SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Clinical researches in idiopathic inflammatory myopathies

by Nagy-Vincze Melinda M.D.

Supervisor: Katalin Dankó MD, PhD, DSc

UNIVERSITY OF DEBRECEN
GYULA PETRÁNYI DOCTORAL SCHOOL OF ALLERGOLOGY AND CLINICAL IMMUNOLOGY
DEBRECEN, 2018

CLINICAL RESEARCHES IN IDIOPATHIC INFLAMMATORY MYOPATHIES

By Melinda Nagy-Vincze, MD.

Supervisor: Katalin Dankó, MD., PhD, DSc

Doctoral School of Gyula Petrányi Doctoral School of Clinical Immunology and Allergology, University of Debrecen

Head of the Examination Committee:
Andrea Szegedi, MD, PhD, DSc

Members of the Examination Committee:
Emese Kiss, MD, PhD, DSc
Gabriella Szűcs, MD, PhD, DSc

The Examination takes place at the library of Building C, Department of Internal Medicine, Faculty of Medicine, University of Debrecen on 14th November 2018. at 11:00

Head of the Defense Committee:
Andrea Szegedi, MD, PhD, DSc

Reviewers:
Péter István Temesvári, MD, PhD
János Gaál, MD, PhD

Members of the Defense Committee:
Emese Kiss, MD, PhD, DSc
Gabriella Szűcs, MD, PhD, DSc

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen on 14th November 2018. at 14:00

1. INTRODUCTION

The idiopathic inflammatory myopathies (IIM), which collectively are also known as myositis, are characterized clinically by muscle weakness, decreased muscle endurance and by muscle inflammation. These are rare diseases with average incidence of 2,8-7,7/million and prevalence of 5-10/ million. The male/female ratio is ½-1/3. Dermatomyositis can occur in children and in adults as well. However polymyositis is mainly the disease of adults. Considering the ethiology, IIMs are multifactorial disorders, genetic and environmental factors (like UV radiation, smoking, infections, medications) also influencing the disease onset and course. The pathomechanism is not clearly known.

The leading symptom is progressive weakness of proximal limb muscles, causing difficulties with everyday tasks like stair-climbing, combing, shaving. All the striated muscles affected, so difficulty in chewing, swallowing, breathing difficulty can be present. In IBM not only proximal but also distal muscle weakness occurs. General symptoms are fatigue, malaise and weight loss. Beside the weakness pain and atrophy can be observed in muscle. Although slow onset of muscle fatigue is the most commonly presenting symptom, the skin or lungs might also be initially affected. During disease progression, symptoms might occur in different organs at different times. Arthralgia and arthritis signed the involvment of joints. Rarely signd of myocardial involvement like myocarditis or arrhythmias are present as well. The multi-organ involvement is generally leads to severe complications and poor prognosis.

The skin symptoms of DM classified into three types, pathognomic (diseases specific), characteristic (can occur in other diseases) and less frequently occurring symptoms. The skin lesions often accompanied by intense itching and photosensitivity is very unpleasant.

As in other systhemic autoimmune diseases autoantibodies can also be detected in IIM. Main groups are: myositis-associated (MAA) and myositis-specific (MSA) autoantibodies.

The dignosis is based on a system of generally accepted criteria by Bohan and Peter:

1. criteria: proximal muscle weakness
2. criteria: positive muscle biopsy
3. criteria: eleveted enzyme levels in the serum (CK, GOT, GPT, LDH, Aldolase)
4. criteria: myopathic pattern on the electromyogram (EMG)
5. criteria: characteristic skin rashes in DM

1.2. Subsets based on clinicopathological features

I. Polymyositis (PM) is the most frequent form of IIM, affected mainly women between the age 45 and 60. In this subset, proximal and axial muscle weakness increase gradully without any pain.

II. Dermatomyositis (DM) is the most common subset in childhood and the second in adults. Considering the gender, women dominancy also presented in both group. Juvenile DM is associated with classical skin symptoms, more frequent calcification of muscles, severe isomatrophy, rare malignancy and association with other connective tissue diseases. In the case of adult DM skin symptoms are prevented by the development of muscle weakness and there are more tumor association and overlap forms.

III. Inclusion body myositis: after the age of 50 this is the most common chronic progressive muscular disease. It mostly affects men. Symptoms usually, start on the lower limbs with proximal and also distal muscle weakness and then affect the muscle groups of upper limbs.

IV: Necrotyzing autoimmun myopathy: shows similar symptoms as PM and DM. This group includes several syndromes different in hystology and caracteristics like statin induced NAM, autoantibody induced NAM and cancer associated NAM.

1.3. Disease activity, treatment

Based on the recommendation of the International Myositis Assessment & Clinical Studies Group (IMACS), 6 so-called "core set measure" tests are used to evaluate the disease activity at onset and during the disease course. These scores also help us to evaluate the therapic response and effectivity. These measures includes muscle strength test, levels of muscle enzymes (CK and LDH), extramuscular symptoms, and the changes in overall disease activity scored by both patient and physician.

Before selecting the pharmacological therapy, muscular and extramuscular symptoms has to be considered as well as the patient's comorbidities and general physical status. High or medium doses of corticosteroids are recommended as first line therapy. In case of no improvement of muscle strength after one month of steroid therapy, treatment is considered ineffective and additional immunosuppressive therapy needs to require. In this case, the so-called second-line drugs can be used like azathioprine, mycophenolate mofetil, methotrexate, cyclosporin A, cyclophosphamide. Also a second-line drug is needed even in the first few days when the overall condition of the patient rapidly deteriorates and also in case of anti-synthetase syndrome or severe extramuscular involvement. If the steroid does not induce remission in severe, rapid progressive cases, intravenous immunoglobulin (IVIG) therapy should be preferred. In patients who respond to steroids, our aim is to reduce the dose to the lowest dose, which will still control the disease. This is also achieved by using a "steroid-saving" immunosuppressive therapy.

In addition to medication therapy, regular and adequate exercises help improve the quality of life.

1.4. Myositis in Hungary

As myositis are rare diseases at the beginning of my PhD work I was trying to obtain epidemiological data in Hungary. Searching in the database of National Health Insurance Fund Administration and the University of Debrecen I've identified 1119 new myositis patients diagnosed between 1999 and 2010. The average incidence of the disease was found to be 0.95/100.000/year. The male/female ratio was 1/1 in children and ½-3 in adults. Dermatomyositis occurred both in children and adult, but polymyositis was found mainly in adults. These epidemiological data partly correlate with those published in the international literature.

