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Editor's Message

There have been a lot of advancement in the diagnosis and treatment of systemic lupus erythematosus (SLE) over the past few decades. Patients with SLE, nowadays, enjoy better survival and quality of life. Nevertheless, management of lupus patients is not the sole responsibility of rheumatologists, but a multidisciplinary task involving other medical specialists for treatment of their multiorgan involvement, psychologists and psychiatrists for management of their psychosocial and psychiatric complications, physiotherapists and occupational therapists during rehabilitation and rheumatology nurses for education and counseling.

In this issue of CHARM, different specialists have contributed to articles with updated knowledge on different aspects of diagnosis and management of patients with SLE. There are articles on the update of management of this disease over the past decades and the presentation and management of paediatric lupus. Our rheumatology nurse is happy to share with you the role of 'lupus nurse' adopted from western health care system. A summary of some useful serological tests to help diagnosis and monitoring of lupus disease is provided by our clinical immunologist. Our obstetrician has also written on an important topic of pregnancy and contraception issues in lupus as this disease affects mostly young women. In the Orthopaedic's column, you can read about management of avascular necrosis of joints, a common complication in SLE patients on long-term corticosteroid treatment. Our clinical psychologist also shares with us the stress and emotional problems faced by these patients and the approach to help them to cope with their disease.

CHARM is an official publication of the Hong Kong Arthritis & Rheumatism Foundation (HKARF). We have provided a little introduction of the HKARF in this issue for your reference. We hope that you can proactively participate in the various activities organized by our charitable Foundation and eventually contributed to our rheumatic patients with better living and health care!

Update in the management of systemic lupus erythematosus

Dr. Temy Mo-yin MOK
Assistant Professor, Honorary associate Consultant, Department of Medicine, Queen Mary Hospital, The University of Hong Kong

Systemic lupus erythematosus (SLE), may have been known to many readers, to be characterised by butterfly rash on the face of many young women. This female predominant autoimmune disease is, in fact, more devastating with multi-organ involvement leading to significant suffering and death. SLE is more common among Chinese than the Caucasian population. Its prevalence among Chinese has been estimated to be around 0.07% i.e. 700 per 100,000 general population. Physicians have been fighting this 'wolf' since more recognition has been made in the 1870s. Over the past few decades, there have been major advances in the diagnosis and treatment leading to lengthened lifespan and improved quality of life of these patients.

Update in disease diagnosis

SLE is actually more a syndrome than a disease. Patients suffer from multiple organ involvement with predominantly skin rash and articular symptoms. Variable systemic manifestations may be observed among different patients and during each of the exacerbations in their life time. The clinical course of lupus is marked by exacerbations and remissions. Prolonged sunlight exposure, consumption of female sex hormone and sulphur containing drugs, viral and bacterial infections are some known precipitating factors. Because of the heterogeneity of this condition, the American Rheumatism Association, former American College of Rheumatology (ACR) in 1982, has compiled a collection of 11 criteria to standardise definition of lupus. Presence of any 4 of these criteria makes a diagnosis of SLE. These criteria include photosensitivity, malar rash, discoid rash, oral ulcers, arthritis, serositis, renal, nervous system, haematological and immunological disorders and anti-nuclear antibody (ANA). Other than the useful screening test of ANA which is present in over 95% of patients with lupus, anti-double stranded DNA antibodies which are highly specific for lupus, also served as one serological diagnostic criteria.

As more lupus manifestations have been recognised subsequently, a subset of patients who develop recurrent arterial or venous thrombosis has been better defined in 1987 to have been suffering from secondary antiphospholipid syndrome. These patients are also characterised by the presence of serological antiphospholipid antibodies. Common recognised subsets of antiphospholipid antibodies measurable by widely available immunoassays and functional assays include lupus anticoagulant and anticardiolipin antibodies. Antiphophoslipid antibodies belong to another serological marker that has been included in the revised SLE classification criteria in 1997.

Update in the management of systemic lupus erythematosus

Lupus nephritis is a common manifestation of SLE and may involve around 40% of patients. Asians and blacks may have more and worse nephritis than Caucasians. Lupus nephritis is often asymptomatic and the condition may be brought to attention by positive urine albustix or elevated systemic blood pressure. The patient may develop ankle edema when there is significant proteinuria in the nephrotic range. The World Health Organisation classification of lupus nephritis, based on the histological features of renal tissue under light microscopy and the site of immune complex deposition demonstrated on electron microscopy, has been used clinically since 1974 to classify different types of lupus nephritis that carries variable prognosis. This has now been replaced by the classification criteria issued by the International Society of Nephrology/Renal Pathology Society in 2004 where finer details of histological features are described including activity index and chronic index that reflects the level of inflammation and the extent of sclerosis and atrophic changes in the diseased kidneys respectively, providing more information with prognostic and therapeutic implications.

Nervous system involvement is the least understood among all lupus manifestations. The central and peripheral nervous systems can be involved and the symptoms may be as trivial as migrainous headache or as stormy as cerebral lupus. Patients suffering from cerebral lupus may present with seizure, confusion and psychosis and often carry poor prognosis. A high index of suspicion is often necessary for diagnosis. Investigations must exclude infection, in particular when the patient is feverish, and may involve modalities including cerebrospinal fluid examination which may be normal or may show pleocytosis and/or increased protein level, and MRI scan of the brain typically showing white matter lesions in the periventricular region. Due to the heterogeneity of this condition, the ACR has set up a task force in 1999 and laid out 19 classification criteria to define nervous system involvement by lupus so that case definitions can be standardised for future research to bring about earlier definitive diagnosis and more effective treatment.

Update in disease treatment

The clinical course of lupus has revolutionalised since the corticosteroid era from the 1950s. With the introduction of cyclophosphamide, a cytotoxic together with high dose corticosteroids in the treatment of lupus nephritis, the survival of these patients improved further but the medication is associated with significant side effects including bone marrow suppression, haematuria and premature ovarian failure. Adoption of mycophenolate mofetil since almost 10 years ago from the therapeutic regimen of renal transplantation, in the treatment of Class IV lupus nephritis that runs an aggressive course and carries poor prognosis, has been demonstrated favourable efficacy to side effect profile. However, there are still patients with refractory disease and the goal of treatment of disease is not restricted to better control of active disease but to achieve long term remission. A number of biologic agents that direct against different targets involved in the pathogenesis of SLE are down the pipeline. B cell based biologic therapy adopted from the treatment of lymphoproliferative disease has been increasingly used in the treatment of refractory lupus. Post marketing surveillance on these novel agents is needed to provide safety data for long term treatment implication.

Pattern of mortality

SLE patients now live longer with earlier and better diagnosis and more effective treatment. Major organ involvement refractory to conventional therapy and severe systemic infection remain the chief causes of death. Patients are also facing complications that arise from severe disease conditions like cerebrovascular accident or from cumulative side effects of medications including avascular necrosis of hips, osteoporosis and cardiovascular disease. Interdisciplinary effort from different health care professionals is of utmost importance in the management to bring about better clinical outcome and quality of life of these patients.

Reference

Tan EM et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725

Weening JJ et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521

ACR ad hoc committee on neuropsychiatric lupus nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599

Chan TM et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis: Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156

Pregnancy and Contraception in Systemic Lupus Erythematosus (SLE)

Dr. Wing-Cheong LEUNG

Consultant Obstetrician, Subspecialist in Maternal Fetal Medicine, Department of Obstetrics & Gynaecology, Kwong Wah Hospital
Honorary Clinical Associate Professor, Department of Obstetrics & Gynaecology, University of Hong Kong

SLE is an important multisystem disease affecting mainly women of childbearing age. In the 1960s, women with SLE were recommended to avoid pregnancy. Nowadays with better medical control of disease activity, adequate obstetric care and perinatal management, pregnancy outcome in SLE women has improved significantly. On the other hand, maternal and fetal complications still occur. Multidisciplinary effort in pre-pregnancy counseling, prenatal, labour and postnatal management is the key for successful pregnancies in women with SLE. A combined clinic setting whereby the SLE pregnant women can be attended by both the obstetrician and rheumatologist together would be ideal.

