

predictive testing can be made. Reduction in morbidity or mortality as a result of genetic testing for late-onset disorders has not yet been demonstrated, and the risk of adverse psychological response and discrimination by insurers and employers appear to be real concerns. Further, the complexities of genetic testing for complex disorders have not been worked out.

In summary, the AAP Committee on Bioethics points out that pediatricians must be well informed about these issues and understand that there are both positive and negative aspects of genetic screening that are part of proper informed consent. Furthermore, potential harm does exist in screening programs, and testing

should be deferred until adulthood unless there would be significant benefit to the child to undergo genetic testing.

Committee on Bioethics. *Pediatrics* 2001;107:1451-1455.

Editor's comment: *The AAP report on genetic testing should be required reading for pediatricians since there are pitfalls to all genetic testing. These must be understood by both the pediatrician and the person giving permission for testing of a child before testing is undertaken. Therefore, search out the complete article.*

Judith G. Hall, OC, MD

Development of Renal Cell Carcinoma in Living Donor Kidney Grafts (in Association With hGH Administration)

Tyden et al report 2 cases of young boys (~4 years of age) who received kidney transplants from their fathers. De novo development of carcinoma was diagnosed by biopsy 9 and 11 years after transplant. One patient received a new transplant and the other received dialysis therapy. Progressive cyst formation was observed in each kidney for many years before carcinoma was diagnosed. The kidneys remaining in the 2 fathers did not develop cyst formation. The boys received human growth hormone (hGH) for a total of 7 years and approximately 5 years. For the latter, administration was intermittent.

The authors state that although renal cell carcinomas have developed previously in kidney allografts (cadaver source), it is not known whether in those reported cases the carcinomas were de novo or whether they had been present at transplantation. The authors, however, state that these are the first de novo cases reported in living donor transplants. The authors conclude that it is possible that hGH stimulates the growth of renal cell carcinoma, or perhaps induces the development of such carcinoma more quickly, in acquired disease of the kidney transplant. They also state that the findings emphasize the importance of annual ultrasonographic surveillance of renal grafts, especially in the pediatric population.

Tyden G, et al. *Transplantation* 2000;11:1650-1656.

Editor's comment: *Regardless of whether coincident with, or attributable to, hGH administration, the fact that renal cell carcinoma occurred in these 2 kidney recipients who were receiving hGH deserves significant attention. All transplanted patients should be followed closely for the possible development of renal carcinoma. Development of cysts should prompt suspicion that carcinoma might develop. The development of solid tumors superimposed on the cystic kidney should be reason for immediate surgery. The development of cysts in patients receiving hGH, in my opinion, should prompt discontinuation of hGH. Fortunately, the time intervals appear to be lengthy before renal cell carcinoma develops after transplant. The possibility that hGH might be an inductive agent for renal carcinoma, again in my opinion, should be discussed with the parents, and with the child if he/she is the age of consent, before hGH is administered. hGH should be given under the auspices of a research protocol.*

Robert M. Blizzard, MD

Growth Hormone Deficiency (GHD) Caused by Pituitary Stalk Interruption in Fanconi's Anemia

Fanconi's anemia can be associated with growth retardation. The authors describe the presence of isolated growth hormone deficiency (GHD) or GHD associated with thyrotropin deficiency in the pituitary stalk interruption syndrome, which was demonstrated by magnetic resonance imaging (MRI) in 5 patients with Fanconi's anemia. GH treatment produced catch-up growth in all cases. The authors concluded that the combination of these findings suggests a common genetic origin.

Dupuis-Girod S, et al. *J Pediatr* 2001;138:129-133.

Editor's comment: *Fanconi's anemia is a rare autosomal recessive disease of variable penetrance that arises from an abnormal processing of DNA. The first of the genes responsible for this syndrome was identified in this decade (Nature*

1992;358(6385):434). Fanconi's anemia patients may present with multiple congenital abnormalities, including bone marrow failure, and increased susceptibility to cancer. They have a 15,000 times greater risk of developing acute myelogenous leukemia (Blood 1994;84:1650-1655).

