Oral presentations

V1.2 RECOGNITION OF MULTIPLE HSP60 EPITOPES IN PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS OPENS THE WAY FOR ANTIGEN-SPECIFIC IMMUNOTHERAPY

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Objective: We previously showed that in Juvenile Idiopathic Arthritis (JIA) patients human and bacterial heat shock protein 60 can be the target of (autoimmune) T cell responses. To determine potential target epitopes for immunotherapy, we needed to identify hsp60 epitopes recognized by a majority of JIA patients. The polymorphic HLA background in JIA has hampered this before.

Methods: With the usage of a novel computeralgorithm (Sette, Eppimmune, La Jolla, CA), predicting potential pan-DR binding sites on a given protein sequence, eight different T cell epitopes on both human and mycobacterial hsp60 have been identified and tested for T cell responses in JIA patients.

Results: All eight peptides yielded clear T cell responses (T cell proliferation and cytokine production), each in a majority (60-100%) of JIA patients. Interestingly we found production of TNF-α, IFN-γ and IL-10; the production of both IL-10 and IFN-γ strongly suggests the induction of regulatory T cells. One of the identified mycobacterial epitopes, had only minor changes compared tot the peptide that induced protection in Adjuvant Arthritis, and there was a clear correlation between the T cell response to this mycobacterial peptide and its human analogue. This underlines that we have found a subset of T cells crossreacting between self and non-self hsp60.

Conclusion: We have identified eight hsp60 epitopes recognized by a majority of JIA patients. The cytokine response induced by these peptides suggests the induction of regulatory T cells. Further analysis is currently being performed to unravel in detail the nature of the found T cell responses.

V1.3 HUMAN HSP60 INDUCES REGULATORY T CELLS EXPRESSING CD30 IN THE REMITTING FORM OF JIA

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Of Juvenile Idiopathic Arthritis (JIA) the oligoarticular form has a relative benign clinical course, whereas polyarticular and systemic JIA are non-remitting, crippling diseases. We reported earlier that patients with JIA show T-cell reactivity to human and mycobacterial heat shock protein 60. Most of this reactivity is found in children with oligoarticular disease and seemed correlated with disease remission. Now we analyzed in a group of oligoarticular and polyarticular JIA patients the expression of CD30 (a Th2-marker) and the induction of regulatory cytokines in responsiveness to human and mycobacterial hsp60. We found that in vitro activation of PBL and SF derived mononuclear cells with both human and mycobacterial hsp60 induces an high expression of CD30 on a subset of CD4+ and CD8+, activated (HLA-DR-positive), memory (CD45RO-positive) T-cells. The expression of CD30 induced by human hsp60 was much higher than induced by mycobacterial hsp60 and almost exclusive to oligoarticular patients.

In the same culture conditions, we found that T-cells activated with hsp60 showed characteristics of regulatory cells. We detected IL10 and IFN-γ by ELISA in the supernatants of with mycobacterial and human hsp60 activated cells, a well as by intracellular staining and flowcytometry in the cytoplasm of CD4+ T-cells. Even more, using the latter technique we found IL10 and IFN-γ double positive T-cells, suggesting the involvement of regulatory T-cells.

Conclusion: Disease remission in oligoarticular JIA is due to T-cell regulatory events leading to the expression of CD30 and the production of disease suppressive cytokines. The earlier documented raised expression of hsp60 in the inflamed synovial may be a crucial trigger for the development of such regulatory T-cells.

V1.4 FUNCTIONALLY SIGNIFICANT IL-6 ALLELIC ASSOCIATIONS IN SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS (SJIA)

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We have previously reported the under-representation of the CC-174 genotype of interleukin-6 (IL-6) in children with sJIA with early onset (poorer prognosis) disease at ⩽5 years of age, and that the G-174 allele is a higher expresser of IL-6 than C-174. The potential influence of other 5'-flanking region polymorphisms of IL-6 (G to A at position –598 and G to C at position –572) in combination with –174, was investigated in genotyping studies of 92 sJIA patients and 383 healthy controls, in transient transfection studies and electrophoretic mobility shift assays (EMSA).

A-598 showed strong allelic association with C-174, and G-598 with G-174 in controls and sJIA patients (linkage disequilibrium:δ=0.704). C-572 (rare allele) showed weak allelic association with G-174 (LD:δ=0.195). In transfection studies in HeLa and 3T3 cells, common haplotype G-598G-572G-174 was a significantly higher expresser of IL-6 than haplotype A-598G-572C-174 (p=0.049), consistent with –174 allelic effects. There was no independent functional effect of the –598 polymorphism when G-598G-572G-174 and A-598G-572G-174 were compared. G-598C-572G-174 was a higher expresser than G-598G-572G-174 (p=0.005), indicating an independent functional effect of the –572 polymorphism. There was no significant difference in IL-6 expression between haplotypes in Huh 7 cells suggesting that these functional effects are cell specific. In EMSA studies, the C-174 allele bound a HeLa nuclear factor between –184 and –134 more strongly than the G-174 allele, with C-174 requiring higher concentrations of cold probe to compete the band out than G-174 (approx. 2-fold difference). C-174 cold probe was a stronger competitor than G-174 cold probe. There were no differences between G-598 and A-598.

In conclusion, there are functionally significant allelic associations between –174, -572 and –598 polymorphisms of IL-6, but only –174 and –572 exert independent effects on IL-6 regulation with implications in disease severity for sJIA.

V1.5 STUDY OF THE INSULIN-LIKE GROWTH FACTOR-I (IGF-I) SYSTEM IN INTERLEUKIN-6 (IL-6) TRANSGENIC MICE

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Low levels of IGF-I and IGF binding protein-3 (IGFBP-3) are present in chronic inflammatory diseases associated with stunted growth. IL-6 transgenic NSE/hIL-6 mice, expressing elevated levels of IL-6 since birth, present growth impairment associated with low levels of IGF-I and IGFBP-3. Here we demonstrate in NSE/hIL-6 mice proteolytic degradation of IGFBP-3 by a serum protease activity that appears, by zymogram, to be secondary to metalloproteinase-2 (MMP-2). Therefore, decreased circulating levels of IGFBP-3 are, at least in part, due to increased degradation. Gel chromatography show that low levels of IGFBP-3 cause impaired formation of the ternary complex, comprising IGF-I, IGFBP-3 and ALS. Pharmacokinetic studies following an i.v. bolus of IGF-I show a 2-fold increase in total plasma clearance in transgenic (0.029ml/min/g) compared to wild-type mice (0.015), associated with a decreased $T_{1/2(beta)}$. Therefore, impaired ternary complex formation causes an increased clearance of IGF-I. Administration to NSE/hIL-6 mice of IGF-I (1μg/gr s.c. twice daily) or of IGF-I complexed with IGFBP-3 (9 μg/gr s.c. twice daily) led to increased mortality ($p<0.05$) in transgenic mice with no deaths in wild-type littermates. Defective ternary complex formation due to low IGFBP-3 levels and increased proteolytic

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degradation of IGFBP-3 appears to explain the increased mortality to administration of IGF-I alone and of IGF-I complexed with IGFBP-3 respectively, exposing the animals to the acute toxic insulin-like effects of IGF-I. This study provides information relevant to the development of therapeutic approaches aimed at correcting abnormalities of the IGF-I system and subsequently of stunted growth in chronic inflammatory diseases.

V1.6 A NOVEL 5' FLANKING REGION POLYMORPHISM OF MACROPHAGE MIGRATION INHIBITORY FACTOR (MIF) IS ASSOCIATED WITH UK JUVENILE IDIOPATHIC ARTHRITIS

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Background: MIF is a ubiquitously expressed protein that has pro-inflammatory, hormonal, and enzymatic activities. Uniquely, MIF release from immune cells can be biphasically regulated by glucocorticoids. Meazza et al. recently described significant increased levels of MIF within the serum and in the synovial fluids of children with JIA. We used dHPLC to screen the 5' flanking region of the MIF gene and identified a G to C polymorphisms at position –173 (ref: Genbank Accession no: L19686). This nucleotide change creates an AP-4 transcription factor binding site. The MIF-173 G/C polymorphism was used to screen a large panel of UK caucasian JIA patients and unrelated healthy controls.

