Review

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Temporomandibular joint arthritis in juvenile idiopathic arthritis: the last frontier

Juvenile idiopathic arthritis (JIA) is a heterogeneous condition defined by arthritis in children under age 16 at onset, lasting at least 6 weeks, without any identifiable etiology. The last 2 decades have witnessed an explosion of research into therapeutics that have allowed most children with JIA to live normal lives. One joint that has lagged behind is the temporomandibular joint. Long neglected in studies of JIA, there has been increased attention paid to this joint, with studies showing that not only is it difficult to treat with systemic therapies, but it may be uniquely vulnerable to local therapy. This review will summarize the scholarship on the epidemiology, diagnosis and management of temporomandibular joint arthritis in children with JIA.

Keywords: biologic therapy • functional orthotic appliance • infliximab • intra-articular corticosteroids • juvenile idiopathic arthritis • temporomandibular joint • triamcinolone

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The temporomandibular joint (TMJ) is an often neglected joint in children with juvenile idiopathic arthritis (JIA) [1]. Unlike most other joints, TMJ arthritis does not result in visible swelling, nor is there significant pain or stiffness at onset in most cases; thus, advanced imaging is required for early diagnosis. Studies using MRI as a diagnostic tool have reported TMJ involvement in upward of 80% of children with JIA [2], and when present, TMJ arthritis can have devastating consequences on the shape and function of the jaw and midface [3].

Treatment of JIA has advanced rapidly over the last decades, with novel therapeutic approaches now available that have dramatically changed the long-term outlook for affected children [4]. However, modern therapies may not be as effective in the management of TMJ arthritis as they are for most other joints [5]. Thus, a number of centers use local therapy in the form of intra-articular corticosteroids (IAC), which appear to be effective in the short term but have as yet uncertain effects on long-term mandibular growth [6,7]. In this review, we summarize the data on the diagnosis and management of TMJ arthritis in children with JIA.

Overview of juvenile idiopathic arthritis

JIA is an umbrella term referring to cases of arthritis of unknown etiology occurring in children with onset below age 16 years [8]. JIA consists of multiple distinct subtypes (Table 1), some of which bear similarities to adult counterparts. For example, rheumatoid factor+ polyarticular JIA is for the most part clinically, genetically and demographically indistinguishable from adult rheumatoid arthritis [9]; enthesitis-related arthritis is essentially the same as undifferentiated spondyloarthritis [10] and systemic JIA has identical clinical features albeit different diagnostic requirements as adult-onset Still disease [11].

In contrast, oligoarticular, polyarticular, and psoriatic JIA all appear to differ substantially from adult arthritis phenotypes. Although older onset psoriatic JIA is similar to the adult counter type [14], all of these disorders frequently have onset in early childhood and are characterized by a joint distribution, complication of chronic uveitis and associa-

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Table 1. Juvenile idiopathic arthritis categories.

Feature	Oligoarticular	RF$^-$ polyarticular	RF$^+$ polyarticular	Systemic	ERA	Psoriatic
Analog in adult arthritis	None	Older onset may resemble RF$^-$ RA	Rheumatoid arthritis	AOSD	Undifferentiated SpA	PsA, among older onset
Peak age of onset	1–3	1–3 Teenage	Teenage	1–3	Teenage	1–3 teenage
Sex	F > M	F > M	F > M	Equal	M > F	F > M (young-onset only)
ANA$^+$	Majority	Majority	Rare	Rare	Rare	Majority (young-onset only)
RF$^+$	Rare	None	Present	Rare	Rare	Rare
HLA-B27$^+$	Uncommon	Uncommon	Uncommon	Uncommon	Common	Common (old-onset only)
TMJ involvement	35–100%	50–100%	33 – 100%	35–65%	15–38%	50–90%

Categories of JIA. ANA: Anti-nuclear antibody; ERA: Enthesitis-related arthritis; JIA: Juvenile idiopathic arthritis; RF: Rheumatoid factor; SpA: Spondyloarthritis; TMJ: Temporomandibular joint.
Adapted with permission from [4].
Data on the frequency of TMJ involvement taken from [5,12,13].

tion with the anti-nuclear antibody test that make them a potentially homogeneous entity [15] and distinguish them from adult arthritides. Finally, the diagnosis of undifferentiated JIA is given to children with features that, due to various exclusion criteria, do not meet criteria for any of the other subtypes, or meet criteria for two or more. An example would be a child with clear systemic features who also has a first-degree family history of psoriasis. The criteria are not perfect [16], and nonbiased approaches combining genetics, clinical and laboratory features, and pathobiologic approaches are being explored to develop novel criteria [17].

