Endocrine, *vol. 18, no. 2, 135–136, July 2002* 0969–711X/02/18:135–136/$10.50

Low Hemoglobin Levels in Children With in Idiopathic Growth Hormone Deficiency

Erica A. Eugster, Mark Fisch, Emily C. Walvoord, Linda A. DiMeglio, and Ora H. Pescovitz

Department of Pediatrics, Section of Pediatric Endocrinology, James Whitcomb Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, IN

Multiple lines of evidence have implicated the growth hormone (GH) axis in the regulation of erythropoiesis. To test the hypothesis that GH deficiency is associated with hematologic abnormalities, we analyzed pretreatment hemoglobin levels in 100 children with GH deficiency. Hemoglobin levels were decreased in children with GH deficiency compared with age-corrected norms.

Key Words: Growth hormone deficiency; hemoglobin; hematopoiesis.

Introduction

A functional role for the growth hormone-insulin like growth factor (GH-IGF) axis in the regulation of hematopoiesis has long been recognized *(1)*. Clinical evidence in support of this association has included the demonstration of impaired erythropoiesis in adults with GH deficiency as well as increases in hemoglobin concentration and hematopoietic precursor cells following GH replacement therapy *(2)*. Similarly, changes in red blood cell indices and hemoglobin levels following GH treatment have been observed in children with and without GH deficiency *(3)*. A further link suggesting common regulators for growth and erythropoiesis comes from reports of GH deficiency in children with congenital anemias such as Fanconi, Blackfan-Diamond, and cartilage hair hypoplasia *(4)*. Interestingly, polycythemia vera has been reported in rare cases of endogenous GH hypersecretion *(5)*. Despite these observations, the mechanism through which GH may be involved in hematopoiesis is unknown. Furthermore, no large-scale study of hematopoiesis has ever been reported in children with GH deficiency. To investigate this further, we undertook a retrospective analysis of baseline hemoglobin levels in a large cohort of children with documented idiopathic GH deficiency prior to the initiation of GH therapy.

Received April 16, 2002; Revised May 20, 2002; Accepted May 20, 2002.

Author to whom all correspondence and reprint requests should be addressed: Erica A. Eugster, M.D., Pediatric Endocrinology, Riley Hospital #5960, 702 Barnhill Drive, Indianapolis, IN 46202. E-mail: eeugster@iupui.edu

Results

Of 100 eligible patients, 73 were male and 27 female. The age range for boys was 1–15 yr, and for girls, 2–14 yr. Additional pituitary hormone deficiencies were present in 9 patients, and isolated GH deficiency was found in the remaining 91 patients. The average age at diagnosis of GH deficiency was 8.7 ± 4.0 yr. Imaging studies revealed a normal hypothalamic-pituitary region in 50 patients, whereas a variety of radiographic abnormalities, including pituitary hypoplasia, were present in the remainder (Table 1). A total of 12 patients (12%, $p < 0.08$) were anemic, defined by hemoglobin >2 SDs below the mean for age, as shown in Table 2. Moreover, a statistically significant decrease in overall mean hemoglobin levels was observed, with a mean hemoglobin SD score of –0.74 ± 1.26 (95% CI: –0.99, –0.43), suggesting a trend toward anemia even in patients without overt abnormalities.

Discussion

During recent years, significant in vitro and in vivo data have accumulated that clearly demonstrate a relationship between the GH axis and the regulation of blood cell production. Whether this results in a measurable difference in hematopoietic indices in children with idiopathic GH deficiency compared with control subjects has not previously been investigated. In the present retrospective study, a significant reduction in average pretreatment hemoglobin levels for age in children with idiopathic GH deficiency was observed, lending further support to the association between GH and blood cell production. The incidence of overt anemia, detected in 12% of our patients, was not statistically different from that observed in the general population. It is unknown whether GH therapy will correct these hemoglobin abnormalities.

