

Klinefelter Syndrome: Phenotype and New Research

In August of 2000, the National Institutes of Health sponsored a meeting (co-sponsored by the March of Dimes and Klinefelter Syndrome and Associates) to address gaps in understanding this condition. In an effort to prioritize research initiatives, the participants summarized research data and developed consensus conclusions. Domains covered included: cytogenetic origin and molecular pathogenesis; gonadal and hormonal dysfunction; somatic anomalies; IQ and language development; adult-onset disorders; predicted phenotype and genetic counseling after *in utero* detection of XXY; genetic risks for offspring of the 47, XXY male; and, research priorities.

In contrast to autosomal trisomies in which maternal errors predominate (95% of cases), the origin of 47, XXY is far more variable with regard to source (maternal vs. paternal), as well as form of error (meiotic or mitotic origin). Adverse phenotypic outcomes are assumed to result from the action of excess genes on the X chromosomes that are not inactivated. Researchers are focusing attention on approximately 40 genes on the X short arm that escape inactivation.

Testicular histology in Klinefelter syndrome (KS) is normal or near normal in early infancy, and is followed by a progressive loss of germ cells throughout childhood. Animal models of sex chromosome aneuploidy have been developed to determine whether germ cell and Leydig cell defects are somatic or germ cell in origin.

Although testosterone concentrations fall within the normal range for 50% of late adolescent and young adults with KS, gonadotropins are universally elevated. Does this observation reflect compensated hypergonadotropic hypogonadism, or partial androgen resistance? Should testosterone levels in the normal range serve as the "gold standard" for guiding the timing and dosage of hormone replacement? The suggestion was made (but without supporting evidence) that prepubertal testosterone treatment (even in the early months of life) may normalize aspects of the behavioral phenotype in KS.

The relationship between hypogonadism and reduced libido in men is well documented, as is its effective treatment through testosterone replacement. Less well recognized and understood is the possibility of an increased prevalence in atypical psychosexual development (eg, paraphilias) among men with KS. Because the majority of individuals with KS go undiagnosed, ascertainment bias may be a factor in the association between sex chromosome aneuploidy and sexual disorders.

Neurodevelopmental studies reveal that XXY infants show decreased truncal tone and atypical gross motor skills with delays in walking (mean of 18 months) which can be ameliorated through intervention (mean of 12 months). IQ falls in the low normal range. Intellectual

functioning and career attainment are typically lower in boys with KS as compared with unaffected siblings. Language skills, in particular, are delayed with first words spoken between 18 to 24 months (vs. 12 months normally). These delays persist, and affect multiple aspects of language development. The characteristic passive personality, which is sometimes accompanied by paradoxical behavioral outbursts, may result out of frustration related to deficits in verbal skills under socially challenging circumstances.

Accumulating evidence indicates that XXY is associated with autoimmune disorders. The link in pathogenesis may be chronic estrogen stimulation. Breast cancer appears to be markedly increased in older XXY men, as are extragonadal germ cell cancers and mediastinal teratomas. The authors speculate that constitutional chromosomal abnormalities and extragonadal aneuploidy germ cells predispose to malignant degeneration.

Simpson JL, de la Cruz F, Swerdloff RS, et al. Klinefelter syndrome: expanding the phenotype and identifying new research directions. *Genet Med*. 2003;5:460-468.

Editor's Comment: *Just when you thought you knew all you needed to know about KS, along comes a summary of a conference indicating that research continues unabated. When the diagnosis of KS is made during childhood or adolescence, the pediatric endocrinologist should be the lead healthcare professional involved with the child's care. In light of evidence that neurocognitive deficits associated with KS are apparent at an early age, a developmental assessment should be performed. A referral to a psychologist should be accompanied with background readings (such as this conference proceeding) to orient that clinician to the most current syndrome-specific findings. The objective here is to ameliorate the predictable deficits, thereby improving developmental and quality-of-life outcomes. Such interventions would ideally occur long before issues of testosterone replacement become the focus of clinical management.*

The suggestion that early testosterone treatment may normalize socialization difficulties in boys with KS is intriguing. Although changes in clinical care await conclusive evidence of such benefits, the discussion forces us to think about testosterone acting in ways beyond induction of pubertal development.

Finally, recent findings regarding adult-onset disorders in KS provide the pediatric endocrinologist with the opportunity to emphasize the importance of regular visits with adult specialists.

David E. Sandberg, PhD