Материал поступил в редакцию: 12-01-2015
Материал принят к печати: 04-02-2015
УДК: 616-002.77

Recent developments in biomarkers used for evaluation of juvenile idiopathic arthritis

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Juvenile idiopathic arthritis (JIA) is the most common inflammatory disease in childhood. JIA is subdivided into six categories, all of which differ in etiological factors, clinical phenotype, prognosis, laboratory tests and response to therapy. To start appropriate treatment in patients with JIA and to inform patients correctly, it is essential to know the individual prognosis. This emphasizes the need for research on novel and more accurate biomarkers to assess disease acitivity. A biomarker comprises small samples from the patient such as blood, urine and saliva, obtained by non-invasive techniques. These serum biomarkers such as S100 proteins (S100A12,S1008/9), myelin related proteins (MRP8/14), single nucleotide polymorphism (SNPs) and newly vectra DA have been suggested for the prediction of disease course and relapse risk. İn this review we summarize the biomarkers for JIA.

Keywords: Biomarker, juvenil idiopathic arthritis.

J Clin Med Kaz 2015; 1(35):11-14
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ЖЕТКІНШЕКТЕРДІҢ ИДИОПАТИЯЛЫҚ АРТРИТІНІҢ АҒЫМЫН БАҒАЛАУДА ҚОЛДАНЫЛАТЫН БИОМАРКЕРЛЕР БОЙЫНША ҚАЗІРГІ ЗАМАНҒЫ ЗЕРТТЕМЕЛЕР

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Жеткіншектердің идиопатиялық артриті (ЖИА) балалық шақтағы буын қабынуы ауруларының ішіндегі ең жиі таралған түрі болып табылады. ЖИА этиологиялық факторларына, клиникалық фенотипіне, болжамына, зертханалық көрсеткіштері мен емге деген жауабына қарай 6 түрге бөлінеді. Науқасқа ауруы жайлы дұрыс ақпарат беру мен қажет емді тағайындау үшін науқастың жеке болжамын анықтай білу өте маңызды. Бұл өз кезегінде аурудың белсенділігін бағалау үшін жаңа әрі нақты жолмен анықтауға мүмкіндік беретін биомаркерлерді қолдану қажеттілігін негіздейді. Биомаркерлер науқастан инвазивті емес жолмен алынған аздаған үлгілер (қан, зәр немесе сілекей) болып табылады. Аурудың ағымы мен рецидив болуы қаупін болжау үшін биомаркерлер сарысуының келесі түрлері ұсынылды: S100 ақуызы (S100A12, S1008 / 9), туыс миелинлі сарысулар (MRP8 / 14), бірен-саран нуклеотидтің полиморфизмі (SNP) мен Vectra DA. Берілген шолуда біз ЖИА кезінде қолданылатын биомаркерлер бойынша қорытынды жасадық.

Маңызды сөздер: биомаркер, жеткіншектердің идиопатиялық артриті.

СОВРЕМЕННЫЕ РАЗРАБОТКИ БИОМАРКЕРОВ, ИСПОЛЬЗУЕМЫХ ДЛЯ ОЦЕНКИ ИДИОПАТИЧЕСКОГО ЮВЕНИЛЬНОГО АРТРИТА

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Ювенильный идиопатический артрит (ЮИА) является наиболее распространенным воспалительным заболеванием суставов в детском возрасте. ЮИА делится на 6 подтипов, каждая из которых отличается по этиологическим факторам, клиническому фенотипу, прогнозу, лабораторным показателям и реакцией на лечение. Для правильного информирования пациента и назначения необходимого лечения, важно знать индивидуальный прогноз. Это подчеркивает необходимость проведения новых видов обследования, в том числе с помощью более точных биомаркеров для оценки активности заболевания. Биомаркеры включают в себя небольшие образцы (кровь, моча, слюна), полученные у пациента с помощью неинвазивных методов. Для прогнозирования течения заболевания и рецидива риска предложены следующие виды сывороток биомаркеров: белок S100 (S100A12, S1008 / 9), родственные миелиновые белки (MRP8 / 14), полиморфизм единичного нуклеотида (SNP) и Vectra DA. В данном обзоре мы подводим итоги по биомаркерам для ЮИА.

