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Annals of Medicine and Healthcare Research

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Online Medical Conference*



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Proceedings of the 2009 International Online Medical Conference

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With forewords by

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Foreword

Wellness & Well-being

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Achieving wellness and hence well-being is the ultimate goal of every human being. On the global scale this is articulated through the Millennium Development Goal (MDG) of the United Nations. Three out the eight MDG provisions directly deal with enhancement and improvisation of health and medical components. At the personal level, it is widely acknowledged that the largest determinant of wellness is health. Holistically, the term health within the context of wellness embraces social, economic, political, physical, spiritual, and mental components. Its hierarchy of societal continuum extends from the person through the community to the nation and global entities. Consequently medical and health issues need to be addressed at each of these levels, on the global scale. Diseases and impairment know no boundary. Understanding, measuring, evaluating, diagnosing, and prognosing are the essential tools of learning and implementing effective and efficacious intervention strategies and tactics. Every domain of knowledge, as explored and articulated in the conference and the ensuing book, is pertinent. New and renewed information are critical in the process of addressing health and wellness issues: including nanotechnology, biology, biochemistry, ecology, medicine, medical practice, traditional health and its practice, physical sciences, cognitive sciences, neurosciences, spiritual enhancers, information communication technology (ICT), and the measuring-analyzing-evaluating tools (diagnostic, mathematic, statistic). As such medical and health issues are pervasive, of persis-

tent concern, and impact on everyone in every community. The need for community-based social-cultural health action strategy, as predicated primordially on the premises articulated in the Ottawa Health Promotion Strategy of 1986, is evidently implicated here. Moreover the World Health Organization (WHO) 2008 Report stressed the overriding importance of primary health, which dominates community or public health concerns, especially in the rural areas.

Life being a dynamic entity, we are witnessing the evolution of biological characteristics and impactful action of many disease causing organisms. Despite man's impressive progress through science and technology, no disease-causing organism has been subdued forever, let alone being exterminated or driven to extinction. On the contrary, resurgence and reemergence of deadly scourges and plagues, both silent and ostentatious, prevail. Our research explorations need to be in tandem with the pace of evolution and dynamic changes in nature's ecological processes. Biological and ecological changes and changing environment are the very essence of life. As such continually-updated evidence-based-knowledge is most relevant to ensure that medical and health theory and practice stay relevant and current with time. This is a tall order especially for the developing and poor countries. With limited resources these countries need to depend mostly and largely on global open accessed knowledge and information.

Consequently, the role of the International Online Medical Conference (IOMC) and its web entity is timely and pertinent. With the advent of real-time online colloquiums, workshops, newsletter, and impending web-based journal, IOMC is expanding its entity and it is fast emerging as a world-class educational portal and knowledge forum especially for the medical and health domains. Its online 24/365 availability and accessibility are a testimony to its resolve and resilience to becoming a repository and virtual centre of education. As educated men in this era of knowledge society, we deeply know that such endeavour deserves applause and compliments. The overwhelming success of IOMC second conference (2009) as further evi-

denced by its ensuing book publication is another major landmark contribution towards developing a global knowledge society. The involvement of every delegate to the global conference is laudable. This second book also simultaneously delineates IOMC's achievement in embedding an online map or ontology of interactive knowledge provision and dissemination involving every committed stakeholder and beholder. After all health and its knowledge and ramifications are everyone's concerns.

A Crucial Role for Health Promotion in the 21st Century

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At a time when healthcare costs are soaring worldwide, the emphasis is placed on prevention to try to contain and hopefully reduce them, particularly in the USA. The cornerstone of prevention is awareness and the gateway to comprehensive population health management is health risk assessment (HRA). The aggregate data gathered from HRAs provide a road map for delivering health promotion and disease management interventions to targeted individuals, which aim at improving clinical and financial outcomes. Science-based information is essential to successful health initiatives. The Stanford Prevention Research Center and the Stanford Health Improvement Program (HIP) have been at the forefront of the preventive field at every step of health promotion: Designing an HRA called the Stanford health and lifestyle assessment and administering it to staff, faculty and their families and disseminating it state-wide, nationally and internationally; Creating motivation assessment tools; Assessing readiness for change; Developing and implementing health promotion programs; Providing primary, secondary and tertiary prevention to the Stanford population and the community-at-large.

