It's not all about the testes: medical issues in Klinefelter patients

Rebecca Z. Sokol, M.D., M.P.H.

Keck School of Medicine, University of Southern California, Los Angeles, California

Important medical conditions associated with Klinefelter syndrome (KS) are categorized as: 1) motor, cognitive, and behavioral dysfunction; 2) tumors; 3) vascular disease; and 4) endocrine/metabolic and autoimmune diseases. Earlier diagnosis of KS may lead to earlier intervention with effective treatment. (Fertil Steril® 2012;■:■–■. ©2012 by American Society for Reproductive Medicine.)
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Klinefelter syndrome (KS) is the most common cause of primary testicular failure. Prevalence is estimated to be 120–153 per 100,000 live-born male births. However, the actual prevalence is probably greater owing to failure to identify and diagnose these patients. The diagnosis is rarely made at birth, with most patients identified after the age of puberty (1–4). Delayed effective treatment and increased morbidity is the consequence of the missed diagnosis. This increased morbidity pertains not only to delayed testosterone treatment, but also to decreased awareness of medical conditions associated with KS. In addition to the classic phenotype of the patient with seminiferous tubule dysgenesis and androgen deficiency, the spectrum of KS includes a number of equally important medical issues (1, 4, 5). Epidemiologic data from Denmark and Britain report a significant increase in morbidity (70%) and mortality (50%) from a variety of causes in KS men compared with control men (6–10). The most frequently associated medical disorders can be categorized as: 1) motor, cognitive, and behavioral dysfunction; 2) tumors; 3) vascular disease; and 4) endocrine/metabolic and autoimmune diseases.

MOTOR, COGNITIVE, AND BEHAVIORAL DYSFUNCTION

Longitudinal studies have documented that many KS children have difficulties in school because of learning disabilities, behavioral problems, and poor athletic ability (11–14). The prepubertal child with KS is often diagnosed by his mother because of his learning or behavior issues or his poor motor skills (4). It is not unusual for the parents of KS children to find similarities between their child and descriptions reported in the literature and on the web (author's clinical experience).

Reductions in gross and fine motor skills, coordination, dexterity, running ability, poor muscle tone and strength, synkinetic movements, and tremor are usually identified in early childhood and may persist into adulthood (4, 13).

The KS cognitive phenotype is manifested as deficits in the specific domains of language and executive functions. KS patients are reported to demonstrate difficulties with language and language-based learning (11–17). Ross et al. (15) tested the neuropsychologic measures of memory, attention, visual-spatial abilities, visual-motor skills, and language of 50 KS boys aged 4.1–17.8 years with the use of well established standardized tests. The cohort was divided into two groups by age: 4.0–9.9 and 10.0–17.9 years. Most of the subjects had deficits in language processing, auditory processing, and auditory memory. General conceptual ability was slightly better in the younger group compared with the older group ($P<.04$). There was no significant effect of previous testosterone treatment on performance result. Although IQ scores fell within the average range, achievement tests indicated a learning disability in reading, spelling, and arithmetic, findings that were similar to earlier reports (12–14).

KS patients also have an increased rate of executive dysfunction, which results in judgmental problems and poor decision making (12). Core executive functions include cognitive flexibility, inhibition (self-control, self-regulation), and memory retention of previous experiences and their consequences. More complex executive functions include problem solving, reasoning, and planning (18). These neurologically based skills that involve mental control and self-regulation are commonly reported to be impaired in patients with attention deficit disorder, an associated disorder identified in a subset of KS patients (12, 15, 19, 20). However, the increased distractibility

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Reprint requests: Dr. Rebecca Z. Sokol, M.D., M.P.H., University of Southern California, Obstetrics and Gynecology, Keck School of Medicine, Los Angeles, CA 90033.

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reported in KS patients may be in response to their language-based learning disability (17). The abnormalities of early speech during the first years of life, and motor disturbances that are identified in most XXY infants are hypothesized to be interrelated and possibly to be the early presentation of the central nervous system dysfunction associated with the XXY genotype (20). These cognitive deficits are even more prevalent in XXYY patients (21).

Because KS patients have less difficulty with nonverbal or visual-spatial tests, as well as difficulties with rapid auditory processing, investigators hypothesize that left-hemisphere dysfunction may explain these findings (15, 20–26). High-resolution magnetic resonance imaging has revealed significant reduction of left temporal gray matter volume in KS adults which positively correlated with language-related skills (22–25). Others have reported decrease in total cerebral volume and increase in lateral ventricle volume in KS children and young adults (22). To further evaluate this hypothesis, cerebral blood flow was evaluated in right-handed KS adults naïve to testosterone replacement by brain single photon emission computerized tomography perfusion profiles and compared with profiles of nine age-matched right-handed male control subjects. The goal was to determine whether perfusion abnormalities in KS correlate with neurocognitive function (25). Perfusion asymmetry toward the left hemisphere was noted in the control subjects, whereas perfusion was mostly symmetric in KS patients in the temporal and lower parietal brain areas, regions that are involved in language processing. Scores on verbal tests were inversely correlated with these perfusion changes, suggesting that the findings were consistent with anomalous cerebral laterality.

