Temporomandibular Involvement and Craniofacial Development in Juvenile Idiopathic Arthritis

Marinka Twilt

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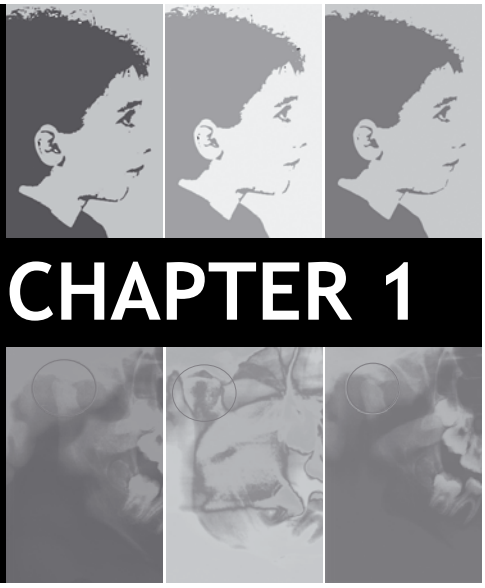
CHAPTER 1



Juvenile Idiopathic Arthritis

The first descriptions of cases of chronic childhood arthritis go back to the 1880 when Moncovo from Brasil described one personal case and added eight from the literature in Paris.[1] In 1891 Diamantberger reported 35 cases from the literature and added three personal observations in Paris.[2] A few years later in 1896 in London, Still gave an outstanding description of chronic childhood arthritis, especially of most of the features of the systemic form.[3] It was based on 22 cases, 19 of whom he personally observed. Despite the fact that Still suggested that chronic arthritis in childhood includes a number of different conditions, the prevailing view for many subsequent decades was that childhood chronic arthritis did not represent a different disease from that observed in adults.
During the late 1960s this view started to be challenged and during the late 1970s both American (Juvenile Rheumatoid Arthritis, JRA) and European (Juvenile Chronic Arthritis, JCA) criteria for the diagnosis and classification of idiopathic chronic arthritis in childhood were proposed.[4,5]
These criteria were not uniform and therefore new criteria and a new international name, Juvenile Idiopathic Arthritis (JIA), were developed. These criteria for JIA were established by the International League of Association for Rheumatology (ILAR) in 1994 in Santiago, Chile and revised in 1997 in Durban and in 2001 in Edmonton.[6-8] JIA is a chronic disease present longer than six weeks that starts before the age of 16 years, and is characterised by inflammation of one or more joints.[7] It is the most common rheumatic disease in childhood, affecting approximately 1 child per 1000.[9] In different international studies an incidence of 0.008-0.226/100.000/year and a prevalence of 0.07-4.01/1000 are described.[9]
JIA is divided into seven subtypes based on clinical symptoms during the first six months of the disease according inclusion and exclusion criteria.[7,8] These subtypes all have a different initial presentation, course and prognosis.[7,10]

The subtypes are:

- Systemic arthritis; arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented to be daily ("quotidian") for at least three days, and accompanied by one or more of the following:
  1) evanescent (nonfixed) erythematous rash
  2) generalised lymph node enlargement
  3) hepatomegaly and/or splenomegaly
  4) serositis

- Oligoarthritis; arthritis affecting one to four joints during the first six months of disease. Two subcategories are recognised:
  1) persistent oligoarthritis; affecting not more than four joints throughout the disease course
  2) extended oligoarthritis; affecting a total of more than four joints after the first six months of the disease
- Polyarthritis Rheumatoid Factor Negative; arthritis affecting five or more joints during the first six months of disease; a test for RF is negative
- Polyarthritis Rheumatoid Factor Positive; arthritis affecting five or more joints during the first six months of disease; two or more test for RF at least three months apart during the first six month of the disease are positive
- Psoriatic Arthritis; arthritis and psoriasis, or arthritis and at least two of the following:
  1) dactylitis
  2) nail pitting or onycholysis
  3) psoriasis in a first degree relative
- Enthesitis Related Arthritis (ERA); arthritis and enthesitis, or arthritis or enthesitis with at least two of the following:
  1) the presence of a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain
  2) the presence of HLA-B27 antigen
  3) onset of arthritis in a male over six years of age
  4) acute (symptomatic) anterior uveitis
  5) history of ankylosing spondylitis, enthesitis related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome, or acute anterior uveitis in a first-degree relative
- Undifferentiated Arthritis; arthritis that fulfils criteria in no or in two or more of the above categories.

The subtypes are also defined by exclusion criteria, to avoid overlap of patients in the different categories.[7,8]

JIA tends to attack certain joints. In oligoarticular JIA the knee is the most commonly joint affected, followed by the ankle. In polyarticular JIA the knee, proximal interphalangeal (PIP), wrist, ankle, metacarpophalangeal, metatarsophalangeal, and elbow joints are the most frequently involved joints. In systemic JIA the knee, ankle and 2nd and 3rd PIP joints are more frequently involved joints.[11]

The course of the disease can vary from severe and irreversible joint destruction to a spontaneous and restless recovery. A study in patients with 5-26 years of

follow-up reported 24-76% achieved remission, depending on the onset subtype.[12] It is important to start therapeutic interventions at an early stage, because of the potential destructive character of the arthritis.

Medical treatment

The insights on treatment regimes in JIA have changed markedly in the last 15 years.[12-16] The greatest change is the tendency to switch to second-line anti-rheumatic drugs (sulfasalazine and immunomodelating agents) earlier in the course of the disease and in accordance with the subtype represented. There is now a shift in treatment focus from chasing failure (gradual add-on approach to the use of medications) to early aggressive combination treatment.[12]

The treatment of JIA combines anti-inflammatory and immunomodulatory medications with physical and occupational therapy, occasional surgery and psychosocial support for patients and parents.

The schedule for medical treatment in JIA consists of the following components:

- Non-steroidal anti-inflammatory drugs (NSAIDs) as mono-therapy can be effective, however only for a minority of patients, mainly those with oligoarthritis. If a NSAID alone is used, the patient should be subjectively improved in one month, and on examination in 8 weeks.[12] In the other subtypes of JIA NSAIDs are often given as concomitant therapy.
- Corticosteroids; systemic and intra-articular. It has not been proven that systemic corticosteroids are disease modulating. The indications for systemic corticosteroids are systemic arthritis with fever and serositis, macrophage activation syndrome or as bridging medication until other medications become effective. Sometimes intravenous pulses are given instead of daily high-dose oral corticosteroids, although there are no controlled studies indicating less adverse events.[17] Intra-articular corticosteroid injections are very effective for oligoarthritis. Studies have shown that as many as 70% of patients with oligoarthritis do not have reactivation of the disease in the injected joint for at least one year and 40% for more than two years.[18-21]
- Immunomodulating medications. Methotrexate is effective for treatment of extended oligoarthritis and is the cornerstone in the treatment of polyarthritis.[22,23] It is however less effective for systemic JIA. Sulfasalazine and leflunomide may be alternatives to methotrexate. Sulfasalazine has showed to be effective in the treatment of oligoarthritis and polyarthritis.[24] Methotrexate was more effective than leflunomide, although a high response rate was also found in the leflunomide group.[25] In a 2-year open label extension study most of the patients responsive to leflunomide maintained their response.[26]

- Recently biologicals, especially TNF-alpha blocking agents were successfully introduced. Etanercept is highly effective for poly-articular course JIA not responsive to methotrexate.[27] Etanercept has shown to be safe and well tolerated in JIA patients with a poly-articular course irrespective of their onset-type.

The Temporomandibular Joint

The human jaw articulation is a so-called secondary joint, because it develops separately and not as a modification of a primary joint.[28,29] The essential morphogenetic events in the formation of the joints of the jaw occur between the seventh and twentieth embryonic weeks.[30,31] It is one of the few joints in the body with a meniscus, an articular disc dividing the joint in upper and lower cavities. The most important site of growth of the mandible in vertical and sagital direction is located on the articular surface of the condylar head.[32,33]

The mandibular condyle

The condyle, at first cartilaginous, develops between the tenth and eleventh weeks from an accumulation of mesenchymal cells.[34] The articulating surfaces of the joint are covered by a dense connective tissue that contains varying amounts of chondrocytes, chondroblasts, fibroblasts, proteoglycans, elastic fibers and oxytalan fibers.[35,36]

Joint surface cartilage must permit frictionless sliding of the articulating structures while at the same time it must be able to transmit compressive forces uniformly to the subchondral bone.[37]

The temporomandibular joint (TMJ) is enclosed in a thin fibrous capsule. The interior surface of the capsule is covered by synovial membrane.[38,39]

TMJ function

Opening of the mouth leads to a rotation (suprahyoid muscles) that always progresses with a translational component (lateral pterygoid muscles).[40] During lateral movements of the mandible, the condyle on the working side moves in laterotrusion and the condyle on the nonworking side in mediotrusion. In centric condylar position all the structural components of the TMJ are in equilibrium and are not subjected to any nonphysiological loads.[41]

TMJ treatment

Treatment of TMJ complaints originated from the condyle or muscles is based on splint therapy. The functional pattern of the mandible and occlusal contact can

be altered by an occlusal splint.[41] The occlusal splint is a removable artificial occlusal surface of plastic that the patients wears temporarily to alter the occlusal contacts. The occlusal splint serves to primarily reposition the mandible and decompress joint and muscle structures.[41]

The temporomandibular joint in Juvenile Idiopathic Arthritis

JIA may affect several joints, including the temporomandibular joint. The TMJ can be affected both unilaterally and bilaterally, early or late in the disease, and it can even be the initial joint affected.

The reported prevalence of TMJ involvement varies from 17% to 87% depending on the population investigated, the subtypes of JIA represented and the radiological method by which involvement is diagnosed.[47,49-50]

Alterations in the craniofacial structure of patients with JIA have been described in several studies.[47,49-50] Patients with JIA demonstrated retrognathia and increased mandibular posterior rotation. Usually the characteristic facial morphology has been associated with condylar destruction.[45-50] Most studies were performed in patients with an oligo- and polyarticular course with more retrognathia and posterior rotated mandibles in the polyarticular course.[45-47] Only one study reported a mild downward and backwards rotation of the mandible in the systemic arthritis.[49]

Aim and outline of this thesis

This thesis describes a cohort of patients with JIA, with and without involvement of the temporomandibular joint, diagnosed by an orthopantomogram (OPT). Consecutive patients visiting the paediatric rheumatology outpatient department of the Erasmus MC- Sophia Children's Hospital, University Medical Center Rotterdam over a period of six months, were included in the "Temporo-mandibular joint Rheumatologic Involvement Project" (TRIP) in 1999.
The cohort of patients was studied at baseline (TRIP 0), after one year of follow-up (TRIP 1), and after 5 years of follow-up (TRIP 5).

Objectives of this thesis

The main objectives of the studies described in this thesis were to evaluate the prevalence and incidence of TMJ involvement in patients with JIA in relation to JIA subtype, and the influence of condylar alterations on the craniofacial morphology. Three studies (TRIP 0, 1 & 5) were conducted to answer the following research questions:

1) What is the prevalence of condylar alterations in a population representing all subtypes of JIA?
2) Are clinical signs and symptoms good predictors for TMJ involvement in patients with JIA?
3) What is the yearly incidence of condylar alterations in a cohort of patients representing all subtypes of JIA?
4) What is the course of the condylar alterations during follow-up?
5) Is the facial morphology of patients with JIA comparable to the facial morphology of the normal population? Do patients with an alteration on the OPT have more alterations of the facial morphology?
6) Is there a correlation between improvement of the alterations on the OPT and changes in retrognathia and posterior rotation of the mandible.

Outline of this thesis

In **Chapter 1** of this thesis an introduction on JIA and the TMJ is given, followed by the main objectives and outline of this thesis. **Chapter 2** gives a historic review of the literature on TMJ involvement in JIA. **Chapter 3** describes the prevalence of OPT alterations in patients with JIA and possible signs and symptoms for TMJ involvement. Abrupt condylar destruction in JIA is described in **Chapter 4**. In **Chapter 5** the incidence of OPT alterations and changes during one-year of follow-up is described. The results of the five-year follow-up study are discussed in **Chapter 6**. The **Chapters 7**, **8** and **9** describe the craniofacial structures in JIA, respectively the prevalence, changes during one-year of follow-up and changes during five-year follow-up. The general discussion in **Chapter 10** answers the main research questions of this thesis, as described in Chapter 1.

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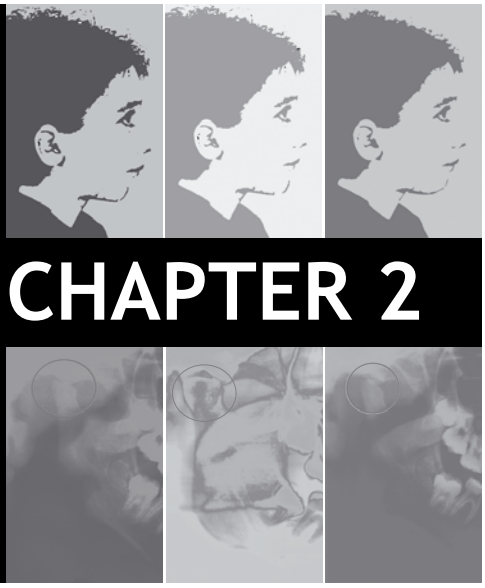
Temporomandibular joint involvement in Juvenile Idiopathic Arthritis; A historic review



CHAPTER 2

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Submitted

Abstract

Objective: Several studies on TMJ involvement in patients with Juvenile Idiopathic Arthritis (JIA) were conducted in the past. This review aims at supplying a clear view of what is known of TMJ involvement in JIA and to give recommendations for future research.

Methods: The search was carried out on MEDLINE (1964-April 2006). MeSH terms used were Temporomandibular joint and Juvenile Idiopathic Arthritis, Juvenile Rheumatoid Arthritis or Juvenile Chronic Arthritis.

Results: Thirty-three papers were included. Patients population selection, subtypes included and radiological techniques (OPT, MRI, CT-scan) used to define TMJ involvement varied greatly in the different surveys. TMJ involvement based on clinical examination varied from 13-100%. TMJ involvement based on radiological examination varied from 21-100%.

Conclusion: TMJ involvement based on radiological examination was and is a frequent feature in JIA. New techniques even imply underestimation of the number of patients with TMJ involvement in the past. Clinical examination alone cannot sufficiently determine condylar involvement.

Keywords: Temporomandibular joint, TMJ, Juvenile Idiopathic Arthritis, JIA, Juvenile Chronic Arthritis, JCA, Juvenile Rheumatoid Arthritis, JRA

Introduction

Juvenile Idiopathic Arthritis (JIA), formerly known as Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis (JCA) is a chronic disease present longer than six weeks that started before the age of 16 years.[1] It is the most common rheumatic disease in childhood.2 The criteria for JIA are established by the International League of Association for Rheumatology (ILAR) in 1994 in Santiago, Chile and revised in 1997 in Durban and in 2001 in Edmonton.[1,3] JIA is divided into seven subtypes based on clinical symptoms during the first six months of the disease according inclusion and exclusion criteria.[1,3] The different subtypes are; systemic arthritis, oligoarticular arthritis (persistent and extended), polyarticular rheumatoid factor (RF) positive arthritis, polyarticular RF negative arthritits, enthesitis related arthritis, Psoriatic arthritis, undifferentiated arthritis.[1,3] These subtypes all have a different initial presentation, course and prognosis.[1,4]

Several joints can be involved, including the temporomandibular joint (TMJ). Diamantberger first described mandibular underdevelopment in juvenile arthritis patients in 1890.[5] Still described involvement of the TMJ in 3 of his 22 patients in 1896.[6] In JIA one or both TMJs can be involved, early or late in the course of the disease, and can even be the initial joints involved.[7] The most important site of growth of the mandible is the chondrogenic zone on the articular surface of the condylar head, other growth sites are located at the ramus of the mandible.[8,9] As a consequence of this superficial position, the growth centre of the mandibula is more vulnerable to damage of the surface, due to arthritis.[7] Early destruction of the chondral part of the condyle due to arthritis may subsequently affect mandibular development and growth.[10-12] A well-known example of these complications is the so-called “bird-face”, a small backwards-positioned jaw, associated with micrognathia.[13]

The aim of this review was to systematically identify and summarise the surveys available on TMJ involvement in patients with Juvenile Idiopathic Arthritis.

Materials and Methods

Search strategy

The search was carried out on MEDLINE (1964-April 2006). MeSH terms used were Temporomandibular joint and Juvenile Idiopathic Arthritis, Juvenile Rheumatoid Arthritis or Juvenile Chronic Arthritis. We included only articles written in English. We required the papers to describe patients with JIA, JRA or JCA. Papers on oral health in Juvenile Idiopathic Arthritis were omitted.

Outcome measures

We extracted data on overall prevalence of TMJ involvement, method used to diagnose TMJ involvement, population studied, the criteria where upon patient selection was based, subtypes represented in the survey and the mean age.

Results

As shown in the flow diagram (Figure 1), 60 potentially relevant papers were identified.[7-10,12,13,14-21,22-29,30-36,37-46,47-58,59-67] Of these, 27 papers were excluded because there was evidence of duplication of data, and the limited number of cases presented in the papers.[7,14,17-19,21,24,25,29-33,37,42,43,45,46,48,51,55,56,58,61,66-68]

Description of Studies

Finally 33 papers were identified as being appropriate for inclusion in the review, summarised in Table 1. TMJ involvement was described as alterations in a clinical examination,[20,23,44,54] a radiological examination[10,13,49,50,52,57,59] or both clinical and radiological examination.[8,9,12,15,16,22,26-28,34-36,38,40,41,47,53,60,62-65] The papers included in this review reach from 1964 to April 2006. If not otherwise stated condylar alterations were assessed by means of an orthopantomogram (OPT). Details such as the included number of patients, the number of controls, the frequency of TMJ involvement, diagnostic technique used, in all the different studies are given in Table 1. Other specific details, such as craniofacial alterations, and remarkable clinical signs, are mentioned here in chronologic order to give a complete view.

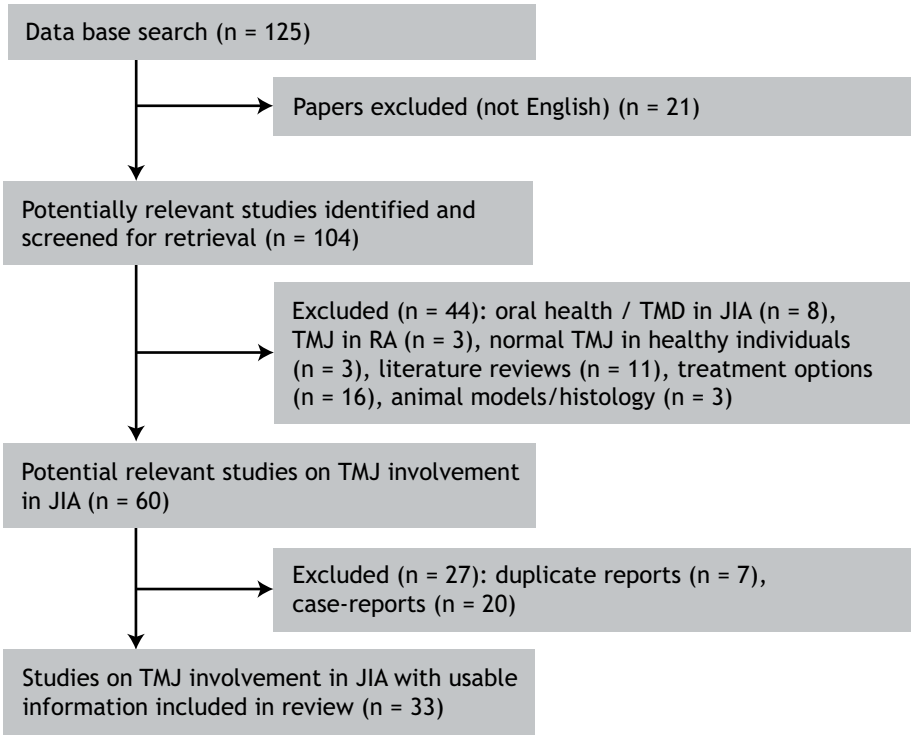

Figure 1. Flow-diagram review.