Methods: The presence of a C at –173 of MIF introduces an AluI restriction enzyme site. Polymerase chain reaction—restriction fragment length (PCR-RFLP) was used to genotype UK caucasian JIA patients and healthy caucasian controls.

Results: The allele and genotype frequencies were significantly different between the JIA patients and control panel. Possession of a MIF-173*C allele gives an approximately 2 fold increased risk of JIA susceptibility (OR 1.9; 95% CI 1.4 –2.7).

Table 1 Comparison of MIF –173 C/G allele frequencies (%) in JIA patients vs Controls

Allele	*JIA cases (2n=1052)*	*Controls (2n=518)*	*P value*
MIF-173*G	852 (81.0)	460 (88.8)	
MIF-173*C	200 (19.0)	58 (11.2)	P<0.0001

Conclusions: Polymorphisms within MIF may predict both an individual's predisposition to chronic inflammation and their sensitivity in terms of response to exogenously administered steroid treatment. The –173 G/C polymorphism we describe is the first report of a SNP in the MIF gene. This polymorphism is strongly associated with JIA.

V2.1 THE PROLONGATION OF QT INTERVAL IN INFANTS WITH TRANSPLACENTALLY ACQUIRED ANTI-SSA/RO ANTIBODIES IS REVERSIBLE UPON DISAPPEARANCE OF MATERNAL AUTOANTIBODIES FROM THE BABIES' CIRCULATION

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We have recently shown that infants born to mothers who carry anti-SSA/Ro autoantibodies may show a QT interval prolongation at EKG even in the absence of congenital heart block. Since a QT prolongation is a risk factor for arrhythmias and sudden death during the first year of life, we have followed these children with EKG until disappearance of autoantibodies. Twenty-one anti-Ro positive infants born from mothers with connective tissue diseases entered our study. Sera were analyzed for anti-Ro antibodies after birth and during the follow-up. A standard 12 lead-EKG was recorded in each subject during the first months of life and at one year of age. QT interval was corrected for heart rate.

At 1 year all infants were antibody-negative. PR interval and QRS duration did not change significantly, while QTc (442 ± 35 msec in the first EKG) significantly decreased, to 413 ± 20 msec at 1 year (P = 0.001). Moreover, 9/21 of the infants had a QTc 440 msec (the upper normal limit) in the first EKG, while all infants had a QTc within the normal limits at 1 year of age. In the five infants with the more prolonged QTc, a 24-hour Holter analysis confirmed this prolongation; at 1 year, the Holter recordings showed normal QTc values during the 24 hours.

In conclusion, a QT interval prolongation at EKG can be associated with transplacentally acquired SSA/Ro autoantibodies, but normalizes within the first year of life. This supports the hypothesis that autoantibodies can be pathogenic.

V2.2 INTERNATIONAL CONSENSUS FOR CORE SETS OF OUTCOME MEASURES FOR DISEASE ACTIVITY (DA) AND DISEASE DAMAGE (DD) ASSESSMENT. PART I: JUVENILE SYSTEMIC LUPUS ERYTHEMATOSUS (JSLE)

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Objective: To identify core sets of outcome variables for JSLE DA and DD assessment.

Methods: 2 consensus methodologies were used: Delphi Technique, a set of well defined mail surveys, and Nominal Group Technique, a structured meeting designed to reach consensus. The 1st survey was designed to select variables used in current clinical practice to assess if a child has responded to therapy. The 2nd survey was to rank the top 10 variables listed by ⩾ 10 physicians in the 1st survey. Next 40 pediatric rheumatologists from 34 countries met to select the domains (broad concepts that groups variables) and the list of variable(s) to measure each domain of both core sets.

Results: First survey: 174/267 (65%) physicians responded with 41 variables listed by ⩾ 10 responders. Second survey: 221/277 (80%) responded with the same top 17 variables selected by both PRINTO and PRCSG members. Consensus conference results: for each core set domains are listed with variables to measure each domain reported in parenthesis. JSLE DA core set: 1) physician's global DA assessment (10 cm visual analogue scale-VAS); 2) health related quality of life (HRQOL) assessment (Child Health Questionnaire-CHQ); 3) parent/patient's global assessment of overall well being (10 cm VAS); 4) immunological laboratory assessment (anti-DNA titer); 5) kidney assessment (24 hour proteinuria and serum creatinine); 6) global JSLE DA tool (Systemic Lupus Erythematosus Disease Activity Index-SLEDAI). Domains (and variables in parenthesis) included in the JSLE DD core set were: 1) global JSLE DD tool (Systemic Lupus Collaborating Clinics/American College of Rheumatology Damage Index-SLICC/ACR DI); 2) physician's global DD assessment (10 cm VAS); 3) HRQOL assessment (Child Health Questionnaire-CHQ); 4) growth and development (height, weight, menses, Tanner Stage).

Conclusion: We propose DA and DD core sets as a minimum list of domains (and variables to measure those domains) for future short and long term JSLE clinical trials, and for current clinical practice to decide if a child has responded to treatment. A prospective large-scale international data collection effort is in progress to validate the DA/DD core sets. A second consensus conference will establish a definition of improvement that may be used in future JSLE clinical trials.

V2.3 CENTRAL NERVOUS SYSTEM COMPLICATIONS IN TWO CASES OF JUVENILE ONSET DERMATOMYOSITIS

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Juvenile dermatomyositis is now recognised to be a disorder based upon a primary vasculopathy of small blood vessels with a significant risk of internal organ involvement, such as interstitial lung disease and gastrointestinal perforation. Central nervous system (CNS) complications are rarely reported in inflammatory myositis conditions with only 3 previous cases published.

We report two children aged four and ten years respectively with a diagnosis of juvenile dermatomyositis, both of whom developed clinical features of severe CNS involvement consistent with cerebral vasculopathy.

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Case 1 was a 4 year old girl with onset of severe ulcerative JDM with typical features from 2 ½ yrs. She had a poor response to oral steroid therapy and was deteriorating steadily to be nearly bed bound with severe ulcers, and thus started cyclophosphamide and IV steroids. Rapid clinical improvement followed this initially, but she then developed sudden onset of status epilepsy, and subsequent rapid neurological deterioration and died from apparent brainstem disease. MRI confirmed multiple small lesions in the brainstem which were considered both new and old (lacunae like), indicating possible previous ongoing CNS disease. MRA was negative

Case 2 is a 10 ½ year old girl who had onset of classic JDM with a marked polyarthritis at 10 years which was initially responding slowly to treatment with steroids and methotrexate. She developed a sudden onset of seizures, increasing in frequency over one week. MRI, MRA and EEG were unremarkable, and she responded to IV methyprednisolone and cyclophosphamide treatment. She then went on to have pseudo seizures in the subsequent months, and clinical depression thought possible to be either disease related or due to high dose steroid use. These have improved steadily over time as has her overall disease. She was ANA positive and anti-RNP antibodies but in low titre. She has subsequently developed a mild Raynauds and mild sclerodactyly appearance to her fingers, and avascular necrosis of the tibia and humerus.

Conclusions: CNS involvement has rarely been reported, in JDM but may be under-recognised. The vasculopathy or "vasculitis" underlying JDM is known to have a systemic distribution, and may be responsible for these complications. MRA and angiography might be useful, but in small vessel disease may be insensitive. Biopsy or post mortem was not done in either case.

V2.4 ETHNIC DIFFERENCES IN THE INCIDENCE OF VASCULITIS IN CHILDREN

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The aim of this study was to determine the incidence and ethnic distribution of Henoch-Schönlein Purpura (HSP), Kawasaki Disease (KD), and rarer primary systemic vasculitis (PSV) in children resident in a region of the UK with a richly diverse ethnic mix.

Methods: Prospective monthly questionnaires were sent to 321 paediatricians, and other relevant hospital consultants, with a mean return rate of 71.1% over 3 years (1996-99). Case ascertainment was verified by review of a further 406 case notes with diagnostic codes for vasculitis, and a single questionnaire sent to 2860 primary care doctors (return rate 59.7%).

