Hughes Syndrome: A Comprehensive Review

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Abstract
Hughes syndrome is also known as antiphospholipid antibody syndrome (APS). Hughes syndrome is an autoimmune condition that causes thickening of the circulating blood. There are many autoimmune diseases (AID), some are rare but others are very frequent. Autoimmune diseases (AID) are the outcome of abnormal activity of the immune system. Their meaning is auto self immune reaction, or in other words, the activity of one’s immune system against himself. This disease affects women nine times more than men, usually at reproductive age and it might be characterized by various clinical manifestations such as arthritis, skin eruption, renal damage, oral ulcers, photosensitivity, pericarditis and pleurisy, epilepsy and cytopenia. Treatment of thrombosis in Hughes syndrome is determined based on several factors: overall patient’s condition, type of thrombosis and the affected organs. Treatment with intravenous immunoglobulin (antibodies which neutralize or decrease production of aPL) is helpful in most of the cases.

Keywords: Hughes Syndrome; Antiphospholipid Anti Body; Hyper -Coagulability; Auto Immune Diseases

Abbreviations
APS: Anti Phospholipid Syndrome; aCL: Anti Cardiolipin Antibodies; aPL: Antiphospholipid Antibodies; TTP: Thrombotic Thrombocytopenic Purpura; LMWH: Low-Molecular Weight Heparin

Introduction
Definition of Hughes syndrome
Hughes syndrome is an autoimmune condition that causes thickening of the circulating blood. The immune system produces abnormal blood proteins called anti-phospholipid antibodies, which cause blood platelets to clump together.

What are Autoimmune Diseases?
Autoimmune diseases (AID) are the outcome of abnormal activity of the immune system. Their meaning is auto self immune reaction, or in other words, the activity of one’s immune system against himself. Due to various reasons including genetic factors and environmental factors as well (including infectious agents), the activity of the immune system is impaired, and part of it is directed against the self (Figure 1) [1].

Figure 1: Autoimmune disease are usually the result of a combination of hereditary factors and an environmental factor which translates the hereditary tendency into a disease. This factor can be any infectious agent, various medications, or stress.
Hughes Syndrome: A Comprehensive Review

There are many AID, some are rare but others are very frequent. This disease affects women nine times more than men, usually at reproductive age, and it might be characterized by various clinical manifestations such as arthritis, skin eruption, renal damage, oral ulcers, photosensitivity, pericarditis and pleurisy, epilepsy, and cytopenia.

Treatment of AID

The treatments of AID includes non-specific therapies for immune suppression, or in other words, to suppress the activity of some parts of the immune system which acts against the self. These drugs include corticosteroids, Cyclophosphamide, Methotrexate, intravenous immune globulins (IVIg), or antibodies to cytokines (which are secreted from cells of the immune system and aggravate disease), or alternatively drugs which supplement the deficiency caused by the disease (i.e. insulin in diabetes, thyroxin in hypothyroidism [2].

The Hughes Syndrome

Hughes syndrome is a relatively ‘young’ syndrome which has been defined only 20 years ago. This disease includes several of clinical manifestations. The syndrome is characterized on the one hand by clinical manifestations, but on the other hand by the presence of one or more auto antibodies to phospholipids, a component of human cells envelope. These auto antibodies help to diagnose Hughes syndrome, but they also have a pathogenic role in the syndrome, as they are not just a sign for Hughes syndrome but also probably cause it [3,4].

Historical Background

Identification of antiphospholipid antibodies and their association with the main clinical features of Hughes syndrome (vessel thrombosis and recurrent pregnancy loss) began in the early 1960s. At first, several patients having AID and also several healthy subjects had false positive test for syphilis (i.e. a positive blood test in the absence of syphilis). In 1952 coagulation inhibitor lupus anti-coagulant (LAC) was identified in both healthy subjects and patients, mainly in those having the false positive test for syphilis. LAC was absent from patients having syphilis. This name is a misnomer as most patients having LAC do not have lupus (SLE), and even though it causes anticoagulation in blood tests, its activity in human body is mostly opposite: it enhances coagulation and leads to thrombosis. In the early 1980s a test was developed for detection of anti-cardiolipin antibodies (aCL) in patients’ plasma. Similarly to LAC, the presence of aCL was also associated with thrombosis and recurrent pregnancy loss. In the next years, it became clear that these auto antibodies are similar but not identical. In 1990 it has been found that a cofactor is required for aCL to bind its target, cardiolipin. This factor was α2-glycoprotein-I (α2GPI), which is considered to be the actual auto antigen in Hughes syndrome, to which aCL really bind. Upon progression in research, it has become clear that antiphospholipid antibodies (aPL) can cause the various clinical manifestations of Hughes syndrome, and therefore they are a marker of the syndrome, but probably also cause it.

There is a false-positive test for syphilis. The test is only false positive. aPL bind the lipids found within the test kit and turn the test result into positive whilst there is no syphilis.

In parallel to developments of aPL, a close relationship was established between them and thrombosis. In 1963, it has been surprisingly reported that patients having LAC, which seemed in laboratory tests as a coagulation inhibitor, had thrombosis-intra-vascular blood clotting, and do not have bleeding diathesis. In 1954, the first patient having LAC and seven recurrent abortions has been reported. In 1983 the clinical manifestations of thrombosis and recurrent pregnancy loss were connected with aPL into a syndrome. Through the years, the definition of Hughes syndrome has expanded and nowadays many other auto antibodies and clinical manifestations of Hughes syndrome are known [5].

Hughes Syndrome - A Prevalent Disorder

The prevalence of aPL in the general population is around 2 - 5%. The prevalence of many auto antibodies increases with age and the same s truth for aPL as their prevalence in the elderly can be very high. Since Hughes syndrome is characterized by various clinical manifestations, it is difficult to estimate its real prevalence. However, Hughes syndrome is the cause of a significant number of thrombotic episodes and recurrent abortions.