Ключевые слова: биомаркер, ювенильный идиопатический артрит.

Introduction

Juvenile idiopathic arthritis (JIA) is the most commonly seen inflammatory disease in childhood. JIA is subdivided into seven categories. All subtypes differ in etiological factors, clinical phenotype, prognosis, laboratory tests and response to therapy. To start appropriate treatment in patients with JIA and to inform patients correctly, it is essential to know the individual prognosis. This emphasizes the need for research on more accurate biomarkers to assess disease activity.

Biomarkers

A biomarker comprises small components which can be found in material taken from the patient such as blood, urine and saliva by non-invasive techniques. An appropriate biomarker must remain in the material for a long time, be measureable, and for use in the paediatric population, not change with age. The use of biomarkers in clinical practice is becoming more widespread and provides valuable information. However, the use in paediatric patients is not yet widespread. In recent years, proteins, cellular components, mRNA and genetic components such as single nucleotide polymorphism (SNP) have been developed in new research as promising biomarkers. Biomarkers can be used to determine the disease phenotype, course, progression, response to treatment, potential complications and remission periods [1].

Juvenile idiopathic arthritis

JIA is the most frequently seen chronic inflammatory rheumatismal disease in childhood at a reported prevalence of 1 per 1000 children [1,2]. The etiology of JIA is not known and the genetic component is confusing. Biomarkers for JIA which will be useful in the choice of medication and monitoring of early remission are being researched in new studies.

JIA is characterised by severe joint inflammation lasting for at least 6 weeks in one or more joints in the under 16 years of age population. There are 6 subtypes, differentiated by clinical characteristics and physical and laboratory findings. The subtypes of JIA are:

Systemic onset;
Oligoarticular;
Polyarticular;
Psoriatic arthritis;
Enthesitis-related arthritis;
Undifferentiated arthritis.

The varying characteristics in a wide spectrum in the sub groups creates difficulties for physicians in making a diagnosis and defining prognosis and treatment [1-3].

Etiopathogenesis of juvenile idiopathic arthritis

The etiopathogenesis of JIA is not yet fully understood. Many genes are important in the determination of the disease onset and clinical characteristics. IL2RA/CD25 gene and VTCN1 genes are the gene loci of JIA predisposition. A relationship has been found between specific HLA alleles and JIA subtypes [3,4].

Humoral and cell mediated immunity plays a role in the pathogenesis of JIA. T lymphocytes play a central role with the expression of pro-inflammatory cytokines (TNF-alpha and IL-6). It is thought that the relationship between Types 1 and 2 lymphocytes is disrupted in JIA. Evidence of the humoral immune system is the complementary activation of increased serum auto-antibodies (especially ANA), immunoglobins and immunocomplexes. Chronic inflammation in the synovium is characterised by B lymphocyte infiltration and expansion. In addition, synoviocyte proliferation stimulated from cytokine expression is responsible for macrophage and T-cell activation. Some authors have classified systemic onset JIA as an "autoinflammatory disease", similar to Familial Mediterranean Fever (FMF) or Cryopyrin-Associated Periodic Syndrome. This theory is supported by the demonstration of similar phagocytic protein (S100A12) patterns in JIA and FMF and the evident response to IL-1 receptor antagonists [5].