From 1999 to 2010, 289 new patients were hospitalized because of myositis in our Clinic. The average age of patients was 47.73 years. The most common phenotype in our patients was polymyositis (61.93%) and dermatomyositis (32.17%). Other systemic immune diseases, so-called " overlap myositis" occurred in 14 cases, 5 cases of Sjögren syndrome, 6 patients with progressive systemic sclerosis and 3 patients with rheumatoid arthritis. In these 14 overlap syndrome cases, myositis component were PM in 11 and DM in 3 patients.

Tumor-associated myositis was found in 10.72% of our patients. Autoantibodies were detected in 57.43% of patients (n = 166). Frequency of myositis-associated autoantibodies were 35.64% (n = 103) in the serum of our patients.

1.5. Vascular changes in IIM

Several autoimmune rheumatic diseases have been associated with accelerated atherosclerosis or other different types of vasculopathy depending on the underlying disease, leading to increased cardio- and cerebrovascular disease risk. In autoimmune rheumatic diseases besides the traditional risk factors, such as hypertension, diabetes, dyslipidemy, smoking and sedentary lifestyle, the chronic inflammation and endothelial dysfunction also increase the cardiovascular disease (CVD) risk and mortality

Although some data have been shown previously on the cardiovascular involvement and risk factors in Idiopathic Inflammatory Myopathies (IIM), yet there have been no studies performed concerning vasculopathy in the disease. The reported prevalence of cardiac involvement in patients with PM/DM varies between 3% to 100%, based on the definition of the disease, time of the investigation in the disease course, etc. The only disease-specific CV involvement is myocarditis which occurs rarely and could be associated with the presence of auto-antibodies, specially the anti-SRP antibody. Other cardiac involvements in IIMs are unspecific; including myocardial infarction, conduction abnormalities, arrhythmias, mitral valve prolapse, congestive heart failure, hyperdynamic left ventricular contraction, dilated and restrictive cardiomyopathy, pulmonary hypertension and pericarditis. The basic abnormality is inflammation with necrosis and fibrosis of the myocardium, similar to the pathological changes seen in the skeletal muscle. Vascular alterations in coronary arteries have also been reported such as vasculitis, intimal proliferation, media sclerosis and micro-vessel disease of the heart with vasospasm angina. Left ventricular failure occurs due to increased chamber stiffness caused by fibrosis or disturbances in calcium regulation. Clinical assessment including history and signs of cardiac involvement is important at the time of diagnosis as well as during follow-up of myositis patients.

According to the international literature beside the malignant and infectious diseases, the association of CVD with IIM is usually high. Non-invasive vascular assessments, including flow mediated dilatation (FMD) of brachial artery, carotid artery intima-media thickness (IMT), and augmentation index and/or pulse wave velocity of the aorta can reflect the cardiovascular risk of these patients. Besides there have been no studies performed concerning vasculopathy in these diseases.

1.6. Pregnancy in IIM

Very limited information is available regarding pregnancy outcomes in women with myositis. As other systemic autoimmune rheumatic diseases (SARD), IIM also affect both fetal and maternal outcomes in pregnancy. Every pregnancy in a patient with myositis has to be considered as a high-risk situation requiring close monitoring. Crucial issues for improving pregnancy outcomes include careful planning, ideal timing and treatment considerations. Interestingly, the occurrence or exacerbation of IIM during one pregnancy does not necessarily predict the relapse of symptoms in a subsequent pregnancy. Both fetal and maternal pregnancy outcome is generally favorable whether pregnancy occurred during inactive disease. There are three distinct presentations of myositis that can be seen in relation to pregnancy:

1. flare of pre-existing disease during pregnancy,
2. pregnancy induced myositis (most often in 1st or 3rd trimester),
3. postpartum disease onset or flare.

2. AIMS

2.1. The interaction of HLA-DRB1*03 allele and smoking for the development of Anti-Jo1 antibodies in IIM

Before graduation I've studied the genetic backgroud of IIM in our patients and the changes in quality of life due to these diseases. As follows I've joined to an international project researching how genetic and environmental factors, later specially smoking and the presence of HLA-DRB1*03 allele affect on anti-Jo1 positivity in IIM.

2.2. Vascular changes in IIM

The aim of the present study was to assess the flow mediated dilatation of the brachial artery by a TensioClinic arteriograph and to measure the thickness of carotid artery intima-media, the augmentation index and pulse wave velocity using high-resolution ultrasonography in a cohort of IIM patients. We also investigated the correlation of these parameters with the traditional risk factors of atherosclerosis and overall cardiovascular status within IIM patients.
Besides we searched any relationship between clinical caracteristics, serological findings, therapic management and vascular changes.
We also examined the role and usefullness of non-invasive angiological measurements performing vascular disease in IIM.

2.3. Pregnancy in IIM

As coordinator of an international collaboration I had the opportunity to assess the outcome of pregnancy and of the myositis manifestations during pregnancy in women with IIM. Our aim was to describe the frquency of maternal and fetal complications, finding prognostic markers of pregnancy risk and correlation

between clinical symptoms, autoantibody profiles, therapic protocolls and pregnancy risk in IIM.

3. PATIENTS AND METHODS

3.1. The interaction of HLA-DRB1*03 allele and smoking for the development of Anti-Jo1 antibodies in IIM

During this study, leading by Hector Chinoy, Professor at University of Manchester 557 adult-onset IIM patients were recruited from four European countries, UK, Sweden, Hungary and the Czech Republic. Patients with PM or DM had probable or definite myositis, according to the Bohan and Peter criteria and had a confirmed MSA/MAA.

In the case of Hungarian patients, the muscle biopsy required for diagnosis was made from the musculus deltoideus or musculus quadriceps femoris at the Institute of Surgery, University of Debrecen. Immunohistochemistry was performed in the histology laboratory of Department of Neuropathology. EMG tests were performed at the EMG laboratory of the Neurology Clinic. The muscle enzyme levels of patients' serum were detected at the Institute of Laboratory Medicine. Muscle weakness was evaluated by manual muscle strength test (MMT80). For detection of extramuscular manifestations, like myocardial involvement ECG and echocardiography, in some cases myocardial MRI were used. In order to objectify the lung involvement, HRCT and diffusion capacity measurements were performed. In the assessment of gastrointestinal symptoms anamnesis and oesophagus x-ray examination was carried out. Joint involvement was measured by physical examination and also X-ray examination was performed to exclude erosive arthritis.

Antibody profiles were analyzed in the Regional Immunological Laboratory of University of Debrecen using membrane-based immunoblot or ELISA technique Confirmatory and supplementary studies were performed in London (Kennedy Insitute) with recombinant protein blot technique, "line-immuno assay".

Smoking history was ascertained through a retrospective questionnaire including the statement, “Have you ever smoked as much as one cigarette a day for as long as a year?”.