Demographics of temporomandibular joint involvement

TMJ arthritis can be overlooked in the absence of a systematic effort to recognize it. For example, several studies that have reported on the overall distribution and frequency of joint involvement in children with JIA have completely ignored this joint [18,19], hence its nickname the 'forgotten joint' [1]. In contrast, retrospective and prospective studies performed at centers that do evaluate systematically for TMJ involvement have reported arthritis in 29–96% of subjects, with an important source of variation among the studies likely attributable to the source of ascertainment (see below). Several studies have evaluated for risk factors of TMJ arthritis among subjects with JIA, with mixed results (summarized in Table 2). Children with oligoarticular JIA have lower risk than those with other categories of arthritis in some [13,20] but not all [21] studies. Disease duration was positively associated with risk in some studies [13,22], but negatively associated in another, which the authors attributed to effects of chronic immunosuppressive therapy [5]. Markers of disease activity are often [13,20–21] but not always [5] associated with TMJ arthritis. Sex does not appear to be a risk factor for TMJ arthritis, beyond its association with JIA as a whole.

Anatomy & pathophysiology

The TMJ is classified as a ginglymoarthrodial joint, meaning that it is a hinge joint also permitting gliding motion [23]. As implied by the name, it is located at the junction of the mandible (jaw) and the temporal bone of the skull. The mandibular component consists of the condyle, a 10–20 mm articulation that sits atop a narrow neck which leads to the body of the jaw. The condyle sits within the glenoid fossa within the inferior temporal bone, just anterior to the external auditory meatus. Within the joint space sits the articular disc, a small piece of fibrocartilage that separates the joint into superior and inferior spaces and is responsible for the hinging and gliding motion of the joint [23]. The disc is connected to the mandible and temporal bones by loose fibrous tissue [24]. In addition to the fibrous tissue within the joint, the TMJ is surrounded by a fibrous capsule reinforced laterally by the temporomandibular ligament [24]. The growth zone of the TMJ is located intra-articularly near the surface of the condylar head, and this joint is the only articulation with an intra-articular ossification center [25]. The articular surfaces of the bones contain avascular fibrocartilage, distinct from the hyaline cartilage that characterizes most joints [24]. The cartilage contains chondrocytes and is surrounded

Table 2. Risk factors for temporomandibular joint arthritis.

Study	n (% with TMJ arthritis)	Risk factors evaluated			Ref.
		JIA category	Disease duration	Disease activity	
Abdul-Aziez *et al.* 2010	20 (80%)	↑risk in sJIA, pJIA	Not associated	↑ESR, CRP, CHAQ	[20]
Abramowicz *et al.* 2011	48 (96%)	↓risk in psJIA	Not evaluated	Not evaluated	[12]
Argyropoulou *et al.* 2009	46†	↑risk in sJIA	↑risk with long disease duration	Not evaluated	[22]
Cannizzaro *et al.* 2011	223 (39%)	↓risk in sJIA, eoJIA	↑risk with early age of onset	↑ESR	[13]
Cedstromer *et al.* 2014	158 (43%)	Not associated	Not associated	↑risk with use of 'potent' medications	[21]
Stoll *et al.* 2012	187 (43%)	Not associated	↑risk with short disease duration	Not associated	[5]

†Number with any abnormality not provided.
CHAQ: Childhood health assessment questionnaire; CRP: C-reactive protein, eo: Extended oligoarticular; ESR: Erythrocyte sedimentation rate; JIA: Juvenile idiopathic arthritis; P: Polyarticular; psJIA: Psoriatic JIA; S: systemic; TMJ: Temporomandibular joint.

by proteoglycans and other large molecules, which help defray the compressive forces involved with regular use of the jaw [24]. The disc also serves to absorb compressive forces at the TMJ [25]. The joint volume is small, with capacity of about 0.5 ml in the lower compartment and 1.2 ml in the upper compartment [23], which is likely less in children.

Mouth opening is largely mediated by the lateral pterygoid muscles, with contributions from the geniohyoid, mylohyoid and the digastric muscles [26]. It is a somewhat complex movement, characterized by rotation between the disc and the inferior mandible as well as anterior translation of the temporal bone to the disc superiorly, with both TMJs acting in concert [26]. Although the fibrocartilage in the TMJ is generally able to withstand significant compressive forces, excessive mechanical loading can result in bone destruction and localized inflammation [27,28]. Degenerative disease of the TMJ is rare in children, but such changes may be more likely in a TM joint already damaged by an inflammatory arthritic process [29,30].

Complications of temporomandibular joint arthritis

Anatomically, long-lasting JIA can result in substantial changes to the shape and appearance of the TMJ, as visualized by MRI or even CT. These changes include flattening of the condyle; shortening of the mandibular ramus; erosive changes noted at the articular surface, analogous to other joints impacted by long-standing arthritis and generalized remodeling of the joint as evidenced by bone ossifications present within inflammatory pannus [31,32]. The articular disc as well can be affected by long-standing arthritis. Early changes include alterations in the shape, with frank perforations as well as dislocation observed in long-standing cases [32]. Arvidsson *et al.* (2010) performed MRI and CT scan in 60 adults with long-standing JIA, many of whom had damage for decades as evidenced by plain radiography [33]. Among those with TMJ involvement, 70% had growth disturbances, and in a subsequent reappraisal of the data, the authors reported ruptured, fragmented or absent discs in upward of 90% of the subjects with TMJ involvement [32].

