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Rīgas Stradiņa universitāte

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TEMPOROMANDIBULAR JOINT ARTHRITIS DEVELOPMENT INFLUENCING FACTORS, CLINICAL AND RADIOLOGIC SYMPTOMS IN CHILDREN WITH JUVENILE IDIOPATHIC ARTHRITIS

Summary of the Doctoral Thesis
for obtaining the degree of a Doctor of Medicine
Speciality – Paediatrics, Paediatric Rheumatology

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The Doctoral Thesis was carried out at Children`s Clinical University Hospital, Clinic for General Paediatrics, Department of Radiology and Joint Laboratory of Clinical Immunology and Immunogenetics of Rīga Stradiņš University.

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The Doctoral Thesis is available in the RSU library and at RSU webpage: www.rsu.lv.

Secretary of the Doctoral Council:

Dr. med., Professor **Jana Pavāre**

CONTENT

ABBREVIATIONS USED IN THE SUMMARY

ACR	American College of Rheumatology
USA	United States of America
ANA	antinuclear antibodies
CHAQ	Childhood Health Assessment Questionnaire
CI	confidence interval
CRP	C-reactive protein
CT	computed tomography
ESR	erythrocyte sedimentation rate
HLA	human leukocyte antigen
IFN-γ (gamma)	interferon gamma
IL	Interleukins
ILAR	International League of Associations for Rheumatology
i/a	intraarticular
JADAS 10 (or 27, or 71)	Juvenile Arthritis Disease Activity Score, number means how many joints are evaluated
JIA	Juvenile idiopathic arthritis
CIIJ	Joint Laboratory of Clinical Immunology and Immunogenetics
Max.	maximum value
mg/L	milligrams per litre
MHC	major histocompatibility complex
Min.	minimal value
mm/h	millimeters per hour
MRI	magnetic resonance imaging
MRP8/14	myeloid related protein

MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drugs
OR	odds ratio
p	probability
pGALS	paediatric Gait Arms Legs and Spine
RF	rheumatoid factor
RSU	Rīga Stradiņš University
RT-PCR	multiprimer real time polymerase chain reaction
SD	standard deviation
TNF	tumour necrosis factor
TMJ	temporomandibular joint
US	ultrasound
VAS	visual analogue scale
CCUH	Children`s Clinical University Hospital
k	Kappa coefficient
χ^2	Chi-square test

1. INTRODUCTION

1.1. Topicality of the research

Temporomandibular joint (TMJ) arthritis in patients with juvenile idiopathic arthritis (JIA) has been a topical issue in Society of Paediatric Rheumatologists, Orthodontists, Radiologists, Dentists in about last ten years. International conferences dedicated to this problem have been organized every year since 2010. The aim of these activities is to avoid complications of TMJ arthritis that can be different faciodental developmental problems with functional limitations.

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of conditions which encompasses all forms of arthritis of unknown aetiology lasting for at least 6 weeks and with onset before the age of 16 years. However it is known that JIA has a genetic predisposition, including different JIA types association with concrete HLA II class alleles (Cassidy et al., 2011; Ravelli, Martini, 2007).

Every joint may become inflamed in JIA including TMJ. The damage of this joint starts very early in case of inflammation because of specific anatomic features – the growth centre of mandibula is located below the cartilage of the joint and therefore affects the growth of mandibula (Ringold et al., 2009; Fam et al., 2006; Cassidy et al., 2011). TMJ arthritis with active inflammatory signs and/or structural damage signs (consequences of chronic inflammation) can be detected even in 87% of JIA patients and very often is diagnosed only after irreversible changes of joint structures have developed (Arabshahi et al., 2006; Küseler et al., 1998).

TMJ arthritis can interfere with normal dentofacial development and such pathologies as micrognathia, retrognathia, asymmetric face, restricted mouth opening, and pathologic dental occlusion can be seen in these patients.

Also craniomandibular functional problems can arise as difficult chewing, even speaking (Perttiniemi et al., 2009; Fjeld et al., 2010). These problems in turn can cause emotional problems and lowered quality of life. Temporomandibular joint dysfunction has been mentioned as the second most often musculoskeletal problem after lower back pain (Ahmad, Schiffman, 2016).

Different factors influencing TMJ arthritis development have been researched. Most often TMJ arthritis has been diagnosed in JIA patients with polyarticular and systemic disease, but it can also be the only affected joint (Cassidy et al., 2011). Stoll and colleagues conclude that there is a similar risk for developing TMJ arthritis in all JIA subtypes and it can also persist during a remission in other joints (Stoll et al., 2012). Positive antinuclear antibodies and rheumatoid factor can be as risk factors (Arabshahi et al., 2006).

Different HLA II class alleles have been associated with concrete JIA subtypes, the age of the onset of disease (Hollenbach et al., 2010). There have been no studies about associations of TMJ arthritis and HLA II class alleles in JIA before this.

To diagnose TMJ arthritis there is a need for combination of different methods – both clinical and radiological. Some studies show that patient`s subjective and objective symptoms do not correlate with MRI findings very often, however standardised questionnaires for subjective complaints or protocols for objective findings rarely have been used. TMJ arthritis symptoms can be pain with jaw movements, when chewing harder food, asymmetry of mandibula, intraarticular crepitation, clicking, even torticollis, but these symptoms as mentioned in previous studies have high specifity but low sensitivity (Cannizzaro et al., 2011; Twilt et al., 2004). Hyperdiganostics of TMJ arthritis can be another problem when using only clinical symptoms (Koos et al., 2014).

Comparing with other radiological methods as ultrasound and conventional X-rays, magnetic resonance imaging (MRI) with contrast enhancement has been proved as the most informative for detection of TMJ arthritis (Müller et al., 2009). Bones, intraarticular joint disk and fibrous cartilage as well as intraarticular fluid and synovial contrast enhancement can be diagnosed with MRI. Also TMJ arthritis can be detected early in asymptomatic JIA patients (Argyropoulou et al., 2009; Pedersen et al., 2008; Weiss et al., 2008). However MRI is an expensive method and in Latvia and other European countries mostly it is impossible to do this investigation for all JIA patients, considering that it should be done not only in the beginning but also at different stages of the disease. Therefore we have to find out those JIA patients with concrete disease characteristic clinical, laboratory criteria and symptoms for which MRI would be me more indicated. It is important when we choose the treatment.

Results of MRI can change our approach to systemic treatment – to stay on synthetic antirheumatic disease modifying drugs as methotrexate or to add biologic antirheumatic drugs. There are also some options for local treatment besides systemic medications as oral splints, local intraarticular glucocorticoid injections (Ringold et al., 2008; Stoll et al., 2012). In Latvia we use JIA treatment guidelines based on international recommendations and treatment options are chosen depending on specific risk joints which are inflamed and the disease activity (*Juvenila idiopātiska artrīta klīniskās vadlīnijas*, 2016). Early, effective systemic and in some cases local treatment is very important to keep TMJ without structural damage and to eliminate consequences of this damage what can affect all faciodental structures (Arabshahi et al., 2005).

To take good care of JIA patients with TMJ arthritis and to avoid faciodental developmental problems with functional limitations, we need to know what factors influence development of TMJ arthritis and also we have to understand what symptoms – both subjective and objective are more

correlating with MRI findings. This information can help decide which patients need MRI investigation not only at the beginning of the disease but also during all the course of the JIA.

1.2. Hypothesis, aim and objectives

Hypotheses of the study:

1. Demographic, clinical, laboratory and genetic factors influence the risk of the development of TML arthritis in JIA patients.
2. Subjective and objective clinical symptoms of TML arthritis are connected with MRI findings.

Aim of research: to investigate demographic, clinical, laboratory and genetic factors influencing the development of TML arthritis, to detect clinical (subjective and objective) and radiologic findings connected with paediatric juvenile idiopathic arthritis.

