Melanocytic Nevi in Children Treated With Growth Hormone

David Wyatt, MD

ABSTRACT. There is concern that growth hormone (GH) therapy may influence the growth of melanocytic nevi. In a review of the experience of the National Cooperative Growth Study, we found no excess of skin cancer in children who were treated with GH. We also reviewed our experience in 90 children with GH deficiency and 24 with Turner syndrome. We found no difference in the nevi count between control subjects and children with GH deficiency, even after many years of GH therapy. Nor was there any relation between the duration of therapy and the nevi count. Children with Turner syndrome had more nevi, but there was no relation to the duration of GH therapy. These findings and the absence of a greater frequency of skin cancer in acromegaly are reassuring. It is unlikely that GH therapy has a significant influence on nevi count or the risk of skin cancer. Pediatrics 1999;104:1045–1049; acquired melanocytic nevi, growth hormone, melanoma, Noonan syndrome, Turner syndrome.

ABBREVIATIONS. GH, growth hormone; AMN, acquired melanocytic nevi; GHD, growth hormone deficiency; NCGS, National Cooperative Growth Study; SCI, skin color index.

Growth hormone (GH) therapy has been reported to have a reversible stimulatory effect on the size of acquired melanocytic nevi (AMN) in children with isolated GH deficiency (GHD) and with Turner syndrome. Recent reviews of safety issues in the use of GH have reflected the concern that it may influence mole growth. However, increased AMN count rather than size is a known risk factor for melanoma. Furthermore, acromegaly, a condition of chronic GH excess, is not associated with an increased risk of skin cancer. It is believed generally that the number of AMN is greater in Turner syndrome, but there does not appear to be an increased risk of melanoma in this condition either. It is not known whether GH ther-

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apy increases the number of AMN or the associated risk of melanoma in these children.

The National Cooperative Growth Study (NCGS) database and studies of AMN counts in a large group of GH-treated children\(^ {15-17}\) were reviewed to evaluate a possible relation between such therapy and AMN counts.

METHODS

NCGS

The safety database of the NCGS, including reports submitted from the US Food and Drug Administration MedWatch program, was searched for the following terms: pigmented nevi, moles, benign skin neoplasms, skin hypertrophy, skin nodules, skin tumors, melanoma, skin cancer, basal cell carcinoma, and squamous cell carcinoma. Individual report forms were reviewed for relevance.

Milwaukee Studies

Patients were examined for count and location of AMN and for clinical atypia, defined as the presence of two or more of these features in any nevus: size >5 mm, heterochromia, nondistinct or irregular borders, asymmetry, and evidence of inflammation. The AMN were registered on a standardized chart\(^ {18}\) in 30 topographic body areas, excluding the scalp, breasts, and genitalia. Skin color was assessed with a reflectance spectrophotometer\(^ {19}\) in sun-exposed (back of the hand) and unexposed (upper inner part of the arm) areas, and skin color index (SCI) was determined. Generally, a higher SCI indicates a lighter skin color. For reducing the likelihood of sun-induced hyperpigmentation of freckles, all children were examined during the fall, winter, and early spring.

Four groups of patients, all of white northern European ancestry, were examined: 90 children (65 boys) who were being treated with GH (GHD group); 24 girls with Turner syndrome (all but 1 of whom were being treated with GH); 52 children (40 boys) of similar age who were seen consecutively at endocrine clinics for the evaluation of short stature (endocrine control subjects); and 48 children (24 boys) of similar age who were seen consecutively at dermatology clinics for the treatment of warts or acne (dermatology control subjects). Growth hormone was always given at a dose of 0.3 mg/kg per week. The average duration of therapy was 4.3 years (range, 0.33 to 9.08 years) in the GHD group and 2.0 years (range, 0 to 4.4 years) in the Turner syndrome group. In the GHD group, 51 subjects had idiopathic or developmental (eg, septooptic dysplasia) isolated GHD; 17 had idiopathic short stature; and 22 had multiple endocrine deficiencies, either idiopathic, developmental, or attributable to resection of craniopharyngioma. No child had been treated with radiation or chemotherapy. In the Turner syndrome group, 1 patient also was treated with thyroxine, 2 with estrogen, and 1 with both.

