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Case Report

Familial primary antiphospholipid syndrome: A report of co-occurrence in three Malaysian family members

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Abstract

Here we present a case report of three familial primary antiphospholipid syndrome (PAPS) patients from Malaysia. The three familial patients comprised two females and one male with a mean age of 26.3 years. The first diagnosis was made between 2005 and 2009, and all patients demonstrated deep vein thrombosis, high levels of IgM and IgG anticardiolipin antibodies, and received warfarin treatment international normalized ratio (INR) 2.0-3.0. The patients ceased to show clinical symptoms after treatment. Recently (August 2014), we investigated whether the levels of antiphospholipid antibodies remained elevated, and we found that seronegativity occurred in the patients. We suspect that prolonged anticoagulant treatment might be one of the causes of reduced levels of antiphospholipid antibodies in these familial PAPS patients.

Keywords: Primary antiphospholipid syndrome, deep vein thrombosis, antiphospholipid antibodies

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease that mainly manifests as venous or arterial thrombosis and/or pregnancy morbidity, all of which are associated with the presence of antibodies [lupus anticoagulant (LA), anticardiolipin (aCL) antibodies, or anti-β2-glycoprotein I (anti-β2GPI) antibodies] (1). According to the International consensus statement on preliminary classification criteria, patients can only be confirmed as having APS when at least one laboratory marker and one clinical feature are present (2).

Primary APS (PAPS) occurs in the absence or presence of other autoimmune diseases such as systemic lupus erythematosus. The prevalence of antiphospholipid antibody (aPL) in the general population ranges between 1% and 5%. However, only a minority of these individuals develop APS. Some estimates indicate that the incidence of APS is approximately 5 new cases per 100,000 individuals every year and the prevalence is approximately 40–50 cases per 100,000 individuals (3). Even though APS can affect people of all ages, it is usually observed in young to middle-aged (20–50 years) adults (4).

In this report, we present three PAPS patients originating from the same family. The patients were suspected to have APS since 2005 and were diagnosed with PAPS according to the Sapporo criteria (5) between 2005 and 2009 at Sarawak General Hospital, East Malaysia. However, in August 2014, laboratory results showed that none of the three patients have elevated levels of antiphospholipid antibodies based on the criteria by Miyakis et al. (2). In this case report, we present the family background, pedigree, clinical presentations, and a comparison of the levels of antiphospholipid antibodies before and after warfarin (international normalized ratio: 2.0–3.0) treatment.

Case Presentation

Patient A [sister of patient B and cousin of patient C (Figure 1)] is a 22-year-old married woman who initially presented her symptoms in 2005 with complaints of leg swelling, and she was diagnosed with deep vein thrombosis (DVT). Initial biochemical tests indicated that the levels of aCL antibodies were within the normal range (IgM: 7.6 units; IgG: 3.57 units) and produced negative results for antinuclear antibody (ANA) and rheumatoid factor. She received warfarin treatment.

The case of patient A was reviewed in 2009 when her sister (patient B), who was admitted for cranioplasty, developed proximal lower limb DVT. Subsequently, patient A was tested for and showed moderately elevated levels of aCL antibodies (IgM: 20.89 units; IgG: 11.64 units). In addition, she had a recurrent DVT in 2011 during her second pregnancy. Biochemical tests indicated the presence of aCL antibodies with moderately elevated levels of the IgM (15.56 units) and normal levels of the IgG (9.99 units) (Table 1). She was not affected by any other autoimmune diseases, thus supporting her PAPS diagnosis.

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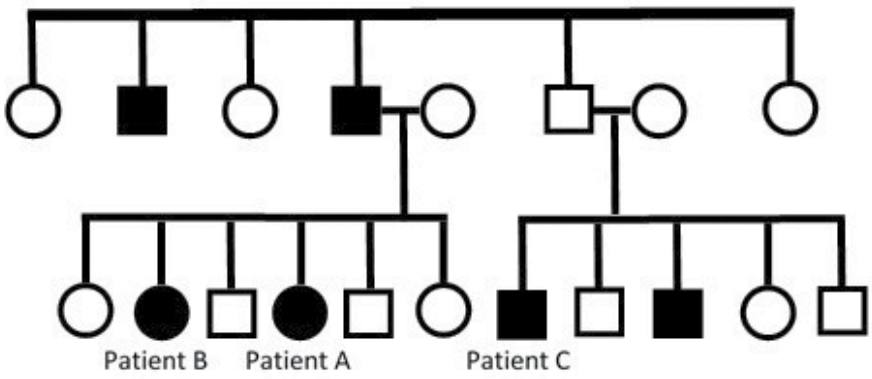

Figure 1. Family pedigree showing three family members (patient A, patient B, and patient C) diagnosed with primary antiphospholipid syndrome (PAPS), while three other family members have also shown signs of PAPS

Table 1. First diagnosis (2005-2009): Clinical and laboratory information of the three family members with PAPS

Criteria*	Patient A (22, F)	Patient B (29, F)	Patient C (28, M)
A. Clinical			
1. Thrombosis	+	+	+
2. Pregnancy morbidity	No information available	No information available	N/A
3. Other Autoimmune diseases	-	-	-
B. Laboratory			
1. Lupus anticoagulant	No information available	+	X
2. Anticardiolipin antibody	+	+	+
Diagnosis of PAPS	+	+	+

