Thromboembolic tendency (TE) in IBD (Inflammatory bowel disease) patients

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BACKGROUND: *The incidence of TE events in IBD patients is higher then in population control. The main reason of it, is the hypercoaugulable state. Our aim was to detect serum markers related to TE, that can assume preventing and prognostic meanings.*
MATERIALS AND METHODS: *We performed a 3 years study on 71 patients with IBD, evaluating hypercoaugulability, and then we compared the results with a 71 patients non IBD group control. We also investigated patients of both groups concerning TE events occurred already.*
RESULTS: *In IBD group we found out that 16 patients (22.5%) had history of TE versus >1% of group control. Nineteen of them, already had knowledge of their previous hypercoaugulating condition. 48 (67%) had increased markers value versus less then 6% detected in group control. In IBD group 43% ,20% and 4.2% had respectively 1, 1-3 or > 3 markers higher levels then normal range. Among the markers investigated, we detected increased levels of plated in 33%, homocysteine in 26.7%, d-dimero 25.3%, c3 in 15.4%, apcr in 5.6%.*
CONCLUSIONS: *From our study we detected highest incidence of TE events, and hypercoaugulating status in IBD group. In our previous investigations, plated, homocysteine, d-dimero, c3, and apcr, seems to be the TE markers with higher sensibility. It seems reasonable, according our experience, to propose a new TE risk score index for IBD patients: low, mild and high risk respectively for patients with 1, 1-3 and >3 markers with higher serum levels then normal range.*

KEY WORDS: Inflammatory bowel disease, Thromboembolism risk score.

Introduction

The acronym IBD identifies the ulcerative colitis (URC), Crohn's disease (CD) and the undeterminate colitis (UC) [7].

Inflammatory bowel diseases are characterized by variegated etiopathogenesis, probably autoimmune. They have in common a histological damage of a granulomatous/ulcerative kind and also the same manifestations which includes the alternation of remissions and exacerbations [1]. They have a remarkable familiarity (13.5%) although it is more evident in CD than in URC [1,2]. The incidence of IBD varies according to different geographical areas but with a steady increasing trend [2-6,25] above all in CD [2,4,6], and the diffusion seems to be linked to genetic factors (association with HLA-A2 and

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B 18) [8] and to geographical factors [1,2,4,9,25]. Today the etiopathogenesis is still debated. The latest theories seem to confirm an autoimmune genesis [10,11]. IBD show a remarkable tendency in developing secondary remote manifestations in a different location from the intestinal one: extraintestinal manifestations (EM). They can appear simultaneously with the primitive intestinal manifestation or they can precede or follow after years [1,2,25]. According to the most reliable etiopathogenetic hypothesis, EM give rise to "metastasizations" of autoantibodies activated in the bowel from the "ideational intestinal brain"; once the autoantibodies are activated, they are able to attack any organ, tissue or system causing damage directly or mediated. In support of this theory there is the evidence that almost all EM regress with a cortison-based/immunosuppressant treatment [2,12]. In literature we have descriptions of the extraintestinal remissions of symptoms after total proctolectomia and ileo-anal pouch [2,13,23]. Among EM we find following manifestations: hepatobiliary, osteoarticular, muscular, dermatological, stomatological, ophthamological, gynaecological, urological, metabolic, perianal etc. [2,12]. Recently another manifestation has appeared which consists in a remarkable thromboembolic tendency (TE) in IBD patients [2,12-20,25]. TE and IBD are an important field of research as TE occurs in young patients aggressively causing significant morbidity (stroke, retinal vascular occlusive thrombus deposition in cerebral, retinal and mesenteric vessels, massive pulmonary embolism), [2,12-20]. Several studies describe thrombosis in venous and arterial district in IBD patients as 4% but according to autopsy studies the percentage is more than 30% [2]. Among the causes of the TE disease we have: thrombocytosis, increase of the coagulation factors [2,12,8], mutation of V factor of Laiden [8], hyperhomocysteinemia [8,12,21], (due to the combined deficit of methylene-hydrofolate-tetra reductase (MTHFR), B12 vitamin and folate) [2,8,21], observed mutation of MTHFR gene in some IBD patients [8]. Finally, surgery determines an additional TE risk in these patients compared to non-IBD patients who have the same operation [2,14,15,22]. Some studies describe mortality of 1-1,2% after restorative proctolectomia due to TE complications (pulmonary-cerebral and mesenteric district [13,15,16,21,23].

