IGF-1 May Help Some Children With Short Stature

BY MIRIAM E. TUCKER
Senior Writer

LISBON — Primary insulin-like growth factor deficiency is one and a half times more common than growth hormone deficiency among children with short stature and a deficiency of insulin-like growth factor-1, George M. Bright, M.D., reported at the 12th International Congress of Endocrinology.

Both deficiency groups have low levels of insulin-like growth factor-1 (IGF-1), and the two groups cannot be distinguished clinically. But the difference is important, because children with primary insulin-like growth factor deficiency-1 (IGFD) are often insensitive to growth hormone (GH) therapy and may respond better to IGF-1 replacement, said Dr. Bright, vice president of clinical affairs for Tercica, a biopharmaceutical company based in San Francisco.

The company plans to file a new drug application in early 2005 for the use of recombinant human IGF-1 in children with primary IGFD.

In an observational study of 6,447 children referred for evaluation of short stature to 197 U.S. pediatric endocrinology clinics between 1993 and 1996, 72% actually had short stature, defined as height shorter than 2 standard deviations below the mean. Of those 4,663 children, 42% had IGFD (IGF-1 levels less than 2 standard deviations below the mean). Among those 1,955 children, 40% had growth hormone levels below 5 ng/mL using a Hybritech immunoradiometric assay and were therefore considered to have classical GH deficiency ("secondary IGFD"), and 60% had normal GH levels (above 5 ng/mL), or so-called primary IGFD.

The 1,179 children with primary IGFD and the 776 with GHD were phenotypically similar, with mean ages of 10.6 years and 10.3 years, respectively. The GHD children were slightly shorter (3.3 vs. 3.0 standard deviations below the mean). This difference was statistically significant, but probably not clinically so; it translates to just about 2 cm, Dr. Bright noted.

> **'It's difficult to distinguish between primary IGFD and GHD based on presenting clinical characteristics.'**
>
> **DR. BRIGHT**

"The take-home message is that it's difficult to distinguish between primary IGFD and GHD based on presenting clinical characteristics," he said.

Measuring serum IGF-1 levels alone is also inadequate, since both groups are deficient (–3.0 standard deviation score [SDS] for IGFD and –3.8 SDS for GHD). However, discrimination between the two groups is possible using an "IGF-1 standard deviation score generation test" derived from baseline and stimulated IGF-1 levels from four groups of children (23 with GHD, 22 with a GH receptor mutation, 65 heterozygotes for the mutation, and 72 normal subjects), Dr. Bright said in a separate presentation.

Blood samples taken on day 8 following GH stimulation demonstrated that an IGF-1 cut-point of 2.5 standard deviations below the mean was 95.7% sensitive and 95.5% specific for discriminating between primary IGFD and GHD. In contrast, IGF-1 concentrations alone gave a specificity of only 86.4% (with the same sensitivity). Among the 1,955 children from the observational study with short stature and low IGF-1, that 9.1% improvement in specificity would translate to 178 patients prevented from being misclassified, he said. For a given level of GH exposure, the change in IGF-1 SDS in the IGF-1 generation test might be helpful.

"For example, when there is a robust change in IGF-1 SDS, you can reasonably expect that GH replacement therapy would be useful in the short and long term. But when there is very little change in the [SDS], your treatment of choice would be IGF-1. If it's intermediate, we would need a separate exercise to determine whether the best treatment is GH, IGF-1, or a combination," Dr. Bright explained.

Earlier this year at the Endocrine Society meeting, Steven Chernausek, M.D., reported Tercica's phase III clinical trial data of recombinant human IGF-1 (rhIGF-1) in 65 children with severe short stature and IGF-1 deficiency caused by GH insensitivity, of whom 54 were treated for at least 1 year (45 had Laron syndrome, 7 had GH antibodies, and 2 had unspecified defects). At the start of therapy, the children had a mean age of 6.5 years (age range 2-10 years), and mean height 88.7 cm (–6.7 SDS). They received twice-daily injections of rhIGF-1 in doses of 80-120 mcg/kg. Mean duration of treatment was 3.6 years.

At 1 year, height velocity had improved from 2.6 cm/year to 8.0 cm/yr, with a mean of 5.3 cm/yr over a period of 8 years. The ratio of bone age to height age decreased from 2.5 at baseline to 1.8 over 3 years in 24 of the patients for whom serial bone age data were available, said Dr. Chernausek, professor of pediatrics at Children's Hospital Medical Center, Cincinnati.

Improved Height Velocity After rhIGF-1

None of the 65 patients dropped out of the study because of adverse events. Hypoglycemia was the most common adverse event attributed to the rhIGF-1 treatment, documented in 26 patients (40%) during the study in contrast to just 12 (18%) prior to starting therapy. Growth of lymphoid tissue was also common, with snoring in 16 patients (25%), tonsillar hypertrophy in 10 (15%), and tonsillectomy/adenoidectomy in 3 (5%).