Medicine is only at the infancy of adopting really cost-effective prevention as the mainstay of healthcare. Indeed, the most productive and novel approach is to think globally but to operate locally. Although we have nation-wide figures and profiles, they can be misleading and induce erroneous prioritization, design and implementation of health promotion programs resulting in wasted resources. A good example of potential pitfall would be smoking cessation programs. The average percentage of current adult smokers was 19.8% in the United States popu-

lation in 2007 whereas it was only 3.7% among the 13,546 benefits-eligible employees at Stanford in 2008. Similarly, smoking prevalence is declining in several developed countries but it is rising in many developing countries. Furthermore, men and women are often unevenly consuming tobacco in different milieus. The mode of consumption may also differ. Therefore, the need for accurate and relevant information is urgent on a whole range of health issues. With the availability of HRAs on the internet as well as intranets, statistics can be collected and analyzed and baselines established on various scales and in a prompt manner. Additionally, HIP can provide proven experience and expertise in health promotion to deciders, policy makers and opinion leaders globally. We hope that the know-how we have accumulated over the last twenty six years will be tapped by those who can benefit from it.

IOMC & Our Vision

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The IOMC organizes an annual online conference (<http://www.iomcworld.com/>) where participants from all over the globe present their papers and research using web conferencing. The 2nd annual conference held on March 14 & 15, 2009 received over 100 abstracts and full papers with topics ranging from infectious disease management in India to health policy in Bosnia. The Scientific Committee of the IOMC was delighted to see this rich exchange of information at the conference and unanimously felt that the IJCRIMPH was an idea whose time had come.

On behalf of the Editorial Board, we are pleased to introduce the first issue of the International Journal of Collaborative Research on Internal Medicine and Public Health (IJCRIMPH). As the official publication of the International Online Medical Council (IOMC), the IJCRIMPH provides a forum for clinicians, researchers and policy advocates in medicine and public health to publish not only their research, but also discussions and commentaries on current topics of general interest.

As the official publication of the IOMC, the journal will review submissions from authors who participated in the online conference. Furthermore, we also want the journal to serve as a resource for trainees and young professionals world-wide, to introduce them to the peer-review process and make medical publication a less onerous undertaking. We have assembled an editorial board of scientific reviews of wide-ranging specialties. The journal has so far been indexed in the EBSCO Academic Search Premier, IndexCopernicus Journals Master List, Open

J-Gate, Medical Journals Index (MJJ), SJSU Library Catalog, GFMER, getCITED and the Standard Periodical Directory. It is hoped that the web-based open-access online format of the journal will be particularly helpful for readers where resources may be scarce.

None of this would have been possible without the initiative, drive and resourcefulness of the Executive Editor, Mr. Mostafa Nejati, who conceived the IOMC in 2007 and remains the driving force behind the annual online conference and the journal.

We look forward to this and your contribution to the issues of the IJCRIMPH.

For more information please see
<http://iomcworld.com/ijcrimph/>

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Hypercoagulability Due to Protein S Deficiency in HIV-Seropositive Patients

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Abstract

Background: Thrombosis due to a hypercoagulable state is a serious clinical problem in HIV-infected individuals that can lead to life-threatening thromboembolic phenomenon. Reported causes of thrombophilia in HIV-infected subjects include antiphospholipid syndrome, increased platelet activation, elevated homocysteinemia, elevated plasma factor VII activity, lupus anticoagulant, activated protein C resistance, protein C deficiency, and acquired protein S deficiency.

Aims & Objectives: To report our experience with 12 HIV-seropositive subjects with laboratory-confirmed evidence of protein S deficiency, with and without venous or arterial thrombosis, and discuss the diagnostic approach to hypercoagulability in HIV infection, and the clinical management of thromboembolic complications in patients with protein S deficiency.