It has long been recognized that growth retardation with normal or decreased GH response to pharmacologic stimuli may be present in this disease. The International Fanconi's Anemia registry reported that short stature is a common finding in these patients (mean, 22.37 SDS) with an 81% prevalence of endocrinopathy. Forty-four percent of the tabulated patients had a subnormal response to GH stimulants; 100% had an abnormal response to GH profile (Pediatrics 2001;107:744-754). Dupuis-Girod et al in the present paper

demonstrated that Fanconi's anemia is frequently associated with GHD and pituitary stalk interruption syndrome. The demonstration by MRI of the latter abnormality is a new finding, which had not been documented in the past in such patients. The pathogenesis of pituitary stalk interruption syndrome is unknown. It could be related to injury at birth or perhaps to the same deletions in the genes that lead to Fanconi's anemia. It is interesting to note that patients with Fanconi's syndrome might not always have the severe type of GHD. Pituitary stalk interruption probably needs to be considered only in patients with Fanconi's anemia who are severely growth retarded and in whom treatment with GH will induce catch-up growth. However, it should be kept in mind that patients with

chromosomal abnormalities, including patients with Fanconi's anemia, in particular are at a higher risk for malignancies when treated with GH. Therefore, the question has been raised about the dilemma of initiating a treatment that may improve growth but also might increase the risk for cancer. Although the incidence of leukemia in GH-treated patients without predisposing risk factors is believed not to be different from that of the general population (J Clin Endocrinol Metab 1996;81[693]:1692-1696 and 1704-1710), in patients with Fanconi's anemia this complication might ensue (Lancet 1994;343:1576).

Fima Lifshitz, MD

Neonatal Diabetes Mellitus Due to Complete Glucokinase Deficiency

Diabetes mellitus is a heterogeneous disorder. Neonatal diabetes, defined as insulin-requiring hyperglycemia occurring within the first month of life, is a rare form of diabetes but also is heterogeneous. Transient or permanent neonatal diabetes can occur. Recently, it has been recognized that transient neonatal diabetes is often associated with abnormalities of chromosome 6, including imprinting abnormalities. Mutations of insulin promoter factor 1, resulting in pancreatic agenesis, are seen in permanent neonatal diabetes.

This report describes 2 patients with permanent neonatal diabetes due to complete glucokinase deficiency, the result of identified mutations in the glucokinase gene. The affected individuals had poor fetal growth and intrauterine growth retardation, and required insulin in the first days of life. Interestingly, diabetes of many forms was seen within the family among the carriers (heterozygotes) of the gene defects. Among the carriers (heterozygote), maturity-onset diabetes, diabetes of the young, type 1 diabetes, and type 2 diabetes were all observed. One affected infant also had total situs inversus, which was not seen in any other family members.

Glucokinase mutations are relatively common in diabetes, and the homozygous state may actually be a common cause for neonatal diabetes. Glucokinase plays a key role in the regulation of insulin secretion in humans. Thus, the authors tested for mutations in other genes along the pathway, including hepatocyte nuclear factors 1 and 4, insulin promoter factor 1, NK-2 homeobox homologue 2, neurogenic differentiating factor 1-beta-cell, and E box transactivator 2. They found no abnormalities in any of those genes.

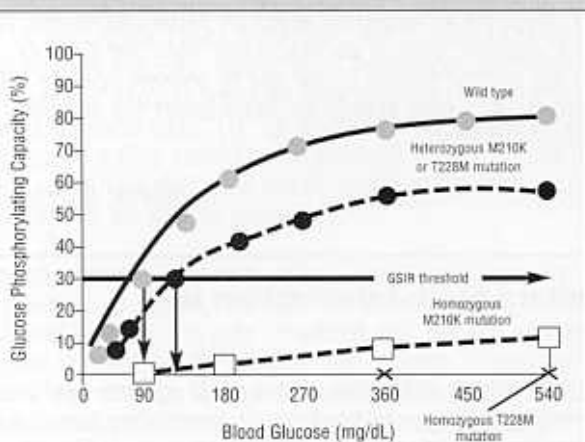
Interestingly, mouse models of glucokinase deficiency also have growth retardation and hypoglycemia at birth, but they also have hypertriglyceridemia, hepatic steatosis, and reduced stores of glycogen, which apparently are not seen with the human mutations.

Njølstad PR, et al. *N Engl J Med* 2001;344:1588-1592.

Editor's comment: The variabilities seen in the families of these infants with neonatal prone diabetes are quite remarkable, suggesting that heterozygotes have problems of many varieties. The authors worked out the kinetics of complex control of glucose metabolism and showed very nicely that the homozygous state simply does not produce enough enzyme to have a normal role, whereas the heterozygous state has variable levels and thus must interact with other factors to produce the various types of diabetes seen (Figure).

Judith G. Hall, OC, MD

Figure



Comparison of the modeled functional properties of wild-type glucokinase, glucokinase with the M210K mutation, and glucokinase with the T228M mutation in the homozygous and heterozygous state. GSIR, glucose-stimulated insulin release.

Reprinted with permission from Njølstad PR, et al. *N Engl J Med* 2001; 344:1588-1592.