Pre-pregnancy

Pre-pregnancy counseling helps in careful planning of pregnancy in women with SLE. Fertility rate in SLE is comparable to general population except in patients who have severe renal impairment, receiving high dose corticosteroids, irregular menstruation or amenorrhoea, and premature ovarian failure secondary to the use of alkylating agents e.g. cyclophosphamide. In general, SLE women are discouraged to get pregnant when the disease is active, in particular, active renal disease with impaired renal function. The following information should be discussed during pre-pregnancy counseling. Local data showed the live birth rate and fetal loss rate of 88% and 12% respectively in SLE pregnant women. The results lie in the favorable end of the spectrum in the world literature. Fetal loss is associated with the presence of anti-Ro, anti-La, antiphospholipid antibodies including IgG anticardiolipin antibodies and lupus anticoagulant (associated with recurrent miscarriages) and significant proteinuria at conception. Poor fetal outcome is expected in 35% of

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live births, mainly related to premature births and intrauterine growth retardation (IUGR). Premature births are related to significant proteinuria during pregnancy and SLE flare-up during pregnancy (especially in the 2nd trimester). IUGR is related to active lupus within 6 months before and at conception. Pre-eclampsia occurs in 10% of pregnant SLE women. SLE flare-up occurs in 15-20% of pregnant SLE women, the risk increases with active disease at conception. The neonatal complications of congenital heart block (anti-Ro +ve) and neonatal lupus erythematosus, although uncommon, should also be mentioned.

It is thus important to achieve a good control of SLE before contemplating pregnancy. An adjustment of medications is sometimes necessary (Table 1). A baseline assessment of complete blood count (CBC), liver & renal function tests (L/RFT), anti-dsDNA, C3/C4, anti-ENA screen (anti-Ro & anti-La), lupus anticoagulant, IgG anticardiolipin antibodies, 24 hour urine for protein & creatinine clearance (CrCl) is recommended.

Prenatal

Joint antenatal and medical care provided by a maternal fetal medicine subspecialist and a rheumatologist simultaneously in a combined clinic setting would be ideal. If this setting is not available and the pregnant SLE woman has to be seen separately in the antenatal clinic and rheumatology clinic, close collaboration and effective communication between the two parties are essential. The pregnant SLE women will have early antenatal care and more frequent antenatal follow-ups to watch out for various pregnancy complications as mentioned in pre-pregnancy counseling. Signs & symptoms of SLE flare-up can be difficult to differentiate from physiological changes in pregnancy and pregnancy complications such as pre-eclampsia (Table 2). Serial ultrasound examination will be performed for dating (early 1st trimester scan to ascertain the expected date of confinement / EDC), fetal anomaly screen at 18 weeks, cervical length (at 22-24 weeks to assess the risk of preterm labour), fetal growth, fetal heart rate (5-10% risk of complete heart block with anti-Ro +ve), amniotic fluid volume and Doppler studies. Doppler studies include assessment of uterine arteries at 22-24 weeks (high resistance flow with notching increases the risk of pre-eclampsia and IUGR); serial assessment of umbilical arteries (UA) and middle cerebral arteries (MCA) (high UA with low MCA resistance flow indicates placental insufficiency / pre-eclampsia / IUGR); and ductus venosus (DV) (abnormal DV flow indicates severe fetal compromise / acidosis). Cardiotocogram (CTG) and biophysical profile (BPP) will be added for fetal monitoring when IUGR is suspected. Low-dose aspirin and low molecular weight heparin can be considered in those women with antiphospholipid antibodies and / or history of poor obstetric outcomes such as pre-eclampsia, IUGR and stillbirths.

Labour

Early induction of labour has to be considered in the presence of pre-eclampsia &/or IUGR, the exact gestation depends on the severity of pre-eclampsia / IUGR versus the risk of prematurity. Even in the absence of pre-eclampsia / IUGR, delivery beyond 40 weeks gestation or EDC is not recommended for pregnant women with SLE. On the other hand, the mode of delivery (vaginal delivery or Caesarean section) is to be determined by standard obstetric indications rather than the presence of SLE per se. Intravenous hydrocortisone is required to cover the stress of labour for those women taking corticosteroids. The newborns will be assessed by paediatrician for congenital heart block (anti-Ro +ve) and neonatal lupus syndrome. Those premature babies will have to stay in neonatal ICU or nursery for some time.

Postnatal

SLE flare-up can occur during the postnatal period. The woman has to be assessed by the rheumatologist before going home. An adjustment of medications is sometimes necessary. Breast feeding is generally encouraged except for those mothers taking cytotoxics, immunosuppressives and NSAIDs. Prednisone, prednisolone, and hydroxychloroquine are compatible with breast feeding. Family planning is another major concern.

Contraception

Oral contraceptive (OC) pills seem safe for women with inactive or stable active SLE without increasing the risk of disease flare-up as shown by the SELENA (Safety of Estrogen in Lupus Erythematosus National Assessment) study. However, OC pills are not recommended for women with antiphospholipid antibodies because of increased risk of thromboembolism. For women with active SLE, barrier methods such as condoms and progestogen-only pills are good alternatives. Women using progestogen-only pills have higher discontinuation rate because of irregular vaginal bleeding. Three-monthly IM medroxyprogesterone acetate is another convenient option but might be problematic in women taking corticosteroids because of increased risk of additional bone loss. Because of high infection rate associated with intrauterine contraceptive device (IUCD), IUCD is relatively contraindicated for SLE women who are taking corticosteroids, immunosuppressives and cytotoxics.

Table 1. Use of drugs in pregnant SLE women

Drugs	Use in Pregnancy	Remarks
Corticosteroids (Prednisone)	Yes	• <10% of active drug reach the fetus • Risk of cleft palate only in animal studies • Screen for gestational diabetes & monitor blood pressure
Antimalarials (Hydroxychloroquine)	Yes	No known teratogenicity
Cytotoxics / Immunosuppressives • Methotrexate • Cyclophosphamide • Azathioprine	 No No Controversial	 Teratogenic Teratogenic Intrauterine fetal growth retardation
NSAIDs	Avoid in last few weeks of pregnancy	Premature closure of ductus arteriosus in-utero

Table 2. SLE flare-up vs. physiological changes & pregnancy complications

SLE flare-up	Physiological changes & pregnancy complications
Malar rash	Pregnancy rash
Easy fatigue	Tiredness
Lupus nephritis	Pre-eclampsia (high BP, proteinuria & oedema)
Autoimmune thrombocytopenia	Gestational thrombocytopenia
Elevated anti-dsDNA, decreased C3/C4	Elevated ESR, elevated complements

Reference

Mok CC, Wong RW. Pregnancy in systemic lupus erythematosus. Postgrad Med J 2001;77:157-65.

Mok MY, Leung PY, Lao TT, et al. Clinical predictors of fetal and maternal outcome in Chinese patients with systemic lupus erythematosus. Ann Rheum Dis 2004;63:1705-6.

Sammaritano LR. Therapy insight: guidelines for selection of contraception in women with rheumatic diseases. Nat Clin Pract Rheumatol 2007;3:273-81.