Methods/Study Design: A retrospective review of the medical records of 12 HIV-seropositive patients diagnosed with protein C and S deficiencies at the Lawnwood Regional Medical Center and Heart Institute, Fort Pierce, Florida, from July 2005 through December 2005. All patients were seen by one of the authors (DO), an infectious diseases consultant. Lawnwood Regional Medical Center is a 341-bed, acute care institution and regional referral center for four counties of Treasure Coast, FL, USA.

Results/Findings: Seven subjects had symptomatic thromboembolic manifestations that included deep venous thrombosis (5 subjects), pulmonary embolism (4 subjects), inferior vena cava thrombosis (2 subject), and/or stroke (1 subject). An additional five patients were identified with asymptomatic protein S deficiency. All subjects were African-American. Mean patient age was 44 years (range, 21 to 60 years), and the male:female ratio was 5:7. The mean CD4+ cell count was 102 per mm³ (range 0-343), and the mean HIV RNA level was 71,772 copies/mL (range 1,421-554,237 copies/mL). Only three patients were receiving highly active antiretroviral therapy (HAART) at the time of clinical presentation. All symptomatic subjects received heparin, with or without warfarin, for their thromboembolic event and all but one recovered.

Conclusion: HIV-infected patients should be screened for acquired protein S deficiency, which contributes to hypercoagulability and risk of clinical thromboembolic events. Asymptomatic patients with reduced plasma free protein S levels may benefit from aspirin primary prophylaxis.

Keywords: Protein S deficiency, hypercoagulable, thromboembolic, HIV/AIDS

Introduction

Infection with the human immunodeficiency virus (HIV) is a type of hypercoagulable state that predisposes to the development of serious and potentially life-threatening thromboembolic disorders such as deep venous thrombosis, pulmonary embolism, and arterial thrombosis. Reported causes of thrombophilia in HIV-infected subjects include antiphospholipid syndrome (Shen & Frenkel, 2004), increased platelet activation (Shen & Frenkel, 2004), elevated homocysteinemia (Soentjens et al, 2006), elevated plasma factor VII activity (Soentjens et al, 2006), lupus anticoagulant (Majluf-Cruz et al, 2004), activated protein C resistance (Majluf-Cruz et al, 2004), protein C deficiency (Erbe et al, 2003; Majluf-Cruz et al, 2004), and acquired protein S deficiency (Bissuel et al, 1992; Erbe et al, 2003; Hassell et al, 1994; Pulik & Lebret-Lerolle D, 1992; Soentjens et al, 2006; Sorice et al, 1994; Stahl et al, 1993; Sugerman et al, 1996). We herein report our experience with 12 HIV-seropositive subjects with laboratory-confirmed evidence of protein S deficiency, with and without venous or arterial thrombosis, and discuss the diagnostic approach to hypercoagulability in HIV infection, and the clinical management of thromboembolic complications in patients with protein S deficiency.

Patients and Methods

We retrospectively reviewed the medical records of 12 HIV-seropositive patients diagnosed with protein C and S deficiencies at the Lawnwood Regional Medical Center and Heart Institute, Fort Pierce, Florida, from July 2005 through December 2005. All patients were seen by one of the authors (DO), an infectious diseases consultant. Lawnwood Regional Medical Center is a 341-bed, acute care institution and regional referral center for four counties of Treasure Coast, FL.

Hyperoagulability testing was performed on all 12 subjects and included protein C and S assays, lupus anticoagulant, factor V Leiden, and antithrombin levels. Protein S and C deficiencies were the only coagulopathies detected. All subjects were screened for common risk factors for thrombophilia including

family history, immobilization, recent surgery, and thrombotic medications. No patient had concurrent malignancy.

