Uveitis Associated with Juvenile Idiopathic Arthritis, our Observations

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ABSTRACT
Introduction: Uveitis as extra-articular manifestation of juvenile idiopathic arthritis (JIA) is present in 20% of children with the persistent form, in 30% with the extended oligoarticular form, while it is present in psoriatic and polyarticular rheumatoid factor (RF) negative ar-thritis in 10% and 14%, respectively. Aim: The aim of the study was to evaluate the frequency of uveitis and its complications in children with JIA. Material and Methods: A retrospective study was conducted with an analysis of the medical records of children with JIA who were treated for the last 5 years. The analysis included the following: the child’s age and sex, age at onset of arthritis, of uveitis, complications, RF values and antinuclear antibodies (ANA). Results: The study included 97 children with JIA; in 14 (14.4%) uveitis was observed; the most common form of JIA was the oligoarticular extended form (6/14), oligoarticular persistent form was observed in 5 children, while 3 children with uveitis had polyarticular RF negative JIA. The age of arthritis onset was lower in children with uveitis (4.7 vs 8.2 years); ANA positivity was more common in children with JIA and uveitis (64% vs 41%). Uveitis was the first manifestation of the disease for 2 children; 28.6% of children had clinically asymptomatic uveitis, while 42.4% of children developed uveitis within 4 years from the JIA onset. 8/14 children developed uveitis complications: 3 cases of synechia, 2 band keratopathy, 2 cataracta, 1 glaucoma. Conclusion: Uveitis as significantly present manifestation of JIA requires to timely recognize, treat, monitor children in order to prevent complications. Keywords: uveitis· arthritis· children.

1. INTRODUCTION
Uveitis is a serious ocular complication of juvenile idiopathic arthritis (JIA), most commonly involves the anterior segment of the eye, and can result in impairment and/or loss of vision in children. The incidence of uveitis in children with JIA ranges from 12% to 38%, it occurs most frequently in children with the oligoarticular extended and oligopersistent form (25% and 16%) of JIA (1-4). It is more common in girls who develop the oligoarticular form earlier in life, who have a positive antinuclear antibodies test (ANA), however, clinical manifestations, course and complications of uveitis may be significantly severe in boys (3, 5, 6). In about 10% of children, uveitis may be present before the manifestation of arthritis, it occurs during or immediately after the diagnosis of arthritis in almost half of affected children, whereas a significant number of children develop uveitis within 7 years after the onset of their arthritis, its activity does not follow the activity of JIA (7, 8, 9). 66% of children with JIA associated uveitis develop ocular complications which prevail in children with longer duration of the disease as well as in children in whom arthritis is more active; about 51% of develop synechia, 34% develop band keratopathy, one-fifth of affected children have cataracts, while approximately 17% of children develop glaucoma (9, 10, 11). However, at the time of diagnosis of uveitis a significant number...
of children already have some of the structural complications (1, 10, 11, 12).

Therefore, the aim of this study was to evaluate the frequency of uveitis and its complications in children with JIA.

2. MATERIALS AND METHODS

A retrospective study was conducted with an analysis of the medical records of children with JIA who were treated at the Department and/or at the Outpatient Clinic for Rheumatology, Allergy and Immunology, Clinic for Children's Diseases, University Clinical Center Tuzla from January 2011 to July 2016. The diagnosis and classification of subtypes of JIA was done in compliance with The International League of Associations for Rheumatology-ILAR (13). The analysis included the following: the child's age and sex, age at onset of arthritis, the prevalence of specific subtypes of JIA, age at onset of uveitis, its localization, characteristics, manifestations (headaches, eye redness and pain, photophobia, vision changes), complications, findings and RF values determined by an agglutination test (cut-off of 0.0-8.0 IU/ml), which was considered positive if the value was above 8.0 IU/ml in two measurements within three months; and ANA Elisa Hytec (cut-off 23 IU/ml), which was considered positive if the value was above 23 IU/ml. For this research we had the consent of the Ethics Committee of University Clinical Center in Tuzla Statistical analyses were performed using the biomedical application software “MedCalc for Windows, version 15.11.4” (MedCalc Software, Ostend, Belgium). Numerical data is shown using a measure of central tendency and an appropriate measure of dispersion. The variables with skewed distribution are shown using the median and interquartile range (IQ).

3. RESULTS

The study included 97 children with JIA: 38 boys and 61 girls. The median age was 7.1 years (IQ range, 2.3-10.6 years), with the prevalence of oligoarticular extended form observed in 48.4% of children. The characteristics of 97 children with JIA are shown in Table 1.

Approximately half of the children included in the study had positive ANA test results, while a significant number of them 13/47 (27.6%) had slightly positive test results with the values very close to the cut-off values. 14/97 (14.4%) of children with JIA included in the study had uveitis (9 girls, 5 boys). The median age of the onset of arthritis in children with uveitis was 4.7 years (IQ range, 1.4-7.9 years), whereas the median age of the onset of arthritis in children who did not develop uveitis was 8.2 years (IQ range, 2.3-10.7 years). The most common form of arthritis in children with uveitis was the oligoarticular extended form in 42.6% of children. The characteristics of 14 children with uveitis and JIA are shown in Table 2.

The ANA test (Table 2) was more frequently positive in children with uveitis and arthritis than in children without uveitis (64% vs 41%), while the frequency of positive RF test was similar in both groups of children, 21.4% in children with uveitis and arthritis and 19% in children with arthritis but without uveitis. Uveitis was the first manifestation of the disease for 2 children who developed JIA within 4 months. 28.6% of children had clinically asymptomatic uveitis, while 71.4% of children with uveitis had some of the symptoms (Table 3).

