

Juvenile idiopathic arthritis

Manifestations in the jaws

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To my father

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ABSTRACT

Juvenile idiopathic arthritis (JIA) is an inflammatory joint disease in children that can involve the temporomandibular joint (TMJ), consequently affect craniofacial growth, jaw function creating discomfort and pain. It is possible that the TMJ is one of the most frequently involved joints in JIA. Earlier studies have often comprised a limited number of patients and different classification criteria have been used. The introduction of new medical therapies might have influenced the prognosis for JIA in the jaw system. The overall aim was to investigate how JIA manifests in the jaws by evaluating symptoms from the orofacial region in adults once diagnosed with JIA. Also investigate clinical, subjective and radiological involvement of the TMJ on panoramic radiographs of children with JIA. Facial growth as judged on cephalometric radiographs was also evaluated. All the findings were related to medical treatment and disease activity over time. We found that adult patients with JIA report more pain and dysfunction in the orofacial region compared with healthy controls. Our study shows associations between orofacial signs, symptoms and overall disease activity in children with JIA. TMJ condylar alterations on panoramic radiographs are fairly common and active disease appears to increase the risk of alterations despite medication. Children with JIA seems to have a changed growth pattern compared with a healthy reference group and patients with condylar alterations have more retrognathia and posterior rotated mandibles. An early TMJ diagnosis in children with JIA is important in order to prevent a negative effect on the TMJs. There is a lack of consensus on when and how to treat JIA in terms of the TMJ. Longer follow-up studies and further prospective studies with the emphasis on the progress of TMJ arthritis and the influence on facial growth are necessary.

Keywords: children, adults, juvenile rheumatoid arthritis, retrospective, temporomandibular joint

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SAMMANFATTNING PÅ SVENSKA

Juvenil idiopatisk artrit (JIA) är den vanligaste inflammatoriska ledsjukdomen som drabbar barn och ungdomar under 16 år. I Sverige är incidensen 14/100000 och prevalensen 1 på 1000. JIA karaktäriseras av inflammation i en eller flera leder med symptom i form av smärta och tillväxtstörningar. Man har sett att käkleden är en av de mest drabbade lederna. En påverkan på käkleden kan ge smärta, försämrad underkäksfunktion och störd tillväxt. Det är inte alltid inflammationen i käkleden ger några kliniska symptom varför den ibland kallas "tysta leden". Detta kan leda till att grava inflammatoriska förändringar kan hinna uppstå innan sjukdomen upptäcks. Genom en panoramaröntgen undersökning kan man se förändringar på käkledshuvudet och genom en profilröntgen (kefalometri) kan man studera tillväxtmönster av under- och överkäke. Den farmakologiska behandlingen syftar till att minska smärta och dämpa inflammationen i lederna. Syftet med avhandlingen var att utvärdera manifestationer i käkar hos barn och vuxna med JIA genom en enkätstudie. Ett annat syfte var att genom en retrospektiv genomgång av medicinska och odontologiska journaldata, granskning av befintliga röntgenutredningar i form av panorama och profilröntgen analysera och se eventuella samband mellan kliniska symptom och kliniska tecken från det orofaciala området. Vi vill också undersöka käkledsförändringar på panoramaröntgen, tillväxtförändringar på profilröntgen samt analysera effekten av medicinering och sjukdomsaktivitet över tid. Vi fann att vuxna som tidigare diagnosticerats med JIA har en ökad förekomst av besvär från det orofaciala området än motsvarande friska kontroller. Vi har sett att det finns ett samband mellan symptom och kliniska tecken och sjukdomsaktivitet hos barn med JIA. En aktiv sjukdom över tid ökar risken för käkledsförändringar trots medicinering. Käkledstillväxten hos barn med JIA var annorlunda mot en referensgrupp av friska svenska barn. De barn som hade käkledsförändringar på panoramaröntgen hade också ett förändrat tillväxtmönster av ansiktstillväxten. Det är viktigt att utreda och följa upp patienter med JIA avseende smärta och käkfunktion för att tidigt upptäcka inflammatoriska förändringar i käkleden och undvika besvär och tillväxtstörningar av käkarna. Det finns idag ingen consensus över hur vi ska följa och behandla käkleden på patienter med JIA därför är större prospektiva studier i området av betydelse

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

- I. Engström A-L, Wänman A, Johansson A, Keshishian P, Forsberg M. Juvenile arthritis and development of symptoms of temporomandibular disorders. A 15-year prospective cohort study. *J Orofac Pain* 2007; 21: 120-126.
- II. Cedströmer A-L, Andlin-Sobocki A, Berntson L, Hedenberg-Magnusson B, Dahlström L. Temporomandibular signs, symptoms joint alterations and disease activity in juvenile idiopathic arthritis-an observational study. *Pediatr Rheumatol Online J* 2013; 11:37 doi: 10.1186/1546-0096-11-37.
- III. Cedströmer A-L, Ahlqwist M, Andlin-Sobocki A, Berntson L, Hedenberg-Magnusson B, Dahlström L. Temporomandibular condylar alterations in juvenile idiopathic arthritis most common in longitudinally severe disease despite medical treatment. *Pediatr Rheumatol Online* 2014; 12: 43 doi: 10.1186/1546-0096-12-43
- IV. Cedströmer A-L, Andlin-Sobocki A, Berntson L, Abbu N, Hedenberg-Magnusson B, Dahlström L. Facial growth in juvenile idiopathic arthritis. Submitted

CONTENT

ABBREVIATIONS	IV
1 INTRODUCTION	1
1.1. Evolution of classification in childhood arthritis	1
1.2. Clinical manifestations of JIA	4
1.3. Treatment of JIA	5
1.4. Disease activity	5
1.5. Outcome of JIA	6
1.6. Temporomandibular disorders (TMD) in children and adolescents	6
1.7. Pain and jaw function in JIA	7
1.8. Temporomandibular joint involvement in JIA	7
1.9. Condylar growth of the TMJ in JIA	8
1.10. Imaging of the temporomandibular joint	8
1.11. Facial growth in JIA	9
1.12. Long-term effects of JIA on jaw function	9
1.13. Outcome of JIA in the jaw system	9
2 AIMS	11
3 PATIENTS AND METHODS	12
3.1 Study I	12
3.1.1 Study population	12
3.2 Studies II-IV	13
3.2.1 Study population	13
3.2.2 Study II	15
3.2.3 Study III	16
3.2.4 Study IV	17
3.3 Statistics	18
3.4 Legal and ethical aspects	19
4 RESULTS	20
4.1 Study I	20

4.2 Study II.....	20
4.3 Study III.....	21
4.4 Study IV	22
5 DISCUSSION	23
5.1 Methodological aspects	23
5.1.1 Study design.....	23
5.2 Imaging.....	23
5.3 Clinical examination.....	24
5.4 General discussion.....	24
5.5 Representativity of the study population.....	30
6 CONCLUSIONS.....	31
7 FUTURE PERSPECTIVES	32
ACKNOWLEDGEMENTS	33
REFERENCES	35
APPENDIX.....	45

ABBREVIATIONS

ACR	American College of Rheumatology
ANA	anti-nuclear antibodies
COVs	core outcome variables
CT	computed tomography
DMARD	disease-modifying anti rheumatic drug
ERA	enthesitis-related arthritis
EULAR	European League Against Rheumatism
HLA	human leukocyte antigen
IBD	inflammatory bowel disease
IL	interleukin
ILAR	International League of Associations for Rheumatology
JAS	juvenile ankylosing spondylitis
JCA	juvenile chronic arthritis
JIA	juvenile idiopathic arthritis
JPsA	juvenile psoriatic arthritis

JRA	juvenile rheumatoid arthritis
MDA	minimal disease activity
MRI	magnetic resonance imaging
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
RA	rheumatoid arthritis
RF	rheumatoid factor
SpA	spondyloarthropathy
TMD	temporomandibular disorders
TMJ	temporomandibular joint
TNFalpha	pro-inflammatory cytokine tumour necrosis factor alpha

1 INTRODUCTION

Juvenile idiopathic arthritis (JIA) is primarily an inflammatory joint disease that affects children and in many cases involves the temporomandibular joint (TMJ). The consequence can be a change in craniofacial growth, together with affected jaw function that can create discomfort and pain.

JIA is the most common systemic autoimmune disease in children and adolescents and the incidence varies in different countries. In a Nordic population-based, study the incidence in Sweden was 14/100,000 (Berntson et al. 2003). Worldwide, the incidence varies greatly (Ravelli et al. 2007). The course of the disease fluctuates. The prevalence in Sweden is one in 1,000 children (Andersson Gäre et al. 1992, Berntson et al. 2003). Girls are more susceptible than boys, with a ratio of 3:1 (Andersson GGde et al. 1992). The course of the disease is very heterogeneous.

