Condylar asymmetry in patients with juvenile idiopathic arthritis: could it be a sign of a possible temporomandibular joints involvement?

Short Title: condylar asymmetry in juvenile idiopathic arthritis

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Abstract
Objectives: The aim of the study was to evaluate the condylar and ramal asymmetry of the mandible in patients with Juvenile Idiopathic Arthritis (JIA) using orthopantomographies (OPTs).
Methods: 30 JIA patients with confirmed diagnosis of JIA and a routine OPT, seeking for orthodontic therapy, free of specific symptoms of temporomandibular joint involvement, and 30 normal matched subjects with OPT were comprised in the study. The method of Habets et al. was used to compare the condyles and rami in OPT. The significance of between-group differences were assessed using Mann-Whitney test.
Results: the results showed a high significant difference in the range of asymmetry of the condyle, being the patient group highly asymmetrical ($P<0.0001$). No differences were found in the range of asymmetry of the ramus between groups ($P=0.47$). The intra-group comparison between males and females showed a difference in the patient group ($p=0.04$), being the females more asymmetric.
Conclusions: knowing that the temporo-mandibular joint (TMJ) is highly susceptible to inflammatory alterations during growth, even in absence of symptomatology, and being the OPT a cost-benefit favorable imaging tool widespread in the dental field, the latter could be used as a first screening examination in JIA patients to calculate the condylar asymmetry index. The use of this screening tool will help the physicians in addressing the patients that should undergo a more detailed TMJ imaging to early detect TMJ abnormalities and to early set up a targeted therapy of the related cranial growth alterations.

Keywords: Juvenile idiopathic arthritis (JIA), asymmetry index, orthopantomography (OPT), early diagnosis

Introduction

Juvenile idiopathic arthritis (JIA) relates to an heterogeneous group of diseases of unknown aetiology, characterized by chronic inflammation of one or more joints, with an onset before the age of 16 years and a minimum duration of 6 weeks [1]. The prevalence of JIA is reported as 0.07 – 4.01 per 1000 children, while the annual incidence is 0.008 – 0.226 per 1000 children, and it

manifests in girls more frequently [2].
The disease spectrum goes from self-limited monoarthritis to ongoing multiple joints destruction, and may involve severe systemic manifestations [3]. The classification system, first proposed in 1994 (Santiago criteria)[4], was revised twice: in 1997 (Durban)[5] and in 2001 (Edmonton)[1] by the International League of Associations for Rheumatology (ILAR). A new set of criteria for childhood-onset idiopathic inflammatory arthritis, called JIA, was developed, and it is still used. Nowadays JIA can be classified according to the onset of the disease and to the number of joints affected, as oligoarthritis, when four or less joints are involved and as polyarthritis when five or more joints are involved. A systemic type of the disease also exists (Still's disease)[6].
TMJ involvement by JIA was recognized long time ago, by Still in 1897 [7]. Due to the diagnostic difficulties, the prevalence of TMJ involvement is reported, in several studies, with a wide range, from 17 to 87 per cent [8-12]. The TMJ can be involved by JIA unilaterally or bilaterally and in several studies [10, 11, 13] it has been shown that, among patients with TMJ involvement, 40-50% experience unilateral manifestations while bilateral involvement can be up to 74%[14, 15].
It has been well established that the TMJ is characterized by adaptive growth and maintains greater remodelling capacity in the adulthood, with respect to other joints [16, 17]; when JIA involves the TMJ, one of the two side might be affected more severely with respect to the other, leading to asymmetrical mandibular growth, unstable occlusion, disturbed TMJ and masticatory function, asymmetrical loading of joints and muscles, TMJ pain, and a compromised aesthetic appearance [8, 18, 19]. Joint asymmetries may develop with reduced growth especially on the affected side, and the chin deviating to the same side, often associated to a molar asymmetrical Class II malocclusion [20-22]. Recent studies show that early and appropriate treatment of TMJ involvement by JIA determines positive results and can improve mandibular vertical growth [19, 23-25].
Advances in diagnostic technology have allowed us to gain accuracy in identifying early signs of impairment of joint structures. Using the Cone Beam Computed Tomography (CBCT) method, it was shown that condylar asymmetry was a common feature in children with JIA. The degree of asymmetry was variable, but significant in the majority of the subjects. [2, 26, 27]. Farronato et al.[27] showed a significant difference between the volumetric values of the affected versus normal side; this was true especially for the condyle region, but there was no statistical difference between right versus left side [28].
Orthopantomography is a widespread, non-invasive method for evaluating the dental development during growth; sophisticated methods for diagnosing condylar lesions [29] are used for a precise diagnosis.
The aim of the study was to evaluate, using OPTs, the condylar and ramal mandible asymmetry of JIA patients, with respect to normal subjects. The hypothesis was to detect condylar and ramal asymmetry in OPT, as an indicator of TMJ involvement.

