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Cumulative Incidence of Orofacial Manifestations in Early Juvenile Idiopathic Arthritis

A Regional, Three Year Cohort Study

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Cumulative Incidence of Orofacial Manifestations in Early Juvenile Idiopathic Arthritis: A Regional, Three Year Cohort Study

Short title: Orofacial conditions in JIA

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Abstract:

Objectives: To estimate the cumulative incidence of arthritis-induced orofacial symptoms, dysfunctions, and dentofacial deformities in growing individuals with juvenile idiopathic arthritis (JIA) in a 36 month regional cohort study, and to identify predictors for the development of arthritis-induced dentofacial deformities.

Methods: Data was retrieved from the Aarhus JIA TMJ cohort register, which contains standardized, longitudinal, observational data regarding orofacial conditions in patients with JIA (n=1040). This regional cohort represents the majority of all subjects with JIA from the western part of Denmark between 1990 and 2016, regardless of temporomandibular joint (TMJ) arthritis status. Cumulative incidences of orofacial conditions were reported using Kaplan-Meier methods and predictors for dentofacial deformity was identified using Cox proportional hazard analysis.

Results: Follow-up data from 351 subjects over thirty-six months was included in this study. Median age at first clinical examination was 6.6 years (25/75 centiles: 4.9 and 9.9 years). Orofacial symptoms and dysfunction were common findings at 36 months after the first clinical examination and approximately five years after JIA onset, with a cumulative incidence of 38% and 53%, respectively. Dentofacial deformities were found in 35% of

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subjects at the 36-month follow-up, and were significantly associated with the presence of orofacial dysfunction.

Conclusions: Orofacial conditions were frequent findings in JIA and were represented in all JIA subcategories in this regional study. One third of subjects had arthritis-induced dentofacial deformities requiring orthopedic appliance treatment at the 36-month follow-up.

Significance and Innovation

- Orofacial symptoms was reported in 38 percent of the cohort and orofacial dysfunctions occurred in 56 percent of the cohort early in the JIA disease course.
- Arthritis-induced dentofacial deformity was diagnosed in 35 percent of skeletally immature subjects early in the JIA disease course and occurred in almost all JIA subcategories.
- The development of arthritis-induced dentofacial deformity was significantly associated with the presence of orofacial dysfunction.

Temporomandibular joint (TMJ) arthritis is a recognized feature of juvenile idiopathic arthritis (JIA), and TMJ involvement is seen in a substantial number of patients with JIA [1-4]. TMJ involvement can cause joint degeneration and hamper mobility and masticatory function, potentially leading to asymmetric loading of joints and muscles, eventually causing orofacial symptoms and dysfunction and impacting the health-related quality of life of the affected individuals [1, 3, 5-7]. In growing individuals, TMJ inflammation can also critically affect dentofacial growth and development [8-13]. The TMJ has an intra-articular mandibular growth site of crucial importance for normal mandibular growth and

development [14], and therefore is considered particularly vulnerable to TMJ arthritis. Arthritis-associated dentofacial growth disturbances are among the primary long-term concerns for patients with JIA and TMJ involvement [15], and the orofacial consequences of TMJ arthritis are well described in the literature [1-4, 6, 8, 11, 13, 16]. In spite of this knowledge, the most commonly used clinical tools to assess JIA disease activity and physical function including the JADAS 27, the CHAQ, and the JAMAR pay little specific attention to the TMJs during the general disease assessment of patients with JIA [17-19].

Treatment of TMJ arthritis-induced mandibular growth disturbances involves non-surgical orthopedic splints and surgical orthognathic or distraction osteogenesis procedures over a long period, involving substantial intervention, and requiring an interdisciplinary treatment approach [20-22]. Outcomes are dependent on early intervention initiation and excellent patient cooperation [22].

Few prospective studies have elucidated the incidence rates of orofacial conditions in non-selected JIA cohorts [7, 23]. The establishment of accurate population-based estimates of TMJ arthritis-related orofacial conditions and the identification of predictors for dentofacial deformities would improve risk assessment, family counseling, and the development of standardized interdisciplinary treatment approaches combining the efforts of pediatric rheumatologists, orthodontists, maxillofacial surgeons, and orofacial pain specialists.

In this regional cohort study of growing patients, we aimed to estimate the cumulative incidences of patient-reported symptoms, clinical orofacial dysfunctions, and arthritis-induced dentofacial deformity in JIA, and identify predictors for the development of arthritis-induced dentofacial deformities.

