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Introduction

The antiphospholipid syndrome (APS) is an autoimmune disorder presenting with tissue injury in various organs attributed to large or small vessel thrombosis or, in some instances, possible nonthrombotic inflammatory mechanisms, associated with in vitro evidence of antibodies to certain proteins, or protein–phospholipid complexes [1]. Clinical manifestations range from no symptoms to imminently life-threatening catastrophic APS [2]. Primary APS has generally been defined as the presence of antiphospholipid antibodies (aPL) in patients with idiopathic thrombosis but no evidence of autoimmune disease or other inciting factor, such as infection, malignancy, hemodialysis, or drug-induced aPL [3]. The term secondary APS has been used when patients with a wide spectrum of autoimmune disorders and thrombosis are also found to have aPL [4].

According to the 2006 International Consensus Statement on APS classification criteria, identification of APS requires the presence of vascular thrombosis and/or pregnancy morbidity, along with at least one of the following aPL antibodies: lupus anticoagulant (LA) test, anticardiolipin IgG and IgM antibodies, and β2-glycoprotein I (β2-GPI) IgG and IgM antibodies [5]. Deep venous thrombosis is the most frequent clinical manifestation of APS. Venous thrombosis, with much less frequency, in almost every organ of the body has been described, causing related clinical manifestations [6]. The hypercoagulable state in the APS may lead to adrenal vein thrombosis and subsequently to hemorrhagic necrosis of the adrenal gland [7]. There is no available data regarding adrenal gland abnormalities in our local antiphospholipid syndrome population.

Magnetic resonance imaging (MRI) provides a highly sensitive method of detecting hemorrhage, and offers exquisite detail of the adrenal glands. Acute hemorrhage (days 1–6) will be rich in deoxyhemoglobin, which is isointense relative to muscle on gradient-echo T1-weighted

Tab. 1 Clinical manifestations of the study group patients and controls

	Patients *N* = 20 (%)	Controls *N* = 20 (%)	P
Age (year)	32.45 ± 9.93	30.3 ± 4.2	0.378
Age of onset (year)	28.70 ± 10.31	24.3 ± 4.61	0.089
Duration (month)	46.65 ± 58.71	72 ± 44.04	0.131
Adrenal affection	7 (35)	0	0.004*
DVT	11 (55)	4 (20)	0.02*
Recurrent pregnancy loss	9 (45)	1 (5)	0.004*
Pulmonary embolism	2 (10)	0	0.244
Stroke	2 (10)	0	0.244
Cerebral venous sinus thrombosis	3 (15)	0	0.115
Levido reticularis	1 (5)	0	0.5
Thrombocytopenia	3 (15)	0	0.115
Budd chiari	2 (10)	0	0.244
Digital gangrene	3 (15)	0	0.115
Raynaud's phenomenon	7 (35)	3 (15)	0.104
Lupus nephritis	10 (10)	17 (85)	0.018*
Arthritis	8 (40)	4 (20)	0.109
Malar rash	8 (40)	13 (65)	0.074
Discoid rash	1 (5)	3 (15)	0.249
Serositis	11(55)	15 (75)	0.112
Convulsions	0	3 (15)	0.115
Psychosis	0	2 (10)	0.244
Transverse myelitis	1 (5)	0	0.5
Heart valve disease	2 (10)	8 (40)	0.028*

DVT deep venous thrombosis, *N* number
* $p < 0.05$

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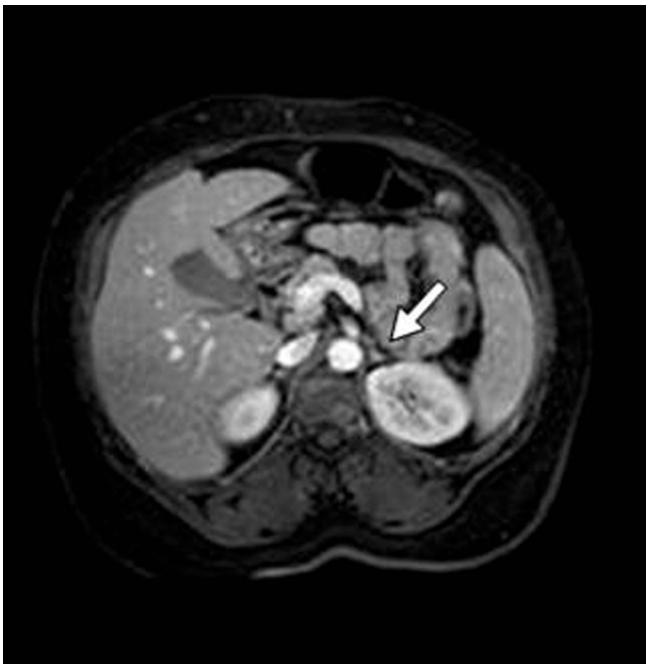