The genotype was investigated in all the 4 patient groups in local laboratories. Subsequently, the DRB1 locus was repeatedly tested in Manchester. In the case of Hungarian patients, DNA from the entire peripheral blood was isolated. MHC-II alleles, HLA-DBR1, DQA1, DQB1 haplotypes were identified by Polymerase Chain Reaction (PCR) and SDS-Polyacrylamide Gel Electrophoresis. During PCR, DNA was amplified by using different "Master Mixes" for 5 microliters of purified DNA sample.

During statistical analysis, a chi square test and a Fischer’s exact test were used, and logistic regression analysis was performed using Stata software (version 9.2, Stata Corp., College Station, TX).

3.2.Vascular changes in IIM

Twenty-seven patients (21 females, 6 males; mean age at diagnosis: 39.48 years) with Idiopathic Inflammatory Myopathies (IIMs) were enrolled in this study, that were followed-up regularly at the Division of Clinical Immunology, Institute of Internal Medicine, University of Debrecen. The average age of patients was 39.48 years at diagnosis, 14 of them suffered in DM, 13 patients had PM. We investigated the development of cardiovascular changes (hypertension, peripheral vascular, ischemic heart and cerebrovascular diseases) during the disease course, as well as traditional CVD risk factors, such as dyslipidemy.

For comparison, 38 healthy individuals matched for sex (25 females, 13 males) and age (mean: 50.3 years) served as controls. None of the controls smoked, had overt atherosclerosis, cardiovascular, cerebrovascular, or

peripheral vascular disease, hypertension, dyslipidemy, or other confounding conditions.

During the examination of vascular parameters, the measurements were made in the morning, at room temperature of 21 ° C, on an empty stomach. Before testing, patients and control persons were rested for 30 minutes in a lying position, and strong light or sound effects were eliminated. We asked them not to drink coffee or tea or take antioxidants for 24 hours prior to the measurements and patients should not take any medicines that could affect the vascular system.

The following measurements were made:

- Assessment of flow-mediated vasodilatation of brachial artery
- Evaluation of carotid artery intima–media layers' thickness
- Assessment of augmentation index and pulse wave velocity in the aorta

Statistical analysis was performed by the SPSS 17.0 software using Pearson's correlation analysis for normal distribution variables and Spearman's test for non-normal variables. Statistically significant was the $p \leq 0.05$ value.

3.3. Pregnancy in IIM

I studied clinical symptoms and laboratory parameters before and during pregnancy in our IIM patients. 9 women had a pregnancy after myositis diagnosis or at the same time. In addition to their data, I collected data of 8 Czech, 5 Swedish and 1 Polish IIM patients. I examined the course of these 23 women's 33 pregnancies. In addition to the retrospective analysis of the clinical databases, our patients also completed a questionnaire edited together by the participating physicians. The diagnosis was also based on the criteria of Bohan and Peter.

To characterize the disease activity, manual muscle testing (MMT), serum CK, LDH values and presence of skin symptoms were used accordig to IMACS' recommendation.

Normal delivery was defined when healthy, more than 2500 g weight newborn delivered after the ended 37 weeks of pregnancy. Premature delivery was defined when the pregnancy ended between its 28 and 37 weeks. Abortion was defined when the pregnancy ended before its 12. weeks, not specified as spontaneous or induced.

Serological profiles were measured in local labs by ELISA or immunoblot techniques. Anti-TIF1γ, anti-NXP2, anti-SAE, anti-MDA5 and anti-Zo antibody test were performed at University of Bath by immunoprecipitation.

We used the Fisher's exact test for statistical analysis and logistic regression with the sotware SPSS 17,0. Statistically significant was the $p \leq 0.05$ value.

4. RESULTS

4.1. The interaction of HLA-DRB1*03 allele and smoking for the development of Anti-Jo1 antibodies in IIM

We enrolled 557 Caucasian patients with adult IIM in this study: 181 patients from Hungary, 183 from the Czech Republic, 94 from Sweden and 99 from the United Kingdom. 75% of patients were female, with a mean age of 48 years (37-58 years) at time of diagnosis. There was no significant difference between nationalities, either considering the sex ratio or the age ($p = 0.065$). 50% of patients had PM, 38% had DM and 12% suffered from overlap myositis. In the Hungarian population there were significantly fewer DM cases compared to the others (OR: 0.36, 95% confidence interval (CI) (0.24-0.54), $p < 0.0001$). Overlap cases, however, were significantly more frequent (OR 3.06, CI: 1.83-5.14, $p < 0.0001$).

There was no significant difference in the frequency of HLA-DRB1*03 allele in the study in the 4 patient groups. The DRB1*03 allele was detected in 32% of Hungarian patients, 43.2% in Czech Rep., 54.3% in Sweden and 52.5% in the UK.

Anti-Jo1 autoantibody positivity was confirmed in 21% of patients, specially in 16% of Hungarian patients. There was no significant difference in the antibody frequency in the 4 subgroup.

39% of our patients were smokers, most of them from the UK, least of them in Hungary. A significant difference had been shown in the distribution of smokers ($p < 0.0001$) in the 4 nationalities.

Examinig the 4 nations together, the proportion of smokers was significantly high among anti-Jo1 positive patients. 50% of antibody positive patients were smokers, while in the anti-Jo1 negative group only 36% used cigarettes (OR: 1.83, 95% CI: 1.18-2.83, $p = 0.004$). In the 4 patient populations,

only the Hungarian patients showed significant differences between the smoking habits of anti-Jo1 positive and negative patients. 45% of our antibody positive patients were smoked, whereas in the antibody negative group, only 17% (OR: 3.94, 95% CI: 1.53-9.89, p = 0.0009).

Investigating the genetic background, a close correlation was verified between carrying HLA-DRB1*03 allele and anti-Jo1 antibody positivity. The presence of the HLA-DRB1 * 03 allele was detected in 74% of antibody positive IIM patients (OR 5.55, CI: 3.42-9.14, p <0.00001).

The frequency of HLA-DRB1*03 allele was higher for smoking patients than for non-smoker patients. The difference was also statistically significant only for Hungarian patients, 59% vs. 25% (OR: 4.39, CI: 1.96-9.92, p <0.00001).

Subsequently, we investigated the relationship between smoking and the presence of HLA-DRB1*03 allele in conjunction with anti-Jo1 autoantibody positivity. In order to ensure that the low sample size of each group does not affect the statistical significance of the results, in this case, the patients were divided into groups independently from nationality. Since all 4 nationalities belong to the Caucasus race, genetic features do not affect the results obtained if individuals of different nationalities are classified into one group, and examine exclusively the smoking habits and anti-Jo1 positivity. The HLA-DRB1*03 negative, non-smoking patients were considered as control group, and their results were compared to the others.

