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The morbidity of some rheumatic diseases in Kazakhstan

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Background: Osteoarthritis (OA) is the most prevalent among other rheumatic diseases (RD), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are threatened by frequency of disability, development of complications and shortening of life expectancy.

Objectives: To research of prevalence and growth rate of RD in Kazakhstan from 2006 to 2011.

Methods: The official statistical data of the MoH was analyzed (1).

Results: Patients with MSD were 706 458 with growth for period – 10.4%. Patients with RA were 44 773, SLE – 2568, OA – 115 318, and women 66.6%, 82.3%, 66.8% correspondingly. The highest growth for period was matched at OA patients–287.6%, less uplift at RA – 60.6%, SLE – 45.7%. The number of new diagnosed patients was 9793 in 2011, women – 62%. The growth rate was 49.4% in compare with rate in 2006, at women – 60.9%. The number of patients with SLE – 361, women 80%, with growth rate – 52.3%. The number of patients with OA – 32 289, women – 63.9% with growth rate – 302.4%. The highest prevalence was observed at OA – 691.5; less prevalence at RA – 268.5; SLE – 15.6 on 100 thousand of population (2).

Conclusion: The growth rate of rheumatic diseases testifies about saving social significance of problem. The level of prevalence SLE in Kazakhstan is lower in compare with other Asian population (in China – 30, in Japan – 19.2 on 100 000 of population) (3,4). It is explained with low diagnostic level of disease in country. The growth of morbidity RA and OA at new diagnosed patients is needed to pay special attention.

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Presentation and prognosis of peripheral ischemic lesions in rheumatic diseases

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Introduction: Peripheral ischemic lesions in rheumatic diseases may have variable presentation and prognosis varying from complete recovery to amputation. Responsible patient related, disease related and other factors have not been well described in literature.

Aims and Objectives: To study presentation and outcomes of peripheral ischemic lesions in rheumatic diseases and analyse factors responsible for them.

Methods: All patients with peripheral ischemic lesions, attending the Rheumatology department of a tertiary teaching institution between March 2013 and January 2015 were prospectively analysed for demographic factors, disease related factors and outcomes.

Results: Of 50 patients presented with peripheral ischemic lesions, 40 (80%) had rheumatic causes and 10 (20%) had non - rheumatic causes. In the group with rheumatic diseases, mean age was 34.5 years. Of these, 32 were adults (with 81% females) and 8 were children (with 62% females). 87.5% patients presented in winter season. Early ischemic / pregangrenous lesions were present in 47.5 % cases while gangrenous lesions were present in 52.5% cases. The most common rheumatological cause was vasculitis 18 (45%) either primary or secondary, followed by systemic sclerosis 7 (17.5%). Other causes were SLE with APS (15%), primary APS (7.5%), MCTD (5%) and undifferentiated vasculitis (10%). Amputation (either surgical or auto-amputation) was the outcome in 55% cases, while 45% lesions recovered completely with medical treatment.

Conclusions: Peripheral ischemic lesions may present either as initial or predominant manifestation of a rheumatic disease. Vasculitis was the most common cause. Factors associated with peripheral ischemic lesions were female gender, winter season and higher age, while those associated with poor outcome were delayed referral/presentation, delayed specific management and vasculitis. Early diagnosis and aggressive multidisciplinary management should be warranted for optimal outcomes in these cases.

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Macrophage activation syndrome (MAS) an under recognized hematological manifestation: case series of 21 patients -experience from South India

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Macrophage activation syndrome (MAS) is characterized by excessive activation of well differentiated macrophages and T cells which clinically presents as fever, cytopenias, lymphadenopathy, hepatosplenomegaly, coagulopathy and in severe cases multiorgan failure mimicking sepsis and high mortality rate, posing a big clinical challenge to the physician in the diagnosis and treatment. The MAS is often under recognized by rheumatologist and was reported in 7–13% of systemic onset JIA and 0.9-4.6% of SLE patients. Aim of the Present study is to analyze clinical, laboratory parameters and outcome of rheumatology patients with macrophage activation syndrome

Methods: Patients satisfying criteria for hemophagocytic lymphohistiocytosis (HLH-2009) were identified from inpatient case sheets and discharge summaries from department database from 2008 to 2014, collected: age, sex, clinical features, laboratory data, underlying rheumatic disease and short term outcomes and analyzed.

