Serum Erythropoietin Levels in Von Hippel-Lindau Syndrome

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Introduction

Von Hippel-Lindau syndrome (HLS) is an autosomal-dominant inherited cancer-prone disorder associated with hemangioblastomas (Hbl) of the CNS, angiomatosis retinae (AR), renal cysts, renal cancer, pancreatic cysts, pancreatic cancer, and pheochromocytoma [10]. The main cause of death in this disease are Hbl of the CNS, followed by renal cancer and pheochromocytoma. AR can lead to unilateral or even bilateral loss of vision [11]. Manifestations of the syndrome usually develop in young adults [8].

As increased production of erythropoietin (EPO) has been reported in association with Hbl of the CNS [13], we investigated whether the serum EPO concentration is an indicator of HLS manifestation, which may facilitate an early diagnosis of affected individuals.

Methods

Assay of Serum EPO and Normal Values

Serum for EPO radioimmunoassay was prepared from venous blood sampled without anticoagulant. The assay was carried out in duplicate using $^{125}$I-labelled recombinant human EPO (specific activity 11–33 TBq/mmol; Amersham Buchler, Braunschweig, FRG) and antiserum (1:5000) from a rabbit immunized with human urinary EPO. Human urinary EPO was also used as the standard (10 concentrations in the range 0–250 mU/ml in dilution buffer: phosphate buffered saline, pH 7.4 with bovine serum albumin 0.5 g/l and sodium acid 0.5 g/l, to which bovine gamma globulin 12 g/l was added).

Mixtures of 100 µl antibody solution and 100 µl test serum or EPO standard were incubated at 4°C for 48 h, before 100 µl $^{125}$I-EPO (5 × 10$^{-15}$ mol/l in dilution buffer) was added for another 24 h. Thereafter, the antibody-bound $^{125}$I-EPO was precipitated with polyethylene glycol 6000 (160 g/l).

The EPO concentration of the serum samples was calculated from semilogarithmic plots of the standards (radioactivity of the pellet versus log
EPO concentration). The mean within and between assay coefficients of variation was 7% and 19% in the EPO range 40–50 mU/ml. The detection limit was 5 mU/ml.

Comparative measurements of immunoreactive EPO were performed on serum samples from 14 normal subjects (5 females, 9 males; age 20–38 years). Their EPO values were essentially normally distributed with a mean of 18.1 ± 7.5 mU/ml (± 1 SD).

Thus, with the assay described, 95.5% of all normal values are in the range 3.1 – 33.1 mU/ml (mean ± 2 SD).

Subjects

Participating in this study were patients with proven positive gene carrier status of HLS. According to the minimal criteria for the diagnosis [9, 10], Hbl or AR in combination with one CNS, ocular, renal, adrenal, or pancreatic lesion were found in two first-degree relatives. Also included were asymptomatic gene carriers without manifestations of HLS. In these cases, a gene carrier status was confirmed by pedigree analysis.

Results

We studied 44 subjects with HLS (21 male, 23 female). The mean age was 38.7 (16–79) years. The following manifestations of HLS were found: Hbl of the CNS in 5, AR in 25, renal cancer in 2, renal cysts in 3, pheochromocytomas in 7 patients; there was a history of surgical treatment for Hbl of the CNS in 4, and for pheochromocytoma in 11 patients. Fifteen subjects presented with multiple lesions. Three individuals were identified as asymptomatic gene carriers by pedigree analysis; our standard screening protocol [11] did not reveal lesions of the HLS.

The results are summarized in Table 1. Serum EPO was elevated (>33.1 mU/ml) in 2 of 5 (40%) patients with Hbl, in 2 of 25 (8%) with AR, in 1 of 7 (14%) with pheochromocytoma, but in none of the patients with renal and pancreatic lesions. No significant correlation was found between elevated EPO values and serum hemoglobin concentrations. One patient with AR and one patient with a history of pheochromocytoma surgery presented with polyglobulia (hemoglobin > 180 g/l), but serum EPO was normal in both cases.

Discussion

The association of polyglobulia and cerebellar hemangioblastoma was first reported by Carpenter et al. in 1943 [2]. Waldman et al. [16] described the production of an erythropoiesis-stimulating factor in Hbl, which was later