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POST-THROMBOLYSIS AND ANTITHROMBOTIC-INDUCED BLEEDING IN THE ELDERLY: ARE WE MISSING SOMETHING?

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ABSTRACT

Stroke management in the elderly is a bit different from people of other age groups. Acute stroke treatment has a higher risk of bleeding due to thrombolysis or mechanical thrombectomy. During follow-up, elderly patients face an increased risk of bleeding from antithrombotics (especially anticoagulants) because they often experience metabolic derangements, coagulation abnormalities, cancer-related coagulopathies, multiple drug interactions, and changes in vessel architecture. The bleeding risk is higher with the Asian population. Therefore, we must ensure the elimination of any preventable cause of bleeding. One condition is autoimmune clotting factor deficiency (AiCFD). It is a bleeding problem that happens when the body's immune system makes antibodies that attack one specific coagulation factor. Most of these autoantibodies are polyclonal and are either neutralizing antibodies that inhibit the function of coagulation factors or non-neutralizing autoantibodies that promote clearance of the clotting factors. The autoantibodies are generated when the immune system is heavily influenced by inflammation, which can come from any infection, cancer, or certain treatments/replacement therapy. This event can happen at any point in a person's life and can be long-lasting. The prior knowledge about the existence of these antibodies in a specific part of the world (which may have regional/racial variation) is important because we can stop avoidable bleeding episodes in susceptible elderly individuals. In case of significant bleeding secondary to this abnormality, however, we can reverse the situation with the specific coagulation factor replacements or immunosuppressants to keep the antibodies under control.

KEYWORDS: Autoimmune clotting factor deficiency, Thrombolysis induced bleeding, Elderly population of Asia, Antithrombotic related bleeding.

Text:

We are aware that antithrombotic(s) are a common prescription in our elderly population. Many of them even need dual antiplatelets or anticoagulants. The risk of bleeding is also high in this population group, particularly among those of Asian origin. Many of them already have other existing risk factors for bleeding, and some of them have life-threatening bleeds. The individual response to antithrombotic(s) is variable and often unpredictable in elderly population. There is also no reliable method yet to monitor their activities.

Hence, we need to make sure that we rule out any precipitator of bleeding that is preventable. Autoimmune clotting factor deficiency (AiCFD) is one of them, which needs serious consideration. Acquired immune coagulation factor deficiency (AiCFD) is a bleeding disorder that happens when the body's immune system makes antibodies that attack one specific coagulation factor. Most of these autoantibodies are polyclonal and primarily neutralizing antibodies that inhibit the function of coagulation factors. There are, however, non-neutralizing autoantibodies that promote clearance of the clotting factors as well.[1] Thus, they may result in either a decrease in the concentration of the specific coagulation factor or make them nonfunctional or both.

Although AiCFD is prevalent in all age groups, like other autoimmune diseases the autoimmune coagulation abnormality is commoner in elderly population. The increased incidence of autoimmune disorders in older adults is thought to be related to age-related changes in the immune system, often referred to as immunosenescence. Key factors include immune dysregulation (aging is associated with alterations in T-cell function and other regulatory immune mechanisms that normally prevent autoimmunity). Increased incidence of chronic inflammation, autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus), and malignancies (e.g., solid tumours and hematological cancers) trigger autoimmune clotting factor deficiencies. Older adults have had greater cumulative exposure to various antigens, which can increase the likelihood of triggering an autoimmune response.

Researchers have reported AiCFD in nearly all coagulation factors, which can lead to fatal hemorrhage in a significant number of cases.[1]

Autoantibodies against coagulation factor VIII cause acquired hemophilia A, a well-known autoimmune disorder. Thus, some autoimmune disorders not only cause devastating systemic diseases but also precipitate symptomatic bleeding. This sometimes may be fatal by silently creating antibodies against one's own clotting factors.

Autoimmune acquired clotting factor deficiency is less common than "nonimmune" acquired clotting factor deficiency, which makes it harder to diagnose and treat. Due to less awareness of the disease, specific tests are not widely available, complicating definitive diagnosis and appropriate management. There are situations when there is an unexplained reason for increased bleeding, and it is finally concluded that patients have a “bleeding disorder of unknown cause.” In patients admitted to critical care units, we have noted a significant number of cases with unexplained excessive bleeding. After ruling out other possibilities, like disseminated intravascular coagulation, it is possible that some of them have autoimmune coagulation factor abnormalities.[2] Similarly, during neurosurgical or other surgical procedures, surgeons may face catastrophic bleeding if they cannot identify these disorders. AiCFD is a possible reason in some of these cases.

Treating them appropriately may turn an unfavourable outcome into a favourable one. In cases of significant bleeding, we need coagulation factor replacement therapy, fresh frozen plasma transfusions. Special agents that can bypass the faulty coagulation cascade (responsible for the bleeding), and immunosuppressants in special situations may be required to keep the antibodies under control.[3]

Without reliable epidemiological data, the condition should be presented as under-recognized rather than definitively “rare.” In elderly patients, the AiCFD is probably the second most common occurrence, following the use of pharmacologic agents like warfarin that decrease coagulation factors. These antibodies may develop secondary to any disease process that may affect dysregulation of the immune system. The body can generate autoantibodies against specific clotting factors when the immune system is heavily influenced by inflammation, which can come from any infection like COVID-19, cancer, or certain treatments/replacement therapy, and this event can happen at any point in a person's life.

The development of antibodies against clotting factors after an infection, or after exposure to replacement therapy for conditions like hemophilia, can take several weeks to months, potentially even longer. Some antibodies may be transiently present in our body while some

may resolve on their own. More research is required in this field, considering the variable nature of these antibodies' origin and behaviour.

As an initial evaluation, we need to make a basic laboratory correlation: the presence of coagulation inhibitors typically manifests as prolonged PT or aPTT, depending on the affected factor. Then, we can make assays widely available to detect antibodies against all coagulation markers, similar to the Bethesda assay, which quantifies the level of inhibition for factor VIII and also determines the extent of factor VIII required in the system to overcome the antibody for the same.

We need to introduce this concept to all clinicians, including family physicians, to enable them to apply the process and treat patients with greater confidence. We can also keep track of the prevalence of these antibodies in the community (they may have regional or racial variations). These will also help patient management in the near future.[4]

In acute stroke patients, when we need to administer thrombolysis, on many occasions we have to seriously consider bleeding risk. Considering susceptible individuals like those with chronic kidney disease, those having cancer, those with prior bleeding episodes, or those having relative contraindications, we have to balance between the risk and benefit of administering thrombolysis. In those cases, if we already have a record of increased bleeding possibilities owing to antibodies against coagulation parameters, we may avoid catastrophic bleeding. Similarly, in non-acute cases, we can choose antithrombotic numbers, adjust doses, and make dietary restrictions (for example, fish oil, Ginkgo biloba, ginger, and vitamin E can interfere with haemostasis).

We need to identify these patients by proper screening and treat them appropriately beforehand so that they are ready for the best possible treatment in emergency situation. Not all, but we should search for AiCFD in the following high-risk situations: 1. Patients, especially elderly, who are undergoing thrombolysis for acute stroke. 2. Patients undergoing major surgery (e.g., neurosurgery). 3. Patients with unexplained or disproportionate bleeding. We need to introduce special screening tests in the emergency room itself so that we can confidently isolate doubtful cases of these bleeding disorders, provide acute treatment, and ensure more effective and scientific management on follow up.

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