various programs, as part of the training schedule or as a warming-down/relaxation procedure after an exercise session. Along with walking, warm water activities are best tolerated, but there are no contra-indications to endurance activities.

Compliance has been described as one of the major problems in exercise programs for FM patients. An inactive lifestyle is associated with poor physical fitness, and pain may further discourage participation in physical activities. If exercises are started in the deconditioned body, the unaccustomed physical activity may lead to more complaints and to further avoidance of physical activity. A vicious circle leading to less and less activity may ensue. This vicious circle is probably one of the reasons of low rates of volunteering, poor compliance with the program and/or program follow-up prescriptions, or drop-outs.

Self-management based programs will be illustrated with examples drawn from the literature and from our experience in Geneva.

Review session N° 3: Pregnancy and R. D. – Friday 15 June, 10.00-11.45/South Hall

SP0068 PREGNANCY AND RHEUMATOID ARTHRITIS

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Women will hardly ever get their first signs of rheumatoid arthritis (RA) during pregnancy, whereas the onset of RA seems to cluster in the postpartum period. This clinical and epidemiological observation may be explained by a postponement of the onset of symptomatic RA by pregnancy, which is in line with the observed amelioration of disease activity in women with established RA. Up to 75% of women with RA improve during pregnancy, starting in the first or second trimester with maximum improvement during the third trimester of pregnancy. More than 90% of these patients will experience a flare of their disease within two to six months after delivery. Women who have ever been pregnant have a lower risk of developing RA, particularly when they had their first pregnancy at an early age. Several biological mechanisms have been put forward to explain the favourable effect of pregnancy on the onset and course of RA, but there is still no fully satisfactory explanation. The profound hormonal shifts (e.g. increased estrogens, progesterone and corticosteroids) have been implicated in the favourable effect of pregnancy through their effect on the immune system. Pregnancy is an immunological challenge requiring immunological protection or tolerance for the partly non-self fetus. Cellular immunity is decreased during pregnancy, which may play a role in the positive effect of pregnancy in RA. Pregnancy is associated with decreased production of TH1 associated cytokines (IL2, interferon gamma), increased production of TH2 associated cytokines (IL-4, IL-10), and decreased production of proinflammatory cytokines (TNF alpha, IL-12). Alterations in the glycosylation of IgG have also been put forward as a possible explanation. The question why not all women improve during pregnancy is still not answered by the above mechanisms. There is some evidence that HLA disparity between mother and fetus will play a role in the suppression of autoimmunity, which will differ between different pregnancies. A better understanding in

how pregnancy exerts its effect on the onset and course of RA will help to unravel possible immunological mechanisms in RA and may lead to more effective treatments.

SP0069 PREGNANCY OUTCOME AND ANTI-RO/SSA ANTIBODIES

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Autoimmune phenomena seem to play a major role in the pathogenesis of unexplained pregnancy loss. The strong association of antibodies against ribonucleoproteins and neonatal lupus syndrome became soon apparent. Neonatal lupus syndrome, a classical model of passively acquired autoimmunity, results from the transplacental transfer of IgG anti-Ro/SSA between the 20th and the 24th week of pregnancy causing histopathological damage on developing tissues. It consists of congenital heart block (CHB), non-scarring cutaneous lesions, hepatitis, haemolytic anaemia and thrombocytopenia. A recent report supports that a significantly greater number of mothers whose children had CHB were asymptomatic compared with mothers of children with cutaneous disease. Specific maternal MHC class II genes seem to correlate with specific outcomes in neonatal lupus syndrome. A Japanese study suggests that certain maternal specific haplotypes were associated with CHB and cutaneous lesions.

The exact mechanism through which antibodies against ribonucleoproteins affect the fetal conductive system remains largely unknown. Maternal IgG anti-Ro/SSA and anti-La/SSB antibodies have been isolated from affected fetal hearts, while studies on human and animal models revealed possible arrhythmogenic effects of these antibodies. Apoptosis is proposed as a mechanism of translocation of intracellular Ro/SSA and La/SSB antigens to the cell surface of fetal cardiac myocytes, where they can be bound by cognate autoantibodies. In addition, it was shown experimentally that embryonic expression of certain constituents of the Ro/SSA molecule occurred some weeks before the clinical detection of CHB. Particularly, hYRNAs molecules between the 6th and 16th week of gestation, while an alternative 52b protein, recognised by the sera of mothers whose children had CHB, between 14–16 weeks. Finally, antibodies against a human endogenous retrovirus (ERV-3), which is expressed in fetal tissues particularly in the heart, were found to be elevated in mothers of children with CHB. IgG antibodies against a 57 kd protein and calreticulin are also proposed as additional risk factors in the pathogenesis of neonatal lupus syndromes.

Based on the hypothesis that unexplained pregnancy loss in autoimmune patients may represent intrauterine expression of neonatal lupus, several studies explored the possible association of anti-Ro/SSA autoantibodies and pregnancy loss in autoimmune patients. In initial studies such association was confirmed only among black women with SLE. Subsequently, in a large cohort study it was revealed that although the presence of anti-Ro/SSA antibodies did not affect the pregnancy outcome in SLE patients, it was strongly correlated with recurrent pregnancy loss in non-SLE patients, including patients with Sjögren's syndrome, rheumatoid arthritis and scleroderma. In a further study, a clear gradation risk between recurrent pregnancy loss and the number of different Ro/SSA peptides (Ro52, Ro60, p57) recognised by the sera of autoimmune patients was demonstrated. It is of interest that the association of these peptides with adverse pregnancy outcome did not alter by the presence of other autoimmune

factors as antithyroid and anticardiolipin antibodies. Particularly, the presence of antibodies against thyroglobulin appears to be an independent marker of recurrent pregnancy loss in these patients.