The median age of developing uveitis after the onset of JIA was 24 months, and 42.8% of children developed signs of uveitis over a period of four years from the JIA onset (Table 4). In our study 78% of children had bilateral uveitis, with most common anterior uveitis (64%). Fewer than half of the children 8/14 or 57.1% developed uveitis complica-
4. DISCUSSION

Juvenile idiopathic arthritis (JIA) associated uveitis is the most common extra-articular manifestation of JIA with a potentially significant risk of visual impairment. The prevalence of uveitis in children with JIA widely ranges 10-38%, due to different classifications and differences in schemes for monitoring affected children (1, 4, 14). Heiligenhaus et al (15) reported on the frequency of uveitis 12% in all children with JIA, and Clarke et al (16) observed uveitis in 13.1% of children with JIA. Similarly, we found uveitis in 14.4% of children with JIA; the incidence was significantly higher in girls (64.3%) than in boys (35.7%). Saurenmann et al (6) also reported the significantly higher incidence in girls (37%) compared to boys, where the incidence was only 7%, although their study included the children with JIA up to the age of 2. Depending on the JIA subtype children are at various risks of developing intraocular inflammation, so Paroli et al (17) found the oligoarticular form in 87.3% and polyarticular form in 12.7% of children with uveitis; whereas Angeles-Han et al (18) reported that 41% of children had the oligoarticular persistent form of JIA and uveitis. They concluded that the oligoarticular subtype of JIA was one of the important predictors of uveitis development. Our results were in accordance with that, 78.3% of children with uveitis had the oligoarticular, while the polyarticular form was present in 21.4% of children with JIA and uveitis. The median age of JIA onset in boys was slightly higher (5.7 years), while the median age of JIA onset was significantly lower in girls (3.5 years). Paroli et al (17) reported that the mean age of children included in their study was 4.5 years, while Angeles-Han et al (18) found that the age of arthritis onset in girls with uveitis was significantly lower than in boys (2.3 years vs. 6.6 years). The risk of developing uveitis in children with JIA is significant in girls in whom arthritis occurs early in life, who are ANA positive (19). The role of ANA in the pathogenesis remains unclear since the intraocular antigen which would be a target for ANA has not been identified yet, and that raises the question whether ANAs are pathogenic or an epiphenomena of JIA associated uveitis (20). Our results are to some extent in accordance with the above stated. Although approximately half of the children included in the study had positive ANA, a significant number of them 13/47 (27.6%) had slightly positive test results with the values very close to the cut-off values. ANA was more frequently positive in children with uveitis and arthritis than in children without uveitis (64% vs 41%). Also, Angeles-Han et al (21) more frequently found ANA positivity in children with JIA and uveitis than in children without uveitis (66.7% vs. 16.7%), while Kasapcoglu et al (22) reported that 25/37 children with oligoarticular JIA were ANA positive, and 10 of them developed uveitis; the children with the extended form of JIA neither were ANA positive nor had uveitis. On the other hand, the results of the study carried out in Italy results suggested that ANA positivity was the greatest risk factor of developing uveitis, and 30% of children with positive ANA developed uveitis regardless of the child’s age or sex (3). In the United States approximately 10-25% of 300,000 children with JIA developed uveitis within the first 4 years of the arthritis diagnosis (1,3). Angeles-Han et al (21) also found that 80% of children developed uveitis within 4 years after the JIA diagnosis; about 24% had uveitis before JIA, 22% within the first year of JIA developed uveitis, while 4% of children developed uveitis in the fifth year after the arthritis onset. Our results are in accordance with the previously stated, in 14.3% of children uveitis occurred before JIA, 85.7% of children developed uveitis within four years after the onset of arthritis; 28.6% of them developed uveitis within the first 13 months of JIA. Since slightly different results were presented by Sabra et al (7) who found that the median age of uveitis development after the JIA diagnosis was 1.8 years. However, uveitis may predate the diagnosis of JIA, thus eye inflammation may remain unnoticed for some time. JIA associated uveitis is the most common form of anterior uveitis in childhood (23) which was proved by Heiligenhaus et al (24), in their study 83% of children with uveitis had anterior form, Clarke et al (16) observed chronic anterior uveitis in 68.3% of children, acute anterior uveitis in 16.2% and recurrent anterior uveitis in 12% of children; Qian and Acharya (25) reported that 83% of children had anterior uveitis and intermediate uveitis 9% of children with JIA. Our results comply with theirs, the most common form of uveitis was the anterior for 64% children. Studies show that 50% to 70% of eyes have at least one structural complication at the initial ophthalmology examination (band keratopathy, posterior synechiae, cataract, glaucoma, hypopyon, macular edema, epiretinal membrane and optic disc swelling) while vision loss may be a drastic sequel of having many of those complications (3,8,20). Angeles-Han et al (18) reported results, given that both cataracts and synechiae were frequently present in 31% children, while keratopathy was less common in 25%, and glaucoma in 17% of children, but our results are slightly different, 57.1% of children developed structural ocular complications, most frequently synechiae (21%), while both keratopathy and cataracts were equally present; only one child had glaucoma; but the bad final outcome resulting in vision loss in 14.3% of eyes.
5. CONCLUSION

Uveitis as significantly present, severe extra-articular manifestation of JIA requires a thorough approach to timely recognize, treat and monitor children in order to prevent drastic complications such as vision loss in children.

• Conflict of interest: none declared.

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