BRIEF REPORT

Genetic Diagnosis in Adulthood
A Case Report

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While family physicians may readily entertain genetic diagnoses in their pediatric patients, they may fail to consider such diagnoses in their adult patients. We present the case of a man with recurrent leg ulcers who was recognized as hypogonadal and was ultimately given the diagnosis of Klinefelter's syndrome (XXY) at age 47. Although there is no primary treatment for XXY, significant associated conditions, including osteoporosis and testosterone deficiency, can be ameliorated. We review the clinical condition of XXY at various ages and summarize age-specific interventions. We discuss the importance of genetic diagnosis throughout the life span.

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With continued progress in clinical genetics, family physicians can assist in the recognition and diagnosis of genetic conditions in their patients. At present, the incidence of single gene disorders at birth is estimated to be 1 in 100; that of chromosomal disorders is estimated to be 1 in 150.[1] Many adults with genetic conditions grew up before their disorder had been characterized, or before the means to diagnose the condition were developed. The following case study illustrates the potential benefits and complexities involved in genetic diagnosis in adulthood.

Case Report

A 47-year-old man was hospitalized with deep venous thrombosis of the left leg 3 weeks after arthroscopic knee surgery. He had a 10-year history of recurrent venous stasis ulcers. While on hospital rounds, the attending physician observed that the patient had a boyish-looking face with a paucity of facial hair, which prompted speculation about possible hypogonadism.

Further evaluation of his eunuchoid facial appearance was performed after hospital discharge. The patient was six feet tall and weighed 270 pounds. He had gynecomastia, a penis 2 1/2 cm in length, and small testicles measuring 1 cm by 2 cm. Hypogonadism was confirmed by laboratory testing, with free testosterone 0.24 nmol/L (5.5-11.5), and total testosterone of 0.52 nmol/L (10.4-30.8). This was clarified as hypergonadotrophic hypogonadism by follicle stimulating hormone (FSH) level of 26.7 mIU/mL and leutenizing hormone (LH) level of 10.3 mIU/ml. Chromosomal karyotype revealed 47,XXY pattern.

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Testosterone replacement was instituted with two 2.5 mg transdermal patches, applied nightly. After 3 months of therapy, the patient noted no significant changes in energy level, strength, mood, or sleep requirements. He did note increased libido and increased frequency of erections occurring with sexual fantasy.

Because of the XXY diagnosis, bone-mineral density testing was performed and revealed osteopenia of the fourth lumbar vertebra and of the femoral neck of the left hip. He began treatment with calcium 1500 mg daily, vitamin D 400 IU daily, and osteoclast inhibition therapy with alendronate 10 mg daily.

Psychosocial information relevant to the XXY diagnosis was obtained over subsequent office visits. The patient had been married twice; each marriage lasted less than 1 year. The second marriage ended 17 years ago because of his wife's drug use and marital infidelity. His second wife bore a son during their marriage. After the divorce she and the child moved out of state and the patient has had infrequent contact with his son. The patient had always wondered about the boy's true paternity, but continued to pay child support. The XXY diagnosis forced him to confront the issue of the boy's paternity once again. He ultimately decided to keep his XXY diagnosis from his ex-wife and their son, but would consider disclosing it if she ever requested an increase in the child support payments.

Within the past year he had been involved in another heterosexual relationship. After he developed difficulties in maintaining erections, the couple ceased the physical aspects of their relationship, but maintained their friendship. This occurred prior to the XXY diagnosis. The patient was hopeful that testosterone replacement therapy would improve his sexual functioning and allow a resumption of the sexual relationship.

During the office visits following diagnostic disclosure, the primary physician was surprised at the calm acceptance the patient exhibited toward the diagnosis. He expressed no shame or guilt, but was relieved that

TABLE 1

Recognition, Diagnosis, and Management of XXY

Recognition, by age	**Features**
Toddler	Developmental speech delay
Grade school	Learning disabilities (problems with immediate memory, auditory processing)[11] Attention Deficit Disorder
Adolescent	Persisting gynecomastia Psychosocial maladjustment[18]
Adult	Infertility Small testes
Diagnosis, by test	**Results**
Serum testosterone	Decreased or normal
Serum FSH	Elevated
Serum LH	Normal to elevated
Karyotype	90% have classic XXY
Management, by problem	**Comments**
Testosterone deficiency	Replace with transdermal testosterone; adjust dosage according to serum testosterone levels
Risk for osteoporosis	Screen with bone- mineral density test; assure optimal calcium and vitamin D intake
Risk for breast cancer	Instruct in breast self-exam
Risk for autoimmune disorders	Screen for diabetes mellitus and hypothyroidism