Five patients (8%) had middle ear effusions at least once, and 16 (25%) had abnormal tympanometry or audiograms, with tube placement in 8 (12%). Increases in the size of the kidneys and spleen by ultrasound occurred in the first 2-3 years of therapy, but no adverse changes of renal function were observed. There were no deaths or neoplasias, Dr. Chernausek reported. ■
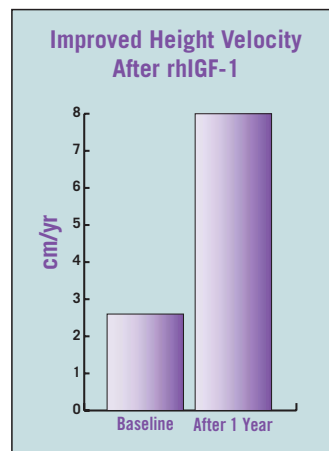
Metabolic Syndrome Predicts Subclinical Atherosclerosis in Adults

BY BRUCE JANCIN
Denver Bureau

NEW ORLEANS — Young and middle-aged adults who meet criteria for metabolic syndrome are at a 2.5-fold greater risk of having subclinical atherosclerosis, Kwame O. Akosah, M.D., said at the annual scientific sessions of the American Heart Association.

This is true regardless of whether they have a low Framingham risk score or a normal-range C-reactive protein (CRP) level. The risk of subclinical atherosclerosis associated with metabolic syndrome is also independent of—and even greater than—that associated with diabetes mellitus, a coronary heart disease equivalent, added Dr. Akosah of the Gundersen Lutheran Health System, La Crosse, Wisc.

"It appeared in our study that metabolic syndrome was the driving force for developing early atherosclerosis, not high-sensitivity CRP or diabetes mellitus," he said.

Dr. Akosah reported on 253 consecutive men and women, mostly in their 40s and 50s, who were evaluated for possible coronary arte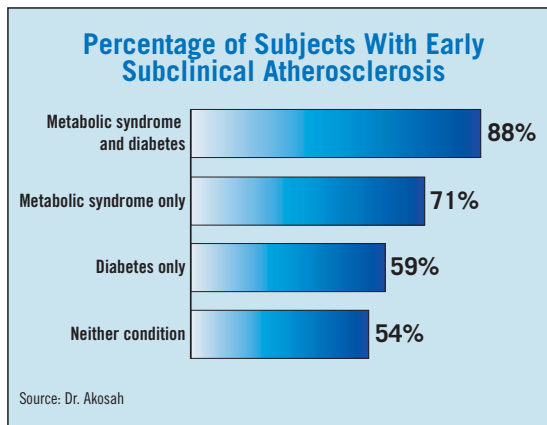ry disease. All underwent carotid ultrasound assessed by blinded cardiologists for the presence of subclinical carotid atherosclerosis, a well-established marker for atherosclerosis in other vascular beds.

Subclinical carotid atherosclerosis—as defined by focal plaque and/or a mean intimal-medial thickness of 1.0 mm or more—was identified in 59% of subjects. Yet 89% of study participants had a low-risk Framingham risk score. And 37% didn't even have multiple major cardiovascular risk factors, Dr. Akosah said.

Among the 75 subjects who met criteria for metabolic syndrome, 18 had concomitant diabetes. Another 17 subjects had diabetes without metabolic syndrome. The prevalence of subclinical carotid atherosclerosis was significantly greater among participants with metabolic syndrome than in those with diabetes only or with neither condition. (See graph.)

In a multivariate logistic regression analysis, metabolic syndrome independently conferred a 2.5-fold increased risk of having subclinical atherosclerosis.

Percentage of Subjects With Early Subclinical Atherosclerosis

Metabolic syndrome and diabetes	88%
Metabolic syndrome only	71%
Diabetes only	59%
Neither condition	54%

Source: Dr. Akosah

Of note, CRP was not useful in risk stratification. For example, the prevalence of subclinical atherosclerosis among 64 subjects with elevated CRP but without metabolic syndrome was 50%, yet it was 59% among 109 individuals with neither an elevated CRP nor metabolic syndrome.

Despite the increasing emphasis devoted to metabolic syndrome in medical circles since the 2001 National Cholesterol Education Program guidelines identified it as a secondary therapeutic target, 56% of subjects in the study didn't have a fasting blood glucose level taken along with their lipid measurements, making it impossible to properly assess them for the presence of metabolic syndrome.

"We cardiologists are very good at preaching what to do and talking about the things that we do," Dr. Akosah said. "But if you go look back in our records, you'll find out that we're not doing as well as we're convincing everybody. Sure, we need to check blood pressure and lipid levels, but fasting glucose is no longer something that should be measured only at the endocrinologist's office." ■