Juvenile idiopathic arthritis clinical and laboratory tests

Diagnosis is based on patient history and the findings of physical examination. There is no diagnostic laboratory test for JIA, and a child with JIA may even have completely normal laboratory test results. However, laboratory test results can be useful in the differential diagnosis and in the definition of the JIA subgroups especially characteristics apart from the joint. In routine practice, the values examined in the laboratory evaluation are sedimentation rate, C-reactive protein, full blood count, metabolic panel, liver and kidney function tests (inluding serum creatinine), antinuclear antibody (ANA), rheumatoid factor, anticyclic citrulline peptide (anti-CCP). In addition analysis may also be made of protein, albumin, fibrinogen, ferritin, D-dimer, angiotensing converter enzyme (ACE), antistreptolysin (ASO), antiDNAse B and urine [2,3].

Acute phase reactants, ESR and CRP levels are often high in systemic onset and polyarticular disease and may be used in the monitoring of disease activity. However, as many diseases may affect these two parameters, sensitivity and specificity for JIA is low [1-3].

In the active period of systemic onset JIA, serum protein and albumin levels are often low, while fibrinogen, ferritin and D-dimer levels are high. ACE levels are examined in the differential diagnosis for sarcoidosis, ASO and anti-DNAse B for rheumatic fever and post-streptococcal arthritis [1-3].

Clinical research on the relationship between biomarkers and disease course in juvenile idiopathic arthritis

In recent years, the pro-inflammatory S100 proteins, S100A8/9 (also known as calprotein or myelin-related protein) have been found to be a sensitive test in the measurement of JIA activity. S100 proteins are measured with ELISA (enzyme –linked immunosorbent assay). In the course of severe disease, particularly in the polyarticular type, serum S100 proteins are found to be high. In a study by Gerss et al [6], which was aimed at predicting JIA relapse risk, S100A12 and myeloid-related protein 8/14 (MRP 8/14) levels were found to be high in patients expriencing attacks.

In addition to the correlation of S100 proteins to disease activity, they are also used in monitoring the response to treatment. After 6 months of treatment with methotrexate (MTX), serum MRP8/14 was found to be low in those responding to treatment and high in those not responding. In addition, in those treated with IL-1 antagonist or anti-TNF, the correlation between MRP8/14 level and disease activity was found to be low. Patients with high disease activity together with relapse were found to have a high level of serum MRP8/14. In the prediction of patients at high risk of relapse, a value of MRP8/14>740ng/ml^{-1} was found to be signficant with sensitivity of 92% and specificity of 82% [7-9].

The polyarticular type JIA group is divided into 2 subgroups with the presence of RF. These two groups display different genetic properties, age of onset, clinical findings and progno-

sis. In up to almost 70% of children with oligoarticular JIA, the ANA test is positive. ANA positivity is also necessary in the differential diagnosis to exclude systemic lupus. The relationship of ANA with JIA and disease has been thought to be a risk factor in the development of chronic anterior uveitis. Although uveitis is painless, it is a significant complication leading to serious sight loss. These two antibodies, RF and ANA, which can be easily measured in the blood and remain stable for a long time are two valuable biomarkers indicating disease type, predicting the course and indicating the treatment path [10,11].

In systemic onset JIA, when there is low ESR, low/normalised white blood cells, thrombocytopaenia, raised liver enzyme, high ferritin, low fibrinogen, high temperature and bleeding (in a disseminated intravascular coagulation pattern), it should be taken as a warning of the life-threatening macrophage activation syndrrome (MAS). Gene expression studies have been conducted to predict children who may develop MAS and various gene loci have been found to be related to MAS development [12].

In the last 20 years, with the use of intra-articular steroids, MTX and biological agents, especially in the early stage, a very good prognosis has been seen in children with JIA. A different prognosis is seen for each subgroup, so there is therefore a need for assistive methods in the determination of prognosis [10-12].

Early stage hip or wrist involvement, symmetric disease, the presence of RF and extended active systemic disease are related to a poor prognosis. A better course is seen in children with rheumatoid pulmonary disease or vasculitis compared to children with RF positive JIA. Although the anti-CCP test is a more specific test than RF, it has not been studied sufficiently in children. In paediatric patients with JIA, anti-citrulline fibrinogen and alpha-enolase isotypes may be found and citrulline antibody isotype may be associated with a poor disease progression [13].