In the general population, Hughes syndrome is the leading cause of acquired hypercoagulability (blood tendency to coagulate and form thrombosis). aPL are found in higher frequency in several manifestations attributed to blood hypercoagulability (sticky blood):

- The prevalence of aPL among patients having venous thrombosis (usually involving deep veins of the thigh and legs) is between 5 - 30%. Finding of aPL possess a risk for first event of venous thrombosis, recurrent events and death.
- The presence of aPL is a risk factor for myocardial infarction (heart attack).
- Stroke (either permanent cerebro vascular accident, or transient = transient ischemic attack) is the most frequent feature of arterial thrombosis in Hughes syndrome. aPL are found in 2 - 46% of patients less than 50 years of age having stroke. Approximately, one in every five strokes in patients under 40 is due to APS. Most studies also report high prevalence of aPL in older stroke patients [7].

The association between aPL and abortions is stronger in late pregnancy loss, but also exists in abortions before 10th week of gestation. Thrombotic events are very frequent in the general population as a leading cause of disability and mortality due to heart attacks and strokes. One should suspect an association between these events and Hughes syndrome especially in young patients having thrombosis, and in any women having recurrent pregnancy loss. Establishment of an association between the clinical manifestations and aPL is of highly importance since a proper treatment would be able to prevent in most cases recurrent events and even death [8].

The Genetic Background of Hughes Syndrome

Most AID has a genetic background, but this hereditary component is not as obvious as diseases which are transferred from a parent to his children in half of quarter of cases. On the other hand, it is relatively common that members of the same family would have different AID. For example, a mother might have hypothyroidism, her sister could have diabetes mellitus whilst her daughter having SLE. The conclusion of the genetic research in the field of primary Hughes syndrome is that this syndrome is significantly different in its genetic aspects from SLE (even though secondary SLE might occur during lupus). The genetic predisposition for Hughes syndrome is partially explained by markers called human leukocyte antigens (HLA). Some of these HLA molecules are related to aPL: HLA type DR4, DR7, DRw53, and DQB1*0302 are associated with the presence of aCL. The genetic background is also responsible for the structure of α2GPI; this structure in turn may induce the production of anti-α-2GPI auto antibodies. The replacement of one amino acid in the structure of α-2GPI could turn this molecule immunogenic and produce auto antibodies. The genetic findings in the research of Hughes syndrome can explain only partially the development of Hughes syndrome, and like in other AID, disease occurrence depends both on hereditary factors and environmental factors such as infectious agents [9].

Classification Criteria of Hughes Syndrome

A definite diagnosis of Hughes syndrome requires the presence of at least one clinical criterion and one laboratory criteria.

The Clinical Criteria

1. Thrombosis - at least one episode of thrombosis within artery, vein or small vessels within any organ or tissue.
2. One of the following during pregnancy:
   a. One or more pregnancy loss after 10th gestational week, when anatomical, genetic and hormonal reasons for abortions have been excluded.
   b. One or more episode of a pre-term delivery before 34th gestational week, due to severe pre-eclampsia or severe placental insufficiency.
   c. Three or more recurrent pregnancy loss before 10th gestational week, when anatomical, genetic and hormonal reasons for abortions have been excluded.

The Laboratory Criteria

1. Detection of IgG or IgM aCL in medium to high titers, in two different measurements at least six weeks apart.
2. Detection of LAC in two different measurements at least six weeks apart. The clinical manifestations of Hughes syndrome are numerous and various, and by far exceed those used for Hughes syndrome definition. Usually Hughes syndrome patients have more than one clinical Manifestation. However, in order to definitely diagnose Hughes syndrome, the above-mentioned criteria should be met. Patients having laboratory criteria for Hughes syndrome in the absence of clinical criteria, but yet have a clinical manifestation suggesting the presence of Hughes syndrome, have probable Hughes syndrome even though they are not included under Hughes syndrome definition. Similarly, Hughes syndrome is characterized by many aPL, and therefore patients having a clinical criteria for Hughes syndrome but without a laboratory criteria, but do have another autoantibody which is found in Hughes syndrome, also have probable Hughes syndrome even though the year not considered having definite Hughes syndrome [6].

Hughes Syndrome: A Comprehensive Review

Primary and Secondary Hughes Syndrome

Primary Hughes syndrome

Primary Hughes syndrome is found in patients without an associated disease, or without evidence of any agent that could have induced production of aPL. Many of the cases of idiopathic recurrent pregnancy loss in the past are now known to be part of Hughes syndrome upon detection of aPL.

Secondary Hughes syndrome

Secondary Hughes syndrome is found in patients with another disease or in those having another cause suspected as the one which induced aPL production. It does not mean that secondary Hughes syndrome differs from primary Hughes syndrome, as the clinical manifestations of Hughes syndrome in both cases can be identical [6].

Drugs, Symptoms and Treatment

Drugs

Certain drugs are used for the treatment of primary and secondary Hughes syndrome. These include as follows

- Oral contraceptives,
- Procainamide,
- Phenothiazines,
- Ethosuximide,
- Phenytoin,
- Quinine,
- Chlorothiazide,
- Hydralazine and
- Interferon-alpha.

Some of these drugs also induce

- Autoantibodies and
- Lupus-like disease [10].

Symptoms of Hughes Syndrome

Without treatment, Hughes syndrome can cause many symptoms and complications, including:

- Migraine headaches
- Mottled skin tone (livedo reticularis)
- Low blood platelet count (thrombocytopenia)
- Vein thrombosis
- Deep vein thrombosis (DVT)
- Arterial thrombosis
- Heart attack
- Stroke

Diagnosis of Hughes Syndrome

Tests used in the diagnosis of Hughes syndrome include:

- Medical history
- Physical examination
- Blood tests [12].

Treatment for Hughes Syndrome

There is no cure for Hughes syndrome. Treatment aims to ease symptoms and reduce the risk of complications. Options include:

- Medications to stop platelets from clumping together, such as low-dose aspirin.
- Medications to thin the blood, such as heparin.
- Cortisone drugs to control the inflammation associated with autoimmune diseases such as lupus.

