Antiphospholipid syndrome in Africa: a review

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Abstract

Objective: To review the extent of research findings on Antiphospholipid Syndrome (APS) across the African continent.
Data source: Published original researches and reviews were searched in English related to APS in Africa.
Study design: Only studies conducted on Africans living in Africa were reviewed. Related review articles done with main focus on the African experience of APS, its manifestations and laboratory findings were also included. Articles summarizing international consensus and background of APS were also included.
Data extraction: A PubMed search using the keywords "Antiphospholipid Syndrome" was done. This yielded 9167 results. The results were filtered in two arms. First, studies of APS in Africa were extracted. These were 63 out of which 27 relevant studies on Africans living in Africa were selected. Second, studies on international consensus and background of APS were filtered. These were 51 out of which 13 with relevant contents were selected. This brings the total selected articles to 40.
Data Synthesis: Data added and summarized.
Conclusion: The Antiphospholipid Syndrome (Hughes' syndrome, APS) was first described in 1983 and has since been reported all over Africa. Over the years, several studies have been undertaken in Africa focused on different aspects of APS and new findings keep emerging revealing atypical manifestations and pointing to a likely under-recognition of the magnitude of APS in the causation of thromboembolic diseases and pregnancy morbidities in Africa. Recent findings repeatedly refute the old belief that many systemic autoimmune and rheumatic diseases are rare in Africa. APS, in the "primary" form and in the setting of Systemic Lupus Erythematosus (SLE) and other autoimmune diseases may not be uncommon in Africa. It is recognized that much work still needs to be done in understanding the true burden and the probable peculiarities of APS among Africans.

Key words: Antiphospholipid syndrome, Africa, Abortion, Thrombosis, Rheumatology, Systemic lupus erythematosus

Introduction

Antiphospholipid Syndrome (APS) is a well studied composite of clinical and immunological disorders with protean manifestations and sometimes bizarre complications. Since its first description in 1983[1], several cases have been reported from all over Africa[2-7], and like across the rest of the world, the core features have been repeatedly affirmed. These features include arterial and venous thromboses, recurrent spontaneous miscarriages, thrombocytopenia and the presence of high titres of antiphospholipid antibodies (aPLs) in the blood of the subject.

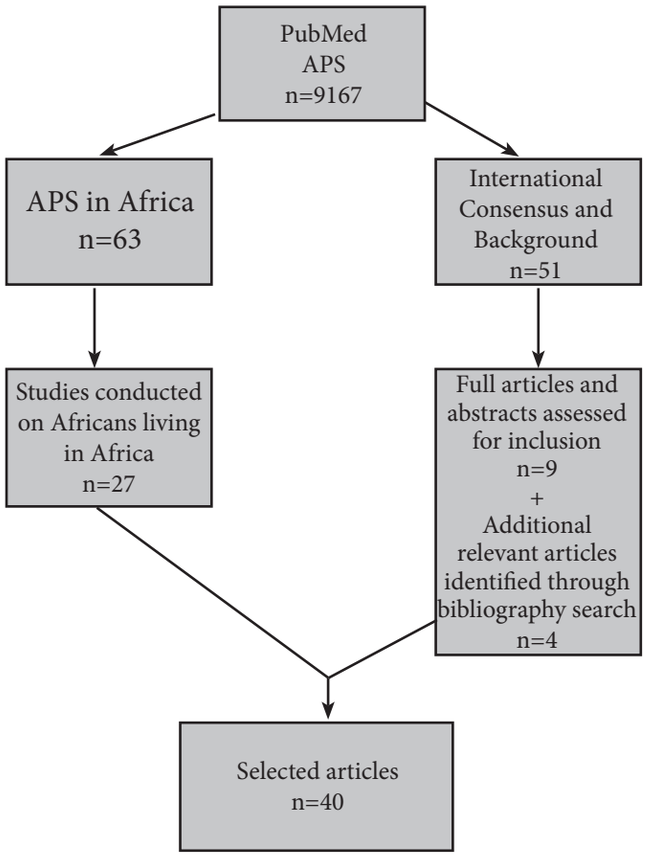
Not many systemic syndromes have been better researched than APS and despite the apparently incorrect erstwhile belief of the rarity of many systemic autoimmune and rheumatic disorders in Africa, extensive documentation of APS has been done. APS has emerged as the most important treatable cause of recurrent miscarriage accounting for approximately 15% of cases of recurrent miscarriage. It is also an important cause of early onset pre-eclampsia and of Intra-Uterine Growth Restriction (IUGR)[8, 9]. Fourteen percent of patients with recurrent venous thromboembolic disease have aPLs[10]. The frequencies of antiphospholipid antibodies (aPL) in general-population patients with pregnancy morbidity, deep vein thrombosis, myocardial infarction, and stroke are 6%, 10%, 11%, and 14% respectively[11].