Fig. 1 ◀ Dynamic MRI of normal suprarenal glands, delayed phase showing homogeneous enhancement of the left adrenal gland with clear surrounding fat planes (control group)

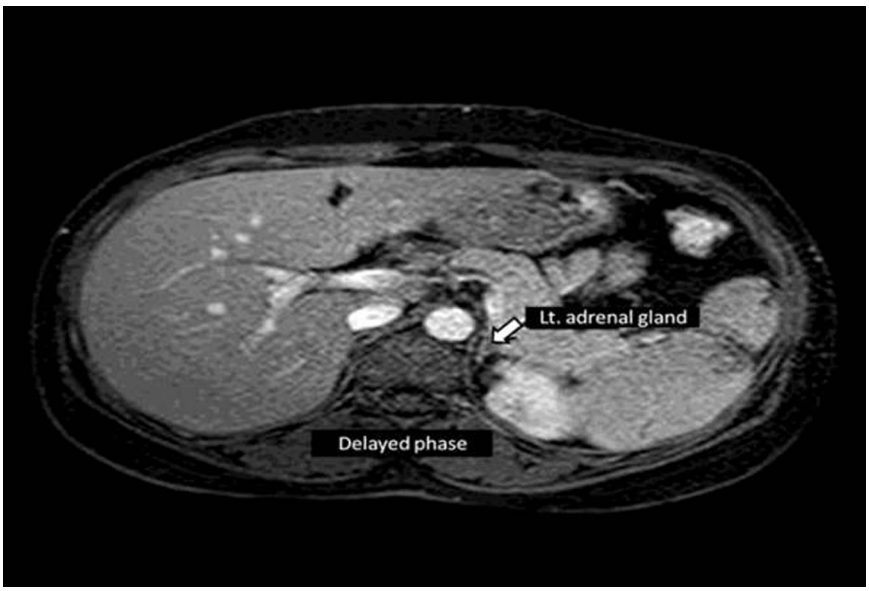

Fig. 2 ▲ Enlarged left adrenal gland measuring 1.3 cm in its maximal width with evidence of subacute hemorrhage. No enhancement in the arterial phase (not shown) with persistent capsular enhancement in the delayed phase, and stranding of the surrounding fat planes

MRI and has low signal intensity on T2-weighted MRI. Methemoglobin, present in the subacute phase (1–5 weeks after onset), causes high signal intensity on T1-weighted images and variable signal intensity on T2-weighted images. Chronic hemorrhage (after 5 weeks) shows the gradual formation of hemosiderin as areas of low signal intensity on both T1- and T2-weighted. MRI T2-weighted images show edematous change related to the inflammatory swelling of the adrenal gland [8].

The purpose of this study was to detect and study the MRI findings of adrenal gland involvement in a group of Egyptian patients with APS.

Materials and methods

The current study is a cross-sectional study comprising 20 patients with primary or secondary APS, recruited from the Rheumatology and Rehabilitation Department, Kasr Alaini Hospital, Cairo University, from January 2012 until December 2012, and classified according to 2006 International Consensus Statement on APS classification criteria [5]. Twenty systemic lupus erythematosus (SLE) patients without aPL antibody syndrome classified according to the American College of Rheumatology (ACR) revised criteria for the classification of SLE [9] were enrolled as a control group. The protocol of the search was approved by the institution within which the work was undertaken and it conforms to the provisions of the world association's Declaration of Helsinki. All participants gave informed consent.

