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HUGHES SYNDROME: A COMMON PROBLEM IN KUWAIT HOSPITALS

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SUMMARY

The objective was to study antiphospholipid antibody syndrome (APS or Hughes syndrome) in two major teaching hospitals in Kuwait. Patients with suspected Hughes syndrome were investigated with tests for anticardiolipin antibodies (aCL) and lupus anticoagulants (LAC) over 1 yr. Diagnosis was considered confirmed if significant levels of either or both antibodies with no obvious cause (primary), or with systemic lupus erythematosus (SLE) or SLE-like illness (including SLE serology) (secondary) were present. Twelve (37.5%; seven females, 58%) primary and 20 (62.5%; 18 females, 90%) secondary Hughes syndrome patients were seen during this period. Patients were Kuwaiti, Middle-Eastern and North-African Arabs (29), Filipinos (2) and White (1). None were from the Indian subcontinent. The main presentation was thrombosis in 75% (arterial in 25% and venous in 50%), and recurrent abortions in 50% of married women. Haematological and dermatological manifestations were limited entirely to the secondary variety, seen in 25% and 19%, respectively. Clinical manifestations were severe, leading to death in one, intensive-care management in 31% and with partial or complete warfarin resistance or brittleness in 25%. Neurological/eye and cardiac manifestations were not seen, as these patients may be attending separate speciality hospitals for these diseases in Kuwait. The approximate prevalence of this syndrome was 2.66/1000 admissions in medical wards. Projected to the total referral areas of the two hospitals, an approximate figure of 52 patients/million population/year was obtained. Hughes syndrome was a common problem among Arabs, Filipinos and possibly Whites in Kuwait. Its manifestations were severe, often requiring intensive-care management, and in one case it was fatal. Patients from the Indian subcontinent were conspicuous by their absence, despite the fact that they were well represented in all other rheumatic disease groups. Ethnic and/or geographical factors could be important in this syndrome. To the best of our knowledge, this is the first report of Hughes syndrome from the Middle East.

KEY WORDS: Hughes syndrome, Middle East, Kuwait, Anti phospholipid syndrome.

MORE than 10 yr have elapsed since the unifying concept of the antiphospholipid syndrome (APS) was put forward by Hughes and his group [1]. Over these years, several centres have confirmed the occurrence of this syndrome and added to its ever-widening clinical spectrum [2–7]. According to some workers, APS is the commonest form of acquired hypercoagulable state [2].

The present article describes Hughes syndrome seen in Kuwait over a period of ~12 months. An attempt has been made to compare the clinical severity and approximate hospital-based numbers of this syndrome with those reported earlier from India and from Western countries. To the best of our knowledge, this is the first report of Hughes syndrome from the Middle East.

PATIENTS AND METHODS

In the present prospective study, only new patients suspected of having Hughes syndrome of the primary type or secondary to systemic lupus erythematosus (SLE) or lupus-like illness seen at Mubarak Al-Kabeer and Amiri hospitals over a period of 1 yr (approximately) were included. A specially designed proforma was used for this purpose. Diagnosis of APS was made according to standard criteria [5]. Anticardiolipin antibody (aCL) screening and quantitation for IgG and IgM isotypes was carried out using commercially available enzyme-linked immunosorbent assay kits (Pasteur Institute, France). Only 'moderate' or 'high' positives were considered to be significant [5]. The second marker antibody screened was lupus anticoagulants (LAC) by the diluted Russell's viper venom test [8]. Although there is no such 'international standard' available for LAC, levels below 0.17 units were considered negative, those between 0.17 and 0.29 were considered 'low positive', and those between 0.3 and 0.69 were considered 'medium positive'. Levels above 0.7 units were considered 'high positive'. For the present report, medium and high positives were considered significant.

As the aCL screening test became available in the last 4 months, and since many of the patients with manifestations localized to a single organ may have attended speciality hospitals (e.g. neurology, ophthalmology, cardiology), the present study is likely to be an underestimate of the actual problem.

The findings were compared with published reports of this syndrome from India and Western countries [9–12].

RESULTS

At the time of this study, the size of the referral population of Mubarak Hospital was 413 153

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TABLE I
Demographic and clinical data of patients included in the study

Hughes syndrome	Primary (n = 12)	Secondary (n = 20)
Age		
Range	20–61 yr	18–50 yr
Median	31 yr	25.5 yr
F:M ratio	1.4:1	9:1
Ethnic group		
Kuwaiti	6 (50%)	12 (60%)
Egyptian	5 (42%)	5 (25%)
Other Middle-Eastern Arabs	1 (8%)	2 (10%)
Whites	0	1 (5%)
From the Indian subcontinent	0	0
Major clinical feature		
Thrombosis	12 (100%)	12 (60%)
Fetal wastage	3/6 (50% of married women)	5/10 (50% of married women)
Thrombocytopenia	0	5 (25%)
Dermatological	0	11 (55%, livedo reticularis, livetoid mottling of hands, non-healing leg ulcers)
Others	0	2 (1 benign intracranial hypertension, 1 diplopia)
Laboratory results	aCL (done in 10); moderate to high range (IgG and/or IgM) 9/10 LAC (done in 8); significant levels 7/8 Autoimmune serology negative	aCL (done in 16); moderate to high range (IgG and/or IgM) 15/16 LAC (done in 13); significant levels 12/13 Autoimmune serology for SLE (high ANA, in some antiDNA) positive
Treatment	Anticoagulation	Anticoagulation, treatment of SLE manifestations with antimalarial, steroids
Outcome	Stormy course in 5, 1 death due to myocardial infarction, partial warfarin resistance in 5 patients	Stormy course in 5, partial warfarin resistance in 3 patients