Similar changes detected on MRI have cosmetic as well as functional consequences. Long-standing unilateral or one-side dominant TMJ arthritis can result in asymmetric jaw growth, and long-standing bilateral TMJ arthritis can result in micrognathia and retrognathia [30]. As indicated above, such changes were very frequent prior to the advent of modern therapies. The cosmetic alterations are obvious, these changes resulting in the so-called 'bird-mouth' shape [34,35]. Additionally, anatomic changes can complicate chewing (particularly if maximal incisal opening [MIO] is limited), swallowing and intubation [36].

Diagnosis of temporomandibular joint arthritis

Like any joint, clues for the diagnosis of TMJ arthritis can potentially be obtained by history of subjective symptoms, abnormal exam findings referable to the

TMJ, and ancillary imaging studies. Cedstromer *et al.* (2014) used two clinical indexes, one consisting of subjective symptoms such as TMJ fatigue and pain, the other consisting of objective findings such as tenderness to palpation or to range of motion (ROM), to evaluate for condylar abnormalities evidenced by panoramic views of the TMJ [21]. Although both clinical and subjective findings of the TMJ correlated with disease activity as a whole, neither correlated with radiographic findings. As discussed below, an important limitation of this study is their use of plain films, which only detect advanced chronic changes.

Koos *et al.* (2014) prospectively evaluated five physical exam maneuvers (asymmetric mouth opening, pain on palpation of masticatory muscles, pain on palpation of the TMJ, TMJ clicking and reduced MIO) as predictors of TMJ arthritis, using MRI as the gold standard [37]. They reported that each item individually had a sensitivity ranging from 21 to 65%, while any single finding from the five potential exam maneuvers had a sensitivity of 85%, indicating that a substantial number of cases would still be missed. Likewise, Stoll *et al.* (2012) reported jaw deviation in 49% of patients with, versus 12% of patients without, TMJ arthritis, a highly significant finding that would nevertheless still miss half the cases [5]. In this study, a low MIO was also independently associated with risk of TMJ involvement, but receiver operating curve analysis revealed it to be unsatisfactory as a screening test, with an AUC of only 0.63. In a prospective study involving 32 newly diagnosed subjects with JIA, symptoms such as jaw pain and dysfunction were highly specific (100%) for TMJ arthritis as assessed by MRI, with sensitivity of only 26%; while the sensitivity and specificity of a battery of physical exam maneuvers were a disappointing 38 and 50%, respectively [2]. Abramowicz *et al.* (2013) reported that a combination of abnormal MIO for age and jaw deviation had a positive predictive value of 100%; however, with a negative predictive value of only 46%, they were also found to be unacceptable as screening tests [38]. An important reason that MIO is an insufficient screening test is the wide variation in normal MIOs among healthy children, as evidenced by a study of over 22,000 children attending a dental clinic in Zurich, Switzerland [39]. While in this study, the mean, 10 percentile and 90 percentile for a 10-year-old child of either sex were, respectively, 4.6, 4.0 and 5.3 cm, it was visually evident that normal school-age children can range anywhere from 3.0 cm up to 6.5 cm. Thus, a single measurement on any given child has little informative value. However, we have in our practice found MIO to be useful in tracking the presence of TMJ involvement in an individual patient followed longitudinally. An important caveat to MIO assessments is that there is intrinsic variability in their measurements, such that changes of less than 0.6–0.9 mm can represent measurement error [40].

Among imaging studies, plain radiographs are inexpensive and easily obtainable, but can only be used to evaluate for chronic bony changes; not acute arthritis [41]. Likewise, cone-beam computed tomography, which differs from traditional computed tomography in that it is highly focused on the TMJ with less radiation exposure, is more focused and likely to be more accurate than plain films at detecting chronic TMJ changes, although at the expense of a higher burden of exposure to radiation [42]. It may also be more accurate than MRI at detecting chronic bony changes [42], although to our knowledge, they have not been compared head-to-head. Additionally, computed tomography, unlike MRI, will not detect pannus, which is considered to be an indicator of chronic arthritis [43]. Computed tomography is frequently used for bony detail when planning orthognathic surgery [44] and for evaluation of heterotopic bone formation [45]. Figure 1 shows an example of condylar loss seen on computed tomography associated with JIA.

MRI is considered the gold standard for evaluation of TMJ arthritis [32]. The normal appearance of the TMJ on MRI was described by Kellenberger *et al.* (2015) [32], with an example shown in Figure 2. The condylar head of the mandible should be visible as an ovoid structure with a convex upper contour. On some sequences, the articular disk can be visualized between the condylar head and the inferior temporal bone. In children with arthritis, joint fluid can be seen as hyperintensity on fluid-sensitive (T2-weighted) sequences, although this is not a sensitive finding for the detection of arthritis [5]. Additional findings suggestive of acute arthritis are bone marrow edema and particularly contrast enhancement (Figures 3 & 4). Findings suggestive of chronic arthritis include changes to the changes in the shape of the condyle or disk, pannus and osteophytes [43] (Figures 3 & 4). Limitations of the MRI include its cost and requirement for sedation in young children.