Management of CHB remains largely empirical. Several anecdotal reports have supported the use of steroid and non-steroid treatment including theophylline, salbutamol, furosemide, plasmapheresis and intrauterine fetal heart pacing with various results. Both therapeutic modalities improved hydrops fetalis, but only steroids seemed to reverse incomplete CHB. Recent study suggests the use of fluorinated steroids which are minimally metabolised in the placenta in fetuses with unstable conduction defects or hydropic changes. In conclusion, it is evident that pregnancy in anti-Ro/SSA positive women remains a diagnostic, pathogenetic, family counselling and therapeutic challenge.

REFERENCE

Abstract presented by H. M. Moutsopoulos

Genetic diseases with rheumatic manifestations – Friday 15 June, 14.00-15.30/Congress Hall

SP0071 COMPLEMENT GENE MUTATIONS

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Homozygous complement protein deficiencies are rare. However, the study of inherited deficiencies of complement proteins *in vivo* offer insights into the physiological activities of the complement system that are not readily available from *in vitro* analysis. The phenotype of complement deficiency varies according to the position of the missing component within the complement activation pathways. This demonstrates that different parts of the complement system subserve particular functions. For example, terminal complement component deficiency predisposes to recurrent Neisserial infections. Furthermore, individuals with classical pathway component deficiencies develop SLE. These observations have led to the hypothesis that the classical pathway protects against the development of SLE. However, the mechanism underlying this association has not been fully established. Recent findings obtained using animal models of complement deficiencies, suggest that the classical pathway plays an important role in promoting the physiological clearance of apoptotic cells. The discovery that apoptotic cells may be the source of autoantigens in SLE has led to the hypothesis that complement deficiency may promote autoimmunity by impairing the clearance of apoptotic cells.

To prevent host tissue injury and depletion of complement components, the complement system is tightly regulated by a series of proteins circulating in plasma and present on cell membranes. The major inhibitory protein of the alternative pathway is factor H (FH). Deficiency of this protein results in secondary depletion of C3 due to uncontrolled alternative pathway (AP) activation. This occurs commonly in individuals with C3 nephritic factor, an IgG autoantibody that stabilises the alternative pathway C3 convertase. Both individuals deficient in FH and

those with C3 nephritic factor develop membranoproliferative glomerulonephritis (MPGN). To explore the mechanisms by which uncontrolled C3 activation predisposes to MPGN, we have developed an *in vivo* model of factor H deficiency. FH deficient mice have secondary C3 deficiency, show large amounts of C3 deposited preferentially on the glomerular basement membrane and develop MPGN. Both partial and complete FH deficiencies have been associated with haemolytic uraemic syndrome (HUS) and the pathogenesis is poorly understood. This animal model will allow us to investigate the mechanisms by which C3 dysregulation predisposes to glomerulonephritis and HUS.

In conclusion, individuals and experimental models of complement deficiency prove to be an invaluable tool to investigate the role of the complement system in health and in disease.

REFERENCE

- 1 Pickering MC, Botto M, Taylor PR, Lachmann PJ, Walport MJ. Systemic lupus erythematosus, complement deficiency, and apoptosis. *Adv Immunol.* 2001;**76**:227-324

SP0072 THE GENETIC BASIS OF FMF

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Familial Mediterranean Fever (FMF) is a hereditary inflammatory disorder characterised by short self resolving attacks of fever and serositis, especially peritonitis and arthritis. The discovery of the FMF gene in the summer of 1997 has provided the first specific biological tool for FMF diagnosis, which can be pinpointed among various inflammatory disorders through mutation screening.

FMF is classically transmitted as an autosomal recessive trait. The FMF gene, MEFV, is located on chromosome 16p13.3 and comprises 10 exons. To date, 29 point-mutations have been detected in exons 1, 2, 3, 5, 9 and 10, but no gross rearrangement has been found. There are three mutational "hot spots": two in exon 10 (at codons 680 and 694) and one in exon 2 (codon 148). The 5 most frequent mutation M694V (42%), V726A (9%), M680I/C (8%), M694I (5%) and E148Q (5%) derive from a founder effect which likely accounts for their high prevalence. The other mutations are found in „T 1% FMF chromosomes, and about one third of the FMF alleles are to be identified. It is quite likely that a broad number of cases are not MEFV linked and suffer from "FMF like" symptoms. Four populations are commonly affected: Armenians, Arabs, Non-Ashkenazi Jews (NAJ) and Turks. Italians, Ashkenazi Jews and Spaniards should probably not be considered as rarely affected populations any longer, because the prevalence of FMF mutations is also relatively high in them. The disease is also sometimes suspected and genetically confirmed in patients with no classic ancestry (French, BritishK). Rare mutations are preferentially found in those cases.

The FMF clinical panel ranges from total absence of symptoms (incomplete penetrance) to amyloidosis. This relies at least partly on allelic heterogeneity. Homozygosity for M694V has been reproducibly demonstrated to be associated with a severe disease course. This genotype is practically fully penetrant. In contrast, about two third of E148Q homozygous individuals are asymptomatic. The trend is that genotypes including either E148Q or V726A are associated with low penetrance and low risk of amyloidosis, whereas genotypes including two of either M694V, M694I or M680I are associated with full penetrance