Multiple regression analysis was used with a suitable log transformation (with a shift) of the AMN counts. Model search methods were used to identify the important covariates, and partial F tests were used to determine the significance of the group classification and of the duration of the GH treatment. Analysis of large nevi (size, >5 mm) was performed with logistic regression for the ratio of this count to the total AMN count in each subject.

RESULTS

NCGS

There were 25 reports of nevi at entry in the NCGS database (Table 1). The prevalence of reports is higher in patients with Turner syndrome, as might be expected.\(^ {14}\) The category “other” also has a higher prevalence. Of the 6 patients with reports of nevi in this category, however, 3 had dermatologic conditions that are associated with greater numbers of nevi (basal cell nevus syndrome in 2, incontinentia pigmenti in 1); 1 had Noonan syndrome, which, like Turner syndrome, may have greater numbers of nevi; 1 had juvenile arthritis and a lifelong, diffuse pruritic rash; and 1 had “areas of hyperpigmentation” rather than nevi.

Malignant melanoma was reported in 2 patients: a 9-year-old girl with previous craniospinal irradiation (unspecified central nervous system tumor) who had been treated with GH for almost 3 years, and a 15-year-old boy who had been treated with GH for 1.5 years. Basal cell carcinoma was reported in 2 patients: a 17-year-old boy with Gorlin syndrome, which is associated with an increased incidence of basal cell carcinoma, who had been treated with GH for 0.5 year, and a 10-year-old girl with previous head irradiation (unspecified central nervous system tumor) whose carcinoma was in the radiation field. Finally, a dysplastic nevus was reported in a 14-year-old boy who had been treated with GH for 3 months and whose nevus was present before the therapy.

Milwaukee Studies

We approached the possibility of an effect of GH on nevi in three ways. First, we studied group effects by using analysis of covariance. Second, we analyzed the effect of the duration of therapy on AMN counts within the two GH-treated groups, GHD and Turner syndrome. Third, we looked at the frequency of large AMN (>5 mm) in all groups.

Group Effects

We tested several covariates to develop a model to explain the variance in AMN count: age; sex; group (GHD, endocrine control subjects, dermatology control subjects); SCI-exposed; SCI-unexposed; and sunburn history. (The Turner syndrome group was not included in this initial analysis, because these patients were expected to have higher AMN counts.) There were only two significant covariates: age and SCI-unexposed (\( P < .0001\)). As an additional check, tests of interaction between-group and the two co-

<table>
<thead>
<tr>
<th>TABLE 1. Reports of Nevi at Entry in the NCGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic GHD</strong></td>
</tr>
<tr>
<td>(n = 12,482)</td>
</tr>
<tr>
<td>Number with nevi reported</td>
</tr>
<tr>
<td>Prevalence (no./1000)</td>
</tr>
</tbody>
</table>

Data are through December 31, 1997. Idiopathic GHD indicates maximum stimulated GH level \( \leq 10 \mu g/L \), no organic cause noted; organic GHD, maximum stimulated GH level <10 \( \mu g/L \), organic cause (eg, central nervous system tumor) noted; idiopathic short stature, maximum stimulated GH level >10 \( \mu g/L \), no organic cause noted; other, syndrome or chronic medical condition noted (regardless of GH level).
variates were made, both showing nonsignificant effects ($P = .918$ and .223). This means that the relation between AMN count and either age or SCI-unexposed was the same within each group—AMN count increased to the same degree with either covariate regardless of the group (GHD, endocrine controls, dermatology controls). Thus, by several approaches to the combined data, we found no differences for AMN counts (or the increase in AMN counts with age and SCI-unexposed) among these groups.

With the Turner syndrome group ($n = 22$ with all data) added to the analysis and with all others ($n = 181$) treated as control subjects (because there were no differences in AMN counts among the other three groups), age and SCI-unexposed remained highly significant ($P = .0001$ for each) covariates with AMN count. Now, however, there was also a highly significant group effect ($P = .0004$), with the Turner syndrome group having a higher mean AMN count.