Results: 586 new cases of vasculitis fulfilling established diagnostic criteria were collected prospectively from the 1.2 million children resident in the region. All Asian children originated from the Indian subcontinent. Asian children had the highest incidence of KD and rarer PSV, whilst Asian and black children had the highest incidence of SLE, and juvenile dermatomyositis (JDMS).

The annual incidence of HSP was 22.1/100,000 under 14 years (95% CI 19.2-25.0), and 70.3*/100,000 between the ages of 4-6 years (95% CI 54.2-86.4). The annual incidence of KD rose to 5.5/100,000 in children under 5 (95% CI 3.1-7.8), and 14.6* /100,000 (95% CI 1.3-27) in Asian children under 5 years. In girls over 11 years the annual incidence of SLE was 12.3*/100,000 (95% CI 7.3-17.3). Clusters of KD (time: 180 days, space: 1500m) and HSP (time:120 days, space: 1500m) reached significance p=0.05.

Conclusion: This study has estimated a high incidence of vasculitis in non-oriental Asian and black children, and a higher incidence of HSP than previously reported. Genetic and environmental influences may be involved.

V2.5 THE CLINICAL FEATURES OF KAWASAKI DISEASE AND INCOMPLETE KAWASAKI DISEASE IN INCIDENCE COHORTS

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The American Heart Association criteria for Kawasaki disease (KD) identify a core group of children at risk of coronary artery aneurysms (CAA), but children who fail to fulfil these criteria remain at risk of CAA. Identifying these children is a difficult clinical dilemma. Our aim was to compare the clinical features of incidence cohorts of children with and without complete diagnostic criteria.

Methods: 1.1 million resident children were surveyed over 3 years. Data were collected by monthly questionnaires sent to 321 hospital consultants, a single questionnaire sent to 2860 general practitioners, and review of 406 case notes with hospital codes for vasculitis. KD cases fulfilled the AHA diagnostic criteria. Incomplete Kawasaki disease (IKD) was defined as children with typical fever, and three other diagnostic criteria.

Results: 73 children with KD and 20 with IKD were identified from 164 reported to the study. 58 additional children lacked sufficient criteria for either group and were rejected. The estimated annual incidence <5 years old was 5.5 per 100,000 (95%CI 4.2-7.1 per 100,000) for KD, and 2.4 per 100,000 (95%CI 1.4-3.9 per 100,000) for IKD. 3 children with KD, 1 child with IKD and 1 child in the rejected group developed CAA (risk compared to KD = 0.8 IKD, 0.4 rejects). Lymphadenopathy and conjunctivitis were reported less in IKD than KD (ratio 0.4:1), misery was more often reported (2.5:1). In all groups late peeling of the extremities was more frequently recognized than early erythema and oedema. There was no significant difference in the mean time to presentation (10.6 (0-54): 9.6 (0-37) days), the ethnic mix (comparative risk for Asian children 0.73) or the median age (3.2:3.5 years) between KD and IKD respectively.

Conclusions: Inclusion of children missing one criterion for the diagnosis of KD identifies an additional 40% who had a comparable risk of CAA, similar population characteristics to children with KD, and other non-criteria features of the illness. The enormous contribution of all consultants, general practitioners and medical records staff in the West Midlands supporting this study is acknowledged. J Gardner-Medwin is an Arthritis Research Campaign clinical lecturer.

V2.6 EXPRESSION OF CALCIUM-BINDING PROTEINS MRP8 AND MRP14 IN INFLAMMATORY MUSCLE DISEASES

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Idiopathic inflammatory myopathy (IM) encompasses a heterogeneous group of muscle diseases including dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). To investigate the pathological role of monocytes in all these disorders we analysed the expression of two calcium-binding proteins (MPR8 and MRP14), which are expressed by inflammatory active subpopulations of monocytes. We have investigated the expression and local distribution of MRP8 and MRP14 in muscle biopsies of 33 patients with IM immunohistochemically. In DM (n=12), PM (n=12) and IBM (n=9) perimysial monocytes and macrophages (CD68) do almost not express MRP8 and MRP14. In contrast, MRP8 and MRP14 high expressing monocytes are the most abundant cell type in necrotic myofibers, which was confirmed by double-labeling experiments (MRP8 or MRP14 and CD68). Using cell culture experiments we found a direct inhibitory effect of MRP8/MRP14 on proliferation and differentiation of C2C12 myoblasts and a time and concentration dependent induction of apoptosis after treatment with purified MRP8/MRP14.

*Table 2 Incidence of vasculitis (95% CI) per 100,000 children/year. *p<0.01 from other ethnic groups*

	% paediatric HSP (2 year data)	*KD n = 463*	*SLE n = 73*	*JDMS n = 28*	*Rare PSV n = 14*	*population n = 8*
All		20.4 (18.6-22.4)	2.1 (1.7-2.7)	0.8 (0.5-1.2)	0.4 (0.2-0.7)	0.24 (0.1-0.5)
Asian	10%	24.0 (18.2-31.2)	4.9* (2.8-7.8)	5.6 (3.0-9.5)	0.6 (0.1-2.1)	1.7* (0.5-4.4)
Black	3%	6.2* (1.7-16.0)	2.1 (0.3-7.5)	3.1 (0.6-9.1)	2.1* (0.3-7.5)	–
White	86%	17.8 (16.0-19.8)	1.9 (1.4-2.4)	0.4* (0.2-0.7)	0.3 (0.2-0.6)	0.14 (0-0.4)

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Conclusion: The expression of MRP8 and MRP14 in DM, PM, and IBM correlate with disease activity and inflamed destruction of muscle fibers in IM. Our results indicate that activated monocytes exhibit a destructive effect in the inflammatory process of IM by secretion of MRP8/MRP14.

V3.1 KL-6, THE NEW MARKER OF INTERSTITIAL PULMONARY INVOLVEMENT IN CHILDREN WITH AUTOIMMUNE RHEUMATIC DISEASES

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Background: Interstitial pulmonary fibrosis is the most severe pulmonary manifestation of autoimmune rheumatic diseases in children. Noninvasive, serological marker which would be specific and sensitive enough is still missing in diagnostic procedure of this condition. Several papers published during last few years suggest that mucin-like mucoprotein KL-6 could meet these requirements.

Objective: To compare KL-6 concentrations in sera of children with autoimmune rheumatic diseases with and without pulmonary involvement and follow the effect of methotrexate treatment on circulatory KL-6.

Material and methods: In the group of 39 children (29 patients with juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis and vasculitis and 10 healthy controls) blood KL-6 concentrations were measured using ELISA test (EISAI, Japan). Functional pulmonary test and blood gases measurement were used to discover pulmonary involvement. Mann-Whitney test was performed for statistical analyses.

Results: Circulating KL-6 concentrations in patients with pulmonary involvement were significantly higher compared to mean concentration in the group without pulmonary involvement and healthy controls (800,17 ± 448,06 vs 421,67 ± 151,7 vs. 315,2 ± 120,73 IU/ml, p<0,05). KL-6 concentrations correlated negatively with capillary blood oxygen saturation (R = -0,067, p<0,001) and FVCex% (R = -0,425, p<0,05). Methotrexate treatment did not influence KL-6 concentrations (446,38 ± 178,06 v s 445,83 ± 239, NS).

Conclusions: KL-6 seems to be a good marker of interstitial pulmonary involvement in children with autoimmune rheumatic diseases.