1.1. Evolution of classification in childhood arthritis

Mayer S. Diamantberger first distinguished chronic arthritis in children from adult arthritis in his doctoral thesis in 1891 (Diamantberger 1890). In 1897, the British physician George F. Still, published a paper in which he reported that arthritis in children differed in clinical respects from rheumatoid arthritis (RA) in adults (Still 1897). Since then, several publications have addressed the differences between chronic arthritis in childhood and RA in adults. Chronic childhood arthritis is a group of several distinct diseases and the diagnosis is based on clinical assessments, without pathognomonic findings or objective confirmatory laboratory tests, and the exclusion of other diseases. (Nistala et al. 2009, Prakken et al. 2009, Frosch et al. 2008).

Classifications of the disease have varied over time and in different parts of the world. In recent decades, different classifications have been primarily suggested.

In the United States and Canada, a definition of juvenile rheumatoid arthritis (JRA) was presented and revised in 1977 by the American College of Rheumatology (ACR). They described JRA as an idiopathic arthritis with a minimum of six weeks' duration in an individual under the age of 16 years. After six months' of duration, the disease is divided into systemic,

pauciarticular (one to four joints affected) or polyarticular (more than five joints affected) (Brewer et al. 1977).

In the European classification, which was also presented in 1977, the European League Against Rheumatism (EULAR) used the term “juvenile chronic arthritis (JCA)”. The idiopathic condition has to last for three months in an individual less than 16 years of age. The criteria were listed as systemic, pauciarticular and polyarticular. In order to encompass all forms of chronic inflammatory arthritis, it also included juvenile ankylosing spondylitis (JAS), juvenile psoriatic arthritis (JPsA) and arthropathy associated with inflammatory bowel disease (IBD) (EULAR 1977).

In 1995, the Paediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) devised the present classification, which is used worldwide (Petty et al. 2004, Southwood et al. 1997). The ILAR committee grouped the different categories of disease under the umbrella term “juvenile idiopathic arthritis (JIA)”. The criteria were revised in 1997 and 2001 (Petty et al. 2004). The condition must last for more than six weeks and appear before the age of 16 (Fink et al. 1995, Martini et al. 2010, Ravelli et al. 2007, Cassidy et al. 1986). The ILAR criteria divide clinically distinguishable disease groups into seven categories based, first and foremost on the number of joints involved, and they are now used worldwide. Importantly, the ILAR classification represents the first attempt to reach an international consensus, aiming to facilitate the comparison of scientific studies. Table 1 summarises the definition of the seven categories of JIA according to the ILAR classification criteria.

Table 1. Classification of juvenile idiopathic arthritis

Category	Definition
Systemic arthritis	Fever lasting at least two weeks and arthritis in ≥ 1 joint, plus one or more of the following: erythematous rash, generalized lymph node enlargement, hepatomegaly and/or splenomegaly serositis Exclusions: a, b, c, d
Oligoarthritis	Arthritis affecting ≤ 4 joints during the first six months of disease. There are two subcategories: Persistent = affecting ≤ 4 joints throughout the disease Extended = affecting > 4 joints after the first six months of disease Exclusions: a, b, c, d, e
Polyarthritis, RF-	Arthritis affecting ≥ 5 joints during the first six months of disease, RF negative Exclusions: a, b, c, d, e
Polyarthritis, RF+	Arthritis affecting ≥ 5 joints during the first six month of disease, RF positive at least 2x on tests at least three months apart. Exclusions: a, b, c, e
Psoriatic arthritis	Arthritis + psoriasis, or arthritis and at least two of the following: dactylitis, nail pitting or onycholysis, psoriasis in a first-degree relative Exclusions: b, c, d, e
Enthesitis-related arthritis	Arthritis + enthesitis or arthritis or enthesitis with at least two of the following: presence/history of sacroiliac joint tenderness and or inflammatory lumbosacral pain HLA-B27+ Onset of arthritis in a male over six years of age Acute (symptomatic) anterior uveitis History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis in a first-degree relative Exclusions: a, d, e
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or in two or more of the above categories

The principle of this classification is that all the categories of JIA are mutually exclusive. This principle is reflected in the list of possible exclusions for each category:

- a) Psoriasis or a history of psoriasis in the patient or a first-degree relative
- b) Arthritis in an HLA-B27-positive male beginning after his sixth birthday
- c) Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis or a history of one of these disorders in a first-degree relative
- d) The presence of IgM rheumatoid factor and at least two occasions at least three months apart

The presence of systemic JIA in the patient
RF = Rheumatoid Factor

Adapted from Petty et al. (2004)

Systemic JIA is characterised by prominent systemic features, such as fever, rash and serositis (Ravelli et al. 2007). Today, this category is considered to have an autoinflammatory origin rather than an autoimmune one. Patients with RF-positive polyarthritis represent 1-3% of all cases of JIA and are believed to be similar to those suffering from adult RF-positive RA (van Rossum et al. 2003). Enthesitis-related arthritis (ERA) is a form of undifferentiated spondyloarthropathy (SpA). (Colbert et al. 2010). In all 75-80% of patients with ERA are HLA-B27 positive and the occurrence of the antigen is one of the inclusion criteria for ERA. The category of oligoarthritis is the most common category of JIA, heterogeneous and well defined, which is only seen in children (Martini et al. 2003). There are two subcategories of oligoarthritis: a persistent form in which the disease affects four joints or fewer and an extended form in which more than four joints are affected after the first six months of disease (Petty et al. 2004). RF-negative polyarthritis is a heterogeneous group of JIA patients comprising patients with the involvement of five or more joints during the first six months of the disease but negative in RF. The occurrence of ANA, age at onset and remission status are very similar to the oligoarticular extended category. In adult rheumatology, it is well known that patients with psoriatic arthritis run the risk of developing sacroiliitis (McGonagle et al. 2005, McGonagle et al. 2007). The ILAR criteria keep the juvenile psoriatic arthritis strictly apart from the ERA category. If a child with JIA develops signs of sacroiliitis, it can only be classified as ERA or as undifferentiated. The undifferentiated category is fairly common, approximately 14% in Swedish population-based studies. Many of these children have been excluded from the ERA category or fit into more than one category. This demonstrates a weakness of the ILAR criteria. The classification is under evaluation (Nordal et al. 2011) and, as a result, the discussion George Still initiated in 1896 concerning the definition is ongoing even today.

1.2. Clinical manifestations of JIA

The vast majority of children with JIA have arthritis. The definition of arthritis by the ILAR is based on clinical findings of joint swelling or limited range of joint mobility with pain and tenderness. Any joint may be affected. The initial changes in a joint with arthritis take place in the synovial membrane. The immunological reaction with oedema and the accumulation of plasma cells, T- and B-lymphocytes and macrophages leads to the production of pro-inflammatory mediators, such as cytokines. The cytokines activate more inflammatory cells, the vascularity increases and there is an increase in the synovial layer thickness. The hyperplastic synovium changes

to villous hyperplasia termed “pannus”. The pannus infiltrates and erodes the articular cartilage and adjacent bone (Textbook of pediatric rheumatology 2011). Enthesitis is defined as inflammation of the sites where the tendons, ligaments, capsules or fascia are attached to bone and it can be difficult to differentiate clinically from arthritis (Borman et al. 2006). Enthesitis is seen primarily in the JIA category of ERA. Other extra-articular manifestations that are common in JIA include uveitis, tenosynovitis, dactylitis and occasionally systemic involvement such as lymph node enlargement, hepato- and splenomegaly, serositis and fever.

1.3. Treatment of JIA

The management of JIA is based on a combination of pharmacological interventions, physical and occupational therapy, as well as psychosocial support. The pharmacological treatment of JIA is a challenge, because no single drug is able to cure the many variants of the disease. The treatment is mainly symptomatic, employing a multidisciplinary approach and is directed at minimising inflammation that causes joint damage, impaired growth and development, long-term disability and a secondary decrease in quality of life (Ravelli et al. 2007). Over the past few decades, new medical therapies have improved disease control (Textbook of pediatric rheumatology 2011). In the majority of patients, non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment, because they suppress the mediators of inflammation, reduce pain and improve mobility. Intra-articular corticosteroid injections prevent deformities and are commonly used (Lanni et al. 2011). Disease modifying anti-rheumatic drugs (DMARD) are the next choice and methotrexate (MTX) has been chosen most frequently since the first publication on its use in 1986, while the most effective dose was proposed in a randomised trial (Ruperto et al. 2011). New drugs that bind and inactivate the pro-inflammatory cytokine tumour necrosis factor alpha (TNFalpha), have led to important improvements in the management of JIA in recent years (Ravelli et al. 2007). Other so-called biological therapies have added further opportunities to modify the action of cytokines involved in the inflammatory process. Even though studies of medical therapies in JIA have increased, the basis for therapy largely relies on experience (Hashkes et al. 2005).