Hughes Syndrome: A Comprehensive Review

- Drug therapy to control other health problems, such as hypertension (high blood pressure) or diabetes, that may increase the risk of complications including stroke or heart attack.
- Regular medical check-ups to monitor the medications and reduce the risk of side effects: for example, blood thinners may cause uncontrolled bleeding in some cases lifestyle changes such as quitting cigarettes, eating a healthy diet and exercising regularly.
- Ongoing medical treatment allows most people with Hughes syndrome to live long and healthy lives. However, you may need to take medications for long periods of time, perhaps for the rest of your life. Some people are troubled by complications, despite the best of care [13].

Other

Clinical manifestations

The clinical manifestations of Hughes syndrome are diverse and might include every organ in the human body (Figures 2, 3). Though the diagnosis of Hughes syndrome requires the presence of thrombosis or pregnancy morbidity, Hughes syndrome patients can have disorders in various body systems including every organ in the human body.

Figure 2: Clinical manifestations.
Figure 3: Hughes syndrome is a systemic disease which can affect every organ in the human body. Her major characteristics include: deep venous thrombosis, pulmonary emboli, myocardial infarction, stroke, live do reticularis, heart valve disease, recurrent abortions, skin ulcers, impaired blood supply the fingers, budd-chiari syndrome, and small vessel disease of the kidneys [14].

Hughes Syndrome and the Heart

Case Report: A 25 year old woman, usually healthy, suddenly felt chest pains. Since the pain did not resolve and was also accompanied by dyspnea and nausea - she admitted to the emergency room. Electrocardiogram examination revealed acute myocardial infarction (heart attack). Coronary angiography demonstrated obstruction of the left anterior descending artery. The obstruction was opened and an intra-
Hughes Syndrome: A Comprehensive Review

arterial stent was placed in order to reduce the risk of re-stenosis. She was later found to have high titers of aCL. Involvement of the heart in Hughes syndrome is associated with significant morbidity and mortality [15].

**Coronary artery disease**

This disease is found in many patients within the general population, and is the leading cause of death in the Western world due to myocardial infarction and other manifestations of the diseases coronary arteries which supply the heart. Hughes syndrome is associated with enhanced atherosclerosis. Atherosclerosis is characterized by deposition of lipids and cells of the immune system within arterial walls, and once it occurs within the coronary arteries it results in coronary artery stenosis.

**Angina pectoris**

During physical exertion occurs due to the inability of these narrowed arteries to provide sufficient amount of blood to the heart. Angina pectoris is manifested by mid-chest pain, and it resolves following rest or use of vasodilating drugs.

**Unstable angina pectoris**

Some of the patients have unstable angina pectoris which is characterized by pain appearing also during rest, and it is caused due to almost complete obstruction of a coronary artery or alternatively due to complete arterial obstruction which spontaneously resolved. Atherosclerosis might lead to thrombosis within the coronary arteries and blockade of blood flow within these arteries. The part of myocardial muscle which is supplied by the obstructed artery is undergoing necrosis, and this is actually

**Myocardial infarction (heart attack)**

It is usually manifested by chest pain that can radiate to other regions such as the arms, upper abdomen, and lower jaw. The pain is not relieved during rest, and might be accompanied with vomiting, perspiration and extreme weakness. Even though in some cases myocardial infarction can be mild and not lead to significant impairment of heart function, in other cases it can cause heart failure, dangerous arrhythmias and even sudden death. Myocardial infarction occurs in about 7% of Hughes syndrome patients, even though in different studies the prevalence of myocardial infarction was up to 30%. An objective evidence for coronary artery disease is found in 10% of Hughes syndrome patients who also have SLE. Apart from aPLs, several risk factors contribute to cardiovascular diseases in these patients (smoking, hypertension, hypercholesterolemia, diabetes mellitus), and therefore treatment of these risk factors is of a great importance in these patients. The presence of aPL signifies an increased risk for cardiovascular diseases, and thus it is not surprising that even in the general population without Hughes syndrome the presence of these auto antibodies was associated with a two-fold increased risk for myocardial infarction. In addition, aPL could be detected in 5-15% of patients having acute myocardial infarction [16].

**Respiratory Manifestations in Hughes Syndrome**

**Case Report:** A 40 year old man complained of pain and swelling of his right leg following an inter-continental flight. The pain spontaneously dissolved but recurred following a long-distance flight two years later. In the latter episode the pain was associated with shortness of breath. The patient was diagnosed as having a deep venous thrombosis of his thigh vein with pulmonary emboli, and treated with heparin. His blood test was positive for the presence of lupus anticoagulant. This autoantibody causes the hyper-coagulability which developed during the immobilization characterizing long-distant flights. The hyper coagulability led to venous thrombosis and subsequently to embol to the lungs [17].

**Pulmonary emboli**

Vessels thrombosis is one of the most common features of Hughes syndrome (Figures 4). Deep venous thrombosis (usually of the lower extremities) is the most common manifestation of thrombosis in Hughes syndrome. About third of the cases of deep venous thrombosis are associated with pulmonary emboli. Depending on its size, the embolus occludes one of the arteries in the lungs and interferes with gas exchange so that blood cannot be adequately oxygenated. The clinical manifestations of pulmonary emboli include chest pain, dyspnea, tachypnea, decreased blood oxygen saturation, cardiac dysfunction and even sudden death.
Pulmonary thrombosis

This is a rare manifestation of Hughes syndrome. However, as thrombosis can occur in every vessel in the human body, it can also occur in one of the major arteries of the lung. The thrombosis can also affect multiple small lung vessels.

Pulmonary hypertension

The blood pressure within lung arteries is significantly lower than blood pressure in the arteries supplying the rest of the body. Increase in arterial lung blood pressure indicates a disease, can lead to lung dysfunction and even to death. Pulmonary hypertension occurs in 2% - 3% of Hughes syndrome patients and is usually the result of recurrent pulmonary emboli.