Results: Tweny one patients (15 females) (fourteen were SLE, 3 were JIA, one each of Adult onset Still's, dermatomyositis, RA, primary HLH)were identified, Median duration of the underlying disease was 6 (range: 3–60) months, Mean duration from first symptom to diagnosis is 18.8 ± 10.6 days; Mean Hospital stay 14.3 ± 7.6 days, Pancytopenia was observed in 19, and bicytopenia in 2 patients. Bone marrow examination done in 17, marrow hemophagocytosis is seen in 3 patients. Multiorgan failure occurred in 6 (33.33%) of which 3 (3/21 = 14.28%) died. Infection in 11 (52.38%) and cyclophosphamide in one was the triggering cause of MAS.

Conclusions: (i) Fever and sepsis like syndrome,elevated serum ferritin, altered liver enzymes, pancytopenia are the most common findings in Macrophage activation syndrome (MAS) and pancytopenia with elevated ferritin levels should raise the suspicion of MAS. (ii) Infections are common triggers. (iii) Mortality is high (50%) in patients with multi organ failure. (iv) Absence of Marrow hemophagocytosis does not negate the diagnosis.5. High index of clinical suspicion and early treatment may improve the outcome.

Fibromyalgia

APL15-0340

The polysymptomatic score allows easy identification of central sensitivity in chronic illness

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The polysymptomatic score (also known as the polysymptomatic distress scale) is derived from the 2011 ACR fibromyalgia diagnostic criteria. While this instrument was originally made for fibromyalgia, the clinical utility of this instrument is beginning to be used in additional populations of chronic illness.

Aims: To compare this instrument with other standardised clinical instruments commonly used in other chronic illness cohorts.

Methods: We examined outpatients from 3 different clinical groups, fibromyalgia, rheumatoid arthritis (RA) and chronic cardiac failure (CCF). Participants undertook a short questionnaire encompassing the RAPID-3, SF-36, 2011 fibromyalgia ACR criteria as well as undergoing a standardised tenderpoint exam. Fibromyalgia clinic participants additionally completed the FIQR.

Results: 234 participants (70.1% female, mean age 61.2) were recruited in total: fibromyalgia (n = 60), RA (n = 117) and CCF (n = 57). Across the total population PS had a strong, positive correlation with tenderpoint count ($r = 0.807$, n = 234, $P < 0.001$), RAPID-3 ($r = 0.659$, $P < 0.001$), self-rated pain ($r = 0.590$, $P < 0.001$) and FIQR ($r = 0.703$, $P < 0.001$). Similar strong, negative correlations were observed for SF-36 overall physical health ($r = -0.623$, $P < 0.001$) and mental health ($r = \times 0.539$, $P < 0.001$).

Increasing PS also strongly correlated with larger numbers of associated central sensitivity syndromes ($r = 0.715$, $P < 0.001$).

Conclusion: The polysymptomatic score is a 1 min test that shows promise as a disease severity measure. The PS allows for rapid assessment of the contribution of central sensitivity in a number of chronic illnesses. This may allow further insight into assessment and management of difficult to treat patients, as well as, providing indications of further comorbidities.

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Increased risk of coronary heart diseases in patients with fibromyalgia especially in those with concomitant comorbidity–a nationwide population-based cohort study

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Objectives: Fibromyalgia has seldom been associated with coronary heart disease (CHD). The aim of this study was to evaluate the risk of CHD in patients with fibromyalgia.

Methods: We used a dataset of 1 million participants, systemically scrambled from Taiwanese national insurance beneficiaries, to identify 61 612 patients with incident fibromyalgia (ICD-9-CM 729.0-729.1) and 184 834 reference subjects matched by sex, age and index date of diagnosis from 2000 to 2003. Risk of CHD was analyzed by Cox proportional hazard modeling.