Finally, the other imaging modality that can pick up on acute changes is ultrasound (US). Although it has advantages of MRI with respect to cost and lack of requirement for sedation, the evidence is mixed as to whether it is as sensitive at detecting acute inflammation. Three recent studies demonstrated that US can detect signs of arthritis in the majority of patients. Assaf *et al.* (2013) reported abnormal findings in 124 out of 160 sequences in a total of 20 patients known to have TMJ arthritis on the basis of clinical findings and abnormal MRI, although it is unclear whether any of the cases were missed by US [46]. Likewise, Jank *et al.* (2007) reported findings of destructive changes to the

TMJ in 53 of 96 TMJs studied, although MRI was not used in this study [47]. Melchiorre *et al.* (2010) reported joint effusion in 46 of 68 and condylar abnormalities in 62 of 68 subjects [48]. Although these subjects did not undergo MRI, their findings are comparable to studies that were based on MRI. In contrast, Weiss *et al.* (2008) performed US and contrast MRI of the TMJ on 32 unselected children with newly diagnosed JIA [2]. In their study, MRI identified active arthritis in 24/32 (75%), while US did not detect active arthritis in any subjects. Similarly, chronic changes were identified by MRI and US in 22/32 (69%) and 9/32 (28%), respectively. Analogous results were reported by Muller *et al.* (2009), as they noted US missed 67% of JIA patients with TMJ arthritis [49]. The reason for the variation in these findings is not clear, although US is clearly very highly operator dependent, and the smaller anatomy of young children make TMJ evaluation by US challenging.

An important limitation of all of the studies that use imaging as a gold standard is the potential for overdiagnosis of arthritis. Clearly, it would be unethical to subject children to biopsy to test the performance characteristics of the MRI, so the only potential approach is to evaluate MRI of the TMJ in healthy children. Even this poses ethical challenges, as MRI requires contrast and thus intravenous access to attain maximal sensitivity [5], it requires sedation in young children, and is furthermore fairly expensive. An approach to address the issue of the specificity of abnormal MRI findings is to study children whose TMJs have been imaged incidentally during MRI of the brain. This type of study was performed retrospectively by Tzaribachev *et al.* (2009), who evaluated the TMJ in 96 such children, reporting that the vast majority of the studies were normal [50]. Specifically, only three of 96 had effusions, all of which were considered small, and another three had mild synovial enhancement, for a total of six out of 96 that would be considered suggestive of arthritis. However, different findings were reported by von Kalle *et al.* (2013) and by Kottke *et al.* (2014). The former was a retrospective study of 46 children who underwent contrast MRI of the brain and who had TMJs visualized during the procedure [51]. In their study, fluid-sensitive sequences did not detect any joint abnormalities, yet contrast enhancement was observed in 14/92 joints (15%). The authors proposed a dynamic scoring system that would take into account the ratio of signal intensity 6 min postcontrast administration to the signal intensity 1 min postcontrast administration, with values >1.23 likely indicative of true contrast enhancement [52]. An even higher frequency of contrast enhancement was reported by Kottke *et al.* (2014), who prospectively evaluated 27 children who were simultaneously undergoing MRI of the head, excluding subjects with known arthritis or with abnormal exams involving the TMJ [53]. Of 54 TMJs, 45 (83%) had evidence of intra-articular fluid, and some degree of contrast enhancement was observed in 52 (96%) of TMJs; when present, the joint fluid enhanced in 43/45 (96%) of cases. These findings were typically mild, leading the authors to conclude as well that when present in children with JIA, mild degrees of contrast enhancement should be considered normal. Significant chronic changes were not observed in either study. These studies are consistent with a study in adults, in which noncontrast MRI of the TMJ revealed joint fluid in 33 of 62 asymptomatic volunteers [54]. Importantly, site-specific imaging protocols differ, and evaluation of the joint post-contrast push is critically time dependent.

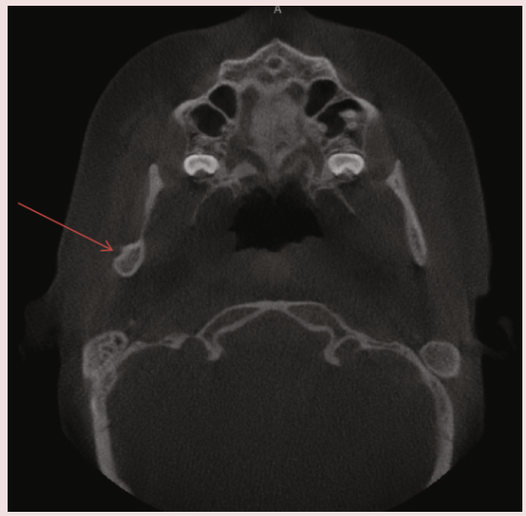

Figure 1. Computed tomography appearance of chronic temporomandibular joint arthritis in a 12-year-old female with polyarticular juvenile idiopathic arthritis. Her right condyle has undergone erosive changes (arrow.)