PAPS: primary antiphospholipid syndrome; F: female; M: male; N/A: not applicable
*Based on the Sapporo criteria (5)

Table 2. Updated laboratory information of the three family members

Features	Patient A	Patient B	Patient C	Reference range*
LA (APTT)	44.9 s	43.2 s	62.2 s	33.0–49.0
aCL	3.99 GPL/3.83 MPL	7.89 GPL/6.01MPL	13.12 GPL/2.32 MPL	>40 GPL / >40 MPL
Anti-β2GPI	0.3 nmol/L (IgM)	1.0 nmol/L (IgM)	0.0 nmol/L (IgM)	>99th percentile
	1.2 nmol/L (IgG)	2.7 nmol/L (IgG)	0.6 nmol/L (IgG)	

LA: lupus anticoagulant; APTT: activated partial thromboplastin time; aCL: anticardiolipin antibody; GPL: immunoglobulin G phospholipid antibody; MPL: immunoglobulin M phospholipid antibody; Anti-β2GPI: anti-beta-2-glycoprotein I; IgM: immunoglobulin M; IgG: immunoglobulin G
*According to the Sydney criteria (2).

Patient B is a 29-year-old married woman who first presented her symptoms in May 2006 at six-months postpartum. At the time of admission, she complained of headache, right–left confusion, and right-sided body weakness. A computed tomography (CT) scan showed a left middle cerebral artery territory infarction that was complicated by a hemorrhagic transformation and midline shift. She underwent decompressive craniectomy. During the postoperative period, she developed right leg DVT. Biochemical tests confirmed the presence of protein C at 61% (normal range: 50–130%), protein S at 37% (normal range: 30–124%), and antithrombin at 59% (normal range: 75–125%). Lupus anticoagulants (LA) were negative; the activated partial thromboplastin time (APTT) was 31.3 s, while factor V Leiden was normal. She was treated with warfarin and remained well until she was re-admitted to the hospital for cranioplasty in November 2009. During this admission, her warfarin treatment was discontinued for two days, and she developed a recurrent right lower limb proximal DVT. Biochemical tests confirmed normal levels of aCL antibodies (IgM: 9.48 units; IgG: 13.66 units) and positive LA with prolonged APTT (58 s) (Table 1). She did not have a history of any other autoimmune diseases; therefore, her PAPS diagnosis could be confirmed.

Patient C is a 28 year old who initially presented his symptoms when he was 20 years old in 2006 with painful swelling of the left leg for four days. Further investigation confirmed the presence of extensive left leg DVT involving the inferior vena cava. A CT scan revealed features of a pleural effusion in a right pulmonary artery embolism, while a lung biopsy confirmed the presence of a pulmonary infarction. Enzyme-linked immunosorbent assays confirmed the presence of high titer aCL antibodies (IgG) and was negative for LA (Table 1). ANA was weakly positive, but double-stranded DNA was negative. Since then, patient C was treated with warfarin. He showed no signs, symptoms, or criteria of other autoimmune diseases.

According to the latest (August 2014) diagnostic reports (Table 2) of these three confirmed PAPS patients, none had a significant level of any of the antibodies, indicating that all patients were negative for PAPS. Even though patient C's APTT was a bit high (62.2 s), it was possibly due to the long transportation time of blood samples from East Malaysia to Peninsular Malaysia.

Discussion

To the best of our knowledge, this is the first reported familial case of PAPS from Malaysia. Most published APS cases were from older age groups (mean age of 56.5 years) (6, 7); however, these Malaysian PAPS patients are younger (mean age of 26.3 years). All three patients showed high levels of aCL antibodies with DVT; further, two patients (patient A and C) suffered from peripheral edema and one (patient B) suffered from a postpartum cerebral infarction. According to the "International consensus statement on an update of the classification criteria for definite APS" (2), these symptoms are the core clinical and laboratory manifestations of PAPS.

On the basis of their latest diagnosis (August 2014), none of the patients showed significant level of autoantibodies. The reason might be that the chronic treatment of warfarin for an extended time (more than 8 years) reduced the level of phospholipid antibodies (8). Another possible reason is the prolonged effect of warfarin on the gene expression level of phospholipid-inducing antibodies.

We were unable to determine the genetic status of each patient due to the absence of individual DNA samples. The reason for the reduction of

autoantibodies still remains a mystery.

We identified a rare cluster of familial PAPS cases in Malaysia who turned out to be seronegative after a long warfarin treatment as described by Hughes and Khamashta (9). Due to the occurrence of PAPS within three family members, it is likely that hereditary (genetic) factors play an important role in triggering disease onset; however, there might be an effect of drugs or other factors on genetics as well that might have reduced the level of autoantibodies as shown by Wang et al. (10). Therefore, future genetic studies are warranted to identify other possible antibodies that might have an association with the pathogenesis of APS and the association of drugs used to treat PAPS on the genetic expression level of familial cases.

Ethics Committee Approval: Ethics Committee approval was received for this study from the National Medical Research Register, Ministry of Health (NMRR-11-1110-10749).

Informed Consent: Verbal informed consent was obtained from patient who participated in this study.

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