

Hypogonadism and Pubertal Development in Prader-Willi Syndrome

Genital abnormalities are common in Prader-Willi Syndrome (PWS) and are one of the eight major clinical criteria for diagnosis. Previous reports of the type and frequencies of these abnormalities were not necessarily from individuals with genetically confirmed PWS. Crino and associates report data from patients evaluated by the Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology. Eighty-four patients (42 males), mean age 15.8 ± 8.2 years were studied. Sixty-three percent were over 14-years-old. All satisfied the Holm and Cassidy clinical criteria for the diagnosis of PWS and the methylation test was positive in all subjects. Microdeletion of chromosome 15(15q12-13) was demonstrated in 66%, while uniparental disomy or an imprinting defect was suspected in the others.

All males showed cryptorchidism (86% bilateral). Small testes and scrotal hypoplasia were observed in 76% and 69%, respectively. Micropenis was seen in 36%. Twenty-two of 29 males had spontaneous onset of puberty at 14.0 ± 3.2 years but it was incomplete in all cases. Specifically, pubertal changes past Tanner 2-3 genital stages were rarely observed.

In females there was hypoplasia of the labia minora and/or of the clitoris in 71% and 69% of cases. Thirty-four of 39 females had spontaneous onset of puberty at 12.6 ± 2.7 years, with very slow progression. Menarche occurred at a mean age of 17.3 ± 5.2 years in 44% of cases over 14 years of age. Primary amenorrhea was diagnosed in 56%. Menstrual cycles were seldom regular and secondary amenorrhea occurred in 33% who had spontaneous menarche. Of note, premature

pubarche occurred in 12 subjects (6 males) and true precocious puberty in 3. It is suggested that premature pubarche might have been related to obesity. Genital and pubertal abnormalities were evenly distributed among subjects with microdeletion and UPD-imprinting defects. Treatment of various types for hypogonadism was discussed, including the use of dihydrotestosterone transdermally. However, no systematic trials on treatment with sex hormone treatment in adolescents or adults are available.

Crino A et al. *Eur J Pediatr* 2003;162:327-333.

Editor's Comment: *This paper provides interesting information concerning genital abnormalities in individuals diagnosed with PWS, confirmed with genetic testing. The large number of subjects in this descriptive study and the careful presentation of the findings should assist all who work with these patients and who must counsel them and their families in regard to expectations for pubertal development and fertility. It is interesting that sexual precocity was observed at a frequency that should be considered high in this group. This suggests that examination of the genitalia should be performed at each clinical visit. Whether or not current treatment with exogenous GH, which has been shown to significantly alter body composition in PWS, will affect pubertal development remains to be shown.*

William L. Clarke, MD

Growth and the Tyrosine Kinome

Tyrosine kinases (TKs) add phosphate moieties to tyrosine residues on proteins that typically serve as docking sites to recruit other molecules that bind and propagate signals. As such, they function as central regulators of signaling pathways that control transcription, cell cycle progression, differentiation, apoptosis and other processes that are highly relevant to growth of cells and tissues. Given this central position in regulation of growth, Bardelli et al raised the question: why have mutations in TK genes been found in only a small number of instances including certain human cancers? They speculated that mutations do exist, but have yet to be detected because the vast number of TK genes is only now becoming apparent as the human genome project unfolds. To test this idea, they took advantage of high-throughput sequencing and bioinformatics from the human genome project to search

for TK mutations in a select group of cancers, colorectal cancers.

A recent analysis organized the protein kinase complement of the human genome (the "kinome") into a dendrogram containing nine broad groups or branches of genes. Bardelli et al selected one major branch, which contained three groups including 90 TK genes, 43 TK-like genes and 5 receptor guanylate cyclase genes. Mutation analysis of 813 exons from the genomic database carried out on DNA from 35 colorectal cancer cell lines yielded 14 mutations. Further analysis of DNA from 147 tumors identified 46 novel mutations in 14 genes. All of the mutations were somatic in nature based on comparison of DNA from tumor to matched normal tissues.

The authors suggested that mutations found in seven genes, which were detected in more than one tumor,