The World Forum on Rheumatic and Musculoskeletal Diseases, in its white

paper on the global challenges and opportunities in the practice of rheumatology, states that developing countries in Africa are worst hit with the spate of inadequacy of rheumatologists and limited understanding of the burden of rheumatic and musculoskeletal diseases among public health professionals and policy makers means that these diseases are often not considered a public health priority[12].

Methodology

A PubMed search using the keywords "Antiphospholipid Syndrome" was done. This yielded 9167 results. The results were filtered in two arms. First, studies of APS in Africa were extracted. These were 63, out of which 27 relevant studies on Africans living in Africa were selected. Second, articles on international consensus and background of APS were filtered. These were 51 out of which 13 with relevant contents were selected. This brings the total selected articles to 40.



The antiphospholipid antibodies

The antiphospholipid antibodies include antibodies to cardiolipin (aCL) and beta-2-glycoprotein-1 anti-beta(2) GPI, as well as the Lupus Anticoagulant (LAC). These antibodies, which used to be thought as mere laboratory nuisance, have been linked to APS and the presence of at least one of them is required for the diagnosis of APS[13]. In Benin City, Nigeria, LAC has been shown to be present in 8% of multiparous women and in 15.4% of pregnant women with pre-eclampsia[14, 15]. In Dakar, Senegal, a two year retrospective study showed 11 patients of a dermatology clinic fulfilling the diagnosis of APS[16]. These studies and many more to be discussed have shown that, although there is endless room for researching the epidemiology of APS in various regions of Africa, there are ample pointers to the abundance of it around the continent.

It is known that the presence of aPLs in the serum does not translate to invariable manifestation of symptom. Certain infections are associated with a higher likelihood of developing aPLs. In a study of 137 individuals chronically exposed to malaria and living in Africa or Asia, high prevalence of serum co-factor-independent IgG and IgM aCL were detected and IgG aCL levels were found to be related to the clinical/endemic status of the subjects[17]. In another study of 272 South African patients with various infectious diseases, raised levels of aCL, anti-beta(2) GPI, and anti-prothrombin (aPT) antibodies were found in all patient groups studied[18]. aCL was found in 7%, anti-beta (2) GPI in 6%, and aPT in 43% of 100 HIV patients, in 29%, 89%, and 21% of 112 patients with leprosy, in 8%, 8%, and 28% of 25 patients with syphilis, in 12%, 8%, and 28% of 25 patients with malaria, and in 20%, 30%, and 30% of 10 HCV patients studied, respectively[18]. The prevalence of LAC was, however, found to be low in a group of 104 HIV-infected Nigerian patients: 2.9% and 1.9% HIV-infected patients and controls, respectively ($p = 0.973$)[19].

On account of the knowledge that aPLs may be found in a small proportion of normal individuals and in patients with infective conditions without any clinical symptom of APS, the main indications to test for aPLs have been established. These include systemic lupus erythematosus and other selected autoimmune conditions, spontaneous venous and arterial thrombosis, recurrent fetal losses, and autoimmune thrombocytopenia, among others[20].

Classification of antiphospholipid syndrome

Long before the eventual clarification of the existence of APS in patients without SLE, all patients fitting the description of APS were thought to be manifesting further features of SLE. However, it is now known that a sufficiently homogenous group exists with the features of APS without the other clinical or immunological manifestations of SLE or any other autoimmune disorder. It was first recognized by Asherson in 1985 while at the Hammersmith Hospital when he identified 25 patients conforming to this new class of disease[21]. A publication of these cases was not achieved until 1988 when it was better accepted that "primary" APS indeed existed.

The class of patients with a primary systemic autoimmune disease, mostly SLE, who also fulfill the diagnosis of APS, is now referred to as SLE with APS or as appropriate with the primary disease. This category

was the earliest to be known but has now been overtaken by the cases with isolated APS in number[21].

In 2006, Gould *et al*[22] published a cross-sectional study of 100 South African SLE patients in whom the clinical characteristics, including features of APS, disease activity, and damage were observeved. Positive aCL, anti-beta (2) GPI, aPT and LA were found in 53, 84, 20 and 2 patients, respectively. This study also showed that IgA anti-beta (2) GPI was associated with both a history of thrombosis alone ($p<0.05$) and a history of any clinical feature, thrombosis, and/or spontaneous abortion of the APS ($p<0.05$). IgA aCL was also associated with a history of any clinical APS event ($p<0.05$). Cooper *et al*[23], in another study conducted in Capetown, South Africa, found a good positive predictive value (70%) between aCL and overall SLE disease activity. A strong association was also observed between aCL and renal involvement (80%). Out of the 57 SLE patients studied by Cooper *et al*[23], 9 fulfilled both the clinical and serological criteria for APS and a further 18 patients fulfilled the serological criteria.