Systemic onset disease either fully responds to medical treatment or progresses into adulthood by showing a serious polyarticular course. While remission develops in the majority of children with oligoarticular involvement, the others progress to permanent polyarticular disease. In studies of patients with oligoarticular involvement, the two different courses are explained by immunological differences. For example, T cell types (regulator T cells and TH17 with high inflammatory property) and their prevalence show differences in these two clinical subtypes. In children showing more severe joint involvement, T cells, inflammatory protein levels and gene expressions have been found to be different. In the synovium of these children, while the CD4/CD8 ratio is lower, in those showing persistent oligoarticular involvement, serum CCL5 chemokine has been found to be higher [14,15].

Differences in the response to treatment is defined genetically. Therefore, genetic factors are each a good potential biomarker. In a previous study, 5-Aminoimidazole-4-Carboxamide Ribonucleotide-Transformilase (ATIC) gene with 2 SNPs and inosine triphosphate pyrophosphatase (ITPA) gene have been related to a poor response to MTX and 1 SNP of adenosine triphosphate binding cassette transporter 1 has been related to a good response to MTX [16].

Even though treatment choices in JIA are targeted at long-term, medication-free, clinical remission, complete remission is achieved in very few patients. Patients who obtain full remission pass into a 'controlled disease stage' rather than normal inflammatory status. There are studies supporting that T cells and expressed granulocytes are seen to have a function in the disease control genes of hepatocyte nuclear factor 4 alpha (HNF4-α) [17].

A multi-biomarker, new blood test, named Vectra DA, which will predict disease activity in polyarticular or widespread oligoarticular JIA, was presented as the research of Ringold S et al [18] at the 2014 Congress of the European League against Rheumatism (EULAR). This test contains 12 serum proteins which are in the pathobiology of JIA. An algorithm has beeen created to form a single Vectra DA score. According to this algorithm, JIA is classified as low, moderate or high disease activity. The biomarkers included in the test are vascular cell adhesion molecule 1 (VCAM-1), epidermal growth factor (EGF), vascular endothelial growth factor A(VEGF-A), interleukine 6 (IL-6), tumour necrotising factor receptor type 1 (TNF-R1), matrix metalloproteinase 1 (MMP-1), matrix metalloproteinase 3 (MMP-3), YKL-40, leptin, resistin, serum amyloid A and C-reactive protein. The juvenile arthritis disease activity score (JADAS) is a combined scale including the disease activity evaluation score of the doctor, the global wellness evaluation score of the patient/parent, number of active joints and ESR. In a previous study, Vectra DA results and JADAS results were found to be compatible. The efficacy of Vectra DA with multibiomarkers for JIA is supported by the heterogenity of the disease process and the ability to apply it in the monitoring of disease activity [19].

To be able to give the appropriate treatment to patients with JIA, individual prognoss is of great importance. In a study by Dijkhuizen et al [20] in which 3679 articles were scanned to reveal variables defining disease activity, joint damage, functional disability and quality of life, the results were compared of valid methods such as the Wallace criteria, the Childhood Health Evaluation Survey and the Juvenile Arthritis Damage Index and the study concluded that in all the methods, apart from quality of life, polyarticular onset was related to a poor prognosis, and diagnostic delay and systemic group were often related to the active disease process and ANAs were revealed not to be defining factors of disease activity. In addition, symmetrical involvement and RF positivity were related to less damage, and high disease activity to poor functional results.

Conclusion

The use of biomarkers in childhood arthritis is not widespread. An individual approach is aimed for with these biomarkers defining the clinical phenotype of the disease, the course, response to treatment and whether or not remission is gained. Thus the use of unnecessary medication can be avoided and by bringing the inflammation under control it becomes possible to attain remission in a short time.

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