1.4. Disease activity

Disease activity has been evaluated in different ways over time. According to the recommendations of the European League Against Rheumatism

(EULAR) (Andersson-Gäre et al. 1995), disease activity can be described as active disease (with an increased number of engaged joints), stable disease (where the engaged joints are unchanged), inactive disease (without treatment for less than two years) and remission (with no disease activity and no treatment for more than two years). In 1997, the core outcome variables (COVs) were published (Giannini et al. 1997), with a minimum level of improvement as a primary outcome in JIA (the ACR paediatric 30 response criteria). It requires an improvement of at least 30% from baseline in three of the six COVs, with no more than one of the six deteriorating by > 30%. In 2004, an international consensus group developed preliminary criteria for inactive disease and clinical remission (Wallace et al. 2004). Nowadays, the term “minimal disease activity (MDA)” has come to the agenda. A preliminary definition of MDA was validated in 2008 (Magni-Manzoni et al. 2008).

1.5. Outcome of JIA

In order to study the outcome of JIA, population-based studies are most relevant. In a long-term prospective study of JIA in a population-based Nordic setting, Nordal et al. (2011) found that ongoing disease was evident in 58% of the children after eight years of disease. Flato et al. (2003) conducted a prospective study on 316 patients with JIA. After a median of 14.9 years of disease duration, they found that the disease was in remission for half the patients, 24% had developed joint erosions and 36% had impaired physical function. Generally, patients with JIA had more disability, more bodily pain and poorer general health than the controls. In another study, an 11-year follow-up study of 26 patients, those with JIA with the oligoarticular persistent category had the best prognosis, while growth abnormalities and radiographic changes were more commonly found in those with polyarticular JIA and the systemic onset of disease (Narayanan et al. 2002)

1.6. Temporomandibular disorders (TMD) in children and adolescents

Temporomandibular disorders (TMD) represent a group of conditions characterised by pain and dysfunction in the TMJ and the surrounding tissues (Dworkin et al. 1992). Different indices have commonly been applied to summarise signs and symptoms from the orofacial area in epidemiological surveys. Helkimo’s dysfunction and anamnestic indices (Helkimo 1974) are indices that have been commonly used in epidemiological contexts (Carlsson et al. In: Temporomandibular joint and masticatory muscle disorders 1994)

among children and adolescents (Toscano et al. 2009). A widely accepted and used classification system is the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin et al. 1992). This classification system included an Axis I physical assessment and an Axis II assessment of psychosocial status and pain-related disability. It remains a model for pain research and has now been replaced by the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) (2014) for both clinical use and research (Schiffman et al. 2014). Ranges of TMD pain vary in healthy individuals, from 8-15% for women and 3-10% for men, in population-based studies (Dao et al. 2000). In children before puberty, pain is rare (le Resche et al. 2007).

1.7. Pain and jaw function in JIA

To get the diagnosis of TMD according to Research Diagnostic Criteria, general joint disease must be lacking. It is, however, reported that children with JIA have dysfunction in the TMJ and can have symptoms and signs of TMD, such as clicking, regardless of their general joint disease. In the literature, there are vast discrepancies between reports on pain and dysfunction among patients with JIA. Pain from the jaws during function and rest may be severe in JIA, as well as limited opening capacity, joint sounds, locking and palpatory tenderness in the TMJ and associated muscles (Ringold et al. 2009). The prevalence of signs and symptoms in the masticatory system in patients with JIA has varied between 17%-87% in previous studies, (Billiau et al. 2007, Pedersen et al. 2001, Twilt et al. 2004), with large differences between previous subcategories. This disparity might be due to large variations in patient sample composition but also to the examination methods used. Furthermore, the number of examined subjects has often been limited.

1.8. Temporomandibular joint involvement in JIA

It has been suggested that the temporomandibular joint is one of the most frequently involved joints in JIA, according to radiographic changes (Ringold et al. 2009). Swelling is seldom seen and arthritis in the TMJ is often asymptomatic. As a result, the TMJ has been called “the forgotten joint” in paediatric rheumatology (Arabshani et al. 2006). The reported prevalence of TMJ involvement varies from 17% to 87% depending on the population investigated, the categories of JIA represented and the radiological method by which involvement is diagnosed (Kjellberg et al. 1998, Kùseler et al. 1998,

Mayne et al. 1969, Mericle et al. 1996, Ronchezel et al. 1995). TMJ involvement is thought to occur during the active phase of JIA, when the inflammation generates chondral and subchondral bone lesions and the consequences for mandibular growth and development may be considerable, regardless of whether or not there are signs and symptoms (Kjellberg 1995 a). TMJ arthritis might be present despite limited or otherwise quiescent disease and in the presence of concurrent systemic immunomodulatory therapy (Stoll 2012, Arabshahi et al. 2005). Subjective symptoms display a vast variation (Müller et al. 2009, Svensson et al. 2000, Twilt et al. 2004, Weiss et al. 2008, Olsson et al. 1991)

1.9. Condylar growth of the TMJ in JIA

The TMJ is unique because it presents with special features compared with other joints. The articular layer is composed of dense fibrous connective tissue rather than hyaline cartilage and the condylar growth is situated in close proximity to the articular surface and joint capsule rather than the growth plate, as in long bones. A disc is present for hinging and gliding movements and the two joints are connected and dependent on each other (Pirttiniemi et al. 2009). Arvidsson et al. (2009) suggest that condylar alterations in JIA may be caused by undergrowth, secondary to growth centre damage, or overgrowth, possibly related to inflammation-induced increased vascularisation and growth factor release. The result is a deformed joint due to remodelling (Arvidsson et al. 2009, Arvidsson et al. 2010).

1.10. Imaging of the temporomandibular joint

As involvements of the TMJs are often asymptomatic, imaging examination appears to be important to evaluate JIA involvement in this particular joint (Twilt et al. 2008). Different imaging methods for the TMJ exist. In the last few decades, magnetic resonance imaging (MRI) has become the golden standard for examining the TMJs in children with JIA, as it has been found to be an efficient method for detecting early inflammatory changes (Küseler et al. 1998, Weiss et al. 2008, Cannizzaro et al. 2011). On MRI, it is possible to detect ongoing inflammation (Weiss et al. 2008). Computed tomography (CT) is also a widespread technique and it is often used in this context (Hu et al. 1996, Arvidsson et al. 2010). Arvidsson et al. (2010) found that 70% of JIA patients had TMJ involvement on CT and MRI. MRI and CT are demanding, expensive examinations. In contrast, panoramic radiography is simple, inexpensive, with relatively low radiation doses (Cohnen et al. 2002), commonly available and requires no sedation in young children. On

panoramic radiographs, it is only possible to see old damage and changes on the skeleton. It is often performed prior to MRI or CT examinations in clinical practice. Previous studies have found condylar lesions on panoramic radiographs in 17-78% of patients with JIA (Rønning et al. 1974, Pedersen et al. 2001, Twilt et al. 2004, Billiau et al. 2007, Arvidsson et al. 2009). There is thus a substantial spread in the results relating to the prevalence of condylar lesions among patients with JIA, even when the same radiological technique has been used.

1.11. Facial growth in JIA

TMJ involvement has been regarded as the most important cause of changed facial growth (Kjellberg et al. 1998). The condyle can grow to the third decade (Pirttiniemi et al. 2009), as different from the suture of the maxilla, which is almost completed at 10 years of age (Irie et al. 1975). If the condylar growth is inhibited, the lower jaw rotates backwards in relation to the cranial base, giving a steeper mandibular plane angle and a shorter posterior facial height (Kjellberg et al. 1995 b, Kjellberg et al. 1995 c). The result is a more convex profile and reduced mandibular protrusion. Asymmetries can emerge if the condyles are differently affected. Structural changes seen radiographically can recover and normalise in cases with low disease activity (Arvidsson et al. 2010, Twilt et al. 2009).