Pregnancy complications

Pregnancy related morbidities are among the most common presentations of APS in Africa. Various case reports and clinical studies across Africa have shown the high frequency of pregnancy wastage, pre-eclampsia and premature deliveries in patients with APS. In the first ever case series from Nigeria, Adelowo *et al*[4] reported pregnancy loss as the most common presentation. From the 11 cases of APS in dermatology in Dakar, 9 patients had obstetric incidents which include repeated spontaneous abortions, intra-uterine foetal deaths and precocious deliveries[16].

Recurrent miscarriage, the loss of three or more consecutive pregnancies, affects 1% of couples trying to conceive. This is significantly higher than that expected by chance alone and suggests that some couples have a persistent underlying abnormality to account for their pregnancy losses[9]. A study of the prevalence of antiphospholipid antibodies, factor V G1691A (Leiden) and prothrombin G20210A mutations in early and late recurrent pregnancy loss conducted in Tunisia showed aPL frequencies of 45% and 9% among patients and controls, respectively ($P < 0.001$)[24]. Stemming from the study conducted in Abidjan, Cote d'Ivoire, Kouassi *et al*[25] argued that systematic aPL screening should be done in African women with obstetrical complications, and could further improve the management of patients at risk. They studied patients with recurrent foetal loss, pre-eclampsia, retroplacental haematoma and chronic foetal suffering and found a frequency of 11.8% of aPL positivity as compared to 0% in controls. Similarly, Thiam *et al*[26] found prevalence rates of 14.6 and 21.1% of LAC and aCL, respectively, among Senegalese patients with history of repeated abortion. In another study from Kenya, Mwenda *et al*[27] showed that 33.8% of Kenyan women visiting Kenyatta National Hospital, Nairobi, for recurrent pregnancy losses had APS. Although, it seems worthwhile, routine screening of patients with unexplained recurrent abortions for APS may still be unachievable in most regions of Africa because of the cost implication and sometimes inavailability of facilities for the tests.

Thromboembolism

Venous or arterial thrombosis, which forms another key clinical criterion in the diagnosis of APS, has not seen much research attention from the African continent. Thromboembolism is believed to be the basis for several manifestations of APS affecting varying calibers of vessels. In 2004, Maaroufi *et al*[2] suggested that APS may play an important role in the pathogenesis of retinal vascular occlusion. They found a diagnosis of APS in 33% of patients with retinal vein and artery occlusions. Anakwue *et al*[3], in 2013, reported a case of toe gangrene in a 21 year old Nigerian girl. The prevalence of APS has not been studied in patients with DVT, stroke or Myocardial Infarction (MI) on the African continent. However, Abid *et al*[28], in a study of 21 patients with transmural MI with normal coronary vessels seen in the Hedi Chaker Hospital, Tunisia, were able to identify a subset of these patients with various coagulation disorders including APS.

Vascular occlusion is implicated in the pathology of various neuropsychiatric manifestations of APS and SLE, although studies have not been done in Africa to differentiate the population of patients with pure central nervous system thrombosis from those with inflammation. In a group of 69 SLE patients studied by Whitelaw *et al*[29] in South Africa, a correlation was found between aPL positivity and neuropsychiatric morbidities in SLE patients.

Also, several pulmonary manifestations of APS are known to be directly associated with thromboembolism. Pulmonary embolism and infarction, pulmonary hypertension, pulmonary arterial thrombosis, pulmonary microthrombosis, acute respiratory distress syndrome and postpartum syndrome have all been identified as part of the spectrum of possible thrombotic complications of APS[30]. Albeit, other non-thromboembolic pulmonary features of APS which include intralveolar haemorrhage and non thromboembolic pulmonary hypertension are well known[30].

Catastrophic antiphospholipid syndrome

The earliest and probably the most amount of research works on this very rare subset of APS were led by a

South African, Dr. Ronald A. Asherson, after whom Catastrophic Antiphospholipid Syndrome (CAPS) has been named. Many of Asherson's studies were conducted on African patients. CAPS is an accelerated form of APS which was first described in 1992 and has been shown to be dominated by widespread small vessel thrombosis[31]. Although catastrophic APS patients represent less than 1% of all patients with APS, they are usually in a life-threatening medical situation that requires high clinical awareness[32]. While it is fatal in approximately 50% of cases reported, thrombocytopenia is usually marked, and a Coombs positive microangiopathic-type anaemia may accompany the condition. Features of disseminated intravascular coagulation may be evident in some patients[33].