These studies showing that mild contrast enhancement can appear in nonarthritic subjects may raise the possibility that the physical examination is, in fact, of greater sensitivity for the detection of arthritis than some studies would suggest [2,5]. This might be a fair conclusion if the only MRI findings observed in children with normal examinations consisted of mild degrees of contrast enhancement. However, Weiss *et al.* (2008) showed chronic changes in 69% of JIA subjects at baseline, 50% of whom had normal exams [2]. Thus, there are clearly children in whom the history and exam fail to predict substantive changes.

It must be further emphasized that even if some of the acute findings seen on MRI of the TMJ in chil-

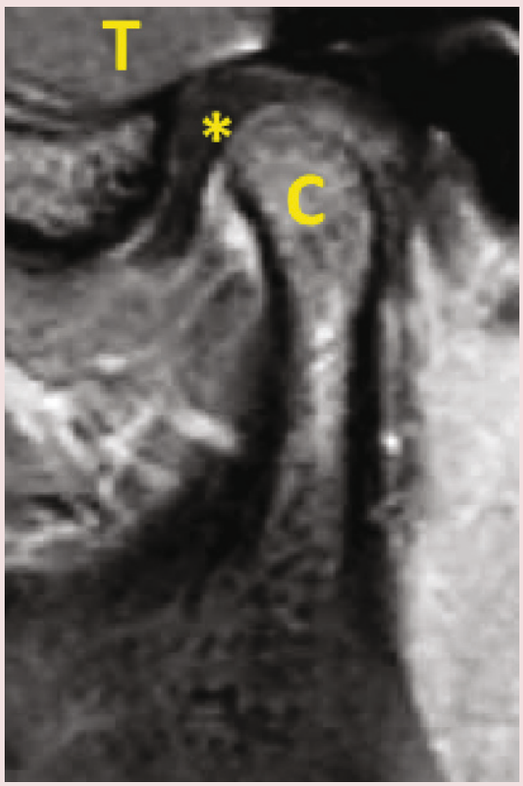

Figure 2. Normal MRI of temporomandibular joint.
The condylar head (C) can be seen atop its neck. The temporal bone (T) comprises the other end of the temporomandibular joint (*).

dren with JIA may in fact be nonspecific, the body of evidence overwhelmingly shows that children with JIA are at substantial risk for TMJ arthritis. This has been clearly demonstrated by long-term follow-up studies of children with JIA, who almost uniformly have developed severe chronic changes of the TMJ resulting in substantial alterations to form and function [30,55].

Treatment

Systemic therapy

A detailed description of the therapies used to treat children with JIA is beyond the scope of this review, and the interested reader is referred to Stoll and Cron [4]. There is very little direct evidence as to whether systemic therapy for JIA is as efficacious for the TMJ as it is for most other joints. Data suggesting that systemic therapies may be less effective in the TMJ as compared with most other joints came from a study showing that nearly 50% of children with otherwise quiescent disease nevertheless had inflammation in the TMJ [5]. The reasons for this potential discrepancy in the response to systemic therapy are unclear, although not without precedent, as the sacroiliac joint also fails to respond to certain systemic therapies (traditional disease-modifying antirheumatic drugs) otherwise generally of benefit in arthritis [56]. Since the TMJ is generally not included as an outcome measure in drug trials, most of the data on the potential benefit of systemic therapy on this joint consists of indirect lines of evidence. The only exception is one randomized trial comparing two arthritis medications on the outcome of TMJ arthritis in JIA [57]; unfortunately, the two medications selected for this trial, D-penicillamine and sodium aurothiomalate, are no longer considered viable therapeutic options.

An indirect line of evidence indicating that systemic therapy may be of benefit for TMJ arthritis comes from studies of children with long-standing disease in the absence versus in the presence of systemic therapy. One of the first studies was published by Larheim and colleagues in 1982, demonstrating radiographic abnormalities in 52 of 100 subjects with JIA [58]. Long-term follow-up studies of adults with JIA diagnosed prior to the modern era likewise demonstrated not only that structural abnormalities of the jaw were common, but that the risk increased in those with long-standing active arthritis [55,59].

These observations of chronic, almost inevitable, worsening of destructive changes over time no longer appear to be the case. Twilt *et al.* (2008) performed baseline and 5-year follow-up radiographs among 70 subjects who were exposed to a variety of immunosuppressive therapies; none had received intra-articular treatment [60]. Despite the passage of time, the number of condyles with radiographically evident changes decreased from 37% at baseline to 26% at follow-up, with clinical evaluation likewise demonstrating improvement in the form of decreased posterior rotation of the mandible. Another study showing potential benefit of systemic therapy was a retrospective study conducted by Ince *et al.* (2000), who reported decreased radiographic evidence of TMJ arthritis among 18 subjects taking methotrexate, compared with nine who were not [61]. Although this was not a randomized study, any potential bias would likely result in increased changes in the patients taking methotrexate, as those are more likely to have active arthritis overall. Finally, as indicated above, the study by Stoll *et al.* (2012) indicated that disease duration was protective against TMJ arthritis, a finding the authors attributed to widespread usage of conventional and biologic disease-modifying therapy at their center [5].