Objectives of research:

1. To investigate demographic and disease-characteristic clinical and laboratory parameters.
2. To study the factors influencing the development of TML arthritis, comparing demographic, clinical, laboratory data, the results of HLA II allele genotyping in the patient groups with MRI positive (MRI+) (the signs of active and/or chronic inflammation) and MRI negative findings (MRI−).
3. To detect the connection between subjective and objective symptoms of TML arthritis and TML MRI findings, comparing MRI(+) and MRI(−) groups and also depending on the signs of active and/or chronic inflammation on MRI.
4. To estimate the results of MRI depending on the signs of active inflammation and/or irreversible structural damage in JIA patients

with subjective and/or objective symptoms of TML arthritis (symptomatic patients) and patients without TML symptoms (asymptomatic patients).

1.3. Novelty of research

1. The factors influencing the development of TML arthritis in paediatric juvenile idiopathic arthritis patients in Latvia are studied for the first time, that way paying attention to the damage of anatomically unique and functionally significant joint and it is timely diagnosis.
2. The HLA class II alleles have not been studied in patients with JIA and TML arthritis; therefore the results of the study are investment in the research of the pathogenesis and classification of JIA and the development of personalized medicine.

1.4. Practical significance

Taking into account demographic, clinical, laboratory factors and HLA II risk and protective alleles influencing development of TML arthritis one can find JIA patients in need of early MRI diagnostics to detect further therapy options to avoid possible irreversible joint damage. The practical recommendations about diagnostics of TML arthritis for paediatric rheumatologists are worked out based on the results of the research.

The study has promoted and continues to develop interdisciplinary cooperation of rheumatologists, radiologists, orthodontists and geneticists and a team work in care for JIA patients.

2. MATERIAL AND METHODS

2.1. Design of the study

Prospective cross-sectional study, consisting of 4 parts:

1) analysis of demographic and disease-characteristic data of JIA patient group;

2) detection of the factors influencing TML arthritis development in the patient groups with the signs of TML arthritis on MRI–MRI(+) and without the signs of arthritis on MRI–MRI(−), comparing demographic, disease characteristic clinical, laboratory and HLA II allele genotyping data;

3) research of subjective and objective clinical symptoms and connection with MRI findings, comparing symptoms in MRI positive and negative groups and depending on the signs of active and/or chronic inflammation;

4) analysis of MRI findings in JIA patients with TML arthritis symptoms (symptomatic) and patients without symptoms from these joints-asymptomatic.

The study was carried out in state tertiary level hospital, Children`s Clinical University Hospital, Clinic for General Paediatrics, Department of Radiology and Joint Laboratory of Clinical Immunology and Immunogenetics of Rīga Stradiņš University in the period from 2010 to 2015.

The study was approved by Central Medical Ethics committee of Latvia (CMEC) in 6 February, 2013 with the issued opinion about the compliance with principles of bioethics: 01-29.1/1 – "Research of the genetic basis of the connection between temporo-mandibular joint and juvenile idiopathic arthritis (Annex 1)". All the children included in the study and their parents signed informed consent for the participation in the research.

2.2. Research sample

There were 91 patients treated and followed up in Children`s Clinical University Hospital, Clinic for General Paediatrics as inpatients or outpatients diagnosed with Juvenile idiopathic arthritis (JIA) according to ILAR criteria who underwent magnetic resonance imaging (MRI) with contrast enhancement for temporomandibular joints in the period from 2010 to 2015.

From 91 patients included in the study 80 children had subjective complaints and/or objective findings of TML arthritis, but also 11 asymptomatic patients without subjective and/or objective TML symptoms were included. These patients had complaints about other joints and according to risk factors mentioned in literature they were in high risk for the development of TML arthritis.

The gold standard of the diagnosis of TML arthritis is magnetic resonance imaging (MRI) with contrast enhancement therefore 2 main groups of the research were formed according to MRI findings:

1) MRI(+) positive group: patients with active signs of synovitis (bone oedema, increased synovial contrast enhancement, intraarticular fluid, pannus) and/or damage of intraarticular structures (condyle head deformation, mandibular fossa flattening, osteophytes, erosions). Light and symmetrical contrast enhancement was not considered as a sign of arthritis (von Kalle et al., 2013) (n = 72);
2) MRI(−) negative group – patients without pathological findings on MRI (n = 19).

The patients with the pathological changes on MRI (MRI(+) group) were further divided according to the structural damage:

1) The patients with structural TML damage with or without the signs of active inflammation (n = 50);

2) The patients with only active TML inflammation signs (n= 22) (Fig.2.1.).

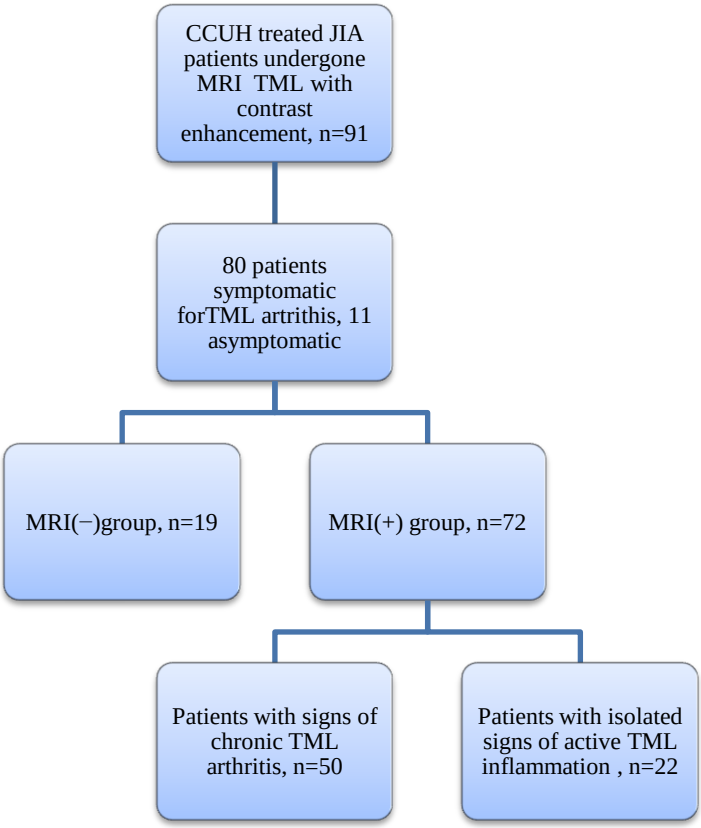

Figure 2.1. **Research groups**

2.3. Control group

During immunogenetic study 100 accidental healthy blood donors without the history of autoimmune diseases were included in the control group – 47 men (47%) and 53 (53%) women, mean age 18.6 years (SD = 3), all of them inhabitants of Latvia. The material included in the study is taken from the blood bank of Joint Laboratory of Clinical Immunology and Immunogenetics of Rīga Stradiņš University.

2.4. Determination of the disease characterising indicators

Active joint count – swollen joints which are not connected with bone hypertrophy or joints with restricted movement and pain with movement or palpation. The joints were considered as active when synovitis was detected by MRI or USG also in circumstances where joints were not active following the previous definition (Consolaro et al., 2016).

CHAQ (Childhood Health Assessment Questionnaire) is validated in Latvian and used to evaluate the activity of the disease and the patient`s functional ability over the past week prior to the visit to doctor during everyday activities. The patients and their parents were assessed during the period when MRI was carried out (± 1 week). CHAQ has score ranging 0 to 3; the highest score means worse functional abilities.

VAS (visual analogue scale):

1) 10-cm visual analogue scale for physician-assessed global disease activity, where 0 means no activity of the disease but 10 means maximum activity;

2) patient-assessed and/or parent-assessed pain severity scale 0 to 10, where lower score means less pain;

3) patient-assessed and/or parent-assessed global assessment of disease status by rating the child's overall level of well-being (WB) on a 10-cm visual analogue scale (VAS) from 0 to 10; the higher rating means worse overall level of well-being, which can be affected by the presence of disease damage, the use of medications, the need for hospitalization etc. (Latvian Children Rheumatologists Society, clinical guidelines of idiopathic juvenile arthritis, The National Health Service, order No. KV 03-2016 21.06.2016.).

