Trabajo número 5:

Moderate hyperhomocysteinemia is a highly prevalent defect in Spanish patients with venous thromboembolic disease.

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Moderate hyperhomocysteinemia is a highly prevalent defect in Spanish patients with venous thromboembolic disease

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Recent studies suggest that mild hyperhomocysteinemia may be a risk factor for venous thromboembolic disease (VTED). In this work we evaluated the prevalence of moderate hyperhomocysteinemia in patients with VTED in our area. We found hyperhomocysteinemia in 23.4% of 64 patients studied compared with 7.35% of 68 healthy controls (p=0.014). Our results suggest that moderate hyperhomocysteinemia is one of the most prevalent abnormalities associated with VTED.

Several studies have concluded that moderate hyperhomocysteinemia is an independent risk factor for atherosclerosis and arterial occlusive diseases in the general population.[1,2] Recent studies suggest that mild hyperhomocysteinemia may also be a risk factor for venous thromboembolic disease (VTED) and its recurrence.[3-6] The objective of this study was to evaluate whether VTED is associated with an increased prevalence of hyperhomocysteinemia in our area. Sixty-four consecutive unrelated Spanish patients with objectively diagnosed VTED (31 females and 33 males, mean age 52.16±15.70) and sixty-eight healthy controls (41 females and 27 males, mean age 46.6±10) were studied in our Institution, between January 1996 and December 1996. The assessment of hyperhomocysteinemia was performed by measuring the concentration of fasting plasma homocysteine and its increase 6 hours after oral methionine loading (PML) (0.1 g L-methionine/kg body weight). Concentrations of plasma homocysteine were determined by high-perfomance liquid chromatography and fluorescence detection.[7] In order to investigate other biological abnormalities causing thrombophilia, we also determined: antithrombin, plasminogen and amidolytic protein C by chromogenic substrates; anticoagulant activity of protein C; total protein S and free protein S by the ELISA method; antiphospholipid antibodies by ELISA; and the factor V Leiden mutation by standardized methods. Hyperhomocysteinemia was defined as fasting plasma homocysteine levels and/or PML absolute increments above the 95th percentile of the level in the control group (respectively 11.43 µmol/L and 28.72 µmol/L).

Hyperhomocysteinemia was detected in 15 patients (23.4%, IC 95% 13.0-33.8), eight females and seven males (mean age 63.18±8.65 yrs) and 5 subjects in the control group (7.35%) (p=0.014). Malignancies were 13 times more frequent in patients with hyperhomocysteinemia than in patients without it. Although the mechanisms underlying this association are unclear, higher plasma homocysteine in patients with cancer has been noted before.[8] It would be interesting to perform more studies to clarify the association between hyperhomocysteinemia and VTED in cancer patients.

Table 1. Patient characteristics.

	Total patients	*No HH*	*HH*
Number of patients	64	49	15
Mean age ±SD	52.1±15.70	49.64 ±15.91	63.18 ±8.65 (p<0.05)
Female:male ratio	33/31	25/24	8/7 (n.s)
Family history of VTED	25 (39.06%)	19 (38.77%)	8 (53.33%) (n.s)
Recurrent VTED	32 (50%)	25 (51.02%)	10 (66.66%) (n.s)
Mean age at first event	44.50	42.08	52.46 (p<0.05)
Malignant disease*	5 (7.81)	1 (2.04)	4 (26.66)
Other defects	5 (7.81%)	3 (6.12%)	2 (13.33%)
Oral contraceptives°	9 (14.06%)	7 (14.28%)	2 (13.33%)

*HH: hyperhomocysteinemia; VTD: venous thromboembolic disease; *when cancer patients are excluded from the analysis, the patients with VTD show a tendency toward higher plasma homocysteine than control group (p=0.06); °only women considered, n.s: non significant. Fisher's exact test.*

Within the group of patients who had had at least one objectively diagnosed VTED, the age at first event was lower in patients without hyperhomocysteinemia than in patients with hyperhomocysteinemia (42.08± 15.41 years compared with 52.46±8.13 years; p<0.05). Recurrences and family history of VTED were more frequent in patients with hyperhomocysteinemia than in patients without hyperhomocysteinemia, but differences were not significant. As for other deficiencies, two patients of the hyperhomocysteinemia group had antiphospholipid antibodies, whereas two patients of the non-hyperhomocysteinemic group had factor V Leiden mutation while another had activated protein C resistance without factor V Leiden mutation. Hyperhomocysteinemia did not seem to add to the thrombotic risk of oral contraceptives (Table 1).

