SHORT REPORT

Effects of human growth hormone therapy on melanocytic naevi

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Melanocytic naevi may grow more rapidly during human growth hormone (hGH) therapy. With standardised skin photographs, the growth rate of the naevi was two-fold greater in 14 hypopituitary and 5 Turner's syndrome girls treated with hGH than in untreated patients or controls. HMB-45 immunoreactivity, a marker of stimulated melanocytes, was absent in naevi from 18 of 19 individuals not treated with hGH, including 5 Turner's syndrome patients studied 2–43 months after stopping hGH. In naevi from 39 hGH-treated patients, 22 showed unusual HMB-45 reactivity in dermal naevocytes. During administration of hGH, melanocytic naevi grow faster and there is reversible stimulation of naevocytes.

Lancet 1993; **341**: 1505–06.

The HMB-45 antibody,[1] which labels actively growing melanocytes,[2-4] stained melanocytes of rapidly growing naevi excised from a Turner's syndrome patient treated with human growth hormone (hGH). This observation prompted us to study the growth and pathology of melanocytic naevi in hGH-treated patients.

With a Yashica Medical 100 camera, colour slides of the skin were taken every 3–12 months in 23 controls aged 8–16 years, 5 hypopituitary patients before beginning hGH, and a Turner's syndrome girl off hGH for 3 months. We also studied 19 unselected patients with hypopituitarism or Turner's syndrome treated with hGH for 3 months to 6 years. Informed consent was obtained from each patient and their parents. We used a computerised image analyser (MOP-Videoplan, Kontron).[5] The growth rate was calculated over 6 months by the change in diameter expressed as a percentage of the initial diameter.

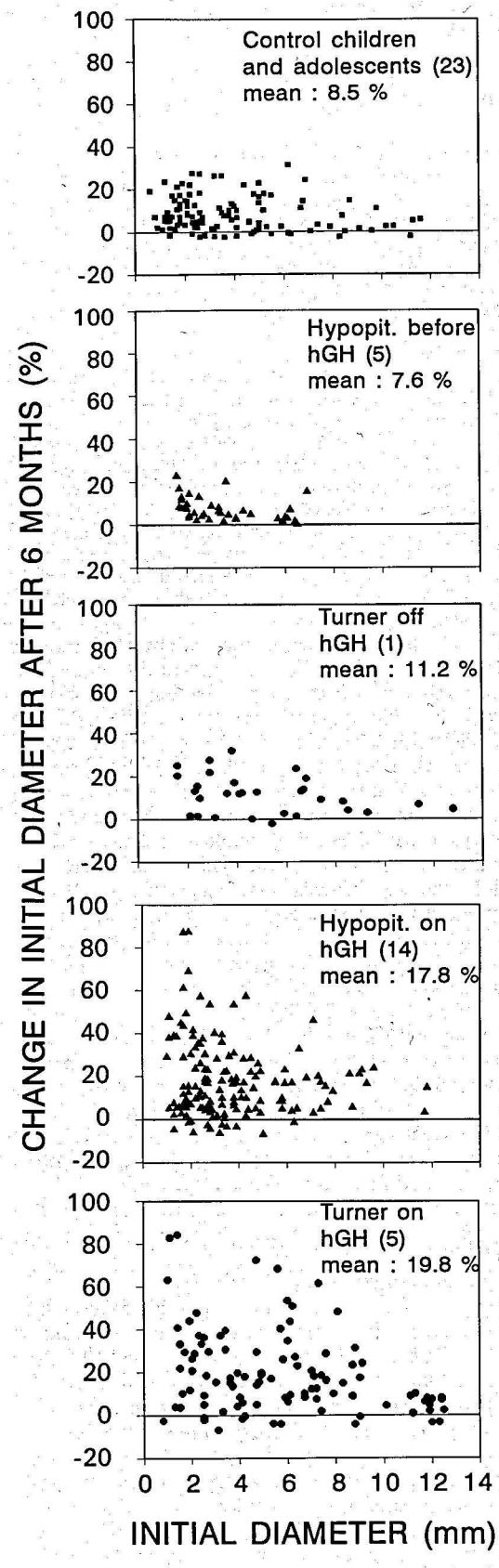
79 naevi were excised in another 58 children and adolescents. In 38, the reason was the appearance or site of the naevi. In 13 the naevus was rapidly growing, whereas in 7 patients, including 3 Turner's syndrome girls off hGH, the naevi were excised for this study after obtaining consent from the patients and the parents. 19 of the 58 were not using hGH, including 2 hypopituitary patients and 2 Turner's syndrome girls before hGH therapy and 5 Turner's syndrome girls off hGH for a median of 7 months (range 2–43). In this untreated group, the mean age was 13·9 years (7·5–21·2) and 9 individuals were prepubertal. Most naevi (15/19) were from areas not exposed to sun. The hGH-treated group consisted of 39 patients (21 with hypopituitarism and 18 with Turner's syndrome). Their mean age was 14·1 (8·7–17·9) and 20 were prepubertal. Most naevi (30/39) were from areas not exposed to sun. When appropriate, the patients were on replacement therapy with thyroxine, hydrocortisone, or sex steroids. Mean (and range) hGH dose and duration of therapy were, respectively, 0·48 (0·36–0·84) IU/kg per week and 56 (18–164) months in hypopituitary patients and 0·85 (0·55–1·05) IU/kg per week and 38 (14–72) months in Turner's syndrome.