All patients and controls were subjected to a full medical history and complete clinical examination. Patients excluded from the study were those younger than 16 years or older than 60 years, those with history of malignancy. At the time of study, only SLE patients in remission (score 0) or who had mild disease activity (score 1–5) according to SLE Disease Activity Index (SLEDAI) were selected [10, 11]. Baseline laboratory parameters were obtained at inclusion. Serum cortisol level (two samples: 8 a.m. and 8 p.m.) was measured and was considered normal if 10–20 µg/dl at usual time of awakening, and less than 5 µg/dl at bed time. Thrombocytopenia was considered when patients had less than 100,000 platelets per 1 mm^3.

Immune profile included serum complement factor 3 (C3) and factor 4 (C4) levels, ANA, and anti-ds-DNA antibody. The evaluation of LA was performed at the time of the diagnosis (before anticoagulation) according to the guidelines of the International Society on Thrombosis and Haemostasis [12]. The levels of IgG and IgM of aCL and anti-β-2GPI antibodies were determined by enzyme-linked immunosorbent assay (ELISA) by using REAADS semiquantitative test kit. The normal ranges for aCL-IgG were less than 23 GPL, and for IgM less than 11 MPL. The normal range for anti-β-2GPI was less than 20 units for each isotype (IgG, IgM, or IgA).

Abdominal ultrasonography was done to all patients. MRI of the abdomen showing the adrenal glands was made. MRI before and after gadolinium administration as axial and coronal T1-weighted gradient echo sequences in and out of phase, axial and coronal T2-weighted echo-train spin-echo sequences, axial T2-weighted sequences after fat suppression, post gadolinium axial and coronal T1-weighted images was done. It was used to detect the size of the gland, normal homogenous signal intensity, evidence of hemorrhage, capsular enhancement, and increased stranding in peripheral fat.

Statistical analysis: Collected data were analyzed using statistical package for social science (SPSS) version 15.0 for windows evaluation. Quantitative variables were described using mean ± standard deviation (SD) and categorical data by frequency and percentage. The difference between the means was tested by standard t test. For comparison of percentages Chi-squared (χ^2) with Fisher Exact test was used. P values < 0.05 were considered significant.

Results

In the present study, none of the patients and the controls was smokers. Sixteen patients were females (80 %) with male to female ratio 0.25. Thirteen patients had secondary APS to SLE and 7 had primary APS. Arterial thrombotic events were present in 5 patients (25 %). Venous thrombotic events were present in 13 patients (65 %). The control group comprised 20 SLE patients (16 females) with the same male-to-female ratio. The demographic data and the clinical manifestations of the study group APS patients and SLE controls throughout the disease course are compared in **Tab. 1**. One patient had diabetes, 6 patients had hypertension, 7 patients had hypercholesterolemia, and 9 patients had hypertriglyceridemia, compared to 2, 8, 6, and 8 patients in the control group (p = NS). The SLEDAI of the 13 patients with secondary APS was 2.5 ± 1.1, while that of the SLE control group was 2.6 ± 0.9 with p = 0.815.

Abstract · Zusammenfassung

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Adrenal gland abnormalities detected by magnetic resonance imaging in patients with antiphospholipid syndrome

Abstract

Background. Adrenal infarction is a rare complication of antiphospholipid syndrome (APS).

Objectives. The purpose of the current study is to detect and study the magnetic resonance imaging (MRI) findings of adrenal glands in APS patients.

Materials and methods. In a cross-sectional study, the data of 20 patients with primary or secondary APS were compared to 20 SLE patients without antiphospholipid antibody (aPL) syndrome (controls). MRI of the abdomen showing the adrenal glands was performed.

Results. Of the patients, 80% were females with a mean age 32.45 ± 9.93 years, and mean disease duration of 46.65 ± 58.71 months. Adrenal gland abnormalities in the MRI study were detected in 35 % of APS patients vs. no abnormalities detected in the SLE controls. Adrenal gland enlargement was found in all patients (35 %). Capsular enhancement (infarction or hemorrhagic infarction) was found in 5 patients, increased stranding of the surrounding fat planes (inflammatory process) in 4 patients and increased signal on T1WI and T2WI (hemorrhage) in 3 patients. In patients with adrenal gland involvement, 71.4 % had triple aPL positivity compared to 23.1 % in patients with normal adrenal findings (p = 0.04).