Pulmonary hemorrhage

The lung nodes form the site in which gas exchange occurs between air and blood. Oxygen transfer into the blood and carbon dioxide transfer out of the blood occur when lung nodes are filled with air. Hemorrhage into lung nodes occurs occasionally in Hughes syndrome and in lupus, and is characterized by cough, fever, dyspnea and hemoptysis [18].

Recurrent Abortions, Pregnancy and Fetal Demise in Hughes Syndrome

Some of the infertility cases remain unexplained. It has been suggested that part of these unexplained cases are caused by aPL. However, aPL classically causes recurrent abortions and obstetric complications.

Case Report: A 35 year old woman had a history of five recurrent abortions, and she was found to have medium levels of anti-cardiolipin autoantibody. Treatment was begun with aspirin and low-molecular-weight heparin during her 6th pregnancy, and she gave birth to healthy child at 36 weeks of gestation [19].

Recurrent abortions

2% - 5% of women of reproductive age experience two or more abortions. Pregnancy loss during any stage of pregnancy may be the first and occasionally the only sign of Hughes syndrome. The characteristics of pregnancy losses in the various research articles dealing with Hughes syndrome differ, but as a whole aPL are associated both with early and late pregnancy loss. Most cases of abortions in women with and without Hughes syndrome occur at early stages of pregnancy. Since Hughes syndrome is also associated with late pregnancy loss, the rate of women with this type of abortions is relatively high. The presence of aPL is important for the diagnosis, but it also has a prognostic significance. The subsequent abortion rate in woman positive for aPL is as high as 90%, and significantly higher than women without aPL. This is the natural course of Hughes syndrome, but once patients receive prophylactic therapy their chance of giving birth to a healthy child significantly increases.

Pregnancy morbidity

Pregnancy is a physiological state, but it might be accompanied by some pathological complications. Some of these complications occur more often among Hughes syndrome patients. Pre-eclampsia is a complication occurring during pregnancy characterized by appearance of hypertension and protein urea (excretion of protein in the urine) during pregnancy. This phenomenon poses a risk for the
Hughes Syndrome: A Comprehensive Review

pregnant women and can be evolved into eclampsia with seizures, and it can also adversely affect the fetus. Pre-eclampsia is not a rare manifestation during pregnancy, but its frequency is higher among Hughes syndrome patients. In Hughes syndrome patients, pre-eclampsia usually occurs at an earlier stage of pregnancy and is more severe than in women without Hughes syndrome. Pre-term delivery is also frequently found among Hughes syndrome patients (approximately in 20% of the cases) and is usually the result of child birth induced by the physician due to pre-eclampsia and fetal growth retardation. This latter complication of Hughes syndrome is usually the result of placental dysfunction in Hughes syndrome, and it has been reported in 10%-30% of the pregnancies of women having Hughes syndrome. aPL can also cause thrombosis during pregnancy in 5% of women which negatively affects maternal health and pregnancy [20].

Cutaneous Manifestations

- Livedo reticularis
- Livedo vasculitis
- Necrotizing purpura
- Leg ulcers
- Atrophic blanche
- Distal cutaneous ischemia
- Widespread cutaneous necrosis
- Peripheral gangrene
- Thrombophlebitis
- Hemorrhage [21].

Skin Manifestations

Skin involvement in Hughes syndrome occurs due to different pathogenic mechanisms, but is usually the result of small vessel thrombosis, thus affecting small arterioles and venules supplying blood to the dermis and sub-cutaneous fat. Hughes syndrome has various dermatological manifestations. The most frequent skin manifestation of Hughes syndrome is livedo reticularis which is characterized by a net-like reddish-blue discolorization. Occasionally a similar phenomenon can be found in healthy subjects following cold exposure. Livedo reticularis can be found in about quarter of APS patients, more in women than in men, and in higher frequency in patients having secondary Hughes syndrome associated with lupus. Other common skin findings in Hughes syndrome are skin ulcers which occur in 55 of the patients. They usually manifest as small and painful lesions with a diameter of 0.5 - 3 cm with a round- or star-shaped borders, circled by brown-purple border and intra-dermal hemorrhage. Skin ulcers usually present over the ankles and feet. As the ulcers heal they usually leave white scars surrounded by black pigment. Superficial skin necrosis can be found in 2% of Hughes syndrome patients, and evolves as skin eruption followed by black necrosis in the buttocks, limbs or face. This manifestation can also be found in other hyper-coagulability states, and sometimes Hughes syndrome patients having superficial skin necrosis have also another hyper-coagulability disorder which also contributes to thrombosis. Some of these patients have other autoimmune, malignant or infectious diseases [22].

Multiple sub-ungual hemorrhages can be a manifestation of various diseases, including for example endocarditis. They have been reported in 1% of Hughes syndrome patients, and are the result of thrombosis of the sub-ungual vessels, or from emboli sent from the heart. Another dramatic manifestation of Hughes syndrome is digital necrosis that occurs in 3% of the patients with Hughes syndrome, even though a higher rate have been also reported, up to 19% of the patients. The risk factors for this manifestation of Hughes syndrome are smoking, hypertension, and oral contraceptive use. Treatment of these risk factors can prevent other clinical manifestations of Hughes syndrome.

Superficial vessel thrombosis can occur in 12% of Hughes syndrome patients, and it involves usually lower limb vessel thrombosis manifested by pain and local tenderness. Once thrombosis is persistent and affects the torso, it might be due to occult cancer states accompanied by aPL. Occasionally Hughes syndrome patients have skin lesions similar to those found in patients with inflammation of skin vessels (vasculitis) [23].