Patients and Methods

Study design and population

Data was retrieved from the Aarhus JIA TMJ cohort register, containing standardized longitudinal observational data on patients with JIA seen at the Regional Specialist Craniofacial Clinic, Section of Orthodontics, Aarhus University, Denmark between 1990 and May 2016. The vast majority of diagnosed patients with JIA are referred to the Regional Specialist Craniofacial Clinic for regular orofacial examinations and management of arthritis-induced orofacial conditions by the pediatric rheumatology hospital centers of western Denmark. The Danish healthcare system is a public, tax-funded system in which decisions related to disease management are independent of financial and insurance status, which means that the Aarhus JIA TMJ cohort is representative of the overall JIA population in western Denmark. Patients with JIA are longitudinally followed at the Regional Specialist Craniofacial Clinic regardless of TMJ arthritis involvement. Orthodontists with specialized expertise conduct the clinical examinations, and all clinical visits are standardized in agreement with international consensus-based recommendations for orofacial examination for JIA and include a 57-items standardized orofacial examination procedure [24].

Data was retrieved from the register using the following inclusion criteria: 1) JIA diagnosis according to ILAR criteria [25], 2) less than 14 years of age at first visit, to ensure remaining potential for dentofacial growth, 3) First clinical visit in 2000 or later, 4) A minimum of 3 years of observation time with a minimum of one clinical orofacial examination per year. The study was approved by the Danish Health and Medicine Authorities (3-3013-1803/1/) and the Danish Data Protection Agency (1-16-02-500-16).

Assessments

The following background information was retrieved from the referring hospital charts: Age at JIA onset, JIA subcategory, total number of active joints at diagnosis, antinuclear antibody (ANA), rheumatoid factor (RF), medication history, and remission on/off medication at last follow-up according to the 2004 preliminary Wallace criteria (See online Supplementary Table S1) [26]. Subjects with a final follow-up visit before 2004, were classified retrospectively according to the classifications by Petty et al. and the Wallace et al. after 2004 [25, 26].

The following information about first patient-reported orofacial symptoms was retrieved from the register. Orofacial symptoms were defined as the first patient or parent report of any of the following: TMJ sounds (crepitation/clicking), TMJ pain, pain from masticatory muscles, TMJ morning stiffness, and reduced chewing function. Information about the first abnormal examination finding of orofacial dysfunction was retrieved from the register. Orofacial dysfunction was defined as the first detection of any of the following signs by a qualified orthodontist performing a standardized orofacial exam: TMJ pain on palpation, masticatory muscle pain on palpation, asymmetric mouth opening, reduced maximal mouth opening compared to age-related non-JIA normative values [27], and TMJ sounds during clinical examination (crepitation/clicking) (for details see online supplementary figure S1). No standardized clinical criteria exist for the definition of arthritis-induced dentofacial deformity, therefore, in the present study, we defined dentofacial deformity as follows: *“Patients with clinical and radiological findings documenting arthritis-induced TMJ deformity and incipient dentofacial deformity, beyond normal variation, requiring orthopedic treatment with dental splint.* Orthopedic treatment with a non-surgical orthopedic functional appliance (distraction splint) was initiated following the diagnosis of dentofacial

deformity. Diagnosis and treatment decisions related to dentofacial deformity were based on clinical findings and guided by radiological findings of TMJ pathology, using 3-dimensional (3D) cone beam computerized tomography scan (CBCT) techniques to assess the severity of the dentofacial deformity [28].

The definitions of TMJ symptoms, TMJ dysfunction, and dentofacial deformity adhere to the Temporomandibular Joint Juvenile Arthritis Work group (TMJaw) consensus-based standardized terminology [29]

Statistics

Descriptive statistics of the median, first, and third quartiles were applied to assess age at first orofacial examination and time span between JIA disease onset and first clinical visit at the Craniofacial clinic. Kaplan-Meier estimates were performed to describe the cumulative incidences of patient-reported orofacial symptoms, orofacial dysfunction, and dentofacial deformity from the first clinical visit and the following 36 months for the total cohort and for the subcategories. First orofacial symptom was defined as the first date any orofacial symptom was reported during the clinical orofacial examination (including TMJ sounds, TMJ pain, pain from masticatory muscles, TMJ stiffness, and reduced chewing function). First orofacial sign was defined as the first date any orofacial dysfunction occurred during clinical orofacial examination (including TMJ pain on palpation, masticatory muscle pain on palpation, asymmetric mouth opening, reduced maximal mouth opening, and TMJ sounds). The event date of dentofacial deformity was defined as the date that treatment with a functional orthopedic appliance was initiated. The first clinical visitation was defined as the event date in cases for which an event was already present. Censor time was 36 months after the date of the first clinical visit. Cox proportional hazard analysis was conducted to

assess the association between predefined candidate parameters and the diagnosis of dentofacial growth deviation. All candidate parameters were dichotomized, and hazard ratios were calculated by univariate Cox proportional hazard analyses. Parameters with statistically significant outcomes in the univariate analyses were included in a multivariate Cox proportional hazard analysis for calculation of adjusted hazard ratios. The level of significance was $p < 0.05$.