1.12. Long-term effects of JIA on jaw function

Few studies have been published on the long-term effects of JIA on jaw function and all are referral based. Follow-up studies have shown the progression of the disease in the TMJs; new abnormalities or the progression of existing abnormalities (Rønning et al. 1981, Pedersen et al. 2008, Mussler et al. 2010). Moreover, improvement in the condylar alterations including normalisation with panoramic radiography, has been reported (Twilt et al. 2007, Twilt et al. 2008).

1.13. Outcome of JIA in the jaw system

Little is known about the outcome of JIA in the TMJs. Earlier studies have often covered a limited number of patients and have not always used the ILAR criteria for classification. In addition, the introduction of new medical therapies might have changed the prognosis for JIA in the jaw system. Our intention was to evaluate how signs and symptoms of the orofacial region,

disease activity and medication over time were associated with condylar alterations on panoramic radiographs in children with JIA.

2 AIM

The overall aim was to investigate how JIA manifests in the jaws.

Specific aims:

1. To evaluate the development of symptoms from the orofacial region over time in a cohort of patients with JIA compared with a cohort of matched healthy control patients
2. To describe systematically the clinical and subjective involvement of the TMJ and associated structures in children diagnosed with JIA and relate the findings to disease activity and TMJ condylar alterations, as assessed on panoramic radiographs
3. To evaluate how longitudinal medical treatment of JIA and the burden of disease activity influence the development of TMJ condylar alterations as assessed on panoramic radiographs
4. To investigate on cephalometric radiographs the facial morphology of children with JIA and relate the findings to disease activity over time and to TMJ condylar alterations assessed on panoramic radiographs

3 PATIENTS AND METHODS

3.1 Study I

3.1.1 Study population

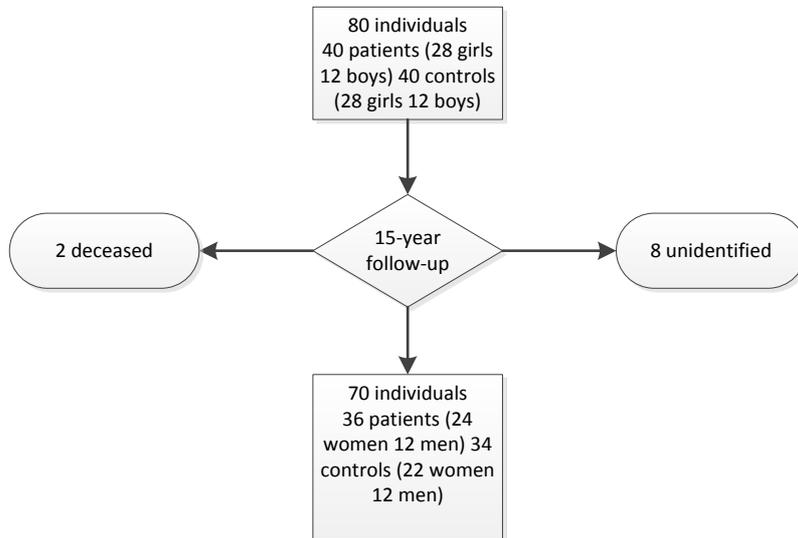


Figure 1. The original cohort and the follow-up cohort of patients with JIA and gender- and age-matched control group

The original cohort comprised 40 patients, 28 girls and 12 boys, who were referred from the Department of Paediatrics and Rheumatology at the University Hospital in Umeå, Sweden. The inclusion criteria were arthritis for at least three months before 16 years of age. Patients with psoriatic arthritis were excluded. The mean age at the original examination was 18 years. The age of onset ranged from one to 14 years and the duration of the disease varied from eight to 24 years. Sixteen had a clinical disease profile like polyarticular and 24 belonged to the oligoarticular category. The control group, $n=40$, was matched in terms of age and gender. The control sample had not been diagnosed with general joint disease and the patients' closest relatives were also free of joint disease.

At the 15-year follow-up, the study comprised 70 individuals, 36 with JIA, 24 women and 12 men, and 34 from the control sample, 22 women and 12 men. Two had died and the addresses for eight subjects could not be found.

The study consisted of a questionnaire in which the first part included the subjects' estimation of their own general health (good, neither good nor bad, bad), intake of medication and chewing ability. The second part of the questionnaire related to whether the subjects had any jaw-related symptoms (pain at rest and function, difficulty opening the mouth wide, stiffness/fatigue, TMJ sounds, headaches and neck and shoulder pain). To determine the frequency of jaw-related symptoms, they were evaluated, using 5 alternatives: never, once/twice a month, once a week, several times a week and daily. Helkimo's anamnestic index (Ai) was calculated to define the severity of the symptoms. The third part included questions relating to awareness of different parafunctions, type of joint disease, employment, quality of life, impairment of daily life (ability to do housework unhindered, to move/walk freely and whether their quality of sleep was good) and utilisation of health care owing to TMD (surgery, steroid therapy, acupuncture, heat, analgesics, occlusal adjustments, splint, transcutaneous electrical nerve stimulation, massage).

3.2 Studies II-IV

3.2.1 Study population

All patients who fulfilled the ILAR criteria for JIA (Petty et al. 2004) and who were referred to one of three specialist dental clinics in Sweden (Department of Surgical Sciences, Oral and Maxillofacial Surgery in Uppsala, the Orofacial Pain Specialist Clinic in Gothenburg and the Department of Clinical Oral Physiology at the Eastman Institute in Stockholm) over an eight-year period (between 1 January 1999 and 31 December 2006) were included. Eligible patients had to be born after 1 January 1986, as they were covered by free dental care and therefore more likely to come to an examination.

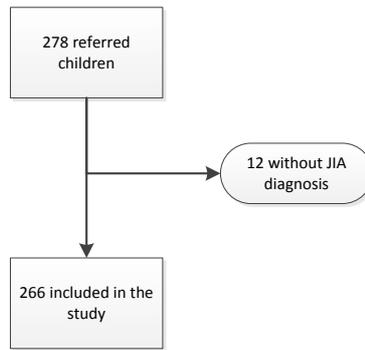


Figure 2. The 266 JIA patients included in Study 2

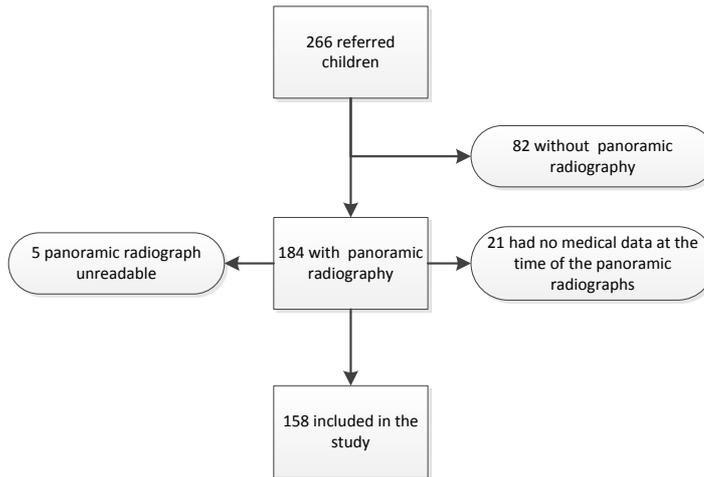


Figure 3. The JIA patients included in Study 3

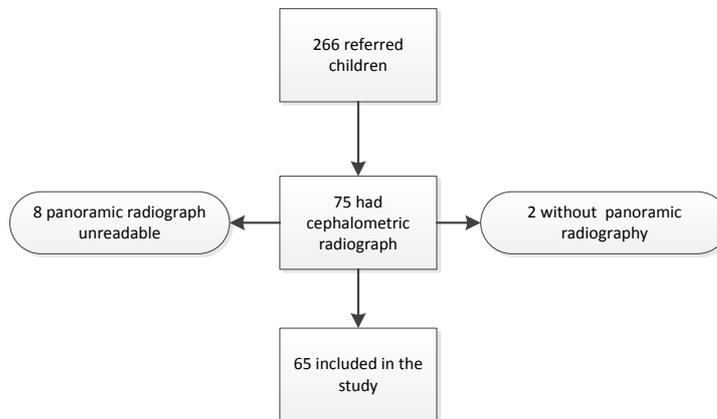


Figure 4. The JIA patients included in Study 4

Method

3.2.2 Study II

A specialist dentist made a clinical assessment, according to structured protocols, of orofacial signs at the study visit. Anamnestic information related to patient-reported symptoms was collected using standardised questions to the patient and/or parents/carers on the same occasion. The evaluations by the specialist dentists were read retrospectively and Helkimo's indices (Helkimo 1974) were calculated. Helkimo's clinical dysfunction index, Di 0-III, evaluates mandibular mobility, TMJ function, muscle pain, TMJ pain and pain on movement of the mandible on a three-point scale of increasing severity; 0, 1 or 5. The sum, 0-25 points, constitutes the dysfunction score, which forms the basis of the clinical dysfunction index. The signs found at the clinical examination can thus be expressed as Di 0 (0 points, no signs), Di I (1-4 points, mild signs), Di II (5-9 points, moderate signs), or Di III (10-25 points, severe signs). Helkimo's anamnestic index, Ai 0-II, summarises TMJ sounds, fatigue/stiffness of the jaw, pain, difficulty moving the jaw, locking and luxation. Ai 0 denotes the complete absence of subjective symptoms, Ai I denotes mild symptoms, such as joint sounds, stiffness or fatigue of the jaws, Ai II denotes severe symptoms, with one or more of the following reported in the anamnesis: difficulty opening the mouth wide, locking, luxation or pain on movement, facial and jaw pain.