Morning stiffness in joints ≤ 15 minutes is one of the criteria for inactive disease (Wallace et al., 2011).

2.5. Radiologic data analysis

The standard MRI with contrast enhancement for TML joints was carried out in: T1 and T2 FS coronary plane, T1 and T2 oblique sagittal plane; after the administration of intravenous contrast T1 sagittal oblique and T1 FS axial (8–10 minutes after the contrast injection). The standard dose of gadolinium containing contrast is 0.2 mL/kg body weight. T1 images show the structure and localization of intraarticular disc. Fat-suppressed T2 sequences are sensitive to bone marrow oedema, intraarticular fluid and synovial proliferation.

The results of MRI imaging were assessed by two independent radiologists. The agreement of opinions was detected by kappa coefficient. Altmann guidelines (1999) (adapted from & Koch, 1977) were used for the interpretation of the results; the strengths of agreement below 0.20 – poor, 0.20–0.40 – fair, 0.40–0,60 – moderate, 0.60–0.80 – substantial, 0.80–1.00 – almost perfect.

MRI results were divided according to the signs of active and/or chronic inflammation, the common number of findings was also evaluated.

2.6. Laboratory data analysis

2.6.1. Laboratory data performed to diagnose JIA and to estimate disease activity

Laboratory investigations – CRP, ESR, RF, HLA B27 antigen detection in JIA patients to diagnose the disease and to estimate the activity of the disease were carried out in Biochemistry Laboratory of Children`s Clinical University Hospital following equal standardized methods. The reference values in the laboratory were as follow: ESR in boys of all the age groups

0.0–15.0 mm/h, girls 0.00–20.0 mm/h, CRP in all age groups and genders 0–5 mg/L.

RF was evaluated as positive or negative without giving the numeric value.

ANA – was detected in The Laboratory of Pauls Stradiņš Clinical University Hospital with immunofluorescence method; titre 1 : 80 considered as positive; the titre was not taken into account but pointed out as positive or negative.

2.6.2. Genotyping of HLA II class alleles

The immunogenetic part of the research was carried out in CIIJ of RSU As a control group 100 samples of CIIJ healthy individuals from genetic bank were taken. DNA was extracted from peripheral blood, using *QiagenQIAamp* DNA kit reagents according to manufacturer (QIAamp DNA Mini and Blood Mini Handbook). The quality and quantity was checked by *Qubit ® fluorometer* (Invitrogen USA*)*. HLA genotyping of the patients and healthy donors was performed by multiparametric real-time polymerase chain reaction (RT-PCR).

The following alleles were genotyped for the patients and the control group: HLA-DRB1*01:01 to 18:01, DQA1*01:01, 01:02, 01:03, 04:01, and 06:01 and DQB1*02:01–02:02, *03:01–03:05, *04:01–04:02, *05:01–05:04 and *06:01–06:08. Genotyping was performed by low resolution RT-PCR, qualitative analysis, melting curve analysis, using sequence specific parameters according to manufacturers methodical principles which allow to identify main HLA-DR and HLA-DQ types of locus alleles.

HLA-DRB1*, HLA-DQA1* and HLA-DQB1* gene amplification was performed in 103 cycles with *DTLite* – thermocyclers (DNA-Technology), which allows to maintain fixed thermal regimen. Initially temperature

(approximately 94 °C) enhances double stranded DNA denaturation and single stranded DNA formation. Afterwards temperature is decreased to approximately 64 °C and hybridization takes place: there are several allele samples or primers in the test system, which attach to complementary DNA regions on single stranded DNA. Temperature is increased up to 80 °C. DNA-polymerase (Taq-polimerase) and nucleotides are added, DNA fragment is elongated with complementary primer and second complementary DNA chain is synthesized. As a result from one DNA strand with specific gene second copy is made which both become matrices in following cycles. The number of searched gene increases in geometric progression and is documented by the device. Results are read automatically by the computer during the amplification programme and after completion.

2.7. Five step screening for TMJ arthritis detection

From 91 patients of the study group 64 underwent objective examination following five step screening for TMJ arthritis orally presented by working group in TML arthritis multidisciplinary conference in 2011 in Kiel but published in 2014 (Koos et al., 2014). Taking into account that our study started in 2010 but the screening was published in 2014 it has not been carried out in all the study patients.

TML arthritis screening (5 steps):

1. TML palpation is painful or painless (during palpation mouth is closed and relaxed);
2. *musculus masseter* palpation is painful or painless (during palpation mouth is closed and relaxed);
3. *musculus temporalis* palpation is painful or painless (during palpation mouth is closed and relaxed);

4. mouth opening (between front teeth; patient opens mouth as wide as one can):
    a) up to the age of 10 years ≤ 35mm or normal;
    b) after the age of 10 years ≤ 40mm or normal;
    c) in repeated visit mouth opening decreased by 7 mm or more;
5. Deviation of lower jaw more than 2mm or normal with maximum mouth opening.

2.8. Statistical analysis of data

Data statistical analysis in overall study group and also in MRI+ and MRI-groups was performed using *IBM SPSS* 22.0 programme. Factor dispersion in groups was detected by frequency tables. The differences of statistical significance of frequency of prevalence were estimated by Pearson's chi-squared test (χ^2) or Fisher's exact test. The p value < 0.05 was chosen as the level of statistical significance. The frequencies of DRB1, DQB1 and DQA1 alleles in patient groups were compared by Pearson's chi-squared test (χ^2). The Cochran-Mantel-Haenszel statistics was used for estimation of the odds ratios. EPI INFO programme version 6 was used to calculate p value and OR with 95% confidence intervals and Fisher's correction for small samples (Harbage, Dean, 1999). Nonparametric Mann–Whitney U test was used to compare CRP and ESR.

TML MRI positive findings correlations with different demographic, clinical and laboratory data was detected by logistic regression models.

3. RESULTS

3.1. Patient group`s demographic and disease characterising data

From 91 study patients 64 (70%) were girls, 27 (30%) boys. Mean age at the moment of MRI investigation was 13.6 years (SD = 3.1 year) (6–17.9 years).

The division of JIA types was: seronegative polyarthritis 55 patients (60%), seropositive polyarthritis 7 (8%), persistent oligoarthritis 2 (2%), progressing oligoarthritis 8 (9%), arthritis with enthesitis 14 (16%), undifferentiated arthritis 3 (3%), systemic arthritis 2 (2%). There were no patients with psoriatic arthritis but 3 (4.4%) patients had uveitis.

The disease-characteristic clinical data were as follows – mean duration of the disease 3 years (SD = 2.4 years) (0.2–11 years), the time interval from the detection of diagnosis 1.8 years (SD = 2.2 years) (0–10 years). The mean Childhood Health Assessment Questionnaire score (CHAQ) in common group of JIA patients was 0.67 (SD = 1.04) (0–8), average pain intensity score in visual analogue scale was 4 (SD = 2) (0–8), average patient assessed well-being was 4 (SD = 2) (0–10), average physician-assessed global disease activity was 5 (SN = 5) (0–10). The mean morning joint stiffness was 19.7 minutes (SD = 45.1) (0–360 minutes). The mean active joint count taking into account those joints were synovitis was detected by ultrasonography or MRI was 7 (SD = 5) (0–22).

From the disease-characteristic laboratory data positive ANA was detected in 24 (27.6%) patients, positive RF was detected in 6 (6.7%) patients. HLA B27 antigen was positive in 18 (19.8%) patients. From the disease activity characterizing laboratory mean CRP was 5.5 (SD = 25.08) mg/L (0–180 mg/L), but ESR 10.5 (SD = 18.62) (0–120 mm/h).

The disease characterizing data in common patient`s group is shown in Table 3.1.

Table 3.1.