V3.2 KL-6 AS A MARKER OF INTERSTITIAL LUNG DISEASE IN PATIENTS WITH JUVENILE SYSTEMIC SCLEROSIS (JSS)

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KL-6 is a mucin-like glycoprotein that is produced mostly by type II pneumocytes and has been shown to be a marker of pulmonary fibrosis and disease activity during interstitial lung diseases. We measured the circulating levels of KL-6 in patients with JSS to investigate the value of this marker in discrimination of patients with pulmonary involvement (PI) and in determination of disease activity. KL-6 levels were measured in 39 serum samples from 12 patients with JSS in different stages of the disease and in 20 age-matched healthy controls using a specific ELISA. All patients had the diffuse cutaneous form of JSS, 6 of them with PI. In 3 patients we measured KL-6 before and after autologous bone marrow transplantation (aBMT). The mean value of serum KL-6 levels in healthy controls was 310,5±113,9 U/ml. In patients with JSS without PI serum levels of KL-6 (345,3±151,7 U/ml) were comparable to those of controls. On the contrary, in JSS patients with PI serum KL-6 levels (1758,9±1172,5 U/ml) were significantly (p<0,001) higher than those of healthy controls and those of patients without PI. Longitudinal studies of patients with PI showed that KL-6 levels generally reflected disease activity and the extension of the fibrosis defined by clinical and radiographic examination, while functional tests showed no correlation. Two of three patients who underwent aBMT showed a marked favorable response and were able to stop immunosuppressive treatment; their KL-6 levels remained unchanged (1688 vs. 1809 U/ml) or decreased (3718 vs. 1286 U/ml). The third patient did not respond to a BMT and the progression of PI was associated with a further increase in KL-6 levels (1206 vs. 4020 U/ml). Measurement of KL-6 in sera is a useful non-invasive marker of pulmonary fibrosis in children with JSS. Its advantage to conventional methods of lung investigation is that it is easy to measure repeatedly and does not need children's cooperation.

V3.3 MACROPHAGE ACTIVATION SYNDROME IN JUVENILE IDIOPATHIC ARTHRITIS: TOWARDS THE DEVELOPMENT OF DIAGNOSTIC GUIDELINES

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Background: Macrophage activation syndrome (MAS) is an increasingly recognized, potentially life-threatening complication of chronic rheumatic disorders, particularly systemic juvenile idiopathic arthritis (JIA), which requires prompt recognition and treatment. Recent therapeutic advances emphasize the need of well established diagnostic criteria.

Objective: To identify potential diagnostic guidelines for MAS complicating JIA.

Methods. Cases of MAS associated with JIA reported in the literature and observed by us were reviewed and the clinical and laboratory manifestations recorded. Sensitivity and specificity of variables were evaluated by using as controls episodes of disease flare that occurred in patients with systemic JIA followed at our department.

Results: Eighty-eight patients with JIA (72 reported in the literature and 16 observed by us) who had 109 episodes diagnosed as MAS were identified. The control sample was composed by 35 episodes of disease flare (first flare) observed in as many patients with systemic JIA. The variables that showed the highest (≥ 0.75) sensitivity and specificity for MAS were the following: ferritin ≥ 10,000 ng/ml (sensitivity 1, specificity 1) , triglycerides ≥ 160 mg/dl (0.9, 1), SGOT ≥ 40 IU/ml (0.93, 0.97), fibrinogen ≤ 250 mg/dl (0.85, 1), SGPT ≥ 40 IU/ml (0.87, 0.93), γ-GT ≥ 40 IU/ml (0.81, 0.97), platelet count ≤ 150,000/mmc (0.76, 1), bone marrow aspirate showing macrophage hemophagocytosis (0.75, 1), hepatomegaly (0.76, 0.86), and splenomegaly (0.77, 0.82). Variables that did not prove sufficiently sensitive and specific included fever ≥ 38°C, lymphoadenopathy, neurological manifestations, arthritis, rash, hemorrhages, WBC ≤ 4,000/mmc, ESR ≤ 50 mm/h, LDH ≥ 900 IU/ml, bilirubin ≥ 1.2 mg/dl, and serum sodium ≤ 130 mEq/L.

Conclusions: We identified variables that may represent suitable candidates for the development of diagnostic guidelines for MAS occurring in patients with JIA. The validity of ferritin, which showed the highest sensitivity and specificity but was tested only in a limited number of patients, should be further investigated in future studies.

V3.4 TOWARDS RADIOLOGICAL SCORING IN JUVENILE IDIOPATHIC ARTHRITIS: CORRELATION BETWEEN CLINICAL JOINT INVOLVEMENT AND RADIOLOGICAL SIGNS

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Objective: To describe clinical and radiological correlation in oligoarticular and polyarticular onset Juvenile Idiopathic Arthritis (JIA) as a first step in order to develop an assessment standard.

Methods: Study entry data of 69 patients who took part in the placebo-controlled sulfasalazine study performed by the Dutch Juvenile Idiopathic Arthritis Study Group were used. A correlation was made between radiological findings and clinical and laboratory data. Radiological abnormalities were defined as swelling, osteopenia, joint space narrowing (JSN), growth abnormalities, subchondral bone cysts, erosions, and malalignement. Statistical univariate and multivariate analysis were performed.

Results: 471 Radiographed joints of 67 patients (mean age: 9.1 years (range 2.5-17.5); disease duration: median 24.3 months (IQR 10.5-40.2) qualified for this analysis. 92/186 (49%) Radiographed joints with clinical arthritis showed radiological abnormalities. Radiographed clinical normal joints often showed radiological abnormalities (e.g. hand/wrist: 35%; foot 39%). Growth abnormalities occurred

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in 48%, JSN in 28%, and erosions in 15% of the patients. Univariate analysis showed increased odds ratios (OR) for the finding of radiological abnormalities (excluding soft tissue swelling from analysis) for the overall severity score (OR=1.4, p<0.00001) and onset age 10 years (OR=2.75, p<0.0001). Multivariate analysis showed increased odds for IgMRF positivity (OR 4.6, p=0.005) and HLA-B27 positivity (OR=3.0, p=0.004). An index joint could not be identified. Evaluation of reproducibility showed a kappa-coefficient (Cohen) of 0.7 (range 0.40-0.86). The scoring took 10-20 minutes per patient.

Conclusion: Our study showed that scoring radiographs in JIA patients was feasible, reproducible, and correlated well with the overall severity score, and showed additional radiological symptoms of disease in clinical normal joints. IgMRF positivity and HLA-B27 positivity appeared independent factors with increased odds for occurrence of radiological abnormalities.

V3.5 SIMILARITY OF HLA-DRB1 ALLELE PATTERNS IN POST- STREPTOCOCCAL REACTIVE ARTHRITIS AND RHEUMATIC FEVER IN ITALIAN PATIENTS

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Aim: There is still debate on the relationship between Poststreptococcal reactive arthritis (PSReA) and rheumatic fever (ARF). Possible associations with HLA class II antigens of either PSReA (DRB1*01) or ARF (DRB1*16) have previously been described. We performed low-resolution HLA-DRB1 typing by a sequence-specific oligonucleotide probing method in 33 PSReA (14 males,19 females) and 15 ARF (10 males, 5 females) patients and compared the occurrence of DRB1*01 and DRB1*16 in patients and normal subjects, from the same area geographic area and typed in the same laboratory with the same methods.

Results: Reciprocal comparisons of frequency of DRB1*01 allele between PSReA, ARF and controls did not show any statistical differences. An increased frequency of the DRB1* 16 allele was seen in PSReA patients when compared with normal controls (OR 6.9, 95% CI= 4.3-9.3, p <0.03), while no significant differences occur between ARF vs controls and between ARF vs PSReA. Cause the allele distributions observed in PSReA and ARF patients were not significantly different from each other (Chi-square test with small numbers, z=0.53; p=0.70), we considered all 48 patients as members of a single group. DRB1*01 allele occurred at similar rates in patients and controls. On the other hand, 7 (5 PSReA and 2 ARF) of 48 patients were DRB1*16 positive versus 2/80 controls. This difference is statistically significant (p<0.02) with a relative risk of 6.6 (95% C.I=4.3-8.9).

Conclusions: The lack of heterogeneity of DRB1 allele distribution, as shown by these preliminary results, seems to suggest that PSReA and ARF are not genetically different, as far as DRB1 locus. However, DRB1*16 seems to confer increased susceptibility for both PSReA/ARF, suggesting that these syndromes belong to the same spectrum.

V3.6 A FAMILY HISTORY OF PSORIASIS DOES NOT AFFECT THE CLINICAL EXPRESSION AND COURSE OF JUVENILE IDIOPATIC ARTHRITIS PATIENTS WITH OLIGOARTHRITIS

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Background: In the recent revision of the proposed classification criteria for juvenile idiopathic arthritis (JIA) (Durban, 1997), the presence of a family history of psoriasis in a first or second-degree relative was included in the list of exclusions for the oligoarthritis category. However, it is unclear whether a family history of psoriasis identify a distinct subset of JIA patients.

