Fibromyalgia (FM) is a syndrome of unknown aetiology characterised by chronic wide spread pain, increased tenderness to palpation and additional symptoms such as disturbed sleep, stiffness, fatigue and psychological distress. Familial aggregation of FM is common. Depressive symptoms and psychological distress is a frequent finding in FM patients and their relatives.¹ These findings suggest that genetic and familial factors may play a role in the etiopathogenesis of this syndrome. In a recent linkage analysis of 40 FM multicase families it was shown that the HLA region might be a candidate for genetic transmission of vulnerability for the disorder.²

The pathophysiological mechanisms underlying fibromyalgia have been linked to disturbances in serotonin (5-HT) metabolism and transmission. Among the different parameters of the serotonin pathway the genes coding for the 5-HT receptors and transporters are interesting candidates to investigate a genetically driven predisposition to FM. Recent studies have analysed silent and functional polymorphic variants of these genes in patients with fibromyalgia.^{3,4,5}

- The human 5-HT transporter (5-HTT) is encoded by a single gene on chromosome 17q12. A functional polymorphism in the transcriptional region has been described ("long allele" L or "short allele" S). In a study of 62 FM patients a higher frequency of the S/S genotype of the 5-HTT was found compared to healthy controls. The S/S subgroup revealed higher means in depression and psychological distress.
- The 5-HT_{2A} receptor gene is located on chromosome 13q14–21. A silent T102C polymorphism of the 5-HT_{2A} receptor gene has recently been detected. In a sample of 168 FM patients a statistically significant different distribution of genotypes was found with a decrease in T/T and an increase in both T/C and C/C genotypes compared to controls. A correlation of genotypes with pain variables revealed higher scores in the tenderpoints score in patients with the T/T genotype. Correlations with psychopathological symptoms were not significant.
- The 5-HT_{2C} receptor gene is located on the X chromosome. In a sample of 65 FM patients the presence of the 5-HT_{2C} (C32S) mutant was significantly correlated with measures of psychological distress. In the same sample the tryptophan hydroxylase (TPH) gene was analysed. The TPH gene is located on the short arm of chromosome 11 and a polymorphism in intron 7 has recently been detected. The TPH is the rate limiting enzyme that determines the concentrations of serotonin *in vivo*. No significant different frequencies of the alleles were found in this group of FM patients compared to control subjects.

The implication of these findings for the etiopathogenesis of fibromyalgia is far from clear and have to be replicated in larger and ethnical different samples. But these results might point to a disturbance on 5-HT-receptor and transporter level at least in a subgroup of FM patients and emphasises the importance of the serotonergic system in the pathophysiology of FM.

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SP0064 DRUG THERAPY IN FIBROMYALGIA. A REVIEW

E Thomas, F Blotman. *Rheumatology, Lapeyronie Hospital, Montpellier, France*

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Since the cause and pathophysiology of fibromyalgia (FM) remain unknown, treatment is often limited; fewer than 50% of patients have significant and sustained clinical improvement. No pharmacologic agent are indicated specifically for FM treatment, although many have been tried to date. Controlled trials with non-steroidal anti-inflammatory drugs have been shown them to be of little help, despite their use in a majority of patients. Steroidal anti-inflammatory drugs are not efficacious and often deleterious. Among analgesics, preliminary data suggest that tramadol, affecting norepinephrine at the receptor site, may be useful for FM pain. No clinical data are available to suggest efficacy of opioids in FM. Tricyclic antidepressants and selective serotonin reuptake inhibitors may diminish the sleep disturbance, pain and depression associated with FM. they remain the cornerstone of drug therapy in FM. Blockade of the serotonin receptor subtype 5-HT₃ with Tropisetron or Ondansetron has been reported to significantly decrease the number of tender points, despite poor digestive tolerance. The findings of low levels of insulin-like growth factor 1 in FM led to give daily growth hormone (GH) injections to 22 women (vs placebo to 23), enrolled in a controlled study. A 9 months, the tender point score was significantly improved with GH. other agents like 5-hydroxytryptophan, gamma-hydroxybutyrate and S-adenosyl-L-Methionine also shown promising results. FM symptoms may be alleviated in a short term manner with various pharmacologic treatments but a minority of patients still experience remission at a few years follow-up.

SP0065 FIBROMYALGIA: PAIN MANAGEMENT STRATEGIES

¹C Cedraschi, ²J Desmeules, ¹TL Vischer. ¹Rheumatology Division, Geneva, Switzerland; ²Clinical Pharmacology and Toxicology Division, Geneva University Hospital, Geneva, Switzerland

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At present, there is no specific treatment for FM, partly because of the lack of understanding of its aetiology and pathogenesis. Self-management based programs have been proposed to help the patients cope with their symptoms and improve their quality of life. These programs mainly use information, physical conditioning, and cognitive-behavioural techniques.

Information in chronic pain patients has been emphasised as an important component as a well-informed patient is an essential member of a successful chronic illness management team. Acknowledging FM patients' pain and suffering is also a key point in these programs.

FM patients have been shown to have functional impairment which include their ability to perform daily activities. They have decreased muscle strength and endurance, and low levels of physical fitness. Exercise programs are various and may include range-of-motion exercises, cycling, walking, swimming, specific muscular reinforcement, etc. Pool exercises have been used in

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

M Hazes. *Department of Rheumatology, University Hospital Rotterdam – Dijkzigt, Rotterdam, The Netherlands*

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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

C Mavragani, HM Moutsopoulos. *Department of Pathophysiology, School of Medicine, National University of Athens, Athens, Greece*

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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