

D-dimers: their's place in ischemic stroke initial evaluation, in the Emergency Department

Radu Jipa, Daniela Motoc, Bogdan Pitis

"Vasile Goldis", Western University of Arad, Faculty Of Medicine Pharmacy And Dentistry

ABSTRACT. The ischemic stroke represents one of the most frequent pathology patients present with in the Emergency Department (ED). Because of the wide range of symptoms, sometimes the diagnosis process requires significant time and resources, not always available in a busy E.D. To reduce the necessary time to establish a diagnosis, apart of physical exam and CT-imaging, new methods and protocols could be proposed. The value of D-dimers represent a tool that can be used to assess the probability of the presence of new thromboses, including cerebral. This preliminary study investigates the utility of the use of D-dimers in clinical practice and the possibility to be integrated in a more elaborate protocole focused on ischemic stroke.

KEYWORDS: D-dimers, ischemic stroke, Emergency Department

INTRODUCTION

The process of stopping the bleeding and maintaining the integrity of the blood circulatory system is part of a highly sensitive mechanism, represented by a balance between thrombogenesis (thrombus synthesis), and the destruction of these clots (thrombolysis). Thrombogenesis is a complex process that involves a vascular time (vasoconstriction of the injured vessel, activation, adhesion, agglutination and the secretion of substances contained in granules of platelets), followed by coagulation (the process by which the filaments of fibrinogen are "gelled" in a fibrin network, including, also, cellular components of blood, realizing the final thrombus). To prevent an extensive thrombogenesis, which could obstruct free blood vessels and produce ischemic phenomena, thrombus formation is kept under control by a dynamic balance, highly sensitive, of lysis of thrombus and fibrin into small fragments, called degradation fibrin products. These end products thrombolysis, of different sizes, will be released into plasma, where their concentration can be determined; finally, they will be catabolized at different levels. They represent the final product of the normal synthesis of thrombus.

When the value of these degradation products of fibrin increases in plasma we face a situation of increased thrombus synthesis, with clinical implications that can vary from benign, that do not pose any danger, up to extremely serious situations, potentially fatal. These latter cases are represented by all the conditions that lead to exaggerated and extensive thrombus synthesis: deep

vein thrombosis or disseminated intravascular coagulation. The consequences of the presence of these exaggerated production, found in deep vein thrombosis, are represented by the ischemic local events and by the dislocation of thrombus with its migration in the venous bloodstream (embolization); finally, the clot will impact and block the circulation at various levels, far from the site of synthesis (pulmonary embolism, ischemic stroke, myocardial or intestinal infarction). Disseminated intravascular coagulation is a continuous process of thrombogenesis, followed by a process of consuming the platelets and plasma coagulation factors, with extensive hemorrhagic phenomena, usually lethal.

In all these situations the excessive synthesis of thromboses and its consequence, thrombolysis (fibrinolysis), can be demonstrated and quantified using the plasma levels of the final products of degradation of fibrin (fibrin fragments called D-dimer). However, these end products of degradation of fibrin may be present in large amounts in plasma also in other situations, related to excessive consumption of fibrinogen and unrelated to thrombogenesis (certain diseases of liver, chronic inflammation, tumoral processes, pregnancy, recent surgery). The normal value of D-dimer is below 0.5 mg / mL FEU. The clinical utility of D-dimers is represented by the possibility of being used as a "marker" of thrombogenesis, or, in the case of low values of D-dimers in plasma, to exclude an exaggerated synthesis of thromboses. The value of plasma D-dimer resides in its potential to be integrated in protocols specialized in investigating the probability of deep vein thrombosis and

pulmonary thromboembolism, along with other parameters, like the score Wells.

Among pathological processes that may be accompanied by increased synthesis of thrombus has to be included the ischemic stroke (thrombotic occlusion of cerebral vessels). The presence of thrombi and their's extension, could be assessed by investigating plasma D-dimer's amount. The analysis could provide important data for the evaluation of patients with variable neurological deficit, along with other specific analyzes and investigations.