[Kuwaitis 168 258 (40.7%), expatriates 244 895 (59.3%)]. The hospital had 400 beds. There were 18 823 admissions during the period of the study, of which 6356 were in medicine. Kuwaitis made up 55% of the in-patient admissions, while 45% were expatriates. During the same period, 32 120 patients were seen in the medical out-patients, of whom Kuwaitis made up 47.6% and expatriates 52.4%.

At the time of this study, the size of the referral population of Amiri Hospital was 192 800 [Kuwaitis 97 094 (50.35%), expatriates 95 706 (49.65%)]. The hospital had 350 beds. There were 13 319 admissions during the period of this study, of whom 5651 were in medicine.

A total of 32 patients were diagnosed as having Hughes syndrome in these two hospitals during this

TABLE II
Details of clinical manifestation of primary and secondary Hughes syndrome

Hughes syndrome			Primary	Secondary
Thrombosis			11/12	1220
	Arterial		2/12	5/20
		Peripheral	2/12	3/20
		Organ-localized	2/12 (myocardial infarction, stroke)	2/20 (stroke)
	Venous		9/12	7/20
		Peripheral	8/12	5/20
		With pulmonary embolism	3/12	2/18
		Without pulmonary embolism	5/12	3/18
		Organ-localized	1/12 (retinal)	2/20 (Budd–Chiari)
Recurrent abortions			3/6 married women	5/10 married women
Haematological			0/12	13/20
	Thrombocytopenia			5/20
	Haemolytic anaemia			4/20
	Evans' syndrome			1/20
	Leucopenia			3/20
Dermatological			0/12	11/20
	Livedo reticularis			2/20
	Livetoid mottling of hands			4/20
	Others			5/20 (non-healing ulcers 2, Raynaud's 3)
Miscellaneous			0/12	Benign intracranial tension in 1; diplopia in 1

In Tables I and II, some of the parameters add up to more than the number of patients. This is because some patients had more than one manifestation of the syndrome.

TABLE III
Comparison of antiphospholipid antibodies (APA) and clinical occurrence of Hughes syndrome in different geographical regions

Ethnic group	Western reports [2, 3, 13, 14]	India [9, 10]	Kuwait (present study)*
APA	25–50% of SLE	aCL 27.6%; LAC 13%	aCL +ve in 75% of 44 SLE patients
Thrombotic events in Hughes syndrome	40–50% of those with APA, i.e. 10–25%	142% (9); 7.7% (10)	30%, severe, serious with warfarin resistance seen frequently

*No patient of Indian-subcontinent origin was seen in spite of the fact that ~20% of the hospital attendances, including those of the rheumatology service, are of Indian subcontinent origin [15]. This racial group is well represented in most other rheumatic diseases [15].

period. This gave an approximate frequency of 2.66 patients/1000 admissions in these hospitals. At the population level, these figures gave an annual incidence of 52 cases/million population. Demographic characteristics and main clinical features are given in Table I.

Among primary Hughes syndrome patients, one female could not be controlled by heparin or warfarin and died of massive inferior myocardial infarction. Four patients had a stormy course requiring intensive care due to pulmonary embolism; three required emergency vascular surgery. Warfarin resistance or brittleness in control of the international normalization ratio (INR) was found in five cases. Among patients with secondary Hughes syndrome, five had serious life-threatening complications with pulmonary embolism requiring intensive care. Warfarin resistance or brittleness in control of INR was present in three patients.

Thus, within a short period, 12 patients with primary and 20 patients with secondary Hughes syndrome were seen in two major hospitals in Kuwait. Table II gives details of the clinical manifestations of Hughes syndrome.

It can be seen that both in primary as well as in secondary Hughes syndrome, thrombosis was the commonest manifestation, more often seen in the primary (>90%) than in the secondary variety (52%). Venous thrombosis was seen in >75% of the primary type, but in only 35% of the secondary type. Arterial thrombosis was seen in 17% of the primary variety, which was slightly less than the 25% seen in the secondary variety. The frequency of abortions seen in both types was comparable (50% of the married women). The most striking difference between the two types of Hughes syndrome in this study was the complete absence of haematological and dermatological manifestations in the primary variety. In addition, in the secondary variety there were two patients with rather unusual manifestations. One patient had severe headache which was due to benign intracranial hypertension relieved on acetazolamide and warfarin. The second patient had diplopia whose cause could not be investigated further, but which improved with treatment.

