EVALUATION OF THE MAIN DATA OF INFLAMMATORY RESPONSE TO THE BASE THERAPY OF THE JUVENILE IDIOPATHIC ARTHRITIS

Yulia Vyzhga
PhD, Associate Professor
Department of pediatric No. 2
N. I. Pirogov Vinnytsya National Medical University
56 Pirogova str., Vinnytsya, Ukraine, 21018
yulia_tokarchuk@yahoo.com

Abstract: The activity of the juvenile idiopathic arthritis evaluates the speed of the process progression, intense of its clinical manifestation, effect of the carried treatment.
The aim of our study was to estimate changes of the inflammatory response signs as well as content of NF-kB due to basic therapy of the JIA.
Materials and methods. At our study, we had checked 68 children with JIA, who passed their treatment at Vinnytsya regional children's hospital within the period from 2011 to 2014 years.
Results. At the patients we studied currency of the JIA was characterized with articular variant of the disease, mainly in monoarthritis type. Laboratory activity of the inflammatory response characterized with increased content of the C-reactive protein (71.2±3.7 %), inflammatory cytokines – IL-1β (54.8±4.1 %) and IL-6 (56.2±2.4 %), as well high quantity of the nuclear factor-kB (70.5±3.1 %). Currency of the JIA in children characterized with high increasing of the inflammatory response signs especially C-reactive protein (6.55(4.2;9.8)), IL-1β (7.3(3.5;11.9)), IL-6 (6.8(4.5;10.6)) and NF-kB (6.76 (4.8; 9.1)), that are in correlative connections with clinical signs (number of the injured and swelled joints, evaluation of the general condition of the child according to doctors and own response) of the disease activity (rxy=+0.34 up to 0.62, p<0.01).
Conclusion. During the managing of the basic therapy in children with JIA we estimated decreasing of the IL-1β content in patients at the background of methotrexate administration (38.7±3.7 %), at the second group with use of sulfasalazine (28.5±3.5 %) and the third with leflunomide prescription (29.1±5.1 %), but significant decreasing of the IL-6 content, that is one of the main inflammatory mediators and as well NF-kB was found just in group of the patients with methotrexate administration (on 36.3±3.8 % and 32.4±2.4 % for NF-kB).
Keywords: juvenile idiopathic arthritis, children, inflammatory markers, treatment, NF-kB, cytokines.

1. Introduction

According to the statistical findings in Ukraine there are more than three thousands of children with juvenile idiopathic arthritis (JIA) (0.4 on 1000 of the children's population), morbidity rate is from 2 up to 16 persons on 10000 of children at the age to 16 years old, from 30–50 % of the patients loose work abilities after three-five years of the disease. Even in case of active treatment, up to the 25 years of age in 30 % of the patients that started JIA in early childhood, high activity of the disease is saved [1, 2]. The activity of the disease evaluates the speed of the process progression, intense of its clinical manifestation, effect of the carried treatment. Very important is to study development of the pathogenesis of the JIA for the evaluation of the common changes on the cellular level to demonstrate diagnostic and therapeutic abilities of the disease due to estimation of the mechanisms of the adaptation and injury of the cell systems with managing of the inflammatory response creation [3, 4]. At the backstage of the inflammatory response in case of JIA we can find biochemical and immune-chemical processes with regulation of exact biological active substances, especially with cytokines, stimulating growth factors, nuclear components [5]. Development of the inflammatory response in case of JIA can be due to damage of the apoptosis mechanisms, that lead to its over need activation or stop [6, 7].

Transcriptional factors, especially nuclear-kB (NF-kB) – one of the most important signs that mediate immune and inflammatory response, regulate apoptosis. In the study in vitro was demonstrated important role of the NF-kB in forming of the response for drug therapy in case of reproduction of the disease that comes with active chronicle inflammatory reaction [8, 9]. That is why now seriously interested at studying of the main antirheumatic drug action due to their influence at NF-kB and as well modulation of the signal pathways with different drugs [10].