Material and methods

Subjects

30 patients (23 girls and 7 boys; mean age 12,87 ± 4,8477 years) with a confirmed diagnosis of JIA according to the ILAR 2003 criteria and 30 orthodontic subjects were included in this retrospective study after informed consent was obtained. Patients were included if they had 1) a confirmed diagnosis of JIA, 2) regular follow-up by a pediatric rheumatologist, and 3) no history of temporomandibular disease (TMD). All patients had a panoramic radiograph.
Patients were excluded if they had 1) incomplete medical records, 2) presence of congenital or acquired facial anomalies (eg, hemifacial microsomia, cleft lip and palate, Treacher Collins syndrome, or TMJ ankylosis), 3) a history of facial fractures, 4) previous intra-articular procedures (eg, steroid injections or operations), 5) TMD, 6) presence of medical comorbidities not allowing for OPT radiography (eg, severe scoliosis limiting neck movement).
Patients were referred to the Orthodontics divisions for routine orthodontic and dental screening; until that moment, patients were free of specific symptoms and no involvement of TMJ was

suspected. Patients were asked about the first manifestation of JIA and if they have ever suffered of TMJ symptomatology (articular clicking, locking or functional limitations).
The control group was selected to be age and sex matched with the first group and was comprised of 30 patients, JIA free, with normal occlusion, 23 girls and 7 boys; mean age 13,69 ± 4.822 years. The inclusion criteria were: (1) no significant medical history (2) normal growth and development (3) bilateral molar class I with minor or no crowding (4) no crossbite (5) no functional deviation of the mandible and (6) no history of trauma or previous orthodontic or prosthodontic treatment or maxillofacial or plastic surgery. The age and sex distributions in the 2 groups are shown in Table I.
Clinical and instrumental data
For each patient, the occlusal diagnosis was evaluated clinically and on the model casts.
To quantify asymmetries between the mandibular condyles and the rami the method introduced by Habets et al. was used [30]. This method compared vertical heights of the mandibular right and left condyles and rami. Panoramic radiographs were traced and measured with a digital calliper by one operator (R.C.) in a blind way, not knowing whether they belonged to patient or control group.
The outlines of the condyle and the ascending ramus of both sides were traced on acetate paper. On the tracing paper, a line (A, the ramus tangent) was drawn between the most lateral points of the condylar image (O1) and of the ascending ramus image (O2). A line perpendicular to the ramus tangent (A) was drawn from the most superior point of the condylar image. The vertical distance on the ramus tangent from B line to the most lateral point of the condyle (O1) was measured. This distance was called condylar height (CH). The distance on the ramus tangent between the two originally marked most lateral points of the image (O1 and O2) was called ramus height (RH) and measured (Fig. 1, 2). To express the symmetry between the condyles and the rami on the OPT image, the following formula $|(R-L)/(R+L)|x100\%$ was used.
The absolute value of the difference between the measured condylar or rami sizes of the right (R) and left (L) were divided by the sum of the same condylar or rami sizes and respectively expressed in percentages.
This calculation allows individual differences in sizes and provides a value for (a)symmetry of each individual. The result of this ratio-formula gives a range of asymmetry from 0% (complete symmetry) to 100%. According to the study by Habets et al. a 6% difference between the condylar vertical sizes in an OPT is an acceptable limit for diagnosing a condylar asymmetry [30].

Statistical analysis
Data were expressed as mean ±SD and interquartile range. The statistical distribution of the quantitative measures was found to be non-gaussian (tested by Shapiro-Wilk test) and the significance of between-group differences were assessed using Mann-Whitney test. All the tests were two tailed and statistical significant level was set at 5%.