Yuen SY, Krizova A, Ouimet JM, Pope JE. Pregnancy outcome in systemic lupus erythematosus (SLE) is improving: results from a case control study and literature review. The Open Rheumatology Journal 2008;2:89-98. [with an updated list of references]

Osteonecrosis in Patients with Systemic Lupus Erythematosus

Dr. Hang-cheong CHENG
Senior Medical Officer, Department of Orthopaedics & Traumatology, United Christian Hospital

Introduction

Osteonecrosis (ON), also known as avascular necrosis, is characterized by death of bone marrow and trabecular bone as a result of impaired blood supply. The disease can affect femoral heads, knees, humeral heads, talus, capitellum and other parts of the body. As the disease progresses, flattening and collapse of the articular surface occurs and this can result in end-stage arthritis. The condition is especially disabling if weight bearing joints are involved and joint replacement surgery may be required for pain control. Systemic lupus erythematosus (SLE) is one of the non-traumatic conditions associated with ON. The reported frequency of symptomatic ON in SLE patients is 3-30% (average 10%) but is likely to be higher as ON can be asymptomatic (1).

Corticosteroid therapy, Raynaud's phenomenon, vasculitis, antiphospholipid syndrome, arthritis and Cushingnoid appearance have previously been examined in relation to the development of ON in SLE patients. Corticosteroid therapy was found to be the major contributing factor and was associated with an 18-fold increased risk of development of ON in SLE patients (2). ON is extremely rare among SLE patients who are corticosteroid naïve and is rare among patients treated with mean dose of prednisolone <20mg daily. Using MRI as a screening tool, 44% of SLE patients were found to have ON involving the hip and knee 3.1 months after commencement of high dose corticosteroid therapy, with virtually all ON appearing within 6 months (3). The exact mechanism by which corticosteroid precipitates the development of ON is unclear. Corticosteroid therapy might lead to increase in size and number of intramedullary lipocytes causing increased bone-marrow pressure and thereby vascular compression and reduced perfusion to bone tissue (4). Corticosteroid has also been shown to suppress osteoblastic activity leading to deficient repair of microfractures in ON (1).

Since the prevalence of ON in SLE is much higher than that seen in other clinical conditions requiring chronic corticosteroid use, SLE related factors are likely contributory to the development of ON (5). Although factors like Raynaud's phenomenon, vasculitis, hypercoagulopathy, arthritis, Cushingnoid appearance were found to be associated with the development of ON in SLE, the link between these factors was not as strong as that with corticosteroid.

Clinical Features and Investigations

ON should always be suspected when joint pain develops in SLE patients treated with high dose of corticosteroids as synovitis is rare in these patients. However, ON can be asymptomatic. Patients with symptomatic ON usually present with sudden onset of joint pain. The pain worsens as the disease progresses with collapse of the articular surface and development of secondary osteoarthritis. Because of the analgesic effect of the corticosteroid, joint destruction can be accelerated in mechanisms similiar to Charcot-like arthropathy (1).

In SLE patients, ON can be localized to one joint or may affect multiple joints. As the other joints may be asymptomatic, detection of ON at one site should be followed by screening of other joints. The femoral head is the commonest site of involvement. Bilateral involvement occurs in up to 90% of SLE patients. The next common site is knee and bilateral involvement is also common. Shoulders, ankles, elbows and wrist can also be involved.

Initial investigation includes plain radiographs of the affected joints. Typical radiological changes include areas of radiolucency and sclerosis. Crescent sign represents the presence of subchondral fracture which is highly specific for ON. Collapse of the articular surface and secondary osteoarthritic changes are observed in advanced disease.

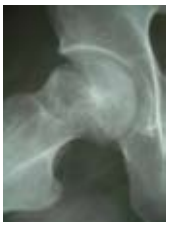

Figure 1- X-ray showing the crescent sign

Plain radiographs can be normal in early stages. MRI which is 99% specific and sensitive is the recommended mode of investigation. A single density line on T1-weighted images demarcates the normal - ischaemic bone interface and double density lines on T2-weighted images represent the hyper-vascular granulation tissue between the necrotic and viable bone tissue at the periphery of the site of ON (6).

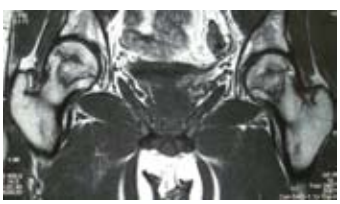

Figure 2 – MRI showing ON of both femoral heads

Bone scan which shows decreased activity in the area of ON was used for diagnosis in the past. However, with a false-negative rate of 25-45%, bone scan is less commonly performed nowadays (6). CT scan can identify collapse but is not commonly used because of higher accuracy of MRI.

The site and size of ON, collapse of articular surface and osteoarthritic changes are the determinating factors for the prognosis and treatment of ON. Various disease classifications of prognostic and therapeutic implications have been developed for ON. Ficat and Arlet, Steinberg, Assoication Research Classification Osseous (ARCO) and the Ohzono classification are the most widely used ones for ON involving the femoral head.

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Treatment of ON in SLE

The treatment strategies for ON and clinical outcome in SLE is similar to that of ON in general. If not treated, the disease progresses in particular for large lesions such that 20% of femoral heads with ON will collapse at 1 year and 75% will collapse at 3 years (7). Prosthetic joint replacement is often required within 3-4 years of diagnosis. In fact, ON accounts for 10% of primary total hip replacement in the US and 45% in Taiwan. The choice of treatment depends on disease stage which is determined by symptoms, site and size of lesion, collapse of articular surface and osteoarthritic changes. Treatment ranges from non-operative treatment, joint preserving procedures for early lesions to arthroplasty for end stage lesion.

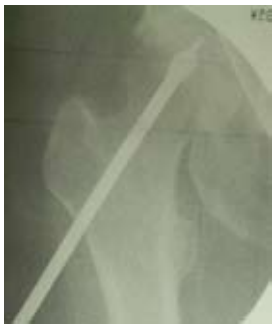
Non-operative treatment

Non-operative treatments including analgesic use, physiotherapy and non-weight bearing and are indicated for asymptomatic and small symptomatic ON lesions because these lesions may heal or remain stable. It usually takes 7-11 months for early resolution to appear on MRI and 19-44 months for complete resolution (8). Previously, non-weight bearing was proposed to allow the necrotic bone to heal and hence slow down disease progression. However, restricted weight bearing has been found to be associated with a failure rate of >80% at a mean of 34 months and is thus not clinically useful (9).

Operative Treatment

For symptomatic sizable lesions, surgical treatment should be considered.

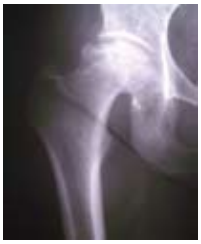
1. Joint Preserving Procedures



Core decompression is used to treat ON before collapse of articular surface. The procedure aims to decrease intramedullary pressure and improve perfusion to the ON area by removing a core of bone from the region. The result of core decompression is controversial. The successful rate varies from 30% to 70% for ON of femoral heads. The outcome is less favourable for big lesions and those with high percentage of weight bearing area.

Figure 3- Core decompression of femoral head

Osteotomy and bone grafting are other joint preserving procedures for ON. However, the efficacy of these treatments in SLE patients is unclear.



