Immuno-biological Assessments of Temporomandibular Joint Disease in Patients with Immune-mediated Rheumatic Conditions

A cross sectional study of 273 cases

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Temporomandibular joint (TMJ) is commonly involved in various immune-mediated rheumatic disorders accounting for significant disability and impaired quality of life. The aim of our study was to assess inflammatory and immune parameters in patients with TMJ arthritis related to rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) and to identify potential relation with severity and dysfunction of TMJ pathology. We performed a cross-sectional study in a cohort of 433 consecutive RA, 32 JIA, 258 AS, and 103 PsA. Only patients presenting with clinically significant TMJ involvement (273) related to their rheumatic condition were included in the final analysis. TMJ involvement is traditionally described in chronic inflammatory rheumatic disorders, particularly in patients with higher levels of inflammation as detected in rheumatoid arthritis and psoriatic arthritis. Disease activity and severity, as well as biological and positive serological assessments (rheumatoid factor, anti-cyclic citrullinated peptide, IL-1) remain significant determinants of the severity of TMJ arthritis.

Keywords: *temporomandibular joint (TMJ), acute phase reactants, immune-mediated rheumatic diseases*

Temporomandibular joint (TMJ) is commonly involved in various immune-mediated rheumatic disorders including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA) and spondyloarthropathies such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA), leading to significant disability as well as impaired quality of life [1-16].

Up 98% of patients with RA (Franks, 1969; Syrjanen, 1985; Uotila, 1964; o'Connor 2017), 63% of PsA patients (Kononen, 1987; Lundberg and Ericson, 1967; Rasmussen and Bakke, 1982; o'Connor 2017), about 32% of those diagnosed with AS (Maes and Dihlmann, 1968; Resnick, 1974; Wenneberg, Hollender, and Kopp, 1983; o'Connor 2017), and up to 72% JIA (Niibo, 2016) will develop TMJ arthritis during the course of their disease, presenting with a variable clinical spectrum that range from asymptomatic to clinically significant arthritis characterized by severe pain, articular noises, mandibular deviation during maximum extrusion, joint stiffness, difficulties in opening the mouth [1-14].

The magnitude of TMJ involvement depends on the type of rheumatic pathology and seems to be related to disease activity and severity status [1-16]. Therefore, it is clearly that inflammatory parameters such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as immune abnormalities including the level of rheumatoid factor (RF) and plasma tumour necrosis factor-α (TNF-α) are related to the severity of TMJ disease, particularly in RA patients [1-14].

Both RA and spondyloarthropathies are characterized by complex pathobiology meaning cytokine imbalances with the preponderance of systemic as well as articular inflammatory mediators (TNF-α, IL-6, IL-1, prostaglandins), subsequent inflammation, immune (T and B cells, macrophages) and non-immune (osteoclast, synoviocytes, chondrocytes) cell activation, (neo)angiogenesis and, as a final step, structural damage (erosive lesions in RA, as well as destructive and proliferative lesions in spondyloarthropathies) [1-16].

It is currently accepted that TNF-α is associated not only with severe active and advanced joint damage, but also with TMJ inflammation and pain. Furthermore, TNF-α is able to endorse the release and activation of destructive mediators including matrix enzymes [6-8,11-13].

IL-1α and IL-1β are widely recognized as potent pro-inflammatory and destructive cytokines, promoting a broad spectrum of local as well as systemic events e.g. vasodilatation, cellular trafficking, induction of matrix-metalloproteinases. Moreover, high serum concentrations of IL-1β are typically related to both inflammation and damage in RA with TMJ arthritis [6-8,11-13].

Finally, another interleukin (IL-6) seems also to be important for TMJ pathology as certain authors reported correlation between IL-6 levels, the degree of acute synovitis and acute perforation of the TMJ joint disc as supported by arthroscopic assessment [6]. However, no relation was demonstrated between pain, joint dysfunction and the total protein concentration in synovial fluid [5].