This study is the first report on the prevalence of hyperhomocysteinemia in a Spanish population with VTED. It was present in about 23% of patients with VTED and our results suggest that moderate hyperhomocysteinemia is a common biologic abnormality in these individuals.[9] We are, therefore, of the opinion that homocysteine assessment should be included in the laboratory evaluation of patients with VTED. Measurements of fasting plasma homocysteine and post-methionine levels should be performed because the detection of hyperhomocys-

teinemia is considerably increased by using the latter test. After confirmation of the existence of hyperhomocysteinemia, other tests to study its possible origin (such as folate and vitamin B6 and B12, and investigation of renal function) as well as its treatment should be considered.

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Key words

Homocysteine, venous thrombosis, cardiovascular disease

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Trabajo número 6:

Lack of association between venous thrombosis and subsequent malignancy in a retrospective cohort study in young patients.

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Lack of Association Between Venous Thrombosis and Subsequent Malignancy in a Retrospective Cohort Study in Young Patients

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Since the publication of Trousseau in 1865, several studies have documented an increased incidence of cancer in patients with deep venous thrombosis (DVT) especially those with idiopathic or recurrent DVT, but in young patients this association is not clear and is therefore a subject of controversy. We performed a retrospective study in a consecutive cohort of 40 young patients (age <40 years) with a DVT and without a known cancer. All patients were diagnosed in our hospital during the period of 1988–1992. At the time of diagnosis, a routine examination to detect the presence of malignant disease was made. For the follow-up, all patients included in the study were asked to return to our unit and were interviewed for symptoms that could suggest a malignant disease. The mean follow-up was five years (from three to eight years). Twenty-four patients had DVT in the lower limbs and three in the upper extremities, nine had pulmonary embolism (six of them with DVT) and four had DVT in other sites. Sixteen patients (40%) had secondary DVT due to nonbiological causes, abnormalities in hemostasis were found in 14 patients (35%), and biological or environmental triggering factors were not identified in 10 patients (25%). Malignancies were not detected at diagnosis and in the follow-up. In our experience, venous-thrombotic patients under the age of 40 have a low incidence of subsequent cancer. Further studies should be performed to confirm this observation and to ascertain whether extensive screening for cancer is a cost-effective approach. Am. J. Hematol. 60:181–184, 1999. © 1999 Wiley-Liss, Inc.

Key words: deep venous thrombosis; cancer, young people

INTRODUCTION

In 1865 Trousseau [1] published his initial observation of cancer associated with deep venous thrombosis (DVT). Since this observation several studies have examined the relationship between DVT and subsequent cancer. Some studies have reported an increased incidence of subsequent cancer in patients with DVT when compared with the general population [2–4]. Others have shown that patients with idiopathic DVT (no known associated risk factors) or recurrent DVT have a high incidence of cancer when compared with patients with secondary DVT or no recurrent thrombosis [5–13]. Recently Rance et al. [14] have communicated an increased incidence of cancer in patients with bilateral DVT. Nevertheless, some authors have not observed any association between DVT and subsequent cancer [15,16] whereas others differ about the increased risk of cancer in patients with idiopathic or recurrent DVT [17,18]. The relationship between the age of the first thrombotic event and the development of subsequent cancer has been investigated by some authors, but the results are contradictory. Some studies show that patients under 50 years of age have a particularly increased risk for cancer during follow-up when compared with healthy controls [2,19–21]. Other studies fail to find any relationship between the age of first thrombotic event and occult cancer [9,12], and some of them suggest that the incidence of cancer is higher only after the age of 50 years [11,13]. Two questions arise from these observations: Is screening for occult

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cancer indicated, and How extensive should it be? Authors currently differ about the need for investigating occult cancer in patients with DVT and for extending screening. Some authors propose only anamnesis and physical examination [2,18,19,21]. Others perform a nonextensive screening that includes: anamnesis, physical examination, blood cell counts, lactate dehydrogenase, carcinoembryonic antigen and chest X-ray [3,7,22]. These authors recommend that additional tests should be guided by abnormalities detected in the clinical evaluation. Others favor performing extensive screening including an abdominal ultrasonography or a CT scan [5,9,12,23], and finally, some of them also include colonoscopy and gastroscopy [11]. Several investigators have observed that patients with idiopathic or recurrent DVT are a high-risk group for developing subsequent cancers. For this reason, extensive screening has been proposed only for these patients [21–24]. However, the question remains: Are young patients included in the high-risk group and should screening for cancer be performed? Thus, because of these contradictory results and opinions, the intensity of screening for cancer in young patients with DVT remains a matter of individual clinical judgement.