Results

The Aarhus JIA TMJ cohort consisted of 1040 subjects with JIA in May 2016. 351 subjects (33.7%) met the predefined inclusion criteria (Figure S2). Reasons for exclusion were: first visitation before 2000 ($n=70$), ≥ 14 years of age at first orofacial examination ($n=168$), no initial examination at first visit ($n=17$), other reasons ($n=27$), less than three examinations ($n=307$), less than 36 months total follow-up ($n=83$), three examinations more than 12 months apart ($n=17$). The most common reason for exclusion was less than three years of follow-up. The median time between JIA onset and first orofacial clinical examination was 668 days (25 and 75 centiles: 364 days and 1026 days), and median age at first clinical visit at the Craniofacial Clinic was 6.6 years (25 and 75 centiles: 4.9 years and 9.9 years). All JIA subcategories were represented in the study-cohort, including systemic JIA ($n=19$), oligo persistent JIA ($n=137$), oligo extended JIA ($n=69$), polyarticular RF-negative ($n=80$), polyarticular RF-positive ($n=7$), psoriatic arthritis ($n=15$), enthesitis related arthritis ($n=16$), and undifferentiated arthritis ($n=8$). Cohort characteristics are described in Table 1. 70.1 percent of the included subjects were females.

The secondary excluded subjects (n=407, Figure S2) were significantly older than the included subjects (Median: 9.5 years, 25 and 75 centiles: 5.6 and 11.9 years). The group of excluded subjects was comparable to the study cohort in terms of JIA category distribution and male/female ratio.

Orofacial symptoms

Twenty-five percent of the included subjects reported at least one symptom at the first clinical visit (Figure 1a, table 2), and the cumulative incidence of orofacial symptoms reached 38% at the 36-month follow-up, corresponding to an annual incidence of 4.3% from the clinical baseline visit. Substantial variations in the cumulative incidences of orofacial symptoms were observed between JIA subcategories at the 36-month follow-up, varying from 21% to 62% (Figure 1.b, Table 2). At the 36-month follow-up, the highest and the lowest incidences of orofacial symptoms were seen in the undifferentiated (62%) and systemic subcategories (21%). The most frequently reported orofacial symptoms were TMJ pain (25.1%), chewing limitation (20.5%), and TMJ sounds (14.2%) (Table 3). Symptomatic patients presented variable numbers of symptoms over the 36 months of observation, and the presence of multiple symptoms was rare. Most symptomatic subjects reported one (16.5%) or two symptoms (9.4%) over the 36 months of observation.

Orofacial dysfunction

Thirty-six percent of the total cohort had at least one clinical sign of orofacial dysfunction at the first clinical visit (Figure 1c, Table 2). The cumulative incidence increased to 53% at the 36-month follow-up, corresponding to an annual incidence of 6.7% from the baseline orofacial examination. Substantial variations in the cumulative incidences of orofacial

dysfunctions were observed between JIA subcategories at the 36-month follow-up, varying from 27% to 75% (Figure 1.d, Table 2). The highest and the lowest incidences of orofacial dysfunction were seen in the enthesitis-related (75%) and psoriatic arthritis (27%) subgroups. The most frequent orofacial dysfunctions were asymmetric mouth opening (25.1%) and muscular pain on palpation (21.7%) (Table 3), and the number of clinical signs of orofacial dysfunction also varied among the subjects over the 36 months of observation. The presence of > 2 signs of orofacial dysfunction was rare (Table 3).

Arthritis-induced dentofacial deformity

Two percent of the subjects had already received orthodontic/orthopedic treatment for dentofacial deformity at the first clinical visit (Figure 2a, Table 2), and the cumulative incidence of subjects receiving treatment for arthritis-induced dentofacial deformity increased in a non-linear fashion to 35% at the 36-month follow-up. Substantial variations in cumulative incidences of dentofacial deformity were observed between JIA subcategories at the 36-month follow-up, varying from 0% to 51% (Figure 2b, Table 2). The highest and lowest follow-up subcategory incidences of dentofacial deformity were seen in the polyarticular RF-negative JIA subgroup (51%) and in the polyarticular RF-positive JIA subgroup (0%).

