly revealed that he had been taking ‘feminizing hormones’ for ‘a few months’. Although he was unable to recall the exact percentages of each hormone in the combination, he verified them as estrogen and progesterone. He also admitted to having had laser treatment to his face recently, which resulted in severe acne, to which he attributed his flushed appearance.

Biochemical markers showed the presence of hypokalemia (2.9 mmol/l) leukocytosis ($15.9 \times 10^9/l$) and neutrophilia ($10.2 \times 10^9/l$). An X-ray report showed minimal soft tissue swelling and that the underlying bones appeared normal. The examination and biochemical parameters were equivocal for a possible infective process in his left ankle. We explained that if there had indeed been no trauma to his ankle and the symptoms and signs were present spontaneously, we would have to err on the side of caution and treat him for septic arthritis. We decided to wash out his ankle and commence intravenous antibiotics. At this point he admitted that the night before he had been dancing in stiletto heels for 6 h and had possibly twisted his left ankle.

He was given analgesics and his ankle was placed in a tubigrip bandage. He was advised to rest and elevate his ankle for a few days. He was also advised to come back if the fever persisted and if he began to feel unwell.

Discussion

Cross-gender hormone treatment is an important component in the medical treatment of transsexual people [Gooren *et al.* 2008]. Because transsexuals who undergo treatment are typically young to middle-aged and healthy, there are usually few or no contraindications to sex hormone treatment [Gooren *et al.* 2008].

Correspondence to:

Muhammad Adil Abbas Khan

Specialist Registrar,
Department of Plastic and
Reconstructive Surgery,
James Cook University
Hospital, Middlesbrough,
UK
adilaku@hotmail.com

Zain A. Sobani

Student, Medical College,
Aga Khan University,
Stadium Road, Karachi,
Pakistan

Mark Gorman

Core Trainee, Department
of Plastic and
Reconstructive Surgery,
Castle Hill Hospital, Hull,
UK

In Europe, widely used drugs for the suppression of androgen secretion include cyproterone acetate. Other less-effective alternatives are medroxyprogesterone acetate, spironolactone, finasteride and long-acting gonadotropin hormone-releasing antagonists (GnRH), which inhibit gonadotropin release [Corman and Legros, 2007; Gooren *et al.* 2008]. Among the estrogens, oral ethinyl estradiol and 17 β -estradiol valerate are commonly used. Typical estrogen doses for transsexuals are two to three times as high as the recommended doses for hormone replacement therapy (HRT) [Moore *et al.* 2003]. Transsexuals favor injectable estrogens as they produce high levels of circulating estrogen, even though they have the highest risk for overdose [Gooren *et al.* 2008].

The effects of sex steroids vary between men and women. Estrogens are known to have a positive effect on bone mass in male to female transsexuals [Gooren *et al.* 2008; Sosa *et al.* 2003]. The effects of anti-androgens in men can be extrapolated from data obtained on men with prostate cancer who are treated with these drugs. These patients develop an increase in fat mass, with an altered lipid profile, insulin resistance, hyperinsulinemia, hyperglycemia and increased high-density lipoprotein levels [Gooren *et al.* 2008]. On the other hand, a decrease in low-density lipoproteins is observed [Gooren *et al.* 2008].

Serious complications of sex hormone therapy are underreported. A website has recently been created for the reporting of cross-gender hormone side effects (see http://www.wpath.org/resources_transgender.cfm). The most frequent side effect is venous thromboembolism [Corman and Legros, 2007]. Moore and colleagues reported a number of side effects in their retrospective study from the Division of Endocrinology and Andrology at the Free University Hospital in Amsterdam [Moore *et al.* 2003]. Of those listed as negative, they observed increases in venous thromboembolism (around 20-fold), cholelithiasis, hyperprolactinemia, elevated liver enzymes, depression (increased compared with the general population) and a decrease in hemoglobin [Moore *et al.* 2003].