Intra-articular therapy

Stoll *et al.* (2015) reviewed the literature on safety and effectiveness of IAC therapy as treatment of TMJ arthritis, reporting on eight studies, two of which had overlapping subjects [7]. These studies are highly het-

erogeneous with respect to inclusion criteria, imaging guidance used for IAC delivery, selection and dose of IAC therapy, and outcome measures. Despite this variability, these studies have reported improvement in symptoms, MIO measurements and MRI findings of acute inflammatory changes following a single dose. For example, Arabshahi *et al.* (2005) reported improved pain in 10/13 and improved MRI findings in 67% of TMJs (2005) [62]; Habibi *et al.* (2012) reported decreased pain in 17/17 and improved jaw deviation in 13/14 among whom this was assessed [63] and Stoll *et al.* (2012) reported improved MRI evidence of arthritis in 24 of 62 TMJs, compared with only eight that worsened [64]. Effectiveness of subsequent doses in patients who did not respond to an initial injection appears to be less robust [64]. Six of the studies reported on safety, with no serious adverse events (SAEs) reported in a total of 255 subjects [7].

Limitations of these studies were reviewed by Stoustrup *et al.* (2013), including their retrospective and uncontrolled designs, nonblinded interpretations of the imaging studies and absence of standardized end points [6]. Additionally, concerns have been raised about the long-term safety of IAC therapy of the TMJ. Although IAC therapy of most peripheral joints is widely used and generally found to be safe [65], in some animal models of TMJ arthritis, corticosteroid injections into the TMJ have resulted in decreased mandibular growth [66,67]. This was also reported in children who received IAC into the TMJ [68]. The authors retrospectively evaluated 33 subjects who underwent IAC of the TMJ. A unique aspect of this study was that, at time of the injection, they used MRI to evaluate for intra-articular versus extra-articular placement of the drug. Not unexpectedly, improvement of the inflammatory grade of the TMJ arthritis was seen in 53% of 82 TMJs in which the delivery was intra-articular, compared with only 20% of 59 instances of extra-articular placement ($p = 0.0002$). Of concern with respect to the safety of this therapy is that at the time of the second follow-up MRI, the mandibular growth rate decreased by 0.5 mm/year among those with intra-articular placement, compared with an increase of the same amount in those subjects with extra-articular placement ($p = 0.021$). This discrepancy between improvement of the underlying arthritis and worsening of the growth rate indicated that the injection itself, rather than the underlying disease, was likely responsible for the worsening growth. An additional safety event reported in children was development of heterotopic bone in 12 subjects with long-standing TMJ arthritis who had received multiple rounds of IAC [45]. Although the report did not indicate how much of this was due to the arthritis as opposed to its local therapy, most previous studies have reported bone loss; not bone gain [3,29]. Finally, severe damage including ankylosis has been reported in adults who have received IAC to the TMJ [69–71]. Thus, there have been recommendations to limit or avoid IAC of the TMJ [6,60]. One other approach for IA therapy was initially proposed by Alstergen *et al.* (2008), who performed seven rounds over 36 months of IA infliximab (5 mg/injection), with long-lasting improvement initially observed following the first dose [72]. Subsequently, Stoll *et al.* (2013) reported on 24 children who received IA infliximab after failing IAC and, in most cases, therapy with systemic biologics in addition to conventional disease-modifying antirheumatic drugs [73]. Although there was benefit noted in individual cases, in the group as a whole, no evident improvement was seen in the acute changes, and there was worsening over time in the chronic findings. Whether IA infliximab, or other IA anti-TNF therapy, will be more effective as initial IA therapy for TMJ arthritis is unknown.

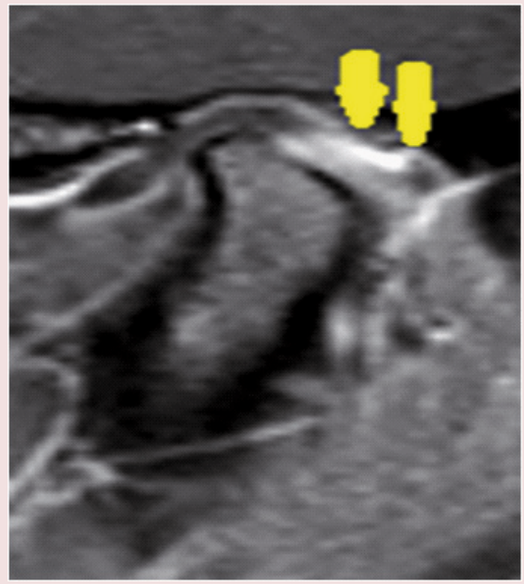

Figure 3. Temporomandibular joint MRI (sagittal T1-weighted post-contrast image) of 17-year-old female with juvenile idiopathic arthritis limited to her temporomandibular joint, who has received multiple rounds of IAC and IA infliximab. A thickened and enhancing synovium (pannus) is evident (arrows).