Data from medical records at the paediatric rheumatology clinics where the participating patients were treated were collected and interpreted under the supervision of one paediatric rheumatologist. General disease activity during the last two years before the study visit was recorded.

Table 2. A modified version of the European League Against Rheumatism (EULAR) criteria, as presented by Andersson-Gäre (Andersson Gäre 1995), was used with the addition of one further category (five categories).

EU	Disease activity according to EULAR
1	Active disease (increasing number of engaged joints)
2	Stable (unchanged number of engaged joints)
3	Inactive with treatment (no disease activity)
4	Inactive without treatment (no disease activity and no treatment for less than two years)
5	Remission (no disease activity and no treatment for more than two years).

Presence/absence of condylar alterations, morphological (flattening, osteophyte) or structural (erosion, sclerosis, subchondral cysts), was evaluated on panoramic radiographs. The dichotomous assessment, alteration/no alteration, was made by one dentist, together with an oral radiology specialist, until consensus was reached; all on one occasion. Both were blinded to all other dental and medical information.

3.2.3 Study III

Evaluations of the TMJs on panoramic radiographs were made as in Study II. The latest panoramic examination was used for analysis. Seventy-two patients had only one panoramic radiograph performed. Moreover, any toadstool appearance of the condyles, as described by Petrovski et al. (2009), was registered separately. In this condition the condyle is flattened, elongated and dorsally inclined. The condylar neck is shortened or absent.

If one or both condyles were judged as “unreadable”, the individual was excluded. Eighty-six percent of the radiographs were digital and analysed on monitors, while analogous radiographs were analysed in an X-ray light box. Fifty randomly selected cases were evaluated until consensus was reached a second time after three weeks, in order to establish the reliability of the evaluation over time.

The total pharmacological treatment was evaluated longitudinally from disease onset, established by the rheumatologist, to the time of the panoramic examination. Medication with DMARDs, which included MTX, and/or biologically modifying medications, including tumour necrosis factor alpha inhibitors (TNF-alpha) and/or corticosteroid injections in the TMJ, was denoted “potent medication”. The use of “potent medication” for six months or more was denoted a “medication period”. An evaluation of medical treatment was performed for each six-month period during the first year after onset and then once every year until panoramic examination. A shorter period than six months of “potent medication” or patients only using non-steroidal anti-inflammatory drugs (NSAID) were not included.

The disease activity groups were the same as in Study II, except that activity was evaluated longitudinally from disease onset to the time of the panoramic examination and not only the last two years. Disease activity, defined as EU 1 and/or 2 for six months or more, was denoted “active disease”. The first year after onset was evaluated for each six-month period and thereafter once every year. The time from disease onset to the date of the radiological examination could thus be described as the number of “medication periods”

and “active disease periods”. The number of “medication periods” and “active disease periods” varied from 0 to 8 and patients were followed for seven years at most.

3.2.4 Study IV

At least one cephalometric radiograph had to be performed during the study period to be included in this study. Seventy-five patients of the 266 previously included had a cephalometric radiograph performed. Eight were judged as unreadable and two patients had no panoramic radiograph to compare with and as a result, 65 patients were included, 50 girls (77%) and 15 boys (23%). Their median age was 12.0 years.

The facial morphology evaluated on the cephalometric radiograph was compared with condylar alterations on panoramic radiographs that were performed approximately the same year as the cephalometric radiograph. The evaluations of the TMJs on the panoramic radiographs were performed as previously described.

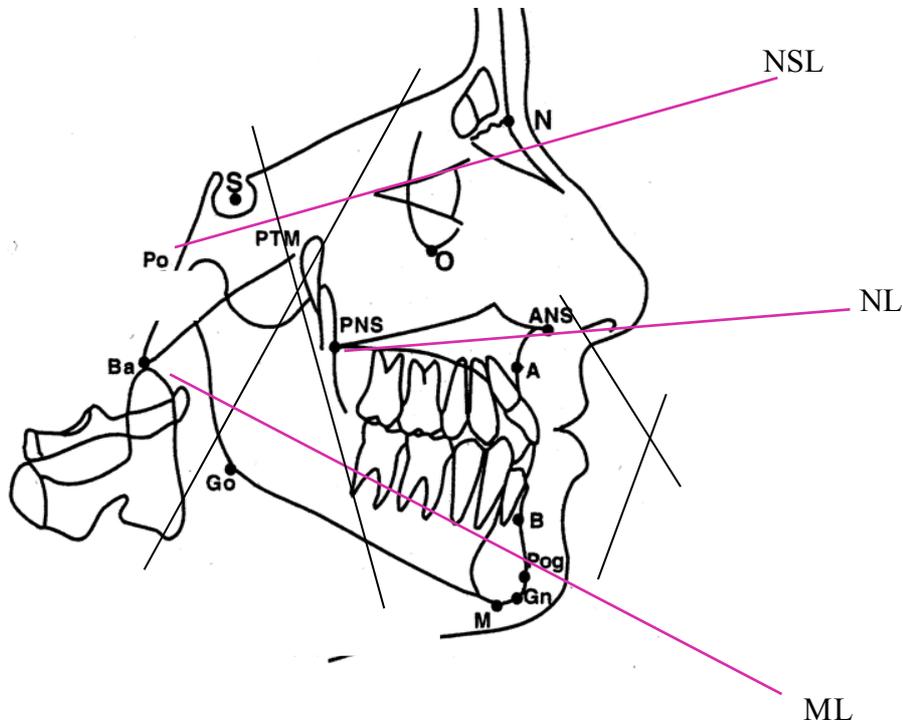


Figure 5. Reference points and lines used in the cephalometric analysis.
Reference points: A (subspinale, the deepest point in the concavity of the anterior maxilla between the anterior nasal spine and the alveolar crest), ANS (anterior

nasal spine, the tip of the anterior nasal spine), B (supramentale, the deepest point in the concavity of the anterior mandible between the alveolar crest and pogonion), Ba (basion, the most inferior point on the anterior margin of the foramen magnum, Gn (gnathion, the most antero-inferior point on the bony chin), Go (gonion, a mid-planned point at the gonial angle of the mandible located by bisecting the posterior and inferior borders of the mandible), Me (menton, the lowest point on the lower border of the mandibular symphysis, N (nasion, the junction of the frontal and nasal bones at the naso-frontal suture), Pg (pogonion, the most anterior point on the mandibular symphysis), PNS (the tip of the posterior nasal spine), S (sella, the centre of the sella turcica),), Ii (the incisal tip of the lower central incisor) Is (the incisal tip of the upper central incisor), Ili (the incision line inferius), IIs (the incision line superius).

Reference lines: NSL (nasion-sella line, the line through points N and S) NL (nasal line, the line through points ANS and PNS), ML (mandibular line, the tangent to the lower border of the mandible through M and Go).

The cephalometric radiographs were performed under standardised conditions with a natural head position and the teeth in centric occlusion. The lateral cephalometric radiographs were analysed using the FACAD 3.0 software cephalometric tracing program. Cephalometric measurements were carried out using conventional reference points and reference lines, see Figure 5. The analysis included antero-posterior skeletal relationships, including maxillary protrusion (SNA), mandibular protrusion (SNB) and the sagittal jaw relationship (ANB). The vertical skeletal relationship included mandibular angulation (ML/NSL), maxillary angulation (NL/NSL), the vertical jaw relationship (ML/NL) and the relationship between the upper and lower facial height (U/L FH).