The disease characterizing data in common patient`s group

Parameter	Patient number, n	Mean	SD	Min.	Max.
Duration of the disease, years	91	3.0	2.4	0.2	11
Time interval from the detection of diagnosis, years	91	1,8	2,2	0	10
Active joint count, n	91	7	5	0	22
CHAQ	64	0.67	1.04	0	8
VAS – pain	65	4	2	0	8
VAS – overall well-being	65	4	2	0	10
VAS – physician`s performed assessment	66	5	5	0	10
Morning stiffness in joints, minutes	89	19.7	45.1	0	360
CRP, mg/L	90	5.5	25.08	0	180
ESR, mm/h	91	10.5	18.62	0	120

SD = standard deviation, Min. = minimal value, Max. = maximum value.

3.2. Factors influencing the development of TMJ arthritis

3.2.1. Demographic, disease characterising clinical and laboratory data

To detect the factors influencing development of TML arthritis 91 patients were divided into two groups depending on MRI findings: MRI positive group (n = 72) and MRI negative group (n = 19). The only statistically significant differences were detected in CRP values – mean value in MRI(+) group with proved TML arthritis was 6.8 (28)mg/L but MRI(−) group 0.3 (0.4) mg/L, p = 0.0078 (Table 3.2.).

Table 3.2.

TML arthritis development influencing factors in MRI (+), MRI (−) and common JIA patient`s group

Factors	MRI+ group (n = 72)	MRI− group (n = 19)	Common group (n = 91)
Demographic parameters Gender: Girls, n (%) Boys, n (%)	 55 (76.4) 17 (23.6)	 9 (47.4) 10 (52.6)	 64 (70.3) 27 (29.7)
P value	0.014		
Age at MRI performance, years, mean (SD)	13.8 (3.02)	12.6 (3.24)	13.6 (3.1)
P value	NS		
Disease characterizing parameters Duration of the disease, years, mean (SD)	2.9 (2.5)	3.3 (2.0)	3.0 (2.3)
P value	NS		
Time interval from the detection of diagnosis, years, mean (SD)	1.6 (2.2)	2.2 (2.0)	1.8 (2.2)
P value	NS		
Active joint count*, mean (SD)	7 (5)	7 (6)	7 (5)
P value	NS		
CHAQ, mean (SD)	0.76 (1.13) n = 52	0.45 (0.47) n = 12	0.67 (1.04) n = 64
P value	NS		
VAS – pain, mean (SD)	4 (2) n = 53	3 (2) n = 12	4 (2) n = 65
P value	NS		
VAS – overall well-being, mean (SD)	4 (2) n = 53	3 (2) n = 12	4 (2) n = 65
P value	NS		
VAS – physician`s performed assessment, mean (SD)	5 (8) n = 54	3 (1) n = 12	5 (5) n = 66
P value	NS		
Morning stiffness, minutes, mean (SD)	21.9 (45.0) n = 70	11.8 (16.8) n = 19	19.7 (45.1) n = 89
P value	NS		

Table 3.2. continued

Factors	MRI+ group (n = 72)	MRI− group (n = 19)	Common group (n = 91)
Laboratory data ESR, mm/h, mean(SD)	11.8 (20.6)	5.5 (5.5)	10.5 (18.6)
P value	NS		
CRP, mg/L, mean(SD)	6.8 (28)	0.3 (0.4)	5.5 (25)
P value	0.0078		
ANA positive, n (%)	19 (26.4)	5 (26.3)	24 (27.6)
P value	NS		
RF positive, n (%)	6 (8.3)	0 (0)	6 (6.7)
P value	NS		
HLA B27 positive, n (%)	15(20.8)	3(16)	18 (19.8)
P value	NS		

* Active joint count – swollen joints not connected with bone hypertrophy or joints with restricted movement and pain with movement or palpation. The joints were considered as active when synovitis was detected by MRI or USG also in circumstances where joints were not active following the previous definition. NS - statistically non significant.

3.2.2. HLA II class alleles of risk and protection that influence the development of TMJ arthritis

HLA II class allele DRB1, DQA1, DQB1 polymorphism was analysed in MRI(+) and control group, MRI(−) and control group, as well as between MRI(+) and MRI(−) groups. The following alleles were detected more often in MRI (+) in comparison with healthy control: DRB1*07:01 (OR = 7.9, p = 0.001), DRB1*11:01 (OR = 2.14, p = 0.035), DRB1*13:01 (OR = 2.27, p = 0.022), DRB1*15:01 (OR = 2.65, p = 0.003) and DQB1*05:01 (OR = 1.87, p = 0.042) (Table 3.3.).

Table 3.3.

HLA class II alleles more common in JIA MRI (+) group in comparison with healthy control group

HLA class II alleles	MRI positive group (n = 72)		Control group (n = 100)		χ^2	p	OR	OR 95% CI	p
	Allele count (n = 144)		Allele count (n = 200)						
	Abs.	Rel.	Abs.	Rel.					
DRB1 *07:01	20	0.14	4	0.02	18.23	0.001	7.90	2.64–2.67	0.001
DRB1 *11:01	20	0.14	14	0.07	4.46	0.035	2.14	1.04–4.40	0.038
DRB1 *13:01	21	0.15	14	0.07	5.27	0.022	2.27	1.11–4.63	0.024
DRB1 *15:01	27	0.19	16	0.08	8.85	0.003	2.65	1.37–5.14	0.004
DQB1 *05:01	27	0.19	22	0.11	4.12	0.042	1.87	1.02–3.43	0.045

P < 0. 05. Abs. – absolute frequency. Rel. – relative frequency. χ^2 – chi square. OR – *odds ratio*. CI – confidence interval.

Allele DRB1*07:01, DRB1*13:01, DRB1*15:01 relate to the risk of TML arthritis development. Allele DRB1*11:01 and DQB1*05:01are found more often also in MRI negative JIA group as well as in control group, therefore are considered to be risk allele for JIA but not TML arthritis (Table 3.4.). Allele DRB1*12:01is more often found in MRI negative group in comparison with healthy controls (OR = 2.7, p = 0.029).

Table 3.4.

HLA class II allele more common in MRI negative JIA patients group in comparison with control group

HLA class II allele	MRI negative group (n = 19)		Control group (n = 100)		χ^2	p	OR	OR 95% CI	P
	Allele count (n = 38)		Allele count (n = 200)						
	Abs.	Rel.	Abs.	Rel.					
DRB1* 11:01	7	0.18	14	0.07	5.18	0.023	3.00	1.12–8.02	0.029
DRB1* 12:01	8	0.21	18	0.09	4.77	0.029	2.70	1.08–6.75	0.034
DQB1 *05:01	9	0.24	22	0.11	4.54	0.033	2.51	1.05–5.99	0.038

P < 0.05. Abs.– absolute frequency. Rel. – relative frequency. χ^2 – chi square, OR – *odds ratio*, CI – confidence interval.

Allele possibly connected with lower risk for the development of TML arthritis more common in healthy control group in comparison with JIA MRI positive group – DRB1*08:01 (OR = 0.05, p = 0.003), DRB1*16:01 (OR = 0.18, p = 0.001), DRB1*17:01 (OR = 0.23, p = 0.004) un DQB1*06:01 (OR = 0.12, p = 0.017) (Table 3.5.).

Table 3.5.

HLA class II allele less common in MRI positive group in comparison with healthy control group

HLA class II allele	MRI positive group (n = 72)		Control group (n = 100)		$\chi 2$	p	OR	OR 95% CI	P
	Allele count (n = 144)		Allele count (n = 200)						
	Abs.	Rel.	Abs.	Rel.					
DRB1* 08:01	0	0.00	12	0.06	8.95	0.003	0.05	0.01–0.89	0.041
DRB1* 16:01	4	0.03	28	0.14	12.50	0.001	0.18	0.06–0.51	0.001
DRB1* 17:01	4	0.03	22	0.11	8.10	0.004	0.23	0.08–0.69	0.009
DQB1* 06:01	1	0.01	11	0.06	5.74	0.017	0.12	0.02–0.94	0.044

$p < 0,05$. $P < 0,05$. Abs. – absolute frequency. Rel. – relative frequency. χ^2 – chi square. OR – *odds ratio*. CI – confidence interval.