Association between subject characteristics and dentofacial deformity

The following characteristics were significantly associated with the risk of dentofacial deformity in the univariate Cox proportional hazard analysis (Table 4): A) The presence of orofacial symptoms at the baseline orofacial examination (Odds ratio [OR]): 2.22, 95% confidence interval (CI): 1.45-3.41. B) The presence of orofacial dysfunctions at the baseline

orofacial examination (OR: 3.28, CI: 2.23-4.83). Only the presence of orofacial dysfunctions at the baseline orofacial examination was significantly associated with dentofacial deformity in the multivariate hazard analysis (OR: 1.86, CI: 1.24-2.8) (Table 4).

Discussion

To date this is the largest study to investigate the orofacial complications to JIA. This study demonstrates that orofacial symptoms and dysfunction are common features and characteristics 36 months after the first clinical examination and approximately five years after JIA onset, with cumulative incidences of 38% and 53% respectively. Orofacial symptoms and dysfunction are present in all JIA subcategories, and dentofacial deformity occurs in one third of subjects at the 36 month follow-up, approximately five years after JIA onset. These findings represent new and important insights into the prevalence of orofacial complications in growing subjects with JIA.

Previous cross-sectional and longitudinal observational studies have consistently reported the presence of TMJ arthritis in a substantial proportion of children and adolescents with JIA [1, 3, 7]. However, prior studies have also implied that JIA-induced orofacial symptoms and dysfunction are rare in young individuals with recent JIA onset. Olson et al. reported that symptoms of dysfunction were almost absent in subjects younger than seven years in a cross-sectional study [30]. In 2008, Weiss et al. demonstrated that TMJ arthritis was present in the majority of patients with new-onset JIA (median age 8.6 years), despite the fact that 71% were asymptomatic [4]. The findings in the present study conflict with these previous findings and indicate a high incidence of orofacial complications in children in a JIA cohort with a median age of 6.6 years at first orofacial examination. The multivariate cox proportional analysis showed a significant association only between clinical orofacial

dysfunction and dentofacial deformity underlining the unpredictable nature of the arthritis-induced growth deviations that can occur in all JIA subcategories. It is noteworthy that age at onset, number of involved joints at diagnosis, and biological prescription were not significantly associated with the presence of dentofacial deformity. It is also noteworthy that a small proportion of subjects diagnosed with dentofacial deformity presented isolated TMJ arthritis with no other involved joints at onset, as recently described by Hügler et al. [31]. This specific group was characterized by a longstanding and complex course before JIA diagnosis was established.

Clinical aspects

The cumulative incidences reported in this study can be used to approximate the general risk of orofacial complications within all JIA subcategories. We recognize, that not all kinds of orofacial symptoms and dysfunctions necessarily require active disease treatment, nor has a significant impact on health. However, the reported incidences underline that clinical orofacial examination is an essential element in the general health assessment of individuals diagnosed with JIA, regardless of JIA subcategory. Contrast-enhanced magnetic resonance imaging (MRI) is the gold standard for TMJ arthritis diagnosis, and previous studies have shown that clinical orofacial examination has a low sensitivity for diagnosis of TMJ arthritis [16]. However, the standardized orofacial examination serves three additional and important purposes: 1) Standardized routine orofacial examination provide a solid basis for the general assessment of dentofacial growth and development, when sudden onset of orofacial symptoms, alterations in TMJ function, and/or development of dentofacial deformity should prompt increased attention and appropriate referral of the patient for further clinical and radiological orofacial examinations, 2) It enables the diagnosis of TMJ

arthritis-induced orofacial symptoms, dysfunction, and growth deviations in previously asymptomatic subjects, and 3) It allows for the assessment of dentofacial growth and development and the progression of symptoms and dysfunction in subjects who were diagnosed with TMJ involvement. These complications may occur as a consequence of previous TMJ arthritis and are not always associated with the presence of MRI findings of active TMJ inflammation.

Recently, international, multidisciplinary, consensus-based recommendations have highlighted important aspects for inclusion in the orofacial examination of subjects with JIA within each of the following domains: background information and general disease history, orofacial symptoms, masticatory muscle and temporomandibular joint function, and orofacial function and dentofacial growth [24]. An international multidisciplinary task force under the TMJaw network is currently validating a standardized patient symptom questionnaire and a 3-minute clinical examination protocol exclusively for JIA.