Interestingly, IL-1β, IL-6, IL-8 and TNF-α concentrations are significantly increased in patients with TMJ involvement

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than in healthy controls, without any correlation with signs and symptoms as reported by other [6-8,11-13].

Finally, higher synovial fluid concentrations for IgA, IgG and β-glucuronidase were described in patients with clinically important TMJ disease (severe pain, mandibular stiffness) as compared to healthy individuals [4].

Despite consistent evidence of TMJ involvement in chronic inflammatory rheumatic conditions, signs and symptoms of TMJ pathology are typically underestimated by rheumatologists and even by patients, especially when treatment is focused on other peripheral joints [1-14].

The aim of our study was to assess inflammatory and immune background in patients with TMJ arthritis related to different immune-mediated rheumatic disorders (rheumatoid arthritis, juvenile idiopathic arthritis, spondylartropathies) and to identify potential relation with severity and dysfunction of TMJ pathology.

Experimental part

Material and method

We performed a cross-sectional observational study in a cohort of consecutive patients diagnosed with RA (433 cases, fulfilling the 1987 ACR diagnostic criteria), JIA (32 cases, ILAR classification), AS (258 cases, 1984 modified New York diagnostic criteria) and PsA (103 cases, 2006 CASPAR classification criteria), attending at least once the rheumatology department from January 2005 to July 2007.

Only patients presenting with clinically significant TMJ involvement related to their rheumatic condition were included in the final analysis. TMJ disorder was identified irrespective of the rheumatic disease by the means of a specific questionnaire enquiring about patients' main complaints about pain and stiffness in the TMJ, articular sounds, bruxism, mouth opening derangements as well as restricted movements.

We systematically evaluated *inflammatory parameters* (ESR and CRP), irrespective of the background disease, while several *immune parameters* were tested according to the disease specificity.

We focused on the assessment of *rheumatoid factor* (latex and Waaler Rose precipitation reactions; normal range between 8 and 512 UI/mL) and *anti-cyclic citrullinated peptide antibodies (ACPA)* (ELISA; normal < 4.5 U/mL) in patients with RA, whereas *anti-nuclear antibodies* (ELISA, cut off value 1/80) for both RA and JIA.

Interleukin-1, a cytokine with pro-inflammatory and destructive properties, was evaluated only in RA patients by ELISA, with a normal range <10U/mL.

Since AS and PsA are not characterized by any specific antibody, such patients were tested only for the presence of the *histocompatibility antigen HLA B27.*

Disease activity and disability scores were calculated using validated indexes, comprising disease activity scores on 28 joints for RA (DAS28-ESR and DAS28-CRP), disease activity in psoriatic arthritis (DAPSA), disease activity index for ankylosing spondylitis (BASDAI) and ankylosing spondylitis disease activity score (ASDAS-CRP for AS).

Data were compared with biological assessments registered in healthy controls.

All patients have signed a written informed consent before their enrolment and the project received the Ethical Committee approval.

Statistical analysis was done in SAS 4.3 program (descriptive and analytical statistics including chi-squared, Pearson's correlation, Breakdown one way ANOVA in all the groups described above).

Results and discussions

As previously mentioned only patients with clinically significant TMJ involvement were analysed; thus, TMJ disorder was detected in 152 RA (35.10% of all RA), 55 AS (21.70% of all AS), 44 PsA (42.71% of all PsA), and 22 JIA (68.75% of all evaluated JIA).

Inflammatory and serologic abnormalities in RA

Acute-phase reactants were positive in more than half of RA patients developing TMJ involvement, with the increase in both ESR (54. 61%) and CRP (56.58%) levels as shown in table 1.