Other less often quoted side effects of estrogens in transsexuals are focal arthritis and bone marrow disorders. Sex hormones play a vital role in the modulation of onset and continuation of autoimmune diseases. Estrogens are implicated as enhancers of humoral immunity, with

androgens and progesterone acting as natural immunosuppressants [Cutolo *et al.* 2004]. Cutolo and colleagues showed that levels of proinflammatory estrogens relative to androgens are significantly elevated in the synovial fluid of both male and female patients with rheumatoid arthritis compared with controls, which they attributed to an increase in local aromatase enzyme activity [Cutolo *et al.* 2004]. Studies have shown that major reproductive events such as menstruation, ovulation, implantation and cervical ripening are characterized by increased numbers of invading leukocytes in the tissues [Stygar *et al.* 2007]. This migration has been shown to be influenced by estrogen. On the other hand, estrogens have been implicated in the pathogenesis of immune disorders such as systemic lupus erythematosus (SLE) [Cutolo *et al.* 2004]. These estrogens, which include 17 β -estradiol and other metabolites, are implicated in the production of cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-12 etc. Stygar and colleagues demonstrated that peripheral blood leukocytes are responsive to estrogens via the receptors ER- α and ER- β [Stygar *et al.* 2007].

The effects of estrogens are not limited to the immune system. Zheng and colleagues conducted a study to determine whether there was a gender difference in plasma Na⁺ and K⁺ concentrations between male and female Sprague–Dawley rats. They found no difference in plasma Na⁺ concentrations between the groups, but plasma K⁺ concentration was reduced in females compared with males. This was attributed to the effect of 17 β -estradiol acting on estrogen receptors α and β [Zheng *et al.* 2006].

Conclusions

Because our patient admitted to taking hormones, we concluded that the effect of estrogen on leukocyte and plasma K⁺ levels was consistent with that seen in the literature. Both medical and surgical methods of gender reassignment benefit transsexuals psychologically. In the short term, using cross-gender hormones remains relatively safe. However, potentially adverse effects in the longer term are currently unknown. The physician should exercise caution when treating such patients and be on the lookout for side effects that may mimic other disorders, such as the arthritis in our patient. Awareness of these side effects can only come from close monitoring and

meticulous reporting of adverse effects in the literature.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

- Corman, V. and Legros, J.J. (2007) [Hormonal treatment in transsexual patients. Metabolic consequences]. *Ann Endocrinol (Paris)* 68: 258–264.
- Cutolo, M., Sulli, A., Capellino, S., Villaggio, B., Montagna, P., Serio, B. *et al.* (2004) Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity. *Lupus* 13: 635–638.
- Gooren, L.J., Giltay, E.J. and Bunck, M.C. (2008) Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. *J Clin Endocrinol Metab* 93: 19–25.
- Moore, E., Wisniewski, A. and Dobs, A. (2003) Endocrine treatment of transsexual people: a review of treatment regimens, outcomes, and adverse effects. *J Clin Endocrinol Metab* 88: 3467–3473.
- Sosa, M., Jodar, E., Arbelo, E., Dominguez, C., Saavedra, P., Torres, A. *et al.* (2003) Bone mass, bone turnover, vitamin D, and estrogen receptor gene polymorphisms in male to female transsexuals: effects of estrogenic treatment on bone metabolism of the male. *J Clin Densitom* 6: 297–304.
- Stygar, D., Masironi, B., Eriksson, H. and Sahlin, L. (2007) Studies on estrogen receptor (ER) alpha and beta responses on gene regulation in peripheral blood leukocytes in vivo using selective ER agonists. *J Endocrinol* 194: 101–119.
- Zheng, W., Shi, M., You, S.E., Ji, H. and Roesch, D.M. (2006) Estrogens contribute to a sex difference in plasma potassium concentration: a mechanism for regulation of adrenal angiotensin receptors. *Gen Med* 3: 43–53.

Visit SAGE journals online
<http://tae.sagepub.com>

SAGE JOURNALS
Online