We have performed a retrospective study in a consecutive cohort of 40 consecutive patients (age <40 years) with a first episode of venous thrombosis to determine the incidence of subsequent cancer in young patients with DVT.

PATIENTS AND METHODS

The cases were obtained from the registry of our hospital. We reviewed the clinical records of consecutive patients under 40 years of age without known cancer and with a first episode of DVT between January 1988 and December 1992. Forty patients were identified. All of them showed clinical signs or symptoms of venous thromboembolism and objective tests were used in the diagnosis. DVT of the lower limbs was diagnosed by ultrasonography or phlebography. DVT was detected by ultrasonography examination in the upper extremities. Pulmonary embolism was diagnosed by high probability defects on ventilation-perfusion lung scanning and pulmonary angiography was used to confirm diagnosis in one patient with inconclusive defects in lung scanning. CT scan was used for diagnosis of mesenteric or *vena cava* thrombosis and magnetic resonance imaging was used for diagnosis of intracranial vein thrombosis. At the time of diagnosis, anamnesis, physical examination, blood cell counts, erythrocyte sedimentation rate, lactate dehydrogenase, liver and renal chemistry, carcinoembryonic antigen, blood coagulation parameters and a chest X-ray were done in all patients. Specific studies were performed when a malignancy was suspected. Biological abnormalities of blood coagulation associated with thromboembolic disease were screened in all patients. These included antithrombin activity (Coamatic antithrombin III, Chromogenix, Möndal, Sweden), protein C activity (Coamatic protein C, Chromogenix), antigenic protein C (Asserachrom protein C, Diagnostica Stago, Asuières, France), total and free protein S (Asserachrom protein S, Diagnostica Stago), and activated protein C resistance (Coatest APC Resistance, Chromogenix). Lupus anticoagulant was detected by the method of Exner et al. [25] and antiphospholipid antibodies by a method reported elsewhere [26]. The presence of an abnormality was confirmed in a second sample. Patients were classified as having secondary or idiopathic DVT. DVT was considered to be secondary if there were predisposing abnormalities of blood tests or if DVT occurred after trauma, a prolonged immobilization, surgery, during pregnancy or puerperium, or if patients suffered from morbid obesity, chronic inflammatory bowel disease, nephrotic syndrome, venous compression, varicose veins, dehydration, or prolonged traveling. DVT occurring in the absence of these conditions was defined as idiopathic.

All patients selected for the study were asked to return to our unit and were interviewed for symptoms that could suggest malignancies. The same physician, in accordance with a standardized questionnaire, performed all the interviews. Patients were asked about major illnesses, hospitalizations, visits to their family physician, overall health, and also underwent a full physical examination.

RESULTS

The study cohort comprised 16 male and 24 female thrombotic patients. Their mean age was 26 years (range 3–37). Twenty-four patients suffered from lower-limb DVT and three from DVT in the upper extremities. Nine had pulmonary embolism, six with coexisting DVT. Two patients suffered from mesenteric thrombosis, one from *vena cava* thrombosis and in one, the thrombosis was intracranial. Sixteen patients (40%) had a secondary episode without biological abnormalities predisposing thrombosis. Prolonged immobilization after trauma or surgery (11 cases) and pregnancy-related thrombosis (five cases) were the most common predisposing factors. Fourteen patients (35%) had a secondary DVT due to biologic abnormalities associated with thromboembolic disease. Seven patients had protein S deficiency, two had protein C deficiency, one had antithrombin deficiency, two had activated protein C resistance, and two had antiphospholipid antibodies. In 10 patients (25%) neither biological nor clinical predisposing factors were found and thrombosis was considered to be idiopathic.