Purpose of the study

The purpose of this study is to assess the true incidence of TE in IBD, to identify risk factors and predictive serological markers of TE risk. A secondary purpose is to find risk differences among patients affected by URC and CD. Finally, we have wondered, how to prevent the risk of TE? What aids or medicines shall we use in the different timings? How shall we select those patients to be treated with heparin and those with elastic compression?

Material and methods

From February 2007 up to today we have enrolled 71 IBD patients in our study. Of these, 39 were affected by RCU e 32 by CD. We have investigated the tendency to thromboembolism by using serological markers: D-Dimer, plasma homocysteine, PT, APPT, APCr, fibrinogen, folate, Vitamin B12, C3, factors of coagulation, piastrinemia, MCHC; through special questionnaires on TE past events; through clinical analysis. Finally we have compared the results with those obtained from a homogeneous class of control patients with no intestinal disease (control group 1) and from a second class of patients affected by another intestinal disease (control group 2).

Results

The questionnaires provided to the IBD group revealed following aspects: 16 out of 71 (22.5%) had a positive anamnesis for TE manifestations. In 11 cases (15.4%) patients were affected by RCU, in 5 cases (7%) by CM. Nineteen patients (26%) out of 71 showed alterations of the clotting ability with the same results of RCU and CD. In these patients had occurred 21 TE manifestations (29%): 15 (21%) deep venous thrombosis (DVT), 3 (4.2%) thromboflebitis (TF), 2 (2.8%) thrombosis v. SFA (TVSS), 1 (1.4%) central retinal vein thrombosis (TVCR). 6 patients (8.4%) showed a vasculitis or another autoimmune disease. TE manifestations are the same in the two control groups 1 (0.71%) and 2 (1.42%) respectively in the control group 1 and 2. In the questionnaires provided to the IBD group we observed: malabsorption in 19 cases (26.7%) (vs. 3-4%), malnutrition in 14 (19.7%) (vs. 5-7%), major bedding than the population control, thrombocytosis in 27 patients (38%), 3 cases of chronic venous insufficiency (CVI) (4%) in IBD patients (data similar to that of non-IBD patients). We observed that in several groups more than one of the serological markers were at basal levels higher than normal in patients with IBD, compared with the two control groups, which explains the tendency to hypercoagulability and to TE. Some of the supplied markers proved to be predictive markers of TE risk, and their use could be taken into consideration as predictive and prognostic value in order to identify patients at risk for TE. In our study the markers with more specificity are: piastrinemia, homocysteine, D-dimer, APCr, C3. In the IBD group, 48 patients (67%) had alteration of the marker's basal values. In 31 (43%), only one of them was altered, in 14 (20%) from 1 to 3 had been growing, in 3 cases (4.2%) more than 3 markers were increased compared to the threshold values. We have observed thrombocytosis in 24 patients (33%), hyperhomocysteinemia in 19 (26.7%), increased D-Dimer in 18 cases (25.3%),

an increase of C3 in 11 cases (15.4%), and APCr increased in 4 patients (5.6 %). Alterations prevail in patients with RCU (29), (40%) compared with CD (19), (26.7%). Only 23 (32.4%) of the IBD patients showed no alteration of the clotting ability. In a control population, only 4 patients (5.6%) had alterations of the clotting parameters, and only 5 (7%) in group 2.