The frequency of Hughes syndrome in SLE in Mubarak Hospital was also studied. A total of 44 confirmed cases of SLE were seen during this period, only four of whom were Indians. Hughes syndrome was suspected in 21 patients, all of whom were Kuwaiti, other Middle-Eastern Arabs or Egyptians. On investigation, 13 were confirmed as having the syndrome. This gives an approximate frequency of 30% secondary Hughes syndrome in SLE occurring mainly in Middle-Eastern or the Afro-Arab population in Kuwait. Table III compares the occurrence of antiphospholipid antibodies (APA) and Hughes syndrome in SLE in different geographical regions [2, 3, 9, 10, 13–15].

The results showed a conspicuous absence of patients of Indian subcontinent extraction among those with Hughes syndrome in Kuwait.

DISCUSSION

The present study, the first of its kind from the Middle East, is a report on Hughes syndrome seen prospectively at two major hospitals in Kuwait. The clinical picture was dominated by thrombosis, both arterial and venous. Thrombosis has been confirmed to be the main feature of Hughes syndrome [1–7, 16]. Organ-localized thrombosis of vessels (coronary, cerebral, retinal, hepatic), another well-recognized complication of Hughes syndrome [2, 4–7, 17] was present in some cases. The second major clinical feature was fetal wastage [1–7]. The other associated clinical features were haematological and dermatological. Haematological manifestations included thrombocytopenia, haemolytic anaemia and leucopenia, frequently reported in Hughes syndrome [2, 4–6, 18, 19]. One young girl had typical Evans' syndrome, a disease often associated with antiphospholipid antibodies [4, 18, 19]. Among the dermatological manifestations were livedo reticularis on the forearms or legs and/or livetoid mottling of the hands in several patients. One patient had a typical non-healing ulcer which responded to full dose of prednisolone and anticoagulation. These are well-recognized manifestations of Hughes syndrome [2, 20–22]. Most interestingly, while thrombosis and abortions were seen with almost similar frequency in the primary and secondary variety, dermatological and haematological manifestations were entirely limited to patients with secondary Hughes syndrome associated with SLE or SLE-like illness. A recent international multicentre study has also reported that autoimmune haemolytic anaemia, endocardial valve disease and neutropenia (in addition to low C4 levels) are more common in the secondary form [23, 24]. Two unusual clinical manifestations were seen in patients with secondary Hughes syndrome, namely benign intracranial hypertension and diplopia. While benign intracranial hypertension has been reported as a non-thrombotic complication of primary Hughes syndrome [25], our patient had a lupus-like disease. We are not aware of diplopia as a manifestation of Hughes syndrome.

Approximately 2.66 new cases of this syndrome were seen for every 1000 in-patient admissions in these two hospitals. Projected to the referral population of these hospitals, this gives a yearly incidence of 52 cases/million population. The prevalence of antiphospholipid antibodies has been studied by several workers (reviewed in [4]). Figures have varied from 1.79 to 30%, depending on the population screened. However, data on the epidemiology of Hughes syndrome are scant, and population surveys are not available. In a secondary and tertiary referral practice in California, 70 patients were seen over a period of 5 yr [11]. In an internal medicine department of a large hospital in France, screening of 1014 patients for antibodies against non-cardiolipin antiphospholipid yielded 20 patients who could be diagnosed as Hughes syndrome; 70% had venous and/or arterial thrombosis, 20% had stroke and 10% had thrombocytopenia [12]. Thus, in comparison to the Californian study, the prevalence of Hughes syndrome in Kuwait would appear to be much higher. However, in comparison to the French study using a different type of APA, the numbers appear lower.

Comparative data from different geographical areas (Table III) show that the syndrome, at least its thrombotic form, is much less common among Indians. There was no patient in the present series from the Indian subcontinent. This was despite the fact that ~50% of the patients attending the hospitals in Kuwait were expatriates, of whom Indians, Pakistanis, Bangladeshis, Sri Lankans and Nepalese made up 20% [15]. Also, people from the Indian subcontinent (India, Pakistan, Sri Lanka, Bangladesh, Nepal) made up one-fifth of the patients in the rheumatology clinic at Mubarak Hospital (unpublished) and they were well represented among other rheumatic diseases [15]. There is some evidence that the frequency of aCL and its relationship to thrombotic events may be related to ethnic and racial differences [26, 27].

Thus, the present study showed that, in Kuwait, Hughes syndrome was a frequent problem among hospital patients. The illness was severe and in a significant proportion it was difficult to achieve the recommended INR of three or more [5, 28, 29]. Persons from the Indian subcontinent were conspicuous by their absence from this group, in spite of their proportionate representation among hospital patients.

Neurological, ophthalmological and cardiac manifestations, among the well-known manifestations of Hughes syndrome [1, 2, 4–7, 30–35], were uncommon in the present study.

ADDENDUM

Since the submission of this paper at the end of 1995, 14 new cases of this syndrome have been seen among Kuwaitis and Egyptians, and a few other Arabs. Over the same period, one young Indian woman with SLE has been found to have mild thrombocytopenia and significant levels of aCL. Recently, Professor K. V. Johny, Chairman of the department, brought to our notice a Pakistani woman with Hughes syndrome presenting as DVT and PE.

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