The aim of our study was to estimate changes of the inflammatory response signs as well as content of NF-kB due to basic therapy of the JIA.

2. Materials and methods

At our study we had checked 68 children with JIA, who passed their treatment at Vinnytsya regional children's hospital within the period from 2011 to 2014 years. Among them we presented 32 boys and 36 girls. The first group was presented with 32 patients that received methotrexate as a main drug for the treatment of the JIA. The second group was presented with 25 children that accepted as a basic treatment strategy sulfasalazine. To the third group we included 11 patients that were given leflunomide as a basic treatment. Groups were statistically similar according to the age, sex and duration of the disease findings. The average duration of the disease in the group of the children we examined was 18.2±1.3 months. For the patients of the first therapeutic group indications for the methotrexate use were: high signs of the process activity, systemic variant of the disease, absence of the use of other antirheumatic drugs at the anamnesis and contraindications against treatment strategy. To the second and third features for the indication of such therapy ere: minimal or moderate activity of the disease, articular variant of the injury, specially mono- or oligoathritis contraindications and refuse of the parents for such a treatment. Methotrexate for the children of the first group was given at a middle dosage 7.5 up to 15 mg/m^2/week, which was 2.5 mg every 12 hours. At the background of methotrexate indication children accepted folic acid at the middle dosage not less than 5 mg/week. Therapeutic dosage of the sulfasalazine in children with JIA was at the average meaning of 20 to 50 mg/kg/day, but not more than 2 g/week and of the leflunomide – 20–30 mg/day. System corticoids (methylprednisolone) children received in a dosage not more than 0.2 mg/kg/day according to the prednisolone equal dose. Patients accepted as well non-steroid anti-inflammatory drugs with duration not over 14 days in an age dosages.

During the study we estimated general condition of the patients with using of the clinical and laboratory methods according to main features of the disease. As well we checked visual analogy scores, Childhood Health Assessment Questionnaire (CHAQ). Laboratory-instrumental methods included routine studies as well estimation of the main signs of inflammatory response activity – inflammatory cytokines in serum (Interleukin-1β and Interleukin-6), content of the nuclear facor-kB while using ELISA method.

Effect of the basic therapy of the JIA provided according to the criteria of ACR and checked changes of both clinical and laboratory signs of the inflammatory response. Criteria that we checked in all patients included: count of the painful and swell joints, as a signs that indicate clinical activity of the disease, degree of the functional insufficiency according to the CHAQ test, evaluation of the 10-points score of the pain in both variants (patient and doctor), as well ESR and CRP content. The duration of the observance at the children of all groups lasted for 1 year, with control studies in6 and 12 months after the start of the basic therapy. All results were statistically proved with program Statistica 6.0. All data were expressed as mean ±SD. Estimation of differences between average meanings was done by coefficient «t» to Students method, percentage values were detected by Fishers method. Approvement of the differences was counted by standard possibility (p) – $p<0.05$. For difference between comparative values was evaluated ratio of risks. Assessment of the degree of influence of factor characteristics was evaluated by odds ratio for 95 %.

3. Results of the study

At the patients we studied currency of the JIA was characterized with articular variant of the disease in 52 (76.4±2.6 %) cases, monoarthritis type was estimated in 41.2±3.4 %. Systemic variant of the disease was presented in 16 (23.6±3.6 %) children with JIA. In 29 (42.6±3.2 %) patients disease characterized with a high activity of the process, in 28 (41.2±3.2 %) and 11 (16.2±2.1 %) cases we managed mild and severe signs of the JIA process.