To detect whether this implied a greater rate of change in AMN count with age or with SCI-unexposed for the Turner syndrome group, we tested the presence of group interactions with these variables. Neither was found to be significant ($P > .35$), indicating parallel relations in the two groups between AMN count and age and between AMN count and SCI-unexposed. This means that the increase in AMN count was the same in Turner syndrome and in all other groups for each year or for each unit of SCI; the margin between the AMN count in Turner syndrome and the control subjects was constant across this age and SCI range.

To summarize these relations, using the best model that relates AMN count to age and SCI-unexposed, the estimated regression equation can be expressed as:

$$\log(\text{AMN count} + 5) = -0.40 + (0.13 \times \text{age}) + (0.023 \times \text{SCI-unexposed})$$

for Turner syndrome, and

$$\log(\text{AMN count} + 5) = -0.93 + (0.13 \times \text{age}) + (0.023 \times \text{SCI-unexposed})$$

for the other three groups.

The $P$ for each variable is $<.0001$, and the adjusted $R^2$ is .40. For both groups, the slopes are equal and are determined only by age and SCI-unexposed.

The means and 95% confidence intervals for these variables are presented in Table 2. Using one-way analyses of variance and attendant multiple comparisons, we found no significant differences among any of the groups for any independent covariable used in the multiple regression analysis. The AMN count was higher in the Turner syndrome group ($P = .0046$ for group effect, with this group being the only significantly different group by Tukey multiple comparisons).

**TABLE 2. AMN Counts and Significant Covariates in the Milwaukee Studies**

<table>
<thead>
<tr>
<th></th>
<th>Endocrine Control Subjects (n = 52)</th>
<th>Dermatology Control Subjects (n = 48)</th>
<th>GHD (n = 90)</th>
<th>Turner Syndrome (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMN count</td>
<td>20.0 (15.3–25.8)</td>
<td>25.4 (19.2–33.2)</td>
<td>25.4 (20.5–31.3)</td>
<td>46.9 (31.3–69.2)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>11.2 (10.2–12.3)</td>
<td>11.2 (10.2–12.3)</td>
<td>12.1 (11.4–12.9)</td>
<td>11.9 (10.5–13.3)</td>
</tr>
<tr>
<td>SCI-unexposed</td>
<td>125 (123–128)</td>
<td>124 (121–126)</td>
<td>122 (119–124)</td>
<td>123 (118–127)</td>
</tr>
</tbody>
</table>

Values are mean (95% confidence interval) (geometric mean and confidence interval, back-transformed from log [AMN + 5]) for AMN.

* $P = .0046$, Tukey multiple comparisons.

† $n = 81$.

‡ $n = 22$.

Duration of GH Therapy

The second analysis focused on the GH-treated groups. With duration of therapy, age, and SCI-unexposed as covariates in the predictive model for transformed AMN count in the GHD group, age and SCI-unexposed again were highly significant ($P = .0001$ for each variable), but duration of GH therapy was not ($P = .159$). Age remained significant in the Turner syndrome group ($P = .0008$), SCI-unexposed showed a trend toward significance ($P = .099$), and duration of therapy was not significant ($P = .441$).

Large Mole Ratio

The third analysis looked at the numbers of large nevi in each patient group. The distribution is shown in Table 3. The counts were small in the great majority of subjects, and the frequencies of large nevi counts of 0, 1, and 2 were similar in all groups. There is a significant difference only for large nevi counts of three or more, which were seen in ~12% of both the GHD and the Turner syndrome groups. An analysis of the logarithmic-transformed frequency of large AMN similar to that performed for total AMN count was inadequate for these data, in which the large nevi were sparsely distributed. Therefore, we used the ratio of the number of large nevi to the total AMN count for each subject. Logistic regression of this proportion showed no relation with age, sex, SCI-exposed, SCI-unexposed, or the number of reported sunburns. There was a difference between groups: both of the GH therapy groups differed from the control groups ($P = .009$ vs endocrine controls; $P = .042$ for dermatology control subjects), but did not differ from each other ($P = .102$). Additional logistic regression analysis within each GH-treated group showed no relation between the duration of GH therapy and the ratio of large to total AMN count ($P = .910$ for GHD; $P = .978$ for Turner syndrome). No atypical nevi were seen in any subject.