Objective: To investigate whether there are differences in the clinical features and course of JIA patients with oligoarthritis with or without a family history of psoriasis.

Methods: All consecutive patients with JIA and oligoarthritis (arthritis affecting 1-4 joints during the first 6 months of disease) seen at our department between September, 2000 and May, 2001 were included. At the study visit, a family history of psoriasis confirmed by a dermatologist in any first or second-degree relative was carefully elicited. Prospective clinical assessments included the search for nail abnormalities, dactylitis, or psoriatic rash, and a complete joint assessment; parents completed the Childhood Health Assessment Questionnaire (CHAQ) and the Childhood Health Questionnaire (CHQ). Retrospective analyses included registration of demographic data, joint involvement (including dactylitis) at 0, 3, 6, 12 months and then every 12 months after the disease onset, occurrence of uveitis, previous drug therapies, results of antinuclear antibody and HLA B27 determinations, and radiographic joint lesions. Laboratory indicators of JIA activity were recorded at disease onset and at the time of the first observation at our department and were repeated at the prospective evaluation. Patients were divided into two groups according to the presence (Group 1) or absence (Group 2) of a family history of psoriasis. Patients fulfilling the criteria for psoriatic arthritis (Group 3) were excluded.

Results: 140 patients were enrolled, 102 (73%) in Group 1, 27 (19%) in Group 2, and 11 (8%) in group 3. The comparison of the clinical and laboratory features, including the articular course over time, among Group 1 and Group 2 did not show any statistically significant difference.

Conclusions: We found a close similarity in the clinical features and course among patients with oligoarthritis with or without a family history for psoriasis. These results argue against the exclusion of patients with a family history of psoriasis from the oligoarthritis category of JIA.

V4.1 SAFETY AND EFFICACY OF TWO ANTI-TNF PREPARATIONS (ETANERCEPT AND INFLIXIMAB) IN PATIENTS WITH JIA RESISTANT TO CONVENTIONAL THERAPEUTIC REGIMENS

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The aim of this study was to assess safety and efficacy of etanercept (ET, Enbrel®) and infliximab (INFL, Remicade®) in patients with persistently active JIA despite treatment even with combined DMARDS. 16 such patients with various types of JIA were enrolled in the study and were scheduled to receive ET or INFL on the basis of the distance from our center they lived. The ET group consisted of 6 patients (F/M=4/2, mean age 9.33 yrs) and the INFL group of 10 patients (F/M=7/3, mean age 10.6 yrs) with various types of JIA. The mean duration of disease activity was 61.3 and 67.2 mo for the ET and INFL groups respectively. ET was given at a dose of 0.4mg/kg and INFL 3-5mg/kg according to the manufacturers' directions. Both preparations were administered concurrently with methotrexate (15mg/m^2/w), NSAID and prednisone (14/16). Assessment of the efficacy was based on the "Core Set of Outcome" for JIA. Hematologic, biochemical and immunologic work-up prior to treatment and at monthly intervals thereafter was performed. Cardiologic assessment prior to treatment and at 6-month intervals was also done. No adverse reactions during the INFL infusions or at the time of ET injections were observed. Two patients (one from each group) developed flu-like symptoms recurrently. 3/6 patients of the ET and 5/10 of the INFL groups developed new autoantibodies (ANA=1/6 and 4/10, RF=1/6 and 1/10, Sm=0/6 and 1/10 respectively) after the 2nd month of treatment. At the end of 6 months, improvement was found in 5/6 patients of the ET and in 9/10 of the INFL groups. These preliminary results indicate that anti-TNF preparations may be a safe and effective additional treatment in patients with persistently active JIA of various types.

V4.2 18 CHILDREN AFTER AUTOLOGOUS STEM CELL TRANSPLANTATION FOR REFRACTORY JUVENILE IDIOPATHIC ARTHRITIS: 1 TO 51 MONTHS OF FOLLOW UP

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Since 1997 we treated 14 children with systemic JIA and 4 children with polyarticular JIA with ACST. Before ASCT all children had progressive disease despite the use of corticosteroids, MTX up to 1 mg/kg/wk, CsA (2,5 mg/kg/day) and anti-TNFα therapy. The bone

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marrow was T cell depleted (CD34+: 0,4 to 6 x10^6/kg and CD3: 0,1 to 2,8 x 10^5/kg). The conditioning regime included ATG (5 mg/kg/day x 4), cyclophosphamide (50 mg/kg/day x 4) and low dose TBI (4Gy). The aplastic period lasted 13 to 30 days.

Momentarily, 9 patients with a follow up rang from 1 to 51 months (median 31 months) are in drug free complete remission. All patients in remission show an impressive growth catch up and gained profound general well being. Seven patients developed a relapse within 4 to 30 months after ASCT, requiring treatment with low dose prednison, MTX and in one case Enbrel.

Due to the prolonged immunosuppressive therapy and the conditioning regimen, which induced a profound lymphopenia during 6 to 9 months, infectious complications were high. As reported earlier we had two cases of transplantation related mortality. Both patients died of a Macrophage Activation Syndrome.

Conclusion: With a maximal follow up of 51 months after ASCT 50% of the JIA patients (9 out of 18) are still in drug free complete remission of the disease and gained a remarkable increase in quality of life. One third of the patients (6 of 18) showed a relapse with active arthritis, treated with corticosteroids and MTX. After adaptation of our protocol no more cases of MAS have occurred.

V4.3 SUSTAINED SAFETY AND EFFICACY OF ETANERCEPT (ENBREL®) IN THE EXTENDED TREATMENT OF POLYARTICULAR-COURSE JRA

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Background: Etanercept safely and effectively treated juvenile rheumatoid arthritis (JRA) in a previous randomized, double-blind, placebo-controlled trial. Patients received etanercept during Part 1 of the study and etanercept or placebo during Part 2.

Objectives: This ongoing, open-label extension study is assessing long-term safety and efficacy of etanercept in 58 of 69 pediatric patients with JRA who were enrolled in the initial trial.

Methods: Patients receive 0.4 mg/kg (maximum 25 mg) etanercept SC twice weekly. Drug exposure analysis includes time on study drug in the initial trial. Adverse events (AEs) are assessed regularly. Efficacy is assessed using the JRA Definition of Improvement at 30%, 50%, and 70% response levels.

Results: Median exposure to etanercept was 2.3 years. Of 58 patients enrolled, 7 (12%) discontinued for suboptimal response, 2 (3%) for AEs, and 6 (10%) for reasons unrelated to safety or efficacy. Six patients were hospitalized for infections; 4 patients had noninfectious serious AEs. Types and rates of infections and noninfectious AEs were similar to those observed with placebo in the previous study. Of 43 patients assessed at the 2-year timepoint, 81% had a 30% response, 79% had a 50% response, and 67% had a 70% response. Ninety-six percent (24/25) of patients who previously received etanercept then placebo in the initial study regained responses in this trial.

Conclusions: Etanercept is safe and well-tolerated. The frequency of adverse events has not increased with prolonged exposure to etanercept. Therapeutic response to etanercept has been sustained for up to 3 years by patients with JRA.

V4.4 COMPARISON BETWEEN INTRAARTICULAR TRIAMCINOLONE HEXACETONIDE AND ACETONIDE IN OLIGOARTICULAR JIA

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Aim: To compare the efficacy of intraarticular Triamcinolone Hexacetonide (THA) and Triamcinolone Acetonide (TA), in a cohort of children with oligoarticular Juvenile Idiopathic Arthritis (JIA) followed prospectively.

Methods: Patients undergoing intraarticular injections from January 1996 to January 2001 were selected to receive either THA or TA according to a random sampling code. Clinical assessment was performed at baseline and 1, 3, 6, 9, 12, 18 and 24 months afterwards using an articular score (P.C.S. of Outcome Measures, Marco Island, 1994). Inflammatory markers (ESR, CRP) were tested at baseline, and disease duration, NSAIDs and DMARDs treatments were noted. A good response was defined as a decrease of the articular score $\geq$ 60%. The χ^2 test, t-test, multivariate analysis stepwise and Kaplan-Meier life tables were used to estimate differences between the 2 study groups.