Laboratory activity of the inflammatory response characterized with increased content of the C-reactive protein (71.2±3.7 %), inflammatory cytokines – IL-1β (54.8±4.1 %) and IL-6 (56.2±2.4 %), as well high quantity of the nuclear factor-kB (70.5±3.1 %). Increased level of C-reactive protein was found in children with JIA without any connection with a duration of the disease, more often in case of monoarthritis (61.7±3.5 %), with moderate signs of the clinical activity of the disease (72.05±2.8 %), functional insufficiency (80.9± ±1.9 %) and start elements of degenerative-destructive changes in the joints (83.8±2.3 %). In group of the children with a duration of the JIA less than 2 years more often (on 19.4±1.2 %) we got increased level of IL-1β, at the same time overloading of the IL-6 content was more common for the patients with a duration of the process more than 2 years (on 26.1±1.8 %). We should estimate that higher meanings of the NF-kB (on 14.0±1.1 %) we found in children with a smaller period of the disease and this findings depended on quantity of the injured and swelled joints, activity of the disease, severity of the degenerative-destructive process in the joints (r_{xy}=+0.34 up to 0.62, $p<0.01$). With increasing of the JIA duration we found as well enlargement of the patients number with positive NF-kB test (on 16.0±1.3 %), but with small decreasing of its content.

According to the clinical form and activity of the disease, speed of its progression, all our patients were divided for 3 subgroups according to the therapeutic influence. We should manage that clinical currency of the disease in children of the first group was more severe with higher signs of the JIA activity (on 19.2±1.4 %), degree of the functional insufficiency (on 26.4± ±2.1 %) and destructive-degenerative signs (on 41.3±3.5 %) in compare with features of the other two groups of children. According to the laboratory signs of the JIA in children, it was also more elevated in children of the first group before the administration of the treatment ($p<0.05$) and based at the background of CRP content (10.73±0.89 mg/l), IL-1β (7.55±0.61 pg/l), IL-6 (6.38±0.68 pg/l), as well NF-kB (6.42±0.56 pg/l) estimation.

We found high clinical effect of the drug therapy in 6 positions from 8 possible in children of the first group, that received methotrexate as basic drug, especially it concern decreasing of the painful joints count (on 24.2±2.8 %), pain index (on 23.7±2.1 %), estimation of the general condition in patients version (on 16.6±1.9 %) and doctors variant (on 12.8±1.8 %), also significantly decreased laboratory signs of the inflammatory response – ESR (on 35.4±4.9 %), content of the CRP (on 30.8±3.7 %). In children of the second group, such positive changes were found in 4 categories from 8 possible and in the third group of the children we estimated 5 points from 8 possible result.

Between the children of the first group clinical effect of the drug therapy on the level of ACR 30 was achieved in 37.5±2.7 % patients, in 46.8±2.4 % we got ACR 50 and in 9.3±2.9 % cases of JIA received ACR 70 response. At the second group of the patients in a term of 12 months of basic therapy currency level of ACR 30 was achieved in 56.0±3.4 % children, 20.0±2.8 % got ACR 50 and 4.1±1.2 % received ACR 70 stage of the drug therapy response. At the third group of the patients with JIA response level ACR 30 was achieved in 54.5±2.1 % cases, 27.2±1.9 % more demonstrated ACR 50 result.

Effect of the inflammatory response suppression was demonstrated in all three groups of patients with JIA at the background of drug therapy use. But significantly better response was received in the first group of the patients that used methotrexate and presented with decreasing of IL-1β (on 38.7±3.7 %) and especially IL-6 (on 36.3±3.8 %), NF-kB (on 32.4±2.4 %) in compare with signs before the treatment and overcame the same results of the patients of two other clinical groups. Intense suppression of the IL-6 synthesis confirm active pathogenic-spread action of the methotrexate, cause IL-6 is one of the most important inflammatory cytokines that regulates synthesis of both IL-1β and CRP. And decreasing of the NF-kB amount prove more actual anti-inflammatory target-action of the methotrexate as a drug of basic strategy therapy in compare with other drugs.

4. Discussion

1. Currency of the JIA in children characterized with high increasing of the inflammatory response signs especially C-reactive protein (6.55(4.2;9.8)), IL-1β (7.3(3.5;11.9)), IL-6 (6.8(4.5;10.6)) and NF-kB (6.76 (4.8; 9.1)), that are in correlative connections with clinical signs (number of the injured and swelled joints, evaluation of the general condition of the child according to doctors and own response) of the disease activity (r_{xy}=+0.34 up to 0.62, $p< 0.01$).