To establish the intra-examiner reproducibility, sixteen randomly selected cases were evaluated a second time, approximately two months apart. The intraclass correlation (ICC) was calculated according to Shrout and Fleiss (1979). The differences between the two measurements were compared. No significant differences between duplicate recordings were identified.

3.3 Statistics

All statistical analyses were performed using SPSS. A 5% significance level was used throughout, unless otherwise stated. Study I: to test for differences in the distribution of symptoms general health and disability, the X² test was used. If the expected count on one or more cells was less than 5, the Fisher's exact test was used after transferring data to 2 x 2 tables.

Studies II, III: for comparisons of Di, Ai and EU between study clinics and all eight categories, the Kruskal-Wallis test was used. In order to test the difference between every two categories, clinical and radiographic, and to test the difference between condylar alterations or not the Mantel-Haenszel chi-square test was used. For comparisons of gender and age between all sites, the Pearson chi-square test and the Kruskal-Wallis test respectively were used. For comparisons between every two categories of gender and age, condylar alterations or not, Fisher's exact test and the Mann-Whitney U-test respectively were used. Spearman's rank correlation was used for the correlation analysis. Kappa statistics were used to evaluate reliability over time for condylar alterations. Bivariate logistic regression analysis was used to establish the risk of condylar alterations.

Study IV: for descriptive purpose the median, the 25th and 75th percentiles were given for age at onset and at cephalometric radiograph and disease duration. Cephalometric tracings were presented with the mean and standard deviation (SD). Categorical variables were presented with number (n) and percent (%). In order to test the difference between condylar alterations, Fisher's exact test was used for dichotomous variables and the Mann-Whitney U-test for continuous variables. Univariate linear regression was used to evaluate cephalometric tracings related to the number of "active disease periods". Two-tailed statistical analyses were performed at a significance level of 5% ($p < 0.05$)

3.4 Legal and ethical aspects

Study I has no ethical application. It was intended as an examination project that did not require ethical application. Due to interesting results, the study expanded into a full article. The journal did not demand an ethical application for publication. In a later inquiry, members of the ethical committee found that an ethical application in hindsight was not possible.

The multicentre studies (study II-IV) was approved by the Ethical Committee at the University of Gothenburg, Göteborg, Sweden (342-07).

4 RESULTS

4.1 Study I

Both the controls and the patients with JIA had more symptoms from the orofacial region at the follow-up after 15 years compared with the examination at baseline. A larger proportion of the JIA sample had an anamnestic dysfunction index of II compared with the control group. The prevalence of signs in the craniofacial region was higher at the follow-up examination compared with baseline data among both cases and controls. TMJ clicking sounds were the most commonly reported symptom among both cases and controls. At the 15-year follow-up, patients with JIA reported a statistically significantly higher prevalence of jaw and facial pain, impaired maximum jaw-opening capacity and feelings of tiredness in the jaws compared with controls. The patients with JIA were more aware of toothclenching and grinding habits at both examinations, but the difference only reached a significant level for tooth-clenching at the follow-up examination. The prevalence of headaches and neck pain increased three and five times in the JIA group from 1986 to 2001. Cases that reported frequent pain in the jaws and/or pain on jaw movements reported frequent pain in the neck/shoulder region.

Nine individuals (32%) in the JIA group reported that they had no ongoing joint disease at the follow-up study. The JIA group had significantly more difficulty to performing housework and an impaired ability to move freely compared with the control group.

Almost a third of the JIA sample had consulted a dentist because of TMD symptoms compared with 8% of the controls.

4.2 Study II

When it came to gender, age at disease onset or at examination or frequency of Di and Ai among the included patients, no differences were found between the study centres. The specialist dental clinic in Gothenburg had most patients with extended oligoarthritis while Stockholm and Uppsala had most patients with persistent oligoarthritis. Patients at the specialist dental clinic in Gothenburg had most active disease, EU 1. The clinic in Gothenburg performed fewer radiological examinations than the clinics in Uppsala and Stockholm.

The specialist dental examination was performed at a mean of 2.9 years after disease onset. Clinical signs in the patients, Di I-III (mild, moderate or severe), were found in 57.7% to 92.0% in the different ILAR categories, while subjective symptoms in the patients, Ai I-II (mild or severe), were found in 32.0% to 76.0%. There were significant differences between the JIA categories in both Di and Ai. The psoriatic category had most orofacial signs and symptoms, according to Helkimo's indices, while patients diagnosed with persistent oligoarthritis had the fewest. There was a correlation between Ai and Di. Seventy-six per cent had a disease activity of 1 or 2. Patients with systemic arthritis had most disease activity, EU 1. Severe disease activity, (EU 1 and EU 2) was associated with clinical signs, Di, and subjective symptoms, Ai.

A panoramic examination was performed in 134 patients at the study visit. No differences in the proportion of radiological examinations between categories, gender, age at onset or age at examination, Di or Ai, was found. In patients with disease activity EU 2, radiological examinations were performed more frequently. Four of the panoramic radiographs were judged as "unreadable". Of the remaining radiographs in 130 patients, 48 (37.0%) were rated as having a condylar alteration. No significant association between condylar alterations and category, gender, age at onset, age at examination, clinical signs (Di), subjective symptoms (Ai) or disease activity was observed.

4.3 Study III

Of the total of 266 patients with JIA, panoramic radiographs were exposed in 184 patients, 69% during the eight-year study. Medical data from the same year as the panoramic examination were found in 163. Five radiographs were judged as "unreadable" and 158 patients were finally included. The median disease duration was 2.5 years. Five patients had missing medical data for one or two periods between onset and the panoramic examination. The reliability of the dichotomous radiological assessments (structural and/or shape alteration or not) over time was kappa = 0.68 (95% CI 0.56 to 0.80). This strength of agreement is considered to be substantial (Landis et al. 1977).

Condylar alterations on panoramic radiographs were found in 68 patients (43%) and were not significantly associated with ILAR category, gender and age at onset or duration of disease. Sixty-seven patients had shape alterations, 25 structural alterations and 12 toadstool appearances. Eight of these also had condylar alterations.

Patients with any “potent medication”, increased numbers of “medication periods”, patients with “EU 1 or potent medication” and “EU 1 and potent medication” ran an increased risk of condylar alterations. The risk of condylar alterations with a larger number of “active disease periods” was not statistically significant, only close to it ($p = 0.06$). There was a significant positive correlation between EU 1 and “potent medication”.

4.4 Study IV

Condylar alterations were found in 38 patients (58%) of the 65. All 38 had structural changes and 15 had shape alterations. As a reference, the cephalometric standards of healthy Swedish children reported by Thilander et al. in 2005 were used. The whole group of children with JIA had a more retrognathic mandible (SNB, ANB) and a steeper mandibular plane (ML/NSL, ML/NL) compared with the reference group. A statistically significant difference between children with and without condylar alterations was found. Children with condylar alterations had a more retrognathic mandible (SNB, $p=0.04$), SnPog, $p=0.02$) and a steeper mandibular plane (ML/NSL, $p=0.01$, NL/NSL, $p=0.03$).

The number of “active disease periods” varied between 0 and 15. The median number of “active disease periods” was 3.0 in the total group of 65 children.

A univariate linear regression analysis revealed that the number of “active disease periods” was not associated with any of the 12 cephalometric variables, but the study cohort was small.

5 DISCUSSION

5.1 Methodological aspects

5.1.1 Study design

The first study was a longitudinal follow-up of adult patients with previously diagnosed JIA and symptoms from the orofacial region. Moreover their general health, type of joint disease, utilisation of health care, employment, quality of life and impairment of daily life, were compared with a control group matched in terms of age and gender. One of the risks in follow-up studies is a loss of a significant number of patients. In our study, 10 patients dropped out (13%) due to death and unobtainable addresses. Fifty-four returned the questionnaire, but, considering that it was 15 years between the two examinations, a response rate of 68% is acceptable. The design of Studies II-IV was suitable for analysing TMJ arthritis, craniofacial growth and disease activity over time. One strength of the studies was the fairly large cohort, in contrast with many previously described case series, with both objective and subjective variables involved and with radiological findings and cephalometric analyses as an end point. The percentage of all patients diagnosed with JIA that were referred to specialist dental clinics is not known and the number of patients in some of the ILAR categories was small, which weakens the results. The observational design also implies that the impact on the condyles in the event of no medication in active disease is unknown.