Results
Demographic characteristics, type of JIA and occlusal characteristics are presented in Table 1.
As regard to the type of JIA, 25 patients (83,3%) were diagnosed with oligoarticular type, 3(10%) with polyarticular type and 2(6,6%) with other type of JIA.
Class II malocclusion (symmetric and asymmetric) was observed in 16 patients (53, 3%) and crossbites (unilateral and bilateral) were present in 8 patients (26,6%).
As regards the time interval between the first symptom of JIA and the OPT, the average difference is of 4,95±4,68 years.
The results showed a highly significant difference in the range of asymmetry of the condyle, expressed in percentage from 0 to 100%, between the patient versus the control group($P<0.0001$), being the condylar asymmetry index in the patient group of 15.58% ±10.98 and in the control group of 1.72% ±1.21 ($P<0.0001$). (fig. 3)
No differences were found in the range of asymmetry of the ramus between groups ($P=0.47$) , being the ramal asymmetry index in patient group of 2.97 % ±2.42 and in the control group of 2.33 %

±1.7.
The intra-group comparison between males and females showed a significant difference in the range of asymmetry of the condyle in the patient group (P=0.04) , being the condylar asymmetry index of 17.45±11.84 in the females and of 9.43±3.24 in the males and a border line value for the control group (P=0.05) , being the condylar asymmetry index of 1.96±1.27 in the females group and of 0.95±0.51 in the males. No differences were found in the range of asymmetry of the ramus both in the patient group (P=0.36), being the ramal asymmetry index of 2.76±2.41in the females and of 3.66±2.51 in the males, neither in the control group (P=0.11), being the ramal asymmetry index of 2.59±1.76 in the females and of 1.49±1.37 in the males (fig. 4).
Among the males, the difference of the range of asymmetry of the condyle between patient and controls resulted significant (P=0.002) and the range of asymmetry of the ramus resulted almost significant (P=0.06).
Among the females, the difference of the range of asymmetry of the condyle resulted highly significant ($p<0.0001$), but no differences were found in the range of asymmetry of the ramus (P=0.78).

Discussion

This retrospective study evaluated the condylar and ramal asymmetry of patients with JIA, compared with normal subjects, also considering males and females separately and intra-group differences. Still few articles addressing the mandibular asymmetry in JIA patients have been published so far and no articles explored possible differences in this asymmetry between males and females.
The distribution of the various subtypes of JIA in our sample does not reflect the distribution reported worldwide, and this is most reasonably due to the sample size. Indeed our aim was not to explore the rate of TMJ involvement among the different ILAR categories of JIA.
The distribution of the malocclusions in our cohort of JIA patients showed a prevalence of class II characteristics, in agreement with the literature [23]. The condyle of the patient group resulted highly asymmetric with respect to the control group. This is in agreement with previous published data [2, 19, 29, 31]. The ramus did not show any asymmetry. Of note, the range of condylar asymmetry is greater in females with respect to males , while there is a tendency toward ramal asymmetry in males, totally absent in females. Even though these differences between sex-groups may be related to the relatively low number of male patients compared to females, future studies on larger cohort are warranted to address this point.
With regard to the time interval between the first sign of JIA and the OPT, it may indicate a period of silent pathology that can result in a considerable impairment of TMJ.
From previous histological studies we know that the TMJ is a unique joint characterized by an adaptive pattern of growth and it shows great capabilities of remodelling in different stages of development [16, 32-35]. This joint is particularly vulnerable to dysplasia [2, 17] and alterations of the cartilage and the subchondral bone may occur in JIA children [36]. This may lead to local growth disturbances that occur as a result of inflammation, increased vascularization and destruction of the growth sites in the mandibular condyle. The severity can range from condylar flattening, sometimes combined with minor lesions, to complete absence of the condylar head [8, 37, 38]. The resultant abnormalities, which are present in up to 69% of subjects with JIA, include micrognathia, downward and posterior growth rotation of the mandible, facial asymmetry, and limited mouth opening as well as various malocclusions, especially hyperdivergent class II [9, 39].
As previously reported, the TMJ could be involved unilaterally or bilaterally and even when the involvement is bilateral, the TMJ shows significant asymmetry in vertical and sagittal directions. In general, the asymmetry observed in the JIA group with bilateral TMJ involvement may be explained by the differences in the severity of the inflammatory process or the onset time of the disease in the two different sides of the TMJ [13]. However, bilateral TMJ involvement showed largest amount of mandibular retrognathia [36, 40]. This finding is not surprising, as the bilateral