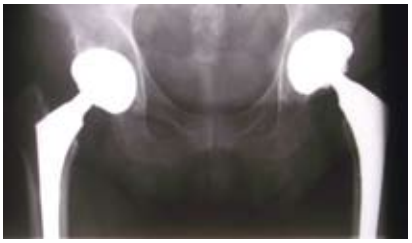


Figure 4 – Collapse of Femoral Head
Figure 5- Bilateral total hip replacement for ON

2. Arthroplasty

Arthroplasty is indicated to control joint pain and improve function when there is collapse of articular surface and secondary osteoarthritis. Favorable outcome have been reported for joint replacement for ON in SLE patients. Survival of total hip replacement in SLE patient has been reported to be 95% at 5 years (10) and 82% at 9 years. With the development of modern implants, survival of these prosthesis is expected to be longer.

Summary

ON can develop in SLE patients who are on high dose corticosteroids. MRI is useful in the detection of early lesions. Core decompression may be useful in selected precollapse ON. Joint arthroplasty is indicated for patients suffering from advanced disease.

Reference

Abu-Shakra M, Buskila D, Shoenfeld Y. Osteonecrosis in patients with SLE. Clinical Reviews in Allergy & Immunology. 2003; 25:13-24

Gladman, DD, Urowitz, MB, Chaudhry-Ahluwalia V, Hallet DC, and Cook R. Predictive factors for symptomatic osteonecrosis in patients with systemic lupus erythematosus J. Rheumatol. 2001; 28, 761–765.

Oinuma K, Harada Y, Nawata Y, Takabayashi K, Abe I, Kamikawa K, et al. Osteonecrosis in patients with systemic lupus erythematosus develops very early after starting high dose corticosteroid treatment. Ann. Rheum. Dis. 2001: 60, 1145–1148.

Zizac TM, Marcoux C, Hungerford DS, Dansereau JV, and Stevens MB. Corticosteroid therapy associated with ischemic necrosis of bone in systemic lupus erythematosus. Am. J. Med. 1985:79, 596–604.

Rascu A, Manger K, Kraetsch HG, Kalden JR, and Manger B. Osteonecrosis in systemic lupus erythematosus, steroid-induced or a lupus-dependent manifestation? Lupus 1996: 5, 323–327.

Samuel J. Parsons, Niall Steele . Osteonecrosis of the femoral head: Part 1—Aetiology, pathogenesis, investigation, classification. Current Orthopaedics, 2007: 21, 457-463

Merle d'Aubigne R, Postel M, Mazabraud A, Massias P, Gueguen J. Idiopathic necrosis of the femoral head in adults. J Bone Joint Surg 1965;47-B:612–33.

Cheng EY, Thongtrangan I, Laorr A, Saleh KJ. Spontaneous resolution of osteonecrosis of the femoral head. J Bone Joint Surg Am 2004;86:2594-9

Mont MA, Carbone JJ, Fairbank AC. Core decompression versus non-operative management for osteonecrosis of the hip. Clin Orthop Relat Res 1996;324:169-78.

Huo, M. H., Salvati, E. A., Browne, M. G., Pellicci, P. M., Sculco, T. P., and Johanson, N. A. (1992) J. Arthroplasty;1992;7,51-56

Immunological tests in diagnosis and monitoring of patients with Systemic Lupus Erythematosus

Dr. Eric Yuk-tat CHAN
Consultant, Clinical Immunologist, Department of Pathology and Clinical Biochemistry, Queen Mary Hospital

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by inflammation of various tissues and organs. Autoimmune diseases are illnesses that occur as a result of attack of the immune system on self targets. Patients with SLE produce antibodies that bind to self molecules called autoantibodies. Autoantibodies may be pathogenic, for example, anti-double stranded (ds) DNA antibodies which bind native or double stranded DNA and form immune complexes. Deposition of immune complexes in organs causes inflammation and dysfunction and organ damage. Involvement of multiorgan is common in SLE, some organs are more commonly involved than others. Similarly a wide variety of autoantibodies can be detected in the peripheral blood of these patients.

Diagnosis of SLE

Anti-nuclear antibodies (ANA) is the recommended initial screening test for suspected lupus. This test is positive in over 95% of SLE patients and hence the diagnosis of SLE can be largely excluded if the test is negative. Positive ANA results are also commonly found in other rheumatic and non-rheumatic diseases. To confirm a diagnosis of SLE, more specific tests such as anti-dsDNA and anti-extractable nuclear antigen (ENA) antibodies are needed. A negative ANA sample is not likely to have anti-dsDNA but is possible to have anti-ENA antibodies. The ANA titre or level is mainly used in determining its significance – the higher the titre, the more clinically significant.

Anti-dsDNA antibody is traditionally measured by radio-immunoassay (Farr assay) or Crithidia immunofluorescence which are highly specific for SLE. In the past 20 years, enzyme-linked immunosorbent assay (ELISA) has been increasingly used in the detection of autoantibodies but anti-dsDNA antibody measured by ELISA is sometimes positive in non-SLE patients. If a false positive anti-dsDNA result by ELISA is suspected, one has to review the clinical features of the patient more carefully or resort to more specific tests for confirmation.

Anti-ENA antibodies are a group of autoantibodies binding soluble nuclear antigens. Commonly measured anti-ENA antibodies include anti-Sm, anti-nRNP, anti-Ro, anti-La, anti-Jo-1 and anti-Scl-70 antibodies, traditionally assayed by immunodiffusion methods. Newer methods like ELISA or line blotting are coming into use recently. Although most samples react in all kinds of assay methods there are exceptions which need to be interpreted carefully. Anti-Sm is only found in SLE patients but the prevalence is rather low (20-30%). Anti-nRNP is typically detected in high level in most patients with mixed connective tissue disease and in 40-50% of SLE patients. Anti-Ro (SS-A) and anti-La (SS-B) are found mainly in Sjogren's syndrome patients and in 60% and 30% of SLE patients respectively. A small percentage of SLE patients with anti-Ro or anti-La antibodies give births to babies with neonatal lupus – a syndrome characterized by dermatitis or congenital heart block. Anti-Jo-1 and anti-Scl-70 antibodies are markers found in dermatomyositis and systemic sclerosis respectively.

Other autoantibodies against nuclear constituents are either not fully established e.g. anti-nucleosome antibodies, or known to be not useful e.g. anti-single stranded (ss)DNA and LE cells. Anti-ssDNA is detected in over 50% of patients with lupus like disease secondary to drugs. A subgroup of drug-induced lupus is characterised by anti-histone antibody. Like ANA, anti-ssDNA can be found in many nonspecific conditions like mononucleosis and hepatitis.

Some SLE patients are complicated by the anti-phospholipid syndrome (APS). This syndrome is supported by three laboratoy tests – lupus anticoagulant, anti-cardiolipin antibody, anti-β2-glycoprotein I antibody. Lupus anticoagulant is a functional assay on the effect of these peculiar antibodies resulting in prolongation of APTT in vitro while causing thrombosis in vivo. It is the most specific of these three tests in the diagnosis of APS. Initially β2-glycoprotein I or Apolipoprotein H is described as a protein required for the recognition of anti-cardiolipin in solid in vitro assays. Recently anti-β2-glycoprotein I is added to the diagnostic panel and is also specific for APS. Anti-cardiolipin antibody is the least specific among the three tests. To support a more certain diagnosis of APS the IgG isotype of anti-cardiolipin antibody and a moderate antibody level are needed. APS is diagnosed with persistently positive result of any of the above tests together with relevant clinical features such as clinical thrombosis or recurrent abortions.

Monitoring of SLE

SLE runs a wax and wane clinical course. A number of laboratory tests are useful to monitor disease activity and guide treatment plan. Complement components 3 and 4 (C3 and C4) levels are low in serum when SLE disease is active. This is because SLE is an immune complex disease and C3 and C4 are both consumed when there is complement activation by immune complexes. Anti-dsDNA antibody level also increases with increased disease activity. It is known in up to 30% of SLE patients C3, C4 and anti-dsDNA levels do not correlate with disease activity, the reason of which is unclear. Also changes in blood results may precede clinical relapses by several weeks or even months. The ANA titre correlates poorly with disease activity and is not used to monitor SLE patients.

