

Kyphosis in Turner Syndrome

Elder and colleagues performed lateral thoracic spine and standing anterior-posterior scoliosis radiographs in 25 of 30 girls between the ages of 5 and 18 years with Turner Syndrome. Excessive kyphosis was defined as an A-P curvature greater than 40%, vertebral wedging as an A-P deformity greater than 5% at any vertebral body, and scoliosis as a lateral curve greater than 10%. Karyotype, age, height, weight, and body mass index percentile, and use and duration of growth hormone, oxandrolone (anavar), and/or estrogen were recorded and entered into a linear regression analysis to determine significant predictors of kyphosis or kyphosis and wedging. Of the 25 subjects studied, 15 (60%) had abnormal radiographic findings. Ten (40%) had excessive kyphosis, 10 (40%) had vertebral wedging, and 5 (20%) had scoliosis. All girls older than 14 years of age (N=8) had excessive kyphosis and wedging.

The subjects were 12.0 ± 3.6 years old. Sixty percent had a 45X karyotype, 80% had received GH therapy, and 36% had received estrogen therapy. Logistic regression analysis revealed that chronologic age alone was predictive of excessive kyphosis/wedging, ($P=0.053$). Stepwise linear regression analysis also showed that chronologic age was predictive of the degree of kyphosis ($P=0.032$). None of the other variables were predictive. The authors remarked upon the high prevalence of vertebral wedging and excessive kyphosis in their study population. They noted that this is markedly increased compared with the reported prevalence of 3% in the general population. The cause of the scoliosis is apparently multi-factorial, but may include mechanical factors, osteoporosis, adolescent growth spurt, and intrinsic bone defect. Girls with Turner syndrome are known to have a significant number of bony abnormalities, including hypoplasia of cervical vertebrae, and hemivertebrae, although these were not found in the study population. The authors also note

that their inability to determine the contribution of age and hormonal therapies to the development of kyphosis may be the result of the small number of subjects studied.

PediaLink.org (Vol. 109) 6/2002. PPE 93.

Editor's Comment: *With such a huge number of Turner subjects (40%) with reported excessive kyphosis, it is surprising that there are not more reports of its prevalence. Indeed this study suggests all girls with Turner syndrome should have routine radiographic screening and should be evaluated by an orthopedist. It is also surprising that more information is not available regarding the probable pathogenesis of these deformities. Since the vast majority of subjects in the study had received or were receiving GH, its contribution to the development of the kyphosis is impossible to determine. However, information from subjects in larger multi-centered databases of individuals who have and have not been treated with GH, would be important to access in order to determine its possible role in the genesis of this deformity. Some information regarding the prevalence of kyphosis in children treated with GH who either had or did not have GH deficiency also could be an important comparison group. Unfortunately this study raises many more questions than it answers, but will probably stimulate other centers to evaluate girls with Turner syndrome. Perhaps a multi-centered survey could help provide a better understanding of this problem. The Growth, Genetics and Hormones Editorial Board welcomes a letter to the editor from readers who have knowledge of data pertinent to the questions raised.*

William L. Clarke, MD

Cancer Risk in Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann Syndrome (BWS) is a well-known syndrome of overgrowth. Macrosomia, neonatal hypoglycemia, midline abdominal defects, macroglossia, ear pits and the predisposition to embryonic cancers in infants and young children, including Wilms tumor, hepatoblastoma and neuroblastoma are the important clinical features of BWS. It is now possible to correlate the phenotypic features with specific genetic disturbances. Most recently, alterations in the imprinting and methylation of several genes in the 11p15 region have been implicated in its etiology. Different patients have different involvement phenotypically and genetically.

De Baun et al have correlated anomalies of DNA methylation of one of the relevant genes, *H19*, in patients with cancer, as compared to those without. Those with cancer are less likely to have abnormalities of the methylation of another gene in the area, *LIT1*. Conversely, abnormalities of methylation of *LIT1* are more likely to be associated with abnormal wall defects and macrosomia. Affected individuals with paternal uniparental disomy of *11p15* are more likely to have associated hemihypertrophy, cancer, and hypoglycemia than those without uniparental disomy.

These findings suggest that all individuals with BWS deserve a precise molecular evaluation in order to be

able to appropriately screen for expected complications. The cluster of genes related to BWS has been studied extensively because of its involvement in the epigenetic phenomenon of imprinting. Abnormal and loss of imprinting of the *IGF2* gene found in this region is present in a number of tumors. *H19* plays a role in the methylation of *IGF2* and so its abnormal methylation or expression may increase the risk of cancer by its relation to *IGF2*.

In the evaluation of BWS, one would expect that cancerous tissue might have different imprinting or methylation than other easier to study tissues. This is particularly frustrating when hemihypertrophy is present. It is interesting to note that any hypertrophy observed in patients with BWS is suggestive of mosaicism. To date, all of the reported patients with paternal UPD of 11p15 are in fact, mosaic. Thus, the two sides of the body probably have different manifestations of the Beckwith-Wiedemann gene cluster.

The hypoglycemia that can be seen in Beckwith-Wiedemann Syndrome also is associated with

uniparental paternal disomy. Since hypoglycemia can result in secondary mental retardation, both screening and watching for hypoglycemia in patients with BWS is extremely important during infancy.

DeBaun, et al. *Am J Hum Genet* 2002;70:604-611.

Editor's Comment: *Most of the conditions recognized to be involved in genomic imprinting are associated with abnormalities of growth. Thus, the possibility of genomic imprinting must be considered in any syndrome of abnormal growth. Further evaluation can obviously lead to unique insights about pathogenesis as are being developed in the BWS. This work is allowing recognition of the heterogeneity existing in BWS that may predispose to severe complications.*

Judith G. Hall, OC, MD

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