A clear relationship between this proposed altered left hemisphere functioning and testosterone levels has not yet been delineated clinically. Swerdloff et al. (26–28) have developed a KS mouse model to study in greater detail the cognitive manifestations of KS in a controlled setting. They demonstrated that the rate of learning is significantly slower in XXY mice compared with their XY litter mates, findings that are consistent with those reported in humans with KS. Based on their studies, they propose that the similarities in phenotype between XXY men and XXY mice suggest that gene-dosage effect from genes that escape X inactivation in the mouse, as well as androgen deficiency, accounts for the clinical manifestations in XXY men, particularly the behavioral and cognitive disorders.

CAGn (trinucleotide repeat in exon 1) polymorphism has also been proposed as an etiology for the variable presentation of motor, cognitive, and behavioral dysfunction reported in KS patients. Zitzmann et al. (29) retrospectively analyzed the clinical traits and phenotype, including karyotype, CAGn length, and X chromosome inactivation of 77 newly diagnosed untreated KS patients. They reported that patients with shorter CAGn length were significantly more likely to work in higher skilled professions. This hypothesis requires further study.

Other psychiatric disorders, such as schizophrenia, psychosis, and bipolar disorder, also have been reported in KS patients (30). However, more studies are needed to clearly establish an association between an extra X chromosome and these psychiatric disorders.

How hormonal influences and genetic factors actually affect cognition, behavior, and motor skills in KS patients requires further study. Although future research will more clearly define the pathophysiology of these disorders in KS patients, consensus exists that earlier diagnosis made in KS boys may provide greater opportunities for earlier effective educational interventions in the treatment of learning and motor skill disabilities (15).

TUMORS

Mediastinal Tumors

An increased incidence of mediastinal germ cell tumors (MGCTs) in KS patients is well documented. MGCT is a very rare tumor, with a reported incidence rate per one million persons in the general population of 1.13 in boys aged 0–9 years, and 1.53 for boys aged 10–19 years based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program for the years 1975–2006 (31). In contrast, the incidence of MGCT in the KS population is reported to be significantly higher. Hasle et al. in 1992 (32) reported a mean frequency of KS in male patients with MGCT of 8%, suggesting this to be 50 times the expected number compared with the predicted prevalence of KS in the general population of 1/600. In a follow-up publication, Hasle et al. (33) used the Danish Cancer Registry to study cancer incidence in KS patients and reported no differences in overall cancer incidence in KS subjects compared with the background population, but a significant increase in mediastinal tumors. Four observed cases in 696 KS men were observed as compared to an expected incidence in the general population of 0.06 for a relative risk (RR) of 67. Using a similar cancer registry in Scotland and England, Swerdlow et al. (6) reported no increased incidence of mediastinal tumors; however, those authors attributed this to the fact that their registry primarily included men >30 years old. Additional studies support the conclusion that there is an increased incidence of mediastinal tumors (9, 10, 34). Clinically, younger patients tend to present with precocious puberty; histologically, their tumors are mixed germ cell tumors. Older children present with thorax-associated symptoms, mainly chest pain, dyspnea, and cough; mixed germ cell tumors are more common, but teratomas and other mixed tumors occur (34). Therefore, clinicians should consider the diagnosis of KS in boys who present with precocious puberty and the diagnosis of MGCT in KS patients who present with precocious puberty or thorax-associated symptoms.

Breast Cancer

The incidence of breast cancer in KS men is controversial. Numerous case reports have suggested an association (10, 35), whereas an early study reported no increase in breast cancer in KS patients identified through a cancer registry in Denmark (8). A subsequent study conducted in Scotland and England reported a significant increase in breast cancer in a cohort of 646 KS patients identified from cytogenetic registries in the country of origin (6). In follow-up studies, based on a cohort of 3,518 KS men, the standardized

incidence ratio increased to 19.2%, which was markedly higher than the incidence in the general male population, but lower than the incidence in the general female population (7). These results are supported by those of a more recent cohort study in Denmark, which reported a marked increase in breast cancer cases (n = 3) in a cohort of 832 KS patients compared with none reported in 4,033 control subjects (9). Based on these reports the estimated frequency in KS men ranges from 3.7%–7.5% (10, 35).

Taking a different approach, Brinton et al. (36) accessed the records of a cohort of 4.5 million men identified through the patient treatment files of the U.S. Veterans Affairs (VA) Medical System and followed the medical conditions of those men over a 30-year period. They identified 3,518 breast cancer patients, of which men with KS accounted for 642 of the breast cancer patients for an adjusted RR of 16.83 with a 95% confidence interval (CI) of 6.81–41.62. The authors attributed the lower prevalence of breast cancer cases in the VA cohort to the fact that the cohort included only those men medically qualified to enter military service and thus be eligible for VA benefits.