The physiologic mechanism through which GH impacts hematologic processes remains enigmatic. Recently, a transgenic mouse model overexpressing a novel peptide product of the GH-releasing hormone (GHRH) gene, *GHRH-RP*, was described *(6)*. Transgenic animals demonstrate increased cell cycling for blood cell progenitor lines as well as marked overexpression of stem cell factor, a protein with known

Table 1
Patient Characteristics

Sex (*n*)	Age at diagnosis (yr)	Endocrine function (*n*)	Radiographic findings (*n*)[a]	Hemoglobin SD score
Male (73)	8.7 ± 4.0	Isolated GH deficiency (91)	Normal (50)	–0.74 ± 1.26
Female (27)	(0.71–19.4)	Additional anterior pituitary hormone deficiency (9)	Hypoplastic anterior pituitary ± ectopic posterior pituitary (30)	(–4.90– 2.53)
		Prader-Willi syndrome (2)	Empty sella (4)	
			Dandy-Walker cyst (2)	
			Tonsillar ectopia (1)	
			Pituitary microadenoma (1)	
			Encephalomalacia (2)	
			Pineal cyst (1)	
			Periventricular leukomalacia (2)	
			N/A (7)	

[a]N/A, not available.

Table 2
Characteristics of GH-Deficient Children with Anemia

Patient no.	Sex	Age (yr)	Peak GH level (ng/mL)	Hemoglobin (g/dL)	SD score	Radiographic findings
1	M	7	9.1	11.5	–2.0	Hypoplastic pituitary
2	M	10	6.3	12	–2.0	Hypoplastic pituitary
3	M	2	8.5	10.1	–4.9	Normal
4	M	14	9.0	12.4	–2.6	Encephalomalacia
5	M	19	0.08	11.6	–4.4	Normal
6	M	13	7.51	11.9	–2.1	Normal
7	M	12	1.39	12.5	–2.0	Normal
8	F	10	9.3	10.9	–3.4	Pineal cyst
9	M	5	7.6	10.8	–2.9	Normal
10	M	12	7.8	11.6	–3.2	Normal
11	M	15	5.8	13	–2.0	Normal
12	M	2	2.8	11.8	–3.2	Leukomalacia

critical hematopoietic functions. This suggests that the site of hematopoietic regulation within the GH axis may in part be hypothalamic. Prospective studies of hematologic parameters in children with GH deficiency differentiating hypothalamic from pituitary GH deficiency will further elucidate the precise nature of the relationship between the GH-IGF axis and erythropoiesis.

Subjects and Methods

Following institutional review board approval, charts of 259 patients ages 2–19 yr with a diagnosis of GH deficiency or who were receiving GH therapy were reviewed. Patients who did not meet criteria for classic GH deficiency (defined as a peak GH level <10 ng/mL on two provocative GH stimulation tests) were excluded, as were those with underlying medical conditions associated with anemia, such as renal disease. Similarly, patients with a history of cranial irradiation or on medications known to affect hematopoiesis were eliminated from analysis. Using age-adjusted normal ranges *(7)*, baseline hemoglobin levels were converted to SD scores.

Acknowledgments

This work was funded in part by NIHR01HD34789 and a fellowship research training grant from Eli Lilly and Co.

References

1. Kurtz, A., Zapf, J., Eckhard, K., Clemons, G., Froesch, R., and Bauer, C. (1988). *Proc. Natl. Acad. Sci. USA* **85,** 7825–7829.
2. Kotzmann, H., Riedl, M., Clodi, M., et al. (1996). *Eur. J. Clin. Invest.* **26(12),** 1175–1181.
3. Vihervuori, E., Sipila, I., and Siimes, M. A. (1994). *J. Pediatr.* **125,** 242–245.
4. Mäkitie, O., Juvonen, L., Dunkel, I., Kaitila, I., and Siimes, M. A. (2000). *J. Clin. Endocrinol. Metab.* **85,** 563–568.
5. Grellier, P., Chanson, P., Casadevall, N., Abboud, S., and Schaison, G. (1996). *Ann. Intern. Med.* **124,** 495,496.
6. Fang, S., Steinmetz, R., Walker King, D., et al. (2000). *Endocrinology* **141(4),** 1377–1383.
7. Dallmann, P. R. and Siimes, M. A. (1979). *J. Pediatr.* **94(1),** 26–31.