GENE IL-8-251A / T AS A PROGNOSTIC TEST OF PROBABILITY OF DUODENAL ULCER IN CHILDREN

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Abstract

We had studied allelic polymorphism of the gene IL-8 and found that heterozygote mutant genotype of IL-8-251A/T may be prognostic criteria probability of duodenal ulcer in children. The bearer of the homozygous mutant genotype of IL-8-251A / A is associated with the most severe inflammation.

Keywords

children, duodenal ulcer, the gene IL-8-251A / T.

BACKGROUND

A number of studies demonstrated the important role of strains of Helicobacter pylori (HP) in formation of ulcer [1, 2]. The second most important factor in the damage of the mucosa is a disturbance of the system of defense mechanisms that are implemented through changes in reparative processes. We observe heterogeneity in the inflammatory response to HP infection that is caused by individual genetic characteristics (allelic polymorphism of cytokine genes) that trigger and control inflammation in the mucosa of duodenum [3]. Leading role in the pathogenesis of HP infection plays interleukin-8 (IL-8), polymorphism which affects the severity of the immune response, thereby causing the clinical phenotype of the disease [1]. IL-8 (Chemokine CXCL8) – glycoprotein that is mapped on 4q12-q21 chromosome, is one of the major proinflammatory cytokines. The gene encoding IL-8 has several allelic variants that differentially affect gene expression. It is important to study regional molecular genetic mechanisms of ulcer duodenum in children in the Chernivtsi region in order to improve treatment results of disease.

MATERIALS

Under our supervision we had 62 children with duodenal ulcer (main study group) and 57 healthy children (comparison group) aged 6 to 18 years. Children in both groups were HP-positive. The studied groups were representative for age, sex and place of residence ($p > 0.05$). Criteria for inclusion of children in the study: residence (Chernivtsi-sity, Chernivtsi region); Helicobacter pylori; age: 6–18 years; signed informed consent for research. Exclusion criteria: antibiotic therapy during the last three months, bad habits.

METHODS

Instrumental methods included esophagogastroduodenoscopy using fiberoptic gastroduodenoscopy (Pentax FG-24P) to verify the diagnosis, assessment of morphological changes in the mucosa by visual analogue scale, a biopsy of the gastric mucosa (Antrum and body of the stomach) and duodenum. Samples of genomic DNA for the study of gene polymorphism of IL-8 were isolated from peripheral blood leukocytes, stabilized using EDTA anticoagulant, followed by amplification of polymorphic sites by polymerase chain reaction using individually selected temperature program and appropriate primers. The presence of allele A (IL-8-251A/T) forms a restriction site for Mfe I. Analyses of amplification products were performed by electrophoresis in 3% agarose gel with ethidium-bromide and visualized under UV light using computer video. Statistical analysis of the data was performed using software package «Statistica 6.0». To assess compliance with the distribution of genotypes expected value at equilibrium Kolmogorov-Smirnov test using Pearson (χ^2). In the absence of normal distribution criteria used *Mann–Whitney–Wilcoxon test.* Association of alleles and genotypes of IL-8-251A/T with a tendency to develop duodenal ulcer evaluated by analysis of contingency tables, 2×2, 3×2 with the expectation criterion χ^2 (df = 1) and the odds ratio (OR) with genotype calculator. To assess the impact of polymorphism of IL-8 -251A/T on manifestations of the disease was used criterion H (*Kruskal — Wallis one-way analysis of variance*) [4].

RESULTS

Analysis of the distribution of alleles of the gene IL-8-251A/T showed that children from the main group had significantly more common A allele in comparison to children from comparison group ($\chi^2 = 8,99$, $p < 0.01$). The frequency of the T allele in affected children was slightly lower than in healthy ($\chi^2 = 4,32$, $p < 0.05$). The distribution of genotypes of IL-8-251A/T in the studied groups is presented in Fig. Normal genotype IL-8-251T/T was found in 19.4% of patients, mutant heterozygotes (IL-8-251A/T) –

67.7% of children in the main group, homozygous (IL-8-251A/A) – in 12.9% of children. In the comparison group of children we observed a slightly different distribution of genotypes of the gene IL-8-251A/T. Thus, the genotype of the IL-8-251T/T was found in 49.1%, IL-8-251A/T – in 29.8%, IL-8-251A/A – 21.1% of children. Frequency of occurrence of genotype IL-8-251A/T in patients was significantly higher in comparison to the healthy individuals (χ^2 = 17,08, p <0.0001), which gives reason to evaluate this genotype as a risk criterion of ulcer duodenum in children. A genotype of IL-8-251T/T, which is significantly more often diagnosed in children of comparison group (χ^2 = 11,79, p <0.001), can be considered to have a protective effect.