Surveys in chronological order

In the 1960's two studies were conducted.[8,53] Bache observed a marked reduction in mandibular growth in patients with an onset at an early age, and patients with a disease course of a series of unremitting attacks.[8] Sairanen *et al.* observed clinical abnormalities in 40% of the patients with condylar alterations.[53]

In the 1970's three studies were performed.[13,16,23] Barriga *et al.* reported retrognathia in 12% of the patients, and posterior rotation of the mandible in 44% of the patients, associated with the polyarticular and systemic subtype.[16] The study of Rönning *et al.* is the only study reporting the prevalence (0.04%) of condylar alterations in 2244 healthy controls.[13]

In the 1980's eight studies were reported.[20,22,38,40,41,52,60,62] Larheim *et al.* studied 20 patients selected on the presence of micrognathia, a restricted mouth opening and TMJ complaints in 65%, consequently TMJ involvement was present in 100%.[38] In a 17 year follow-up study Larheim et al. included 9 selected patients of the initial 19 patients included in the study of Barriga *et al.*, of whom 6 already showed condylar alterations at baseline.[40] A longitudinal study of Rönning and

Tabel 1: Studies on TMJ involvement in patients with JIA

Author (year)	ref. nr			Nr of pte	Nr of co	Mean age (yrs) or range	Prevalence clinical examination*	Prevalence with radiology**	Patient selection	Radio-graphic tool used
		criteria used		subtypes represented						
Bache (1964)	8	19	JRA	–	–	14.4	78%	78%	–	Plain Rx
Sairanen (1966)	53	24	JRA	–	55	–	13%	21%	unselected	OPT
Grosfeld (1973)	23	100	JRA	–	–	–	65%	–	consecutive	–
Barriga (1974)	16	27	JRA	7 sys, 7 pauci, 13 poly	27	*3.7–18.6*	44%	30%	–	Plain Rx
Rönning (1974)	13	249	JRA	–	2244	*0.75–19*	–	29%	–	OPT
Larheim (1981)	38	20	JRA	20 poly	22	24	100%	100%	selected	OPT
Larheim (1981)	40	9	JRA	9 poly	–	30	78%	100%	follow–up	OPT
Rönning (1981)	52	195	JRA	–	–	–	–	32% 63%	baseline follow–up	OPT
Larheim (1982)	41	100	JRA	14 sys, 64 pauci, 22 poly	130	9.0	38%%	41%	consecutive	OPT
Stabrun (1987)	62	103	JRA	13 sys, 65 pauci, 25 poly	55	9.0	–	21%	consecutive	OPT
Forsberg (1988)	20	40	JRA	24 pauci, 16 poly	40	18.5	55%	–	consecutive	–
Grosfeld (1989)	22	160	JRA	–	–	*3–15*	65%	80%	–	OPT
Stabrun (1989)	60	103	JRA	13 sys, 65 pauci, 25 poly	50	9.0	41%	–	consecutive	OPT
Karhulahti (1990)	28	121	JRA	–	104	15	30%	55%	–	OPT
Stabrun (1991)	59	26	JRA	11 pauci, 15 poly	26	8.4	–	100%	follow–up	OPT
Olson (1991)	47	70	JCA	1 sys, 48 pauci, 21 poly	–	11.9	56%	41%	consecutive	OPT
Taylor (1993)	64	15	JRA	2 sys, 9 pauci, 4 poly	–	10.4	100%	90%	selected	MRI
Kjellberg (1995)	34	26	JCA	12 pauci, 14 poly	120	13.4	–	65%	–	OPT
Ronchezel (1995)	9	26	JRA	10 sys, 11 pauci, 5 poly	10	10.0	69%	50%	randomly	CT
Hanna (1996)	10	24	JRA	24 sys	–	9.0	–	29%	–	OPT

Author (year)	ref. nr			Nr of pte	Nr of co	Mean age (yrs) or range	Prevalence clinical examination*	Prevalence with radiology**	Patient selection	Radio-graphic tool used
		criteria used		subtypes represented						
Hu (1996)	26	37	JRA	6 sys, 8 pauci, 23 poly	—	11.2	57%	62%	consecutive	CT
Mericle (1996)	12	30	JRA	17 pauci, 13 poly	—	10	83%	48%	—	OPT
Pearson (1996)	49	71	JCA	—	—	15	—	38%	selected	OPT
Küseler (1998)	36	15	JCA	2 sys, 9 pauci, 4 poly	10	12.0	60%	87%	new JIA pts	MRI
Marini (1999)	44	41	JRA	10 sys, 14 pauci, 17 poly	46	*8—15*	73%	—	—	—
Ince (2000)	27	45	JRA	18 pauci, 27 poly	—	14.0	>50%	63%	—	OPT
Svensson (2000)	63	105	JCA	8 sys, 78 pauci, 19 poly	—	12.0	26%	39%	—	OPT
Bakke (2001)	15	42	JCA	33 pauci, 9 poly	21	31.4	73%	67%	referral—based	OPT
Pedersen (2001)	50	169	JCA	21 sys, 110 pauci,38 poly	—	9.8	—	62%	consecutive	OPT
Sidiropoulou (2001)	57	66	JIA	30 pauci, 36 poly	37	11.9	—	50%	—	OPT
Savioli (2004)	54	36	JIA	22 sys, 7 oligo, 7 poly	13	10.8	94%	—	—	—
Twilt (2004)	65	97	JIA	15 sys, 41 oligo, 9 poly rf+, 17 poly rf—, 8 ERA, 3 art psor, 4 undifferen	—	10.7	41%	45%	consecutive	OPT
Küseler (2005)	35	15	JIA	2 sys, 9 pauci, 4 poly	—	12.0	75%	93%	follow—up	MRI

* Prevalence of TMJ involvement in the JRA/JCA/JIA patients based on clinical examination of the TMJ

** Prevalence of TMJ involvement in the JRA/JCA/JIA patients based on radiographic examination of the TMJ

Väliaho of 195 patients with JRA, reported condylar alterations in 32% at baseline and in 63% after at least 3 years of follow-up.[52] Larheim *et al*. observed that condylar alterations were significantly associated with an early onset, long duration of the disease, a polyarticular course, and a high disease activity.[41] Stabrun *et al*. reported a correlation between a reduced mouth opening and a reduced translation, related to condylar alterations.[62] In another paper Stabrun *et al*. described how the combination of a reduced mouth opening, a vertical difference between the two mandibular angular regions, and a deviation of the mandible at maximal protrusion can discriminate the presence or absence of alterations on full-face photography in 93% of the 56 patients of the subset used.[60] Forsberg *et al*. showed presence of at least one clinical sign in 20% of the 40 matched controls.[20] A temporomandibular disorder (TMD) was present in 65% of the 160 JRA patients studied by Grosfeld.[22] Radiological examinations were only performed in 70 patients; selection criteria are unclear, 80% of these patients showed condylar alterations.

In the 1990's twelve surveys were reported.[9,10,12,26,28,34,36,44,47,49,59,64] Stabrun observed a progression of the condylar alterations in 26 patients with initial condylar alterations after six years of follow-up.[59] During follow-up all patients also showed a progression of morphology changes, such as mandibular retrognathism, and posterior rotation. Olson *et al*. only performed a radiological examination in 56 of the 70 patients.[47] The selected population studied by Taylor *et al*. all had clinical TMJ abnormalities.[64] Küseler *et al*. used contrast enhanced MRI and OPT to examine the condyle of patients with newly diagnosed JIA.[36] 67% showed condylar alterations on the OPT, while alterations on the MRI was seen in 87%. The frequency of alterations diagnosed with MRI increased during a 2-year follow-up study, reporting inflammatory enhancement in 93%.[35] Marini *et al*. observed the stomatognathic function, no radiological examination was performed.[44]

From 2000 until 2005 another eight surveys were reported.[15,27,35,50,54,57,63,65] TMD in JIA is described by Savioli *et al*.[54] Clinical signs and symptoms were inadequate for predicting condylar alterations, according to Ince *et al*.[27] Svensson *et al*. reported clinical symptoms in only 50% of the patients with condylar alterations.[63] Bakke *et al*. reported most condylar alterations in patients with pauciarticular extended JCA, a long disease duration, and a high disease activity.[15] Sidiropoulou *et al*. reported a tendency toward retrognathism with a short mandible in patients with polyarticular JIA.[57] Twilt *et al*. observed condylar alterations in all subtypes of JIA, and more frequently in patients with a polyarticular course.[65]

Discussion

In the literature the term "TMJ involvement in JIA" embraces a broad scale of abnormalities, and the outcome TMJ involvement is not uniformly defined. Therefore it is difficult to compare the different studies. Besides the missing uniform description of TMJ involvement, imaging techniques, and medical strategies have changed over time. In the last three decades an increase in the number of studies performed is remarkably. The most important conclusion of this historic review is that TMJ involvement is acknowledge as a frequent feature in patients with JIA, however in the daily medical practice of patients with JIA regularly forgotten.

Imaging techniques used to determine TMJ involvement are the OPT, CT, and MRI. The most used radiological technique to determine condylar alterations in the past was the OPT. Unfortunately only erosive lesions can be detected on the OPT. These erosive lesions are usually late signs of TMJ involvement. The OPT is not capable to distinct active and old lesions. Recently new techniques are used to determine TMJ involvement. Contrast enhanced MRI cannot only identify condylar alterations, but also inflammatory enhancement indicating actual synovitis. MRI is therefore a much more sensitive technique for determining TMJ involvement in JIA. The frequency of TMJ involvement was higher in the surveys using MRI. Consequently this implies TMJ involvement to be underestimated in the past, while using the OPT. At this moment studies on ultrasonography for TMJ involvement in JIA are being performed, but are not yet published. It seems that ultrasonography is also possible to distinct between active and old lesions. Ultrasonography will be of great interest in paediatric patients, as no sedation is necessary.

Many studies also report abnormalities during clinical examinations or complaints of the patient. All studies use different signs, symptoms and ways to determine these alterations, however almost all studies do conclude signs and symptoms to be present in both patients with and without condylar alterations; hence are not useful in discriminating between presence or absence of condylar alterations. Signs and symptoms related to condylar alterations in different surveys are: early onset of the disease, long duration of the disease and a polyarticular course. Arthritis of the TMJ is difficult to assess with a clinical examination alone. Therefore an imaging examination is necessary.

Some studies also describe craniofacial involvement in the patients with JIA. These studies only describe an increased frequency of retrognathia and posterior rotation in patients with JIA with condylar alterations, and not in patients without condylar alterations.

Besides the different techniques used to define TMJ involvement, also the therapeutic options for the patients in the different studies lead to difficulty in comparing the results of the different surveys. In the last 15 years insights in the treatment regimens, and consequently treatment in JIA have changed markedly. The greatest change is the tendency to switch to second-line anti-rheumatic drugs earlier in the course of the disease in accordance with the subtype represented. The treatment has shifted from chasing failure (gradual add-on approach) to early aggressive combination therapy.[69] This new strategy is aimed at early control of the disease activity, and consequently also the arthritis in the TMJ.
Patient selection techniques differed greatly in the different surveys. In some studies a selection bias has occurred as only patients with already known condylar alterations, or patients with complaints concerning the TMJ were included. These surveys consequently report a higher frequency of TMJ involvement. Also in other studies selection bias has occurred, as most studies do not include all subypes of JIA, but mainly patients with a polyarticular course of the disease. These biases explain the great differences in the frequency of TMJ involvement.
After evaluating all these surveys describing TMJ involvement it is clear uniform arrangements need to be made on the terminology TMJ involvement. Few follow-up studies are performed and almost all were performed in a biased population with condylar alterations at baseline in all patients. Ideally a prospective follow-up study should be performed, including patients with all seven subtypes of JIA. Besides the prevalence and course of TMJ involvement, also the incidence of TMJ involvement can be studied. Ideally OPT, MRI, and ultrasound should be compared for the sensitivity and specificity of these techniques. These three techniques can also help to distinguish between new active lesions and old lesions and their course over time.

Conclusion

TMJ involvement embraces a broad scale of alterations, which makes comparison between the different studies difficult. Over the years TMJ involvement is acknowledge to be a frequent feature in JIA. However no clinical implication studies for the daily practice are described. The ability of new techniques to detect active synovitis, imply the frequency of TMJ involvement to be underestimated in the past.

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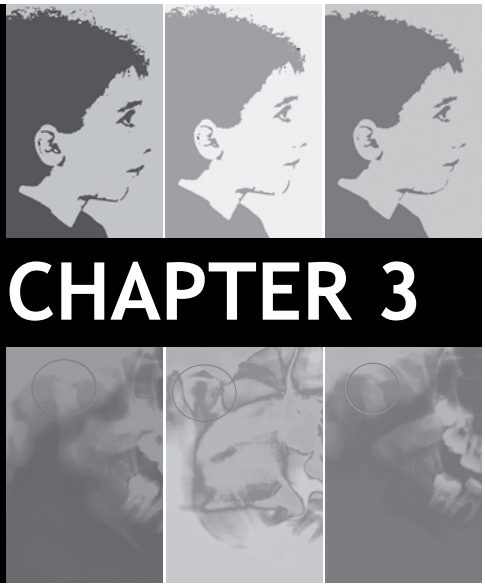

CHAPTER 3

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Abstract

Objective: To study occurrence as well as clinical signs and symptoms of temporomandibular joint (TMJ) involvement in juvenile idiopathic arthritis (JIA) in a population representing all subtypes of JIA.

Methods: Ninety-seven consecutive children with JIA underwent orthodontic evaluation including an orthopantomogram (OPG). Further evaluation included patient characteristics, disease onset, course, and medical treatment.

Results: Forty-five percent of all children had TMJ involvement. Frequencies according to JIA subtypes: systemic 67%, oligoarticular (persistent and extended) 39%, rheumatoid factor (RF) negative polyarticular 59%, RF positive polyarticular 33%, enthesitis related arthritis 13%, psoriatic arthritis 33%, and other arthritis 50%. In children with a polyarticular course, irrespective of their disease onset, TMJ involvement was more frequent (55% versus 31% in oligoarticular course). In children with disease onset at a young age and/or an extended course of the disease, TMJ involvement was also more frequent. Pain during jaw excursion, absence of translation, asymmetry during maximal opening and protrusion, as well as crepitation during evaluation are predictors for TMJ involvement with a good specificity but a low sensitivity. Not all patients with TMJ involvement have clinical signs.

Conclusion: Because of the high prevalence and discrepancy between clinical signs and presence of arthritis of the TMJ, regular orthodontic evaluation and OPG is recommended to recognize TMJ involvement and enable early intervention.

Introduction

Juvenile Idiopathic Arthritis (JIA), formerly known as Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis (JCA), is a chronic inflammatory disease present for longer than 6 weeks starting before the age of 16 years.[1] The criteria for JIA were established by the International League of Association for Rheumatology (ILAR) in 1994 in Santiago, Chile and revised in 1997 in Durban. JIA is divided into 7 subtypes based on clinical symptoms during the first 6 months of the disease.[1]

Underdevelopment of the mandibula is a characteristic feature of patients with JIA, recognized as early as 1890.[2] Involvement of the Temporomandibular joint (TMJ) was first reported by Still when he described chronic arthritis in childhood in 1897.[3] The reported frequency of TMJ involvement varies from 17% to 87% in the literature depending on the population investigated, the subtypes of JIA represented, and the methods by which involvement is diagnosed.[4-6] In all subtypes of JIA, one or both TMJ can be involved and may even be the initial joints involved.[4,7,8]

The most important site of growth of the mandible is the chondrogenic zone on the articular surface of the condylar head.[9,10] As a consequence of this superficial position, the growth center of the mandibula is more vulnerable to damage of the surface, due to arthritis.[8] Early destruction of the chondral part of the condyle due to arthritis may subsequently affect mandibular development and growth.[11-13] A well known example of these complications is micrognathia, the so-called bird-face, a small backward-positioned jaw.[5]

Unfortunately, in many cases TMJ involvement evolves without any symptoms, causing a delay in detection.[7] Clinical symptoms (pain, local morning stiffness, and impaired function) alone have shown to be quite unreliable as indication of arthritis.[5] Decreased opening of the mouth, earache, and pain during eating, chewing or yawning can also point at TMJ involvement.[4,6-8] The severity of TMJ symptoms is directly related to the inflammatory variables of JIA. As the disease progresses it may lead to severe destructive changes in the TMJ.

It is therefore important to recognize clinical symptoms that indicate TMJ involvement in an early stage. Combining these symptoms with radiological abnormalities may lead to early detection of imminent condylar destruction. When clinical symptoms are detected by the pediatrician, this should lead to referral for an extra orthodontic evaluation.

As symptoms of TMJ involvement coincide with flares of disease activity, the primary goal is to control the synovitis with medication. Further, guidelines for

conservative treatment that follow basic principles in rheumatology like heat and cold therapy and exercises to improve range of motion are added. After initial general medical care, treatment is aimed at normalization of mandibular growth in anterior and vertical direction.[10] In most patients orthodontic treatment can be carried out satisfactorily during growth by using both functional and fixed appliances.[11,14]
Our aim was to study occurrence of TMJ involvement in a population representing all subtypes of JIA according to Durban criteria and to determine which clinical signs are indicative for TMJ involvement.

Materials and Methods

Patients

In this survey patients who visited the pediatric rheumatology clinic of the Sophia Children's Hospital over a period of six months were investigated. All children with JIA according to the Durban criteria were routinely referred for orthodontic evaluation, even in the absence of complaints of the TMJ-region.

Data collection

Data were obtained from medical records and through clinical investigation. The following data were collected: patient characteristics (including sex, age at onset, and age at orthodontic examination), type of disease onset and course, disease activity, and laboratory data. Therapeutic interventions during the course of the disease were used as an indicator for the assessment of the disease activity and severity since onset of the disease. Drug treatments considered were nonsteroidal antiinflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), and immunosuppressive drugs such as corticosteroids and methotrexate.
The data collected by the orthodontist included: mandibular function estimated by measuring (in mm) the interincisal distance at maximal mouth opening adjusted for overbite, protrusion adjusted for overjet, side deviations at maximal opening and protrusion, and lateral movements between the midlines adjusting for midline discrepancy at intercuspal position. Other symptoms, such as masticatory problems and difficulty in opening of the mouth, were recorded as present or absent. Full-face photography was performed for assessment of facial asymmetry and thorough documentation, which makes comparison during follow-up or re-evaluation possible.

Radiological examination consisted of an orthopantomogram (OPG) taken after clinical examination and scored according to Rohlin[15] by two blinded examiners (M.T and M.L.M.M). The scoring system of Rohlin for TMJ involvement consists of 6 grades: 0 normal situation, 1 slight abnormality, 2 definite early abnormality, 3 moderate destructive abnormality, 4 severe destructive abnormality, 5 mutilating abnormality.[15] We defined TMJ involvement as present when the score was grade 1-5.

Although OPG is not the most sensitive in detecting resorption and change in the cranial area, it can be used to show joint involvement.[11,16] Magnetic resonance imaging (MRI) or lateral tomograms may be more efficient in diagnosing early TMJ involvement; however, OPG is less expensive and patient exposure to radiation is less. OPG is widely used in most dental and orthodontic clinics and therefore the best tool for routine investigation.[4,15]

Statistic analysis

Continuous group data were summarized as medians and interquartile ranges. Comparisons of continuous variables between the groups of children with and without TMJ involvement were performed by a *t*-test for normally distributed variables, by a Mann-Whitney test for variables not normally distributed, and by a Pearson's chi-square for categorical variables. To determine independent prognostic factors of TMJ involvement, simple and multiple logistic regression analysis were performed. The following variables were tested univariately as well as in a multivariately procedure: swelling, pain, pain during jaw excursion, morning stiffness, clicking, and crepitation noticed by the patient and asymmetric opening and protrusion, or crepitation, absence of translation, limited rotation of the head, limited head extension and/or flexion, and clicking noticed by the orthodontist during examination.

All analyses were performed with the SPSS version 10.0 package (SPSS-PC, Chicago, IL, USA).

Results

Patients

Over 6 months, 110 children with JIA according to the ILAR criteria visited the pediatric rheumatology clinic. Of these patients, 97 were evaluated by the orthodontist and 13 patients did not show up at their appointment, or refused to make one. The orthodontist had evaluated 19 of the 97 children earlier in the

course of their disease. To include these 19 patients, orthodontic measurements and anamnestic data of the initial visit were obtained from medical records.
The survey consisted of 60 girls and 37 boys, with a mean age of 10 years, 8 months (range 2 yrs, 10 mo, to 18 yrs), mean age at onset 5 years, 10 months, and mean duration of the disease of 4 years, 9 months.

Table 1: JIA subtype and frequency of TMJ involvement (n = 97).

JIA type and -course	n	TMJ Involvement %
Systemic	15	67
oligo	1	0
poly	14	71
Oligoarticular	41	39
persistent	37	34
extended	4	75
Polyarticular rheumatoid factor positive	9	33
Polyarticular rheumatoid factor negative	17	59
Enthesitis related arthritis (ERA)	8	13
oligo	4	0
poly	4	25
Psoriatic arthritis	3	33
oligo	2	50
poly	1	0
Other arthritis	4	50
oligo	3	33
poly	1	100
Total	97	45

TMJ changes

OPG was performed for all children. In 44 of the 97 patients (45%), TMJ involvement (grade 1-5) was found. The percentage of TMJ involvement in relation to the different subtypes of JIA and the course of the disease are summarized in Table 1. The frequency of TMJ involvement increased if the arthritis had progressed to a polyarticular course (55% compared to 31% in oligoarticular course). Of the 44 patients with TMJ involvement, 22 have unilateral involvement of the TMJ and 22 patients have bilateral TMJ involvement. In total 66 condyles were involved: 28 right-sided and 38 left-sided. The Rohlin score for severity yielded 30 condyles with grade 1, 3 condyles with grade 2, 8 condyles with grade 3, 22 condyles with

grade 4, and 3 condyles with grade 5. TMJ arthritis is associated with an earlier onset of the disease compared to JIA without TMJ arthritis (5 years versus 6 years, 7 months). The children with TMJ arthritis also had a longer duration of the disease than children without (5 yrs, 2 mo, vs 4 yrs, 5 mo).
Disease severity and activity in the past were assessed by means of drug intervention used as therapy. Of the patients treated with local corticosteroids, NSAIDs, and DMARDs (N=69), 29% had TMJ involvement. Of the patients with NSAIDs, DMARDs and immunosuppressive therapy (N=28), 68% had TMJ involvement. Treatment as a sign of disease activity showed a linear by linear association with TMJ involvement (p=0.013). If therapy included NSAID, DMARD and immune suppressive drugs, chances of TMJ involvement increased 5-fold (odds ratio, OR, 4.75) compared with no medication.

Table 2: Symptoms of TMJ involvement in patients with JIA (n = 97).

Signs	Patients with Signs (%)	Patients with TMJ involvement (%)	Odds Ratio	95% confidence interval	P
Noticed by the patient					
Swelling	5 (5)	4 (80)	5.6	0.6 — 5.2	0.17
Pain	11 (12)	6 (55)	1.6	0.67 — 12.1	0.53
Pain during jaw excursion	9 (9)	6 (67)	5.2	1.02 — 26.5	0.04*
Morning stiffness	8 (8)	4 (50)	1.4	0.32 — 5.8	0.72
Clicking	12 (13)	8 (67)	2.9	0.82 — 10.5	0.087
Crepitation	9 (9)	6 (67)	2.8	0.67 — 12.1	0.17
Orthodontic examination					
Asymmetric opening and/or protrusion	24 (28)	17 (71)	4.9	1.74 — 13.5	0.002*
Crepitation	8 (8)	7 (88)	10.1	1.2 — 85.5	0.011*
Absence of translation	22 (23)	16 (73)	4.9	1.7 — 14.1	0.002*
Limited rotation of the head	25 (28)	14 (56)	2.1	0.81 — 5.3	0.13
Limited head extension and/or flexion	36 (41)	17 (41)	1.3	0.56 — 3.1	0.52
Clicking	13 (13)	9 (69)	3.3	0.94 — 11.6	0.052

* $p < 0.05$

Clinical signs of TMJ changes

Signs and symptoms that could indicate TMJ involvement are summarized in Table 2. Of the symptoms noticed by the patient during the course of the disease, only pain during jaw excursion ($p < 0.05$) is a valid predictor. If the other signs were present, the possibility of TMJ involvement increased, but not significantly

($p > 0.05$). Of the signs noticed by the orthodontist during orthodontic examination, absence or impaired translation during maximal mouth opening, crepitation during jaw movement, asymmetric opening, and protrusion seem to be important predictors ($p < 0.05$). Clicking appears to be a borderline sign ($p < 0.06$). Trough backwards selection procedure absence of translation during maximal opening ($p < 0.009$) and asymmetry during maximal opening and protrusion ($p < 0.021$) appeared to be the most important factors, as the other factors in Table 2 did not increase the risk of TMJ involvement significantly ($p > 0.05$).
Orthodontists' observations are summarized in Table 3. Of the measurements performed by the orthodontist only maximal opening of the mouth and protrusion were significantly decreased in patients with TMJ involvement compared to those without.