Serology for RF and ACPA classified as negative (for both types of antibodies), low positive (RF or ACPA), and high positive (RF or ACPA) was also determined, highlighting the severity of aberrant immune response in our RA patients. Classically, RF (an unspecific antibody for RA) and ACPA (RA biomarker antibodies) feature the same trend, defining seropositive disease subtype in about 80% of cases. Indeed, the majority of our patients (72.37%) were seropositive for RF, with high titres in more than half (63.16%); however, ACPA positivity was reported in only 40% of RA cases (table 1).

Serum IL-1 concentrations

Serum IL-1 was randomly checked in 33 of the RA enrolled in the study. In 55% of cases we demonstrated very high levels of serum IL-1, particularly in severe active disease with secondary TMJ involvement (table 1).

We reported a statistically significant relation between the duration and severity of TMJ arthritis and increased ESR ($r=0.278$, $p=0.001$), high RF levels ($r=0.274$, $p=0.001$) and increased serum IL-1 concentrations ($r=0.264$, $p=0.001$).

Although the relation between the activity and severity of synovitis and CRP level is generally recognized in RA,

ESR (mm/h)	Normal ESR		Moderate increased ESR		High ESR	
	N	%	N	%	N	%
	8	5.26	61	40.13	83	54.61
CRP (mg/dl)	**Normal CRP**			**High CRP**		
	N	%		N	%	
	66	43.42		86	56.58	
RF (UI/mL)	**Absent**		**Positive**		**Important positive**	
	N	%	N	%	N	%
	42	27.63	14	9.21	96	63.16
ACPA (UI/mL)	**Absent**			**Present**		
	92	60.53		60	39.47	
IL-1 (UI/mL)				33	100%	

Table 1
IMMUNO-BIOLOGICAL ASSESMENTS IN RA PATIENTS

ESR (mm/h)	Normal ESR		Moderate increased ESR		High ESR	
	N	%	N	%	N	%
	7	12.73	38	69.09	10	18.18
CRP (mg/dl)	Normal CRP			High CRP		
	N	%		N	%	
	38	69.09		17	30.91	

Table 2
ACUTE-PHASE REACTANTS IN AS PATIENTS

ESR (mm/h)	Normal ESR		Moderate increased ESR		High ESR	
	N	%	N	%	n	%
	0	0	9	20.45	35	79.55
CRP (mg/dl)	Normal CRP			High CRP		
	n	%		n	%	
	18	32.73		26	67.27	

Table 3
ACUTE-PHASE REACTANTS IN PsA PATIENTS

ESR (mm/h)	Normal ESR		Moderate increased ESR		High ESR	
	0	0	18	81.82	4	18.18
	0	0	18	81.82	4	18.18
CRP (mg/dl)	Normal CRP			High CRP		
	n	%		n	%	
	18	81.82		4	18.18	
ANA (UI/mL)	Normal CRP			High CRP		
	n	%		n	%	
	14	63.64		8	36.36	

Table 4
IMMUNO-BIOLOGICAL ASSESSMENTS IN PATIENTS WITH JIA

the link with the severity of TMJ involvement was reported only in several papers [7,10]. Remarkably, in our patients we found the same positive correlation between TMJ pain and dysfunction and CRP levels

Inflammatory abnormalities in AS

AS is classically characterized by low to moderate systemic inflammation; therefore, AS patients present with modestly increased ERS and CRP serum concentrations.

Up to 70% of our cases had moderate to high ESR and about one third (30.90%) of them abnormal CRP levels (table 2). In addition, patients with clinically symptomatic TMJ arthritis featured higher ESR as compared to those without TMJ pain (89.50% vs. 66.67%; $\chi^2 = 4.49$, p=0.03).

Inflammatory and serologic abnormalities in PsA

Increased acute-phase reactants always reflect the inflammatory process in PsA.

When performing the same biological assessments in our PsA patients, we reported abnormal ESR in all subjects included in the study: the majority (80%) presented high ESR and one out of five patients had moderately increased ESR. However, only 67.27% reported increased CRP concentrations, one third of PsA featuring serum CRP in the normal range (table 3).