Results

Twelve HIV-seropositive with laboratory-confirmed protein S deficiency were identified, and their clinical features are summarized (Table 1). Isolated protein S deficiency was seen in 9 patients, and combined protein S plus protein C deficiency occurred in 3 subjects. Other primary or secondary risk factors for hypercoagulability were not present. Five patients were asymptomatic, and seven subjects had symptomatic, acute thromboembolic manifestations including: deep venous thrombosis plus pulmonary embolus (4 subjects), inferior vena cava thrombosis (1 subject), deep venous thrombosis plus inferior vena cava thrombosis (1 subject), and stroke (1 subject). Thromboembolic events were diagnosed using venous angiograms and high resolution computed tomography (CT) of the lung or abdomen. No patient had previous thrombosis, family history of thrombosis, or prothrombotic conditions. The mean patient age was 44 years (range, 21 to 60 years), and the male:female ratio was 5:7. All subjects were African-American. The mean CD4+ cell count was 102 per mm³ (range 0-343), and the mean HIV RNA level, determined by polymerase chain reaction (PCR) testing, was 71,772 copies/mL (range 1,421-554,237 copies/mL). Only three patients were receiving highly active antiretroviral therapy (HAART) at the time of clinical presentation. All symptomatic subjects received heparin, with or without warfarin, for their thromboembolic event and all but one recovered.

Discussion

Infection with HIV is an independent risk factor for developing venous thromboembolic events.

But HIV is also associated with a variety of acquired coagulopathies that increase the incidence of venous and arterial thrombosis, including antiphospholipid-anticardiolipin antibo-

dies, increased platelet activation, elevated serum homocysteine levels, lupus anticoagulant, elevated plasma factor VII activity, activated protein C resistance, protein C deficiency, and protein S deficiency (Bissuel et al, 1992; Erbe et al, 2003; Hassell et al, 1994; Pulik & Lebret-Lerolle D, 1992; Majluf-Cruz et al, 2004; Shen & Frenkel, 2004; Soentjens et al, 2006; Sorice et al, 1994; Stahl et al, 1993; Sugerman et al, 1996).

The prevalence of protein S deficiency among persons with HIV infection has been reported in 33% to 94% of patients with HIV infection (Bissuel et al, 1992; Hassell et al, 1994; Pulik & Lebret-Lerolle D, 1992; Sorice et al, 1994; Stahl et al, 1993; Sugerman et al, 1996). A study of protein S deficiency among 25 randomly-selected HIV-seropositive men found 19 subjects (76%) with decreased plasma free protein S levels, and this was a statistically significant difference compared to healthy male controls (Stahl et al, 1993). A decrease in protein S levels did not correlate with CD4+ cell count, CDC class, p24 antigen positivity, zidovudine use, or *Pneumocystis carii* prophylaxis, but a linear correlation was seen with duration of HIV infection. Sugerman and coworkers conducted a prospective laboratory evaluation of 34 HIV-infected children and detected free protein S deficiency in 76.5% of subjects; 55.9% had functional protein S deficiency levels < 2SD below the mean of laboratory controls (Sugerman et al, 1996). These authors found no association between protein S deficiency and CD4+ lymphocyte count, cy (CMV) status, HIV p24 antigen, von Willebrand factor antigen, IgG anti-cardiolipin antibodies, or serum beta-2-microglobulin levels. Similarly, a prospective study of 74 HIV-seropositive men found protein S deficiency in 33% of the cohort, with no significant association seen between protein S deficiency and medication use, opportunistic infection, or CD4+ cell count (Hassell et al, 1994). Bissuel et al. (1992) found plasma free protein S deficiency in 41 of 61 (65%) symptomatic and asymptomatic patients infected with HIV-1, and a significant decrease in plasma free protein S levels was observed in HIV-seropositive subjects compared with healthy controls ($p = 0.0001$). In contrast to the above authors,

however, protein S deficiency was associated with disease severity, namely CD4+ lymphocyte count and CDC class. Sorice and coworkers (1994) also found that protein S levels were significantly lower in patients with < 100 CD4+ cells/ul compared to those with higher counts.