Table 3: Jaw mobility and TMJ involvement in children with JIA (n = 97).

Symptoms	Patients without TMJ involvement		Patients with TMJ involvement		p-value (*t*- test)
	n	mean (mm)	n	mean (mm)	
Protrusion	48	8.7	35	8.3	0.05*
Maximal opening	54	50.2	42	44.9	0.001*
Overjet	54	4.0	43	5.4	0.81
Overbite	53	2.4	43	1.4	0.54
Lateral movement					
right	54	9.8	42	9.4	0.41
left	54	10.5	42	8.9	0.77

* $p < 0.05$

Maximal opening capacity of the mouth in our population was also compared with the normal ranges for age described in different surveys, summarized in Table 4.[17,18] Maximal opening capacity of patients with TMJ involvement was in the lower range, but within the normal standard deviation. For protrusion, normal ranges are described in literature for 10- and 15-year-old children (10-year-old mean protrusion 10 mm, 15-year-old mean protrusion 9.7mm).[7,17] In our survey, children aged 9 to 11 years with TMJ involvement (n = 4) had a decreased mean protrusion (7.3 mm) compared to those without (n = 7, mean protrusion 9.5 mm). In children aged 14 to 16 years there was no difference in mean protrusion in those with (n = 6, protrusion 9.9 mm) and those without (n = 6, protrusion 9.25 mm) TMJ involvement.

Table 4: Maximal opening in JIA referred to age categories and normal mobility. Ranges are shown in brackets.

Age	0-6 years	6-11 years	11-16 years	16-21 years
Ingervall		49 mm (37 – 66 mm)		51mm (33 – 64 mm)
Sheppard	42 mm (35 – 49 mm)	46 mm (37 – 53 mm)	51 mm (40 – 72 mm)	49 mm (38 – 59 mm)
This study	n = 9	n = 15	n = 24	n = 6
patients without OPG alterations	43 mm (37 – 51 mm)	48 mm (38 – 56 mm)	53 mm (38 – 71 mm)	53 mm (50 – 56 mm)
This study	n = 12	n = 13	n = 13	n = 4
patients with OPG alterations	42 mm (33 – 50 mm)	43 mm (20 – 51 mm)	47 mm (40 – 56 mm)	57 mm (45 – 57 mm)

Discussion

In this cross-sectional survey of pediatric patients including all JIA subtypes according to the Durban criteria, the mean frequency of TMJ involvement was 45%. A considerable variation depending on subtype was seen, with the highest prevalence in children with a polyarticular course. A wide variability in the frequency of TMJ involvement is reported in the literature (17% and 87%); however most surveys do not include all subtypes of JIA and in some, only older children and adolescents are evaluated.[4,7,8,12,13] The frequency of TMJ involvement also depends on the radiographic tool used to diagnose TMJ involvement. In our survey OPG was used to study the occurrence of TMJ abnormalities in JIA.

Our study population was relatively young compared to other studies, and all subtypes of JIA were represented. The highest risk of developing TMJ involvement was in systemic and polyarticular JIA (67% and 50%). Children with an oligoarticular JIA with a polyarticular course also had an increased risk of TMJ involvement (oligoarticular persistent 34%, oligoarticular extended 75%). The high frequency of TMJ involvement in polyarticular JIA was accounted for by the polyarticular RF negative group in which the frequency of TMJ arthritis was 59%. Surprisingly, the polyarticular RF positive group, known for an erosive destructive character, had a relatively low frequency of TMJ destruction on OPG (33%). The RF positive patients had late disease onset compared with the other subtypes. We postulate that older age may make the condyle less vulnerable to damage by arthritis than in young children. When most of the growth of the mandibula is completed and the growth center is closed, arthritis of the TMJ will have less devastating consequences.

In contrast with our expectations, unilateral and bilateral involvement were equally divided in our patients, while in other reports bilateral involvement was more frequent than unilateral involvement.[7]

Of all symptoms noticed by the patient, only pain during jaw excursion was a (weak) predictor of TMJ involvement (Table 2). Abnormalities on orthodontic examination that were significant and good predictors for TMJ involvement included absence of translation during maximal opening of the mouth, asymmetry of the maximal opening, and protrusion, and crepitation (Table 2).

A trained pediatrician/ rheumatologist can detect these predictors. Translation is the second part of the normal jaw movement during opening, the frontal movement of the condyle after the initial rotation. TMJ involvement should be suspected when only rotation is observed during lateral palpation of the TMJ. During this lateral palpation, asymmetry at maximal opening can also be observed. However, the fact remains that the sensitivity of these predictors is less than the specificity. Absence of translation, for example, having a sensitivity of 37% and a specificity of 89 %, is a good predictor for involvement: if translation is present, TMJ involvement remains a possibility. Even when different tests were combined, no conclusive predictors for TMJ involvement were found.

We agree with Stabrun, *et al.*[19] that impaired lateral rotation of the head is not an independent clinical predictor for TMJ involvement. In patients with cervical spine involvement, pain during movement of the head, reduced rotation, extension, and flexion are experienced because of interaction of symptoms. Patients with systemic or polyarticular onset have an increased risk of developing cervical spine involvement.

Measurements analyzed in Table 3 are more limited than those of Table 2 because they depend on normal growth and mobility of the mandibula. These predictors vary according to age and should therefore be compared with healthy controls. The literature provides only normal values for maximal mouth opening and for protrusion.[7,17,18] There is a significantly smaller maximal opening capacity in patients with TMJ involvement compared with those without TMJ involvement.[7,10,12,13,19] This difference may even be underestimated, since patients with initial stages of TMJ involvement with impaired opening but no visible OPG alterations are classified as having no TMJ involvement. Values for maximal opening in our patients were within the normal range (Table 4), although if TMJ involvement was present, the maximal opening is just in the outer limits of normal. In summary, impaired opening of the mouth is an important indicator of TMJ involvement that should be checked regularly.

There was a significantly decreased protrusion capacity in patients with TMJ involvement compared to those without. We were able to compare protrusion measurements of only our 10 and 15-year-old patients with controls because data on normal protrusion values are not available for other age groups. Since we had only a small number of children in these age categories, no definite conclusions can be drawn.

For the clinician it is important to realize that involvement of the TMJ may be present without signs and symptoms. Therefore every physical examination of a patient with JIA should include the TMJ-region. In case of doubt about possible involvement of the TMJ, the patient should immediately be referred to an orthodontist. Even if there is no clinical suspicion of TMJ involvement, periodic evaluation with OPG is recommended in all children with JIA. In our hospital it is standard policy to perform an orthodontic examination in every patient at least once a year; the optimal interval between examinations is not yet defined.

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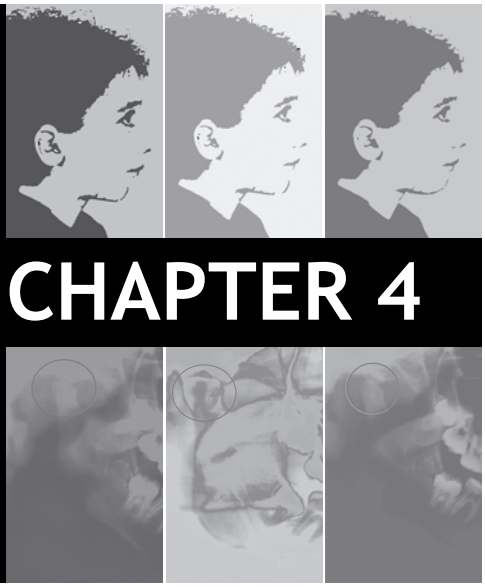
Abrupt condylar destruction of the mandibula in Juvenile Idiopathic Arthritis



CHAPTER 4

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Introduction

Unilateral and bilateral involvement of the temporomandibular joint (TMJ) and subsequent growth disturbance of the mandibula is a common feature in juvenile idiopathic arthritis (JIA).[1] The prevalence varies between 17-87% depending on the subtype of JIA.[2-6] No conclusive measures for local disease activity are found. Arthritis of the TMJ is usually not associated with pain, and clinical signals, such as deviation of the jaw, impaired opening of the mouth, absence of translation, crepitation, or clicking during palpation, are usually scarce, which explains the delay in diagnosis.[7]
The TMJ consists of fibrocartilage, hyaline cartilage, and synovial membrane like other joints. The growth centre of the mandible is located on the articular surface of the condylar caput instead of more distal to the joint[8], therefore the TMJ is more vulnerable to damage of the surface.
Arthritis may cause rapid condylar destruction as the following case history illustrates.

Case report
A 7 year old girl with arthritis in wrist, ankles, and some joints of hands and feet was diagnosed rheumatoid factor negative polyarticular JIA. She was treated with non-steroidal antiinflammatory drugs, sulfasalazine and methotrexate. The wrists and hands, especially, showed active arthritis with a gradual deterioration of function. Radiological evaluation disclosed no erosions.

At a routine check up the patient -than 11 years of age- complained of pain when she opened her mouth with impairment of biting, a clicking sound in her left TMJ, morning stiffness, impaired mastication, and decreased maximal opening which had been present for one month. Results of the immediate orthodontic evaluation were compared with those of the previous completely normal control two months earlier. The only observed changes were a limited translation and corresponding side deviation of the right jaw in rest and during maximal opening. The maximal opening of the mouth was not altered. The orthopantomogram, which was normal at the previous visit, showed severe destructive abnormalities of both condylar heads, disclosing TMJ destruction within two months (figures 1 and 2). Splint therapy was started to decompress the TMJ.

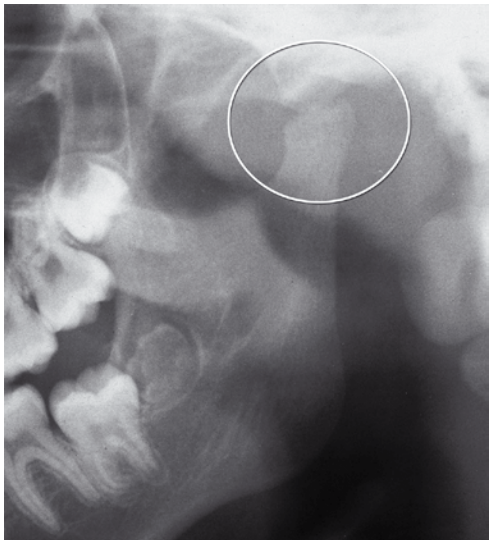

Figure a: Normal OPG

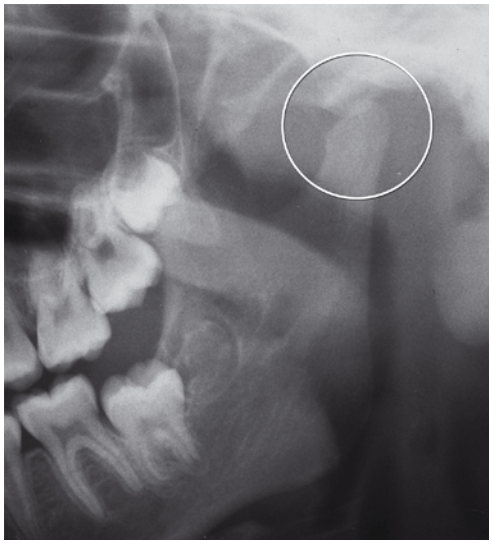

Figure b: Severe destructive abnormality

Figure 1: OPG normal, b. severe destructive abnormalilty, extensive erosions of the lateral and medial parts of the condyle and the temporal joint.

Discussion

Sudden destruction of both condylar heads of the mandibula was seen in the patient only one month after she developed complaints. There is a striking discrepancy between the complaints and the clinical findings. The movements of the jaw compared with the previous measurements were exactly the same, except that the translation of the condylar head at the right side was limited but still present. This demonstrates that even discrete signs make thorough evaluation, including orthopantomography, necessary.

All studies on TMJ involvement agree that orthodontic evaluation is necessary and mandatory, but the frequency of orthodontic evaluation is not yet established.[4,6,7,9,10] In our clinic all children with JIA have a routine orthodontic evaluation once a year. An extra evaluation can be arranged within a few days. Patients and parents should be informed of possible signs of TMJ involvement during the course of disease. The clinician has to be aware of the possibility of acute destruction of the condylar heads of the mandibula.

There is still no conclusive therapeutic regimen for TMJ involvement in JIA. Three possible therapeutic measurements have been reported: intra-articular corticosteroid injection, expanding anti-rheumatic drugs, or splint therapy. In

our clinic splint therapy is the standard policy in condylar involvement in JIA.
The case illustrates the rapid and sudden destruction that can take place in a very limited period of time and emphasises the importance of awareness of clinical signals of TMJ destruction/involvement even when there are no objective abnormalities during evaluation. Treatment will be delayed if clinical signs are misinterpreted and the typical complaints are not attributed to possible involvement of the TMJ. Therefore regular evaluation of the TMJ by the paediatrician/rheumatologist and periodical evaluation by the orthodontist with orthopantomogram assessment is recommended.

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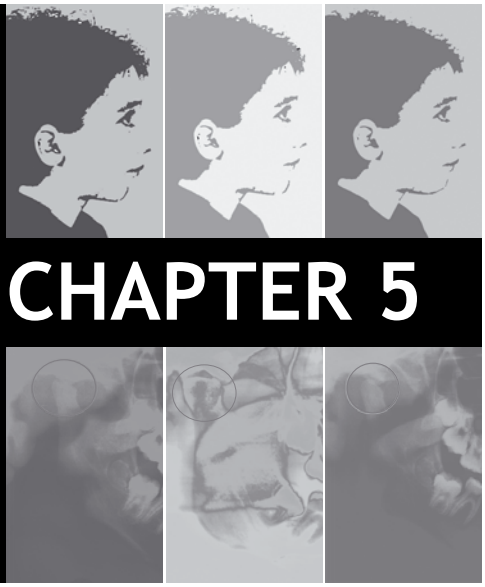
Incidence of Temporomandibular involvement in Juvenile Idiopathic Arthritis



CHAPTER 5

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Submitted

Abstract

Objective: Temporomandibular joint (TMJ) involvement is a frequent feature in cross-sectional prevalence studies among Juvenile Idiopathic Arthritis (JIA) patients. The cross-sectional design makes it almost impossible to study the incidence. Follow-up data on TMJ involvement are sparse. In this study patients were reviewed with an interval of a minimum of one and a maximum of two years to study the yearly incidence of TMJ involvement and to gather follow-up data on TMJ involvement and orthopantomogram (OPT) alterations.

Methods: Children with JIA from a previous study on TMJ involvement were included. OPTs were scored according Rohlin's grading system (grade 0-5). The paediatric rheumatologist measured the level of disease activity during the interval.

Results: 89 of the 97 patients could be included in this study with a mean follow-up of 14 months. The yearly incidence of TMJ involvement was 7.1% in patients with JIA. Improvement on the OPT was seen in 27 patients (66%), of these patients 19 showed no signs of TMJ involvement anymore. Worsening on the OPT was seen in 4 patients (10%). Disease activity was significantly lower in the improved patients than in the patients with worsening.

Conclusion: The yearly incidence of TMJ involvement was 7.1%. Condylar lesions due to arthritis can improve over time, which points at a regenerative capacity of the mandibular condyle. As condylar improvement seems to be associated with a low disease activity, it is important to imply the TMJ when deciding on a therapeutic regimen.

Key words: Juvenile Idiopathic Arthritis, JIA, Temporomandibular joint, TMJ

Introduction

Juvenile Idiopathic Arthritis (JIA) is a term to indicate a disease of childhood onset characterised primarily by arthritis persisting for at least six weeks, starting before the sixteenth birthday.[1]
Several joints can be involved, including the temporomandibular joint (TMJ). One or both TMJs can be involved in JIA, early or late in the course of the disease. In most cases this occurs without any clinical symptoms, but patients frequently have radiographic evidence of arthritic joint changes.[2,3] Diamantberger first described mandibular underdevelopment in patients with JIA in 1890.[4] Since then the reported frequency of TMJ involvement varies in literature from 17% to 87%.[2,5,6-12] Remarkable all studies are cross-sectional, and most studies use the OPT to define TMJ involvement, making it almost impossible to distinguish between active arthritis and old lesions due to arthritis. In the first study, representing all subtypes of JIA, we reported TMJ involvement with a frequency of 45%.[12] Only few follow-up studies have been performed.[8,13-15] These studies all show increased condylar alterations or progression of existing alterations during follow-up. None of these studies report the incidence of TMJ involvement during the follow-up period.
The most important growth centre of the mandible is located on the articular surface of the mandibular condyle heads, therefore destructive changes during the growth period affect mandibular development with subsequent alteration in dental occlusion and may even affect the total craniofacial growth and development, resulting in the so-called “bird-face”, associated with micrognathia.[2]
The aim of this follow-up study (TRIP 1; Temporomandibular joint Rheumatologic Involvement Project 1 year follow-up) is to report the incidence of TMJ involvement, and radiological changes during follow-up.

Patients and Methods

Patients

Initially 97 consecutive patients of the outpatient paediatric rheumatology department of the Erasmus MC Sophia Children’s Hospital, with JIA according Durban / Edmonton criteria were routinely referred for comprehensive orthodontic evaluation, the Temporomandibular joint Rheumatologic Involvement Project (TRIP 0). Consequently it was decided all patients should be evaluated once a year including OPT. In this survey (TRIP 1), patients were retrospectively included

if an evaluation with OPT was available after a minimum of one to a maximum of two years follow-up.

Methods/ Data collection

The actual total disease activity was assessed at both evaluations by the paediatric rheumatologist by using a visual analogous scale (VAS, a rising scale 0 no activity to 100 high activity). We defined the overall disease activity during the follow-up period as the mean of these two measurements and the difference between the two measurements is used as an indicator for changes in disease activity in JIA during the follow-up period. Data on the medical and orthodontic treatment were collected from the medical records.

Radiographic evaluation was acquired by means of OPTs, diagnosed according to the six categories of Rohlin's grading system.[16] The six categories are: grade 0, normal conditions; grade 1, slight abnormality; grade 2, definite early abnormality; grade 3, moderate destructive abnormality; grade 4, severe destructive abnormality; grade 5, mutilating abnormality. TMJ involvement was defined as grade 1-5. Patient information on the OPTs was blinded, and two examiners independently scored the OPTs.

Statistical Analysis

Continuous group data were summarised as means. Comparisons of categorical variables between the groups of children with and without TMJ involvement were performed by a Fisher's exact test. A *t*-test was used for continuous variables between two groups. The inter-observer variation is measured by means of Cohan's Kappa and the intraclass correlation coefficient. Incidence rate was defined as the number of new cases per patient year at risk during follow-up.

SPSS 12.0 package (SPSS-PC, Chicago, USA) was used for all data-analysis.

Results

In the TRIP 1 study 89 of the initial 97 patients were reviewed. 8 patients could not be included as no OPT was available one to two years after the TRIP 0 study. Consequently the TRIP 0 cohort was adjusted and included patients also represented in the TRIP 1 cohort. The mean interval between the consecutive OPTs was 14 months.

Patients

All subtypes of JIA were included with only a few patients diagnosed with enthesitis related arthritis (ERA), psoriatic or other arthritis, corresponding with percentages found in paediatric rheumatology populations. The population of 33 boys and 56 girls had a mean age of 11.5 years and a mean duration of the disease of 5.7 years. In table 1 the number of patients per subtype and mean age at onset per subtype are summarised.

Table 1: TMJ involvement in the TRIP 1 and adjusted TRIP 0 study (n = 89)

JIA type	Number of patients	TMJ involved		% TMJ involvement	Mean age at onset
		uni	bi	meant per subtype	(years) (range)
TRIP study	**1 = 0**	**1 / 0**	**1 / 0**	**1 / 0**	**1**
Systemic arthritis	15	2 / 4	6 / 7	53 / 73	3.9 (0.8-8.0)
Oligoarthritis					
persistent	21	4 / 6	0 / 3	19 / 43	5.5 (1.4-15.8)
extended	16	5 / 3	1 / 3	38 / 38	4.3 (1.2-12.3)
Polyarthritis RF positive	8	0 / 3	0 / 0	0 / 38	11.3 (8.8-15.4)
Polyarthritis RF negative	16	3 / 1	2 / 7	31 / 50	5.1 (1.4-10.3)
Psoriatic arthritis	3	0 / 0	1 / 1	33 / 33	7.8 (6.5-9.2)
ERA	6	1/ 1	0 / 0	17 / 17	10.6 (5.5-13.3)
Other arthritis	4	0 / 2	1 / 0	25 / 50	3.9 (2.3-8.6)
Total	89	15 / 20	11 / 21	29 / 46	5.8 (0.8-15.8)

Frequency of TMJ involvement

TMJ involvement was present in 29% of the TRIP 1 patients compared to 46% of the patients in the adjusted TRIP 0. TMJ involvement related to the different subtypes in TRIP 1 and TRIP 0 is summarised in table 1. The highest percentage of TMJ involvement, mostly bilateral, was found in systemic arthritis at both evaluations. In the oligoarthritis persistent and the polyarthritis RF negative groups the frequency of TMJ involvement was substantially decreased in TRIP 1. None of the polyarthritis RF positive patients showed alterations on the OPT anymore.

TMJ involvement was more frequent when the arthritis had a polyarticular course (35% (20/57) polyarticular course *vs* 19% (6/32) oligo-articular course p = 0.081) irrespective of the JIA onset type.