5.2 Imaging

Panoramic radiography has limited diagnostic value for TMJ, as it only provides an overview of the jaws and only large condylar changes can be evaluated with any confidence. The method has acceptable reliability and specificity but low sensitivity, compared with more advanced radiological techniques, such as MRI, CT or Cone Beam Computed Tomography (CBCT). Compared with adults, children have smaller, rounder condyles. As a result, the influence of the long-axis angulation of the condyle on the radiographic anatomy is less pronounced, making it easier to detect pathological condylar deformations in children (Arvidsson et al. 2009). Panoramic examinations are simple, inexpensive and easily accessible at most clinics, involve low radiation levels and require no sedation in young children. Different scoring systems for lesions on the condyles have been applied (Twilt et al. 2004, Twilt et al. 2008, Billiau et al. 2007, Pedersen et

al. 2001, Arvidsson et al. 2009). To simplify the categorisation, condylar alterations were only registered dichotomously in this study.

5.3 Clinical examination

In Studies II-IV, one dentist summarised all the standardised clinical and anamnestic protocols. A group of experienced but not calibrated examiners were involved in the original data collection. This implies a weakness, in terms of both validity and reliability. Some differences in patient characteristics between the sites were observed, partly reflecting variations in clinical routines.

5.4 General discussion

Study I indicates that the prevalence of pain and dysfunction in the orofacial area increases from childhood to adulthood and increases among the patients with JIA more than among healthy controls. The finding that one third of the JIA patients had seen a dentist due to their symptoms indicates that a considerable number of their symptoms are located in the orofacial area. This suggests a higher risk of pain and dysfunction among patients with JIA. Few JIA patients reported impaired general health when they were children. In 2005, Sawyer et al. reported that children with JIA reported less impaired general health than their parents. The relationship between impaired jaw-opening ability and neck/shoulder symptoms is interesting. Patients with JIA can develop severe damage of the TMJ (Rønning et al. 1974, Hu et al. 1995, Pedersen et al. 2001, Twilt et al. 2004, Billiau et al. 2007, Arvidsson et al. 2009). Zafar et al. (2000) have shown that the jaw and the neck interact during jaw-opening.

Studies II-IV comprise patients with JIA but no healthy control group. Studies indicate that recurrent pain in children and adolescents is common. About 400,000 children in Sweden (20%) have pain in the head, stomach or back once a week (Alfvén et al. 2012). In a study of schoolchildren, 1/3 reported weekly pain. Impaired health-related quality of life (HRQoL) was twice as common in children with recurrent pain compared with children without pain (Petersen et al. 2009).

The study design we have used was unfortunately unable to evaluate quality of life in children with JIA. Different methods to measuring health status are critical when it comes to understanding the health status of children with JIA, for making decisions in clinical practice and for evaluating and comparing the effect of therapies in clinical research studies. The Pediatric Quality of

Life Inventory (PedsQL) is a well-validated, reliable and sensitive measure of HR-QOL in children with chronic disease (Varni et al. 2002, Varni et al. 2003). Disability and pain have been found to be the most important determinants of physical and psychosocial well-being, in a European and Latin American study of HRQOL in JIA patients (Gutiérrez-Suárez et al. 2007). In a Swedish cross-sectional study and a Swedish prospective longitudinal population-based study, children with JIA experienced reduced quality of life (Lundberg et al. 2012, Nordal et al. 2011). Measurements of health-related outcomes need to be evaluated for JIA to generate new therapies and to meet the expectations of patients and families with JIA (Ringold et al. 2007). Well-being in the temporomandibular joints is an important goal for many children.

Different methods for collecting data on temporomandibular signs and symptoms have been used over the years. Helkimo's clinical dysfunction index, Di, and anamnestic dysfunction index, Ai, are coarse quantifications of signs and symptoms in the orofacial area, but the standardised evaluations facilitate comparisons between patients and conditions. The indices have acceptable levels of reproducibility, not only for the same observer but also between different observers (Helkimo 1974, Magnusson et al. 1985) and are strongly correlated with other indices (Schiffman et al. 1992). Di and Ai have been widely used in epidemiological contexts relating to temporomandibular disorders (TMDs) (Carlsson et al. In: Temporomandibular joint and masticatory disorders 1994), also among children and adolescents (Toscano et al. 2009). TMDs with signs and symptoms similar to those in JIA also occur in the healthy, general population. Signs and symptoms have been found to be less frequent in children than in adults in general (Carlsson et al. In: Temporomandibular joint and masticatory disorders 1994). In a three-year longitudinal study of 12- to 19-year-olds in a Swedish county, the incidence of TMD pain was 2.9% and 11.4% reported TMD pain on at least one occasion. The pattern of TMD pain fluctuated and was more common in girls (Nilsson et al. 2007). In a cross-sectional epidemiological investigation covering two decades and involving about 100 children and adolescents aged 3, 5, 10 and 15 TMD-related symptoms were very rare in 3- and 5-year-olds. Among 10- and 15-year-olds, 5-9% reported severe symptoms and up to 50% showed one or more TMD signs (Köhler et al. 2009). Longitudinal studies covering a long time period would provide more detailed information about the natural variation in TMD over time.

Most of the 266 patients with JIA in our study cohort were afflicted in the orofacial area. Cases with severe dysfunction, Di III, were found in all but one of the diagnostic categories. Severe symptoms, Ai II, were found in all

categories. Orofacial engagement in young JIA patients, as found in this study, thus exceeds that in comparable, healthy groups. Severe signs and symptoms among JIA patients, according to Helkimo's indices, have previously been presented, but all the ILAR categories were not represented (Savioli et al. 2004).

The distribution of clinical signs and orofacial discomfort among the 266 patients in Study II differed between the ILAR categories, where the psoriatic arthritis category had more clinical signs and symptoms than the other categories, despite similar disease activity. Previous studies have also found differences between categories, but the results vary. Pedersen et al. (2001) found most TMJ involvement in the polyarticular category, Twilt et al. (2004) in the systemic category and Cannizzaro et al. (2011) in the extended oligoarticular category. In our cohort, we found most symptoms and signs in the psoriatic category. One reason why the psoriatic arthritis category was more affected may be that psoriatic arthritis involves the synovium but also the surrounding tissues, the cartilage and the bone (Mc Gonagne et al. 2005, Mc Gonagle et al. 2007, Haroon et al. 2012). In our study, the RF-positive category had very few patients without any orofacial signs. It is known that the RF factor contributes to joint involvement (Pedersen et al. 2001, Twilt et al. 2004, Bas et al. 2003, Karhulahti et al. 1993), but, as the number of patients in this category was limited, it is difficult to draw confident conclusions.

We concluded that there are associations between orofacial signs and symptoms and overall disease activity, assessed for two years. The findings were perhaps not unexpected, as the TMJ is one joint among others and high disease activity affects both articular and peri-articular structures. TMJ arthritis in JIA is often asymptomatic. Its unique anatomy and biochemical composition makes the TMJ susceptible to damage from arthritis (Ringold et al. 2009). Inflammation from the prenatal period to puberty can damage the growth center at the condylar head and results in alterations in mandibular growth (Ronchezel et al. 1995). The TMJ is also one of the most used synovial joints, with its frequent chewing and speaking, which makes it important to recognise and treat TMJ arthritis during childhood.

In Study III, the radiographically examined group comprised 69% of the total cohort of 266 patients. Radiographic condylar alterations were found in 43% of the examined patients after a median disease duration of 2.5 years. Studies using the panoramic radiographic technique have reported different results in terms of TMJ condylar alterations, 17-78%, and the size of the studied populations has also varied from 97 to 249 JIA patients (Rønning et al. 1974,

Pedersen et al. 2001, Twilt et al. 2004, Billiau et al. 2007, Arvidsson et al. 2009). The divergent results for condylar alterations are most probably due to different scoring systems and different patient populations. Condylar alterations, as judged on panoramic radiographs, were more common in patients with a heavier burden of longitudinal medication and consequently more severe illness. The fact that not all the patients were examined with panoramic radiography, together with missing medical data for solitary periods for some patients, entails a possible bias.

Several authors have studied the importance of longitudinal medication for avoiding TMJ arthritis in JIA, as judged on panoramic radiography, with different results. Arvidsson et al. (2009) found no significant difference in TMJ abnormalities between patients with or without previous MTX treatment and/or the use of biological drugs studied for a mean duration of 3.2 years. Twilt et al. (2004) found TMJ involvement in 68% of the patients with previous or present DMARD (not MTX) as compared to 29% of patients with previous or present immunosuppressive therapy (corticosteroids and MTX) with a mean duration of 4.9 years. The difference between the groups was not discussed in more detail. Ince et al. (2000), on the other hand, found significantly more frequent and more severe condylar involvement in JIA patients without MTX at the time of the panoramic examination. The observation period was eight years for the non-MTX group and 6.9 years for the MTX group. It was concluded that MTX therapy may minimise the TMJ destruction, but longitudinal studies would provide more definitive information.