The underlying causative factors for this increased incidence of breast cancer among KS men remain speculative. Among the proposed mechanisms are altered endogenous hormones, particularly altered testosterone, E_2 ratio, gynecomastia, increased obesity in this population, and genetic predisposition to breast cancer (36). These studies support the recommendation for patient education, regular breast self-exams, and yearly examination by the patient's physician.

Testicular Cancer

Based on the current literature, a relationship between KS and testicular cancer is not documented (1, 7, 9).

VASCULAR AND CARDIAC DISEASE

Vascular disease is reported to be increased in KS patients. In an initial study of 412 patients with KS observed over periods ranging from 1 to 20 years, the prevalence of past or present hypostatic ulceration was 6% (20–50 times higher than in the general population) and the incidence of deep-vein thrombosis in subjects aged 30–70 years was 22.8 cases per 10,000, compared with the incidence in the general population of 4 new cases per 10,000 men. The frequency of pulmonary embolism was 16 cases per 10,000 patient-years at risk, compared with an expected figure of 0.9–3 cases per 10,000 men per year (37). These data were confirmed in the recent Danish Registry. A hazard ratio (HR) of 5.29 (95% CI 3.29–8.50) was reported for thrombophlebitis and venous thrombosis, an HR of 3.60 (95% CI 1.92–6.74) for pulmonary embolism, and an HR of 1.71 (95% CI 1.28–2.29) for ischemic heart disease (9). Abnormalities in clotting and plasminogen activator inhibitor 1 and the underlying obesity in many KS patients have been proposed as possible, but not yet verified, etiologies (38).

Congenital malformations and subclinical changes in left ventricular function have also been suggested to occur in KS. Anderson et al. (39) performed echocardiograms on 25 KS patients and compared them to 25 aged-matched control subjects, reporting minimal disease only in those KS patients who met the criteria for metabolic syndrome, suggesting that the underlying obesity may be more important than the hypogonadism.

ENDOCRINE/METABOLIC DISEASES AND AUTOIMMUNE DISORDERS

In addition to the pathognomonic hypogonadism and associated osteoporosis, an increased incidence of diabetes mellitus, obesity, metabolic syndrome, hypothyroidism, Sjogren syndrome, rheumatoid arthritis, and systemic lupus erythematosis (SLE) have been reported in men with KS (1, 6–9).

KS is an important risk factor for early-onset osteoporosis (10, 40). The etiology is multifactorial, with testosterone deficiency the primary cause. Testosterone, which acts through androgen receptors on bone cells, stimulates longitudinal and radial bone growth. Testosterone also regulates bone metabolism by aromatization to estrogen, which reduces bone resorption. Thus testosterone deficiency can lead to reduced bone formation and higher bone resorption. However, bone mineral density (BMD) is not always correlated with testosterone levels in KS patients, nor does testosterone therapy always increase BMD. Other mechanisms suggested as etiologies for the altered BMD in KS patients include abnormalities of androgen receptor CAG length, low levels of insulin-like factor 3 (produced in the Leydig cells), and X chromosome inactivation (40, 41). Further studies are needed to test these proposed mechanisms.

Based on data generated in cohort studies, the standardized mortality ratios for diabetes mellitus, pulmonary embolism, and peripheral vascular disease are markedly increased in KS patients (7, 9). In a cross-sectional study, Bojesen et al. (42) evaluated 71 KS men, of whom 35 received testosterone treatment, and compared them with 71 control subjects. Based on the National Cholesterol Education Program/Adult Treatment Panel II criteria (three or more of the following criteria: elevated fasting plasma glucose, triglycerides, cholesterol, waist circumference, blood pressure, low HDL), 16 of the KS patients had metabolic syndrome compared with 7 control subjects. Insulin sensitivity was decreased in the KS men. No significant differences were found between the testosterone-treated KS men and the nontreated KS men.

Although chronic estrogen stimulation and testosterone deficiency have been proposed as mechanisms for the metabolic abnormalities and the autoimmune disorders, conclusive studies in KS patients have not been published (1, 37, 43). Prospective randomized studies are needed to ascertain the role that abnormal testosterone:estrogen ratio plays in the association between KS and these medical conditions and the efficacy of testosterone replacement in prevention.

SUMMARY

Earlier diagnosis of KS may provide greater opportunities for earlier intervention with effective treatment. Learning disabilities, poor motor skills, and behavior issues should alert the family doctor to the possible diagnosis of KS. Once the diagnosis has been established, the treating physician should be aware of the medical conditions associated with KS and

institute early educational interventions, cancer prevention awareness, and diet and exercise programs to prevent obesity and possible metabolic syndrome in KS patients.

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