Condylar changes TRIP 1

Changes in condylar involvement between the adjusted TRIP 0 and TRIP 1 are shown in table 2. The majority of the condyles (71%) showed no differences in grades at both evaluations. Improvement of the OPT scores was seen in 40 (65%) of the 62 affected condyles. In 29 of these condyles complete regeneration of the mandibular condyle was seen, there were no signs of TMJ involvement anymore.

Worsening of the OPT scores was seen in 6 of the 62 affected condyles. Newly developed alterations on the OPTs were seen in 5 of the 116 at the moment of the first evaluation non-affected condyles.

Table 2: Changes of TMJ involvement TRIP 1 in respect of TRIP 0, scored according to the grading system of Rohlin (n = 178 condyles).

		TRIP 0					
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
TRIP 1	grade 0	**111**	23	1	0	5	0
	grade 1	2	**2**	1	1	3	0
	grade 2	0	1	**1**	0	0	0
	grade 3	2	2	0	**4**	4	0
	grade 4	1	0	0	3	**7**	2
	grade 5	0	0	0	0	0	**2**

Changes on patient basis

On a patient basis this consequently meant that 27 patients (66%) improved. No sign of TMJ involvement was detected in 19 of these patients of who previously had 14 uni- and 5 bilateral TMJ involvement. Worsening of the OPT alterations was seen in 4 patients (10%).

Newly developed TMJ alterations were seen in 4 of the 48 patients who had no TMJ involvement at the beginning of the follow-up period. This points to arthritis of the TMJ during the follow-up period. Consequently the incidence of TMJ involvement causing radiological alterations is 0.071 per patient year.

The mean VAS during the follow-up period was lower in patients with improvement on the OPT than patients with worsening of the OPT score (respectively mean VAS 10 (range 0-26) and 21 (range 3-56), p = 0.017). The mean VAS was highest in the patients who worsened more than 1 grade and who had newly developed TMJ alterations (respectively mean VAS 27 (range 9-37) and 26 (range 3-56)).

The difference between the VAS at TRIP 0 & 1 was minimal to nothing in patients with improvement of the OPT score (mean difference 0.08). In patients with

worsening of the OPT score the VAS at TRIP 1 was higher than the VAS at TRIP 0 (mean difference 5).
Orthodontic treatment with a splint was given to 27 of the 41 patients with TMJ involvement in the adjusted TRIP 0. The decision to start splint therapy was based on the severity of the TMJ involvement or on the complaints of the patient, possibly due to active arthritis. Consequently the not treated patients were those without complaints or less serious alterations on the OPT. Of the 27 treated patients 50% and of the 14 patients not treated 93% showed improvement.
Improvement or worsening of the OPT score was equally distributed among patients with an oligo- or polyarticular course.

Reproducibility of measurements
The inter-observer agreement for the OPT scores was calculated with Cohan's Kappa. The inter-observer agreement was 0.86 for the right and 0.72 for the left condyles. The intraclass correlation coefficient is 0.91 for the right and 0.97 for the left condyles.

Discussion

This follow-up study (TRIP 1) on TMJ involvement in children with JIA is the first study on incidence of TMJ involvement in JIA. In none of the earlier studies an incidence of TMJ involvement is described, depending on the methods used to define TMJ involvement it was difficult to distinct between old and recent TMJ involvement.[8,13-15] In this study with a relative short follow-up it was possible to define new condylar alterations and calculate an incidence rate. The incidence rate of TMJ involvement was 7.1% (0.071 per patient year). This relatively high incidence rate implies that the TMJ should be included in routine examination of the patient and should be considered when choosing a therapeutic regimen. However as TMJ involvement can be without symptoms or signs, radiological examination on a regular basis is necessary.[17]
Another important finding in this study is the regenerative capacity of the TMJ and its relation to the disease activity. The number of patients with TMJ involvement has decreased with 17% compared to the previous evaluation (29% *vs.* 46% TMJ involvement). This points at a regenerative capacity of the mandibular condyle, which has not been described before in JIA patients.
Comparison with other studies is difficult as in none of the studies on follow-up of TMJ involvement the OPT scores were compared. None of the other

follow-up studies using different techniques to define TMJ involvement describe improvement or regeneration during follow-up. In the MRI follow-up study of Küseler et al. synovial enhancement and joint fluid fluctuate over time. Condylar erosions however remain stable or aggrevate over time.[15] Rönning *et al*. only describe new developed TMJ involvement or aggravated TMJ involvement during the 3-year observation period.[8]

The decrease of TMJ involvement with 17% can be explained by the fact that all patients who improved had a low VAS during follow-up, meaning that their disease was not in an active phase. On the other hand children who showed worsening of the OPT score were in an active phase of their disease. Therefore it can be concluded that the course of the disease, the disease activity and severity, is reflected in TMJ involvement.

What specific orthodontic treatment, besides the general anti-rheumatic medication, has contributed to the improvement is uncertain. Improvement was seen in both the patients with and without splint treatment. As the decision to start splint therapy was also based on the complaints of the patient, the two groups are not comparable and further prospective research will be necessary to determine the effect of splint treatment on TMJ involvement in JIA. Recently data is available on intra-articular injections in arthritis of the TMJ in JIA patients.[18] None of the patients in this study were treated with intra-articular injections and still a great number of patients showed improvement. Intra-articular injections can be considered especially if only the TMJ is involved. In all other patients the systemic therapy should be in accordance with all other involved joints, including the TMJ.

The TRIP studies showed that young age at onset and a long duration of the disease are risk factors for developing TMJ involvement.[12] Patients with systemic JIA, oligoarticular extended JIA and RF negative polyarticular JIA have an increased risk on TMJ involvement. All these patients have a polyarticular course; this enlarges the chance on TMJ involvement. However if TMJ involvement is present the chances of improvement or worsening is irrespective of the oligo- or polyarticular course of the arthritis.

Improvement and regeneration was seen in patients with both minor and severe lesions on the OPT, hence in all grading categories. Together with the high level of the reproducibility tests this indicates that the changes found cannot be contributed to grading differences.

This study has its limitations. Nowadays MRI with gadolinium is the golden standard for diagnosing TMJ involvement. MRI is a more sensitive method for diagnosing and evaluating TMJ arthritis than OPT. The incidence reported here could be an

underestimation as early stages in TMJ arthritis are not expressed in the OPT. However we chose the OPT because it is less expensive, there is no need for sedating young patients and OPTs are widely used in most dental and orthodontic clinics and therefore the best tool for routine evaluations of the TMJ.
A selection bias could have occurred as not all patients were represented in this follow-up study. However the number of missing patients is almost equally divided among the subtypes and the TMJ status in TRIP 0.
The incidence rate should be calculated in a cohort of patients with newly diagnosed JIA at start of the study (an inception cohort), however the incidence rate calculated here is a good proxy of the "real" incidence rate.
Acknowledging arthritis of the TMJ is important since it does not only arise to aesthetic problems, like the well known "bird-face" appearance, but it can also lead to oral health problems, and difficulty in chewing and intubating.

Conclusions

In this cohort the incidence of TMJ involvement was 7.1%. This study also demonstrates a regenerative capacity of the TMJ. Condylar improvement seems to be associated with a low disease activity. Therefore it is important to imply the TMJ in the routine examination of the patient and to consider the TMJ involvement when deciding on a therapeutic regimen.

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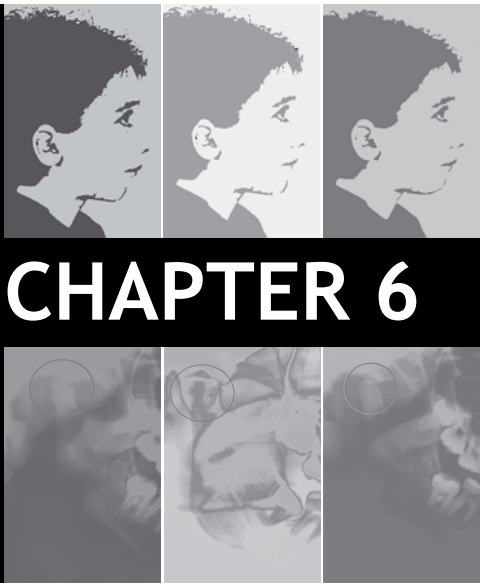
Long-term follow-up of the Temporo-mandibular joint in Juvenile Idiopathic Arthritis



CHAPTER 6

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Abstract

Objective: Temporomandibular joint (TMJ) involvement is a frequent feature in cross-sectional prevalence studies among Juvenile Idiopathic Arthritis (JIA) patients. In this follow-up study patients were reviewed after five years to study the course of TMJ involvement in relation to disease characteristics.

Methods: Children with JIA from a previous study on TMJ involvement were included. A rheumatologic evaluation including the PRINTO-score, and orthodontic evaluation including an orthopantomogram (OPT) were performed. OPTs were scored according Rohlin's grading system (grade 0-5).

Results: The overall prevalence of patients with condylar alterations decreased from 49% to 40%. Improvement of the alterations was seen in 69% of the initial affected condyles, and consequently improvement was seen in 83% of the initial affected patients. Normalisation of the alterations was seen in 67% of the improved condyles, and consequently in 44% of the patients. This proves a regenerative capacity of the condyle. Improvement was related to a low disease activity and a less extensive therapeutic regimen.

Conclusion: In patients with JIA condylar alterations can improve and even regenerate. Condylar improvement is associated with a low disease activity.

Key words: Juvenile Idiopathic Arthritis, JIA, Temporomandibular joint, TMJ

Introduction

Juvenile Idiopathic Arthritis (JIA) is a term to indicate a disease of childhood characterised primarily by arthritis persisting for at least six weeks, starting before the sixteenth birthday. JIA is divided into seven subtypes based on clinical symptoms during the first six months of the disease.[1] These subtypes all have a different initial presentation, course and prognosis of the disease.[2]

All joints can be involved in JIA, including the temporomandibular joint (TMJ). One or both TMJs can be involved in JIA, early or late in the course of the disease, and can even be the initial joint to be involved.[3,4] Diamantberger first described mandibular underdevelopment in patients with JIA in 1890.[5] Since then the reported frequency of TMJ involvement varies in the literature from 17% to 87% and depends upon the population investigated, subtypes of JIA represented and the diagnostic methods used.[6,14]

Most studies describe more bilaterally affected TMJs in JIA, although it should be noted that in 27-50% of the patients with TMJ involvement only one of the TMJs is initially involved.[6,14,15]

The most important growth centre of the mandible is located on the articular surface of the mandibular condyles head, therefore destructive changes during the growth period affect mandibular development with subsequent alteration in dental occlusion and may even affect the total craniofacial growth and development, resulting in the so-called “bird-face”, micrognathia.[6]

The few follow-up studies performed, showed an increased frequency of TMJ involvement during follow-up, and progression of the existing condylar alterations.[3,10,16,17]

The Temporomandibular joint Rheumatologic Involvement Project (TRIP) was initiated as most studies on TMJ involvement in JIA patients were selected based on different criteria, such as onset type, age, disease course and sometimes even TMJ status, and only a few follow-up studies were performed.[3,4,6-17] Also the insights in the treatment of JIA have changed markedly in the past 15 years.[18]

The patient cohort of the TRIP studies is based on a cross-sectional population of 97 consecutive patients representing all subtypes of JIA. In the initial study (TRIP 0), the frequency of TMJ involvement diagnosed with an orthopantomogram (OPT) was 45%.[14] TRIP 1 (one year later) reported a yearly incidence of 7%, and a decrease in the frequency of TMJ involvement, and consequently an improvement of condylar lesions was noticed.[19]

The aim of the TRIP 5 follow-up survey was to study, longitudinally, the course of condylar alterations in relation to disease characteristics after 5 years of follow-up.

Patients and Methods

Patients

In TRIP 0, 97 consecutive patients with JIA according to the Edmonton criteria were routinely referred for a comprehensive orthodontic evaluation. These patients were reviewed 5 years later (TRIP 5) to evaluate changes in condylar alteration during follow-up.

Patients of the initial cohort were included if a rheumatologic evaluation and an orthodontic evaluation with OPT were available at both evaluations. The Medical Ethical Committee (MEC) of the Erasmus MC – University Medical Centre Rotterdam approved the study, and written consent was obtained from all patients.

Methods

Radiographic examination

Standardised radiographic evaluation was acquired by means of OPTs. The OPTs were scored using the six categories of Rohlin's grading system.[20] These six categories are: grade 0, normal conditions; grade 1, slight abnormality; grade 2, definite early abnormality; grade 3, moderate destructive abnormality; grade 4, severe destructive abnormality; grade 5, mutilating abnormality. TMJ involvement was defined as grade 1-5. Two "blinded" examiners independently scored the OPTs.

Disease activity

The PRINTO (Pediatric Rheumatology International Trail Organisation)- score, also referred to as the ACR 30, was used as parameter for disease activity in TRIP 5. The PRINTO-score is an international validated measure for disease activity, and exists of the following six items: 1) global assessment of the severity of the disease by the physician by means of a visual analogous scale (VAS), 2) global assessment of pain and overall wellbeing by the patient or parent by means of a VAS, 3) functional ability by means of the Childhood Health Assessment Questionnaire (CHAQ), 4) number of "active" joints (joints with swelling not due to deformity), 5) number of joints with limitation of motion, 6) Erythrocyte Sedimentation Rate (ESR).[21]

Statistical analysis

Continuous group data were summarised as means. Comparisons of categorical variables between the groups of children with and without TMJ involvement were performed by a Fisher's exact test. A *t*-test was used for continuous variables and

the chi-square for ordinal values between groups. SPSS 12.0 package (SPSS-PC, Chicago, USA) was used for all data-analysis.

Results

General results

In TRIP 5, 84 (87%) of the initial 97 patients were reviewed, 31 boys and 53 girls. Thirteen (13%) patients could not be included, 8 (62%) were not willing to cooperate, 3 (23%) could not be traced, and 2 (15%) lived abroad. Consequently the TRIP 0 cohort was adjusted to included only patients also represented in the TRIP 5 cohort. The mean interval between the consecutive evaluations was 5.7 years (range 4.1 yr - 6.8 yr).

Table 1: TMJ involvement in the TRIP 5 and adjusted TRIP 0 study (n = 84).

JIA type	Nr of patients	TMJ involved uni	bi	% TMJ involvement	Mean age at onset (yrs (range))
TRIP study	**5=0**	**5 / 0**	**5 / 0**	**5 / 0**	**5**
Systemic	15	4 / 4	5 / 7	60 / 73	3.8 (0.8 – 8)
Oligo					
persistent	20	6 / 6	1 / 3	35 / 45	5.8 (1.4 – 15.8)
extended	15	6 / 4	2 / 3	53 / 46	4.8 (1.5 – 12.3)
Poly RF pos	6	0 / 2	0 / 0	0 / 33	10.6 (9.17 – 12.5)
Poly RF neg	14	5 / 1	2 / 7	50 / 57	4.7 (1.25 – 10.3)
Psoriatic arthritis	3	1 / 0	0 / 1	33 / 33	8.6 (7.5 – 9.2)
ERA	7	0 / 1	0 / 0	0 / 14	9.7 (4.1 – 13.3)
Undifferentiated	4	2 / 2	0 / 0	50 / 50	3.6 (1.2 – 8.5)
Total	84	24 / 20	10 / 21	40 / 49	5.8 (0.8 – 15.8)

Patients

All subtypes of JIA were included, corresponding with percentages found in a Dutch paediatric rheumatology population. 52 (62%) of the 84 patients were still visiting the outpatient department of rheumatology and / or orthodontics, 25 patients were visiting both departments, 17 only the rheumatology department, and 10 only the orthodontic department. Of the 42 (38%) patients no longer visiting the rheumatology department, 25 patients were released out of follow-up, and 17 patients were referred to another rheumatologist, mainly a rheumatologist for adults. In TRIP 5 the mean age of the cohort was 15.9 years (range 8.3-4.7 yrs) and a mean period since the diagnosis of 10.2 years (range 6.3-18.9 yrs). Table 1 shows the number of patients per subtype and mean age at onset per subtype.

Frequency of TMJ involvement

TMJ involvement was present in 40% of the patients at TRIP 5 compared to 49% of the patients at TRIP 0. Table 1 summarises TMJ involvement per subtype in TRIP 0 & 5. At both evaluations the highest percentage of TMJ involvement was found in the patients with systemic JIA. None of the polyarticular RF positive patients showed condylar alterations at TRIP 5 anymore.

Condylar alterations in TRIP 0 & 5 were more frequent if the arthritis had a poly-articular course (more than 5 joints involved) irrespective of their JIA onset type (TRIP 0; 58% in poly-articular course *vs.* 36% in oligo-articular course, p = 0.04, TRIP 5; 50% in poly-articular course *vs.* 38% in oligo-articular course, p = 0.03).

Table 2: Patients characteristics in patients without and with TMJ involvement in respectively TRIP 0 and TRIP 5.

Characteristics TRIP 0	**Patients TMJ non-involved (n = 43)**	**TMJ involved (n = 41)**	**p-value**
Female gender*	25 (58)	28 (68)	0.23
Age at onset(years)^	6.7 (1.2 – 15.8)	4.7 (0.8 – 13.1)	0.04
Duration of disease^	4.1 (0.6 – 9.9)	4.9 (0.6 – 12)	0.20
Age (years)^	10.8 (2.8 – 17.2)	9.6 (3.3 – 18.8)	0.24
Characteristics TRIP 5	**TMJ non- involved (n = 50)**	**TMJ involved (n = 34)**	**p-value**
Female gender*	33 (66)	20 (59)	0.33
Age at onset(years)^	6.7 (1.2 – 15.8)	4.3 (0.8 – 9.5)	0.01
Duration of disease^	9.4 (6.3 – 18.8)	11.2 (6.8 – 17.5)	0.02
Age (years)^	16.1 (8.4 – 24.1)	15.6 (8.3 – 24.7)	0.65
PRINTO-score			
VAS physician^	6.9 (0 – 82)	14.1 (0 – 83)	0.02
VAS well-being^	14.5 (0 – 98)	13.9 (0 – 57)	0.53
CHAQ^	0.5 (0 – 3.0)	0.5 (0 – 3.0)	0.71
Active joints^	0.9 (0 – 19)	2 (0 – 18)	0.42
Limited joints^	1.5 (0 – 11)	4.2 (0 – 21)	0.03
ESR^	13.5 (0 – 74)	12.9 (3 – 60)	0.37

* Absolute number (percentage) ^ mean (range)

Table 2 summarises patient characteristics of the patients without and with TMJ involvement in TRIP 0 and patient characteristics of patients without and with TMJ involvement in TRIP 5. In both TRIP 0 & 5 patients with TMJ involvement were younger at onset than patients without involvement (resp p = 0.04 and p = 0.01).

The patients with still present condylar alterations in TRIP 5 had a significantly longer duration of the disease than patients without condylar alterations in TRIP 5 (p = 0.02), this in contrast with TRIP 0 (p = 0.20). Apparently the patients who normalised during follow-up had a relatively shorter duration of the disease than the patients with remaining condylar alterations.

Unilateral and bilateral involvement

Both condyles (*i.e.* bilateral involvement) showed alterations in 21 (51%) of the 41 patients with condylar alterations in TRIP 0, and in 10 (29%) of the 34 patients with condylar alterations in TRIP 5. Normalisation of the condylar alterations (*i.e.* no condylar alterations present in TRIP 5) was seen in 12 (60%) of the 20 patients with unilateral involvement in TRIP 0, and in 3 (14%) of the 21 patients with bilateral involvement in TRIP 0 (p = 0.003). Nine (43%) of the 21 bilateral involved patients in TRIP 0 improved, and showed unilateral involvement in TRIP 5, leading to an increase in the overall prevalence of the unilateral involved patients in TRIP 5.

Condylar changes

In TRIP 5 the number of condyles without alterations increased from 106 of the 168 condyles to 124 of the 168 condyles (resp. 63% to 74%, p = 0.00). Table 3 shows the Rohlin score changes for each condyle during follow-up. Stable non-affected condyles were seen in 92% (97/106), and new developed condylar alterations were seen in 8% (9/106) of the initially non-affected condyles. Persistent identical alterations in TRIP 0 & 5 were seen in 21% (13/62) of the initial affected condyles, worsening was seen in 10% (6/62) of the initial affected condyles, and improvement was seen in 69% (43/62) of the initially affected condyles. Normalisation of the alterations was seen in 63% (27/43) of the improved condyles in TRIP 5; hence the condyles were regenerated.

Table 3: Changes of condylar alterations in TRIP 5 in respect of TRIP 0, scored according Rohlin's grading system (n = 168).

		TRIP 0					
		Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
TRIP 5	grade 0	97	19	2	2	3	1
	grade 1	3	3	0	1	5	1
	grade 2	2	3	0	2	1	0
	grade 3	3	1	1	3	6	0
	grade 4	1	1	0	0	6	0
	grade 5	0	0	0	0	0	1

Changes in TMJ involvement on a patient level

Comparing the alterations on the OPT in TRIP 5 with TRIP 0 showed, 36 (43%) patients with stable normal condyles, 34 (40%) patients with improvement of the condylar alterations, 5 (6%) patients with identical condylar alterations, and 9 (11%) patients with worsening of the condylar alterations. 15 (44%) of the 34 patients with improvement of the initial condylar alterations showed no alterations in TRIP 5 anymore, the condylar alterations were normalised.

Improvement of condylar alterations was seen in 83% of the initial 41 involved patients and in all the different subtypes of JIA; 73% of the patients with systemic JIA, 78% of the patients with oligoarticular persistent JIA, 100% of the patients with oligoarticular extended JIA, 100% of the polyarticular RF positive JIA, 88% of the patients with polyarticular RF negative, 100% of the patients with ERA and psoriatic arthritis, and 50% of the patients with undifferentiated JIA. Patients with improvement of the condylar alterations had a mean age of 15.7 years (8.4-24.7 yrs), mean age at onset of the disease of 5.0 years (1.2-11.8 yrs), and a mean duration of the disease of 10.7 years (6.3-17.5 yrs).

Disease severity

Disease severity and activity in the past were assessed by means of drug intervention used as therapy between TRIP 0 & 5. TMJ involvement is seen more in patients with an extensive therapeutic regimen during this 5-year follow-up period. Patients requiring no treatment anymore or only NSAIDs (n = 26), patients with NSAIDs and DMARDs (n = 19), patients with NSAIDs, DMARDs and immunosuppressive drugs (n = 27), and patients with NSAIDs, DMARDs, immuno-suppressive drugs and biologicals (n = 12) showed respectively 21%, 26%, 60% and 67% TMJ involvement in TRIP 5. Treatment as a sign of disease activity showed a linear by linear association with condylar involvement (p=0.002). If therapy consisted of immunosuppressive drugs and biologicals chances on TMJ involvement increased 5-fold (odds ratio (OR) 5.38) compared with patients treated with no medication, NSAIDs and/or DMARDs.