Iontophoresis

Mina *et al.* (2011) introduced another medical option for treatment of refractory TMJ arthritis: dexamethasone iontophoresis. Previously used as adjunctive therapy for rheumatoid arthritis [74]) and for enthesitis associated with spondyloarthritis [75], this procedure is noninvasive and can be performed in a physical thera-

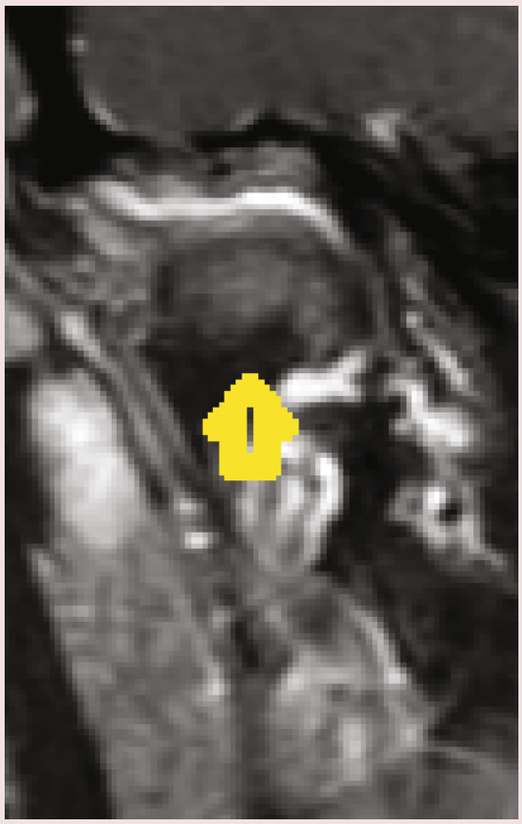

Figure 4. Temporomandibular joint MRI (coronal T1-weighted post-contrast image) of same subject.
Condylar bone loss (arrow) is more evident on this Figure.

pist's office. It consists of transdermal application of the medicine, followed by application of an electrical current to force the medicine into deeper tissues. In their retrospective study, 32 subjects were enrolled, of whom 27 completed the eight episodes of dexamethasone iontophoresis. Decreased pain was reported in 11/15 with pain at baseline, improved MIO was reported in 19/28 and improved maximal lateral excursion in 11/16. The medicine was tolerated without significant AEs, but there have been no subsequent publications on this technique.

Orthodontic devices

Functional appliances are intended to influence the soft tissue and mandibular position so as to support normal growth of the jaw; as a group, they have been termed functional orthopedic appliances (FOA) [76]. By stretching muscles or altering mandibular position, they have the potential to influence favorably bony growth and development [76]. FOA can be classified according to their primary intention of supporting either vertical or sagittal growth [76]. Sagittal advancement is appropriate in cases of bilateral TMJ arthritis in which there is a marked overbite, and is managed by activators; while vertical support is indicated in cases of unilateral involvement where there may be asymmetry in mandibular length and is managed by distraction splints [76]. Activators are similar in appearance to a retainer many children wear after braces, and distraction splints are likewise not cosmetically evident. In general, FOAs are preferably used when the disease is quiescent, although there is no evidence that this need be the case. Their overall effect appears to be positive, but modest. Tulloch *et al.* (1997) randomized 175 skeletally immature children with acquired deformities in TMJ shape (e.g., overbite) to headgear, a FOA worn in the mouth and observation only [77]. The causes of the altered facial shapes in these children were not stated. The results showed improved forward positioning of the mandible and mandibular length among the children who received the FOA, compared with the observation group. However, the differences between the groups were small and of uncertain clinical relevance [76]. There have been studies of FOA in children with JIA, all of which showed encouraging signs although had design flaws that limit their interpretability. For example, a study of a FOA in children with JIA was published by Kjellberg *et al.* (1995) [78]. In this study, 14 children with JIA and evidence of TMJ involvement were treated with an activator for a mean of 1.9 years; during this time, the authors reported improved overbite in 11 of 14, as well as improved facial growth. There was no control group of equally impaired JIA subjects who did not receive treatment, although a control group of healthy children with similar TMJ changes showed that the latter had a more robust response as compared with the former. Although the authors did not account for this finding, the ongoing inflammatory process in the TMJs of these children in the prebiologic era surely contributed. Farronato *et al.* (2009) used a mandibular activator in 72 children with JIA, of whom 22 had follow-up over a 4-year period [79]. They compared their results with historical controls based in a different country and published 18 years prior [34], reporting less retrognathia and improved mandibular shape. Most recently, Portelli *et al.* (2014) used an activator in 15 children with JIA over 2 years, reporting improved pain, function and facial profile following the completion of therapy [80]. However, these were subjective statements, without any data or statistical hypothesis testing. Finally, Stroustrup *et al.* (2014) used custom-designed distraction splints in 28 children with JIA and TMJ involvement for a period of 8 weeks, reporting statistically significant decreased pain and improved mouth opening and

lateral excursion over this period [81]. Because FOA are only effective during growth and must be used for several years to be effective, Pederson *et al.* (2015) recommended that they be used early, as soon as the problem is identified [76].