The melanocytic naevi were formalin-fixed and paraffin-embedded. 5 μm sections were stained with haematoxylin and eosin. Other sections were dewaxed in xylene, hydrated through graded alcohols, and preincubated with 0·05% pronase E (protease XX, Sigma). Endogenous peroxidase was blocked with 3% hydrogen peroxide in methanol for 5 min at room temperature. The peroxidase/antibody-to-peroxidase technique was used with HMB-45 (Dakopath). 3-amino-9-ethylcarbazole was used as chromogen. Because HMB-45 can stain naevocytes at the dermal-epidermal junction in normal adults,[3] we regarded only intradermal expression of HMB-45 as abnormal with a classification into focal or diffuse staining of dermal naevocytes.

In controls and patients not treated with hGH, the naevi grew by a mean of 7·6–11·2% over 6 months (figure). No difference was found between prepubertal and pubertal subjects. In hypopituitary patients and Turner's syndrome girls treated with hGH, growth rate of naevi increased two-fold. In all groups, the growth of naevi with initial diameter under 8 mm was greater than that of large naevi.

Among the excised naevi, 49 were of the compound type with only 3 lentigines, 1 junctional naevus, and 5 intradermal naevi. Standard histological examination was normal. In the 19 individuals untreated or off hGH, 18 did not express HMB-45 reactivity in naevocytes. The only patient with focal HMB-45 expression was a prepubertal girl on thyroxine for congenital hypothyroidism. Among the 39 patients on hGH, 22 had naevi with focal or diffuse intradermal HMB-45 reactivity. Expression was focal in 8 hypopituitary and 7 Turner's syndrome cases, and diffuse in 7 other Turner's syndrome patients. When several naevi were excised in 16 patients, HMB-45 reactivity was similarly distributed in the different lesions from a given patient. In 1 Turner's syndrome patient, in whom naevi were excised twice after 22 months on hGH and 4 months off, staining was diffuse on hGH and absent off hGH. The distribution of HMB-45 staining was not correlated with growth in height, ranging between 2·4 and 8·5 cm per year, or with hGH dose and duration of therapy.

The computerised morphometry is accurate and reproducible. Slight reductions in size of some naevi could result from differences in camera position between pictures. The changes in naevus size could not be explained solely by increases in body size. In the fastest growing patients, the 6 month increase in body surface area could account for only a 3% increase in diameter of the naevi. Although the size and the number of naevi increase up to age 20–30,[6] we found no significant difference in naevus growth with age and puberty in our small series. Turner's syndrome girls develop an increased number of naevi.[7] However, naevus growth rate was similarly increased in hGH-treated Turner's syndrome and hypopituitary patients. Thus a methodological bias, the aged-related increase in size, differences in sexual



Growth rate of individual melanocytic naevi.

Hypopit and Turner = hypopituitary and Turner's syndrome patients.

maturation, and patient's condition could not account for the increased growth of naevi, which suggests that our observations are related to hGH therapy. The hGH-treated patients who had naevi excised were selected for the same reasons as most individuals not treated with hGH. Therefore any selection bias would have affected both groups similarly.

HMB-45 expression is not necessarily associated with neoplastic melanocytes[3,8,9] and could result from stimulation of normal melanocytes by endocrine or paracrine factors.[4] The possible role of hGH as an endocrine factor was supported by the similar HMB-45 reactivity in different naevi from individual hGH-treated patients as well as by no expression in patients off hGH. hGH receptors have been found in human skin.[10]

There are no reports of increased frequency of skin tumours in hGH-treated or in acromegalic patients. Whilst our data indicate that melanocytes can be stimulated during hGH therapy, we found no neoplasms or premalignant transformation. Our findings point to naevocytes possibly being targeted by hGH, with a greater effect during hGH therapy, even at "replacement" doses, than in physiological conditions. Long-term follow-up is required to identify delayed or unknown effects of hGH, especially in patients with Turner's syndrome who are likely to require high doses to obtain substantial growth effect.

We thank Dr J. De Schepper, Prof P. Malvaux, Prof M. Maes, Dr G. Massa, Dr G. Thiry-Counson, and Prof M. Vanderschueren-Lodeweyckx for providing material from their patients and for helpful discussions. We also thank Ms J. Laurent for secretarial assistance. This study was supported by a grant from the Belgian Study Group for Pediatric Endocrinology.

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