2. Due to the provided treatment between all examined children with JIA in 32 (47.0±5.1 %) of the patients we got ACR 30 response, 23 (33.8±4.8 %) achieved ACR 50 and in 4 (5.9± ±1.9 %) estimated ACR 70 level.

3. During the managing of the basic therapy in children with JIA we estimated decreasing of the IL-1β content in patients at the background of methotrexate administration (38.7±3.7 %), at the second group with use of sulfasalazine (28.5±3.5 %) and the third with leflunomide direction (29.1±5.1 %), but significant decreasing of the IL-6 content, that is one of the main inflammatory mediators and as well NF-kB was found just in group of the patients with methotrexate administration (on 36.3±3.8 % and 32.4±2.4 % for NF-kB).

References

1. Ghosh, S., May, M. J., Kopp, E. B. (1998). NF-κB and Rel proteins: Evolutionarily Conserved Mediators of Immune Responses. Annual Review of Immunology, 16 (1), 225–260. doi: http://doi.org/10.1146/annurev.immunol.16.1.225
2. Hahn, Y.-S., Kim, J.-G. (2010). Pathogenesis and clinical manifestations of juvenile rheumatoid arthritis. Korean Journal of Pediatrics, 53 (11), 921–930. doi: http://doi.org/10.3345/kjp.2010.53.11.921
3. Van den Ham, H.-J., de Jager, W., Bijlsma, J. W. J., Prakken, B. J., de Boer, R. J. (2009). Differential cytokine profiles in juvenile idiopathic arthritis subtypes revealed by cluster analysis. Rheumatology, 48 (8), 899–905. doi: http://doi.org/10.1093/rheumatology/kep125
4. Kemper, A. R., Van Mater, H. A., Coeytaux, R. R., Williams, J. W., Sanders, G. D. (2012). Systematic review of disease-modifying antirheumatic drugs for juvenile idiopathic arthritis. BMC Pediatrics, 12 (1), 1471–1479. doi: http://doi.org/10.1186/1471-2431-12-29
5. Isennock, M., Grosel, J. M. (2011). Juvenile idiopathic arthritis: Can you recognize this complex diagnosis? Journal of the American Academy of Physician Assistants, 24 (1), 22–27. doi: http://doi.org/10.1097/01720610-201101000-00005
6. Martini, A. (2012). It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Annals of the Rheumatic Diseases, 71 (9), 1437–1439. doi: http://doi.org/10.1136/annrheumdis-2012-201388
7. Dueckers, G., Guellac, N., Arbogast, M., Dannecker, G., Foeldvari, I., Frosch, M. et. al. (2011). German evidence and consensus based guidelines 2010 for the treatment of juvenile idiopathic arthritis (JIA). Pediatric Rheumatology, 9, 181. doi: http://doi.org/10.1186/1546-0096-9-s1-p181
8. Lin, Y.-T., Wang, C.-T., Gershwin, M. E., Chiang, B.-L. (2011). The pathogenesis of oligoarticular/polyarticular vs systemic juvenile idiopathic arthritis. Autoimmunity Reviews, 10 (8), 482–489. doi: http://doi.org/10.1016/j.autrev.2011.02.001
9. Omar, A., Abo-Elyoun, I., Hussein, H., Nabih, M., Atwa, H., Gad, S., Emad, Y. (2013). Anti-cyclic citrullinated peptide (anti-CCP) antibody in juvenile idiopathic arthritis (JIA): Correlations with disease activity and severity of joint damage (a multicenter trial). Joint Bone Spine, 80 (1), 38–43. doi: http://doi.org/10.1016/j.jbspin.2012.03.008
10. Rosendahl, K. (2011). Juvenile idiopathic arthritis–recent advances. Pediatric Radiology, 41, 110–112. doi: http://doi.org/10.1007/s00247-011-2054-y