Conclusions. Adrenal gland abnormalities on MRI were detected in 35 % of the APS patients (whether primary or secondary); thus, increased focus on management is needed. This percentage is not small and needs to be focused on in terms of management.

Keywords

Antiphospholipid syndrome · Adrenal glands · MRI · Adrenal infarction · Antiphospholipid antibodies

Magnetresonanztomographisch detektierte Nebennierenanomalien bei Patienten mit Antiphospholipidsyndrom

Zusammenfassung

Hintergrund. Ein Nebenniereninfarkt ist eine seltene Komplikation bei Antiphospholipidsyndrom (APS).

Zielsetzung. Ziel der vorliegenden Studie ist die Untersuchung von MRT(Magnetresonanztomographie)-Befunden der Nebennieren in einer Gruppe von APS-Patienten.

Material und Methoden. In dieser Querschnittsstudie wurden die von 20 Patienten mit primären oder sekundären APS mit denen von 20 SLE(systemischer Lupus erythematosus)-Patienten ohne Antiphospholipidantikörper (aPL) verglichen. Durchgeführt wurden abdominelle MRTs mit Darstellung der Nebennieren.

Ergebnisse. Von allen Patienten waren 80% Frauen mit einem Durchschnittsalter 32,45 ± 9,93 Jahre, die mittlere Krankheitsdauer lag bei 46,65 ± 58,71 Monaten. In den MRTs wurden bei 35 % der APS-Patienten Anomalien detektiert, im SLE-Kontrollkollektiv dagegen bei keinem. Eine Vergrößerung der Nebenniere bestand bei allen Patienten (35 %), ein kapsuläres Enhancement (Infarkt bzw. hämorrhagischer Infarkt) bei 5, vermehrtes Stranding im periadrenalen Fettgewebe (entzündlicher Prozess) bei 4 und erhöhte T1W- und T2W-Signalwerte (Blutung) bei 3 Patienten. Von den Patienten mit adrenaler Beteiligung wiesen 71,4 % eine Triple-aPL-Positivität auf, von den Patienten mit unauffälligen Nebennierenbefunden dagegen nur 23,1% (p = 0,04).

Schlussfolgerungen. Nebennierenanomalien wurden magnetresonanztomographisch bei 35 % der APS-Patienten nachgewiesen, was die Notwendigkeit einer stärkeren Fokussierung auf das entsprechende Management verdeutlicht. Hinsichtlich des Patientenmanagements ist dieser nicht unerhebliche Prozentsatz zu bedenken.

Schlüsselwörter

Antiphospholipidsyndrom · Nebennieren · Magnetresonanztomographie · Nebenniereninfarkt · Antiphospholipid-Antikörpern