An inflammatory marker called C-reactive protein (CRP) is very useful in SLE patients with inflammatory or infective complications. Although SLE is an acute inflammatory disease, CRP is normally not increased except in serositis or arthritis where it is increased only slightly. The level of CRP increases markedly in bacterial and moderately in viral infections in SLE patients. Treatment of intercurrent infections lowers the CRP level. This often helps to exclude infection in SLE patients presenting with pyrexia.

Have you heard about Lupus Nurse?

Ms. Jane Lai-hung CHAN
Department Operations Manager, Ambulatory Care Centre,
Queen Elizabeth Hospital, Hospital Authority

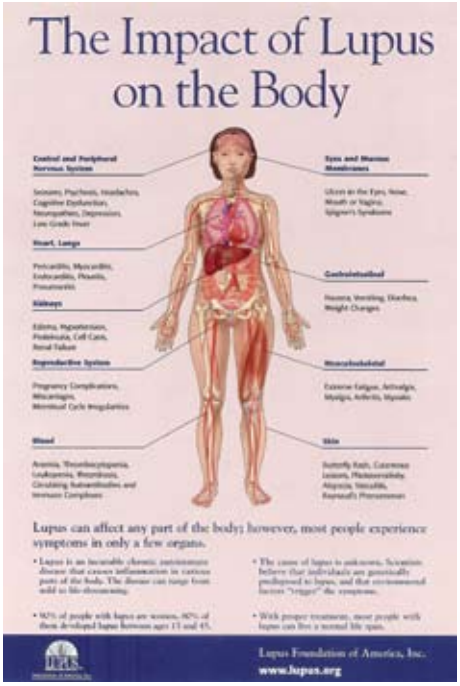
Systemic lupus erythematosus (SLE) is well–known as the clinical picture of a young lady with malar rash over the cheek. Lupus means "wolf", whilst erythematosus means "redness" in Latin. In the 19th century, doctors named the disease because the facial rash looked like a bite from a wolf. Apart from malar rash, SLE is an autoimmune disease with a wide range of symptoms affecting many major organs including brain, heart and kidneys.

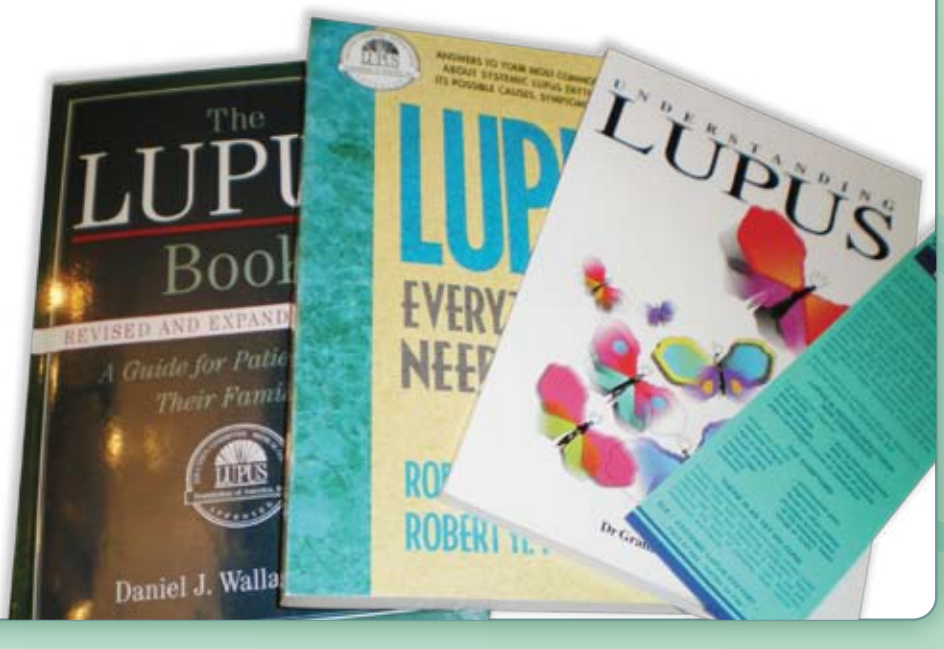
In Hong Kong, SLE patients with prominent renal manifestations are under care of nephrologists, whilst others are looked after by rheumatologists. In recent years, as an emerging nurse specialist in Hong Kong, rheumatology nurse takes care of patients with rheumatic diseases. The role of rheumatology nurse has been elaborated in detail in the last issue of CHARM by Ms. Lindy Wong. Rheumatoid arthritis (RA), ankylosing spondylitis (AS) and SLE are among the commonest rheumatic diseases seen in the rheumatology clinic. Similar to RA and AS, SLE patients commonly present with musculoskeletal complaints. On the other hand, SLE has distinguishing manifestations involving multiple major organs such as kidney, brain, heart and haematological system. Unlike RA and AS, joint deformity resulting in long-term disability does not occur in SLE. Plan on medical treatment and nursing care for SLE, thereby, are quite different compared to RA and AS. For example, anti-TNF which is a novel therapy for RA and AS but its therapeutic effect has not been substantiated in SLE. In the United Kingdom and the United States, lupus nurse specialists evolve from the specialty of rheumatology nursing and specialize in the management of SLE patients. Lupus nurses play a role as a case manager and provide continuity of care. They are particularly helpful for those patients who develop disease complications. The following summarises the role of a lupus nurse:

1. Educate patients on aspects of diagnosis, investigation and treatment in order to empower them for self-care management.
2. Provide information such as drug monitoring, counseling and telephone helpline to ensure patients can take care themselves safely in the community.
3. Provide psycho-social support to patient to enhance their self-efficacy of managing their chronic illness.
4. Coordinate the activities among healthcare professionals.
5. Provide pre-conception counseling since most patients are women in reproductive age.
6. Manage nurse-led clinic for drug monitoring and early detection of signs and symptoms of catastrophic organ involvement.

Being a nurse manager, I look forward to seeing the development of lupus nurse specialists in Hong Kong following the successful establishment of the Specialty of Rheumatology Nursing. This will be important in the development of nursing profession in Hong Kong and will also be of benefit to SLE patients.

If you want to know more about lupus nurse, you may visit following websites for more detail.
http://www.niams.nih.gov/Health_Info/Lupus/Lupus_Guide/chapter_4.asp
http://www.lupusuk.org.uk/whatdonursesdo.asp





Harnessing the curse of SLE

Prof. Peter Wing-ho LEE#, Dr. Amy SM FUNG*, Ms. Joanna WM LAW*
#Honorary Consultant in Clinical Psychology, Hong Kong Sanatorium & Hospital
***Clinical Psychological Services, Hong Kong West Cluster, Hospital Authority**

"The needs of patients with complex chronic illnesses such as SLE often remain unvoiced to health care providers but must be understood if optimal health care services are to be designed and implemented" (S. Danoff-Burg, F. Friedberg, 2009). Lupus is possibly one of the most undesirable diseases in terms of their chronicity, unpredictable flare-ups, adverse influence on almost any part of the body, disfiguring impact on appearance, lacking a cure, and worst of all affecting mostly young women in their prime and child-bearing ages. The lifelong journey with SLE is fraught with challenges and trials. Diagnosis is difficult and uncertain. Toiling initially with multiple and obscure symptoms, fatigue and malaise for prolonged periods, with diagnosis often implicating depression, psychogenic origins, "something to do with the mind", or "having to pull yourself together", the young female patient often finds herself battling grave injustices, frustrations and uncertainties. After being diagnosed, with its scary label and grave implications, youthfulness is instantly robbed away as the patient starts a lifelong journey of more uncertainties along the unsolicited partnership with pains, cosmetic changes, multi-organ impact, periodic disabling fatigue, and the threat of an early and uncertain death.