Central Nervous System and Hughes Syndrome

The most frequent central nervous manifestation of Hughes syndrome is stroke - thrombosis or disruption with blood supply to the brain with subsequent brain tissue damage since no oxygen can be supplied. Stroke can be the result of intra cerebral thrombosis, thrombosis in the large vessels supplying the brain (the carotid arteries in the neck or the vertebral arteries in the spinal column), or alternatively due to emboli of thrombosis in the aorta or the heart. Stroke can lead to permanent vascular occlusion and destruction of the affected brain tissue (CVA cerebro-vascular accident) and then most affected patients would have some degree of disability. However, the blood clot can spontaneously dissolve in some cases and then the manifestations would be only transient (TIA- transient ischemic attack). The outcome of stroke depends on the size of vessel which was blocked and on its location within the brain. The most frequent possible clinical manifestations of stroke include paresis or plegia (usually of the hand and leg of the same side), unilateral face plegia, difficulties in speech or understanding of words, loss of consciousness and even death. Among patients who had stroke, the presence of aPL is associated with a 2 - 7 times increased risk for stroke compared with patients without aPL. Whereas stroke is not a rare manifestation among elderly subjects, it usually occurs in Hughes syndrome among young adults, several decades prior to the general population. Another form of brain thrombosis is venous sinus thrombosis. The venous sinuses are venous channels responsible for blood outflow from the brain. Thrombosis of the venous sinuses can be severe and lead to brain infarcts. Sneddon's syndrome is defined as recurrent strokes and livedo reticularis. The prevalence of aPL in Sneddon's syndrome differs between several researches, but as a general rule they can be detected in about half of these patients; higher rates, up to 85% have also been reported [24].

Dementia

This phenomenon is characterized by cognitive dysfunction, a decline in brain functions with memory disturbances up to inability to perform daily activities. Several diseases can lead to dementia; probably the most famous among them is Alzheimer's disease. The pathogenesis of dementia in Hughes syndrome is recurrent brain infarcts resulting from minor events of thrombosis that over time manifest as dementia. It is also possible that aPL directly gravely affect brain tissue without the need to induce thrombosis. Continuation of thrombosis without appropriate treatment can cause recurrent and progressive brain damage with disruption of superior brain functions such as memory and cognition.

Epilepsy

The etiology of epilepsy is not clear in many cases. It is generally accepted that epilepsy manifested by seizures is due to some kind of brain injury. Some of lupus patients have epilepsy, and aPL was found associated with this manifestation. A possible pathogenic mechanism of epilepsy in Hughes syndrome is thrombosis followed by brain infarct and scar formation. The scarred brain tissue have a dysfunction with respect to signal transmission (such as that affecting muscular contraction) and thus can cause uncontrolled muscle action and practically to seizures. aPL might also have a direct effect of the brain that can promote epilepsy, such as decreasing the activity of neurotransmitter GABA. Anticardiolipin autoantibody which is part of the spectrum of aPL was also found in increased frequency among epilepsy patients without previously known Hughes syndrome. Depression, mood changes and psychosis might also be associated with aPL, and there are few reports about increased frequency of these auto antibodies in those conditions.

Migraine

This is one of the most common manifestations of central nervous system involvement in lupus. Migraine can be classified into several types, but the most frequent presentation is a unilateral headache with vomiting and flashing lights. Migraine is also very frequent among Hughes syndrome patients, but aPL is not found in increased frequency in patients having migraine. Some cases of migraine evolve into complicated migraine in which paralysis can occur. aPL was detected in about a third of the patients with complicated migraine who had transient paralysis or brain infarct. Albeit there are not enough data, it is logical to conclude that even if aPL does not cause migraine, they can contribute to migraine complications.
Hughes Syndrome: A Comprehensive Review

Myelitis

This inflammatory process of the spinal cord is occasionally due to an autoimmune process. Few Hughes syndrome patients had transverse myelitis, which can be detected in about 1% of lupus patients. Once aPL are associated with transverse myelitis, their mechanism of action is probably thrombosis of the small vessels which supply the spinal cord, leading to infarct in a small part of the spinal cord, exactly in the same mechanism of action in which they cause brain infarcts. The clinical manifestations depend on the level of spinal cord affected, and can include paralysis below the level of injury, and urinary incontinence. Some of these cases can be successfully treated with anticoagulation (as a part of other therapies) [25].

Hematological Manifestations of Hughes Syndrome

Thrombocytopenia

Blood platelets have a crucial role in blood coagulation. Formation of blood clots is an essential process in order to stop bleed in. Nonetheless, the very same process leads also to vascular occlusion and thrombosis. The platelets initiates’ blood coagulation, and their deficiency can cause hemorrhage into the skin and mucosa, and rarely into the brain. Hughes syndrome patients have thrombocytopenia in 20%-40% of the cases, but usually in its mild form with a platelet count above 50,000 per milliliter (normal range: 150,000 - 450,000). Severe thrombocytopenia is found in the minority of patients, about 5%-10% of the cases. Severe bleeding accompanies the low platelet counts only rarely, and in these few cases an aggressive treatment should be undertaken. The prevalence of thrombocytopenia among Hughes syndrome patients is similar to that of lupus patients, and occasionally can be the first manifestation of Hughes syndrome [26].

Anemia

This term stands for decreased red blood cell volume accompanied by low hemoglobin levels, and can be encountered in various pathological states, including Hughes syndrome. The pathogenic mechanism of anemia may be autoimmune by auto antibodies directed to auto antigens on red blood cells, leading to their destruction which usually takes place in the spleen. In some of the cases of autoimmune hemolytic anemia, aPL can be detected, usually anti-cardiolipin antibodies. Some of lupus patients with anemia have also aPL, and these auto antibodies probably are involved in red blood cells destruction in lupus and Hughes syndrome. The minority of patients have both thrombocytopenia and anemia (Evan’s syndrome), which can be detected in about 5% of lupus patients and 10% of the patients with primary Hughes syndrome. Other cases characterized by anemia might be life threatening due to anemia caused by cell breakage in thrombosed small vessels. These severe conditions are characterized by multiple small vessel thrombosis. Thrombotic thrombocytopenic purpura (TTP) consists of thrombocytopenia, brain injury, and anemia with red blood cells with distorted shape, whereas hemolytic curemic syndrome (HUS) which affects usually children is associated with kidney rather than brain injury. TTP occurs in the minority of patients with lupus and with primary Hughes syndrome, and there is a possible association between aPL and this manifestation. It is not proved but is likely that these auto antibodies contribute to the pathogenesis of TTP in lupus and primary Hughes syndrome. aPL have been in a significant proportion of HUS patients as well. A similar syndrome is HELLP (heamolysis, elevated liver enzymes, low-platelet count) which includes these manifestations and usually affects women during pregnancy. It is unclear whether aPL are associated with HELLP, but in study they have been detected in 70% of women with HELLP [27].

