

# Thrombophilia

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The coagulation system maintains blood in a fluid state at every moment and, therefore, it is unceasingly active throughout life. However, at the moment a lesion of the vascular system occurs, the coagulation system immediately turns 180° and transforms blood into a perfectly localized solid body, which we call clot. This process, by means of which a clot is formed, is known as hemostasis, which is one of the components of the coagulation system<sup>1</sup>.

The workup of a patient with a coagulation system abnormality is really very simple. All the patient's alterations are classified into two general types: either the patient suffers a hemorrhage or has a thrombosis. There is nothing else. Thus, every pathological state in the human being that predisposes to hemorrhage is known as hemophilia. Conversely, every pathological state that predisposes to thrombosis is called thrombophilia. Hemophilia and thrombophilia can be hereditary or acquired, temporary or permanent, and primary or secondary. The "primary" denotation refers to a state where the alteration is precisely within the coagulation system, such as hemophilia A or deficiency of any of the natural anticoagulant proteins. Secondary disorders refer to any morbid state that reflects on the coagulation system and alters its function, such as pregnancy and antiphospholipid antibody syndrome (APLAS).

Throughout the entire history of humanity, we have been terrified of hemorrhage, and large part of medicine endeavors has been precisely finding out how to control or prevent it. Even in this day and age, the human being holds a deep respect for blood loss (which sometimes verges on terror). Unfortunately, doctors themselves quite often do not escape this

vision. This is one of the fundamental reasons why, rather frequently, we exaggerate blood losses, which drives us to misuse blood and its derivatives, or to make absurd or unnecessary decisions, such as calling off surgeries or invasive diagnostic procedures. The questions then are: Why does the possibility or the presence of hemorrhage affect us that much? Why is it that doctors, even after having been trained as such, do not escape this connotation imprinted on human being's collective memory? Why, if thrombosis is much more deleterious on human beings, we still fail to give it its rightful place? I think the answer is very simple. Hemorrhage can be seen, and this impacts directly on the psyche, thus being coined and imprinted throughout the history of man; conversely, thrombosis is never evident to the eye. However, our biologic destiny played a dirty trick on us, since when all our medical knowledge and attitudes were focused on preventing hemorrhage and treating it at any cost, thrombosis appeared to us gradually, and in a lethal form. In effect, thrombosis is currently recognized as the leading direct cause of death in the world<sup>2</sup>. Perhaps the reader thinks this is an exaggeration, but let's consider some indisputable and well-documented points: In 2010, one out of every four human beings were reported to die directly due to thrombosis<sup>3</sup>, but, today, 5-6 out of every 10 possibly die due to this phenomenon; nearly 90% of myocardial infarctions (until today considered to be the leading cause of death, at least in the western world) occur as a consequence of the formation of an intracoronary thrombus, and nearly 66% of strokes have a thromboembolic origin<sup>4</sup>; pulmonary thromboembolism, which maybe in a few years will be recognized as the

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main cause of mortality worldwide, is another thromboembolic phenomenon that is regarded as the main preventable cause of in-hospital death; consumption coagulopathy (formerly called disseminated intravascular coagulation) is essentially a disseminated thrombosis; maybe between 25% and 35% of cancer patients ultimately die due to thrombosis<sup>5,6</sup>; atrial fibrillation, one of the most important threats to health systems, has in thromboembolism the most significant associated morbidity and mortality<sup>7</sup>; and thrombosis is increasingly observed as an unrecognized cause of maternal death<sup>8</sup>. That is, without ceasing to be still important, hemorrhage has gradually given up ground to the increasing weight of thrombosis.

On the other hand, the concept that thrombosis affects only old patients being taken care of in certain areas of medicine is currently obsolete. We know that, in contrast with what we thought a few years ago, thrombosis affects children and adults, pregnant women, cancer patients, surgical patients, and more commonly non-surgical patients<sup>4</sup>. Moreover, it occurs to patients in whom thrombosis was always assumed to be an impossible complication. In Mexico, an unfortunate example of this is precisely hematology, since for years it was taught that, in hematological patients, especially in those with malignant conditions, thrombosis never occurred. This apparent paradox (the thrombus as an essential disorder of a fluid organ that is called blood, which is not recognized or is denied by the very specialists in this organ) has its origin on the anachronistic concepts that are still being practiced in most hematologist-training schools in Mexico, which continue to consider the study of the coagulation system to be unnecessary and of a lesser importance than malignant conditions. Fortunately, Mexican younger hematologists are generating a very healthy change of attitude. As an example, this *Gaceta Médica de México* issue features an excellent work that describes an association that is sparsely addressed in the literature: Thrombosis in patients with primary myelofibrosis, a blood disorder with very high thrombogenic potential.

On the other hand, one of the most common thrombophilias identified in young patients with thrombosis is APLAS. This thrombophilia, secondary and acquired, is characterized for affecting both the arterial and venous system, just as well-described in another very good case in this *Gaceta* issue. APLAS is a blood disorder essentially defined by the appearance of arterial, venous or placental thrombosis in a pathophysiological scenario where autoantibodies directed

against blood natural antibodies are generated. That is, blood is the organ that is essentially affected. The prothrombotic pathophysiological mechanisms by means of which these autoantibodies clinically manifest themselves can be entirely opposed *in vitro*. This is true and significant when the APLAS essential diagnostic and prognostic test, lupus inhibitor, is evaluated. On this test, the activated partial thromboplastin time is prolonged as if there was an anticoagulant in the patient's blood, although, *in vivo*, it is the factor most strongly associated with the appearance of thrombosis. When the essential hemostasis tests are prolonged, the possibility to assess Vitamin K antagonists' anticoagulant effect with certainty becomes quite troublesome. This difficulty to know with certainty the real level of anticoagulation in a patient with APLAS is a very common and important cause of thrombotic events recurrence.

The fact that the problem of thrombosis in Mexico is comprehensively addressed in formal publications is encouraging. However, there is still much to do and learn. Until now, all the experience on thrombophilia-associated thrombosis remains sparse and uncertain. In fact, all the information we have stems from studies of clinical cases in series that are reduced for a country with more than 100 million inhabitants and with diverse genetic baggage. Although the information published so far is of value as a source of alert on the problem of thrombophilia, from the epidemiological and clinical point of view, it is of no significance. We need large, controlled, prospective trials that include patients from all regions of the country, in order for us to have a more comprehensive view on how primary thrombophilia mechanisms affect our population.

The economic, social, medical and familiar burden imposed by thrombosis is devastating. However, in Mexico, we have a poor vision of what this phenomenon represents. We have no specific strategies to fight it, anticoagulation or antithrombotic clinics are practically inexistent, research on the field is almost absent and, in general, physicians' knowledge about the coagulation system and its disorders is rather poor. Probably, all this has its origin on the fact that thrombosis is not known or continues to be regarded as a non-significant area. Maybe it's time to make a radical change in public policies, in medical thought and in the collective consciousness as well. In effect, public perception on the problem of thrombosis is extremely low and even worse for venous in comparison with arterial thrombosis. Nevertheless, thrombosis is there, at every moment, at any age, lurking in

the darkness of our conscience, feeding on our ignorance and killing more Mexicans than any other pathological phenomenon every day, as in the rest of the world.

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