Results: All subjects were followed up an average of 2 182 823 person-years. Patients with fibromyalgia had a mean age of 44.1 ± 16.5 years. These patients (n = 8280) and reference

subjects (n = 15 162) developed CHD with a significant incidence rate ratio of 1.64 (95% confidence interval [CI]: 1.61–1.68). The adjusted hazard ratio (HR) for CHD in fibromyalgia patients relative to reference subjects was 1.47 (CI: 1.43–1.51), after adjusting for age, gender, occupation, monthly income, traditional cardiovascular comorbidities, depression and anxiety. The CHD risk was higher for younger fibromyalgia patients than for older patients (age <35 years: HR 2.40 [CI: 2.06–2.79]; age >65 years: HR 1.36 [CI: 1.30–1.43]). Fibromyalgia and cardiovascular comorbidities had a significant interaction effect on CHD risk (P for interaction <0.01). We note that CHD risk was markedly enhanced in fibromyalgia patients with concomitant comorbidities.

Conclusions: Our report shows that fibromyalgia patients have an independent risk for CHD development. Fibromyalgia patients with concomitant comorbidities have markedly increased CHD risk relative to those with primary fibromyalgia.

Keywords: Fibromyalgia, coronary heart disease, cohort study

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Construction of a short form scale to assess fibromyalgia patients

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Background: Fibromyalgia Impact Questionnaire is a commonly used instrument in the evaluation of fibromyalgia patients. Depression, anxiety and stress are negative psychological states that are frequently observed in patients with Fibromyalgia Syndrome (FMS). It becomes very tedious for subjects as well as researchers to use more than one instrument to assess different variables. To the best of our knowledge no such combined measure exists which can assess all the above mentioned features in a one single administration. A patient who is depressed and in pain cannot be expected to read, understand and mark lengthy questionnaires. Thus an abridged version to record responses of FM patients in less time and effort is the need of the hour.

Aim: To construct and to establish reliability and validity of short form scale to assess various parameters of fibromyalgia patients.

Materials and Methods: 125 fibromyalgia patients were studied using Fibromyalgia Impact Questionnaire Revised (FIQR), Quality of Life Scale (QoLS), Arthritis Self Efficacy Scale (ASE) and Depression, anxiety, stress scale (DASS21). Factor analysis was done to obtain weights for different items. Top two items (highest weight) of every scale were picked for further analysis. Alpha correlation coefficient was calculated to see strength of their correlation with total scale. Content validity was also evaluated by comparing the individual item score with the total scores of that scale.

Results: Alpha reliability obtained for three parameters (3 items) of FIQR ranges from 0.87 to 0.97, for QoL (3 items) ranges from 0.40 to 0.87, Self efficacy (1 item) 0.93. DASS21 (4 items) reliability ranges from 0.39 to 0.58. All values are significant at 0.01 level.

Conclusion: An abridged version of four scales consisting of 11 items was developed which has good psychometric properties.

Fig1: Summary for Weights, Reliability and Validity obtained by various items

SN	Scale	Code	Items	Factor Loading	Alpha Reliability	Content Validity
1	FIQR Function	FF_9	Go shopping ...	0.939	0.931**	0.932**
2	FIQR Pain	FP_2	I was completely overwhelmed ...	0.986	0.969**	0.986**
3	FIQR Symptoms	FS_9	level of balance problems...	0.901	0.871**	0.894**
4	Quality of Life	QoL_13	Socializing- meeting people, doing things, parties...	0.851	0.869**	0.825**
5		QoL_3	Relationships with sibling & relatives, communicating, visiting...	0.490	0.693**	0.652**
6		QoL_11	Work- job/ home	0.348	0.401**	0.680**
7	Self Efficacy	SE_4	How certain are you that you can regulate your activity?	0.928	0.927**	0.925**
8	DASS_21	DAS_15	I felt I was close to panic	0.694	0.580**	0.665**
9		DAS_17	I felt I wasn't worth much as a person	0.395	0.577**	0.619**
10		DAS_6	I tended to over-react to situations	0.480	0.389**	0.429**
11		DAS_18	I felt that I was rather touchy	0.518	0.417**	0.519**

Genetics

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Molecular analysis of mefv gene polymorphisms and mutations in rheumatoid arthritis in the azari population of Iran

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Objective: The aim of our study was analyzing the Mediterranean fever (MEFV) gene polymorphisms and mutations on exon 2 and 10 in patients with rheumatoid arthritis and to then compare disease activity between mutation carriers and non-carriers in the Azari population of Iran.

Methods: In this cross sectional study we considered the MEFV gene polymorphisms and mutations in exons 2 and 10 in 50 Iranian Azari patients with rheumatoid arthritis by polymerase chain reaction and direct sequencing.