MATERIAL AND METHOD

To study this hypothesis, in the E.D. of Emergency County Hospital Arad, we have decided to study the correlation between acute neurological deficit and the plasma D-dimer value at a number of patients arrived in E.D. For the study we have selected patients who may have any neurological deficit (sensory, motor, balance disorder); in the same time we have excluded the patients who had other explanations for a possible increase of the value of plasma D-dimers: patients with acute or chronic inflammation, other chronic disease, atrial fibrillation (acute or permanent), acute trauma, antiplatelet or anticoagulant treatments. Were excluded, also, the patients at which has been demonstrated a hemorrhagic stroke as the cause of the neurological deficit. At the chosen patients was performed CT scan of the brain, to corroborate clinical symptoms and laboratory data with the imaging. The upper limit for D-dimer value was set at 0.5 mg / mL FEU.

RESULTS

We have had a lot of 18 patients, all with neurological deficit, 10 men (one under 50 years) and 8 women (two under 50 years), aged between 42 and 83 years. Of these, nine men and seven women had elevated D-dimers; 4 men's and 4 women's CT images showed pathognomonic images for acute neurological injury. The correlations found in this group of patients were as follows:

- at 4 women (50%) and 3 men (30%) were present, at the same time, increased D-dimers and CT positive image,
- at 2 women (25%) and 5 men (50%) were present, at the same time, increased D-dimers and CT negative image,
- at one woman (12.5%) and 1 male (10%) were present at the same time, normal levels of D-dimer and CT negative image.

The concordance between elevated D-dimer values and positive CT image for ischemic stroke are expected and represented the idea of this test. Initial

results suggest a direct correlation between presence of thrombus, neurological deficit and D-dimer values increase. Lack of concordance, present at some patients, can be of CT image "false negative" or D dimers in the normal value and can have several explanations:

- the presence of ischemic lesions, large enough to be shown radiologically;
- ischemic lesion, that has not yet produced typical radiological image (E.D. early presentation);
- very small thrombus, which is not yet lysate (no D-dimers production), thrombus that obstructs completely a cerebral vessel (produces neurological deficit);
- lack of platelet lysis (E.D. early presentation);
- thrombus whose pieces do not appear in circulation (circulation locked in a given territory).

UTILITY IN THE E.D.

- determining the plasma D-dimer will not be mandatory for those cases presented with classic clinical picture; presence and extent of motor or sensory deficit, are usually obvious and CT or MRI remains the gold standard for those patients;
- the utility of D-dimer value levels will be higher when other causes of growth (common / probable, except stroke) can be excluded;
- the value of plasma D-dimer will be a useful tool for the evaluation of the patient (grades of severity), will be useful for patients unable to cooperate with the doctor (deficit of cognition, coma), or in cases where CT skull can not be undertaken;
- remains, also, to be investigated the place of D-dimers in assessing the patient prognosis, (a possible predictive role), and the possibility to be integrated in a more complex stroke score (combination score ABCD2 with Wells score or others).

CONCLUSIONS

The plasma value of D-dimers could represent an important tool, part of more detailed protocol, that may improve the process of diagnosing ischemic stroke. Their final importance should be presented after a more complex analysis, on a greater number of patients, including the correlations with age, sex, type of stroke, extension of deficits, time of onset, etc. A detailed protocol should be developed on a much larger number of patients, examining a wide range of parameters and investigating the correlations that result to allow to extract a set of evidence-based conclusions.

BIBLIOGRAPHY

1. D-dimers increase in acute ischemic stroke patients with the large artery occlusion, but do not depend on the time of artery recanalization. Skoloudík D1, Bar M, Sanák D, Bardon P, Roubec M, Langová K, Herzig R, Kanovský P., Semin Vasc Med. 2005 Nov;5(4):379-86., J Thromb Thrombolysis. 2010 May;29(4):477-82. doi: 10.1007/s11239-009-0372-9.
2. D-dimer testing in ischemic stroke and cerebral sinus and venous thrombosis. Squizzato A1, Ageno W. Semin Vasc Med. 2005 Nov;5(4):379-86.
3. Plasma D-Dimer Levels Are Associated with Stroke Subtypes and Infarction Volume in Patients with Acute Ischemic Stroke. Wen-Jie Zi, Jie Shuai, Published: January 20, 2014, <http://dx.doi.org/10.1371/journal.pone.0086465>
4. Plasma Measurement of D-Dimer Levels for the Early Diagnosis of Ischemic Stroke Subtypes, Walter Ageno, MD; Sergio Finazzi, MD; Luigi Steidl, MD; Maria Grazia Biotti, MD; Valentina Mera, MD; GianVico Melzi d'Eril, MD; Achille Venco, MD, [+] Author Affiliations, *Arch Intern Med.* 2002;162(22):2589-2593. doi:10.1001/archinte.162.22.2589