Thrombosis recurred in six patients (43%) with abnormalities of coagulation, in four (40%) with idiopathic DVT, and in two (12.5%) with secondary thrombosis due

TABLE I. Summary of Data From Published Series of Patients Who Develop Cancer After Venous Thrombosis*

Author	No. patients	Type of thrombosis	Age (range)	No. patients with cancer (%)	Patients with cancer, age range (years) (<40 years/40–49 years)
Monreal et al., 1988 [8]	104	DVT	NR	9 (8.6)	51–83 (0/0)
Monreal et al., 1991 [8]	113	DVT	NR	12 (10.6)	36–86 (1/1)
Ranft and Heidrich, 1991 [13]	200	DVT	19–97 years	23 (11.5)	30–over 80 (1/2)
Prandoni et al., 1992 [7]	250	DVT	NR	13 (5.2)	49–84 (0/1)
Monreal et al., 1993 [10]	78	PE	30–89 years	9 (11.5)	44–85 (0/2)
Nordström et al., 1994 [3]	1,383	DVT	NR	150 (10.8)	30–97 (1/2)
Ahmed and Mohyuddin, 1996 [6]	196	DVT	Maximum incidence range 21–40 years	3 (1.53)	33, 53, and 63 (1/0)
Cornuz et al., 1996 [22]	142	DVT	NR	16 (11.2)	40–84 (0/4)
Total	2,466		—	235 (9.5)	4 p < 40 years (0.16%) 12 p 40–49 years (0.48%)

*DVT, deep venous thrombosis; NR, not reported; p, patient; PE, pulmonary embolism.

to nonbiological causes. There were no recurrences during anticoagulant therapy. Family history for thrombosis was present in nine patients (64%) with abnormalities of coagulation, in four (25%) with secondary thrombosis due to nonbiological causes, and in two (20%) with idiopathic DVT.

We were not able to diagnose patients with cancer at the time of the first DVT, during hospitalization, and during follow-up. The mean follow-up was five years, ranging from three to eight years.

DISCUSSION

Since the first publication by Trousseau [1] until the present time, the relationship between the development of subsequent cancer and the age of first thrombotic event has been a subject of controversy. Several studies have obtained contradictory results [2,9,11–13,19–21]. We performed a retrospective study in a cohort of 40 consecutive young patients (age less than 40) without cancer and with a first DVT. The aim of the study was to determine the incidence of cancer in young patients after DVT and to ascertain whether diagnostic work-up for occult neoplasm could be justified. The diagnosis of thrombosis was made by means of objective methods. Secondary DVT, which includes thrombosis related to biological abnormalities, is the most frequent type in young patients. Biological causes are highly prevalent in this group of patients. Sixty-four percent of patients with biological abnormality of coagulation had a family history of thrombosis. This percentage was similar to 61% recently reported by the Spanish Multicentric Study on thrombophilia [27]. Moreover, 20% of patients with idiopathic DVT have a family history of thrombosis. This finding suggests that some of them could have an unknown or congenital abnormality of coagulation that was not studied, such as hyperhomocysteinemia.

None of our patients had an occult cancer at the moment of DVT and none developed cancer during the follow-up. The number of patients recruited in our study is low. Most had secondary thrombosis. We consider that the follow-up period in our patients is sufficient because the shortest period was three years. Most authors suggest that the risk of subsequent cancer is present during the first 12 months after the thrombotic event, and that most malignancies become clinically evident within the first 6 to 12 months after the thrombotic event [21,28].

We reviewed the largest series published to date which included patients with DVT who developed overt cancer during the follow-up (Table I). From a total of 2,466 patients with DVT, 235 developed cancer, only four patients were younger than 40 years of age, and 12 patients were between 40 and 49 years of age, representing 0.16% and 0.48%, respectively, of the total population with DVT. This incidence of cancer resembles that in the general population [29,30]. However, these studies included patients of all ages. Only two reported the precise number of young patients [2,6]. Ranft et al. [6] reported 29 patients under 40 years of age and one (3.4%) developed cancer. In the study by Goldberg et al. [2] four of 87 (4.6%) patients under 50 years of age with DVT developed cancer. We found no cases. The differences be-

tween these series could not be attributed to screening, given that a similar nonextensive screening was applied. Moreover, the number of patients was low in all three.

The results of our study and the findings reported in the literature suggest that young patients with DVT have a very low incidence of subsequent cancer. At present, there is no evidence to support extensive screening in young patients with a first episode of DVT. Nevertheless, further studies should be performed to confirm this observation and to ascertain whether extensive screening is a cost-effective approach in terms of potential gains in life expectancy in young patients.

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