Leukopenia

This term implicates low levels of white blood cells. Leukopenia is much more frequent in lupus and secondary Hughes syndrome than in primary Hughes syndrome patients. Anti-cardiolipin autoantibody of the IgM type might be involved in the pathogenesis of leukopenia in these patients.

Renal Injury in Hughes Syndrome

The kidneys are a target affected in many systemic diseases such as diabetes mellitus, hypertension, and also in SLE. As there is a procoagulant state in Hughes syndrome, renal artery thrombosis can also occur in Hughes syndrome, emboli blocking the renal artery, or alternatively severe arterial stenosis. Disruption of renal blood flow of any reason leads to hypertension, and occasionally to severe and
Hughes Syndrome: A Comprehensive Review

life-threatening hypertension. Restoration of renal artery blood flow by catheterization of the affected artery can improve renal function and blood pressure control as well. In some cases the first and sole manifestation of Hughes syndrome involves the kidneys, and in several cases of uncontrolled hypertension, anti-phospholipid antibodies and renal artery stenosis have been found. Renal vein thrombosis can also be part of Hughes syndrome clinical manifestations, and the tendency to this thrombosis occurs mainly in the presence of nephrotic syndrome (excretion of large amount of protein in the urine). Even though, most of these cases have been reported among SLE patients, those patients having lupus anti-coagulant have increased risk for renal vein thrombosis. Some of these vessels thrombosis can lead to renal infarction, death of some part of the kidney tissue with the subsequent impairment of renal function and induction of secondary hypertension. Emboli from the heart can also cause renal infarction. Thrombosis might also occur within the small vessels of the kidneys, including arterioles and venules and even the glomular vessels through which the serum is infiltrated. Unfortunately, in severe cases when renal transplantation is indicated following chronic renal failure, the presence of anti-phospholipid antibodies is associated with increased chance of transplant rejection and thrombosis in the transplanted kidney.

Abdominal Organs Affected in Hughes Syndrome

The spleen includes many cells of the immune system named lymphocytes, whose primary role is to fight infectious agents. Splenic infarction has been described in Hughes syndrome patients, as well as shrinkage of the spleen following small but persistent thrombotic events leading eventually to dysfunction of the spleen. The pancreas has a central role in secretion of hormones into the bloodstream such as insulin, and it also have an important role in food digestion due to secretion of enzymes which digest fat. Pancreatitis (inflammation of the pancreas) has been described only few times in Hughes syndrome patients. The clinical manifestations of pancreatitis are central or left-sided abdominal pain. However, intestinal manifestations of Hughes syndrome are by far more frequent. Thrombosis of the intestinal arteries can result in intestinal necrosis manifested by sudden severe abdominal pain with abdominal distension.

An earlier pathology is abdominal angina resulting from narrowing and incomplete occlusion of the intestinal arteries. The clinical manifestations in the latter case include post-prandial abdominal pain, as meals induce increase in intestinal blood flow, which is limited in the narrowed vessels. Therefore, the pain which results from decrease in intestinal blood flow develops. The liver has many important functions in the human body including proteins and fat production, and neutralization of various toxins. The liver can be affected in Hughes syndrome in various forms, although these manifestations in general are not frequent among Hughes syndrome patients. Budd-chiari syndrome results from interference of hepatic venous drainage. Liver venous thrombosis can be accompanied by thrombosis of larger veins such as the inferior vena cava which drains the blood to the heart. Budd-chiari syndrome can be acute or chronic, lead to death due hepatic failure, or alternatively can completely resolve. Disruption of blood flow is possible also within the liver, and similar to many other organs, liver infarction has also been described. aPL have been found in many patients having liver cirrhosis (a chronic disease manifested by dysfunction of the liver), portal vein hypertension, and among patients having hepatitis C virus. In these cases, the presence of auto antibodies was not associated with the frequent clinical manifestation of Hughes syndrome, as these patients usually did not develop thrombosis and infarctions [28].

Hearing Impairment in Hughes Syndrome

Hearing loss can be caused due to impairment of blood supply to the cochlear nerve, and aP might affect thrombosis in these small vessels. Indeed, these auto antibodies have been detected in some of the patients having sudden hearing loss, in a varying frequency from very low to even about quarter of the cases. the most frequent autoantibody was aCL. Sudden hearing loss also occurs in increased frequency in other autoimmune diseases such as lupus or Sjogren's syndrome, but even in these diseases it is associated with the presence of aP [29].

Hughes Syndrome and the Eyes

Eyes involvement in Hughes syndrome is relatively frequent, and can be found in most patients. Usually both eyes are involved, due to injury to the central nervous system. However, one eye involvement also occurs in Hughes syndrome, and the underlying mechanism

in the latter case is decreased blood supply to eye or anti-inflammatory reaction. Eye manifestations can be found in 88% of Hughes syndrome patients, but it is less frequent in patients taking anti-coagulants. The specific manifestations of Hughes syndrome involving the eyes include anterior chamber injury including sclerosis, conjunctivitis aneurisms, keratitis, and damage to the pupil. The posterior chamber of the eye can also be involved in injury to the retina, the part of the eye responsible for transmitting vision to the brain. Damage to the retina reflects inflammation or obstruction of blood flow in retinal vessels. Retinal detachment which may evolve can end up in blindness. Another pattern of visual injury is the result of injury to the cranial nerves which supply eyeball muscles, or injury to the optic nerve itself. The symptoms presented by patients having eye manifestations of Hughes syndrome are diverse and can include double vision, ocular pain, headache and visual fields impairment, transient visual loss in one or both eyes. Some of these symptoms were associated with the presence of aCL [30].