Fourteen to fifty one percent of SLE patients had been estimated to suffer from depressive disorders (Hanly et al., 2004, Nery et al., 2008), while 6 to 24% of SLE patients suffer from anxiety disorders (Brey et al., 2002, Afeltra et al., 2003). Apart from the stress of adjusting to the illness, high doses of corticosteroids as well as inherent SLE autoimmune phenomena are also implicated in the patient's mood problems. Regardless of aetiology, effective management of depression and anxiety in SLE patients is mandatory as untreated negative mood interferes with restful sleep, makes pain more intolerable, intensifies fatigue, further reduces life quality and ability to experience pleasure. The better news is that modern day psychological and pharmaceutical treatments of mood and anxiety disorders are effective. However, the common stigma attached to "mental illness" needs to be addressed openly. Assessment and monitoring of psychological well-being should be incorporated as an integral part of the comprehensive SLE management program. Patients should be assured firstly, that psychological sequelae are common and not reflective of inherent weakness, inferiority, or embarrassment, secondly, that positive treatments are available, and thirdly, that effective SLE management should of necessity address all aspects of their physical, emotional, interpersonal, and daily life well-being.

To prevent aggravation and enhance quality of life, routine attention should be given to characteristic symptoms including:

- persistent depressed mood,
- markedly diminished or loss of interest or pleasure,
- unduly low self esteem and sense of worthlessness,
- interpersonal alienation,
- diminished ability to think or concentrate,
- prolonged sleeping problems,
- unexplained and varied physical symptoms, and
- signs/symptoms of chronic physiological arousal.

The healthcare provider should also establish him/herself as a good role model with assuredness in face with their patients' emotional symptoms by proactively enquiring about their presence and being prepared to talk and deal with them as needed. The multiple roles of an effective health care professional should be widened to include problem definition, effective management, care and support, prevention of aggravation, and health education. Monitoring of patients' emotional symptoms should remain an ongoing focus of the primary health care provider. The primary care physician should periodically check and avail him/herself to understand the patient's perspective and adjustment to the illness and how the illness has affected other aspects of his/her life. Individuality and variability across patients in illness response and coping is the rule. Generalization and stereotyping has little place in effective clinical management.

Harnessing the curse of SLE

Harm containment and preserving the most optimal life quality possible is the logical goal in management of SLE given its incurability. Understanding and catering to the needs (or unmet) needs of patients is important. Various studies (Barry et al., 2000, Hale et al., 2006, Hale et al., 2006, Danoff-Burg et al., 2009) have noted that patients often withhold the full range of their needs from health care providers. Building a trusting and open communication with patients from the start is thus an important cornerstone for optimal long term illness management partnership. Danoff-Burg et al. (2009) noted in their sample of 112 patients with SLE that all participants had at least one unmet need. The greatest area of unmet need, understandably, is in the physical domain. A high percentage of the patients reported needing help with tiredness (90%), pain (80%), not sleeping well (75%), feeling worse after physical activity (70%), and needing help for other physical symptoms including dry mouth, headaches, and skin rashes (50%). In the area of daily living, about 70% percent of the patients indicated needing help regarding eye sensitivity to bright light, avoiding sun exposure, and coping with hot or cold temperatures. In the psychological/existential domain, 90% of the patients acknowledged having unmet needs with regards to having inadequate help in dealing with fears about SLE getting worse, dealing with anxiety and stress, dealing with feeling down or depressed, dealing with concerns about changes in appearance, and feeling like a failure as a spouse or parent. Over two-thirds of the patients complained of having insufficient advice in knowing when to see the doctor when changes in symptoms occur, lack of opportunity in talking to someone who understands, getting adequate information from medical staff about treatment side effects, and getting support for explorative use of alterative therapies. Half of the patients complained about continuity of care (or lack of), and (limited) amount of time spent with medical practitioners. The results of the study are important in alerting the busy clinician with regards to important areas of clinical input in promoting better care and patient satisfaction.

Stress and its effective management is always an integral part of coping with SLE. Stress is most intense when unexpected and when there is a marked dis-synchrony between what is expected and hoped for in contrast to the murky reality that needs to be confronted with. In youthful age, life seems rosy and without cares. Plans flourish, optimism abounds, energy brims, and life seems ever full of promise and hope. Lupus unfortunately shatters it all. In coping with the enormous challenge of SLE, McCracken et al. (1995) noted that patients with passive coping strategies (e.g. avoidance, wishful thinking, blaming self) had poorer psychological adjustment and functional status compared to those who adopted realistic problem-focused coping. Bricou et al. (2006) cautioned that while stress was not proven as a causal factor in SLE morbidity (disease activity, organ damage), it seems to "act as an exacerbating factor in disease activity and to have an impact on the quality of life". Effective disease coping was associated with better quality of life. Specific psychosocial interventions, while not targeting disease activity directly, should thus be provided to reduce distress and improve quality of life, which in turn may have a moderating impact on the evolution of the disease itself.

In summary, more (inputs) may be better than less in harnessing the harm of SLE. A trusting and mutually respectful working partnership between the health care provider and the patient is vital for the long-term battle against SLE. Patient competence in understanding of the illness and its management should be promoted. Emotional and psychological condition needs to be routinely monitored and dealt with. Patient mutual support and sharing is beneficial. A clearly demonstrated authority and expertise on the part of the health care provider who is successful in keeping him/herself abreast of ever advancing progress in the field is indispensible. The successful therapeutic regime for SLE needs to be a comprehensive one, addressing physical malaise, emotional and psychosocial functions. Finally, through the effective health care provider who is willing to go out of his/her way to treat, respect and care for the patient – hope is instilled against an illness as elusive and complex as SLE. For after all "Hope is … the earliest and the most indispensable virtue inherent in the state of being alive. . . . If life is to be sustained hope must remain, even where confidence is wounded, trust impaired." Erik H. Erikson (1978).

Reference

Afeltra A., Garzia P., Mitterhofer A.P., Vadacca M., Galluzzo S., Del Porto F. et al. (2003): Neuropsychiatric lupus syndromes – relationship with antiphospholipid antibodies. Neurology, 61, 108-110.

Ainiala H. Loukkola J. Peltola J. Korpela M., Hiertahaju A. (2001): The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology, 57: 496-500.

Barry C.A., Bradley C.P., Britten N., Stevenson F.A., Barber N. (2000): Patient's unvoiced agenda in general practice consultations: qualitative study, British Medical Journal, 320: 1246-1250.

Brey R.L., Holliday S.L., Saklad M.S., Navarrete M.G., Hermosillo-Romo D., Stallworth C.L. et al. 2002): neuropsychiatric syndromes in lupus. Neurology, 58: 1214-20.

Bricou O., Taieb O., Baubet T., Gal B. Guillevin L., Moro M.R. (2006): Stress and coping strategies in systemic lupus erythematosus: a review, Neuroimmunomodulation, 13, 283-293.

Danoff-Burg S., Friedberg F. (2009): Unmet needs of patients with systemic lupus erythematosus, Behavioral Medicine, 35 (Spring), 5-13.

Erikson EH., Ed. (1978): Adulthood. New York, Norton.