Results: 84 patients entered the study: 41 in the THA group, 43 in the TA group. 127 injections were performed, 67 with THA, 60 with TA. The average dose used was 1 mg/kg of THA and 1.1 mg/kg of TA. There was no significant difference between the two groups in disease duration, baseline articular score, ESR and CRP values, dose of drug and NSAIDs and/or DMARTs. The average duration of improvement was 10 months with TA, 21 with THA. After 6 mo. the rate of response was significantly higher with THA than with TA (79% and 54% respectively, p=0.01) and no other variable, such as inflammatory markers, or disease duration, affected the result except the drug used. The Log-Rank test showed that the probability to achieve the joint remission was higher with THA than with TA (56% and 36% after 12 months respectively, p=0.0001). THA maintained good efficacy over time: 40% remission 24 mo. after the procedure with only 12% observed with TA (p=0.0001).

Conclusion: Our results suggest that THA is much more effective than TA for the intraarticular use, both in the short and in the long term follow up, and this observation is not affected by disease duration, degree of local and systemic inflammation.

V4.5 COMBINATION THERAPY WITH METHOTREXATE AND CYCLOSPORINE A IN JUVENILE IDIOPATHIC ARTHRITIS

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Background: Little information exists on the use of combination therapies in juvenile idiopathic arthritis (JIA). Objective. To evaluate the efficacy and safety of the combination of methotrexate (MTX) and cyclosporine A (CyA) in patients with JIA who were refractory to MTX as a single agent.

Methods: Seventeen consecutive patients with JIA, 6 boys and 11 girls, who did not improve or relapsed after 10 to 77 months (median 30.5 months) of MTX therapy at the dose of 15 to 25 mg/m2/week and were continued with MTX with the addition of CyA (4 mg/kg/day) for 6 to 30 months (median 10 months) were analyzed. The disease onset subtype was systemic in 9 pts, polyarticular in 5 pts and oligoarticular (with polyarticular course) in 3 patients. The clinical response to therapy was assessed through the preliminary definition of improvement (PDI) in JIA (A&R 1997;40:1202-9) and the radiographic progression by measuring the carpal length (Radiology 1978;129;661-8). The interobserver and intraobserver correlation coefficients for radiographic assessments were 0.97-0.99 and 0.98-099, respectively.

Results: At the end of the treatment, as compared to the time when CyA was added to MTX, 8 patients (47%) demonstrated a clinical response according to the 30% PDI criteria; five of them (29%) also showed improvement with the 70% PDI criteria and 2 (12%) had achieved the clinical remission. In the whole cohort, the median number of active joints was decreased from 17 (range 6-42) to 8 (range 0-52) (p=0.027) and the median global articular severity score from 68 (range 18-162) to 27 points (range 0-242) (p=0.024). As compared to the treatment period with MTX as a single agent, during combined administration of MTX and CyA the median radiographic progression rate improved from –0.78 to +0.35 in the better wrist (p=0.028) and from –0.66 to +0.09 in the worse wrist (p=0.099). Seven patients (41%) experienced side effects during treatment with MTX + CyA (4 gastrointestinal discomfort, 2 raised creatinine level and 1 liver transaminase increase), which never required treatment discontinuation. The frequency of adverse events was similar to that observed during therapy with MTX alone (47%).

Conclusions: In our JIA patients who were refractory to MTX as a single agent, the addition of CyA led to a significant clinical improvement in a consistent proportion of cases and seemed to reduce the rate of radiographic progression, without increasing the risk of side effects.

V4.6 IMPROVED GROWTH IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA) TREATED WITH ETANERCEPT

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Objective: To assess longitudinal growth in children with JIA, before and during treatment with etanercept - a tumour necrosis factor (TNF) inbibitor.

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TNF - inhibition in JIA has been shown to result in a significant decrease of disease activity, in terms of synovitis, global and functional scoring and ESR. Growth retardation is a hall-mark of chronic inflammation and may be an adverse effect of treatment with corticosteroids as well. We compared the growth in 19 children with polyarticular JIA before and during treatment with etanercept. The group consisted of 14 girls and 5 boys, aged between 6 and 13 years. The duration of therapy was 3 - 18 months (total 185 months). The total growth during treatment in the whole group was 99.5 cm, as compared to 31 cm during the same time interval before start of treatment. Thus, growth rates before and during treatment were 2 cm and 6.5 cm per year, respectively.

Conclusion: Children with JIA undergoing treatment with etanercept approach normal growth rates, as a result of improved disease control, which enables tapering of corticosteroids. Growth should be taken into account when assessing disease activity in JIA.

V5.1 DETECTION OF BACTERIAL DNA IN SYNOVIAL FLUID (SF) AND PERIPHERAL BLOOD (PB) FROM CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

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An infectious aetiology is implicated in juvenile idiopathic arthritis (JIA), although JIA SF culture is, by definition, sterile. The aim of the current project was to use the bacterial 16S ribosomal DNA nested PCR to detect bacterial DNA in SF and PB from patients with JIA.

Methods: Broad range primers specific for conserved regions on the 16S ribosomal gene were used to detect bacterial DNA. Positive PCR products were isolated, sequenced and identified using the BLASTn tool to search for homologous sequences in both the GenBank and EMBL databases.

Results: 110 paired SF and PB samples were obtained from 46 JIA patients (oligoarthritis 23, extended oligo 7, other JIA 16) undergoing therapeutic arthrocentesis, and control PB samples were collected from 12 healthy adults. Bacterial DNA was detected in SF and/or PB in 13/46 JIA patients (28.3%) and 0/12 controls. 26% of oligoarthritis or extended oligo patients were positive, compared with 12.5% of other JIA. In 4/13 patients, bacterial products were detected in SF alone. Bacterial species previously associated with arthritis that were detected in JIA SF included Bacillus, Micrococcus, Nocardia and Staphylococcus. Bacterial species detected that had not previously been recognised as pathogenic in humans included Acidovorax, Bradyrhizobium and Clavibacter. Several previously unrecognised bacterial sequences were also isolated. No bacterial species specific for any subgroup of JIA were found.

Conclusion: Over 25% of this JIA population had detectable bacterial DNA in SF, PB or both compartments. Microbial invasion of these compartments may contribute to the chronic inflammatory process of JIA.

V5.2 CHRONIC HUMAN PARVOVIRUS B19 INFECTION IN RHEUMATIC DISEASE OF CHILDHOOD AND ADOLESCENCE

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To find further evidence of parvovirus persistence in rheumatic diseases of childhood characterised by antibodies against the non-structural parvovirus protein NS1 and to investigate the clinical course of the diseases, an extended study was performed. Methods: 48 children and adolescents (22 males, 26 females, all Caucasians) with joint complaints lasting longer than one year either from active arthritis (oligoarticular 24, polyarticular 7, systemic 1), arthralgias (14), juvenile systemic sclerosis (1), or juvenile dermatomyositis (1) were included in the study. Mean disease duration was 46 months. In no patient antibodies to coxsackievirus, Epstein-Barr virus, ECHO-virus, borrelia, yersinia, campylobacter, chlamydia, salmonella, and streptolysin O were detectable. Laboratory markers of inflammation, specific IgM and IgG antibodies against different proteins of parvovirus B19 and detection of B19-genomes by PCR were investigated. The quantity of arthritis and impaired joint function was compared to patients initial presentation. Disease related complications were recorded. Impairment of activities of daily living was assessed by the Childhood Health Assessment Questionnaire (CHAQ) and the KINDL test.

Results: Nearly half of the patients showed laboratory signs of chronic inflammation. In 24 sera IgM antibodies against parvoviral proteins were detectable (controls: n=124, IgM pos. 7, $p<0.0001$), and in 15 virus specific DNA. (controls: n=124, DNA pos. 9, $p<0.0001$). The number of patients with arthritical joints decreased during the observation period from 44 to 11. Limited joint motion without any further evidence of active arthritis was found in 16 individuals. Overall 4 patients worsened, 27 improved, the others remained stable. 24 children were restricted in their daily activities. The mean disability index was 0.21. All of the children suffered from pain, and nearly all frequently used crutches. No patients developed uveitis. Hashimoto thyreoiditis was seen in 2.