Comparing to the controls, in the HLA-DRB1*03 carrier group, whether smokers or not, anti-Jo1 positivity was more common. In non-smokers among HLA-DRB1*03 positive patients, 39 cases showed antibody positivity, a 2.1-fold increase to the control group (where n = 18, p <0.0001). For HLA-DRB1*03 positive smokers this number is 47 (2.6 times more common than in the control group p <0.0001). Similarly, more frequent antibody positivity was

found in smokers carrying DRB1*03 alleles compared to non-smokers carrying the DRB1*03 allele, although the result was not significant (p = 0.08).

A similar tendency was also observed comparing male and female patients. In both male (4 vs. 15) and female patients (14 vs. 32), more smoker and DRB1 * 03 allele carrier showed anti-Jo1 autoantibody positivity. In men, the frequency of anti-Jo1 antibodies comparing to the control group (non-smoking, DRB1*03 negative male) was 3.75 times higher in the smoking, DRB1*03 positive group (p = 0.005). In women, the carriage of the DRB1*03 allele increases the chance of the appearance of anti-Jo1 antibody alone (n = 33 and 32 vs n = 14). There was no significant difference in the frequency of anti-Jo1 antibodies among smokers and non-smokers in DRB1*03 negative patients. For men this number is 4 vs. 6, females 14 vs 5.

4.2. Vascular changes in IIM

The clinical investigation of CVDs in IIMs showed that 66,7% of patients (n=18; 13 women and 5 men) had hypertension and 29,6% of our patients (n=8; 6 women and 2 men) had ischemic heart disease (IHD) and/or peripheral vascular disease (PAD). None of the patients had major cardio-or cerebrovascular hit. I also examined other cardiovascular diseases, such as valvulopathy, myocarditis, pericarditis or Raynaud's syndrome.

Flow-mediated vasodilatation of brachial artery (abFMD)

Concerning abFMD we observed decreased abFMD in myositis patients, although the result was not significant (p=0,065), while in DM a significantly decreased abFMD was found compared to healthy subjects. Subsequently we assessed correlations between the traditional risk factors of atherosclerosis and cardiovascular diseases. We found significantly negative correlation between the triglyceride levels and flow mediated dilatation (R:-0,412, p:0,041).

Neither hypertension, IHB + PAD, Raynaud phenomenon, myocarditis, pericarditis, nor valvulopathies were correlated with the abFMD values. I did not find any relation between blood pressure values before the tests, cholesterol, LDL-C, HDL-C levels, smoking and abFMD in our patients

The lipid parameters of the control group and their blood pressure values prior the study had no correlation with the abFMD values.

Carotid artery intima–media thickness (acIMT)

Intima-media thickness of the carotid artery showed also a tendency of increased arterial thickness in myositis patients compared to healthy controls (0,61 mm vs. 0,59 mm; p:0,28), which was more pronounced in DM patients (0,64 mm vs. 0,59 mm; p:0,07), although the difference did not reach statistical significance. We also found a significant positive correlation between the values of systolic blood pressure and the thickness of the carotid artery intima-media in IIMs. We found significantly increased carotid IMT thickness in patients with systolic hypertension compared to healthy controls. Significant differences in acIMT have been found both in patients with IHD+PAD compared to healthy controls. The mean carotid IMT of IHD+PAD patients was 0,69 mm, in healthy controls this value was 0,59 mm (p:0,04).

No correlation was found between diastolic hypertension, triglyceride, cholesterol, LDL-C, HDL-C values, smoking and acIMT in our patients.

The lipid parameters of the control group and their blood pressure values prior to the study had no correlation with acIMT.

The acIMT values of myositis patients with previously documented hypertension were significantly higher compared to healthy subjects.

Augmentation index (AIx) and pulse wave velocity (PWV) in the aorta

Concerning pulse wave velocity, we also found a tendency of increased arterial stiffness in the aorta both in all IIM patients (8,79 m/s vs 8,43 m/s; p:0,68) and in DM (8,78 m/s vs. 8,43 m/s; p:0,78), compared to healthy individuals. Concerning the traditional risk factors significantly positive correlation have been found between the triglyceride levels and the augmentation index (AIx) in myositis patients (R:0,567, p:0,029). We verified a clear significant difference in pulse wave velocity between IHD+PAD patients and healthy individuals ($p<0.001$). Neither hypertension, Raynaud phenomenon, myocarditis, pericarditis, nor valvulopathies have been associated with the pulse wave velocity.

Moreover we investigated associations between auto-antibody positivity and vascular abnormalities. 8 patients showed MSA positivity (5 PM, 3 DM), among them in 6 cases anti-Jo1 autoantibodies were detected. One of our patients was positive for anti-Jo1 with severe interstitial lung disease. On the grounds of pulmonary fibrosis, serious pulmonary arterial hypertension developed followed by fatal right and left ventricular failure. One of them had pulmonary fibrosis with slight right ventricular failure. Other cardiovascular diseases like IHD, PAD and hypertension did not present in the Jo1 positive group. Five patients were positive to antiphospholipid antibodies, while 2 had anti-Mi2 autoantibodies; no specific vascular changes were found in these groups.

Concerning the therapy, we have not found any significant differences between groups. Overall, the cardiovascular changes were more frequent in patients who needed combined immunosuppressive treatment.

4.3. Pregnancy in IIM

This project consists of retrospective data analysis from 9 Hungarian, 8 Czech, 5 Swedish and 1 Polish, a total of 23 female IIM patients and 33 pregnancies. The mean age of patients was 23.3 years (7-37 years) at diagnosis. Diagnosis of PM were established in 10 cases, DM was observed in 10, JDM in 3 patients. We observed overlap syndrome in three cases: 2 cases of PM with SLE and SSc, and 1 case of DM with RA. Cancer-associated myositis did not occur in either case.

Regarding clinical symptoms, the most frequent complaint at diagnosis was muscle weakness in 95.6% (n=22) of patients. In addition, extramuscular manifestations were also observed. Most commonly, arthritis (52.17%, n=12), interstitial alveolitis (43.48%, n=10), and mechanic's hand (43.48%; n=10) occurred.

Myositis specific autoantibodies were detected in 8 women's serum at diagnosis, in 6 cases anti-Jo1 and in 2 anti-Mi2 antibodies. Considering myositis.associated antibodies, anti-Pm/Scl (n=2) and anti-SSB (n=1) antibodies were shown. Other autoantibodies, like anti-histone (n=1), double-stranded DNA (dsDNA, n=2), and anti-phospholipid antibodies, namely anti-cardiolipin antibody (n=5) were also present.