DISCUSSION

The safety database of the NCGS, including reports submitted from the US Food and Drug Administration MedWatch program, contains only four reports of skin cancer in children treated with GH. In three of these cases, the patients had risk factors associated with skin cancer (irradiation in two, Gorlin syndrome in one). The remaining case was that of malignant melanoma in an adolescent. Melanoma is uncommon in prepubertal children, but its incidence increases sharply after puberty, with a lifetime risk of 1 in 100, and it is the most common cancer in young...
Table 3. Large AMN in the Milwaukee Studies

<table>
<thead>
<tr>
<th>Endocrine Control</th>
<th>Dermatology Control</th>
<th>GHD (n = 89)</th>
<th>Turner Syndrome (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n = 52)</td>
<td>Subjects (n = 48)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of large AMN (>5 mm)

<table>
<thead>
<tr>
<th>Number of</th>
<th>Endocrine Control</th>
<th>Dermatology Control</th>
<th>GHD</th>
<th>Turner Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42 (81)</td>
<td>34 (71)</td>
<td>63 (71)</td>
<td>15 (62)</td>
</tr>
<tr>
<td>1</td>
<td>8 (15)</td>
<td>11 (23)</td>
<td>9 (10)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>2</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>6 (7)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (6)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>4 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>7</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

An excess of large nevi (>5 mm) was seen in a subset (12%) of both GH-treated groups. But, as with total AMN count, the ratio of large to total AMN did not correlate with the duration of GH therapy. The greater ratio is not attributable to sampling artifact ($P = .009$), but to either unknown factors that are present in a subset of children with GHD or Turner syndrome before therapy or an early, one-time effect of GH therapy (again, in a subset of children). The latter seems unlikely, however, because the overall growth-promoting effect of GH continues for several years in these children; one also would expect an effect on nevi size to also continue.

Bourguignon et al. reported a twofold greater increase in nevus diameter in 19 GH-treated patients (7%–11%) than in 23 control subjects (18%–20%). There are several limitations to the study; it is not clear whether this was a statistically (or clinically) significantly higher rate; the average duration of monitoring was not stated; the data were grouped by patient type, with no mention of the actual nevi count per patient (did only a few of the patients have most of the large moles?); there was no use of body surface area as a covariate; there was no analysis of potential error in the method; and there was no comparison of the nevi growth rates before and after GH treatment in the same subject. In any event, the risk of melanoma is not related to AMN size unless the nevi are atypical or dysplastic, and no dysplastic nevi were seen in any patient in either the study by Bourguignon et al. or the Milwaukee studies. There is a general impression that persons with Turner syndrome have a greater number of AMN. To our knowledge, our study is the first to clearly show this difference in a direct comparison with other children. The Turner syndrome group effect remains unexplained, however. The higher AMN count was present before GH therapy, had no relation to the duration of the therapy, and did not increase relative to the count in the other patient groups across this age and SCI range. There is an increased risk of melanoma with high AMN counts in the general population, but melanoma has been reported only rarely in Turner syndrome. This could indicate either a reporting bias or a different constellation of risks (which does not include AMN count per se) in Turner syndrome.

Because it is unlikely that a prospective, controlled trial can ever be conducted (for example, how would we know which children to monitor before GH therapy?), we may have to rely on large cross-sectional studies for evidence of most of the side effects of GH therapy. There are, of course, limitations to a cross-sectional study. We cannot be certain that there is no excess increase in AMN in a given subject who is treated with GH, because we have neither pretreatment data nor untreated control subjects. Nevertheless, it is reassuring that 1) the AMN count is lower in patients with GHD than in comparably aged control subjects, even after many years of therapy; 2) there is no relation between the duration of GH therapy and the AMN count or the proportion of nevi that are <5 mm; and 3) there are no reports of a greater incidence of skin cancer in GH-treated patients or in persons with acromegaly.

Acknowledgment

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References

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