Hale E.D., Treharne G.J., Norton Y. et al. (2006): "Concealing the evidence": the importance of appearance concerns for patients with systemic lupus erythematosus, Lupus, 15, 532-540.

Hale E.D., Treharne G.J., Lyons a.C., et al. (2006): "Joining the dots": for patients with systemic lupus erythematosus, : personal perspectives of health care from a qualitative study. Ann. Rheumat. Diseases, 65, 585-599.

Hanly J.G., McCurdy G., Fougere L., Douglas J.A., Thompson K. (2004): neuropsychiatric events in systemic lupus erythematosus: attribution and clinical significance. J. Rheumatology, 31: 2156-2162.

McCracken L.M., Semenchuk E.M., Goetsch V.L. (1995): Cross-sectional and longitudinal analyses of coping responses and health status in persons with systemic lupus erythematosus, Behavioral Medicine, Winter;20(4):179-87.

Nery F.G., Borba E.F., Viana V.S.T., Hatch J.P., Soares J.C., Bonfa E., Neto F.L. (2008): Prevalence of depressive and anxiety disorders in systemuic lupus erythematosus and their association with anti-ribosomal P antibodies, Progress in Neuro-Psychopharmacology & Biological Psychiatry, 32, 695-700.

SLE IN CHILDREN

Dr. Reann Wai-po CHU
Specialist in Paediatrics, Union Hospital Consultant, Department of Paediatrics

Introduction:

- SLE in children basically shared the same etiology, pathogenesis, clinical manifestations, and the laboratory findings
- There are some prominent difference between children and adults which modified the clinical expression of the disease and caused additional impact on the clinical expression of SLE. These included:
- early expression of genetically determined abnormalities
- immaturity in immune system
- limited antigenic exposure
- immature skeleton
- potential for growth and development
- gonadal immaturity and variable hormonal levels
- SLE occurs predominantly in the pubertal and post-pubertal age range. Previous data showed girls and boys were affected with equal frequency in early childhood. Overall girls are affected 4.5 times more frequently than boys.
- Previous studies showed the prevalence of all patients with SLE in childhood onset has been estimated at 15% to 17%. There is a trend that it is now higher.

Clinical features:

- The manifestations of SLE in children are as diverse as in adults.
- The most common features are hematological involvements, mucocutaneous lesions, arthritis/ arthralgia in the initial presentation. And renal abnormalities usually presented as nephritis and nephritic syndrome.
- Childhood discoid lupus erythematosus are similar to those of adult type in presentation and chronic course. However, children have particularly high levels of transition to systemic disease.

Diagnosis:

- A low index of suspicion for SLE in children is important.
- Delayed diagnosis may be due to the non-specific complaints (such as weight loss, chronic low-graded fever, or malaise).
- There are many children who do not reached enough clinical criteria in the diagnosis of SLE in the beginning of the disease.
- A false assurance may lead to delayed diagnosis and other new symptoms might be overlooked.
- These children should be monitored over time for the evolution of the disease.

Treatment:

- is best achieved by a team of health care providers as most SLE children benefit from the continued care from the same team over the long course of their disease.
- The team should include a pediatric rheumatologist, nurse, social worker, and psychologist.
- Seek early consultation with nephrologists, dermatologists, nutritionists, and other sub-specialists are important.
- Planning for transition to an adult care environment should begin in the teenage years.
- The skill in treatment for SLE in children is actually learnt from adult experience.
- Due to unique problems related to growth and development in children, more judicious use of glucocorticoids and cytotoxic drugs has to minimized toxicity and maximized effectiveness in the disease.
- New agents such as MMF and the biologics are major advances in the management of severe situation in childhood SLE.

Outcomes:

- SLE is the most common rheumatic disease associated with significant morbidity and mortality in children. The severity of onset of SLE is usually greater in children than adults.
- Organ damage is as common as in the adults. Renal involvement is the most common complication.
- Cognitive impairment in childhood SLE is common. Headache is a frequent complaint. Adolescents commonly present with progressive deterioration in academic performance, withdrawal, and social isolation. Long disease duration was found to correlate with lower intelligence quotient score.
- Intercurrent infections and sepsis contribute significantly to the morbidity of children with SLE.
- Osteonecrosis secondary to steroid treatment and/or due to disease itself occurs in 10% to 12% of patients and contributes to a diminished function and quality of life.
- Although the cardiac disease is often silent and may be underestimated.

General comments:

- The psychological impact of SLE and its treatment make the care of children and adolescents distinct. They frequent have difficulty in internalize the concept of chronic disease, accepting their changed appearance, and facing the unwanted side effects and complications.
- Failure to deal appropriately with these issues often leads to non-compliance and a poor outcome.
- Children with SLE should not restraint on their general activity. Except during periods of severe active disease, regular school attendance should be expected. The child should be encouraged to participate in compatible extracurricular activities as the disease permits.
- There should be no limitations in food choice for children with SLE, but a well-balanced diet with appropriate caloric intake is important. Because of the risk of unwanted weight gain when the child is being treated with corticosteroid, early nutritional counseling should be provided.
- Education of patient, family, and teachers about the effects of treatment on body image assists the child and adolescent adapt to such changes.
- The mortality from SLE has been dramatically reduced in recent few decades. However the disability still remains serious threat to the child with SLE.

SLE IN CHILDREN

Hong Kong experience:

*Lupus nephritis is the mostly commonly present in children with SLE. It is a major determinant of long-term outcome. Clinical evident nephritis occurs in more frequent and of greater severity in children than in adults.

A recent report on a multicenter study of Chinese children in Hong Kong with lupus nephritis was made on children who had onset of disease younger than 19 years old. These patients were diagnosed with SLE between January 1990 and December 2003. After reviewing their clinical features, biopsy reports, treatment and outcome of these patients, there were 128 patients (eight boys, 120 girls; mean age: 11.9+/-2.8 years). About 50% presented with multisystem illness and 40% with nephritic/nephrotic symptoms. Negative anti-dsDNA antibodies were found in 6% of the patients. Renal biopsy revealed WHO Class II, III, IV and V nephritis in 13 (10%), 22 (17%), 69 (54%) and 13 (10%) patients, respectively. The clinical severity of the nephritis did not accurately predict renal biopsy findings. The follow-up period ranged from 1 to 16.5 years (mean+/-SD: 5.76+/-3.61 years). During the study five patients died (two from lupus flare, one from cardiomyopathy, two from infections). Four patients had end-stage renal failure (ESRF) (one died during a lupus flare). All deaths and end-stage renal failure occurred in the Class IV nephritis group. Chronic organ damage was infrequent in the survivors. The actuarial patient survival rates at 5, 10 and 15 years of age were 95.3, 91.8, and 91.8%, respectively. For Class IV nephritis patients, the survival rates without ESRF at 5, 10, and 15 years were 91.5, 82.3 and 76%, respectively. The survival and chronic morbidity rates of the Chinese SLE children in the present study are comparable to those of other published studies.

Reference

Textbook of Pediatric Rheumatology, Cassidy, Elsevier Saunders, 5th Edition, 2005, USA.
Lupus nephritis in Chinese children--a territory-wide cohort study in Hong Kong. Pediatr Nephrol. 2006;21:1104-12

HONG KONG ARTHRITIS & RHEUMATISM FOUNDATION

Organization Background

The Hong Kong Arthritis & Rheumatism Foundation (HKARF) was founded in October 2001 as a government approved non-profit making charitable organization. The primary objectives of the Foundation are to improve the understanding of arthritis and rheumatic disorders commonly seen in Hong Kong, and provide professional, social and financial support to sufferers of these conditions with the aim to improve their quality of life.