Thirty-three of our patients had a total of 33 pregnancies, the mean age was 29.04 years at the beginning of their pregnancy. An average of 68.8 months (0-228) passed between myositis diagnosis and first pregnancy. Pregnancy-induced myositis was observed in 3 cases in the 8th, 17th and 28th weeks of pregnancy in 1-1 SS-PM, RA-DM and DM patients.

In 42.4% of the pregnancies (n=14) fetal complications have been observed. These pregnancies were terminated between gestational week 7 and 31. In 3 cases intra-uterine deaths, in 6 cases miscarriages occurred, 4 of which were spontaneous and 2 induced abortions. In the latest two cases abortion were

induced due to an immunological indication, like the mother's serious, active illness and intake of contraindicated immunosuppressive agents causing fetal malformation. In addition, extra-uterine gravidity in one case, and also 4 premature births were confirmed. Infants born from complicated pregnancies had an average birth weight of 2350 g (168-3220g) and were born on 35.5 weeks (35-36). According to our information, these children later grown up healthy.

The above-mentioned 14 fetal complications were observed in 9 patients, including 6 PM and 3 DM or JDM. Due to the active illness, 7 mothhers (PM=5, DM=2) required immunosuppressive therapy besides corticosteroid treatment before, during or after pregnancy. In 3 cases anti-Jo1 autoantibody positivity was detected in serum of these patients, and anti-cardiolipin and anti-Pm / Scl autoantibodies were also detected in 1-1 cases. In 10 cases of complicated gravidity, conception occurred in the active period of maternal disease, 2 times in remission. 2 pregnancy-induced myositis were observed, one of which ended with spontaneous abortion and the other with premature labor. Myositis remained active after delivery in all these cases.

Based on our results, fetal complications were more common in polymyositis than in dermatomyositis ($p = 0.0729$). The relative risk of fetal complication in PM was 1,923 (95% confidence interval; 1,041-3,553). Probably, besides the PM subgroup, maternal disease activity before or during pregnancy and the presence of autoantibodies may be a risk factor for the development of fetal complications. In the logistic regression analysis, the association of arthritis (OR: 7.5, p: 0.032, 95% CI (1.19-47.77)) and anti-Jo1 autoantibody positivity (OR: 8.9, p: 0.023; 95% CI (1.34-58.88) showed correlation with complications.

5. DISCUSSION

5.1. The interaction of HLA-DRB1*03 allele and smoking for the development of Anti-Jo1 antibodies in IIM

During the observation of four independent European adult IIM patient groups, we tried to find out whether the same smoking-genotype-autoantibody relationship as previously described in RA can be detected in IIM.

In our work, the effect of the HLA-DRB*03 allele positivity and smoking were studied on the expression of the most common myositis-specific autoantibody.

In our patients, the prevalence of anti-Jo-1 autoantibodies was around 20%, which corresponds to previously published data. Interestingly, in all 4 cohorts, there were more smokers among anti-Jo1 positive IIM patients, but this difference only reach statistical significance in Hungarian patients. Carrying the HLA-DRB1*03 allele was also significantly more frequent in Hungarian, smoker IIM patients. Overall, the incidence of anti-Jo-1 antibody is the highest in the HLA-DRB1*03 positive, smoker patient group.

Our findings suggest that smoking is likely to increase the risk of developing IIM in individuals carrying HLA-DRB1*03 alleles. Our current study has shown that the risk of anti-Jo1 autoantibody expression is higher in IIM patients who either smoke and/or carry the HLA-DRB1*03 allele, but due to the absence of age-matched healthy control populations we can not state that these conditions increase the risk of IIM. Our results also indicate that individuals with HLA-DRB1*03 alleles who had ever smoked has a tendency to anti-Jo1 autoantibody production although statistically significant correlation between these 3 parameters could not be verified. It is also possible that HLA-DRB1*03 does not independently influence the appearance of anti-Jo1 antibodies.

Overall, we assume that the presence of HLA-DRB1*03 alleles and smoking together may present a risk for the development of IIM. It is also likely that the risk of the appearance of anti-Jo-1 antibodies continues to increase in those IIM patients who are smokers and have one or more HLA-DRB1*03 copies. These findings help understanding the etiology of IIM and confirm the interaction of the previously described environmental and genetic risk factors in disease onset.

5.2. Vascular changes in IIM

Our present findings underlined that similarly to other systemic autoimmune diseases, impaired abFMD, PWV and increased acIMT were present in IIMs, suggesting the vasculopathy in pathomechanism and increasing the risk of simoultaneous cardiovascular disease. We can establish that the assessments of flow mediated dilation of the brachial artery and the arterial stiffness of the aorta and carotid artery intima-media thickness can be beneficial to predict the CVD risk in myositis patients.

Our findings also confirmed that in DM more vascular abnormalities could be found than in PM. These results could arise from the differences in the pathomechanism of PM and DM. Although striated muscle is the main target of the autoimmune mechanism in both disease entities, in DM, the intramuscular small blood vessels are more dominant effectors' sites, while in PM, the muscle fibres are more direct targets. And more recently, changes in the vascular components were proven to be the primary lesion in this disease because microtubular inclusions and micro vacuoles in endomysial capillaries and MAC deposits were recognized even in otherwise normal muscle of patients with DM.

Among traditional risk factors, hypertriglyceridemy, hypertension leading to the development of ischemic heart or peripheral vascular diseases could be also implicated as one of the forms of vasculopathy in IIM. The elevated

triglyceride levels in our patients could be explained also with sedentary life style due to muscle weakness and impaired physical activity beside the nutritional and hereditary susceptibility of hypertriglyceridemy. We have not found any major cardiovascular events, such as acute myocardial infarction, stroke or critical limb ischemia in our patients.

.

We haven't found any correlation between vascular changes and myositis treatment, but we cannot exclude that the immunosuppressant treatment could also decrease the endothelial dysfunction in chronic inflammatory diseases.

Our group is the first who measured objectively the endothelial dysfunction on such a large myositis population. These results not showed that myositis alone would affect the patient's vascular status. I suggest that in addition to the underlying disease, associated cardiovascular diseases and traditional risk factors play a part in the development of vacular disorders in our patients. This fact emphasise the importance of primary and secondary prevention in decreasing the CVD risk, for example smoking cessation, achievement of appropriate lipid levels, tension control, regular cardiovascular status assessment.