In a 2005 review of 250 patients, Asherson showed that triggering factors are identifiable in approximately 50% of patients and consist predominantly of infections, trauma (including minor surgical procedures such as biopsies), obstetric-related multiorgan failure and malignancy-associated CAPS[34]. The patients present mainly with multiorgan failure resulting from predominantly small vessel occlusions affecting mainly intra-abdominal organs such as bowel, liver, pancreas and adrenals[34].

The international consensus statement on classification criteria and treatment guidelines of 2003 states that the optimal management of catastrophic APS must have three clear aims: to treat any precipitating factors (prompt use of antibiotics if infection is suspected, amputation for any necrotic organ, high awareness in patients with APS who undergo an operation or an invasive procedure), to prevent and to treat the ongoing thrombotic events and to suppress the excessive cytokine 'storm'[32].

Unusual manifestations

From less-than-typical to extremely strange features are sometimes seen in the setting of APS. Many unusual manifestations of APS can be grounds for diagnostic confusion and a potential for worse outcome. A large variety of clinical manifestations have been less frequently described in patients with the APS, with prevalences lower than 5%. These include, among others, large peripheral or aortic artery occlusions, Sneddon's syndrome, chorea, transverse myelopathy, intracardiac thrombus, adult respiratory distress syndrome, renal thrombotic microangiopathy, Addison's syndrome, Budd-Chiari syndrome, nodular regenerative hyperplasia of the liver, avascular necrosis of the bone, cutaneous necrosis or subungual splinter hemorrhages[35]. Although, the largest proportion of APS are primary, secondary cases occurring on primary SLE, Sjogren's syndrome[36], rheumatoid arthritis[37], or systemic sclerosis[38] have been established. Hence, other features of the background connective tissue disease may colour the outlook of the APS. The case of a 57 year old woman was reported from South Africa in 2000 in whom a diagnosis of APS evolved into Waldenstrom's macroglobulinaemia over a 5 year follow up period[7]. In 2008, the case of a woman with primary APS presenting with partial HELLP syndrome, palmar lesions and recurrent DVTs was reported[39]. Variable combinations of usual and unusual manifestations of APS may appear in the same patient thereby presenting a potential diagnostic challenge. APS may also be a part of an evolving systemic disorder. As such, it may accompany or precede an undifferentiated connective tissue disease.

Possible peculiarities of APS in Africa

Since many infectious diseases that have been associated with aPL are more abundant in Africa, it may be an important research focus to compare the true prevalence of clinical APS and the overall prevalence of aPLs in Africa. The scarcity of studies comparing the features of APS in Africans and non-Africans limits the extent of possible distinctions that may be identified between the two groups. It is known that blacks with SLE are more likely to develop lupus nephritis and their renal disease is more likely to run an aggressive course. It is yet to be known if renal vascular thromboembolism, end stage renal disease, glomerular disease or hypertension occurs at higher frequencies in Africans with APS. Also, it is not known if there are uniquenesses to the calibers of affected vessels or preferences of the organ affectations in Africans. APS being a systemic autoimmune disorder of multifactorial cause may show striking differences along racial and continental lines.

Treatment

There has not been much work on the treatment and outcome of APS in Africa. For this reason, it is yet to be known if Africans with APS on standard treatments currently available fare different from non Africans. The only study so far in this line is a non-controlled prospective clinical trial conducted at Khartoum, Sudan, to investigate the efficacy of unfractionated heparin and low-dose aspirin as prophylaxis against pregnancy loss in pregnant Sudanese women with recurrent (≥ 3) miscarriages associated with APS[5]. From this study, 81% of the treated women progressed to have live term deliveries and there was no case of thromboembolic event or maternal death. This is comparable to what is known of similarly treated APS-associated recurrent miscarriages outside Africa. In a 2010 study by Adelowo *et al*[40], they reported that management in the Nigerian setting is variously with heparin, aspirin and warfarin, although other modalities are being used. They also suggested that management is best coordinated by a rheumatologist and an obstetrician.

Conclusion

APS may be in abundance across Africa and probably at a proportion more important than already realized. However, epidemiological data are lacking to assess the magnitude of the burden. The widespread reports of various presentations of the syndrome across Africa give credence to the notion that it may be far underdiagnosed. Hence, APS deserves better heights of clinical consciousness among physicians. Vascular thromboses are known to be the most common presentation of APS but no study has yet been done in Africa to look into the proportions of venous and arterial thromboembolism caused by APS. Also, pregnancy related complications are very important in APS and several cases of recurrent pregnancy wastages may benefit from being routinely checked for aPLs as the detection of this highly treatable condition may mean the turnaround in the clinical outlook for these patients.

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