Another method for assessing disease activity is by means of the PRINTO-score. All items of the PRINTO-score in TRIP 5 showed low mean values; mean VAS physician 9.77 (range 0-83); mean VAS well-being 14.2 (range 0-98); mean CHAQ 0.5 (range 0-3.0); mean joints with active disease 1.32 (range 0-19); mean joints with limited motion 2.55 (range 0-21); ESR 13 (range 0-74), indicating a mean low disease activity in all the patients. If comparing the items of the PRINTO-score in patients with and without TMJ involvement, a significant difference in the VAS physician and the number of joints with limited motion is noticed (see Table 2).

Table 4: Symptoms in the adjusted TRIP 0 related to TMJ involvement in patients with JIA (n=84) in TRIP 0 and 5

Signs	Patients with signs in adjusted	Patients with TMJ Involvement (%)		Odds Ratio		95% Confidence Interval		p-value	
	TRIP 0 (%)	TRIP 0	TRIP 5	TRIP 0	TRIP 5	TRIP 0	TRIP 5	TRIP 0	TRIP 5
Noticed by the patient									
Limited chewing ability	8 (10)	7 (88)	7 (88)	8.91	13.2	1.0 – 76.1	1.5 – 113.1	0.022	0.006
Limited maximal mouth opening	8 (10)	6 (75)	6 (75)	3.7	5.5	0.7 – 19.7	1.0 – 29.4	0.103	0.036
Pain	11 (13)	7 (64)	6 (75)	2.01	1.93	0.54 – 7.45	0.54 – 6.92	0.23	0.24
Pain during jaw excursion	9 (11)	7 (64)	6 (55)	4.2	6.22	0.82 – 21.7	1.21 – 32.1	0.07	0.021
Clicking/ crepitation	18 (21)	12 (67)	7 (39)	2.6	0.92	0.86 – 7.62	0.32 – 2.67	0.074	0.55
Mouth breathing	20 (24)	16 (80)	15 (75)	1.94	2.93	0.69 – 5.4	1.04 – 8.27	0.153	0.036
Orthodontic examination									
Asymmetric opening / protrusion	20 (24)	16 (80)	15 (75)	7.0	7.1	2.0 – 23.9	2.3 – 23.5	0.001	0.000
Absence of translation	22 (26)	17 (77)	15 (68)	5.6	5.1	1.8 – 17.3	1.74 – 14.67	0.001	0.002
Clicking / crepitation	16 (19)	10 (63)	9 (56)	1.44	2.2	0.65 – 6.09	0.73 – 6.7	0.174	0.126

Clinical signs of TMJ involvement

In Table 4, clinical signs noticed by the patient and orthodontist during examination in TRIP 0 are summarised. These signs were even more significantly associated with TMJ involvement in TRIP 5 than in TRIP 0. Signs are not frequently present in patients with JIA, however if present they are more common in patients with (persistent) TMJ involvement during follow-up (see Table 4). Especially complaints of limited jaw function, such as limited chewing ability, limited maximal opening, and pain during jaw excursion in the past are indicators for TMJ involvement. Also patients with mouth breathing in TRIP 0 were significantly more present in the group with condylar alterations in TRIP 5.

Discussion

In this 5-year follow-up study of paediatric patients including all subtypes of JIA according to the Edmonton criteria, a decrease in the frequency of TMJ involvement from 49% to 40% was observed. 83% of the patients with TMJ involvement in the initial cross-sectional survey showed improvement of the condylar alterations. 44% of these patients with improvement of the condylar alterations did not show any condylar alteration (Rohlin grade 0) in TRIP 5 anymore. This is suggestive for a regenerative capacity of the condyle. In the literature the few follow-up studies on TMJ involvement in patients with JIA all show progression of the condylar alterations[3,10,16,17], except the one-year follow-up study of the cohort described in this paper (TRIP 1).[18] The frequency of TMJ involvement among the different subtypes was according to the distribution in TRIP 0, with the highest prevalence in patients with a systemic JIA. The TRIP 5 study also confirms an increased chance of TMJ involvement in patients with a polyarticular course of the arthritis and a long duration of the disease.

Patients with a polyarticular RF positive JIA had a relatively low frequency of TMJ involvement in TRIP 0. Surprisingly none of the polyarticular RF positive patients showed TMJ involvement in the TRIP 5 study anymore. This is remarkable, as this subtype of JIA is known for its erosive destructive character. This subtype is, however, also known for it's late-onset, and in our initial survey we postulated that the condyle is less vulnerable in older patients than in young patients.[14] This late-onset is the reason for the low frequency of TMJ involvement in this group. This postulation is also supported by the fact that patients with TMJ involvement have a much earlier onset than patients without involvement.

Patients with a low disease activity, measured indirectly by means of drug use or PRINTO-score show more improvement of the TMJ than patients with a high disease activity. The TMJ appears to act in the same way as all the other joints that may be involved in JIA. Arthritis of the TMJ can develop individually in each condyle, and TMJ involvement is frequently asymmetrical in patients with JIA. A quiet phase of the disease can lead to normalisation in function and growth of the joint. As a low disease activity can be induced by means of drug treatment, the TMJ should be included when deciding on a therapeutic regimen. All patients in our study were treated with systemic drugs; no local intra-articular injections were given. Intra-articular injections can be used, especially if the TMJ is the only joint with active arthritis.

During the past two decades the insights in the treatment regimen for JIA, and consequently the treatment have changed markedly. The greatest change is the tendency to switch to second-line anti-rheumatic drugs earlier in the course of the disease in accordance with the subtype represented. The treatment has shifted gradually from chasing failure (gradual add-on approach) to early aggressive therapy.[18] This early aggressive therapy will probably lead to a low disease activity earlier in the course of the disease, and might explain why condylar improvement has not been observed in studies performed in the past.

In the initial study we observed that clinical signs are scarce, but if present the chance on TMJ involvement increases.[14] However, if signs were absent chances on TMJ involvement were still high. In TRIP 5 we observed that patients with signs of TMJ involvement in TRIP 0 had an increased chance on TMJ involvement in TRIP 5, or otherwise stated the prognosis of these patients with regard to the condylar alterations is worse than patients without clinical signs. So these clinical subjective signs for condylar alterations noticed by the patient are important predictors for TMJ involvement and the course of condylar alterations. Altogether these symptoms alone are not capable of making a distinction between absence or presence of condylar alterations; a radiological examination remains necessary.

This study has limitations. Nowadays MRI is considered to be the golden standard to diagnose TMJ involvement, however MRI has shortcomings, including the necessity for sedation in small children, and much increased costs. MRI is not available in all orthodontic and dental practices as is the OPT. The OPT is a good diagnostic tool to evaluate erosive alterations. As the kappa-statistics for the intraobserver and interobserver agreement is high for the Rohlin scores, this method is a useful tool in the follow-up of erosive changes in all patients with JIA.[12]

A selection bias could have occurred as not all patients included in the initial cohort were represented in this follow-up study. However the number of missing patients is almost equally divided among the subtypes and the TMJ status in TRIP 0.
Acknowledging arthritis of the TMJ in JIA is important since it does not only arise to growth disturbances of the mandible with consequently aesthetic problems, like the well known “bird-face” appearance, but it can also lead to oral health problems, like difficulty in chewing and can give problems with intubating.

Conclusions
This study shows a drastic improvement of the condylar alterations as determined on the OPT, and even normalisation of the condyle was observed. This proves a regenerative capacity of the condyle. Improvement was seen in all subtypes of JIA, and mostly in patients with a low disease activity. Controlling JIA with systemic drugs is important for the improvement of condylar alterations.

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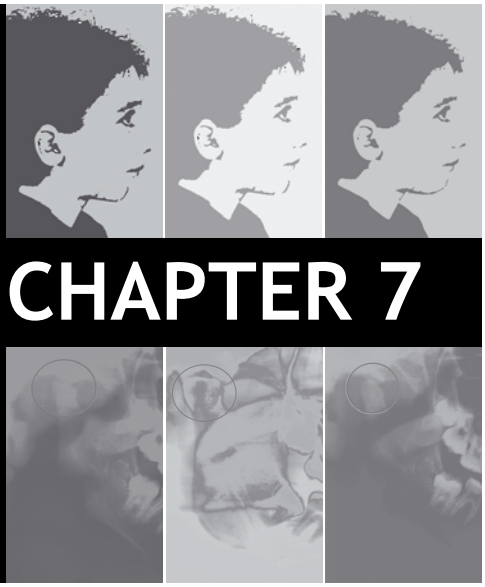
Facioskeletal changes in children with Juvenile Idiopathic Arthritis



CHAPTER 7

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Abstract

Objective: To investigate the facioskeletal morphology in patients with juvenile idiopathic arthritis (JIA) with and without temporomandibular joint (TMJ) involvement.

Methods: Eighty-five patients were included. TMJ involvement was defined by orthopantomogram alterations. Lateral cephalograms were used to determine linear and angular measurements and occlusion.

Results: Patients regardless of their TMJ status had a 67% chance for retrognathia and a 52% chance for posterior rotation of the mandible and, respectively, 82% and 58% if TMJ involvement were present. Changes were not uniformly distributed among the different subtypes.

Conclusion: Patients with JIA have an altered facial morphology, especially in the presence of TMJ involvement.

Introduction

Juvenile idiopathic arthritis (JIA) is characterised by arthritis persisting for at least 6 weeks and onset before the 16th birthday and might affect several joints, including the temporomandibular joint (TMJ).[1]
The TMJ can be affected both uni-and bilaterally, early or late in the course of the disease, and it can even be the first joint affected. The reported prevalence of TMJ involvement varies from 17% to 87% depending on the population investigated, the subtypes of JIA represented and the radiological method by which involvement is diagnosed.[2-6] In a survey representing all subtypes of JIA, the prevalence of TMJ involvement diagnosed with an orthopantomogram (OPT) was 45%.[7] Arthritis of the TMJ results in reduced mandibular growth and subsequent alteration in dental occlusion and may even affect the total craniofacial growth.[2-5]
Alterations in the craniofacial structure of patients with JIA have been described in several studies.[5,8-12] Patients with JIA demonstrated retrognathia and increased mandibular posterior rotation. Usually the characteristic facial morphology has been associated with condylar destruction.[5,8-12]
Most studies were performed in the oligo- and polyarticular subtype with more rethrognathia and posterior rotated mandibles in the polyarticular subtype.[5,8,9] Only one study reported a mild downward and backward rotation of the mandible in the systemic subtype.[11]
The purpose of this study was to determine the influence of arthritis of the TMJ on facioskeletal morphology in a cohort representing all subtypes of JIA.

Patients and methods

Patients

In a 6 month period all children with JIA, according to the Durban criteria, who visited the paediatric rheumatology clinic of the Erasmus MC Sophia Children's Hospital, were routinely referred for orthodontic evaluation, even in absence of complaints. The initial 97 consecutive children were reviewed to evaluate the prevalence of TMJ involvement. Patients with both OPT and lateral cephalogram available were included.

Methods

Radiographic examination

A standardised radiographic examination was carried out by means of lateral cephalograms and OPTs. All lateral cephalograms were digitized with an Epson 1680 Pro scanner (Epson, Long Beach, USA) and traced with QuickCeph 2000 software (Quick Ceph, San Diego, USA). The following values were measured using the lateral cephalograms (see figure 1): ANB, indicating the discrepancy between maxilla and mandible, and GO-GN to S-Na and OP to S-Na, both evaluating the divergency of the maxilla and mandible.[13]

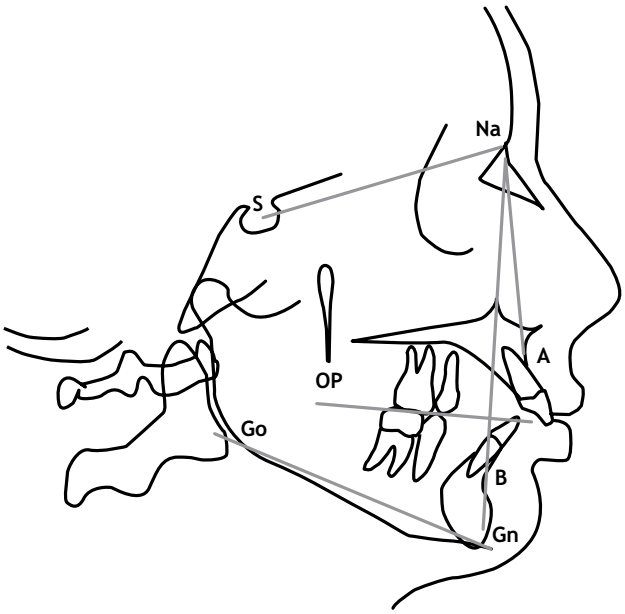

Figure 1: Tracing of a lateral cephalogram. Retrognathia is determined by ANB angle (S-Na-A minus S-Na-B) and posterior rotation of mandible is determined by mandibular plane to cranial base angle (Go-Gn to S-Na) and occlusal plane to cranial base angle (OP to S-Na).

The OPTs were used to determine TMJ involvement and to measure mandibular rami lengths.

TMJ involvement was diagnosed using the six categories of Rohlin: grade 0, normal conditions; grade 1, slight abnormality; grade 2, definite early abnormality; grade 3, moderate destructive abnormality; grade 4, severe destructive abnormality and grade 5, mutilating abnormality.[14]

Some films showed magnification owing to incorrect placement of patients during the X-ray examination, therefore left/right ratios were used instead. Differences between left and right mandibular length were calculated using the formula: [(R-L)/(R-L)] x 100%. Differences > 3% are due to asymmetries of the mandibular

condyle or ramus height, while differences < 3% are caused by technical failures.[15] Therefore asymmetry of the mandible was defined as a rami length difference of > 3%.

Cephalometric standards

Control data for the cephalometric measurements of patients 6-16 years were obtained according to sex and age, based on Riolo *et al.*[16] Normal values for patients older than 16 years were based on Steiner.[17] Posterior rotation of the mandible was defined as the mean + 2 SD of GO-GN to S-Na and OP to S-Na. Retrognathia was defined as a mean ANB value of >4 degrees.

Statistical analysis

SPSS version 12.0 for Windows (SPSS-PC, Chicago, USA) was used for data analysis. To compare differences in means between the group with and without TMJ involvement Student's *t*-test was used for continuous variables and a χ^2 test for ordinal values.

Results

Of the initial cohort, 12 patients were excluded owing to technical failures of the cephalogram (n = 10) and OPT (n = 2). All necessary information was available for 85 patients.

Table 1 summarises information on TMJ involvement, uni- or bilaterally, divided according to subtype. According to the grading system of Rohlin 38 of the 85 patients (45%) had TMJ involvement; 18 patients had unilateral involvement and 20 bilateral involvement.

The only difference found between the different subtypes was age at onset (mean 6.0 years); patients with the polyarticular subtype were 2.7 and 3.5 years older than the oligoarticular and systemic subtypes. The mean duration of the disease was 4.9 years, with minimal differences among the different subtypes. The subtype distribution found in this study is in agreement with the distribution found in a regular paediatric rheumatology department.

As in previous reports, more girls than boys were represented (respectively, 50 and 35). TMJ involvement was almost equally distributed between girls and boys (respectively, 48 and 40 %).

Tabel 1: JIA subtype distribution and TMJ involvement.

JIA subtype		TMJ involvement (%)		
	n (%)	total	unilateral	bilateral
Systemic	14 (17)	10 (71)	3 (30)	7 (70)
Oligoarticular*	38 (45)	15 (40)	8 (53)	7 (47)
Polyarticular RF pos	6 (7)	3 (50)	3 (100)	0 (0)
Polyarticular RF neg	14 (17)	7 (50)	2 (29)	5 (71)
ERA	8 (9)	1 (13)	1 (100)	0 (0)
Psoriatic arthritis	2 (2)	1 (50)	0 (0)	1 (100)
Other	3 (4)	1 (33)	1 (100)	0 (0)
Total	85 (100)	38 (45)	18 (47)	20 (53)

* 34 oligo-articular persitent and 4 oligo-articular extended

Cephalometric analysis

Retrognathia was present in 57/85 (67%) patients with JIA. This percentage was higher in patients with TMJ involvement (31/38 (82%)) than in those without TMJ involvement (26/47 (55%)). On average, ANB was 1.8 ($p = 0.001$) degrees greater in patients with TMJ involvement than in patients without TMJ involvement.

Posterior rotation was present in 44/85 (52%) patients with JIA according to GO-GN to S-Na and in 60/85 (71%) according to OP to S-Na. Posterior rotation measured by OP to S-Na was equal in patients with and without TMJ involvement (71% and 70%). GO-GN to S-Na showed that the mandibles were more posteriorly rotated in patients with TMJ involvement than in those without (58% *vs.* 47%).

The three large subgroups -namely, systemic onset arthritis, oligoarticular arthritis, and polyarticular arthritis (including rheumatoid factor (RF) positive and negative), were used to study the influence of subtype. Comparison between patients within these subtypes showed that retrognathia was most often found in patients with polyarticular JIA (75%), followed by the patients with oligoarticular (68%) and systemic disease (64%).

Posteriorly rotated mandibles were more common in the systemic subtype (93%) than in the polyarticular and oligoarticular subtypes (65% and 63%) when measured by OP to S-Na. Measured by GO-GN to S-Na, posterior rotation was also most frequent in the systemic type (79%), followed by the oligoarticular type and polyarticular types (45% and 45%) of JIA.

The intraobserver agreement measured by κ statistics was 0.79 for ANB, 0.55 for GO-GN to S-Na, and 0.53 for OP to S-Na. The interobserver agreement was 0.85 for ANB, 0.59 for GO-GN to S-Na, and 0.44 for OP to S-Na.

Analysis of orthopantomograms

Mandibular asymmetry was seen in 23/85 (27%) patients. Asymmetry was more common in patients with TMJ involvement than in those without TMJ involvement (37% *vs.* 19%, p = 0.07). No difference in asymmetry was found between patients with unilateral and bilateral involvement (39% *vs.* 37%). Of the 20 patients with bilateral condylar involvement, seven had disproportionate TMJ involvement –that is, one condyle was more severe affected than the condyle on the other side. Of these seven patients with disproportionate involvement, five also showed asymmetry. In patients with proportional bilateral involvement two patients also showed asymmetry.

Discussion

In our survey, patients with JIA, regardless of their TMJ status, had retrognathia and more posterior rotated mandibles than age matched healthy subjects previously reported.[16,17] In agreement with the published reports, we also found that retrognathia and posterior rotation is more common in patients with TMJ involvement.[8,10,11,12] However, in these studies no patients with JIA without TMJ involvement were compared with age matched healthy subjects. Our study also found retrognathia and posterior rotation of the mandible in patients without TMJ involvement, which might be explained by TMJ alterations that were not yet detectable at OPT at the time of evaluation. On the other hand, these patients might have had TMJ alterations earlier, which were no longer detectable on radiographs.

Our study provides a unique possibility to compare the three major subtypes of JIA. Among these subtypes, retrognathia and posterior rotation of the mandible were not uniformly distributed. Retrognathia is most common in the polyarticular subtypes, closely followed by the oligoarticular and systemic subtype. Posterior rotation of the mandible is more common in the systemic subtype. The only study performed with patients with systemic JIA also describes more downward and backward rotated mandibles.[11] No study has compared patients with systemic JIA with patients with oligo- and polyarticular disease. We found no difference in the prevalence of posteriorly rotated mandibles between the patients with oligo- and polyarticular JIA.

In agreement with published reports, we found more retrognathia in the polyarticular subtype than the oligoarticular subtype (75% *vs.* 68%).[6,8,10] However, as no actual percentages of retrognathia were defined in the other studies, no

comparison with our study was possible.
In our survey, posterior rotation is measured in two different ways, giving different results. This discrepancy might be explained because the angle OP to S-Na takes the occlusion into account. Variation of the occlusal plane was believed to be too great because most of our patients had mixed dentitions, resulting in a temporarily altered occlusal plane owing to shedding of primary teeth.
Patients with TMJ involvement have more mandibular asymmetry than patients without TMJ involvement. Although this finding was not significant, this trend might help as a diagnostic tool for TMJ involvement. As the κ statistics for intra- and interobserver agreement is high for ANB, tracing is a useful tool for retrognathia.
In contrast with our expectations, we found no difference in asymmetry between unilateral and bilateral affected patients. This is because the bilateral disproportionate group (that is, one condyle was more severely affected than the condyle on the other side) also showed mandibular asymmetry.
Besides facioskeletal changes, arthritis of the TMJ also leads to difficulty with chewing, oral health problems (for example, caries), problems with intubations and aesthetic problems.
In conclusion, patients with JIA are more likely to exhibit retrognathia and posterior rotation of the mandible in the presence of TMJ involvement. Hence retrognathia and posterior rotation might serve as a predictor for TMJ involvement in patients with JIA.

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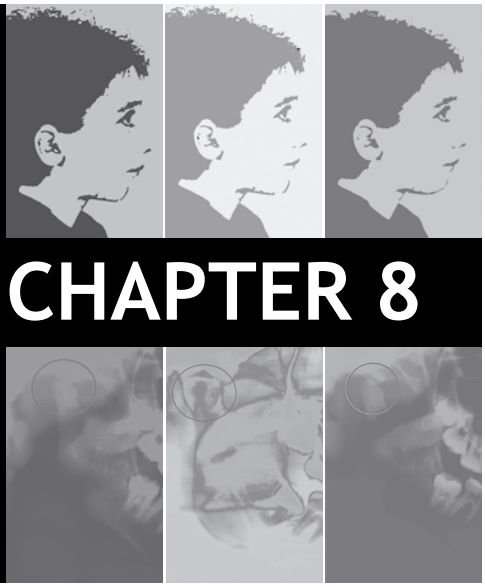
Facioskeletal morphology in Juvenile Idiopathic Arthritis; changes in relation to condylar alterations



CHAPTER 8

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Submitted

Abstact

Objective: To investigate facioskeletal morphology in relation to condylar alterations during follow-up in Juvenile Idiopathic Arthritis (JIA).