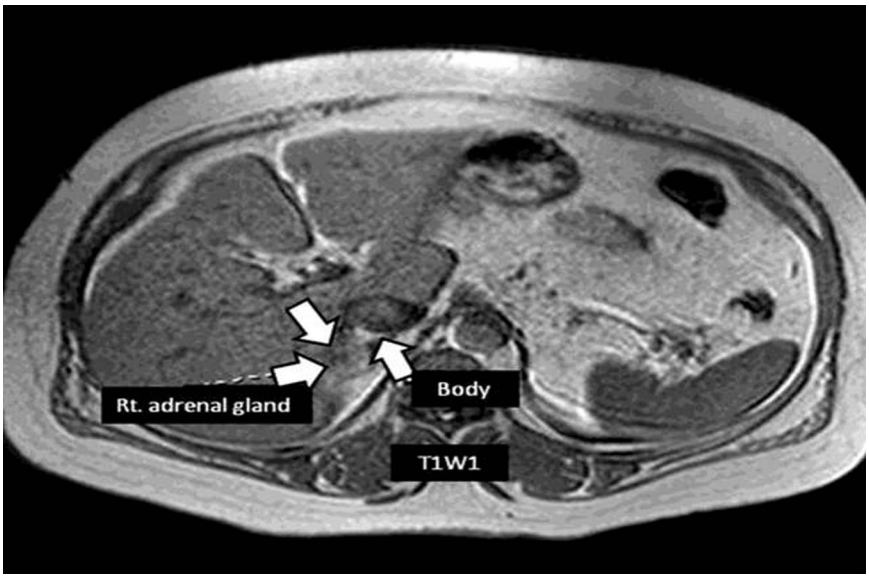

Fig. 3 ▲ Hemorrhagic infarction in the right adrenal gland. An enlarged right adrenal gland (~ 2.5 cm in diameter) with splaying of its medial and lateral limbs, eliciting hyperintense signals in T1WI denoting subacute hemorrhagic infarction

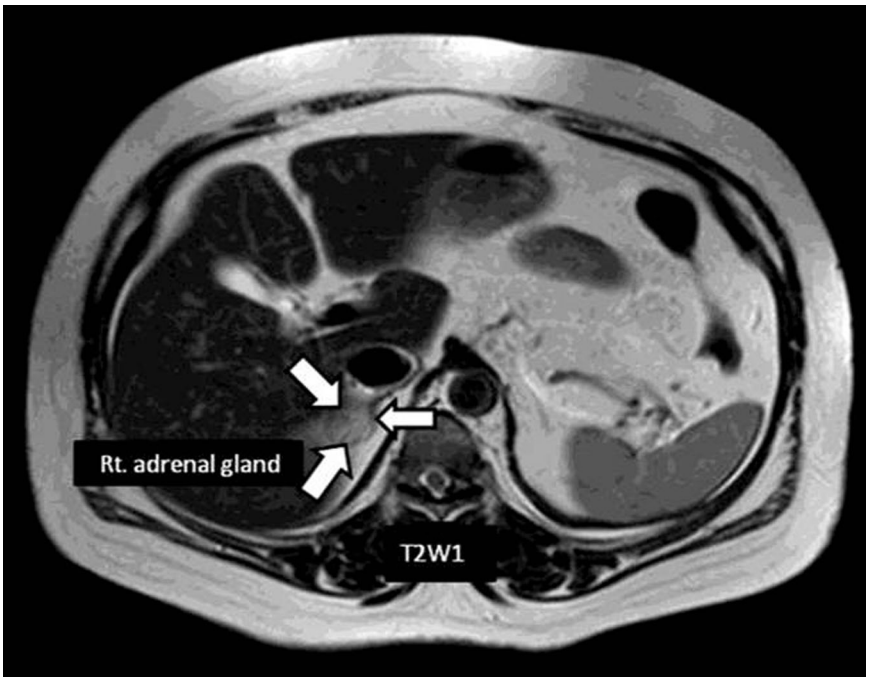

Fig. 4 ▲ Hemorrhagic infarction in the right adrenal gland. An enlarged right adrenal gland (~ 2.5 cm in diameter) with splaying of its medial and lateral limbs, eliciting hyperintense signals in T2WI, denotes subacute hemorrhagic infarction

ANA was positive in 19 patients (95 %), in 13 patients with secondary APS to SLE (100 %), and in 6 with primary APS (85.7 %). Anti-ds DNA was positive in 10 patients. Regarding the aPL, ACL was positive in 13 patients, β2-GPI in 14 patients, and LA in 17 patients. Eight patients had dual positivity (4 had aCL and LA, 3 had β2-GPI and LA, and 1 patient had aCL and β2-GPI), and 8 patients had triple positivity.

At the time of the study, mean prothrombin time (PT) was 23.01 ± 5.57 s and mean international normalized ration (INR) was 1.96 ± 0.99. All patients had normal platelet count, although 3 patients had a history of thrombocytopenia. All patients had normal serum cortisol level with a mean morning sample of 14.1 ± 6.1 μg/dl.