The Endocrine System Involvement in Hughes Syndrome

The endocrine system is composed of several glands whose role is secretion of various hormones having crucial roles in maintenance of normal function of the human body. Several cases of dysfunction of these glands have been described in Hughes syndrome. These include decreased function of the pituitary gland (hypo pituitarism), hyperparathyroidism (increased secretion of the parathyroid hormone which affects the calcium balance), and hyper- or hypothyroidism. In addition, in the minority of diabetes mellitus patients who have insulin deficiency or insulin resistance, aPL have been detected, and in some of these cases an association was found between auto antibodies presence and the vascular complications of the disease.

Nonetheless, the adrenal is the endocrine organ most commonly affected in Hughes syndrome. The adrenal produces male steroids, corticosteroids, and Aldosterone which affect salt balance in the kidneys. It is usually affected in Hughes syndrome by impairment of blood supply. Occasionally adrenal injury forms part of the beginning of catastrophic Hughes syndrome [31].

Figure 10: Two different imaging studies demonstrating adrenal involvement in Hughes syndrome.

Bones and Joints in Hughes Syndrome

Bones, muscles and joints are usually not affected in patients having Hughes syndrome. However, as Hughes syndrome is frequently secondary to other autoimmune diseases, including lupus, these diseases themselves can have manifestations affecting the joints, such as arthritis. Whereas primary Hughes syndrome is not characterized by arthritis, arthralgia (without inflammation manifested as swelling, redness and joint dysfunction) are relatively common in Hughes syndrome. In addition, bone marrow necrosis has also been reported in few patients having Hughes syndrome. This manifestation of Hughes syndrome results from hyper coagulability and leads to severe impairment in blood cells production, manifested by anemia, thrombocytopenia and leukopenia. The main injury to the bones in Hughes

Hughes Syndrome: A Comprehensive Review

syndrome is a vascular necrosis, which results from blood supply impairment. The most characteristic sites of injury are femoral heads, other parts of the femoral bone, tibia, humerus, wrist and foot bones. The minorities of patients are affected, about less than 5%, but this injury is much more prevalent in lupus patients treated with steroids that also have secondary Hughes syndrome. Occasionally a vascular necrosis is detected only in imaging studies of the bones and is not accompanied with symptoms, whilst in other cases it can cause bone or joint pain in the affected region [32].

Treatment of Hughes Syndrome

Treatment of Thrombosis

Thrombosis in Hughes syndrome is determined based on several factors: overall patient's condition, type of thrombosis, and the affected organs. For example, thrombosis in a coronary artery which supplies blood to the heart can be treated early by catheterization of the occluded vessel, turning it into patent and supporting it with intra-arterial stent. Such treatment can prevent myocardial infarction and necrosis, save patients' life or avoid functional disability. Once for one reason or another this catheterization is not an option, treatment for a patient with myocardial infarction includes aspirin and heparin. Aspirin is an anti-inflammatory and analgesic drug which also has a preventive and therapeutic effect on blood coagulation. Aspirin decreases the ability of blood platelets to form blood clots, and thus the blood turns into less 'sticky' (aspirin does not 'dilute' the blood, as generally said by mistake). During the first few hours following coronary artery occlusion, aspirin administration by chewing may decrease blood clot area and also assist in the spontaneous disappearance of the thrombus. Heparin is an anti-coagulant which acts in another mechanism of action: it directly inhibits one of the coagulation factors that promote formation of blood clots. Heparin is given intravenously, but a similar drug called low-molecular weight heparin (LMWH) can be given in subcutaneous injections. Treatment of deep venous thrombosis (such as in thrombosis of the thigh veins) includes heparin or LMWH administered for at least five days. Treatment goal is prevention of blood clot increase, and enhancement of spontaneous disappearance of the blood clot. This is also the treatment in cases of deep venous thrombosis complicated by pulmonary emboli. In the minority of cases, once patient's condition is severe due to large pulmonary emboli or recurrent emboli, other therapeutic interventions are possible such as insertion of an 'umbrella' into the inferior vena cava that should catch the blood clots before they reach the lung, infusion of thrombolytic agent (a drug that actively dissolves the blood clot), and even surgery in order to remove big blood clots in the pulmonary arteries. In most cases, heparin is sufficient, but since it should be given only intravenously, an alternative anti-coagulant drug can be taken orally: Warfarin (Coumadin). The anti-coagulation never starts with Coumadin therapy, as several days are required in order to express the anti-coagulant activity of Coumadin, and therefore heparin treatment continues in parallel with the beginning of Coumadin therapy until there is a proof in the laboratory tests that Coumadin already expresses its anti-coagulation properties. Coumadin dosage differs from patient to another, but its anti-coagulant effect depends on a value named INR (international normalized ratio) which can be measured by blood test. A patient who is not treated with anti-coagulants has an INR level of approximately 1.0. The optimal INR for Hughes syndrome patients having venous thrombosis is around 2.5, and actually between 2.0 and 3.0. The presence of this INR level signifies a tendency of blood coagulation two or three times less than without treatment with Coumadin. In this stage, heparin therapy can be stopped. Coumadin treatment can result in adverse effects, as while it antagonizes coagulation, it also possess the patient at risk for bleeding, including life-threatening bleeding. Coumadin therapy necessitates careful monitoring of INR levels in that range, as higher INR levels are not more effective, while they are associated with increase in bleeding cases.