Strengths

Strengths of the present study include: 1) The distribution of the different JIA subcategories in our study cohort is comparable to previous population-based studies in the Scandinavian JIA population and comparable to the group of excluded subjects from the Aarhus TMJ register [32]. 2) The inclusion of subjects from the large non-selected Aarhus JIA TMJ cohort that represents the JIA population of western Denmark. Orofacial examination and treatment is an integrated part of the pediatric rheumatology care offered to Danish patients with JIA – regardless of financial or insurance status. According to the Danish Rheumatism Association [33], approximately 1200 children (<16 years) in Denmark have a diagnosis of JIA; when including subjects >16 years, approximately 2000 subjects in

Denmark are diagnosed with JIA. Demographically, approximately 60 percent of total JIA population are assigned for orofacial examination at the Western Regional Specialist Craniofacial Clinic. In May 2016, the Aarhus TMJ arthritis cohort consisted of 1040 subjects which approximate the 60 percent of the total Danish JIA population. 3) The routine examination regime for all cohort subjects, regardless of the presence of TMJ involvement. 4) The use of orofacial examination standards in agreement with consensus-based recommendations conducted by specially trained orthodontists. The consensus-based recommendations on clinical orofacial examination were published in 2017 [24]. These JIA-specific recommendations comply with historical recommendations for clinical orofacial examination in subjects with temporomandibular disorders and those recommendations still constitute the scientific foundation for contemporary assessment of orofacial symptoms and dysfunction [34, 35]. We consider it a strength to the present study, that all subjects received the exact same orofacial examination which means that subjects included before 2017 received a standardized orofacial examination complying with the 2017 JIA-specific recommendations.

Limitations

Attrition is a general limitation to the present study where 66 % (n=689) of the total JIA TMJ cohort was excluded due to strict inclusion criteria. During the secondary exclusion (S2), most of the subjects were excluded due to follow-up issues. The fact that the excluded subjects were approximately three years older at first examination, than the included study cohort, could introduce a bias to the presented results. It could be argued, that the high degree of exclusion due to follow-up issues could impact the results with an overrepresentation of subjects with symptoms, dysfunctions and deformities. An argument

against this is, that JIA-induced orofacial symptoms and dysfunctions occur more often during the teenage years similar to general TMD conditions in a non-JIA population [30,36,37]. According to a longitudinal study by Fjeld et al. 2009, the JIA-specific dentofacial deformities are established between 9 and 12 years of age during the dentofacial growth spurt [11]. The higher age at first visitation of the excluded subjects (9.5 years) favors a hypothesis, that an even greater proportion of the excluded subjects could present dentofacial deformities during a 36 months follow-up than the included study cohort with a median age of 6.6 years at first examination. According to Fjeld et al., JIA-specific dentofacial growth abnormalities does not develop to a significant degree between six to nine years of age when compared to a non-JIA control group [11].

We recognize that the delay of 668 days between JIA onset and the first clinical orofacial examination is a limitation to findings of this study. Another limitation is the fact that some of the subcategories includes a limited amount of subjects representing a risk of bias to the reported incidences. Temporomandibular joint arthritis is a sub-diagnosis of the more general temporomandibular disorder (TMD), seen in 7-12% of the population without a JIA background [36, 37]. TMD is considered to be a multifactorial condition encompassing both degenerative, congenital, functional, and autoimmune etiologies [38, 39]. A limitation of the present study is the fact that no diagnostic methods exists to distinguish between JIA-related orofacial symptoms and dysfunction and other TMD-related etiologies. This may only introduce a minor bias to our findings however, since TMD-related orofacial symptoms and dysfunction are most often observed in the late teenage population and infrequently in the age group examined in this study [36]. Another limitation of this study is the lack of standardized clinical definitions of dentofacial growth deviations. Since minor dentofacial deformity, such as dentofacial asymmetry, is a relatively common finding in a 7-year-old

non-JIA population [40], one may question whether the reported 35% cumulative incidence of dentofacial deformity could represent normal variation in non-JIA individuals. In this study, the term dentofacial deformity refers only to the proportion of the cohort receiving orthopedic appliance treatment for a deviating dentofacial growth pattern. The decision to initiate orthopedic appliance treatment was guided by clinical orofacial dysfunctional findings and CBCT evidence of TMJ and dentofacial deformity, and we feel confident that this 35% represents patients with arthritis-induced dentofacial deformity. We initiated early application of orthopedic treatment as soon as radiological evidence of TMJ deformity and/or dentofacial deformity occurred, according to standard procedure. We have previously shown the clinical merits of the early application of orthopedic splint treatment in 7-year-old subjects with unilateral TMJ arthritis-induced dentofacial deformity, and find it unethical to postpone initiation of treatment until dentofacial deformity becomes more severe [22].