5.3. Pregnancy in IIM

IIMs are rare autoimmune disease characterized by female dominance, but disease onset occurs during childbearing years only in 12-14 % of cases. Limited information is found in the literature, I found data on a total of 89 patients and 121 pregnancies, of whom 25.8% (n = 23) participated in my project. The maternal disease were DM in 48 and PM in 33 cases. There has been no accurate data about myositis subgroup in 8 women's pregnancy. Both fetal and maternal pregnancy complications are often reported also in PM and DM and there are data about in pregnancy-induced maternal illness. In contrast, inactive or well-

controlled maternal disease at the time of conception imply less risk both fetal and maternal complications. In 34 cases, limited or incomplete data is available about maternal illness or fetal outcomes. In the other, preciously published cases 97 cases, the mother suffered from PM in 40 and of DM in 57 cases. In DM patients, the myositis of the mother was inactive during 23 pregnancies, active in 8 gravidity and pregnancy induced DM was reported in 16 cases. Examination of PM mothers showed inactive disease during 12, active in 13 and pregnancy-induced mositis in 15 pregnancy. The number of reported fetal complications during pregnancies were 21 in DM mothers, respectively 22 in PM. Silva et al. reported the first retrospective study about this topic, about the examination of 33 ladies 44 pregnancies between 1966 and 2000. They assumed that the best pregnancy outcomes for both mother and foetus would be expected in case of inactive maternal illness. In pregnancies concieved during active maternal illness, they observed 33% of fetal deaths and 43% intrauterine growth retardation.

Overall based on previosly published data, there is no significant difference in fetal outcomes weather the mothers have PM or DM. Considering fetal complications, only active or pregnancy-induced maternal myositis represents a risk factor. Myositis-specific fetal complications have not been identified so far. The most common complications were abortion and intrauterine fetal retardation. Newborns did not show the symptoms of IIM, the authors had not reported any skin symptoms or muscle weakness.

My results confirm the observation as active maternal myositis increases the the frequency of fetal complications. No myositis specific fetal complications were found. Neither the nature nor the timing of the complication differ from others observed in systemic immune diseases. The most common fetal complications were abortion and premature birth. Overall, the birth weight of newborns is lower in active and pregnancy-induced maternal myositis. In

addition, pregnancies of patients with active or pregnancy-induced myositis terminated earlier than those of asymptomatic patients. There was no significant difference in the type of fetal complications between PM and DM mothers. The degree of disease activity (from mild to severe) did not significantly affect the fetal outcomes. None of the infants showed any symptoms of myositis, that's why muscle enzyme levels were not checked.

In our project fetal complications in patients with polymyositis were more common than in dermatomyositis ($p=0.0729$). The relative risk of fetal complication in PM is 1.923. Because of the retrospective analysis, neither histopathological nor detailed immunological laboratory results were available for all patients, I can only assume the cause of more frequent fetal complications observed in PM. The effect of chronic inflammation and the immune response induced by fetal antigens could lead to complications, and also the influence of myositis specific and associated autoantibodies cannot be excluded. Based on the literature, the involvement of the uterus can not be assumed. Nevertheless, it can not be ruled out that myometrium involvement or problems with implantations due to chronic inflammation are in the background of abortions and premature births.

In 26 of the observed 33 pregnancies, mothers were received corticosteroid monotherapy or were medication-free prior to pregnancy, thus the teratogenic side effects of immunosuppressive agents may be excluded as risk factor for the fetus.

In the logistic regression analysis, joint involvement and anti-Jo1 autoantibody positivity were associated with the development of fetal complications. The anti-Jo1 autoantibody is known to be most commonly associated with anti-synthetase syndrome in wich disease one of the leading symptom is symmetric, non-erosive arthritis. In addition, arthritis and arthralgia are common in all IIM subgroups, so these results are not surprising.

The outcome of pregnancies is generally good for mothers. Neither general nor obstetrical complications have been observed. The onset or exacerbation of the underlying disease can cause maternal complaints. Most of the exacerbation of IIM can be controlled by increasing the steroid dosage until delivery. In some cases the symptoms of IIM disappeared after delivery, no further treatment was needed. In severe, rapid progressive cases IVIG treatment could be the best choice. During pregnancy, the proportion of T helper cells is shifting to the Th2 group, and the exposure of fetal antigens is constantly changing the activity of the maternal immune system. All this can explain the exacerbation of IIM during pregnancy and also pregnancy-induced cases.

No maternal complication was observed in our study, most delivery occured without any problem, no information is available about rhabdomyolysis, myoglobinuria or contractional weakness. Except for 2 cases, the mother's underlying disease was well-controlled by corticosteroid monotherapy during pregnancy. In 33.3% (n=11) of cases, immunosuppressive treatment was performed post partum.

My results also show that pregnancies in IIM patients has to be considered as high risk for both the fetus and the mother and require increased observation and multidisciplinary collaboration (internal medicine, gynecologist and neonatologist). Especially in pregnancies with active maternal illness because of the increased incidence of complications and premature births. Planning and ideal timing of pregnancy and continous consultation with the physician is optimal for both mother and fetus.

6. SUMMARY OF NEW RESULTS

1. Carrying the HLA-DRB1*03 allele in Hungarian IIM patients significantly increases the risk of developing anti-Jo1 antibody, and this risk is further enhanced by smoking in men.

2. In myositis increased vascular stiffness could be observed, indicating endothelial dysfunction and may increase cardiovascular risk.

3. Vascular changes are more pronounced in DM than in PM.

4. Besides the underlying myositis, associated cardiovascular diseases and traditional risk factors also play a role in the development of vacular changes in myositis patients.

5. Fetal complications are more common in polymyositis than in dermatomyositis ($p = 0.0729$). The relative risk of fetal complication in PM is 1.923.

6. Considering the characteristics of maternal disease, joint involvement and anti-Jo1 autoantibody positivity negatively affect the fetal outcome of pregnancy.

8. APPENDIX

Genetic reasearches were funded by Myositis Support Group (UK), a Swedish Research Council, the Swedish Rheumatism Association, Ministry of Education, Youth and Sports in the Czech Republic, King Gustaf V 80 Year Foundation, and by Hungarian ETT grant (No: ETT 2 FAE 1 KCOO90819).

"Vascular research was organised within the following program: TÁMOP 4.2.4.A/2-11-1-2012-0001 National Excellence Program - Local convergence program providing personnel support in development and operation for students and researchers. The project was funded by the EU and the European Social Fund."

Pregnncy study was organized within the ESF EuMyoNet Research Networking Programme.