Comparing MRI positive with MRI negative groups we did not find any risk allele, one allele was less common in patients with TML arthritis and probably has protective influence – DRB1*12:01 (p = 0.0001, OR = 0.14, 95% CI = 0.40–0.44).

There were two subgroups formed from the MRI positive group – the group with chronic changes TML (n = 50) and the group without such changes (n = 22). There was no risk allele found in patients with chronic changes, but we found allele DQA1*05:01 (OR = 0.42, p = 0.042) and DQB1*03:01 (OR = 0.40, p = 0.023) probably connected with lower risk for the development of bone structural damage (Table 3.6.). Allele DRB1*11:01 previously mentioned as risk allele for JIA in general in these groups possibly plays protective role towards the development of TML changes (OR = 0.38, p = 0.042). The duration of the disease was not statistically different in the groups with and without the signs of chronic arthritis- respectively 1.49 years (SD = 2.10) and 2.00 (SD = 2.49) (p = 0.159).

Table 3.6.

HLA class II allele frequency in JIA MRI positive group (n = 72) patients with chronic changes on MRI and without chronic changes

HLA class II allele	Patients with chronic changes TML (n = 50)		Patients without chronic changes TML (n = 22)		χ^2	p	OR	OR 95% CI	p
	Allele count (n = 124)		Allele count (n = 20)						
	Abs.	Rel.	Abs.	Rel.					
DRB1* 11:01	10	0.10	10	0.23	4.14	0,042	0.38	0.14–0.99	0.047
DQA1* 05:01	15	0.15	13	0.30	4.13	0,042	0.42	0.18–0.98	0.046
DQB1* 03:01	17	0.17	15	0.34	5.16	0,023	0.40	0.18–0.89	0.026

$p < 0,05$. $P < 0,05$. Abs. – absolute frequency. Rel. – relative frequency. χ^2 – chi square. OR – *odds ratio*. CI – confidence interval.

3.3. Subjective and objective clinical symptoms of TMJ arthritis and their relation to MRI findings

From 91 JIA patients subjective and/or objective symptoms connected with TML region were detected in 79 patients. There was no information about subjective complaints in one patient and no information about subjective complaints and objective examination results in one patient.

There were subjective complaints in 70 patients. Usually the patients complained of the pain during eating, singing, less common during speaking: 54 (60%) patients complained about left sided joint pain, right sided – 50 (56%) patients. Crepitation in TML region was the second most common sign: on the left side 19 (21%), on the right side – 20 (22%) patients. There were complaints about headaches in 19 (21%) patients. Limited opening of the mouth was a complaint in 7 (7%) of the patients. Other complaints were

clicking, sensation of TML limited motion, pain and noise in ears were found comparatively rare. Torticollis was diagnosed in only one patient.

There were 2 or 3 subjective symptoms diagnosed most often- respectively in 27 and 18 patients (37% and 25% of those who had subjective complaints). There were 7 and 8 symptoms detected in only one patient in both occasions.

The objective symptoms were found in 74 patients. There were no objective symptoms in 16 patients, but 11 of them had no subjective symptoms either – these patients constituted purposely selected asymptomatic group. There were no data about examination in one patient.

From the objective symptoms pain was diagnosed most often, during palpation of TML in 59 (65%) patients on the left side, in 43 (47%) patients on the right side. Comparatively less common pain during palpation was detected in jaw muscles – in 22 (24%) patients on the left side, in 14 (15%) patients on the right side; in turn the pain during palpation of temporal muscles was very uncommon – on the left side 6 (6%), on the right side in 5 (5%) patients. Deviation of mandible more than 2 mm from midline more than 2 mm to the left side was observed in 3 (3%), to the right – 5 (5%) patients. Limited opening of the mouth (< 4 cm after the age of 10 years and < 3 cm in younger than 10 years) was observed only in 17 (18%) patients. Visual asymmetry of the jaw was observed in 14 (15%) patients, but micrognathia in 4 (4%) and retrognathia in 2 (2%) patients. Crepitation during mouth opening was detected in (1%) patients, but cracking – 4 (4%) patients.

The number of subjective symptoms in the most cases did not match with the number of objective symptoms ($p = 0.001$). From the patients experiencing two symptoms, in 13 (48%) had also two objective symptoms; 7 (39%) patients with three subjective complaints were found to have two objective complaints, but 5 (18%) patients with two subjective complaints had three objective symptoms. Most patients (n=66, 74%) had up to four objective

and/or subjective findings. There was only one patient with eight subjective and eight objective findings.

There was a five-step TML screening performed in 64 (70%) out of 91 patients. The number of findings was compared with the data of those patients who did not undergo the screening. There were more clinical signs found during the screening, for example, five and eight clinical signs were found only with the help of TML screening ($p = 0.017$).

Mean number of subjective complains in MRI (+) group was 2.3 (SD = 1.9), in turn in MRI(−) group – 1.9 (SD = 1.1), $p = 0.327$. The mean number of objective signs in MRI(+) group was 2.3 (SD = 1.74), MRI(−) group – 2 (SD = 1.12), $p = 0.535$.

The correlation between MRI positive findings, demographic, clinical, and laboratory data was detected by logistic regression model where MRI finding was dependent variable, but independent changing variables were gender, age, CRP, ESR, ANA, uveitis and the number of subjective and objective symptoms. In logistic regression model the number of objective symptoms statistically significantly predicted positive MRI findings ($p = 0.017$; 95%TI 1.16–4.73). The increase of the number of the objective symptoms by 1 showed the probability of 2.3 of positive MRI findings.

There were no signs of active inflammation in 19 patients from the common patients group, but 8 did not have either subjective or objective symptoms however 11 (57%) of them had some subjective or objective symptoms.

Subjective and objective symptoms were analysed in dependence of MRI findings divided in four groups:

1) patients with the signs of active inflammation;
2) patients with the combination of chronic and active signs;
3) patients with isolated chronic signs;
4) patients without changes on MRI.

MRI findings in JIA patients group (n = 91) were as follows: 26 (29%) patients had the signs of active inflammation (including mild synovial enhancement), most of the patients – 49 (54%) had the combination of active and chronic signs, one (1%) patient had isolated signs of chronic inflammation, 14 (16%) patients had no signs of arthritis (no mild synovial enhancement either). Since there was only one patient with isolated chronic changes, data about this group are not statistically significant and were not further analysed.

Judging the number of subjective and objective symptom count in the previously mentioned groups (except isolated chronic inflammation group with just one patient in it), statistically significant differences were detected: more subjective and objective complaints were detected in the group with the combination of active and chronic changes of inflammation. The mean number of subjective complaints in the group of active inflammation was 1.38 (SD = 1.30), in the group with combination of active and chronic inflammation it was 2.65 (SD = 1.90), but in the group without changes on MRI – 1.77 (SD = 1.24), p = 0.020. Objective complaints in the group with signs of active inflammation was 1.46 (SD = 1.36), in the group with the combination of active and chronic signs of inflammation – 2.63 (SD = 1.69), in the group without changes on MRI – 1.85 (SD = 1.34), p = 0.012.

There were statistically significant differences in “sticking” of the jaw sensation in TML (p = 0.038) – patients with active and chronic inflammation signs on MRI (Figure 3.1.).