Conclusion: Parvovirus viremia usually reached a peak at days 8 - 9 after infection and resolved after the development of an antibody response starting at day 10. The detection of viral DNA in sera of 15 patients years after infection, the presence of IgM antibodies against the structural proteins in half of the patients and the presence of IgG antibodies against the non-structural viral protein NS1 indicates viral persistence. Rheumatic disease of childhood with persisting parvoviral infection in most instances takes a benign course unless its starts as a life threatening disorder.

V5.3 NEW RECOMBINANT ANTIGENS FOR THE SERODIAGNOSIS OF LYME ARTHRITIS

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Objective: To evaluate recently described borrelial proteins, Decorin binding protein A (DbpA), and Flagellin A (FlaA) as antigens in the serodiagnosis of Lyme arthritis (LA).

Methods: The *dbpA* and *flaA* genes were cloned and sequenced from three pathogenic Borrelia species common in Europe, *B. burgdorferi* sensu stricto, *B. afzelii*, and *B. garinii*. For expression of the respective recombinant proteins 6xHis-tagged constructs were generated. Serum samples were collected from clinically typical LA patients. Antibodies against the variant recombinant proteins were analyzed using Western blotting and ELISA.

Results: In IgG ELISA 30 of 31 serum samples (97%) were positive for DbpA. Sera from the majority of patients reacted with one DbpA only with no or low cross-reactivity to other two variant proteins. 15/19 samples (79%) were positive for FlaA. With both proteins, the immunoreactivities were observed mainly against variant proteins from *B. afzelii* and/or *B. garinii*. Cross-reactive antibodies of control samples reduced the specificity of FlaA but not DbpA.

Conclusions: DbpA appears to be a sensitive and specific antigen for the IgG serodiagnosis of LA, provided that variants from all three pathogenic borrelial species are included in combined set of antigens. FlaA may also be useful in the serodiagnosis of LA, if the specificity problems can be solved.

V5.4 THE CONTRIBUTION OF GENOTYPES AT THE SAAL LOCUS TO AMYLOIDOSIS AND DISEASE SEVERITY IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Objective: Familial Mediterranean fever is an autosomal recessive disease characterized by recurring attacks of fever and serositis. Amyloidosis, leading to renal failure, is the most severe manifestation. Mutations in the MEFV gene have been identified in the majority of FMF patients. The wide clinical variability of the disease has been partly attributed to MEFV allelic heterogeneity with the M694V mutation and particularly the M694V/M694V genotype being associated with a severe phenotype and amyloidosis. Since patients with identical mutations vary in their clinical manifestations especially as regards the development of amyloidosis, a role for additional genetic and/or environmental modifiers has been proposed. Recently, polymorphisms at the SAA1 (serum amyloid A1) locus, or rather the SAA1α/α genotype, were found to influence susceptibility to renal amyloidosis.

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Methods: In this study we evaluated the contribution of genotypes at both the MEFV and the SAA1 loci to disease severity and amyloidosis. DNA samples from 219 FMF patients (42 of them with biopsy- proved renal amyloidosis) in whom two mutant FMF alleles have been identified, were further analyzed for genotypes at the SAA1 locus. Disease severity score was calculated according to Tel-Hashomer severity score.

Results: Of the 42pt's with renal amyloidosis 33 (78.5%) were homozygote for the M694V mutation, while the rest were compound heterozygote for either M694V or the complex V726A-W148Q mutant alleles. 14(33%) of them manifested the SAA1á/á genotype, in comparison to only 17/173 (10%) of the pt's without amyloidosis. No correlation was found between severity of the disease and the presence of the SAA1á/á genotype.

Conclusion: The results of this study agree with the observation that the SAA1 locus plays a key role in conferring genetic susceptibility to amyloidosis. Otherwise, polymorphisms at the SAA1 locus were not found to be associated with disease severity.

V5.5 MEVALONATE KINASE ACTIVITY DROPS AND γ-IFN PRODUCTION RISES WITH INCREASING TEMPERATURE IN THE HYPER IGD PERIODIC FEVER SYNDROME

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Hyperimmunoglobulinemia D and periodic fever syndrome (HIDS) is an autosomal recessive disease, characterized by recurrent inflammatory episodes with fever, gastrointestinal distress, lymphadenopathy, arthralgia and skin rash. Pro-inflammatory mediators, e.g. serum γ-Interferon (γ-IFN), rise during febrile attacks. Somehow, the attacks are often triggered by minor infections or childhood immunizations. HIDS is caused by a deficient activity of the enzyme mevalonate kinase (MK), mostly due to one common mutation, V377I. Here, we report that in cultured skin fibroblasts this mutation results in a temperature sensitive MK. To investigate whether this phenomenon plays a role in vivo, we measured MK and HMG-CoA reductase activity in mononuclear cells from HIDS patients during and between fever episodes. In all cases HMG-CoA reductase activity was elevated while MK activity was significantly lower during a fever episode. In vitro, γ-IFN production by peripheral blood mononuclear cells from HIDS patients rose sharply with increasing culture temperature. These data indicate that elevated temperature increases both metabolic and inflammatory abnormalities in HIDS. Whether (sub-)febrile body temperature is instrumental in triggering inflammatory attacks in vivo, remains to be demonstrated.

V5.6 INCREASED MEFV GENE POINT MUTATIONS IN SECONDARY AMYLOIDOSIS

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It has been reported that M694V homozygous genotype of the MEFV gene was associated with higher prevalence of amyloidosis in FMF. To test the hypothesis that MEFV gene mutations are associated with amyloidosis secondary to diseases other than FMF, we studied 29 patients with non-FMF secondary amyloidosis (group I) and 29 patients with FMF amyloidosis (group II). The reactive amyloidosis was secondary to juvenile idiopathic arthritis in 6, Behçet's disease in 5, tuberculosis in 5, rheumatoid arthritis in 2, ankylosing spondylitis in 2, osteomyelitis and bronchiectasis in 1 each. In 7 patients no primary cause was identified. None of these 7 patients had symptoms or signs that could be attributed to FMF and all denied a positive family history. Exon 10 mutations (M694V, V726A, M680I, M694I, V744S, R761H, I692 del) were sought by DGGE, ARMS methods and Exon 2 mutation (E148Q) by restriction enzyme analysis. There were 22 mutated alleles in the non-FMF (38%), compared to 47 in the FMF group (81%). M694V accounted more than half of the mutations in group I (59 %) and 89 % in group II. Homozygous M694V mutation was present in 3 of the first and 18 of the FMF group. Of the 6 patients with JIA 4 were carriers of one of the major 3 mutations. The carrier rate in our normal population is 9%. The overall frequency of the tested mutations was significantly increased in patients with amyloidosis secondary to diseases other than FMF. This might imply either a problem of misdiagnosis, or suggest a probable MEFV gene determination in reactive amyloidosis.

V7.1 TO USE A QUALITY OF LIFE QUESTIONNAIRE

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Objective: To find an accurate tool for measuring quality of life in clinical work.

We have long missed an appropriate tool to measure quality of life in patients with juvenile idiopathic arthritis (JIA). The Juvenile Arthritis Quality of life Questionnaire (JAQQ) from Montreal/Canada has been translated into Swedish and used by us during 2001. The instrument consists of a series of statements relating to activities or states that may occur as a result of arthritis or its treatment. There are five sections: gross motor function, fine motor function, psychosocial function, systemic symptoms and pain assessment. For each section except for pain a mean score is calculated. A mean JAQQ score is also computed. When the patient uses the JAQQ the first time the instrument demands an oral information. The test is otherwise a self-administered questionnaire. It can be completed in 20 minutes. We have tested 16 patients mean age 13,7 years (range 7,0 - 20,1), mean disease duration 8,3 years (range 2 - 19).