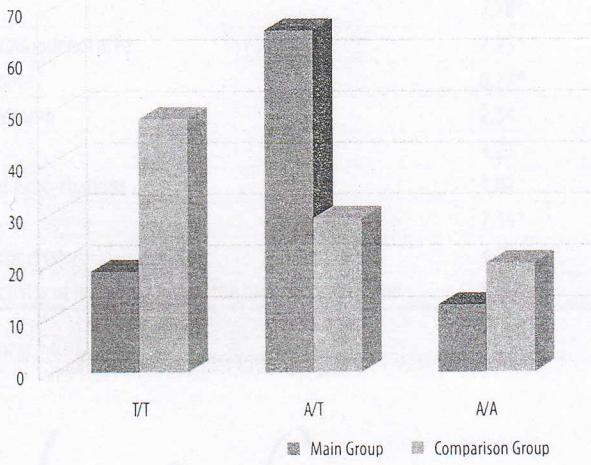

Fig. 1. Frequency distribution (%) of gene genotypes of interleukin-8-251A / T in children of Chernivtsi region

Between genotype IL-8-251A/T and the development of duodenal ulcer in children of the Chernivtsi region revealed a positive association (odds ratio (OR) = 4,94, χ^2 = 17,08, [2,27–10,76], p <0.0001). As shown in Table 1 data, OR greater than 1, indicating the importance of the risk allele A PROMOTER gene of polymorphism of IL-8-251A/T on ulcer duodenum in children. At the same time was shown a statistically significant negative relationship with genotype IL-8-251T/T, indicating perhaps a low risk of disease in carriers of this genotype (table 1).

Our results coincide with the data of other authors concerning the relationship between mutant heterozygous genotype of IL-8-251A/T with the development of duodenal ulcer in Caucasians. Analysis of clinical symptoms and the degree of inflammatory infiltration of the mucosa of the stomach and duodenum in children of the basic group showed significant difference in the intensity of symptoms depending on the distribution of genotypes of IL-8-251A/T. Thus, carriers of mutant A allele were observed with significantly more severe clinical symptoms and the greatest degree of inflammatory infiltration of the mucosa of the stomach and duodenum compared with native "wild" T allele (p <0.05). It is known that if A allele is present we observe increased expression of IL-8, which leads to a more pronounced inflammatory response to infection and persistence of HP.

Analysis of the associative relationship between genotypes of IL-8 and the clinical course of the disease was done (Table 2). We established positive correlative relationship of pain and dyspeptic syndromes, the degree of severity and the degree of active inflammation of the lining of the stomach and duodenum (Table 2).

CONCLUSION

Heterozygous mutant genotype of IL-8-251A/T may be used as prognostic criteria of probability of duodenal ulcer in children. Carriage of the homozygous mutant genotype of IL-8-251A/A is associated with the most severe inflammation. To develop prognostic criteria of risk, severity of duodenal ulcer in children and in order to highlight high-risk groups of the disease is needed further study of the combinations of polymorphisms of genes of various cytokines on more children.

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Table 1. Association of gene genotypes of interleukin-8 with duodenal ulcer

Gene, polymorphism	Genotypes	RR, 95%CI	OR, 95%CI	Log Odds	df=1 χ2 / p
ІЛ-8, (-251 A/T)	TT	0,47[0,29-0,78]	0,25[0,11-0,56]	-1,39	11,79/0,001
	AT	2,13[1,44-3,16]	4,94[2,27-10,76]	1,60	17,08/0,0001
	AA	0,73[0,42-1,29]	0,56[0,21-1,48]	-0,59	1,41/0,235

Table 2. Association of gene genotypes of interleukin-8 with with clinical features and course of treatment of duodenal ulcer of children

Sign	H (Kruskal – Wallis one-way analysis of variance)	p
Epigastric pain	7,38*	0,01
Pain in the pyloroduodenal area	7,25*	0,02
Diarrheal syndrome	6,27*	0,04
Intoxication syndrome	2,54	0,32
Hiperatsydnist	3,21	0,24
The frequency of exacerbations	3,07	0,56
severity	7,34*	0,02
The degree of progression	4,56	0,22
The degree of activity of inflammation of the mucous membrane	8,67*	0,001

*Note: * – Significant at p<0,05.*

in brief...

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Nicht nur Kinder lernen schnell positive und negative Situationen zu unterscheiden – auch Fruchtfliegen sind dazu in der Lage. Im Insektengehirn ist Dopamin für die Bildung des Vermeidungs- als auch des Belohnungsgedächtnisses entscheidend.

Originalpublikation:
A subset of dopamine neurons signals reward for odour memory in Drosophila. H. Tanimoto et al.; Nature;
doi:10.1038/nature11304, 2012

Parkinson: Neuer Antikörper entdeckt

Erkrankungen wie Morbus Parkinson liegen krankhafte Proteinveränderungen zugrunde. Bei der derzeit unheilbaren Krankheit verändert sich das Protein Alpha-Synuclein und wird pathologisch. Forscher haben nun einen Antikörper entdeckt, der Abhilfe schaffen könnte.

Originalpublikation:
An antibody with high reactivity for disease-associated α-synuclein reveals extensive brain pathology Gabor G. Kovacs et al.; Acta Neuropathologica,
doi: 10.1007/s00401-012-0964-x; 2012

MDMA: Partydroge als Parkinson-Heilmittel?

Kann die illegale Partydroge Ecstasy, die Menschen zum Tanzen bringt, tatsächlich in einem Medikament Verwendung finden, das die unkontrollierten Bewegungen bei Parkinsonpatienten verhindert? Ein Forscherteam ist der Meinung, dass das möglich ist.

Originalpublikation:
A novel MDMA analogue, UWA-101, that lacks psychoactivity and cytotoxicity, enhances l-DOPA benefit in parkinsonian primates M.J. Piggott et al.; The FASEB Journal;
doi: 10.1096/fj.11-195016; 2012