Through their disease course, all patients received oral steroids (prednisolone) with mean daily dose of 21.5 ± 9.37 mg and mean duration of 11.7 ± 25.83 months (11.4 ± 2.8 in primary APS and 26.9 ± 6.6 months in secondary APS). Thirteen patients received azathioprine in a daily dose of 50–100 mg, with mean duration of 12.6 ± 28.79 months, while 13 patients received antimalarials (hydroxylchloroquine) in a daily dose of 200–400 mg, with mean duration of 12.3 ± 18.32 months. Seven patients received I. V. pulsed cyclophosphamide (0.75 mg/cm^2), for 6 pulses with mean total dose 2775 ± 3935.3 mg. There was not a significant difference between the patients and the controls regarding the history of intake of these drugs (data of the drugs of controls are not shown). Regarding the history of anticoagulation, 18 patients received warfarin with mean dose of 7.05 ± 3.3 mg and mean duration of 12.5 ± 15.48 months, 11 patients received low molecular weight heparin (LMW heparin) with mean dose of 66 ± 61.25 units and mean duration of 0.9 ± 1.96 months in a daily dose calculated according to the body weight, and 10 patients received both anticoagulation and antiplatelet therapy in the form of low-dose acetylsalicylic acid (aspirin) in a daily dose of 150 mg and mean duration of 10.65 ± 31.96 months.

At the time of MRI, all patients were receiving oral steroids with mean daily dose of 8.5 ± 3.1 mg as well as anticoagulation therapy. Eighteen patients were receiving warfarin with mean dose of 7.4 ± 2.9 mg, 2 patients were receiving LMW heparin with a dose of 60 units twice daily, and 10 patients were receiving low dose acetylsalicylic acid 150 mg daily.

Four SLE patients in the control group had a history of receiving LMW heparin with a dose of 60 units twice daily and were maintained on 150 mg daily dose of acetylsalicylic acid at the time of study.

The SLE control patients had normal adrenal glands on MRI (**Fig. 1**). Adrenal gland abnormalities in the MRI

Tab. 2 Descriptive data and autoimmune profile of the patients with (*group A*) and without adrenal gland abnormalities (*group B*)

	Group A *N* = 7	Group B *N* = 13	P
Age (year), mean ± SD	30.1 10.7	33.7 9.7	0.461
Age of onset (year), mean ± SD	25.9 10.4	30.2 10.3	0.380
Duration (months), mean ± SD	52.3 56.6	43.6 61.9	0.762
LA *N* (%)	7(100)	10(76.9)	0.282
ACL *N* (%)	6(85.7)	7(53.8)	0.329
β2-GPI *N* (%)	6(85.7)	8(61.5)	0.354
Dual positivity N (%)	2(28.6)	6(46.2)	0.642
Triple positivity *N* (%)	5(71.4)	3(23.1)	0.040*
ANA *N* (%)	7(100)	12(92.3)	0.648
Anti-ds DNA *N* (%)	3(42.9)	7(53.8)	0.648
Consumed C3 *N* (%)	2(28.6)	6(46.2)	0.456
Consumed C4 *N* (%)	0	4(30.8)	0.148

C complement, *ANA* antinuclear antibodies, *Anti-ds DNA* anti double stranded deoxyribonucleic acid, *ACL* anticardiolipin, *β2-GPI* B2 glycoprotein, *LA* lupus anticoagulant, *N* number
* $p < 0.05$

study were detected in 7 patients with APS (35 %). Five of them were females (71.4 %). Adrenal gland enlargement was found in all 7 patients (35 %), 6 of whom had unilateral affection (30 %) and 1 patient had bilateral affection (5 %). Capsular enhancement (indicating that the affection is infarction or hemorrhagic infarction) was found in 5 patients (25 %), while contrast was not administered for 2 patients due to renal functional impairment. Increased stranding of the surrounding fat planes (denoting inflammatory process due to infarction or hemorrhage in the gland) was found in 4 patients (20 %; **Fig. 2**).

Evidence of hemorrhage, showing increased signal on T1WI and T2WI, with persistent bright signal on dual out of phase images (denoting subacute hemorrhage within the gland) was noticed in 3 patients (15 %; **Fig. 3 and 4**).

We subdivided the APS patients into 2 groups, i.e., group A: patients with adrenal gland MRI abnormalities, and group B: patients with normal MRI findings. The comparison between the two groups is shown in **Tab. 2**. Five patients (71.4 %) in group A had triple aPL positivity compared to 3 patients (23.1 %) in group B ($p = 0.04$).