Financial support to Needy patients

The Foundation has set up a number of financial schemes to provide direct financial support for needy patients. The Patient Support Fund was set up to provide direct financial assistance to needy arthritis and rheumatic disease patients to purchase non-government subsidized medications and devices for arthritis rehabilitation, as well as home modification. The Patient Emergency Fund is to provide a one-off financial assistance for patients with sudden and unforeseen financial hardship or unexpected change in their health condition which requires immediate treatment. The Patient Activity Fund offers sponsorship to registered patient self-help groups or related organizations to organize social and educational activities that promote the well being of people with arthritis and rheumatism. The Expensive Drug Support Scheme is to make recommendations to pharmaceutical companies to provide discounts to patients who need the use of certain expensive drugs but cannot afford to pay for full cost of these medications.

Public education

The Foundation has also been proactive in promoting the awareness of rheumatic problems among the general public and education of people with arthritis of their conditions. The Foundation produced a number of pamphlets, educational booklets and VCDs for public and health care professionals to promote understanding of the disease as well as to improve health care workers skills in caring for clients with arthritis. Every year, the Foundation organizes regular education activities to echo the International Arthritis Day and arise public concern on the arthritis patients needs.

Education to health care professionals

The Foundation has cooperated with the Hong Kong Society of Rheumatology to set up a joint scholarship for supporting overseas specialty training in rheumatology. The Foundation has also established a research grant to encourage research activities carried out by health care professionals involved in the management of patients with rheumatic disorders. An interdisciplinary bulletin, CHARM (Care, Health, Arthritis & Rheumatism Management) that publishes twice a year, aims to provide health care professionals with up-to-date information in regard to multidisciplinary approach in the diagnosis, investigations, treatment and health care for patients with various rheumatic conditions.

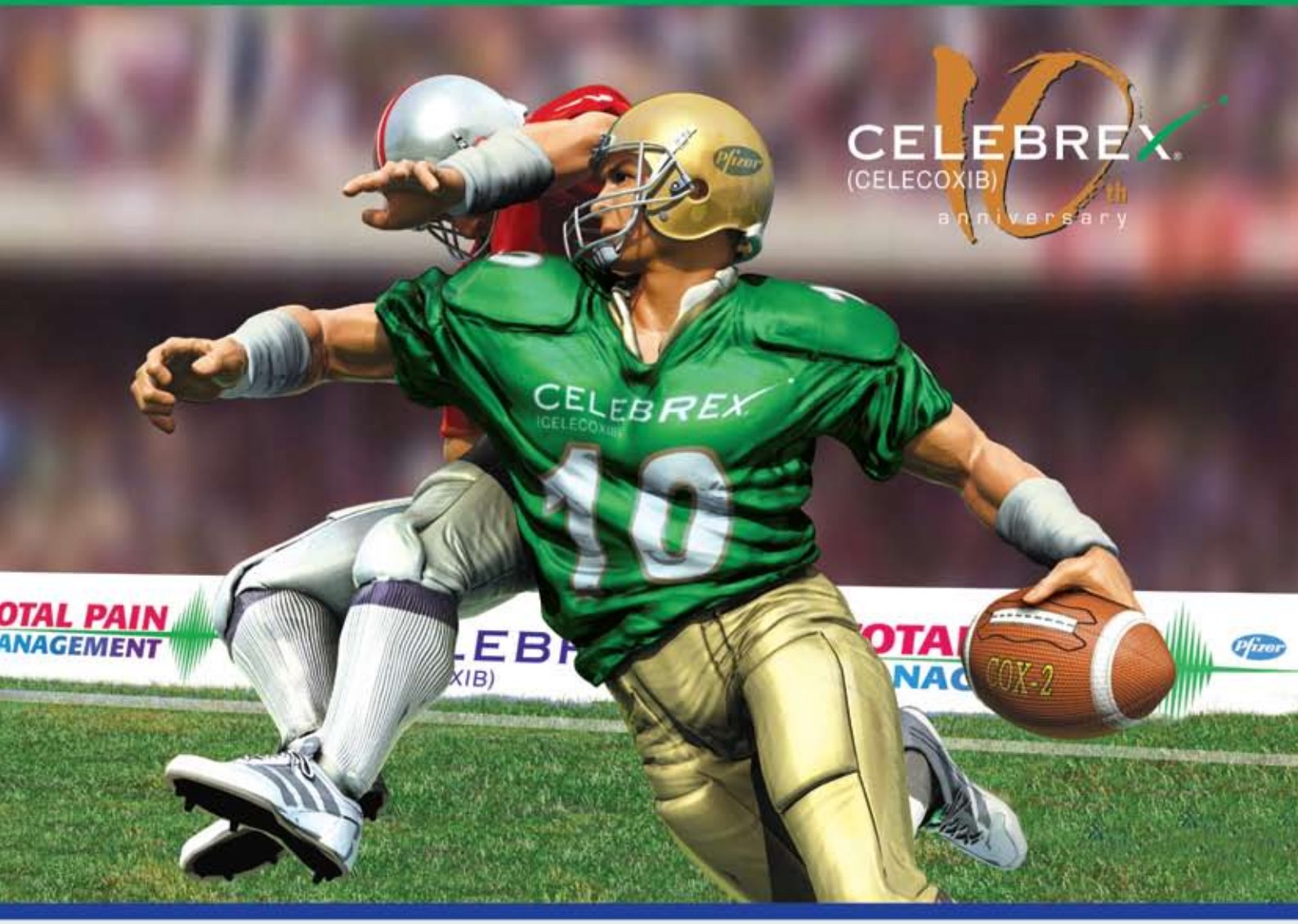
The application guideline and forms of all above programmes can be downloaded from the HKARF website. The updated Educational activities will also be found from HKARF Newsletter "Arthritis Care", "CHARM" and website http://www.hkarf.org/. You are also welcome to become a volunteer member of the Foundation. Please contact Ms Den Law 2346 6336 for further details.

Hong Kong Arthritis & Rheumatism Foundation Ltd.

Rm 14, G/F, HKSR Lam Tin Complex,
7 Rehab Path, Kwun Tong, Kowloon

Tel : (852) 2346 6336
Fax : (852) 2346 6136

Email : mail@hkarf.org
Websi : http://www.hkarf.org



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References: 1. Graham DY, Chan FK. Gastroenterology 2006;134:1240-1257. **2.** Nadarajah A, et al. Singapore Med J 2006; 47:534. **3.** Petri M, et al. J Rheumatol 2004;31:1614-20. **4.** Cheung R, et al. Clin Ther 2007;29 [Theme Issue]:2498-2510. **5.** Silverstein FE, et al. JAMA 2000;284:1247-1255. **6.** European Medicines Agency (EMEA. http://www.emea.europa.eu/. **7.** Food and Drugs Administration (FDA). http://www.fda.gov. **8.** Announcement of the launch of the selective COX-2 inhibitor Celecox(r) tablets in Japan. June 11, 2007. Available at: http://www.astellas.com/global/about/news/2007/pdf/070611_eg.pdf. Accessed September 12, 2008. **9.** Australian Therapeutic Goods Administration. http://www.tga.gov.au/ **10.** COFEPRIS. http://www.cofepris.gob.mx. Accessed September 4, 2008. **11.** Package insert of Celebrex as registered in South Africa. Available at: http://www.arthritis.co.za/celebrex_package.html. Accessed September 4, 2008. **12.** About Celebrex. 2008. Available at URL: http://www.celebrex.com/content/about_CELEBREX.jsp?setShowOn=../content/about_CELEBREX.jsp. Accessed June 26, 2008. **Full prescribing information is available upon request.**

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