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

and a high risk of amyloidosis. Modifiers also affect the FMF phenotype. Recently, a Turkish study showed that patients with the G138 polymorphism in exon 2 are more prone to develop amyloidosis. MICA, the Major Histocompatibility Complex class I chain-related gene A, and SAA are two non-MEFV modifier loci. The impact of M694V homozygosity on the age at onset is aggravated if patients also inherited MICA A9, whereas MICA A4 is associated with a milder form of the disease. Renal amyloidosis is enhanced in patients with the SAA-1 alpha/alpha genotype and in males, each factor acting independently.

The MEFV mRNA is about 4kb length. It is expressed in mature neutrophils, eosinophils, monocytes, and in some cancer cell lines. It is upregulated *in vitro* by some proinflammatory mediators such as IFN. The protein encoded by MEFV was called Marenostin by the French group, and Pyrin by the International consortium. It is a 781 amino acid protein of a predicted 86 kd molecular weight. The predicted rodent proteins have considerable homology with humans, but do not have an intact C terminal domain, in which most FMF-associated mutations have been found in humans! It has been thought for a while that Marenostin/Pyrin was a transcription factor, because of the presence of two nuclear localisation sites in the gene sequence, and because of the presence of a zinc-finger motif. But immunofluorescent staining studies showed that unexpectedly, the protein was cytoplasmic and colocalized with microtubules. These data have been challenged recently by the finding of a deleted isoform that specifically binds to the nucleus. Thus identification of the MEFV function remains a difficult task.

Infection in paediatric rheumatology – Friday 15 June, 14.00-15.30/Forum Hall

SP0075 MACROPHAGE ACTIVATION SYNDROME AND SYSTEMIC JIA

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Systemic JIA is characterised not only by arthritis, but also by systemic features such as intermittent fever, lymphadenopathy, hepato-splenomegaly, exanthema and serositis. The disease occurs predominantly in childhood. It often begins at a young age and usually has a serious outcome, although new therapeutic regimes like high dose methotrexate, cyclosporine-A and TNF- α blockade have improved the prognosis.

A serious complication of systemic JIA is the Macrophage Activation Syndrome (MAS), which is often triggered by infections and medicines like gold and sulfasalazine. MAS is characterised by persistent high fever, mild to serious derangements of liver cell functions, purpura, encephalopathy and disseminated intravascular coagulation. Laboratory investigations often show a leucocytopenia, thrombocytopenia and anaemia in combination with elevated levels of bilirubin and hepatic enzymes. In the bone marrow and other organs like the lymphglands, liver and brain, haemophagocytizing histiocytes are demonstrable. Although they are not specific for MAS, the presence of haemophagocytizing histiocytes together with the other specific clinical symptoms enables the clinician to make the diagnosis.

MAS is a very serious, life-threatening complication of systemic JIA, which has to be treated with high dose corticosteroids, often in combination with cyclosporine. Even with this regimen the mortality rate is high.

Familial Haemophagocytic Lymphohistiocytosis (FHL), a congenital disease of childhood, is also characterised by haemophagocytosis. Recently, a defect in the perforin gene was found in patients with FHL. Because of the resemblance with MAS in systemic JIA, we have also investigated the perforin expression on cytotoxic CD8⁺ effector T-cells and NK-cells. We find a decreased expression of perforins in systemic JIA, which could play a role in the pathogenesis of the disease.

Osteoarthritis – Wednesday 13 June, 14.00-16.00/Forum Hall

SP0005 RISK FACTORS FOR OSTEOARTHRITIS

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Osteoarthritis (OA) is not a disease or a single condition. Diverse observations suggest that it may reflect the repair process of synovial joints. Sites commonly targeted by symptomatic OA include finger joints, knees and hips. These sites have different risk factors for development of structural OA. Different risk factors may relate to structural progression and outcome. Risk factors for pain and disability (such as muscle weakness and adverse psychosocial factors for the knee) may also differ from those relating to structural change.

Risk factors for development of structural OA are divisible into general constitutional factors and local, predominantly biomechanical factors. Important constitutional factors include heredity and ageing (all sites); Caucasian ethnicity (hip); female gender (hands, knees); and obesity (knees). Overt trauma can predispose to OA, but so may specific repetitive activities relating to occupational and recreational usage (eg football, knee bending while load carrying – knee OA; farming – hip OA). Possible negative associations include osteoporosis (hip >knee) and smoking (knee >hip). The role of poor nutrition (especially low antioxidants and vitamin D) in development and progression of knee and hip OA merits further study.

The genetic study of OA promises important insights into pathogenesis. A strong genetic contribution to OA of the hand, knee and hip has been shown using strategies such as: classic twin study; estimation of the relative risk of OA in siblings of OA patients; and segregation analysis of clustering of OA within families. Through candidate and genome wide association studies of affected sibling pairs, genetic associations are now being identified on several chromosomes (notably 2q, 11 and 16) and it is hoped that predisposing genes will shortly be identified. Inheritance is likely to be polygenic and to involve common polymorphisms, each with a relatively low attribution to OA. The next stage will be gene-gene and gene-environmental interaction studies to determine how individual genes and constitutional or environmental factors interrelate to cause OA and to modify its progress.