It is important to recognize that only subjects less than 14 years of age were included, in order to assess dentofacial deformity among growing subjects when interpreting our results. Therefore, our results cannot be extrapolated to the entire JIA population, with an age range between 0-16 years. We hypothesize that the relative population-based incidence of dentofacial deformity would be slightly lower if non-growing 14 to 16 year old subjects had also been included, since late JIA onset rarely leads to dentofacial growth deviation requiring orthopedic treatment. Future population-based research is needed to clarify this issue.

Recently, important progress has been made in the management of TMJ arthritis and the related orofacial complications of JIA: 1) Consensus-based recommendations have been published for clinical orofacial examination of patients with JIA [24]. 2) A consensus-based MRI scoring system has been developed [41, 42] with additional proposals for an objectively reliable way to quantify TMJ synovial enhancement [43]. 3) Reliable and valid 3D morphometric measures have been proposed to assess dentofacial deformity [28]. 4) Concerns have been raised regarding the use of intra-articular TMJ steroid injections for TMJ arthritis in growing individuals, due to relatively low long-term effects on inflammation and marked risk for side-effects [44-46]. We believe that the findings presented here will further aid the management of TMJ arthritis, enabling risk assessment of orofacial complication to JIA. In conclusion, we found substantial cumulative incidences of orofacial symptoms and orofacial dysfunctions at a 36-month follow-up, and it is noteworthy that approximately one-third of these patients had arthritis-induced dentofacial deformity associated only with the presence of orofacial dysfunction.

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Data sharing statement: By Danish regulations, the presented data is considered third-party patient owned data. The data is available upon preceding approval from the Danish Health and Medicine Authorities (reference: 3-3013-1803/1/).

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Contributors: The study was designed by PBS, KDK, MG, TH and TKP. Acquisition, analysis or interpretation of data: PBS, CV, MG, AEB, AEC, TH, KDK, SEN and TKP. Statistics was conducted by AEB and PBS. Drafting of the manuscript: PBS, MG, TH and TKP. Critical revision of manuscript and intellectual content before submission: PBS, MG, AEB, AK, CV, AEC, TH, KDK, SEN, MT, TKP. All authors approved final version before publication.

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Table 1. Cohort characteristics. * From diagnosis of JIA to 3 years after first orofacial examination. **intra-articular steroid injection in any joint from JIA diagnosis to 3 years after first orofacial examination. *** Remission status 3 years after first orofacial examination. Abbreviation: Poly RF-; Polyarticular rheuma factor negative. Poly RF+; Polyarticular rheuma factor positive. ERA: enthesitis related arthritis. Undiff.: undifferentiated arthritis. TNF-a: Tumor necrosis alpha. IA: intra-articular.