destruction of the growth centers located in the cartilage of the mandibular condyles leads to a short mandible undergoing a backward rotation in relation to the anterior cranial base and the maxilla, as often observed in JIA patients [9].
The advantage of early diagnosis and, consequently, early treatment of TMJ involvement in children with JIA is considerable, not only to control the inflammatory process, halting the disease progression, but also because condylar growth can take place even if the condylar bone and cartilage have been already affected. Furthermore, a healing of hard tissue can occur on the head of the condyle and a normal border of compacta bone can develop [23].
TMJ arthritis remains one of the most under-diagnosed and under-treated conditions in JIA, and its delayed detection may lead to severe structural and functional abnormalities of the masticatory system [41]. It is also clear that earlier onset, long duration, and the degree of severity of the disease are directly related to the extent of the maxillofacial abnormalities. Interestingly, Stabrun and colleagues found reduced mandibular growth in affected children without visible condylar lesions [20]. It is likely that early inflammatory alterations of the growing center of the jaw, even in the absence of detectable changes on conventional radiography, may have occurred in these children. Furthermore, even though destructive changes of the TMJ can be observed in OPT and MRI, it happens that only sporadic or no symptoms are referred by the patients [42, 43]. We know that CBCT is able to precisely show the morphological alterations and MRI is able to early detect, from 4 years of age, the TMJ involvement, but the use of gadolinium contrast and, sedation (in the younger patients), are necessary. The quantity of x-rays, the use of contrast medium, the need of a sedation procedure and the high cost of these exams, do not suggest the routine use of this diagnostic imaging. Recently, a study comparing the OPT with MRI with gadolinium in JIA patients, showed that the abnormal panoramic findings (abnormal condyle morphology, accentuated antegonial notch or short ramus and condyle unit), are significantly associated with TMJ synovitis in MRI [44].
Orthopantomography has been used in several studies [44, 45] to evaluate condylar, ramal, and condylar plus ramal asymmetries. These reports concluded that OPT provides acceptable results, especially for vertical measurement, being the asymmetry index, calculated as a ratio, a reliable reference even with different magnifications sheets; moreover this imaging technique has a favorable cost-benefit relationship, exposing subjects to relatively low doses radiation. Given these premises, the results of our study confirm that OPT seems to be a reliable tool to show TMJ abnormalities in patients with JIA. It is seems reasonable to think that the asymmetries found in our patients were secondary to active TMJ inflammation that went undiagnosed, due to the lack of signs and symptoms of TMJ involvement. Given the above-mentioned limits of MRI, our study suggests the use of OPT as a routine tool for screening the possible TMJ involvement in JIA patients and to obtain information on the possible outcome .
For this reason, the routinary use of OPT in JIA children should be suggested from two different points of view:
1- Because OPT is routinely obtained for the orthodontic and dental care diagnosis at an early stage in development, it could be an opportunity for orthodontists and pedodontists to routinely calculate the asymmetry index of the TMJ, to early address, in case of significant asymmetry, further instrumental evaluation and, eventually, the need for referral to rheumatologist.
2. It could be useful for rheumatologists, to routinely obtain an OPT for all JIA children to calculate the asymmetry index, to eventually consider a more detailed imaging and the need for referral to orthodontists for an early functional therapy. Moreover, the OPT obtained at the onset of the pathology could be an important reference to check the progression of the disease during growing.

Key messages
1- The condyle asymmetry, in OPT, resulted significantly higher in JIA patients, especially in

females;
2- TMJs are often early involved in JIA even if asymptomatic and underdiagnosed
3 - OPT could be used as a non-invasive screening in JIA patients for early diagnosis of TMJ involvement and following treatment.

Disclosure statement
The authors declare no conflict of interest

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