There was no statistically significant difference in adrenal gland in patients with primary and secondary APS (3 out of 7 vs. 4 out of 13 patients, respectively, $p = 0.113$). All APS patients with adrenal MRI abnormalities had a history of persistent abdominal pains, nausea, and vomiting compared to 2 out of 13 patients with normal findings ($p < 0.001$). Five out of 7 patients with adrenal MRI abnormalities had a history of persistent fever compared to 1 out of 13 patients with normal findings ($p = 0.007$). All these manifestations improved with steroids.

Discussion

Adrenal gland enlargement was seen in 35 % of the study population, while capsular enhancement (indicating that the affection is infarction or hemorrhagic infarction) was noticed in 25 %. Increased stranding of the surrounding fat planes (denoting inflammatory process due to infarction or hemorrhage in the gland) was noticed in 20 %. Adrenal infarction is known to be a rare complication of APS. The fact that relatively few cases of pure adrenal infarction have been reported likely reflects the fact that MRI is not often performed in such cases [13]. Adrenal infarction is most often accompanied by adrenal hemorrhage either subsequent to ischemic necrosis or as a result of anticoagulant therapy [14]. The pathologic mechanisms involved in the production of adrenal insufficiency in APS are still not clearly understood, but the hypercoaguable state in these patients supports the concept that adrenal hemorrhagic infarction may possibly be related to thrombosis [15]. Another presumed mechanism by which adrenal insufficiency may occur in those patients is the development of adrenal hemorrhage. In these cases, acute adrenal hemorrhage usually occurred after the patient either had undergone surgery or had received anticoagulant therapy for recurrent thromboembolism [7]. It is not possible to pinpoint the exact cause of the adrenal hemorrhagic infarction, e.g., is it related to the disease pathology or to the intake of anticoagulant therapy. A follow-up study is needed to identify the cause accurately.

The adrenal gland involvement in this study was found in primary and secondary APS evenly. ANA was detected in all patients with secondary APS and in 85.7 % of patients with primary APS. It is higher than what is previously reported [16]. This might be related to the ethnic differences. The mean age of all patients was 32.45 ± 9.93 years (range 16–49 years). The mean age of patients with adrenal involvement was 30.14 ± 10.74 years, and 71.4 % of them were females. Espinosa et al. [14] made a computer-assisted search of the literature to identify all cases of primary adrenal insufficiency associated with aPL antibodies published in English, French, and Spanish from 1983 through March 2002. They were 86 patients of mean age 43 ± 16 years; 45 % of them were females.

Patients with adrenal gland MRI abnormalities had a history of persistent fever, abdominal pains, nausea, and

vomiting significantly more than the patients with normal MRI findings. These clinical manifestations might partially be attributed to the adrenal insult itself throughout the course of the disease. Severe abdominal pain was previously reported to be related to the adrenal gland involvement in APS [14] and to be the first presentation in idiopathic adrenal hemorrhage [17, 18]. The symptoms and signs of adrenal insufficiency appear when more than 90 % of the cortex is destroyed [19]. Serum cortisol levels were normal in all patients. However, since the patients were on daily steroids, the cortisol levels measured may not be clinically relevant. It would be interesting to study the clinical and the radiological adrenal involvement in APS patients not taking steroids. In addition, a prospective study is recommended to clarify the real impact of the disease and the anticoagulation drugs in causing the adrenal damage. The triple aPL positivity has been found in previous studies to be associated to pregnancy failure in women with APS [20]. In the recent study, 71.4 % of patients with adrenal gland involvement had triple aPL positivity compared to 23.1 % in patients with normal adrenal findings ($p = 0.04$).

In conclusion, adrenal gland abnormalities on MRI were detected in 35 % of the APS patients (whether primary or secondary). This is not a small percentage. Using MRI should be considered for those patients suspicious of adrenal gland involvement. This will put emphasis on treatment strategies, especially affecting the planning of steroid withdrawal policies undertaken in those patients to avert the development or progression of adrenal insufficiency.

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Compliance with ethical guidelines

Conflict of interest. A. A. Shahin, S. M. El Desouky, M. Y. Awadallah, and D. E. Megahed state that there are no conflicts of interest.