Methods: Temporomandibular joint (TMJ) involvement was defined by orthopantomogram (OPT) alterations. Lateral cephalograms were used to determine linear and angular measurements.

Results: 74 patients could be included; mean follow-up 13 months. The prevalence of OPT alterations decreased, the prevalence of retrognathia and posterior rotated mandibles remained equal. The degree of retrognathia and posterior rotation shows improvement (*resp*. 42% and 39%). The degree of retrognathia improved equally in patients with improved and persistent OPT-alterations (*resp*. 38% and 38%), and more in patients without OPT-alterations (48%). Improvement of the degree of posterior rotation was seen more in patients with improved OPT-alterations than patients without and with stable persistent OPT-alterations, both by OP-SN (*resp*. 58%, 33%, and 14%) or GO-GN-SN (*resp*. 44%, 31% and 0%).

Conclusions: Both condylar and craniofacial alterations can improve in patients with JIA.

Key words: Juvenile Idiopathic Arthritis, Temporomandibular Joint, Facioskeletal changes

Introduction

Childhood arthritis was first described as a distinct disease entity by Still in his paper "On a form of chronic joint disease in children" in 1897.[1] Childhood arthritis has been known as Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis, until the International League of Association for Rheumatology (ILAR) established an international consensus in 1994, leading to the criteria of Juvenile Idiopathic Arthritis (JIA).[2] JIA is divided into seven subcategories, all categories are characterized by arthritis persisting for at least 6 weeks and onset before the 16th birthday.[2] Several joints might by affected by JIA including the temporomandibular joint (TMJ).[1]

Diamantberger first described mandibular underdevelopment in patients with JIA in 1890.[3] In 1897 Stille described involvement of the TMJ in three of his 22 cases.[1] The TMJ can be involved early or late in the course of the disease, and can even be the initial joint involved. Also it is possible to have only one condyle involved (unilateral involvement) or both condyles (bilateral involvement). In the literature the frequency of TMJ involvement in patients with JIA vary from 17-87%. The reported frequency depend on the JIA population studied, and the diagnostic method used to define TMJ involvement.[4-8] In the first study including all subtypes of JIA, a frequency of 45% TMJ involvement was reported.[9] Besides functional limitation TMJ involvement can also lead to reduced mandibular growth. This can lead to subsequent alteration in the dental occlusion and therefore TMJ involvement may even affect the total craniofacial growth.[4-7]

These craniofacial alterations have been described in the literature.[7,10-14] Retrognathia and increased mandibular posterior rotation are present more in patients with JIA, usually it has been associated with condylar destruction.[7,10-14] In most studies not all subtypes were studied, and most information reports on patients with oligo- and polyarticular JIA. Retrognathia and posterior rotated mandibles are more common in the polyarticular subtype.[7,10,11] The systemic onset type is only presented in one study, reporting a mild downward and backward rotation of the mandible.[13]

Recently we performed a study representing all JIA subtypes, reporting altered facial morphology in patients with JIA. Retrognathia and posterior rotated mandibles were more common if TMJ involvement was present, however also patients without TMJ involvement showed retrognathia and posteriorly rotated mandibles.[14]

The purpose of this follow-up study was to determine how the course of condylar alterations influences the facioskeletal morphology in a cohort representing all subtypes of JIA.

Patients and Methods

Patients

The study cohort consists of 97 consecutive patients with JIA according Edmonton criteria visiting the pediatric rheumatology outpatient clinic, referred for comprehensive orthodontic evaluation in the Temporomandibular joint Rheumatologic Involvement Project (TRIP 0) to evaluate the prevalence of TMJ involvement and facioskeletal changes in patients with JIA with and without TMJ involvement. The records of these patients were retrospectively reviewed to evaluate the facioskeletal changes in relation to the changes in TMJ involvement. Patients were included in TRIP 1 if both an OPT and lateral cephalogram were available after a minimum of one and a maximum of two years follow-up.

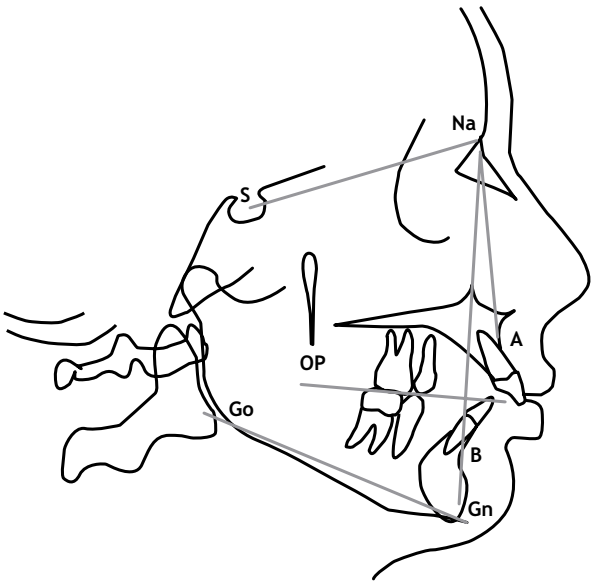

Figure 1: Tracing of a lateral cephalogram. Retrognathia is determined by ANB angle (S-Na-A minus S-Na-B) and posterior rotation of mandible is determined by mandibular plane to cranial base angle (Go-Gn to S-Na) and occlusal plane to cranial base angle (OP to S-Na).

Radiographic examination

The radiographic exams carried out were identical to the exams in the initial survey.[14] In short, lateral cephalograms and OPTs were examined. The lateral cephalograms (LC) were first digitized with an Epson 1680 Pro scanner (Epson, Long Beach, USA). Tracing occurred with QuickCeph 2000 software (QuickCeph, San Diego, USA). The same values as in TRIP 0 were measured (see figure 1). These

measurements were: ANB, indicating the discrepancy, or saggital relationship, between maxilla and mandible, and GO-GN-SN and OP-SN, both evaluating the divergency of, or vertical relationship between, the maxilla and mandible.[15]
Scoring of the OPTs occurred according to the grading system of Rohlin.[16] The Rohlin score divides TMJ involvement in six categories: grade 0, normal conditions; grade 1, slight abnormality; grade 2, definite early abnormality; grade 3, moderate destructive abnormality; grade 4, severe destructive abnormality and grade 5, mutilating abnormality.[16]

Cephalometric standards
Riolo *et al*. provided the control data for the cephalometric measurements of patients 6-16 years according to sex and age.[17] If patients were 16 years or older, Steiners was used as control for cephalometric measurements.[18] An ANB value of > 4 degrees was defined as retrognathia and the mean + 2 SD of GO-GN-SN and OP-SN was defined as increased posterior rotation of the mandible.

Statistical analysis
Data-analysis were performed with SPSS version 12.0 for Windows (SPSS-PC, Chicago, USA). Continuous measurements were described as median with 25th and 75th percentile. The paired *t*-test was used to compare differences in means between the group with and without TMJ involvement for continuous variables and the χ^2 for ordinal values. Statistical significant was defined as a p-value < 0.05.

Results

All necessary information was available for 74 patients. 23 (24%) patients of the initial cohort were excluded due to missing LCs (n = 10 (43%)), invalid LCs (n = 5 (22%)) or OPTs (n = 8 (35%)). Consequently the TRIP 0 cohort was adjusted and only included patients also represented in the TRIP 1 cohort. The mean interval between the consecutive radiographs was 13 months (range 10-18 months).

Patients
All subtypes of JIA were included, corresponding with the percentages found in pediatric rheumatology populations. The population of 27 boys and 47 girls had a mean age of 12 years (range 4 yrs, 1mo – 19 yrs, 9 mo), and a mean duration of the disease of 5 years and 9 months (range 1 yr, 6 mo – 12 yrs, 9 mo). The number of patients per subtype is summarized in Table 1.

Table 1: Overall prevalence of OPT alterations, retrognathia, and posterior rotation divided per subtype in TRIP 0 and 1.

JIA subtype	TRIP 0				TRIP 1			
	OPT alteration	Retrognathia	Posterior rotation		OPT	Retrognathia	Posterior rotation	
		ANB	OP-SN	GO-GN-SN	alteration	ANB	OP-SN	GO-GN-SN
Systemic (n = 13)	10	9	12	10	8	11	11	9
Oligo persistent (n = 19)	9	11	11	7	4	9	11	7
Oligo extended (n = 12)	5	9	6	6	6	8	7	4
Poly RF + (n = 7)	3	5	6	4	0	6	6	5
Poly RF - (n = 13)	6	10	8	5	3	6	9	5
ERA (n = 5)	1	4	4	1	0	4	2	0
Art. Psoriatica (n = 3)	1	1	2	2	1	1	3	3
Undifferentiated (n = 2)	1	1	2	2	0	2	2	2
Total (n=74)	36	50	51	37	22	47	51	35
Degree of alterations^		5.9 (4.8 – 7.0)	21.5 (18.9 – 23.8)	39.5 (36.8 – 42.4)		5.9 (5.0 – 6.6)	21.2 (18.5 – 23.0)	39.4 (36.9 – 43.9)

^Median (25th and 75th percentile)

TMJ involvement

According to the grading system of Rohlin, 22/74 (30%) patients had TMJ involvement in TRIP 1 compared to 36/74 (49%) patients in TRIP 0. Table 1 summarizes the frequency of TMJ involvement, divided per subtype in TRIP 1 and adjusted TRIP 0.

Comparing the OPT scores In TRIP 1 with TRIP 0, 36 (49%)patients had stable normal condyles, 7 (10%) patients had identical condylar alterations, 26 (35%) patients showed improvement of the condylar alterations, and worsening of condylar alterations was seen in 5 (7%) patients.

Cephalometric analysis

Retrognathia

The overall prevalence of retrognathia divided per subtype is summarized in Table 1. This prevalence described is regardless of the TMJ status in TRIP 0 and 1. In contrast to the decrease in the overall prevalence of OPT alterations, the overall prevalence of retrognathia is equivalent during follow-up.

Besides the prevalence of retrognathia we also measured the degree of retrognathia in TRIP 0 & 1. The degree of retrognathia improved in 21 of the 50 patients (42%) with initial retrognathia in TRIP 0 (TRIP 0; ANB 6.5 (4.7-7.5), TRIP 1; ANB 4.4 (3.0-5.7), p = 0.013).

Table 2 shows the changes in the degree of retrognathia in relation to the changes in OPT alterations during follow-up. The degree of retrognathia in the 36 patients with TMJ involvement improved equally in the 26 patients with improvement of the alterations on the OPT as in the 10 patients with persistent alterations on the OPT (*resp.* 8/21 (38%) and 3/8 (38%)).

21 of the 35 patients (60%) without OPT alterations in TRIP 0 & 1 showed retrognathia in TRIP 0. During follow-up 10 of these 21 patients (48%) showed improvement in the degree of retrognathia.

Posterior rotation

The overall prevalence of posterior rotation divided per subtype is summarized in Table 1. The overall prevalence of posterior rotation is almost equal during follow-up.

The degree of posterior rotation improved in 20 of the 50 patients (39%) with initial posterior rotated mandibles in TRIP 0 if measured by OP-SN (TRIP 0; OP-SN 22.4 (17.6-25.3), TRIP 1 OP-SN 17.7 (13.6-21.6), p = 0.18), and improved in 12 of the 34 patients (37%) if measured by GO-GN-SN (TRIP 0; 38.2 (29.7-41.2), TRIP 1; 35.4 (32.2-38.0), p = 0.21).

Table 2: The degree of retrognathia and posterior rotation in relation to changes in OPT alterations during follow-up

OPT changes	Retrognathia (ANB)				
	not initially present		initially present		
	stable	new developed	stable present	improved	worsened
Improved alterations (n = 26)	5 / 3	5 / 2	21 / 9	21 / 8	21 / 4
Persistent alterations (n = 10)	2 / 2		8 / 4	8 / 3	8 / 1
Normal OPTs (n = 35)	14 / 11	14 / 3	21 / 10	21 / 10	21 / 1
New alterations (n = 3)	3 / 1	3 / 2			
	Posterior rotation (OP-SN)				
	stable	new developed	stable present	improved	worsened
Improved alterations (n = 26)	7 / 6	7 / 1	19 / 7	19 / 11	19 / 1
Persistent alterations (n = 10)	3 / 1	3 / 2	7 / 5	7 / 1	7 / 1
Normal OPTs (n = 35)	11 / 6	11 / 5	24 / 12	24 / 8	24 / 4
New alterations (n = 3)	2 / 1	2 / 1			1 / 1
	Posterior rotation (GO-GN-SN)				
	stable	new developed	stable present	improved	worsened
Improved alterations (n = 26)	10 / 8	10 / 2	16 / 9	16 / 7	
Persistent alterations (n = 10)	5 /4	5 / 1	5 / 4	5 / 0	5 / 1
Normal OPTs (n = 35)	22 / 19	22 / 3	13 / 8	13 / 3	13 / 2
New alterations (n = 3)				3 / 2	3 / 1

Table 2 shows the changes in the degree of posterior rotation of the mandible in relation to the changes in OPT alterations during follow-up. The degree of posterior rotation in the 36 patients with TMJ involvement improved more in the 26 patients with improvement of the alterations on the OPT than in the 10 patients with persistent alterations (resp 11/19 (58%) and 1/7 (14%) if measured by OP-SN, and 7/16 (44%) and 0/5 (0%) if measured by GO-GN-SN).
24 of the 35 patients without OPT alterations in TRIP 0 & 1 showed posterior rotation in TRIP 0 measured by OP-SN. During follow-up 8 of these 24 patients (33%) showed improvement in the degree of posterior rotation. If measured by GO-GN-SN 16 patients showed posterior rotation in TRIP 0, 5 patients (31%) had an improved degree of posterior rotation during follow-up.

Discussion

TRIP 1 is the first follow-up study describing changes in the craniofacial alterations in relation to changes in the OPT alterations in a cohort of children with JIA with and without TMJ involvement. All subtypes of JIA are included with only a few patients diagnosed with enthesitis related arthritis (ERA), psoriatic arthritis, and undifferentiated arthritis, corresponding with the percentages found in pediatric rheumatology populations.
In agreement with our previous study retrognathia and posterior rotated mandibles were more common in patients with JIA than in the normal population, and even more if the TMJ was involved in JIA.
Our hypothesis was that if the OPT alterations would improve the facioskeletal morphology would also improve. Although the overall prevalence of OPT alterations decreased drastically the overall prevalence of retrognathia remained equal during follow-up. However the degree of retrognathia diminished in more than a third of the patients, but not more in patients with improvement on the OPT than in patients with persistent alterations. Patients without alterations on the OPT at both evaluations showed the most improvement of the degree of retrognathia. An explanation for the high frequency of retrognathia in all patients with JIA could be that the disease JIA itself has a negative effect on the craniofacial growth. These alterations in craniofacial growth may be restored to normal values if the arthritis in JIA diminishes. In most patients treatment was given sufficiently to control the disease, this may have resulted in normalized craniofacial growth. Craniofacial alterations caused by alterations shown on OPTs are thought to be a result of erosive changes to the growth centre of the

mandibula. These alterations may need more time to restore, if there is still growth potential.
In contrast to the degree of retrognathia, the degree of posterior rotation of the mandible improves more if the alterations of the OPTs improve. Apparently posterior rotation is more capable to follow condylar recovery than retrognathia, since alterations at the condyle affect the vertical relationship more than the sagittal relationship, thus posterior rotation would improve more than retrognathia
This study has some limitations. MRI is considered to be the golden standard to diagnose TMJ involvement, however MRI has shortcomings, including the necessity for sedation in small children, and much increased costs. MRI is not available in all orthodontic and dentist practices as is the OPT. The OPT is a good diagnostic tool to evaluate erosive alterations. As the kappa-statistics for the intraobserver and interobserver agreement is high for the OPT scores and cephalometric measurements, these methods are useful tools in the follow-up of erosive changes in all patients with JIA.[14]
A selection bias could have occurred as not all patients were represented in this follow-up study. However the number of missing patients is almost equally divided among the subtypes and the TMJ status in TRIP 0.
The follow-up period is relatively short to investigate changes in the craniofacial growth in patients with JIA. However as only limited follow-up information is available, even this short period is of interest. This study shows a drastic improvement in the alterations on the OPT and a trend towards improvement of retrognathia and posterior rotation. Long-term research is necessary to evaluate the course of the craniofacial growth over time. We postulate that retrognathia and posterior rotation will normalize more over a longer period of time.
Acknowledging facioskeletal changes in arthritis of the TMJ is important since they do not only arise to aesthetic problems, like the well known “bird-face” appearance, but can also lead to oral health problems, and difficulty in chewing and intubating.

Conclusion

This study shows a drastic improvement in the alterations on the OPT and a trend towards improvement of the degree of retrognathia and posterior rotation. Long-term research is necessary to study the craniofacial development over time.

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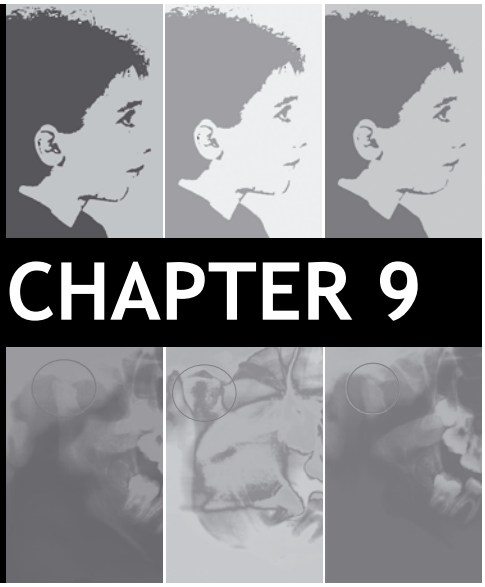
Long-term follow-up of craniofacial alterations in Juvenile Idiopathic Arthritis



CHAPTER 9

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Submitted

Abstract

Objective: To investigate the changes in craniofacial skeleton in relation to the changes in condylar alterations during 68 months of follow-up in patients with Juvenile Idiopathic Arthritis.

Methods: TMJ involvement is defined as a condylar alteration, observed on the orthopantomogram. Lateral cephalograms were used to determine linear and angular measurements.

Results: 70 patients out of the 97 patients of the initial study cohort could be included, with a mean follow-up of 68 months. The overall prevalence of condylar alterations and posterior rotation of the mandible decreased, however the prevalence of retrognathia remained the same. Patients show improvement in the degree of retrognatia and posterior rotation (*resp*. 40%, 51% OP-SN, and 44% GO-GN-SN). Improvement in the degree of retrognathia was seen more in patients with improved condylar alterations, than in patients with stable persistent alterations and without alterations (*resp*. 50%, 33% and 28%) The degree of posterior rotation improved almost equal in patients without TMJ involvement and patients with improved condylar alterations (*resp*. 57% and 50% by OP-SN, and 67% and 38% GO-GN-SN) and did not improve in patients with stable persistent alterations.

Conclusion: Both condylar and craniofacial alterations can improve in patients with JIA.

Keywords: Juvenile Idiopathic Arthritis, JIA, Temporomandibular Joint, TMJ

Introduction

In 1897, childhood arthritis was first described as a distinct disease entity by Still in his paper 'On a form of chronic joint disease in children'.[1] After Still, childhood arthritis was divided into different subtypes. Between 1977 and 1994 two different terms were used, Juvenile Rheumatoid Arthritis (JRA) and Juvenile Chronic Arthritis (JCA). In 1994 the International League of Association for Rheumatology (ILAR) established an international consensus leading to the criteria of Juvenile Idiopathic Arthritis (JIA).

JIA is defined as arthritis starting before the age of sixteen years, persisting for at least 6 weeks and without specific cause. JIA is divided into seven subtypes based on clinical symptoms during the first six months of the disease based on the inclusion and exclusion criteria.[2,3] These subtypes all have a different initial presentation and course and prognosis.[2,4]

The TMJ can be affected both uni-and bilaterally, early or late in the course of the disease and it can even be the initial joint affected. The reported frequency of TMJ involvement varies in the literature from 17% to 87% depending on the population investigated, the subtypes of JIA represented and the radiological method by which involvement is diagnosed.[5-9]

The most important site of growth of the mandible in vertical and sagital direction is located on the articular surface of the condylar head.[9,10] During normal growth of the dentomaxillary complex the vertical dimension increases more than the sagital dimension. Arthritis of the TMJ results in reduced mandibular growth and subsequent alteration in dental occlusion and may even affect the total craniofacial growth.[5-8] Alterations in the craniofacial structure of JIA patients were described in several studies.[8,11-15] JIA patients demonstrated retrognathia and increased mandibular posterior rotation. Usually the characteristic facial morphology has been associated with condylar destruction.[8,11-15]

Most studies were performed in the oligo- and polyarticular subtype with more retrognathia and posterior rotated mandibles in the polyarticular subtype.[8,11,12] Only one study reported a mild downward and backward rotation of the mandible in the systemic subtype.[14]

The patient cohort of the Temporomandibular joint Rheumatologic Involvement Project (TRIP) studies is based on an initial cross-sectional population of 97 consecutive patients representing all subtypes of JIA. In TRIP 0, the frequency of TMJ involvement diagnosed with an orthopantomogram (OPT) was 45%.[16] The craniofacial morphology was altered in patients with JIA regardless of the TMJ status, although more common in patients with TMJ involvement.[15] TRIP 1 (one year later) reported a yearly incidence of TMJ involvement of 7%.[17] Also a drastic

decrease in the prevalence of OPT alterations was observed during follow-up.[17] Equal overall prevalences of craniofacial alterations were seen, but a decrease in the degree of retrognathia and posterior rotation were observed.[18]
The aim of this survey was to study how the course of condylar alterations can influence the craniofacial skeleton in patients with JIA over a five-year period.

Patients and methods

Patients

Initially 97 consecutive patients with JIA according Durban criteria were routinely referred for comprehensive orthodontic evaluation in the TRIP 0 study. In TRIP 5 these patients were reviewed 5 years later to evaluate the prevalence of TMJ involvement and facioskeletal changes in patients with JIA with and without TMJ involvement.
Patients of the initial cohort were included if an orthopantomogram (OPT) and lateral cephalogram (LC) were available at both evaluations.