FSH denotes follicle-stimulating hormone; LH, luteinizing hormone.

this medical diagnosis provided an explanation for his vague sense of feeling "different" from other persons. The patient found information about XXY obtained by his physician from the Internet extremely helpful in understanding his condition.

Additional developmental and psychoeducational history was obtained during a conjoint meeting with the patient and his widowed mother. His mother recalled no developmental delays in his speech or motor development. Educational history revealed school failure in the seventh grade requiring summer school, followed by erratic performance in subsequent years. However, he graduated from a technical program in high school with a "B" average. At age 18, he failed a military physical examination because of "hypogonadism and tall stature." The examining physician referred him to his family doctor who gave him weekly shots that the patient understood were for his thyroid, and pills that he took before each meal for weight loss. Both therapies were discontinued after 6 months. He has been working as a machinist for more than 25 years with no difficulties in job performance. Approximately 10 years ago, he took a written test for job advancement to a supervisor's role, but failed it because he had difficulty with the section that tested reading comprehension.

During this meeting, his mother revealed that neither she nor the son's physician ever considered him likely to be father of the child. Both the patient and his mother were surprised to learn that they each privately questioned his child's paternity. His mother also expressed guilt that in some way she had caused her son's condition. She was relieved to learn that XXY occurs sporadically, unrelated to maternal antenatal behaviors.

Over the next year, the patient has maintained good psychological adjustment to his diagnosis. He has declined any intensive psychological evaluation or support. As evidence of his low bone- mineral density, a minor fall resulted in a fracture of his patella, requiring intraoperative repair. He has had no recurrence of leg ulcers since beginning the testosterone supplement.

Discussion

Approximately 1 in 500 males have the XXY chromosomal complement.[2] As with many chromosomal conditions, the phenotypic expression on XXY is variable. The full syndrome identified by Dr Harry Klinefelter (gynecomastia, testicular atrophy, azoospermia, and sparse facial and body hair) is not found in the majority of XXY males. For this reason, the term "XXY males" has replaced the term "Klinefelter's syndrome."

As in our patient, XXY males may not be diagnosed as such until adulthood, if at all. The family physician needs to recognize features of XXY that might present at different ages. Table 1 summarizes in a developmental fashion the recognition, diagnosis, and management of XXY.

The most consistent physical feature of XXY is small testes, typically measuring less than 2 cm to 3 cm in their longest axis. Phallus size may also be decreased. Diminished pubic and facial hair is common. They have a diminished upper- to lower- segment ratio (crown-to-pubis height is less than pubis-to-floor height).

The laboratory evaluation of an adult suspected to be XXY begins with determination of serum testosterone, FSH, and LH. Since the degree of Leydig cell damage in XXY is variable, serum testosterone and virilization in some individuals may be normal. More consistently, the FSH level is elevated. Chromosomal confirmation of XXY is important to distinguish variant syndromes from pure XXY. These variants include 46,XY/47,XXY mosaicism; 48XXXY; 48XXYY; and 46,XX males, termed sex-reversal syndrome.[3]

Characteristically, most XXY males are azoospermic and infertile. However, XXY males should not assume

TABLE 2

Internet Addresses of Genetic Resources for Patients and Families

- http://www.medhelp.org/www/agsg.htm
  (The Alliance of Genetic Support Groups)
- http://www.pcnet.com/~orphan/
  (National Organization for Rare Disorders)
- http://www.familyvillage.wisc.edu/coffee.htm
  (The Family Village Coffee Shop)
- http://www.waisman.wisc.edu/~rowley/mums/home.htmlx
  (MUMS National Parent-to-Parent Program)

they are infertile without semen analysis. Mosaic individuals with 46,XY/47,XXY have variable phenotypic expression; some have preserved testicular function.[4]