Conclusion

Our study confirms the increased TE incidence in IBD patients (29%) compared to the two control groups 1 and 2: (0.71-1.4%) respectively. TE manifestations prevail in RCU rather than in CD. The most common TE manifestations are DVT (21%); (4.2%), TVSS (2.8%), TVCR 1 out of 71 (1.4). It must be said that in literature you can find cerebral, pulmonary and mesenteric embolism very frequently. In 6 patients (8.4%) with the alteration of the clotting parameters and with TE manifestations, vasculitis appeared, proving the role of the immunity and the vasculitic damage as cause of TE manifestations. TE tendency in IBD depends on many factors and hypercoagulability is the predominant cause of TE risk. From the results obtained in our study, we have listed a sort of "score index" which identifies three classes of TE risk: low risk: patients with the alteration of one marker, intermediate risk: patients with 1-3 markers of higher value than the standard value; high TE risk: patients with 3 or more increasing markers. We also suppose that in the "score index" of TE risk, other risk factors have to be considered such as anamnesis, surgery, malabsorption, malnutrition, bedding, etc. In fact, malabsorption (26.7%) and malnutrition (19.7%), compared to 4 and 7% of control groups 1 and 2, contribute significantly to the TE risk in IBD patients. The most reliable markers are thrombocystosis 24 out of 71 (33%), hyperhomocysteinemia 19 out of 71 (26.7%), D-dimer 18 out of 71 (25.3%), C3: 11 out of 71 (15.5%), and APCr 4 out of 71 (5.6%). Finally, in terms of prevention, preoperative prophylactic heparin as routine is needed in patients with IBD, increasing the dose according to the class of TE risk the person belongs to. While in classes at higher risk, the elastic compression is needed (especially in the preoperative and intraoperative period). There is no absolute contraindication by using heparin in the TE prophylaxis in patients with IBD; of great importance is the use of the elastic compression therapy. Finally, it would be appropriate in selected cases, to prefer the only use of elastic compression instead of heparin [53] especially after a medium or a long time after the risk event (surgery) or TE manifestation. Heparin should not be used, except in special cases, in bleeding patients for whom a constant elastic compression is preferred.

Riassunto

L'incidenza degli eventi trombo embolici nei pazienti con IBD (Inflammatory Bowel Disease) è più alta rispetto al resto della popolazione. La ragione principale di questo è lo stato di ipercoagulabilità. L'obiettivo di questo studio è stato di individuare i marker sierici correlati con il tromboembolismo,il che può assumere un importante significato dal punto di vista preventivo e prognostico. Abbiamo eseguito uno studio di tre anni su 71 pazienti affetti da IBD,valutando lo stato di ipercoagulabilità e comparando i risultati con un gruppo di 71 pazienti non affetti da IBD. Nel gruppo IBD abbiamo trovato che 16 pazienti (22,5%) avevano una storia di tromboembolismo contro l'1% circa del gruppo di controllo. 48 pazienti (67%) mostravano valori sierici dei marker aumentati rispetto a meno del 6% del gruppo di controllo. Nel gruppo IBD il 43%, il 20% ed il 4.2% aveva rispettivamente 1, 1-3 e 3 marker con livelli sierici più alti rispetto ai range di normalità. Tra i marker investigati abbiamo trovato livelli aumentati di piastrine nel 33%, omocisteina nel 26.7%, d-dimero nel 25.3%, c3 nel 15.4%, apcr nel 5.6%. Nel nostro studio abbiamo individuato una più alta incidenza di eventi tromboembolici ed uno stato di ipercoagulabilità nel gruppo di pazienti affetti da IBD. Le piastrine, l'omocisteina, d-dimero, c3 ed apcr sembrano essere marker di rischio tromboembolico ad alta sensibilità. Sembra ragionevole,secondo la nostra esperienza, proporre un nuovo "risk score" tromboembolico per i pazienti con IBD: rischio basso,medio ed alto rispettivamente per i pazienti con 1, 1-3 e > 3 marker con livelli sierici più alti rispetto ai range normali

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