Methods

Radiographic examination

Standardized radiographic examination was acquired by means of LCs and OPTs. All LCs were digitized with an Epson 1680 Pro scanner (Epson, Long Beach, USA) and traced with QuickCeph 2000 software (Quick Ceph, San Diego, USA). The following values were measured (see figure 1): ANB indicating the discrepancy, or sagital relationship, between maxilla and mandible; GO-GN-SN and OP-SN both evaluating the divergency of, or vertical relationship between, the maxilla and mandible.[19]
TMJ involvement was defined as condylar alterations on OPTs. TMJ involvement was diagnosed using the six categories of Rohlin: grade 0, normal conditions; grade 1, slight abnormality; grade 2, definite early abnormality; grade 3, moderate destructive abnormality; grade 4, severe destructive abnormality and grade 5, mutilating abnormality.[20]

Cephalometric standards

Control data for the cephalometric measurements of patients 6-16 years were obtained according to sex and age based on Riolo *et al*.[21] Normal values for patients older than 16 years were based on the Steiner analysis.[22] Posterior rotation of the mandible was defined as ≥ 2 SD of the norms for GO-GN-SN and OP-SN, according to Riolo. Retrognathia was defined as an ANB angle exceeding 4 degrees.

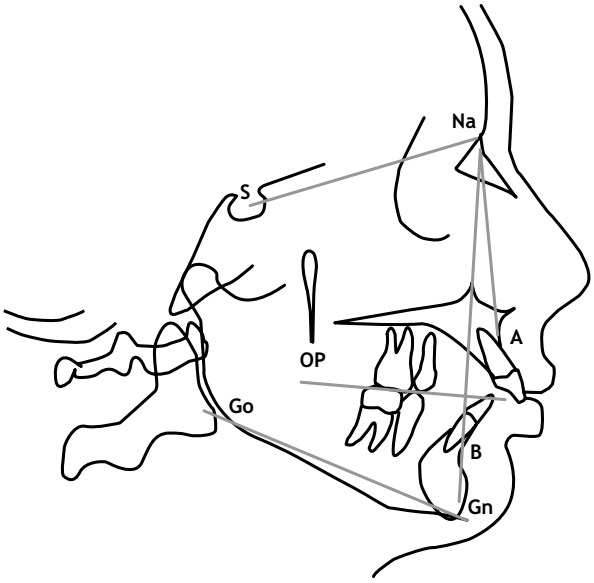

Figure 1: Tracing of a lateral cephalogram. Retrognathia is determined by ANB angle (S-Na-A minus S-Na-B) and posterior rotation of mandible is determined by mandibular plane to cranial base angle (Go-Gn to S-Na) and occlusal plane to cranial base angle (OP to S-Na).

Statistical analysis

SPSS version 12.0 for Windows (SPSS-PC, Chicago, USA) was used for data-analysis. Continuous measurements were described as median with 25th and 75th percentile. To compare differences in means between the group with and without craniofacial alterations the paired *t*-test was used for continuous variables. Statistical significance was defined as a p-value< 0.05.

Results

All necessary information was available for 70 patients. 27 (28%) patients of the initial cohort were excluded due to not consenting in participating in this 5-year follow-up study (n = 13, 13%) or due to invalid LC (n = 1, 1%), invalid OPT (n = 4, 4%), and missing LCs (n = 10, 10%). Consequently, the TRIP 0 cohort was adjusted so that only patients represented in the TRIP 5 study were included. The mean interval between the consecutive radiographs was 68 months (range 53-73 months).

Table 1: Overall prevalence of OPT alterations, retrognathia, and posterior rotation divided per subtype in TRIP 0 and 5

JIA subtype (total n = 70)	TRIP 0				TRIP 5			
	OPT alteration	Retrognathia (ANB)	Posterior rotation OP-SN	Posterior rotation GO-GN-SN	OPT alteration	Retrognathia (ANB)	Posterior rotation OP-SN	Posterior rotation GO-GN-SN
Systemic (n = 13)	9	8	12	10	8	11	10	9
Oligo persistent (n = 17)	8	12	10	7	5	12	8	5
Oligo extended (n = 12)	5	9	6	7	6	6	5	4
Poly RF + (n = 5)	2	4	5	2	0	5	4	3
Poly RF - (n = 11)	6	8	7	4	5	7	7	2
ERA (n = 6)	0	4	3	2	0	3	3	1
Art. Psoriatica (n = 3)	1	1	2	2	1	1	2	2
Undifferentiated (n = 3)	1	1	3	2	1	0	1	1
Total alterations	32	47	48	36	26	45	40	27
Degree of alterations^		5.9 (4.9 – 7.0)	21.4 (18.9 – 24.4)	39.5 (36.7 – 42.1)		5.9 (4.9 – 7.3)	21.5 (19 – 25)	41.1 (37.6 – 44.6)

^Median (25^{th} and 75^{th} percentile)

Patients
All subtypes of JIA were included, and corresponded with the percentages in pediatric rheumatology populations. The population of 27 boys and 43 girls had a mean age of 16 years and 3 months (range 8 yrs, 9 mo – 24 yrs, 8 mo), and a mean duration of the disease of 10 years and 1 month (range 6 yr, 3 mo – 18 yrs, 10 mo). The patients per subtype are summarized in Table 1.

TMJ involvement
According to the grading system of Rohlin, 26/70 (37%) patients had TMJ involvement in TRIP 5 compared to 32/70 (46%) patients in TRIP 0. Table 1 summarizes the frequency of TMJ involvement, divided per subtype in TRIP 5 and adjusted TRIP 0.
Comparing the condylar alterations in TRIP 5 with TRIP 0, 32 (46%) patients had stable normal condyles, 4 (6%) patients showed no change in their condylar alterations, 28 (40%) patients showed improvement of the affected condyles, and worsening of the condylar alterations was seen in 6 (8%) patients.

Cephalometric analysis
Retrognathia
The overall prevalence of retrognathia divided per subtype is summarized in Table 1. This prevalence described is regardless of the TMJ status in TRIP 0 and 5. In contrast to the decrease in the overall prevalence of condylar alterations, the overall prevalence of retrognathia remains the same during follow-up (*resp.* 67% TRIP 0 and 64% TRIP 5). Besides the prevalence of retrognathia, the degree of retrognathia was also measured in TRIP 0 & 5.
The degree of retrognathia improved in 19 of the 47 (40%) patients with initial retrognathia in TRIP 0 (TRIP 0; ANB 6.7 (5-7.7), TRIP 5; ANB 4.0 (3.4-5.8), p = 0.000). Table 2 shows the changes in the degree of retrognathia in relation to the changes in condylar alterations during follow-up. The degree of retrognathia in the 32 patients with TMJ involvement improved more in the 28 patients with improvement of the condylar alterations, than in the 4 patients with persistent condylar alterations (*resp.* 12/24 (50%) and 1/3 (33%)).
18 of the 32 patients (56%) without condylar alterations in TRIP 0 & 5 showed retrognathia in TRIP 0. During follow-up, 5 of these 18 (28%) patients showed improvement in the degree of retrognathia.

Table 2: The degree of retrognathia and posterior rotation in relation to changes in OPT alterations during follow-up.

TMJ		Retrognathia (ANB)				
status		not initially present		initially present		
TRIP 0	OPT changes	stable	new developed	stable present	improved	worsened
TMJ +	Improved alterations (n = 28)	4 / 1	4 / 3	24 / 6	24 / 12	24 / 6
TMJ +	Persistent alterations (n = 4)	1 / 1		3 / 1	3 / 1	3 / 1
TMJ -	Normal OPTs (n = 32)	14 / 10	14 / 4	18 / 10	18 / 5	18 / 3
TMJ -	New alterations (n = 6)	4 / 3	4 / 1	2 / 0	2 / 1	2 / 1
		Posterior rotation (OP-SN)				
		stable	new developed	stable present	improved	worsened
TMJ +	Improved alterations (n = 28)	8 / 8		20 / 8	20 / 10	20 / 2
TMJ +	Persistent alterations (n = 4)			4 / 4		
TMJ -	Normal OPTs (n = 32)	11 / 6	11 / 5	21 / 5	21 / 12	21 / 4
TMJ -	New alterations (n = 6)	3 / 3		3 / 0	3 / 2	3 / 1
		Posterior rotation (GO-GN-SN)				
		stable	new developed	stable present	improved	worsened
TMJ +	Improved alterations (n = 28)	12 /11	12 / 1	16 / 7	16 / 6	16 / 3
TMJ +	Persistent alterations (n = 4)	1 /1		3 / 3		
TMJ -	Normal OPTs (n = 32)	17 / 17		15 / 2	15 / 10	15 / 3
TMJ -	New alterations (n = 6)	4 / 3	4 / 1	2 / 1		2 / 1

TMJ + = condylar laterations in TRIP 0

TMJ - = normal condyles in TRIP 0

Posterior rotation

The overall prevalence of posterior rotation divided per subtype is summarized in Table 1. The overall prevalence of posterior rotation decreased if measured by OP-SN (*resp.* 69% TRIP 0 and 57% TRIP 5) and GO-GN-SN (*resp.* 51% TRIP 0 and 39% TRIP 5).

The degree of posterior rotation improved in 24 of the 48 (50%) patients with initial posterior rotated mandibles in TRIP 0 if measured by OP-SN (TRIP 0; OP-SN 21.4 (18.1 — 25), TRIP 5; OP-SN 17.4 (15 — 19.9), p = 0.009), and improved in 16 of the 36 (44%) patients if measured by GO-GN-SN (TRIP 0; GO-GN-SN 37.6 (28.4 — 41.6), TRIP 5; 34.9 (31.1 — 37.2), p = 0.089).

The changes in the degree of posterior rotation of the mandible in relation to the changes in condylar alterations during follow-up are described in Table 2. Improvement of the degree of posterior rotation in the 32 patients with TMJ involvement was more common in the 28 patients with improvement of the condylar alterations (*resp.* 10/20 (50%) by OP-SN, and 6/16 (38%) by GO-GN-SN). The four patients with persistent condylar alterations showed no improved degree of posterior rotation.

21 of the 32 (66%) patients without condylar alterations in TRIP 0 & 5 showed posterior rotation in TRIP 0 measured by OP-SN. During follow-up, 12 of these 21 (57%) patients showed improvement in the degree of posterior rotation. If measured by GO-GN-SN 15 (47%) patients showed posterior rotation in TRIP 0, 10 (67%) patients had an improved degree of posterior rotation during follow-up.

Discussion

TRIP 5 is the first long-term follow-up study on changes in craniofacial alterations in a cohort of patients with JIA in relation to condylar alterations as determined on an OPT. All subtypes of JIA are represented, corresponding with the percentages found in a pediatric rheumatology department.

In this long-term follow-up study more condyles showed improvement on the OPT than in the one-year follow-up study (TRIP 1).[18] Our hypothesis was that if the condylar alterations would improve, the craniofacial morphology would also improve. Besides the decrease in the overall prevalence of condylar alterations, a decrease in the overall prevalence of posterior rotation was seen, supporting our hypothesis. This in contrast with our one-year follow-up study, which showed the same overall prevalence of retrognathia and posterior rotation.[18] During the five-years of follow-up (TRIP 5), the overall prevalence of retrognathia remained

the same. Beside the overall prevalence of retrognathia and posterior rotation, the degree of retrognathia and posterior rotation was studied. The TRIP 1 study showed a trend towards normalization of the craniofacial measurements; hence an improvement of the degree of retrognathia and posterior rotation. The TRIP 5 continued to show this trend towards improvement of the degree of posterior rotation, supporting our hypothesis. Improvement of the degree was seen more in posterior rotation (both OP-SN and GO-GN-SN) than in retrognathia. Patients with improvement of the condylar alterations, and patients without condylar alterations in TRIP 0 & 5 showed more improvement in the degree of retrognathia and posterior rotation, than did patients with persistent or newly developed condylar alterations.

The difference in overall prevalence of posterior rotation and retrognathia and the continued trend towards normalization in posterior rotation of the mandible, can be explained if the improvement of condylar changes has a greater affect on vertical relationships than sagital relationships. Since the posterior rotation describes the vertical relationship, it does have a greater improvement than retrognathia, which describes a sagital relationship. Sagital growth is also directed from the condylar growth centre by means of bone remodelling. Cytokines involved in JIA, such as IL 6 are known to have influence on bone remodelling processes, which could also explain the remained retrognathia in most patients with JIA. We expect posterior rotation of the mandible to normalize even more over an even longer period of time, as long as there is growth potential of the condyle.

In agreement with our two previous studies retrognathia and posterior rotated mandibles were more common in patients with JIA than in the normal population, and even more if the TMJ was involved. The high prevalence of retrognathia and posterior rotation in all patients with JIA could be explained by a negative effect on craniofacial growth by the disease JIA itself. These alterations in craniofacial growth may be restored to near normal values if the arthritis in JIA diminishes. In most patients the disease activity could be controlled by sufficient medical treatment.

This study has some limitations. MRI is considered to be the golden standard to diagnose TMJ involvement, however MRI has shortcomings, including the need for sedation in small children, and the much increased costs. Also MRI is not available in all orthodontic and dentist practices as is the OPT. The OPT is a good diagnostic tool for condylar alterations.

The kappa-statistics for the intraobserver and interobserver agreement is high for the OPT and the cephalometric measurements, these methods are useful

tools in the follow-up of erosive changes in all patients with JIA.[15]
A selection bias could have occurred as not all patients were represented in this follow-up study. However the number of missing patients is almost equally divided among the subtypes and the TMJ status in TRIP 0.
Eruption of teeth may have an influence on the vertical development, therefore also the dental age of the children should be incorporated in a follow-up study. Dutch cephalometric standards show that Dutch children are more retrognathic than American children, unfortunately the Dutch reference data were not incorporated in the internationally used program to trace the lateral cephalogram.
Acknowledging facioskeletal changes in arthritis of the TMJ is important since they do not only give aesthetic problems, like the well known “bird-face” appearance, but can also lead to oral health problems, and difficulty chewing and intubating. Changes in condylar rating may have an important influence on the aesthetics of the face. If the condylar situation can improve with treatment as demonstrated in this study this may have implications for the timing and indication for treatment. This study also shows that only a longitudinal study design will give the evidence for a relationship between improvement in condylar alterations and the craniofacial morphology.

Conclusion

This study shows a drastic improvement in the alterations of the condyle on the OPT and a trend towards normalization of the posterior rotation. Orthodontists should be aware of the possibility of condylar alterations in children with JIA, especially if they are retrognathic and have posteriorly rotated mandibles.

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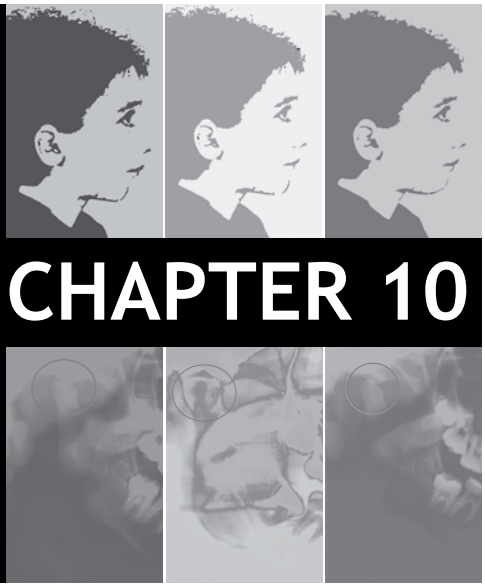
General discussion

CHAPTER 10



General discussion

The aim of the work described in this thesis was to evaluate the prevalence and incidence of condylar alterations in patients with Juvenile Idiopathic Arthritis in relation to JIA subtype, and the influence of condylar alterations on the craniofacial morphology. In this chapter first the main findings are summarised and the TRIP study design is explained. Accordingly a short summary is given on what was already described in the literature, followed by the six research questions, as formulated in the general introduction (chapter 1), and the findings in the TRIP studies. Future perspectives and clinical implications of the findings are discussed afterwards.

Main findings

Condylar involvement in patients with Juvenile Idiopathic Arthritis

- The prevalence of condylar alterations observed in a cross-sectional population representing all subtypes of JIA is 45%.
- Clinical signs and symptoms are scarce, but if present they are good predictors. However if not present the chances of condylar alterations are still high.
- The yearly incidence of condylar alterations in a cohort of patients representing all subtypes of JIA is 7%.
- Damage to the mandibular condyle is reversible, as the prevalence of condylar alterations decreased after 1 and 5 years of follow-up. The condyle can even improve to normal. Improvement of the condyle was associated with a low disease activity.

Craniofacial morphology in Juvenile Idiopathic Arthritis

- Retrognathia and posteriorly rotated mandibles are more common in patients with JIA, regardless of the TMJ status. Patients with condylar alterations do show more retrognathia and posteriorly rotated mandibles than patients without condylar alterations.
- Patients with improvement of the condylar alterations do show more improvement in the degree of retrognathia and posterior rotation, although patients without alterations also show improvement in the degree of retrognathia and posterior rotation.

The TRIP studies

The Temporomandibular joint Rheumatologic Involvement Project (TRIP) was initiated in May 1999 by the department of pediatric rheumatology of the Erasmus MC Sophia Children's Hospital in cooperation with the department of orthodontics. Accordingly three studies (TRIP 0, 1 & 5) were carried out between May 1999 and June 2005 to answer the research questions. The patient cohort of the TRIP studies is based on a cross-sectional population of 97 consecutive patients representing all subtypes of JIA. The TRIP 1 & 5 studies are follow-up studies of this cross-sectional initiated cohort. A clinical rheumatological and orthodontic examination, including OPT and lateral cephalogram were obtained in 97 patients in TRIP 0. The TRIP 1 study contained 89 patients with an OPT, and 74 patients with both OPT and lateral cephalogram. The TRIP 5 study contained 84 patients with a rheumatologic and orthodontic examination, including OPT, and 70 patients with also a lateral cephalogram.

Condylar involvement in patients with Juvenile Idiopathic Arthritis

What was already known

An association between JIA and condylar alterations has been described in the past. In these studies subgroups of patients were studied to determine the prevalence of TMJ involvement. The prevalence of TMJ involvement varies from 17% to 87% in the literature, depending on the subtypes of JIA represented and diagnostic method by which involvement is diagnosed. Most studies had a selection bias as they included only patients with the oligoarticular and polyarticular subtype, almost all with a polyarticular course of the disease. Subsequently the highest frequencies were described in these subtypes. Selection bias also occurred in other studies, for instance patients were included if they had experienced TMJ complaints or if patients already had present condylar alterations.

The imaging tools used were the OPT, the CT-scan, and MRI. Most studies also described clinical signs or symptoms for TMJ involvement in patients with JIA. The only association between condylar alterations and clinical sign and symptoms, were an early onset of the disease, patients with a long duration of the disease, and patients with a polyarticular course of the disease. No studies on the incidence of condylar alterations are described in the literature. Only a few studies have studied the course of condylar alterations in JIA over a longer period of time, all showing an increasing prevalence of TMJ involvement during follow-up.

Research questions

1) What is the prevalence of condylar alterations in a population representing all subtypes of JIA?
2) Are clinical signs and symptoms good predictors for TMJ involvement in patients with JIA?
3) What is the yearly incidence of condylar alterations in a cohort of patients representing all subtypes of JIA?
4) What is the course of the condylar alterations during follow-up?

Findings in the TRIP studies

The results from TRIP 0, 1 and 5 all have demonstrated that condylar alterations are frequent in patients with JIA (*Chapter 3, 5 & 6*). Condylar alterations were not only present in the systemic and polyarticular subtypes, but also in the less aggressive oligoarticular persistent subtype. Patients with condylar alterations have a significantly younger age at onset, and have a significantly longer duration of the disease (*Chapter 3 & 6*). The patients with a polyarticular RF positive JIA show less condylar alterations, in spite of the known aggressive and erosive character of this subtype. This low frequency of condylar alterations is probably due to the late-onset of this subtype. The mandibular condyle seems less vulnerable in older patients. The condylar alterations of these patients all normalised during follow-up (*Chapter 5 & 6*).

Condylar alteration can develop without any signs or symptoms in a short period of time (*Chapter 4*). Signs or symptoms indicating TMJ involvement are scarce. If present they are good indicators for condylar persisting alterations, however if signs or symptoms are not present condylar alterations can still be present (*Chapter 3 & 6*).

In TRIP 1 the yearly incidence of condylar alterations in patients with JIA was 7% (*Chapter 5*). The prevalence of condylar alterations was higher in TRIP 0 than in TRIP 1 and 5 (*Chapter 3,5 & 6*). Improvement of the condylar alterations was observed and even normalisation of the condylar alterations was seen. Patients with initial condylar alterations showed normal condyles during follow-up, indicating a regenerative capacity of the mandibular condyle. Improvement of the condyle was seen more in patients with a low disease activity (*Chapter 5 & 6*).

In summary, the prevalence of TMJ involvement is high in patients with JIA. Condylar alterations are more common in the patients with a systemic and polyarticular RF negative subtype. Also patients with an early disease onset, long duration of the disease, and polyarticular course irrespective of the onset type show more

condylar alterations. Signs and symptoms alone are not able to discriminate between presence and absence of condylar alterations. The mandibular condyle is able to regenerate if the disease is sufficiently controlled.

Craniofacial morphology in Juvenile Idiopathic Arthritis

What was already known

Craniofacial alterations in JIA are already described in the 1890's by Diamantberger and Still. They described mandibular underdevelopment and the so-called bird-face due to arthritis of the mandible. More studies on craniofacial alterations in JIA are reported in the literature. Most studies were performed in patients with either complaints or radiological abnormalities of the condyle. No studies also included patients with JIA without condylar alterations. Most studies were performed in patients with a polyarticular JIA, only one study described patients with systemic JIA.

Research questions

5) Is the facial morphology of patients with JIA comparable to the facial morphology of the normal population? Do patients with an alteration on the OPT have more alterations of the facial morphology?
6) Is there a correlation between improvement of the alterations on the OPT and changes in retrognathia and posterior rotation of the mandible.

Findings in the TRIP studies

The TRIP 0 study demonstrated an increased prevalence of both retrognathia and posteriorly rotated mandibles in patients with JIA, regardless of the TMJ status. If condylar alterations were present retrognathia and posterior rotation were more frequent. Retrognathia was more common in patients with polyarticular JIA and oligoarticular JIA than systemic JIA. Posterior rotation was more common in patients with systemic JIA (*Chapter 7*).