Surgery

Once a child has reached maturation, FOA have no further role in the management of TMJ disorders. As discussed previously, children with longstanding disease can be left with multiple anatomic and functional abnormalities, including a shortened ramus, mandibular asymmetry, condylar instability, malocclusion, impaired chewing mechanics, altered TMJ biomechanics and poor esthetic appearances [30,82]. Thus, surgery is in some cases the only available option [83]. This is preferably done after skeletal growth is complete, and also when the disease activity is fairly quiet [84]. A detailed description of the surgical options is available to the interested reader [84]. Briefly, the options are orthognathic surgery versus distraction osteogenesis. The former can consist of bilateral sagittal split osteotomy, in which the ramus is sectioned, brought forward and stabilized with screws; similar sectioning of the mandible may also be required [84]. In contrast, distraction osteogenesis is a less complicated procedure. In this case, the lateral ramus is exposed by stretching of the overlying soft tissue, so that a distraction device can be adhered to it. A small osteotomy is performed, in other words, a small hole in the bone is created, which is then filled in with new bone, permitting growth of the ramus. This can take about 2–3 months to attain target growth [84]. Unlike orthognathic surgery, distraction osteogenesis can be performed in growing children, and can be done in stages [84]. In addition to the usual surgical risks, there is also a risk of relapse following these procedures.

Conclusion

A generation ago, children with JIA were at high risk of substantial and irreversible changes to the structure and function of their TMJ [58]. Today, such changes appear far less frequently, even perhaps at centers that do not specifically address the TMJ. Thus, it is evident that systemic therapies can target the TMJ, yet in many cases not sufficiently [5]. That some of the inflammatory changes seen on MRI may represent nonspecific findings that may be present in noninflamed children does not account for decades of research showing substantial damage as well as severe inflammatory changes in children with JIA [55,58]; noninflamed children do not have pannus, condylar destructions, disc degeneration or other findings that have been observed over the years in children with JIA [51,53].

It is also clear that TMJ arthritis can be refractory to conventional and biologic immunosuppressive therapy [5]. Although withholding IAC may prevent iatrogenic damage, it does not address the risk of unopposed inflammatory changes in the TMJ. However, in light of the recent study by Lochbuhler *et al.* (2015) [68], more long-term safety data are required on the use of IAC. It is possible that infliximab or even longer lasting TNFi would be more effective as first-line therapy than as salvage therapy in children who have already

Executive summary

Demographics of temporomandibular joint involvement

- Diagnosis of temporomandibular joint (TMJ) arthritis requires a concerted effort to evaluate for its presence.
- There are few reliable predictive factors for TMJ arthritis in children with juvenile idiopathic arthritis (JIA).

Anatomy & pathophysiology

- Excessive mechanical loading of the TMJ can result in bone destruction and inflammation.

Complications of TMJ arthritis

- Long-standing TMJ arthritis can result in substantial damage to the joint, affecting its form and function.

Diagnosis of TMJ arthritis

- Plain radiography and computed tomography can diagnose late stages of bone involvement in TMJ arthritis.
- There are mixed data on the utility of ultrasound, which are operator dependent.
- MRI with contrast is generally considered the gold standard for diagnosis of TMJ arthritis in children with JIA.
- Children without JIA may have some degree of synovial enhancement at the TMJ, in part depending on the MRI protocol and the timing of imaging postcontrast.

Treatment of TMJ arthritis

- TMJ arthritis appears to partially respond to systemic immunosuppressive therapy, but not as well as most other joints.
- Intra-articular corticosteroids therapy for TMJ arthritis appears to be safe and effective in the short term, but concerns have been raised about long-term effects on mandibular growth.
- There are insufficient data on the value and timing of IA injection of infliximab for TMJ arthritis.
- Nonsurgical approaches, such as iontopheresis and functional appliances, may have roles as well in treating TMJ arthritis and normalizing jaw and mid-face growth, respectively.

failed IAC [73]; future studies should compare the safety and effectiveness of IAC with IA infliximab. Finally, functional appliances appear to be a safe and potentially effective means to modulate TMJ growth in children with advanced changes and possibly reduce pain as well as improve form, but data as well as expertise with this approach are limited [76].

Future perspective

As awareness of TMJ involvement in JIA expands throughout the pediatric rheumatology community, studies will be designed evaluating treatment options for TMJ arthritis refractory to systemic immunosuppressive therapy. Such options may include IAC, arthrocentesis without CS injection and IA injection of TNF inhibitors. Additional studies will evaluate nonsurgical approaches, namely FOA and iontophoresis, and there will be more long-term data on the effects of IAC on mandibular growth. This information will permit evidence-based decision making about the optimal therapeutic approach for TMJ arthritis, perhaps even for individual patients.

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