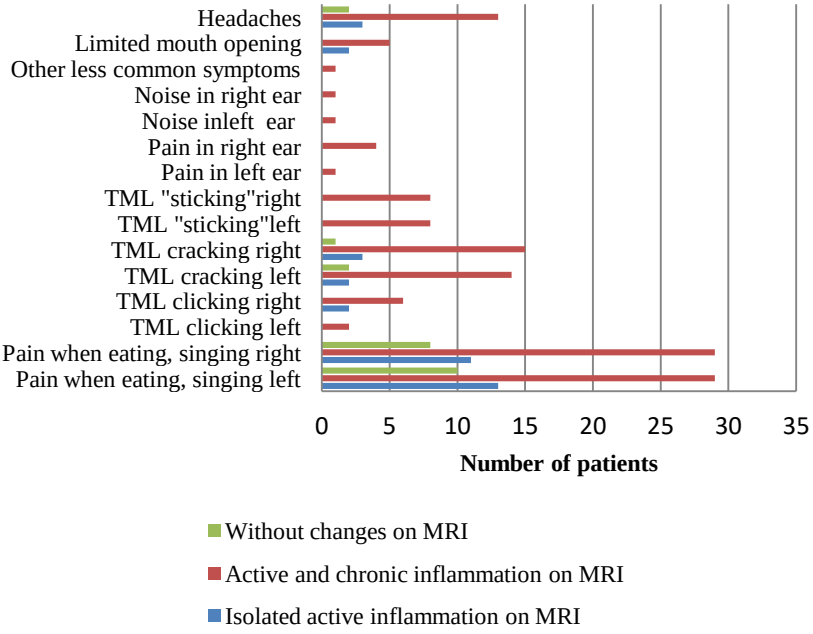

Figure 3.1. **Subjective symptoms in TML patient groups with signs of active inflammation on MRI, active and chronic inflammation and without changes on MRI**

The pain during palpation of TML was the most common objective symptom: in patient group with active and chronic inflammation – 35 (75%) on the left side and 24 (49%) on the right side, in the group of isolated active inflammation – 12 (46%)patients on the left side and 10 (38%) patients on the right side, however in the group without the signs of inflammation – 10 (77%) on the left side and 8 (61%) on the right side. The second most common objective finding was pain during palpation *musculus masseter* region: in the group of active and chronic inflammation – 14 (29%) on the left and 10 (20%) on the right side; in the group of active inflammation – 5 (19%) on the left and 3 (11%) on the right side; in the group without the signs of inflammation –

1 patient (8%) on both TML sides. The other symptoms were comparatively less common, some of them only in both groups with pathological changes on MRI: limited opening of the mouth in 13 (27%) patients in combined inflammation group and 4 (15%) patients in active inflammation group; deviation of mandible from midline > 2 mm on the left side was observed in 2% patients in both groups, on the right side – in 5 (10%) of the patients in combined inflammation group. Micrognathia was detected only in combined inflammation group – in 4 (8%) patients, retrognathia – in 2 (4%) patients, and only one patient had crepitation when opening the mouth. There were no statistically significant differences in groups connected with objective symptoms in correlation with MRI findings (Figure 3.2.).

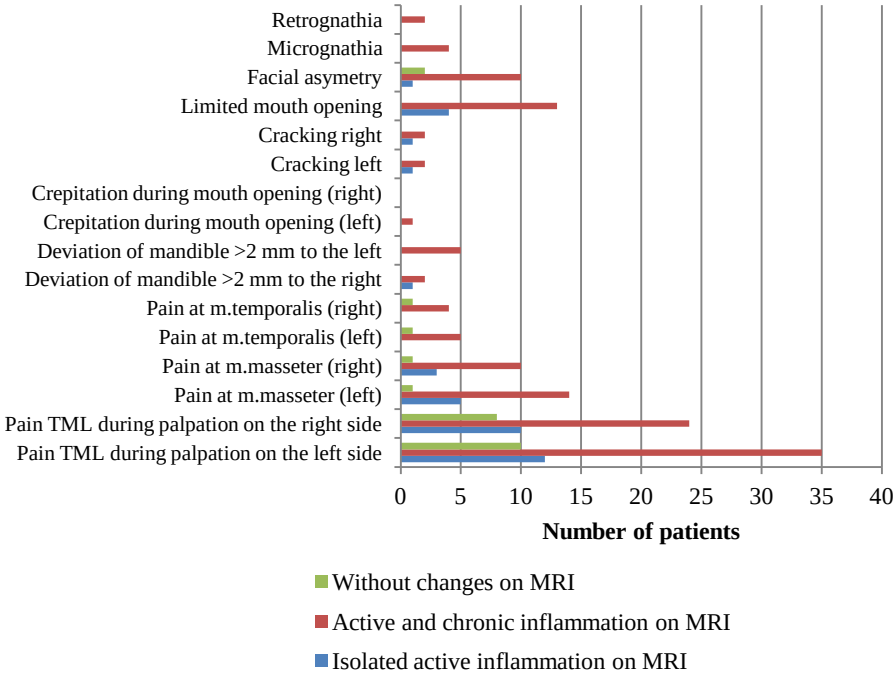

Figure 3.2. **Objective symptoms in TML patient`s group with active signs of inflammation on MRI, with active and chronic signs of inflammation and without inflammation on MRI.**

3.4. MRI findings of TMJ, differences in symptomatic and asymptomatic patients

The results of MRI were reviewed by two radiologists; the coefficient Kappa was calculated to evaluate the agreement of opinions. Mostly the agreement of opinions was strong with Kappa coefficient 0.60–0.80. In some situations the agreement of opinions was moderate for example in evaluation of the activity of synovitis in scale from 0 to 3 (Kappa = 0.33), that did not influence the division of the patients into groups. Moderate agreement was observed in cases of less common signs, for example, pannus was found in only 5 patients (Kappa = 0.32). Strong agreement was observed in evaluation of mandibular condylar heads but moderate in evaluation of other chronic findings (Kappa 0.40–0.60).

As mentioned before, from 91 JIA patient group 26 patients had signs of active inflammation, but in 14 patients no changes were found on MRI. Taking into account the data from literature about possible normal variations, the patients with mild synovial enhancement and symmetrical flattening of condyle heads were included in MRI negative group. As the result there were 72 patients in MRI positive group, but 19 in MRI negative group. There were mainly four signs described on MRI in 21 patients (23%), 15 (17%) children had no changes, 11 children had two and 11 children – six signs (12%). Only three JIA patients were found to have 10 or more radiologic signs of arthritis.

Analysing in details the signs of active inflammation on the right and left TML sides, oedema of condyle heads was found in 25 (27%) patients on the left side, 17 (18%) – on the right side; intraarticular fluid collection was observed in 41 (45%) patients on the left side, 30 (32%) – on the right side. Synovial enhancement in the left joint was found in 68 (73%) patients, but on the right side – 61 (66%), however moderate or severe synovial enhancement

on the left side was observed in 36 (38%) patients, but on the right side – in 25 (27%). Pannus on the left side was detected in 5 (5%), but on the right side in 1(1%) patient.

The signs of chronic inflammation were as follows: deformation of condyle head on the left side in 42 (46%), on the right side in 30 (33%) patients; mandibular fossa flattening on the left side – in 9 (10%), on the right side in 10(11%) patients. Osteophytes in the left joint were found in 5(5%), in the right joint – 7 (7%) patients; erosions on the left side in 21 (23%), on the right side – 9 (10%) patients.

There were 11 patients without subjective and objective symptoms of TML arthritis (asymptomatic patients) included in JIA patients group. Definitive signs of arthritis were found only in 3 (27%) asymptomatic patients.

From 80 symptomatic JIA patients there was combination of active and chronic inflammation signs found in 48 (60%), 20 (25%) had isolated signs of active inflammation, 1 (1%) isolated signs of chronic inflammation, but 11 (14%) patients had no pathological changes on MRI despite having subjective or objective complaints.

There were statistically significant differences ($p=0.003$) in MRI findings of asymptomatic and symptomatic patients, dividing into groups dependent on the signs of active, chronic inflammation or its combination. In general, there were more patients with the signs of active or combined inflammation in symptomatic patient`s group on MRI – 48 (61%), versus asymptomatic patients – 1 (9%). There were comparatively more patients with active inflammation on MRI – respectively 30 (24%) from symptomatic patients, but 2 (18%) in asymptomatic patients.