	Total cohort (n=351)	Systemic JIA (n=19)	Oligo persistent JIA (n=136)	Oligo extended JIA (n= 69)	Poly RF- JIA (n=80)	Poly RF+ JIA (n=7)	Psoriatic JIA (n=15)	ERA (n=16)	Undiff. JIA (n=8)
Age at JIA onset (median years & 1st/3rd quartile)	4.6 (2.1-8.1)	6.4 (3.1-7)	4.1 (2-7.7)	2.9 (1.9-5.2)	4.8 (2.4-8.2)	8.5 (4.7-10.7)	7.1 (3.4-9.3)	8.2 (6.9-9)	7.2 (6.4-10)
Age at first clinical orofacial exam. (median years & 1st/3rd quartile)	6.6 (4.8-9.9)	7.5 (5.1-8.4)	6.5 (4.6-9.9)	5.6 (4.3-8.5)	6.6 (4.9-9.3)	10.6 (8.5-11.6)	9.2 (5.9-10.9)	10.1 (8.5-10.5)	10.5 (8-12.2)
Age at JIA onset < 9 years (%)	287 (81.8)	18 (94.7)	111 (81)	62 (89.9)	65 (81.2)	4 (57.1)	10 (66.7)	12 (75)	5 (62.5)
ANA positive (%)	145 (41.3)	2 (10.5)	58 (42.3)	38 (55.1)	37 (46.2)	2 (28.6)	3 (20)	2 (12.5)	3 (37.5)
Methotrexate user (%)*	218 (62.1)	12 (63.2)	55 (40.1)	44 (63.8)	71 (88.8)	6 (85.7)	11 (73.3)	12 (75)	7 (87.5)
TNF-a user (%)*	88 (25.1)	5 (26.3)	16 (11.7)	14 (20.3)	30 (37.5)	6 (85.7)	5 (33.3)	10 (62.5)	2 (25)
IA. Steroid (not only TMJ) */**	322 (91.7)	14 (73.7)	122 (89.1)	68 (98.6)	78 (97.5)	7 (100)	13 (86.7)	12 (75)	8 (100)
Prednisolon user (%)*	51 (14.5)	16 (84.2)	10 (7.3)	8 (11.6)	10 (12.5)	0 (0)	3 (20)	4 (25)	0 (0)
Active joint count at diagnosis >4 joints (%)	70 (19.9)	3 (15.8)	0 (0)	0 (0)	52 (65)	6 (85.7)	2 (13.3)	2 (12.5)	4 (50)
Remission on medication > 6 months***	90 (25.6)	7 (36.8)	19 (13.9)	22 (31.9)	29 (36.2)	5 (71.4)	3 (20)	3 (18.8)	2 (25)
Remission off medication > 12 months***	137 (39)	7 (36.8)	74 (54)	18 (26.1)	20 (25)	0 (0)	7 (46.7)	6 (37.5)	5 (62.5)

Table 2. Cumulative incidence of orofacial symptoms, orofacial dysfunction, and dentofacial deformity in subjects with JIA within the 36 months after first orofacial examination. *351 subjects were included, but one subject had started treatment for dentofacial deformity before first clinical visit.

	First visit 0 Months	12 Months	24 Months	36 Months	n	Events within first 36 months
Orofacial symptom						
Total cohort	0.25 (0.20-0.29)	0.29 (0.24- 0.34)	0.33 (0.28-0.38)	0.38 (0.33-0.43)	351	133
Systemic	0.16 (0.00-0.31)	0.16 (0.00-0.31)	0.21 (0.00-0.37)	0.21 (0.00-0.37)	19	4
Oligo pers.	0.18 (0.11-0.24)	0.23 (0.15-0.30)	0.26 (0.19-0.34)	0.32 (0.23-0.39)	136	43
Oligo ext.	0.26 (0.15-0.36)	0.29 (0.17-0.39)	0.33 (0.21-0.44)	0.38 (0.25-0.48)	69	26
Poly RF neg.	0.32 (0.21-0.42)	0.35 (0.24-0.45)	0.39 (0.27-0.49)	0.46 (0.34-0.56)	80	37
Poly RF pos.	0.29 (0.00-0.55)	0.43 (0.00-0.70)	0.43 (0.00-0.70)	0.43 (0.00-0.70)	7	3
PsA	0.20 (0.00-0.38)	0.33 (0.05-0.53)	0.40 (0.09-0.60)	0.47 (0.14-0.67)	15	7
ERA	0.44 (0.13-0.63)	0.50 (0.18-0.69)	0.50 (0.18-0.69)	0.50 (0.18-0.69)	16	8
Undiff.	0.62 (0.08-0.85)	0.62 (0.08-0.85)	0.62 (0.08-0.85)	0.62 (0.08-0.85)	8	5
Orofacial dysfunction						
Total cohort	0.36 (0.31-0.41)	0.42 (0.36-0.47)	0.48 (0.42-0.53)	0.53 (0.48-0.58)	351	186
Systemic	0.21 (0.00-0.37)	0.32 (0.07-0.50)	0.42 (0.15-0.61)	0.42 (0.15-0.61)	19	8
Oligo pers.	0.34 (0.26-0.42)	0.39 (0.30-0.46)	0.43 (0.34-0.51)	0.49 (0.40-0.57)	136	67
Oligo ext.	0.39 (0.26-0.50)	0.41 (0.28-0.51)	0.48 (0.35-0.58)	0.54 (0.40-0.64)	69	37
Poly RF neg.	0.36 (0.25-0.46)	0.47 (0.35-0.57)	0.58 (0.45-0.67)	0.64 (0.52-0.73)	80	51
Poly RF pos.	0.14 (0.00-0.37)	0.29 (0.00-0.55)	0.29 (0.00-0.55)	0.29 (0.00-0.55)	7	2
PsA	0.20 (0.00-0.38)	0.27 (0.00-0.46)	0.27 (0.00-0.46)	0.27 (0.00-0.46)	15	4
ERA	0.62 (0.29-0.80)	0.62 (0.29-0.80)	0.69 (0.35-0.85)	0.75 (0.42-0.89)	16	12
Undiff.	0.62 (0.08-0.85)	0.62 (0.08-0.85)	0.62 (0.08-0.85)	0.62 (0.08-0.85)	8	5
Dentofacial deformity						
Total cohort	0.02 (0.01-0.03)	0.24 (0.20-0.29)	0.32 (0.27-0.37)	0.35 (0.30-0.40)	350*	123
Systemic	0.00 (0.00-0.00)	0.11 (0.00-0.23)	0.11 (0.00-0.23)	0.16 (0.00-0.31)	19	3
Oligo pers.	0.03 (0.00-0.06)	0.21 (0.14-0.28)	0.24 (0.17-0.31)	0.28 (0.20-0.35)	136	39
Oligo ext.	0.00 (0.00-0.00)	0.26 (0.15-0.36)	0.39 (0.26-0.50)	0.41 (0.28-0.51)	69	28
Poly RF neg.	0.01 (0.00-0.04)	0.32 (0.21-0.42)	0.48 (0.35-0.57)	0.51 (0.39-0.61)	80	41
Poly RF pos.	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	7	0
PsA	0.07 (0.00-0.18)	0.20 (0.00-0.38)	0.33 (0.05-0.53)	0.33 (0.05-0.53)	15	5
ERA	0.00 (0.00-0.00)	0.19 (0.00-0.36)	0.19 (0.00-0.36)	0.19 (0.00-0.36)	16	3
Undiff.	0.12 (0.00-0.33)	0.50 (0.00-0.75)	0.50 (0.00-0.75)	0.50 (0.00-0.75)	8	4