Conclusion: We find it easy to use the JAQQ and it gives the information requested. The patients have a positive attitude to the instrument and are very much interested in the results.

- Does the instrument give a representative picture of the quality of life?
- Is this our best tool to assess quality of life?
- How do we use the pain assessment?

V7.2 SENSITIVITY OF THE CHILDHOOD HEALTH ASSESSMENT QUESTIONNAIRE (CHAQ) AND THE PEDIATRIC EVALUATION OF DISABILITY INVENTORY (PEDI) IN CHILDREN WITH JIA

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The purpose of the study was to measure the consequences of JIA with respect to childhood daily activities using the CHAQ and the PEDI.

Twenty children with JIA were included in this follow-up study at onset of the disease. Joint swelling and mobility were scored; functional consequences of the disease were measured using the CHAQ (ADL and VAS); functional status was measured using the PEDI. Mean interval between t_1 and t_2: 3.9 (SD = 1.8) months, and between t_2 and t_3: 3.4 (SD = 1.2) months.

Correlation techniques were used to measure the relation between disease parameters and functional outcome, and paired T tests to measure changes over time.

Results: The CHAQ showed significant correlations with most of the disease parameters: BSE (.59), VAS^{pain} (.59), $VAS^{severity}$ (.65), number of affected joints (.62), and swelling (.60). Correlations were strongest at third measurement. The PEDI showed only significant correlations with VAS^{pain} (-.56) and $VAS^{severity}$ (-.72) at first measurement, and with number of joint contractures (-.68) at third measurement. Significant correlation was found between CHAQ and the PEDI (mobility domain, -.65) at first measurement. Significant changes between t_1-t_2 were found in CHAQ (t: 3.67, P .002) and all PEDI scales (P<.003). Between t_2-t_3, significant changes were found only in all PEDI scales (P<.012).

Conclusions: As disease activity improved over time, CHAQ and PEDI showed different sensitivity. The CHAQ expresses the functional consequences of the disease, while PEDI documents functional gain.

Ann Rheum Dis: first published as 10.1136/ard.60.90002.ii7 on 1 October 2001. Downloaded from http://ard.bmj.com/ on April 18, 2024 by guest. Protected by copyright.

V7.3 MEASUREMENT OF FUNCTIONAL LIMITATIONS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS WITH THE JUVENILE ARTHRITIS FUNCTIONAL ASSESSMENT SCALE (JAFAS): A VALIDATION STUDY

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Background and aim: Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease in children and a leading cause of childhood disability. Disability is one of the elements of the PRINTO core set of outcome variables to be included in clinical trials. Functional limitations can be evaluated by questionnaires like the "childhood health assessment questionnaire-CHAQ" or function tests like the "Juvenile Arthritis Functional Assessment Scale-JAFAS". The JAFAS has been developed as an objective measure of functional ability in children with rheumatic diseases. However, since its introduction in 1989 experience with the JAFAS in clinical research is limited. The aim of the study was to further examine the validity of the JAFAS. Methods From January 2001 fourty consecutive children with JIA aged between 6 and 12 years and visiting the outpatient paediatric rheumatology clinic will be invited to participate in the cross-sectional study. Of all patients, basic sociodemographic (age, sex) and disease characteristics are recorded. Functional ability is determined by the JAFAS, the CHAQ and a test for general movement co-ordination ABC.Measures of disease activity include the ESR, the physicians evaluation of disease activity on a visual analogue scale and a tender and swollen joint count. Range of motion (ROM) is measured by the Paediatric EPM-ROM scale. The relationship between the JAFAS and the other measures of functional ability will be determined by computing Spearman Rank Correlation coefficients. By including the ABC movement test, the influence of age on the functional ability scores can be examined. Using the same method, associations between the JAFAS and variables representing the domains disease activity and range of motion will be calculated.

Results: By May 2001 fifteen of the patients have been included. Preliminary result will be presented.

V7.4 EVIDENCE OF AN INVERSE RELATIONSHIP BETWEEN MUSCLE STRENGTH AND JOINT CONTRACTURES IN SUBGROUPS OF JUVENILE DERMATOMYOSITIS

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Aim: To study musculoskeletal function and determine correlation between muscle power and joint contractures in a JDM cohort.

Methods: A retrospective study of 21 patients with definite JDM was conducted at a paediatric rheumatology tertiary referral centre. All patients had a full musculoskeletal assessment by a single assessor (SM) at initial assessment. Data was analysed for: joint range of movement, sex, age, duration of symptoms and strength of major muscle groups (using the MRC Oxford scale). Comparisons were made within the cohort as a whole, and then between 2 subgroups: Classical JDM (CJDM) and JDM with overlap features (OJDM) (such as scleroderma, polyarthritis, and vasculopathic/organ pathology e.g. interstitial lung disease).

Results: There was a high prevalence of joint contractures in the group (76%). The O.JDM group had more contractures per patient (17/child v 5/child, p=0.0017) but greater average overall muscle strength compared with CJDM (Grade 3.0: 2.4). There was no significant difference in age of onset or duration of disease prior to assessment between the subgroups. The CJDM group was predominately female (9F: 2M) and the OJDM had a more equal sex distribution (6F: 5M)

Conclusion: A high rate of contractures was seen overall due to both muscle and joint disease. The OJDM group appears to have more contractures and yet had functionally stronger muscles at initial assessment. The combination of muscle, joint and skin changes may help to distinguish a unique subgroup of JDM. More research, including MRI studies and functional outcome, is needed to confirm these preliminary observations.

V8.1 A RANDOMISED CONTROLLED TRIAL OF A 26 WEEK PHYSICAL TRAINING PROGRAM FOR CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS (JIA): A PRELIMINARY REPORT

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Objective of this study was to evaluate whenever there were statistical significant effects of an aquatic training program for JIA-patients. Fourteen patients with JIA (age range 4 to14 years) participated in this study and were randomised into an experimental (N=7) and a control (N=7) group. The children in the experimental group received the training program. The effects of the program were evaluated using the following instruments : Childhood Health Assessment Questionnaire (CHAQ; functional ability), Juvenile Arthritis Quality of Life Questionnaire (JAQQ; health-related quality of life), Child Health Questionnaire (CHQ; health-related quality of life), Juvenile Arthritis Functional Assessment Scale (JAFAS; functional ability), a range of motion score, and a Wingate anaerobic cycle ergometer test. (anaerobic muscle power).

Results: MANOVA did indicate a positive effect of the training program, on CHAQ, JAQQ and Wingate. However, these effects were too small to reach statistical significance.

Conclusion: at time of analysis, there were no statistically significant effects of our intervention. However positive trends could be distinguished in CHAQ, JAQQ and Wingate. More patients are being studied to gain the appropriate power for the statistical analysis.

V8.2 IS A BACK SCHOOL EFFECTIVE IN THE MANAGEMENT OF YOUNG PEOPLE WITH BACK PAIN?

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This study describes the development and evaluation of a back school programme for young people referred to a Paediatric Rheumatology Department. No other hospital-based back schools for young people were identified. The factors influencing back pain in adolescents (physical, developmental and psychosocial) are incorporated into the development of this back school.

This study uses an experimental, longitudinal same subject design. The outcome measures are pain (visual analogue scale), function (Childhood Health Assessment Questionnaire) and knowledge (quiz). Patients are assessed at baseline, attend the group session (intervention), and are reviewed two- and six-months after the group session. The data was analysed using descriptive and inferential statistics (t-test and one way ANOVA). Patients also completed a satisfaction survey.

Ten group sessions have been held involving 50 patients with a mean age of 13.56 years (Range 11 - 17). Nineteen patients had inflammatory conditions, nineteen had mechanical conditions and 12 had pain syndromes. Significant improvement ($p < 0.05$) is shown both at two-month and six-month reviews in all outcomes (pain, function and knowledge). There were positive responses to the patient satisfaction survey with 50% of respondents particularly enjoying the exercises.

The format and length of the back school has been specially designed for young people. It is not a substitute for physiotherapy or an exercise programme, but offers education and additional support. Despite some methodological shortcomings the results of this study demonstrates its value. This model of back school may be considered effective in the management of young people with back pain.

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