XXY males suffer an increased risk for autoimmune disorders, including type I diabetes, autoimmune thyroiditis, and systemic breast cancer (estimated 20- to 50-fold).[5] There also appears to be an association with lymphoma, leukemia, bladder cancer, and primary mediastinal germ cell tumors. As in our patient, XXY males are predisposed to leg ulcers.[6,7] Physicians need to consider XXY in young men who present with chronic leg ulcers.[8]

Adults with XXY should undergo bone-mineral density testing because of the increased risk for osteoporosis, although in early adulthood, bone-mineral density may be normal.[9] Testosterone replacement alone may not normalize low bone-mineral density.[10]

XXY males should be offered testosterone replacement at the onset of puberty. Testosterone replacement will promote the development of muscle mass, strength, and facial and body hair. It may assist with psychological adjustment through improved body image as well and mood enhancement.[11]

Options for testosterone replacement now include transdermal products, as well as earlier oral and intramuscular forms. The transdermal products eliminate the nonphysiologic hormonal peaks and troughs associated with the other forms. Not surprisingly, some patients report fewer mood swings associated with the transdermal products.[12]

Regardless of age at diagnosis, XXY males should be evaluated for the presence of specific learning disabilities and for negative self-appraisal. Psychoeducational assessment is available through public school systems for any school-age child. Adults can be evaluated through hospital-based learning clinics or by psychologists, learning specialists, and speech therapists in out-patient settings. Comprehensive psychoeducational evaluation for XXY males should include tests of general intelligence, academic achievement, oral and written language, and memory and auditory processing. Identification of specific learning disabilities can lead to individualized educational programming and occupational training at any age.

According to Francis Collins, director of the National Human Genome Research Institute,"...the responsibilities for use and interpretation of genetic tests increasingly will fall to primary care clinicians."[13] Although we have had the ability to detect XXY by chromosomal karyotyping for several decades, this case exemplifies the expanding role that primary care physicians will be playing in the identification of genetic conditions, the utilization of genetic tests, and the medical care of persons with genetic conditions. As caregivers for patients throughout their life spans, family physicians need to consider the possibility of genetic conditions in patients of all ages, not only their pediatric patients. For this reason, medical educators might best teach a developmental approach to clinical diagnosis, as the presenting features of genetic conditions often vary according to the age of the patient. Family physicians need to learn about the more common genetic diagnoses that may evade diagnosis in childhood, such as Fragile X, Marfan syndrome, and neurofibromatosis.

A recent survey assessed the knowledge of primary care physicians regarding medical genetics and genetic tests. One-third of respondents failed to correctly identify the mode of inheritance from a pedigree. The authors of this survey recommended that curriculum planners specifically ensure that primary care resident physicians become skilled in the interpretation of probabilistic results and the counseling of patients.[14] There is some evidence that commercially available gene tests are not fully understood by those physicians who order them. For example, in a nationwide sample of physicians who ordered adenomatous polyposis coli gene testing (for a genetic mutation associated with colorectal cancer), telephone interviews by the com-

TABLE 3

Counseling Strategies Relating to Genetic Diagnosis

Guilt-Alleviating Tactics
Use professional authority: "You took all the necessary precautions."
Normalize patients' feelings: "Others in your position would feel similarly."
Reframe perceptions and actions to ones with less distressful meanings
Limit liability: "You are responsible for A, but not B."
Shame-Reducing Tactics
Develop a working alliance which is nonjudgmental and accepting
Evoke feelings and respond empathetically
Accentuate the positive: identify strengths and competencies
Reward with praise

Adapted from Kessler S, Kessler H, Ward P. Psychological aspects of genetic counseling: management of guilt and shame. Amer J of Med Genetics 1984; 17:673-697.

mercial laboratory performing the test revealed that 31% of physicians misinterpreted the test result.[15]

XXY resembles many other genetic conditions in its variable phenotypic expression of physical, cognitive, and behavioral characteristics. Family physicians may be less familiar with the cognitive and -behavioral aspects of genetic disorders compared withto the medical aspects. In the case of XXY, family physicians are probably more familiar with the associated features of hypogonadism and infertility and less familiar with the associated learning and psychosocial difficulties. The Internet can be a valuable tool for supplementing purely medical sources of information. Through the Internet, patients with genetic conditions, their families, and their primary care physicians can locate relevant lay and professional organizations, obtain patient education materials written in clear, nontechnical language, and link with other persons and families with the same condition (Table 2).[16]