4. DISCUSSION

The study group consisted of 91 JIA patients in whom MRI of TMJ with contrast enhancement was carried out in the period from 2010–2015. We did not consider patient's age, duration of the disease and JIA type. Most of the foreign studies were done, including JIA patients with different types and duration of the disease (Müller et al., 2009; Weiss et al., 2008), however there is at least one study where patients are evaluated with MRI for TMJ arthritis right after the diagnosis of JIA despite subjective complaints or objective findings (Cannizaro et al., 2011). Most of our patients – 98%, where with polyarticular diseases course, mostly with seronegative polyarthritis. Our patient`s group reflects results of other studies where more risk for TMJ arthritis is found in patients with polyarticular disease (including oligoarthritis extended type) (Cannizzaro et al., 2011; Arvidsson et al., 2010).

From demographic data we had two times more girls than boys what is consistent with epidemiology of JIA in the literature. Mean age was 13.6 that also reflects our patient`s group with mostly seronegative polyarthritis. (Cassidy et al., 2011). Regarding that mean active joint count was 7.4, physician`s VAS 5 and patients VAS 4.4, and inflammatory markers were mostly within the normal range, we can conclude that the disease activity was moderate (JIA clinical guidelines. *Latvijas Pediatru reimatologu asociācija, 2016)*. Mean time from the diagnosis was 1.8 years what means that most of the patients already were treated with methotrexate, part of them with biologic medications.

We analysed TMJ arthritis influencing factors considering MRI with contrast enhancement as the gold standard for this diagnose. According to MRI findings 91 patients' group was divided in two main groups – MRI positive (n = 72) and MRI negative (n =19). From all the disease-characteristic clinical and laboratory factors CRP was statistically significantly higher in

MRI positive group that means there was more active disease in patients with TMJ arthritis. We noticed the tendency that in MRI positive group there were higher CHAQ values, VAS results, longer morning stiffness, higher ESR and all RF positive patients were in this group, but it was not proven with statistical methods. Anyway, we can presume that overall disease activity is higher in patients with TMJ arthritis what is consistent with literature (Argyropoulou et al., 2009; Cannizaro et al., 2011; Steenks et al., 2015). Stoll and colleagues in 2012 published the study with a rather big patients' cohort – 187 JIA patients with TMJ arthritis in 43% of them. They concluded that TMJ arthritis development does not depend on active joint count and inflammatory markers (Stoll et al., 2012). In some studies HLA B27 antigen is connected with lower risk for TMJ arthritis, but in our patients there is no difference in both groups (Pedersen et al., 2001; Cannizzaro et al., 2011). In one study positive ANA was mentioned as a risk factor but our study does not confirm it (Argyropoulou et al., 2009). Cannizaro and colleagues from 2005 to 2006 evaluated all patients with newly diagnosed JIA not regarding complaints or objective findings consistent with TMJ arthritis (Cannizzaro et al., 2011). Out of 223 children MRI was done in 102 and as a risk factors oligoarthritis extended, seronegative polyarthritis, younger age of disease onset, arthritis in upper extremities, higher active joint count and higher ESR at the beginning of the disease were mentioned. In our study we can only see some tendency for higher disease activity, but as mentioned previously, these results were statistically insignificant.

The study confirmed the hypothesis that TMJ arthritis development is influenced by genetic factors, in our case HLA class II alleles. HLA class II alleles were compared in MRI positive group with control group, MRI negative group with control group and MRI positive with negative groups. DRB1*07:01, DRB1*13:01 and DRB1*15:01 turned out to be the risk alleles for TMJ arthritis because were detected as risk alleles in MRI positive

group versus controls but not in MRI negative versus control group. In turn alleles DRB1*11:01 and DQB1*05:01 were detected as risk alleles in both groups and we can presume that they are overall risk alleles for JIA. These alleles were detected also in a large study about JIA and HLA II class alleles associations with 802 patients in such risk haplotype: DRB1*11:01/04:01-DQA1*05:01-DQB1*03:01 with no association with disease subtype or age of onset (Hollenbach et al., 2010). DRB1*11:01 (in our study overall JIA risk allele) and DRB1*13:01 (in our study risk allele for TMJ arthritis) have been associated with higher risk for uveitis what in our study was detected only in 4 patients (Angeles-Han et al., 2015). From our 4 patients with uveitis 2 were positive for DRB1*13:01 allele. Hink analysed very large cohort – 5043 JIA patients and compared them with 14 390 healthy individuals (Hinks et al., 2017). In this study most often DRB1*13:01 allele (in our study risk allele for TMJ arthritis) was detected in patients, in turn DRB1*11:01 was more associated with systemic JIA (in our study only 2 patients with systemic JIA). DRB1*13:01 has been associated also with chronic arthritis in adult age – seronegative polyarthritis and seropositive polyarthritis (Helm-van Mil et al., 2005). DRB1*07:01 (our risk allele for TMJ arthritis) in the study done in United Kingdom was associated with lower risk for persistent oligoarthritis.
We had no patients with this type of JIA that can explain our results (Thomson et al., 2002). In Mexican study this allele was less often in seropositive patients (only 7 in our study) (Silva-Ramirez et al., 2010). Allele DRB1*15:01 until now is described as protective in JIA (Hersh, Prahalad 2015).

DRB1*12:01 allele was more often detected in MRI negative group, but not in MRI positive group versus controls – probably it is a risk allele for JIA but with some protective role for TMJ arthritis development.

With probably protective role for TMJ arthritis in our study were alleles DRB1*08:01; DRB*16:01; DRB*17:01 and DQB1*06:01. Murrey and colleagues have mentioned DRB1*08:01 as risk allele for early disease onset

(Murrey et al., 1999). Because our patients mean age was 13 years, we cannot compare this result with ours. About other probably protective alleles there are no significant results in previous HLA and JIA association studies. We can only guess that these alleles probably protect patients not only from TMJ arthritis but also from more active disease course.

We detected no risk alleles in patients with chronic inflammation signs in MRI. DQA1*05:01 and DQB1*03:01 were probably protective for structural bone damage in TMJ. DRB1*11:01 what was also as overall risk allele for JIA turned out to be with protective role in this case. DQA1*05:01 and DQB1*03:01 in Greek study were more associated with oligoarticular disease and uveitis risk – probably these patients have less risk for TMJ structural damage (Pratsidou-Gertsi et al., 1999). There are alleles detected in adult patients' population – DRB1*01:03, *04:02, *11:02, *11:03, *13:01, *13:02 and *13:04 associated with lower disease activity and slower radiological progression. Allele DRB1*13:01 in our study was detected as risk allele for TMJ arthritis but we must take into account that there are different genetic backgrounds in JIA and chronic arthritis in adulthood (Helm-van Mil et al., 2005).

To understand which patients need evaluation with MRI in parallel to TMJ arthritis influencing factors we analysed in detail patients subjective complaints, objective findings and their correlation with two main MRI groups – positive and negative and also in more concrete MRI groups depending on active and/or chronic inflammation signs. Pain in TMJ when eating, singing or speaking was the most common subjective complaint. Cracking of TMJ was the second by frequency, 21% of the patients complained about headaches and only 7% about limited mouth opening. In many studies where objective findings of JIA patients for diagnostics of TMJ arthritis are analysed, there is little or no information about subjective complains (Cannizzaro et al., 2011; Koos et al., 2015; Argyropoulou et al.; 2008; Keller et al., 2015). Keller and

colleagues mentioned that orthodontist was asking about patients' subjective complaints. Steenks in 2015 recommended clinical screening for TMJ arthritis and included specific questions about subjective complaints what should be asked to every JIA patient (Steenks et al., 2015). Steenks study is one of the few studies where information about subjective complaints is included of which problems with chewing noted in 10% of the patients, 14% said that they are eating more slowly, 14% mentioned problems with eating hard food and similar to our study only 11% complained about limited mouth opening.