The optimal therapy for avoiding TMJ arthritis has not yet been confirmed. TNF-alpha inhibitors are supposed to inhibit inflammation more effectively than MTX. Studies comparing TNF-alpha with or without MTX in terms of arthritis in the TMJ have not been performed. The new biological agents are used in approximately 20-25% of children with JIA in Sweden (Kazamia et al. 2014). A review concluded that some children with JIA develop TMJ arthritis despite TNF-alpha inhibitors (Ringold et al. 2009). In another review of randomised controlled trials in JIA on treatment with biological agents no conclusions about efficacy could be drawn, because of the small number of patients and differences in design between the trials (Otten et al. 2013). In our cohort of 266 children with JIA, some patients had TNF-alpha inhibitors for only a short period and it is therefore difficult to draw any conclusions about their effect on TMJ arthritis.

Corticosteroid injections in the TMJ are effective for treating TMJ arthritis (Stoll et al. 2012), but this therapy alone was very uncommon in our study

cohort. Corticosteroid injections are also used to reduce disease activity in other joints in the body.

A modified version of the EULAR was used to describe disease activity in this study, but there are other ways of categorising it. One limitation of EULAR is that the disease activity is only measured on active joints compared, for example, with JADAS 27, where the sums of components are compounded (McErlane et al. 2013).

Several systems for describing disease activity in JIA have been developed. For studies of the effect of medical therapies, core outcome variables (COVs)(Giannini et al. 1997) were developed. Improvement as a primary outcome in JIA (the ACR paediatric 30 response criteria) requires an improvement from baseline of at least 30% in three of the six COVs, with no more than one of the six deteriorating by > 30%. As the care of children with JIA has advanced (Beresford et al. 2009), the minimum acceptable level of improvement has increased accordingly, with improvements of 50%, 70%, 90% and even 100% (ACR Pedi50, Pedi70, Pedi90 and Pedi100). In 2004, an international consensus group drew up preliminary criteria for inactive disease and clinical remission (Wallace et al. 2004). Nowadays, the term “minimal disease activity (MDA)” has been added to the agenda, as it is a more realistic goal than remission. A preliminary definition of MDA was validated in 2008 (Magni-Manzoni et al. 2008) and identifies an intermediate state between active disease and remission. This can be a useful treatment target in future observational studies and clinical trials in patients with JIA. MDA could be defined as a physician global assessment of < 2.5 cm and a swollen joint count of 0 in patients with oligoarthritis and a physician global assessment of < 3.4 cm, a parent global assessment of < 2.1 cm and a swollen joint count of < 1 in patients with polyarthritis. The effect of early aggressive therapy on the course of the disease has not been studied. The long-term effects of methotrexate and biological medication on remission, radiological changes, functional capabilities and the long-term adverse effects were previously unknown (Hashkes et al. 2005). Today, there are a multitude of treatment options, which have allowed children with arthritis to experience normal growth and development. As more is learned about the aetiopathogenesis of the different categories of JIA, it may become easier to target the right drug at the right child. It is clear that most children with non-systemic JIA respond well to TNF-alpha inhibitors and MTX (Stoll et al. 2014).

It is more difficult to diagnose disease activity in the TMJs compared with more easily examined joints like the knee joints. The activity indices that are available should pay more attention to the variables of the TMJ. The Juvenile Arthritis Damage Index (JADI) has a scale on articular damage from 0 to 72 in which 0 = no damage and 72 = maximum damage. Unfortunately this index only counts severe lesions on the TMJs.

According to Wahezi et al. (2013), there have been rapid therapeutic advances in the treatment of JIA and they are reflected in the improvement in physical and functional outcomes, but many children with JIA have periods of active disease despite current medical programmes. Vidqvist et al. (2013) reported several inflamed joints in the last year in 58% of patients with JIA with a median age of 19 years, in spite of medication. The present Study III confirms their result, where it appears that children with JIA have condylar alterations despite medical treatment.

The involvement of the TMJ can influence the facial growth. Unfortunately, only 65 patients were included in the cephalometric study and they were only compared with a previous longitudinal study of healthy Swedish children (Thilander et al. 2005). Our cohort had more posterior rotated and retrognathic mandibles, in agreement with other studies (Kjellberg et al. 1995 b, Sidiropoulou et al. 2001, Twilt et al. 2007, Twilt et al. 2008). We found no differences between boys and girls and we therefore decided not to split the cohort into genders. We found a correlation between condylar alterations and a change in the growth pattern of the mandible, which others have also found (Larheim et al. 1981, Kjellberg et al. 1995 b, Hanna et al. 1996, Sidiropoulou et al. 2001, Twilt et al. 2007, Twilt et al. 2008).

The way disease activity is correlated to facial growth is uncertain and many studies are cross-sectional. In our study of the 65 children with JIA, we were unable to see that many active disease periods were associated with any of the 12 cephalometric variables, but our study cohort was small. Billiau et al. (2007) found no association between disease activity and facial growth. Arvidsson et al. (2010) re-examined 60 adult patients with JIA after an average of 27 years. Patients with facial growth disturbances had more severe disease than patients with normal facial growth at both the initial examination and the re-examination. Serial records have shown that deformity may become worse with age and, the earlier the onset of the disease, the more abnormal the subsequent mandibular development (Barriga et al. 1974, Turpin 1989, Svensson et al. 2000). Twilt et al. (2007) revealed that the radiographic signs of condylar damage were worse five years later in a few

children that exhibited particularly high disease activity at the time of the re-examination.

Patients with JIA appear to undergo a change in facial growth pattern and it appears to be aggravated with condylar alterations. The relationship between disease activity over time and facial growth needs to be studied in larger cohorts.

5.5 Representativity of the study population

One weakness in the first study is that only patients with polyarticular and oligoarticular arthritis were included. The ILAR classification did not exist in 1986 and the patients in Study I were therefore not diagnosed according to the ILAR criteria. The sample was relatively small, but previous studies have shown a regression of disease of 25-50% (Narayanan et al. 2002, Flato et al. 2003, Fantini et al. 2003, Wallace et al. 2005), which is in agreement with this cohort.

The data in Study II-IV were collected retrospectively, were not populationbased and were only discussed in relation to previous studies, which runs the risk of selection bias with an over-representation of severe cases. The merged study cohort was representative of the ILAR categories, gender and age in a distribution resembling cohorts from epidemiological studies.

6 CONCLUSION

Adult patients, with an earlier diagnosis of JIA, report more pain and dysfunction in the orofacial or cervical regions compared with healthy individuals. This means that JIA patients run a higher risk of developing dysfunction in the masticatory system.

There are associations between orofacial signs and symptoms and overall disease activity assessed for two years in children with JIA diagnosed according to the ILAR.

TMJ damage, evaluated as condylar alterations on panoramic radiographs, was fairly common in our cohort of patients with JIA and alterations have been found to correlate with synovitis (Abramowicz et al. 2014). The unique anatomy of the TMJ, with a thin layer of fibrocartilage at the surface of the condylar head, and the biochemical composition make it susceptible to damage caused by arthritis (Ringold et al. 2009). The results suggest, within the limits of this observational study, that active disease over time appears to increase the risk of alterations to the TMJs despite medication.

Patients with JIA have a changed facial growth pattern compared with healthy children. Study IV indicates that patients with condylar alterations have more retrognathia and a posterior rotated mandible. We were unable to confirm that high disease activity influences the facial growth pattern in patients with JIA, but our study cohort was small. Longer follow-up studies and further prospective studies with the emphasis on the way the growth pattern can be influenced are needed.

7 FUTURE PERSPECTIVES

An early and correct TMJ diagnosis in patients with JIA is important in order to treat and prevent a negative effect primarily on the TMJs and secondarily on craniofacial development.

There is a lack of consensus on when to treat and how to treat JIA in terms of the TMJ. In our cohort, we found condylar alterations despite medication, even if the patients were given the new biological agents. Can we reduce the risk of permanent joint damage by general medication or by local treatment with corticosteroid injections? Can we influence craniofacial growth with the new biological agents? What agent is the best to treat TMJ arthritis?

As yet, current medical programmes have not been specified for the TMJ and more knowledge is needed in this area. Longer follow-up studies and further prospective studies, with the emphasis on the progress of TMJ arthritis and the influence of facial growth, are necessary. The need for prospective studies to find risk factors for TMJ involvement have previously been emphasised (Müller et al. 2009) and answering these question must surely be valuable.

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