Much of the literature advising physicians about how to "break bad news" sensitively is readily applicable to the context of disclosing a genetic disorder.[17] Patient response to diagnostic disclosure may range from grateful relief from anxiety and uncertainty to intense feelings of guilt or shame. Table 3 summarizes tactics that family physicians might employ in alleviating guilt or reducing shame when disclosing a genetic diagnosis.

Physicians may need to self-examine their attitudes toward persons with genetic conditions. They need to identify their patients' strengths and competencies, as well as their limitations and health risks.

In our patient, earlier genetic diagnosis may have prevented osteoporotic fracture, recurrent leg ulcers, and financial exploitation related to misattributed paternity. Less tangible, though no less important, benefits of diagnosis included the psychological sense of closure provided to our patient, and the relief of his mother's guilt that she somehow caused his condition. Although earlier diagnosis is ideal, benefits can be accrued when genetic diagnoses are made well into adulthood. Family physicians need to recognize the value in making such diagnoses throughout the life span.

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REFERENCES

1. Seashore M, Wappner R. Genetics in primary care and clinical medicine. Stamford, CT: Appleton & Lange; 1996.
2. Jones KL. Smith's recognizable patterns of human malformation. 5th ed. Philadelphia, Pa: WB Saunders; 1997.
3. de la Chapelle A. Nature and origins of males with XX sex chromosomes. Am J Hum Genet 1972; 24:71-105.
4. DeGroot L, et al, eds. Endocrinology. 3rd ed. Philadelphia, Pa: WB Saunders; 1995.
5. Scheike O, Visfeldt J, Petersen B. Male breast cancer: breast cancer in association with Klinefelter's syndrome. Acta Pathol, Microbiol Scand 1973; 81:352-8.
6. Verp MS, Simpson JL, Martin AO. Hypostatic ulcers in 47, XXY Klinefelter's syndrome. J Med Genet 1983; 20:100-1.
7. Veraart J, Hamulyak K, Neumann H, Engelen J. Increased plasma activity of plasminogen activator inhibitor 1 (PAI-1) in two patients with Klinefelter's syndrome complicated by leg ulcers. Br J Dermatol 1994; 130:641-4.
8. Spier C, Shear N, Lester R. Recurrent leg ulcerations as the initial manifestation of Klinefelter's syndrome. Arch Dermatol 1995; 131:230.
9. Luisetto G, Masttrogiacomo I, Bonanni G, et al. Bone mass and mineral metabolism in Klinefelter's syndrome. Osteoporosis Int 1995; 5:455-461.
10. Wong F, Pun K, Wang P. Loss of bone mass in patients with Klinefelter's syndrome despite sufficient testosterone replacement. Osteoporosis Int 1993; 3:3-7.
11. Mandoki M, Sumner G, Hoffman R, Riconda D. A review of Klinefelter's syndrome in children and adolescents. J Am Acad Child Adolesc Psychiatry 1991; 30:167-72.
12. Matsumoto A. Hormonal therapy of male hypogonadism. Endocrinol Metab Clin North Am 1994; 23:857-75.
13. Collins F. Preparing health professionals for the genetic revolution. JAMA 1997; 278:1285-6.
14. Hofman K, Tambor E, Chase G, et al. Physicians knowledge of genetics and genetics tests. Acad Med 1993; 68:625-32.
15. Giardiello F, Brensinger MS, Petersen G, et al. The use and interpretation of commercial APC gene testing for familial adenomatous polyposis. New Eng J Med 1997; 336:823-7.
16. Black RB, Weiss JO. Genetic support groups in the delivery of comprehensive genetic services. Am J Hum Genet 1989; 45:647-54.
17. Buckman R. How to break bad news. Baltimore, Md: Johns Hopkins University Press, 1992.
18. Graham J, Bashir A, Stark R, et al. Oral and written language abilities of XXY boys: implications for anticipatory guidance. Pediatrics 1988; 81:795-806.