The accompanying manuscript does not include studies on humans or animals.

References

1. Charles E (2009) Antiphospholipid syndrome review. Clin Lab Med 29(2):305–319
2. Levine JS, Branch DW, Rauch J (2002) The antiphospholipid syndrome. N Engl J Med 346(10):752–763
3. Piette JC, Wechsler B, Frances C, Papo T, Godeau P (1993) Exclusion criteria for primary antiphospholipid syndrome. J Rheumatol 20:1802–1804
4. Merkel PA, Chang Y, Pierangeli SS, Convery K, Harris EN, Polisson RP (1996) The prevalence and clinical associations of anticardiolipin antibodies in a large inception cohort of patients with connective tissue diseases. Am J Med 101(6):576–583
5. Miyakis S, Lockshin MD, Atsumi T et al (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 4:295–306
6. Zoghlami-Rintelen C, Vormittag R, Sailer T et al (2005) The presence of IgG antibodies against beta2-glycoprotein I predicts the risk of thrombosis in patients with the lupus anticoagulant. J Thromb Haemost 3:1160–1165
7. Papadopoulos KI, Jönsson A, Berntorp E, Törnquist C, Hulthén UL (1995) Primary antiphospholipid syndrome associated with postoperative primary adrenal failure. J Intern Med 238:175–178
8. Elsayes KM, Mukundan G, Narra VR et al (2004) Adrenal masses: MR imaging features with pathologic correlation. Radiographics 24(Suppl 1):73–86
9. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725 doi:10.1002/art.1780400928
10. Petri M, Genovese M, Engle E, Hochberg M (1991) Definition, incidence and clinical description of flare in systemic lupus erythematosus. Arthritis Rheum 8:937–944
11. Abrahamowicz M, Fortin PR, Berger R du, Nayak R, Neville C, Liang MH (1998) The relationship between disease activity and expert physician's decision to start major treatment in active systemic lupus erythematosus: a decision aid for development of entry criteria for clinical trials. J Rheumatol 25:277–284
12. Brandt JT, Triplett DA, Alving B et al (1995) Criteria for the diagnosis of lupus anticoagulants: an update. On behalf of the Subcommittee on Lupus anticoagulant/Antiphospholipid Antibody of the Scientific and Standardisation Committee of the ISTH. Thromb Haemost 74:1185–1190
13. Takebayashi K, Aso Y, Tayama K, Takemura Y, Inukai T (2003) Primary antiphospholipid syndrome associated with acute adrenal failure. Am J Med Sci 325:41–44
14. Espinosa G, Santos E, Cervera R et al (2003) Adrenal involvement in the antiphospholipid syndrome clinical and immunologic characteristics of 86 Patients. Medicine (Baltimore) 82(2):106–118
15. Arnason JA, Graziano FM (1995) Adrenal insufficiency in the antiphospholipid antibody syndrome. Semin Arthritis Rheum 25:109–116
16. Carvalho JF de, Caleiro MT, Vendramini M, Bonfá E (2010) Clinical and laboratory evaluation of patients with primary antiphopholipid syndrome according to the frequency of antinuclear antibody (ANA Hep-2). Rev Bras Reumatol 5(3):262–272
17. Dahiya S, Bhagavan A, Ooi WB (2012) Spontaneous bilateral adrenal hemorrhage. Endocrine 42(1):226–227. doi:10.1007/s12020-012-9678-z
18. Dhawan N, Bodukam VK, Thakur K, Singh A, Jenkins D, Bahl J (2015) Idiopathic bilateral adrenal hemorrhage in a 63-year-old male: a case report and review of the literature. Case Rep Urol: doi:10.1155/2015/503638
19. Oelkers W (1996) Adrenal insufficiency. N Engl J Med 335:1206–1212
20. Ruffatti AA, Salvan E, Del Ross T et al (2014) Treatment strategies and pregnancy outcomes in antiphospholipid syndrome patients with thrombosis and triple antiphospholipid positivity. A european multicentre retrospective study. Thromb Haemost 112(4):727–735. doi:10.1160/TH14-03-0191