Table 3. Relative prevalence of individual events and number of unique events within the first 36 months. *Two standard deviations below age-related normative values. TMJ; Temporomandibular joint.

	Relative prevalence of individual events within the first 36 months (%)
Prevalence of orofacial symptoms	
TMJ Sounds	14.2%
TMJ pain	25.1%
TMJ stiffness	10.6%
Muscle pain	6.0%
Chewing limitation	20.5%
Number of symptoms (per subject)	
None	62% (n=218)
1	16.5% (n=58)
2	9.4% (n=33)
3	7.4% (n=26)
4	4% (n=14)
5	0.6% (n=2)
Prevalence of orofacial dysfunctions	
Reduced maximal incisal opening*	10.0%
Asymmetric mouth opening	25.1%
TMJ pain on palpation	15.4%
Muscular pain on palpation	21.7%
TMJ sounds	16.0%
Number of dysfunctions (per subject)	
None	47% (n=165)
1	29.9% (n=105)
2	13.4% (n=47)
3	7.4% (n=26)
4	2.3% (n=8)

Table 4. Association between orofacial symptoms, orofacial signs, subject characteristics and the development of dentofacial deformity within three years after baseline orofacial examination. Dentofacial deformity is defined as the need for orthopedic intervention. *Represent events identified during the baseline orofacial examination.

	Univariate crude hazard ratio (95% CI)	P value	Multivariate crude hazard ratio (95% CI)	Adjusted P-value	Subjects with feature
Orofacial symptoms*	2.22 (1.45-3.41)	0.0002	1.4 (0.89-2.2)	0.14	30*
Orofacial dysfunction*	3.28 (2.23-4.83)	0.0000	1.86 (1.24-2.8)	0.003	45*
Age at debut > 9 years	1.18 (0.76-1.84)	0.47	-	-	64
ANA positive	1.4 (0.98-2.00)	0.07	-	-	145
Active joint count at diagnosis > 4 joints	1.42 (0.94-2.14)	0.1	-	-	70

Legends

Figure 1. Cumulative incidences of first orofacial symptoms and first orofacial dysfunction within the 36 months following first clinical orofacial examination. a) First orofacial symptom in the total cohort, b) first orofacial symptom within JIA subcategories, c) first orofacial dysfunction in the total cohort, d) first orofacial dysfunction within JIA subcategories. Dotted lines in figure 2a, 2c represent the 95% confidence intervals.

Figure 2. Cumulative incidence of dentofacial deformity within the 36 months following first clinical orofacial examination. a) Within the total cohort. b) Dentofacial deformity within JIA subcategories. Dotted lines in figure 3a represent the 95% confidence intervals.