The swelling of the thigh and intra-venous thrombus usually disappear following few days of treatment. However, aPL increase the chances to form further blood clots. Therefore, Coumadin therapy should be continued for longer periods in order to prevent or significantly decrease the chances of recurrent thrombosis. In general, long-term Coumadin treatment significantly decreases chances of recurrent thrombosis, and the longer the treatment is, the smaller the recurrence rate of thrombosis after the end of Coumadin treatment. The physician should determine the duration of Coumadin treatment and therapy policy in general. After a first event of deep venous thrombosis it is possible to treat the patient with Coumadin for six months combined with monitoring of other risk factors for thrombosis such as smoking, hypercholesterolemia, obesity, and lack of physical activity. Thrombosis recurrence after the end of weeks to months Coumadin therapy, or alternatively recurrence of thrombosis while under treatment, would necessitate administration of Coumadin for years, maybe for good. In case of Coumadin failure in prevention of recurrent thrombosis, it is possible to increase Coumadin dosage in order to achieve a higher INR level, or to add other anticoagulant which affects platelets. The treatment in this complexes case would be determined by the physician and would be adjusted specifically in every case [33].

Treatment of Recurrent Pregnancy Loss

The chance of pregnancy loss among women having recurrent pregnancy loss as a manifestation of Hughes syndrome is as high as 85%-90%. The approach to treatment of recurrent abortions in Hughes syndrome included therapy aimed at suppression of aPL production, and treatment with anti-coagulants against the pro-coagulant effect of aPL that induce blood clots in the placenta. Steroids can suppress autoantibody production, and they are a leading therapy in many autoimmune diseases. However, steroids are generally not used for treatment of pregnancy complications in Hughes syndrome, as their efficacy is lower than the alternatives, and they also carry associated adverse effects. Treatment with intravenous immunoglobulin (antibodies which neutralize or decrease production of aPL) is helpful in some of the cases, but it is not more effective than anti-coagulation. There is a small sub-group of women in which intravenous immunoglobulin therapy has additive effect to that of anti-coagulants. The regular treatment of recurrent pregnancy loss in Hughes syndrome is with aspirin and heparin, usually in a combination of both. Both drugs antagonize coagulation, and aspirin also have a beneficial effect on placental blood flow. There is controversy regarding the need to add heparin to aspirin therapy. Most researchers support an additive role of heparin combined with low-dose aspirin, as the combination of both drugs beginning with pregnancy confirmation leads to a high rate of live birth rates: around 80%. Infertility, in vitro fertilization need and embryo transfer failure has been suggested as possible manifestations of Hughes syndrome, but they are usually not included in the syndrome and do not mandate anti-coagulation therapy. Women having Hughes syndrome which undergoes in vitro fertilization might be in increased risk of thrombosis due to the high levels of estrogens they are exposed to during ovulation induction. In addition, women treated with anti-coagulant due to previous thrombosis are at risk for bleeding following egg retrieval. In these cases it is recommended to treat the patients during in vitro fertilization cycles with heparin rather than Coumadin, to stop heparin therapy few hours before egg retrieval, and restores heparin administration several hours after the procedure [34].

Hughes Syndrome in Children

The prevalence of aPL among healthy children is 5% - 10%. Among children with lupus, LAC can be detected in 22%, and aCL in 45%, similar to the prevalence of these auto antibodies in adult lupus patients. The clinical picture of Hughes syndrome in children includes mainly deep vein thrombosis, like thrombosis of deep veins of the lower extremities. aPL were also found in most children who had strokes of unknown etiology. Other clinical manifestations include seizures, budd-chiari syndrome which is characterized by disruption of drainage of venous blood from the liver (Hughes syndrome is the main cause of this syndrome in children), and thrombosis in various arteries and veins [35]. Mostly, children having Hughes syndrome are older than 12 years of age. The expression of Hughes syndrome in children, which is an acquired hyper-coagulability state, is related also to inherited hyper coagulability states. A special form of Hughes syndrome in children is a rare manifestation following varicella infection (chickenpox): auto antibodies directed to the natural anti-coagulant ‘protein S’ occur together with aPL, resulting in thrombosis [36].
Hughes Syndrome: A Comprehensive Review

Research

APS ACTION (the Anti-Phospholipid Syndrome Alliance for Clinical Trials and International Networking), is the first-ever international research network that has been created to design and conduct large-scale, multicenter clinical trials in persistently antiphospholipid antibody (aPL) positive patients [37]. The network consists of a multidisciplinary group of physicians and investigators from around the world who are interested in antiphospholipid syndrome (APS) research. The primary mission of APS ACTION is to prevent, treat, and cure antiphospholipid antibody (aPL) associated clinical manifestations through high quality, multicenter, and multidisciplinary clinical research.

Conclusion

Hughes syndrome is an important cause of hyper coagulability, predisposing to both venous and arterial thromboses and recurrent fetal death due to placental insufficiency. Hughes syndrome is a pro thrombotic, autoimmune disorder with heterogeneous clinical presentations. Despite the name, the antibodies associated with Hughes syndrome are predominantly directed against phospholipid-binding plasma proteins, such as β2-GPI and prothrombin, rather than phospholipids themselves. When Hughes syndrome is suspected, confirmatory laboratory tests include coagulation assays for lupus anticoagulant and ELISA detection of anticardiolipin antibodies, the former being more specific and the latter more sensitive. Interpretation of the pathological significance of anticardiolipin antibodies can be problematic since these antibodies are found in various non-thrombotic contexts (certain infections, drug therapy) and even in apparently healthy people. However, this is based on retrospective non-controlled evidence, and high-intensity anticoagulation carries an important risk of hemorrhage. Until definitive data from prospective trials are available, the intensity of anticoagulation will need to be individualized for patients with Hughes syndrome, the risks of hemorrhagic complications being weighed against the benefits of preventing re-thrombosis. Prospective randomized trials have shown the efficacy of aspirin and heparin treatment in the prevention of pregnancy loss in Hughes syndrome. Evidence for the use of other treatment strategies, such as immunotherapy, remains unpersuasive. Despite advances in diagnosis, correctly identifying patients at risk is a challenge. Long-term anticoagulation remains the mainstay of treatment of thrombotic Hughes syndrome. Innovative therapeutic approaches, such as immune modulation, complement inhibition, and targeting inflammation, are under study. Further mechanistic and clinical studies are needed to develop improved therapies for this potentially devastating illness.

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Conflict of Interest

Declared None.

Bibliography


Hughes Syndrome: A Comprehensive Review


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