Protein S deficiency may result in venous thromboembolic phenomena including deep venous thrombosis, pulmonary embolus, inferior vena cava thrombosis, renal or hepatic vein thrombosis, and intracranial venous and dural sinus thrombosis (Dillmon et al, 2005; Iranzo et al, 1998; Majluf-Cruz et al, 2004; Soentjens et al, 2006), as well as arterial thrombosis leading to stroke (Majluf-Cruz, et al., 2004; Mochan et al, 2005; Mochan et al, 2003; Qureshi et al, 1997; Restrepo & McArthur, 2003; Wu et al, 2005). Still, there is a paucity of data on the incidence of clinical thrombosis in HIV-infected individuals with protein S deficiency. Previous literature studies have reported thrombotic events in 1.52% to 18% of HIV-infected patients with protein S deficiency (Majluf-Cruz, et al., 2004; Hassell et al, 1994), but we found a 58% incidence of clotting complications in our small study cohort. Hassel et al (1994) reported an overall incidence of thrombosis of 18% among 74 HIV-infected men, and thrombosis developed in 6.6% of subjects followed prospectively over a median follow-up of 12 months. Development of thrombosis was not significantly correlated with protein S levels. In a case-control study, Mochan and colleagues (2005) found protein S deficiency to be an epiphenomenon associated with HIV infection, and it occurred significantly more frequently in HIV-seropositive subjects compared to HIV-seronegative patients with ischemic stroke ($p < 0.001$). However, when they included HIV-positive patients without stroke as a control group and compared them with the HIV-seropositive stroke group they found that protein S deficiency was statistically related to HIV infection but not to stroke occurrence. Among 35 black South African heterosexuals with stroke, protein S deficiency was the most common coagulopathy causing clinical clotting abnormalities (Mochan et al, 2003).

Highly active antiretroviral therapy (HAART) has altered the expected frequency of hematologic complications in HIV/AIDS (Sloand 2005). Today, acquired protein S deficiency is a relative rare complication of HIV in the US among persons taking HAART, but is much more common in developing regions of the world where antiretroviral treatment is not as widely available. Interestingly, however, the use of protease inhibitors (PIs) has been implicated as the cause of a hypercoagulable state in HIV-infected with myocardial infarction (Shen & Frenkel, 2004). Majluf-Cruz et al. (2004) reported a rate of thrombosis of 1.52% (cumulative incidence = 0.30% per year) during the 42-month follow-up period of their study of 28 HIV-positive male homosexuals with venous thrombosis, compared to a rate of 0.33% (cumulative incidence = 0.055% per year; $p < 0.001$) in 600 patients in the pre-PI era (Majluf-Cruz et al, 2004). Protein C and protein S deficiency was detected in nine and two patients, respectively, and lupus anticoagulant in one.

There is almost no literature on the management of HIV-seropositive patients with protein S deficiency and thromboembolism. In subjects with clinical thromboembolic events, we noted a good response to treatment with heparin, with or without warfarin. One previous study noted a high incidence of thrombotic recurrences and hemorrhagic complications using oral anticoagulants, and acetylsalicylic acid secondary prophylaxis was successfully employed (Majluf-Cruz et al, 2004). In view of the 58% risk of thromboembolism in our small series of HIV-seropositive patients, we suggest that screening of asymptomatic individuals may be indicated, and those with documented protein S deficiency may benefit from aspirin primary prophylaxis, at least.

The pathogenesis of this HIV-related protein S deficiency is poorly understood. Sorice and colleagues screened for specific anti-protein S antibodies using immunoblotting and showed an overall positivity of 28.6% in HIV-seropositive patients, with a higher prevalence in symptomatic than in asymptomatic patients (Sorice et al, 1994). Furthermore, the prevalence of po-

sitivity for anti-protein S antibodies was higher in HIV-positive subjects with protein S levels < 50%. Another group evaluated the possible role of autoimmune mechanisms in the pathophysiology of HIV-related acquired protein S deficiency and detected anti-protein S antibodies in 31 (56.36%) of 55 HIV-1-positive patients vs. three (20%) of 15 control subjects ($p = 0.012$) (Lafeuillade et al, 1994). These antibodies were associated with a significantly low protein S activity compared to controls. Hooper and colleagues postulated that tumor necrosis factor (TNF)-downregulation of protein S may be a mechanism for local and procoagulant activity and thrombosis in patients with HIV/AIDS (Hooper et al, 1994).

Conclusion

HIV-infected patients should be screened for acquired protein S deficiency, which contributes to hypercoagulability and risk of clinical thromboembolic events. Asymptomatic patients with reduced plasma free protein S levels may benefit from aspirin primary prophylaxis.

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