Although the cellular immune response in PsA is largely impaired, specific antibodies are not described for such patients; eventually, RF positivity may be reported during the polyarticular course of PsA.

Inflammatory and serologic abnormalities in JIA

Abnormal inflammatory parameters are commonly described in JIA, particularly talking about ESR. Although the immune response is aberrant, no significant changes in humoral immunity are known; only ANA positivity was reported in about 30% of cases with polyarticular involvement.

All the evaluated JIA had raised ESR levels, the majority displaying moderate increased ESR (81.82%). Conversely, only 18.18% (4 patients) had high CRP concentrations (table 4).

Evidence of positive ANA was detected in more than half of JIA (63.64%) (table 4).

Biological assessments in controls

Healthy controls without any diagnosis of inflammatory rheumatic pathologies were widely (up to 90%) characterized by normal ESR and CRP levels; however 9% had moderate increased ERS.0

Comparative ESR analysis

Data revealed higher ERS levels in patients with TMJ arthritis related to PsA and RA as compared to those with AS and JIA (table 5), with the highest ESR in PsA patients (60.98%) (fig. 1).

Detailed ESR analysis according to normal, moderate and high level categories was further proposed (table 6, fig. 2).

Groups / cases	Mean values	Σ	Min	Max	ESM	-95%	+950%	p
RA (152)	46.54	19.82	12.0	105.0	43.36	49.72	1.61	.0001
AS (55)	33.75	14.69	13.0	105.0	29.77	37.72	1.98	.0000
PsA (44)	60.98	24.78	28.0	127.0	53.44	68.51	3.74	
JIA(22)	36.73	8.66	28.0	67.0	32.89	40.57	1.85	.0000
Controls (33)	14.27	4.11	6.00	23.00	12.82	15.73	.72	.0000

Table 5
ESR IN STUDY GROUPS

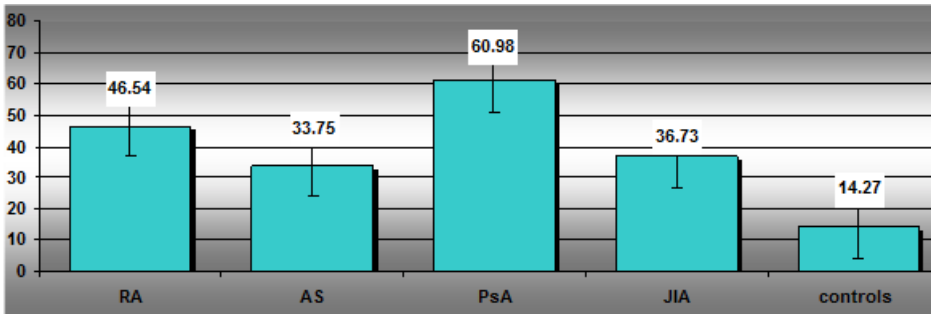

Fig. 1. ESR in study groups and healthy controls

	Normal ESR		Moderate high ESR		High ESR	
	n	%	n	%	N	%
RA	8	*5.26	61	**40.13	83	*54.61
AS	7	*12.73	38	**69.09**	10	*18.18
PsA	0	*0	9	**20.45	**35**	**79.55**
JIA	0	*0	18	**81.82**	4	*18.18
Controls	30	**90.91**	3	**9.09	0	*0
p		**.0000**		**.0003 .0000**		**.003 .0000.**