Results: Thirty three out of 50 RA patients were found to carry MEFV polymorphisms and mutations. The most common were the D102D, G138G, and A165A polymorphisms. In comparison with the normal Azari population the carrier state of MEFV mutations in our study patients was higher. No significant difference was seen in the disease activity between carriers and non-carriers.

Conclusion: MEFV mutations may act as a genetic susceptibility factor for RA. However, it has no major effect on the activity of disease in the Azari population of Iran.

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Survivin is over-expressed in skin fibroblasts of systemic sclerosis patients

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Background: Systemic sclerosis is a multistage autoimmune disorder characterized by three morphological hallmarks in early skin lesions: structural and functional vascular and microvascular abnormalities, perivascular and tissue infiltration of mononuclear inflammatory cells, and increased collagenous and noncollagenous extracellular matrix molecules. Systemic sclerosis patients skin fibroblasts show anti-apoptotic activity, which enhances the fibrosis stage of the disease. We investigated the most important members of IAP family's mRNA expression level. Members of this family are the most important inhibitors of apoptosis.

Material and Methods: Skin biopsy samples were obtained from 21 patients with diffuse SSc diagnosed according to the American College of Rheumatology criteria for SSC. Skin biopsy samples were also obtained from 16 healthy controls. Fibroblasts of skin were cultured and Total RNA was isolated from cell populations followed by cDNA synthesis. Real-time PCR was performed for determination of *cIAP1*, *cIAP2*, *xIAP* and *survivin* gene expression.

Results: Real time data analysis showed significantly higher expression level for *survivin* in patients compared to control group with a ratio of 1.8. No significant difference in *cIAP1* and *cIAP2* and *xIAP* mRNA expression levels were observed between case and control groups.

Discussion: *Survivin* as a member of Inhibitor of Apoptosis family, interact with cdk4, which supports the procaspase 3 and p21 complex, thus resulting in suppression of cell death. It also can inhibit caspase 3 and 7 directly. In vitro experiments show that *survivin* can inhibit caspase activity, fas, and bax mediated apoptosis. *Survivin* also has pivotal roles in cell growth. As far as we know this is the first time that over-expression of *survivin* is being reported, which can open a new path to discovery of the pathogenesis of Systemic Sclerosis. *Survivin* can also be a new potential therapeutic target, as it is in cancer.

Keywords: Systemic Sclerosis, *survivin*, apoptosis, fibroblast, expression

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Analysis of the gene expression of sulf1 and SULF2 in fibroblasts of the skin biopsy of patients with systemic sclerosis

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Background: Systemic sclerosis is an autoimmune or connective tissue disease. It is characterized by thickening of the skin caused by accumulation of collagen, and by injuries to the smallest arteries. It has been identified that *SULF1* can interfere in signaling of many heparan binding growth factors and morphogens. Heparan sulfate (HS) proteoglycans are glycoproteins which regulate many signaling pathways. HS is added to proteins during Golgi modifications. Sulfatase 1 is a catalytic enzyme which removes sulfate groups from HS of proteoglycans. The angiogenesis-related studied molecules which can be regulated by heparan sulfate including *VEGF*, *FGF*, *Wnt*, *BMP*, *HGF*, *HB-EGF* and *SHH*. Most of these molecules play important roles in Systemic sclerosis pathogenesis.

Material and Methods: Skin biopsy samples were obtained from 21 patients with diffuse SSc diagnosed according to the American College of Rheumatology criteria for SSC. Skin biopsy samples were also obtained from 16 healthy controls. Fibroblasts of skin were cultured and Total RNA was isolated from cell populations followed by cDNA synthesis. Real-time PCR was performed using SYBR Green PCR master mix and specific primers for *Sulf1* and *Sulf2*.

Results: Real time data analysis using ΔΔct method showed no significant difference in *Sulf1* and *Sulf2* mRNA expression between case and control groups.

Conclusion: despite all theoretical mechanistic relevance of *Sulf1*, and *sulf2* with scleroderma, we observed no change in both gene's expression. However this finding does not prove the irrelevance of *SULF1* and *SULF2* with scleroderma, it only denies expression change in these two genes and functional relativity of them remains to be studied.

Keywords: Systemic sclerosis, Heparan sulfate, SULF1, SULF2, expression