Analysing objective findings the most common symptom was pain in TMJ localisation, the second in frequency was pain in the region of *m.masseter*, other objective findings were much less often. Limited mouth opening was observed in 18% of our patients and this symptom correlates with MRI findings in different studies. Abramowitz and colleagues concluded that limited mouth opening 6.7 times increases the risk for synovitis in MRI (Abramowitz et al., 2013). Keller`s researchers group concluded that limited mouth opening reflects already deformed mandibular condyles – so this symptom is not usable in early diagnostics of TMJ arthritis (Keller et al., 2015). Mandibular deviation more than 2 cm from midline was observed in 8 of our patients. Stoll concluded that from clinical symptoms correlation of deviation and TMJ arthritis is the strongest (Stoll et al., 2012).

70% of our patients were screened for TMJ arthritis with five step screening, and it increased the possibility to find more symptoms (Koos et al., 2014). It is important because previous studies show that more objective findings give more sensitivity to clinical evaluation – combination of 5 symptoms has sensitivity 0.85 and specificity 0.54 (Twilt et al., 2004; Koos et al., 2014).

The number of subjective and objective findings in our patients was statistically significantly higher in patients with active and chronic inflammatory signs combination in MRI that confirms the results of other

studies that structural changes manifest with symptoms more often than isolated active inflammation (Keller et al., 2015).

Different demographic, clinical, laboratory data were analysed with logistic regression in the two main groups – MRI positive and negative. It was found that objective symptoms count statistically reliably predicted positive MRI findings. Also, other researchers have mentioned that clinical evaluation is very important only it must be structured and unified (Kristensen et al., 2016, Steenks et al., 2015).

During the study time from 2010 to 2015 comprehension about how to interpret MRI results have changed. These problems arise because radiologist has to asses growing joints and there can be some signs that are normal for certain age groups. For example, symmetrical flattening of condyle heads can be normal and also light synovial contrast enhancement (Kalle et al., 2013; Moe et al., 2016; Arvidsson et al., 2009).

We determined the coincidence of opinions of the radiologists with kappa coefficient. In most cases it was 0.6 – 0.8 what means that it is strong. Our radiologist`s opinions were different mostly when evaluating chronic inflammatory signs. Vaid and colleagues have developed scale to systematize TMJ MRI descriptions and conclusions. Two radiologists analysed MRI in this study and opposite to our study kappa coefficient was lower when evaluating active inflammatory signs – 0.51. Mostly disagreement was about intraarticular fluid - opinions coincided only in 38% of cases (Vaid et al., 2014).

We detected TMJ arthritis in 79% of our patients but we must take into account that most of our patients (88%) had symptoms. In a little bit more than a half of patients combination of active and chronic inflammatory signs in MRI were detected. From active inflammatory signs the most frequent radiologic symptom was fluid in the joint space, second in frequency was contrast enhancement. Deformation of condyles was the most frequently detected chronic sign, the second was erosions. Mussler and colleagues in

2010 evaluating 34 JIA patients detected contrast enhancement most often – in 76% of the patients, only it was not clarified whether it was light, medium or severe. Keller`s group evaluated 76 consecutive JIA patients with MRI that was compared to rheumatologic and orthodontic TMJ assessment. TMJ arthritis signs with MRI were detected in 71%, 68% had active inflammatory signs. Synovial contrast enhancement was light in 67 joints, but only in 18 joints it was severe. 33% of the patients had condyle head deformation (Keller et al., 2015). Argiropaulu and colleagues in 2009 published study about 46 JIA patients aged 2–36 years and 32% of the patients had condyle head deformations, 10% intraarticular fluid, 45% had pannus. It is difficult to compare these results with ours because of the wide age group (Argyropoulou et al., 2009).

Our study confirms the other studies that TMJ arthritis can be detected in asymptomatic JIA patients, but also shows that MRI findings in asymptomatic patients are not so severe. Only 3 of our 11 asymptomatic patients had signs of TMJ arthritis in MRI (Argyropoulou et al., 2009; Pedersen et al., 2008; Weiss et al., 2008).

Regarding literature review data and results of our study we can conclude that TMJ arthritis risk has to be evaluated in every JIA patient in every visit. Rheumatologists should evaluate very carefully patients with high inflammatory markers, especially with elevated CRP. Rheumatologist's evaluation for TMJ arthritis should include concrete questions about possible TMJ arthritis subjective complaints as well as systematized objective assessment – it could be five step screening what can be easily integrated into rheumatologic joint assessment (Koos et al., 2011). To get more detailed information about possible TMJ, face and jaw as well as dental problems, all JIA patients should be regularly assessed by orthodontist (Keller et al., 2015; Müller et al., 2009).

HLA class II risk alleles could be included in diagnostics in future but till then we should explore what else besides TMJ arthritis is characteristic in patients with these alleles.

Our study confirms the hypothesis that there are factors that influence development of TMJ arthritis – elevated CRP, concrete HLA II class alleles. It is possible to predict MRI findings after assessing patients very carefully with systematic questions for subjective complaints and using screening for objective symptoms – our study confirms the hypothesis that clinical and radiological symptoms are connected.

CONCLUSIONS

1. There are twice as more girls than boys in common patients group. The mean age is consistent with teenage paediatric population. Most patients have polyarticular course of the disease mainly seronegative polyarthritis. In general, the disease-characteristic clinical variables (active joint count, CHAQ, VAS assessed by patient and doctor, morning joint stiffness) and laboratory data (ESR, CRP) show that patients' group meets moderate activity of the disease.

2. From the factors influencing the development of TML arthritis as demographic, the disease characterizing clinical and laboratory data, elevated CRP was reliably connected with the risk of the development of TML arthritis. The other demographic factors (gender, age), clinical data(duration of the disease, the time from diagnosis, active joint count, CHAQ, VAS assessed by patient and doctor, morning joint stiffness) and laboratory data (ESR, ANA, HLA B27 antigen) in the patient groups with TML arthritis characteristic MRI findings and without the signs of arthritis do not differ statistically.

The development of TML arthritis in patients with JIA is influenced by genetic factors. HLA class II alleles – DRB1*07:01, DRB1*13:01, DRB1*15:01 relate to the risk for the development of TML arthritis. The patients with allele DRB1*08:01, DRB1*16:01, DRB*17:01 and DQB1*06:01 have low risk for the development of TML arthritis. Alleles DRB1*11:01, DQA1*05:01 and DQB1*03:01 are connected with low risk for the structural bone damage in TML.

3. The number of subjective and objective complaints in the common MRI positive and MRI negative groups does not differ statistically; bet there are statistically significant differences in the patient groups dependent on more detailed division of MRI findings (patients with isolated active inflammation, the signs of active and chronic inflammation, the signs of isolated chronic inflammation and without changes). Both numbers of subjective and objective

symptoms are higher in the group with the combination of active and chronic inflammation. The analysis of logical regression shows that the increase in the number of objective symptoms by 1 increases the probability for positive MRI findings 2.3 times. From separate subjective symptoms statistically significant differences are found in sensation of TML joint limited motion which is characteristic for patients with the signs of active and chronic inflammation on MRI. There are no statistically significant differences in objective symptoms in these groups.

4. There was a combination of active and chronic inflammation found statistically more often on MRI in JIA patients with subjective and objective symptoms of TML. However, in JIA patients without subjective and/or objective TML arthritis symptoms MRI is most often without pathological changes or mild synovial enhancement is recognised considered as normal finding.

PRACTICAL RECOMENDATIONS

All JIA patients should undergo a targeted questionnaire to rule out subjective TML arthritis symptoms and the five-step screening for objective symptoms of TML arthritis (section “Methods”).

JIA patients in whom 2 subjective and/or objective symptoms are found should undergo TML MRI with contrast enhancement.

If the patient with JIA and at least 1 subjective and/or objective symptoms has elevated CRP, it is recommended to perform TML MRI with contrast enhancement.

PERSPECTIVE FOR FURTHER INVESTIGATIONS

JIA patients must undergo detection of HLA class II risk allele detected in the study DRB1*07:01, DRB1*13:01, DRB1*15:01, to explore detailed profile of these patients about the course of the disease, clinical and laboratory activity, the involvement of TML and other joints. One can predict the course of the disease and the involvement of TML and other joints and to choose appropriate medication treatment.

REFFERENCES

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