Table 6
DETAILED ESR ANALYSIS IN DIFFERENT RHEUMATIC DISORDERS

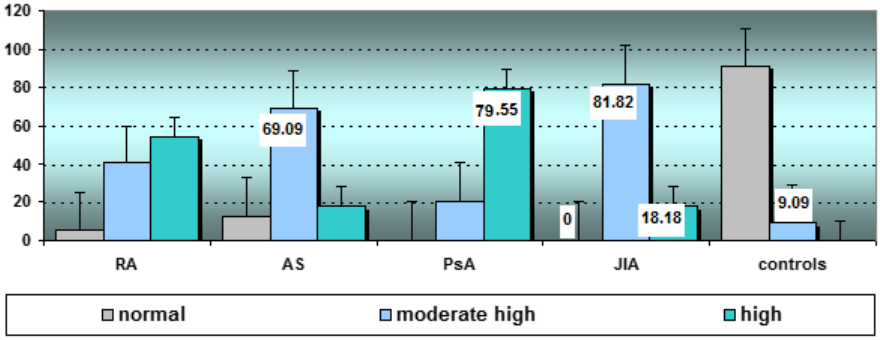

Fig. 2. ESR in patients with TMJ involvement related to rheumatic disorders

Comparative CRP analysis

Finally, comparative data regarding the CPR concentrations in different rheumatic disorders with TMJ arthritis are summarized in table 7. Significantly higher concentrations are reported in both RA and PsA, conditions characterized by severe arthritis, including TMJ damage ($p<0.05$).

Several studies have reported increased prevalence of TMJ involvement in RA, AS, PsA as well as JIA patients [4,5,9,11-13], but data about comparative immuno-biological assessments in a Romanian patient population are lacking.

We have systematically evaluated acute phase reactants in a consistent cohort of patients with chronic inflammatory rheumatic diseases (826 patients), and immunological tests according to the diagnosis (RF and ACPA in all RA, while IL-1 levels in a subgroup of RA, ANA for JIA).

The results of the present study showed that inflammatory rheumatic disorders with TMJ arthritis were more frequently characterized by higher inflammatory parameters as compared with healthy controls.

Although RA patients tend to have more frequent and severe symptoms, signs, and radiographic changes when compared with PsA and AS [o connor], in our study ESR was remarkably elevated among patients diagnosed with either PsA or RA. In addition, CRP levels were also constantly higher in these two entities. Conversely, patients in the AS or JIA groups had lower levels of acute phase reactants.

Taking into account potential relationship between the severity of TMJ arthritis and immuno-biological investigations, patients with RA were characterized by statistically significant correlations between the duration and severity of TMJ involvement and high ESR, CRP, abnormal RF, Positive ACPA and increased serum IL-1 concentrations. However, data could not be totally extrapolated to the SpA groups or JIA patients.

Similar findings were already reported in literature, supporting the direct relation between levels of inflammation (ESR, CRP), immunological syndrome (particularly RF) and activity and severity of TMJ arthritis in patients with RA [9,10]. Moreover, the severity and duration of the systemic disease in RA are the main determinants of painful TMJ [13].

Besides, in a study carried exclusively in patients with PsA and psoriasis, signs and symptoms of TMJ involvement, such as TMJ sounds, bruxism and mouth opening derangements were found to be more frequent and severe than in healthy controls [11]. In addition, the likelihood of TMJ involvement in PsA correlates with the duration and severity of articular disease, while the degree and severity

	Mean	σ	Min.	Max.	ESM	-95%	+950%
RA (152)	6.35	3.25	0.00	17.60	.26	5.83	6.87
AS (55)	5.93	1.90	3.50	14.20	.26	5.42	6.45
PsA (44)	6.58	1.77	4.50	12.60	.27	6.04	7.12
JIA (22)	*5.61	1.59	4.20	10.20	.34	4.91	6.32

Table 7
THE MEAN VLUE OF CRP IN THE EXAMINED LOTS

of skin psoriasis is typically not related to TMJ signs and symptoms [13].

Conclusions

TMJ involvement is traditionally described in chronic inflammatory rheumatic disorders, particularly in patients with higher levels of inflammation as detected in rheumatoid arthritis and psoriatic arthritis. Disease activity and severity, as well as biological and positive serological assessments (rheumatoid factor, anti-cyclic citrullinated peptide, IL-1) remain significant determinants of TMJ arthritis.

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