9. LIST OF PUBLICATIONS

UNIVERSITY of DEBRECEN

UNIVERSITY AND NATIONAL LIBRAY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Registry number: DEENK/242/2018.PL
Subject: PhD Publikációs Lista

Candidate: Melinda Nagy-Vincze
Neptun ID: F3N94U
Doctoral School: Gyula Petrányi Doctoral School of Allergy and Clinical Immunology

List of publications related to the dissertation

1. **Nagy-Vincze, M.**, Dér, H., Kerekes, G., Szodoray, P., Zeher, M., Dankó, K., Soltész, P.: Decreased flow-mediated dilatation with increased arterial stiffness and thickness as early signs of atherosclerosis in polymyositis and dermatomyositis patients. *Clin. Rheumatol. 33* (11), 1635-1641, 2014.
DOI: http://dx.doi.org/10.1007/s10067-014-2561-y
IF: 1.696

2. **Nagy-Vincze, M.**, Vencovsky, J., Lundberg, I. E., Dankó, K.: Pregnancy Outcome in Idiopathic Inflammatory Myopathy Patients in a Multicenter Study. *J. Rheumatol. 41* (12), 2492-2494, 2014.
DOI: http://dx.doi.org/10.3899/jrheum.140438
IF: 3.187

3. Chinoy, H., Adimulam, S., Marriage, F., New, P., **Nagy-Vincze, M.**, Zilahi, E., Kapitány, A., Gyetvai, Á., Ekholm, L., Novota, P., Remakova, M., Charles, P., McHugh, N. J., Padyukov, L., Alfredsson, L., Vencovsky, J., Lundberg, I. E., Dankó, K., Oller, W. E., Cooper, R. G.: Interaction of HLA-DRB1*03 and smoking for the development of anti-Jo-1 antibodies in adult idiopathic inflammatory myopathies: a European-wide case study. *Ann. Rheum. Dis. 71* (6), 961-965, 2012.
DOI: http://dx.doi.org/10.1136/annrheumdis-2011-2000182
IF: 9.111

UNIVERSITY AND NATIONAL LIBRAY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikacio@lib.unideb.hu

List of other publications

4. Diószegi, Á., Tarr, T., **Nagy-Vincze, M.**, Vass, M., Velsz, R., Bidiga, L., Dezső, B., Balla, J., Szodoray, P., Szekanecz, Z., Soltész, P.: Microthrombotic renal involvement in an SLE patient with concomitant catastrophic antiphospholipid syndrome: the beneficial effect of rituximab treatment.
Lupus. [Epub ahead of print], 2018.
DOI: http://dx.doi.org/10.1177/0961203318768890
IF: 2.454 (2016)

5. Botos, B., **Nagy-Vincze, M.**, Dankó, K.: Anti-SRP-pozitív myositises betegeink klinikai sajátosságai és terápiára adott válaszuk.
Orvosi Hetilap. 159 (35), 1382-1389, 2017.
DOI: http://dx.doi.org/10.1556/650.2017.30827
IF: 0.349 (2016)

6. Griger, Z., **Nagy-Vincze, M.**, Bodoki, L., Gherardi, R. K., Dankó, K., Hortobágyi, T.: Dysferlinopathie d'installation tardive imitant une polymyosite résistante aux traitements.
Revue du Rhumatisme. 84 (2), 183-185, 2017.
DOI: http://dx.doi.org/10.1016/j.rhum.2016.12.007

7. Kovács, E., Dankó, K., **Nagy-Vincze, M.**, Csiba, L., Boczán, J.: Long-term treatment of refractory myasthenia gravis with subcutaneous immunoglobulin.
Ther. Adv. Neurol. Disord. 9, 1-4, 2017.
DOI: http://dx.doi.org/10.1177/1756285617722437
IF: 4.192 (2016)

8. Griger, Z., **Nagy-Vincze, M.**, Dankó, K.: Pharmacological management of dermatomyositis.
Expert Review of Clinical Pharmacology. 10 (10), 1109-1118, 2017.
DOI: http://dx.doi.org/10.1080/17512433.2017.1353910
IF: 2.932 (2016)

9. Szabó, K., **Nagy-Vincze, M.**, Bodoki, L., Hódosi, K., Dankó, K., Griger, Z.: Az anti-Jo-1-pozitív antiszintetáz szindróma jellegzetességei gondozott betegeink alapján.
Orvosi Hetilap. 157 (15), 575-583, 2016.
DOI: http://dx.doi.org/10.1556/650.2016.30400
IF: 0.349

10. Griger, Z., **Nagy-Vincze, M.**, Bodoki, L., Gherardi, R. K., Dankó, K., Hortobágyi, T.: Late onset dysferlinopathy mimicking treatment resistant polymyositis.
Joint Bone Spine. 83 (3), 355-356, 2016.
IF: 3.329

11. Szalmás, O., **Nagy-Vincze, M.**, Dankó, K., Farkas, F.: A juvenilis és felnőttkori dermatomyositises betegek klinikai jellemzői.
Orvosi Hetilap. 156 (37), 1491-1496, 2015.
DOI: http://dx.doi.org/10.1556/650.2015.30214
IF: 0.291

12. Bodoki, L., Budai, D., **Nagy-Vincze, M.**, Griger, Z., Betteridge, Z., Dankó, K.: Dermatomyositis-specifikus autoantitesttel rendelkező és autoantitest-negatív betegeink klinikai jellemzőinek és laboratóriumi paramétereinek összehasonlítása.
Orvosi Hetilap. 156 (36), 1451-1459, 2015.
DOI: http://dx.doi.org/10.1556/650.2015.30221
IF: 0.291

13. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Dankó, K.: Dermatomyositisspezifische Antikörper.
Z. Rheumatol. 74, 363-369, 2015.
IF: 0.569

14. Péter, A., Balogh, Á., Szlágyi, S., Faludi, R., **Nagy-Vincze, M.**, Édes, I., Dankó, K.: Echocardiographic abnormalities in new-onset polymyositis/dermatomyositis.
J. Rheumatol. 42 (2), 272-281, 2015.
DOI: http://dx.doi.org/10.3899/jrheum.140626
IF: 3.236

15. Murnyák, B., Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Csonka, T., Szepesi, R., Kurucz, A., Dankó, K., Hortobágyi, T.: Inclusion body myositis: pathomechanism and lessons from genetics.
Open Med. 10, 188-193, 2015.

16. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Betteridge, Z., Szöllősi, L., Jobanputra, R., Dankó, K.: Rare myositis-specific autoantibody associations among Hungarian patients with idiopathic inflammatory myopathy.
Acta Reumatol. Port. 40, 337-347, 2015.
IF: 0.553

17. Bodoki, L., Chen, J. Q., Zeher, M., **Nagy-Vincze, M.**, Griger, Z., Zilahi, E., Dankó, K.: Vitamin D Receptor Gene Polymorphisms and Haplotypes in Hungarian Patients with Idiopathic Inflammatory Myopathy.
Biomed Res. Int. 2015, 1-8, 2015.
DOI: http://dx.doi.org/10.1155/2015/809895
IF: 2.134

18. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Csonka, T., Dankó, K., Hortobágyi, T.: Zárványtestes myositis.
Ideggyogy. Szle. 68 (1-2), 59-67, 2015.
IF: 0.376

19. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Péter, A., Dankó, K.: Anti-NXP2-pozitív dermatomyositis társulása colitis ulcerosával és coeliakiával.
Orvosi Hetilap. 155 (26), 1033-1038, 2014.

20. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Péter, A., András, C., Dankó, K.: Biológiai terápia idiopathiás inflammatorikus myopathiákban.
Orv. Hetil. 155 (1), 3-10, 2014.
DOI: http://dx.doi.org/10.1556/OH.2014.29787

21. **Nagy-Vincze, M.**, Bodoki, L., Griger, Z., Dankó, K.: Epidemiológiai adatok idiopathiás inflammatoricus myopathiákban Magyarországon.
Orv. Hetil. 155 (41), 1643-1646, 2014.

22. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Betteridge, Z., Szöllösi, L., Dankó, K.: Four dermatomyositis-specific autoantibodies-anti-TIF1[gamma], anti-NXP2, anti-SAE and anti-MDA5-in adult and juvenile patients with idiopathic inflammatory myopathies in a Hungarian cohort.
Autoimmun. Rev. 13 (12), 1211-1219, 2014.
DOI: http://dx.doi.org/10.1016/j.autrev.2014.08.011
IF: 7.933

23. **Nagy-Vincze, M.**: Immunglobulin kezelés dermatomyositisben.
Autoimmun Kaleidoszkóp. 2 (7), 20-22, 2014.

24. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Csonka, T., Mumyák, B., Kurucz, A., Dankó, K., Hortobágyi, T.: Inclusion body myositis - a case based clinicopathological update.
Cent. Eur. J. Med. 9 (1), 80-85, 2014.
IF: 0.153

25. Szankai, Z., **Nagy-Vincze, M.**, Bodoki, L., Jakab, A., Betteridge, Z., Dankó, K.: Malignitás társulásának kockázatát fokozó tényezők vizsgálata myositises betegekben: klinikai, immunológiai sajátosságok és az anti-p155/140 antitest szerepe.
Orvosi Hetilap. 155 (36), 1437-1444, 2014.
DOI: http://dx.doi.org/10.1556/OH.2014.29984

26. Bodoki, L., **Nagy-Vincze, M.**, Hortobágyi, T., Griger, Z., Csonka, T., Dankó, K.: Szignálfelismerőrészecske-ellenes autoantitest-pozitív myopathia.
Ideggyogy. Szle. 67 (9-10), 347-353, 2014.
IF: 0.386

27. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Dankó, K.: Az idiopathiás inflammatoricus myopathiák osztályozása.
Immunol. Szle. 6 (1), 4-13, 2013.

28. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Dankó, K.: Intravénás immunglobulin-kezelés idiopathiás inflammatoricus myopathiákban.
Orv. Hetil. 154 (19), 723-728, 2013.
DOI: http://dx.doi.org/10.1556/OH.2013.29600

29. Griger, Z., **Nagy-Vincze, M.**, Bodoki, L., Cseri, K., Hortobágyi, T., Dankó, K.: Nekrotizáló autoimmun myopathia esete.
Metabolizmus. 11 (5), 379-382, 2013.

30. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Garan, D., Constantin, T., Ponyi, A., Dankó, K.: Rituximab kezelés hatásossága juvenilis dermatomyositisben: esetismertetés.
Magyar Reumatol. 54 (2), 107-111, 2013.

31. Bodoki, L., **Nagy-Vincze, M.**, Griger, Z., Csonka, T., Cseri, K., Hortobágyi, T., Dankó, K.: Rituximabkezelés idiopathiás inflammatorikus myopathiákban.
LAM. 23 (1), 16-21, 2013.

32. Labirua-Iturburu, A., Selva-O'Callaghan, A., **Nagy-Vincze, M.**, Dankó, K., Vencovsky, J., Fisher, B., Charles, P., Dastmalchi, M., Lundberg, I. E.: Anti-PL-7 (anti-threonyl-tRNA synthetase) antisynthetase syndrome: clinical manifestations in a series of patients from a European multicenter study (EUMYONET) and review of the literature.
Medicine (Baltimore). 91 (4), 206-211, 2012.
DOI: http://dx.doi.org/10.1097/MD.0b013e318260977c
IF: 4.233

33. **Nagy-Vincze, M.**, Dankó, K.: Dermatomyositis és polymyositis felismerése, általános jellemzői.
Autoimmun Kaleidoszkóp. 3 (1), 10-12, 2012.

34. **Nagy-Vincze, M.**, Dankó, K.: Idiopathic inflammatory myopathies.
Best Pract. Res. Clin. Rheumatol. 26 (1), 25-45, 2012.
DOI: http://dx.doi.org/10.1016/j.berh.2012.01.013
IF: 3.55

35. **Nagy-Vincze, M.**, Bodoki, L., Griger, Z., Dankó, K.: Myositis - gyulladásos izombetegségek klasszifikálása.
Magyar Reumatol. 53, 229-241, 2012.

36. Bodoki, L., **Nagy-Vincze, M.**, Hortobágyi, T., Griger, Z., Cseri, K., Szőllősi, L., Dankó, K.: Nekrotizáló autoimmun myopathia.
Orv. Hetil. 153 (38), 1502-1507, 2012.
DOI: http://dx.doi.org/10.1556/OH.2012.29450

37. Dankó, K., **Nagy-Vincze, M.**: A polymyositis és dermatomyositis modern kezelési lehetőségei.
Orv Hetil. 152 (39), 1552-1559, 2011.
DOI: http://dx.doi.org/10.1556/OH.2011.29176

38. **Nagy-Vincze, M.**, Molnár, P. A., Zilahi, E., Kapitány, A., Dezső, B., Takács, I., Dankó, K.: Primary lung adenocarcinoma associated with anti-Jo-1 positive polymyositis.
Joint Bone Spine. 78 (2), 209-211, 2011.
DOI: http://dx.doi.org/10.1016/j.jbspin.2010.08.018
IF: 2.274

UNIVERSITY of DEBRECEN

UNIVERSITY AND NATIONAL LIBRAY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

39. **Nagy-Vinoze, M.**, Molnár, P. A., Tumpek, J., Szöllösi, L., Gyetvai, Á., Kapitány, A., Dankó, K.: An unusual association: anti-Jo1 and anti-SRP antibodies in the serum of a patient with polymyositis.
Clin. Rheumatol. 29 (7), 811-814, 2010.
DOI: http://dx.doi.org/10.1007/s10067-010-1394-6
IF: 1.687

Total IF of journals (all publications): 66,286
Total IF of journals (publications related to the dissertation): 13,894

The Candidate's publication data submitted to the IDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

31 May, 2018