During one-year of follow-up a decrease in the overall prevalence of condylar alterations was observed. The overall prevalence of retrognathia and posterior rotation remained equivalent. However the degree of retrognathia and posterior rotation after one year of follow-up did show a decrease (*Chapter 8*). After 5 years of follow-up the overall prevalence of retrognathia remained equivalent, while the overall prevalence of posterior rotation showed a decrease (*Chapter 9*). Improvement of the degree of retrognathia and posterior rotation was more

common in patients with improvement of the condylar alterations and patients without condylar alterations (*Chapter 8 & 9*). The fact that the overall prevalence of posterior rotation decreased and the prevalence of retrognathia remained equal could be explained by the fact that the vertical dimension increase more than the sagital. Posterior rotation is a vertical relationship and in case of a remaining growth potential can therefore improve more if the condylar alterations improve. Retrognathia is a sagital relationship and although the condylar growth site is also the driving force behind growth of the mandible, sagital growth is a remodelling process. Nowadays new insides in cytokine profiles and mechanisms show their influence on chondrocytes and chondroblasts; hence their possible negative influence on this remodelling process.
Interestingly retrognathia and posterior rotation were also present in patients without detectable condylar alterations. This could mean that retrognathia and posterior rotation are not only caused by condylar alterations, but also by other mechanisms influencing craniofacial growth. It is already long known that JIA can lead to stature growth retardation, caused by the disease activity of JIA itself. Another known cause for the growth retardation is the use of systemic corticosteroid therapy, necessary in some patients. As retrognathia and posterior rotation are present in patients without corticosteroid therapy and without condylar alterations, growth retardation caused by the disease activity itself plays a major role in craniofacial growth in patients with JIA. Consequently this could mean that the early reports of mandibular underdevelopment by Diamantberger and Still are not solely caused by condylar alterations, but are probably merely a result of the overall disease activity.

Future perspectives for research

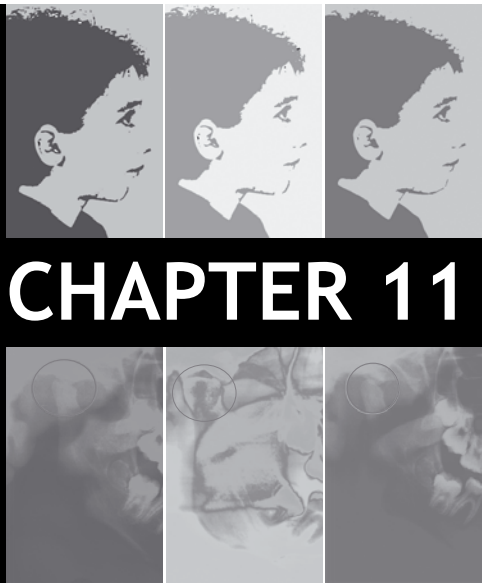
TMJ involvement is a frequent feature in JIA as described in this thesis. Condylar alterations defined on the OPT are late signs of condylar involvement. Only erosive changes can be seen with OPT, no information on active synovitis can be obtained, which limits the therapeutic options. Therefore an extensive study on condylar alterations in JIA with other more sensitive diagnostic methods is necessary. Contrast enhanced MRI and ultrasound are the two most promising techniques. MRI however has its limitations, including necessity of sedation in small children and much increased costs. Ultrasonography is currently making an up rise in rheumatology, and is already included in the standard practice of rheumatologists for assessing knee and wrist involvement. Ultrasonography also is more useable in children and there is no need to sedate a child.

Recently cytokine profiles present in auto-inflammatory diseases, like JIA are discovered and studied. It is already known that some of these cytokines can influence growth processes by interfering in the bone-turnover process and shifting the balance between osteoclasts and osteoblasts. The influence of the different cytokines on the craniofacial growth changes in patients with JIA in relation to disease severity and activity is unclear and should be studied.
Further information on the therapeutic options is necessary. In the TRIP studies, all patients were treated with sufficient drug treatment, as the overall disease activity was low in all 3 studies. Improvement of the condylar alterations were associated with a low disease activity, so condylar arthritis can be controlled with systemic drugs in patients with a polyarticular course of the JIA. If the condyles are the only joints involved intra-articular injections can be administrated. This technique has certain negative side effects; local skin lesions due to corticosteroids leaking back to the skin, sedimentation of crystals in the TMJ, and possibility of an induced infection. Also recent rabbit models showed a reduced mandibular growth when antigen-induced arthritis was treated with intra-articular corticosteroids, even more reduced than when left untreated. So the place of intra-articular injections for TMJ involvement in the treatment algorithm should be studied. Also the role of orthodontic treatment, such as splint treatment, in patients with JIA should be studied. At this moment it is not clear what therapeutic option is the best option in treating condylar alteration in children with JIA.
Frequently the TMJ is neglected in the regular examination of the patient with JIA. Consequently the frequency of TMJ involvement is underestimated. As TMJ involvement is frequent and can occur at any time during the disease course this could influence the counted number of affected joints in the first six months, influencing the distribution of the patients among the oligoarticular and polyarticular subtypes of JIA. Some patients, who are now in the oligoarticular subtype, actually might have an initial polyarticular disease if the TMJs were included. It would be of interest to study these patients to see if they influence the homogeneity of the subtypes.

Implications for clinical care

The TMJ should be included in the regular examination of a patient with JIA. Examination of the TMJ is not easy and a team of specialists, including the (paediatric) rheumatologist and orthodontist, is advisory. TMJ examination should find place on a regular basis throughout the disease course.

Clinical signs are scarce, however if present they are good predictors for TMJ involvement. Signs and symptoms alone are not able to distinguish between absence or presence of TMJ involvement. The chance on condylar alterations in patients with JIA without clinical signs or symptoms is still increased. Therefore the orthodontist should examine patients for at least once a year including imaging techniques. Patients should be evaluated during the course of the active disease, and some patients should be evaluated until they are twenty years of age, as the growth centre in the condylar head is active until then. Patients with complaints should be referred to the orthodontist for an additional evaluation.
The OPT is a possible imaging technique, and can be used in young children. However the OPT is not able to distinct between new and old lesions, and only erosive changes can be detected by OPT. The contrast enhanced MRI is able to distinguish active synovitis and erosive damage of the condyle. However in paediatric patients the MRI is not the most ideal method to examine the TMJ because of the necessity to sedate young children. Ultrasonography in assessing joint alterations in rheumatology and paediatric rheumatology seems promising. Ultrasonography is also capable of identifying active synovitis of the TMJ, and it can be used in patients of all ages, without the necessity of sedation. Ultrasonography should be embedded in the periodical orthodontic care of the patient with JIA.
As TMJ involvement is a frequent feature in JIA, arthritis of the TMJ should be considered when deciding on a therapeutic regimen. Sufficient systemic therapy leading to a low disease activity can lead to improvement or even normalisation of the condylar alterations. Physicians should be restrained in using intra-articular injections as this could have a greater negative effect on the mandibular growth than arthritis of the TMJ itself.



Summary CHAPTER 11

Introduction

Juvenile Idiopathic Arthritis (JIA) is a generalised autoimmune disease, which starts in childhood. JIA is one of the most frequent occurring autoimmune diseases in childhood, and concerns approximately 1 in a 1000 children. JIA is a heterogeneous group of conditions divided into seven different subtypes (see table 1). These different subtypes all should meet some mutual criteria. These criteria are; start of the disease before the sixteenth birthday, arthritis persisting for at least 6 weeks, and all other diagnosis should be excluded. The subtypes are divided based on the clinical symptoms during the first six months of the disease according to inclusion and exclusion criteria. These subtypes all have a different initial presentation, course, and prognosis.

Table 1: ILAR classification JIA.

JIA classification
Systemic JIA
Oligoarticular JIA
persistent
extended
Polyarticular JIA Rheumatoid factor negative
Polyarticular JIA Rheumatoid factor positive
Enthesitis related Arthritis
Arthritis Psoriatica
Undifferentiated arthritis

JIA may affect several joints, including the temporomandibular joint (TMJ). The most important site of vertical growth of the mandible is located on the articular surface of the condylar head. This superficial position makes it more vulnerable for damage and destruction caused by JIA. Early destruction of the condylar head due to arthritis, may subsequently affect mandibular development and growth. Diamantberger already described mandibular underdevelopment in 1890. Involvement of the TMJ was first described by Still in 3 of his 22 cases, when he described chronic arthritis in childhood in 1897. The reported frequency of TMJ involvement in JIA varies from 17-87% in the literature, depending on the population investigated, the subtypes of JIA represented, and the methods by which involvement is diagnosed. Most studies report more bilateral involvement, although TMJ involvement was initially unilateral in 27-50%.

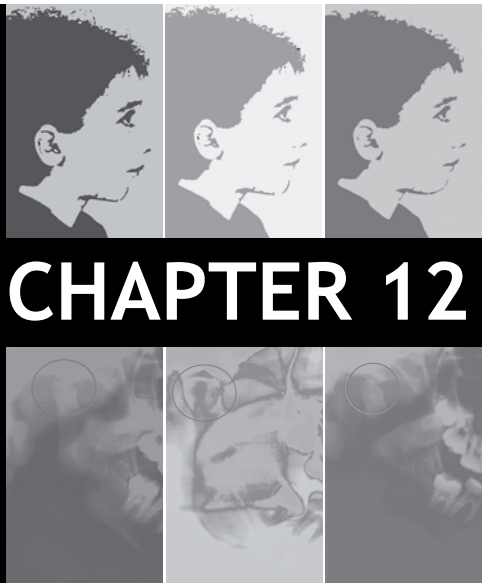
Although many cross-sectional studies on TMJ involvement in JIA were performed during the last three decades, most studies were performed in a selected group of patients. In many studies only a couple of subtypes were represented, only patients of a certain age were included, or inclusion was based on an already existing alteration of the TMJ. Only a few follow-up studies were performed, all reporting an increased frequency of TMJ involvement over time and progression of the existing alterations.
The Temporomandibular joint Rheumatologic Involvement Project (TRIP) was initiated to gather long-term information on TMJ involvement and associated craniofacial alterations. The TRIP cohort consists of 97 consecutive patients with JIA representing all subtypes.
In this thesis the findings concerning condylar alterations, clinical symptoms and craniofacial morphology are described according to a main baseline study (TRIP 0), a one-year follow-up study (TRIP 1), and a five-year follow-up study (TRIP 5).

TMJ involvement in Juvenile Idiopathic Arthritis
In **Chapter 2** a historic view of all studies from 1964 until April 2006 on TMJ involvement in JIA is presented. In **Chapter 3** a baseline frequency of 45% TMJ involvement in patients with JIA is reported. Clinical symptoms are scarce, but if present are good indicators for TMJ involvement. However in the absence of clinical symptoms chances on TMJ involvement are still increased. In **Chapter 4** a patient with abrupt condylar destruction without symptoms is described. In **Chapter 5** a yearly incidence of 7% TMJ involvement in patients with JIA is observed. Improvement of the condylar alterations was observed in most patients with initially affected condyles, implying a regenerative capacity of the condyle. In **Chapter 6** the condylar status after five-years of follow-up is described, confirming the ability of the condyle to improve and regenerate. These improvements are seen more in patients with a low disease activity.

Craniofacial development in Juvenile Idiopathic Arthritis
In **Chapter 7** an increased frequency of retrognathia and posterior rotated mandibles is observed in all patients with JIA, regardless of the TMJ status. Retrognathia and posterior rotation is even more frequent in patients with condylar alterations. In **Chapter 8 & 9** follow-up data on the course of craniofacial alterations are described. After one year of follow-up the overall prevalence of retrognathia and posterior rotation remains equal, although the overall prevalence of TMJ involvement decreased. After 5 years of follow-up

the overall prevalence of retrognathia remains equivalent, but a decrease in the overall prevalence of posterior rotation is reported. In both examinations an improvement in the degree of retrognathia and posterior rotation is observed. Improvement in the degree of retrognathia and posterior rotation is seen most in patients with improvement of the condylar alterations, and in patients without condylar alterations. The difference between the decrease in overall prevalence of posterior rotation and the equal overall prevalence of retrognathia can be explained by the fact that the growth centre in the condylar head influences the vertical relationship more than the sagital relationship of the mandible, which is also influenced by apposition and resorption mechanisms. Posterior rotation is a vertical relationship of the mandible and can therefore improve more than retrognathia, which is a sagital relationship.

In **Chapter 10** the main findings are discussed. Condylar alterations and facioskeletal alterations are a frequent feature in patients with JIA. Signs and symptoms of TMJ involvement are scarce, but if present are good predictors for TMJ involvement. The condylar alterations can improve over time and can even regenerate. Retrognathia and posterior rotation are more common in patients with JIA, regardless of the TMJ status. During follow-up an improvement in the degree of retrognathia and posterior rotation is observed. The overall prevalence of retrognathia remained equal while the overall prevalence of posterior rotation did decrease after five years.



CHAPTER 12

Nederlandse Samenvatting

Inleiding

Juveniele Idiopathische Artritis (JIA), in de volksmond ook wel jeugdreuma genoemd is een gegeneraliseerde auto-immuunziekte die op de kinderleeftijd voorkomt. JIA is een van de meest voorkomende auto-immuunziekten op de kinderleeftijd en treft ongeveer 1 op de 1000 kinderen. JIA is een heterogene groep van afwijkingen waarbij 7 verschillende subtypen worden onderscheiden (zie tabel 1). Deze verschillende subtypen hebben een aantal gezamenlijke criteria waar zij aan moeten voldoen. Deze criteria zijn; begin van de ziekte voor het 16^{e} levensjaar, de artritis moet langer dan 6 weken aanwezig zijn en alle andere mogelijkheden uit de differentiaal diagnose moeten uitgesloten zijn. De subtypen hebben allen verschillende inclusie en exclusie criteria en worden aan de hand van de ziektepresentatie en het beloop in de eerste 6 maanden opgesplitst. Alle subtypen hebben een verschillende initiële presentatie, beloop en prognose.

Tabel 1: ILAR classificatie JIA.

JIA classificatie
Systemische JIA
Oligoarticulaire JIA
persisterend
uitgebreid
Polyarticulaire JIA reumafactor negatief
Polyarticulaire JIA reumafactor positief
Enthesitis-gerelateerde-artritis
Artritis psoriatica
Ongedifferentieerde artritis

JIA kan alle gewrichten aantasten, inclusief het temporomandibulaire gewricht (TMJ). Door de oppervlakkige ligging van het belangrijkste groeicentrum voor verticale groei van de mandibula is dit groeicentrum kwetsbaar voor schade en destructie door JIA. TMJ betrokkenheid kan daardoor de mandibulaire ontwikkeling en groei aantasten. Deze craniofaciale afwijkingen werden voor het eerst beschreven door Diamantberger in 1890. In 1897 vond Still, in zijn onderzoek naar chronische artritis op de kinderleeftijd, betrokkenheid van de TMJ in 3 van zijn 22 casussen. Sindsdien laat de gerapporteerde frequentie van kaakafwijkingen bij kinderen met JIA een grote variatie zien; 17-87%. De gevonden frequentie hangt onder andere samen met de populatie kinderen die

is bestudeerd, de subtypen vertegenwoordigd en de gebruikte diagnostische methoden. De meeste studies tonen aan dat de TMJ's bilateraal zijn aangedaan, hoewel in 27-50% van de patiënten maar één van de TMJ's initieel betrokken is. Hoewel er de afgelopen drie decennia veel cross-sectionele studies met betrekking tot TMJ betrokkenheid zijn verricht, vonden deze vaak plaats in een geselecteerde groep patiënten. In veel studies waren maar enkele subtypen beschreven, alleen patiënten van een bepaalde leeftijd geincludeerd, of vond inclusie soms zelfs plaats op basis van een al bestaande TMJ afwijking. Er zijn maar weinig follow-up studies beschreven, wel beschrijven deze allen meer TMJ afwijkingen tijdens de follow-up duur en progressie van de al bestaande afwijkingen.
Om lange termijn gegevens van zowel de betrokkenheid van kaakgewricht als geassocieerde craniofaciale afwijkingen te onderzoeken werd het Temporomandibular joint Rheumatologic Involvement Project (TRIP) geïnitieerd. Het TRIP cohort bestaat uit 97 opeenvolgende patiënten met JIA, waarbij alle subtypen gerepresenteerd zijn.
In dit proefschrift zijn de bevindingen met betrekking tot condylaire afwijkingen, klinische symptomen en craniofaciale morfologie beschreven naar aanleiding van een algemeen baseline onderzoek (TRIP 0), een 1-jaars follow-up onderzoek (TRIP 1) en een 5-jaars follow-up onderzoek (TRIP 5).

Kaakafwijkingen bij Juveniele Idiopathische Artritis

In **hoofdstuk 2** wordt een historisch overzicht gegeven van de studies in 1964 tot april 2006 die onderzoek hebben verricht naar kaakafwijkingen bij JIA. In **hoofdstuk 3** laat het baseline onderzoek zien dat er sprake is van kaakafwijkingen in 45% van de patiënten. Klinische symptomen voor kaakafwijkingen zijn maar zelden aanwezig, echter indien zij aanwezig zijn dan zijn het ook goede voorspellers voor de aanwezigheid van kaakafwijkingen in patiënten met JIA. In afwezigheid van klinische symptomen is de kans op een kaakafwijking nog steeds verhoogd aanwezig. In **hoofdstuk 4** wordt een patiënt beschreven, die plotseling zonder symptomen ernstige kaakafwijkingen ontwikkelde. In **hoofdstuk 5** wordt een jaarlijkse incidentie van kaakafwijkingen bij JIA van 7% beschreven. Tevens worden er verbeteringen van de condylaire afwijkingen waargenomen, die duiden op een regeneratieve capaciteit van de condyle. In **hoofdstuk 6** worden deze verbeteringen na 5 jaar follow-up nog steeds waargenomen. Deze condylaire verbeteringen blijken voornamelijk voor te komen in patiënten met een lage ziekte-activiteit en minder uitgebreid medicatiegebruik.

Craniofaciale ontwikkeling bij Juveniele Idiopathische Artritis

In **hoofdstuk 7** wordt er een verhoogde frequentie van retrognathie en posterior geroteerde mandibula's in patiënten met JIA, ongeacht of er wel of geen afwijkingen aan het kaakgewricht zijn, waargenomen. Indien kaakafwijkingen aanwezig zijn, stijgt de prevalentie van retrognathie en posterior geroteerde mandibula's. In **hoofdstuk 8 & 9** worden de follow-up gegevens met betrekking tot de ontwikkeling van de craniofaciale morphologie beschreven. Na 1 jaar follow-up is de algehele prevalentie van retrognathie en posterior rotatie gelijk gebleven, terwijl de algehele prevalentie van condylaire afwijkingen is afgenomen. Na 5 jaar follow-up wordt er ook een daling in the prevalentie van posterior rotatie waargenomen. In beide follow-up studies neemt de mate van de retrognathie en de mate van de posterior geroteerde mandibula's af gedurende de follow-up. Patiënten die verbetering van de condylaire afwijkingen laten zien en de patiënten zonder condylaire afwijkingen, laten ook de meeste verbetering in de mate van de retrognathia en posterior geroteerde mandibula's zien. Het verschil in de daling van de prevalentie van posterior rotatie en het gelijk blijven van de prevalentie van retrognathie kan worden verklaard door het feit dat het groeicentrum gelegen in de condyle meer invloed heeft op de verticale ontwikkeling van het aangezicht dan de sagitale ontwikkeling, welke ook beinvloed wordt door apositie en resorptie mechanismen. Posterior rotatie van de mandibula is immers een verticale ontwikkeling, terwijl retrognathie een sagitale ontwikkeling is.

In **hoofdstuk 10** worden de belangrijkste bevindingen besproken. Condylaire en facioskeletale afwijkingen zijn frequent aanwezig in patiënten met JIA. Klinische tekenen voor betrokkenheid van het kaakgewricht zijn zeldzaam, indien aanwezig zijn het echter goede voorspellers van betrokkenheid van het kaakgewricht. Condylaire afwijkingen kunnen verbeteren en zelfs regenereren. Retrognathie en posterior rotatie worden meer gezien in alle patiënten met JIA, onafhankelijk van de status van het kaakgewricht. De mate van retrognathie en posterior rotatie neemt af tijdens de follow-up perioden. De algehele prevalentie van retrognathie blijft gelijk, terwijl de prevalentie van posterior rotatie is afgenomen na 5 jaar.

Dankwoord

Dankwoord

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Curriculum Vitae

Marinka Twilt is geboren op 16 mei 1976 in Spijkenisse. In 1994 behaalde zij haar VWO diploma aan het Riethill college te Raamsdonksveer. Van 1994 tot 1995 studeerde zij biologie aan de Universiteit van Utrecht. In 1995 werd zij nageplaatst voor de studie geneeskunde aan de Erasmus Universiteit te Rotterdam. In 1999 behaalde zij haar doctoraal en in 2001 haar artsexamen.
Hierna heeft zij als arts-assistent (AGNIO) kindergeneeskunde gewerkt in het Erasmus MC Sophia Kinderziekenhuis te Rotterdam en het Amphia Ziekenhuis te Breda.
Van januari 2003 tot september 2006 heeft zij gewerkt als artsonderzoeker bij de kinderreumatologie verbonden aan de polikliniek kindergeneeskunde in het Erasmus MC Sophia Kinderziekenhuis op het project “Inzet en effectiviteit van TNF-alfa blokkerende geneesmiddelen in Juveniele Idiophatische Artritis”, projectleider Dr. L.W.A. van Suijlekom-Smit.
Tijdens haar studie was zij al begonnen aan het Temporomandibular joint Rheumatologic Involvement Project (TRIP) onder leiding van Dr. L.W.A. van Suijlekom-Smit. Tijdens haar aanstelling als artsonderzoeker heeft zij de TRIP 5 studie verricht en de artikelen geschreven, die beschreven staan in dit proefschrift.
In 2005 behaalde zij een Master of Science in Clinical Epidemiology aan de Netherlands Institute for Health Sciences (NIHES) in Rotterdam. In september 2006 start zij de opleiding kindergeneeskunde in het Leids Universitair Medisch Centrum.

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