PSYCHONEUROIMMUNOMODULATION IN SCHIZOPHRENIA

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Основные иммунологические гипотезы шизофрении

- ***инфекционная*** (Bruce, Peebles, 1903; Rosenov E.F., Postgrad, 1947; Г.Ю. Малис, 1948 – 1959 и др.)
- ***вирусная*** (Goodall E.,1932; Морозов М.А., 1954; Морозов В.М, 1954; Вартанян М.Е.,Раппопорт Р.И., 1965; Torrey E.F., Peterson M., 1976; Hare T., 1979; Б.Ф. Семенов с соавт., 1982; Crow T.J., 1983; 1988; 2002; Libikova H., 1983; Rimon, R., 1983; Morosov P.V. ,1983;; Kurstak E. et al. (eds.), 1987; E. Kurstak (ed.), 1991; О.А. Васильева с соавт., 1991, 1992;Vasiljeva O.A et al., 1987; 1991; Rajcani J. et al., 1987; Невидимова Т.И, 1987; Крюкова Л.К. , 1988; Шмелев А.А., 1990; Найденова Н.Н., 1991; А.И. Жанков, 1993-1996; Karlson et al., 2002 et al.; Khandaker G.M. et al, 2013; Horning M. et al, 2013)

Основные иммунологические гипотезы шизофрении

- ***Токсико-аллергическая-аутоиммунная*** (Селецкий В., 1903; Page,1909; Хорошко В.К., 1912; Lehman-Facius H.,1937 – 1941; Heath R.G. et al., 1959-1967; Семенов С.Ф., Попова Н.Н., 1969; Pandey R.S. et al., 1981; Коляскина Г.И., 1972; Вилков Г.А.с соавт., 1984; 1990; Кушнер С.Г., Мазнина Т.П., 1980; 1985;.Куприянова И.Е, 1982; Карась И.Ю., 1988; Коляскина Г.И., Секирина Т.П., 1990; Говорин Н.В., 1998 и др.)
- ***Психонейроиммунная модель шизофрении***

  (F. Villemain et al., 1987; 1989; C.A. Kayfman et al., 1987; Ветлугина. 1993- 2001; О.А. Никифорова, 1994; Т.И. Невидимова, 1997; V. Barak et al., 1995; M. Maes et al., 1995; C.L. Cazzullo et al., 1999; N. Muller et al.,2000; Schwartz M., Silver H.,2000; Коляскина Г.И., 2003; Muller N., Schwaz M., 2006; Pae CU et al., 2006; Akhondzaden S. et.al., 2007; Maino K. et al., 2007; Hinze-Selch D et al., 2007; Vetlugina T. P. et al., 2008; 2013; Leonard BE et al., 2009; 2012; Lobacheva O.A., 2011; Debnath M, Berk M., 2014)

Психонейроиммунная модель шизофрении

Study Aim:

- *To study the regularities of psychoneuroimmunomodulation in schizophrenia and ways to improve the effectiveness of therapy based on immunological approaches*

PSYCHONEUROIMMUNOMODULATION

- Modulation of

of immune parameters depending on form, tempo of progression, stage and duration of pathological process, influence of psychopharmacotherapy

Methods

laboratory assessment of the immune status:

– Cells with receptors CD2, CD3, CD4, CD8, CD16, CD72, HLADR

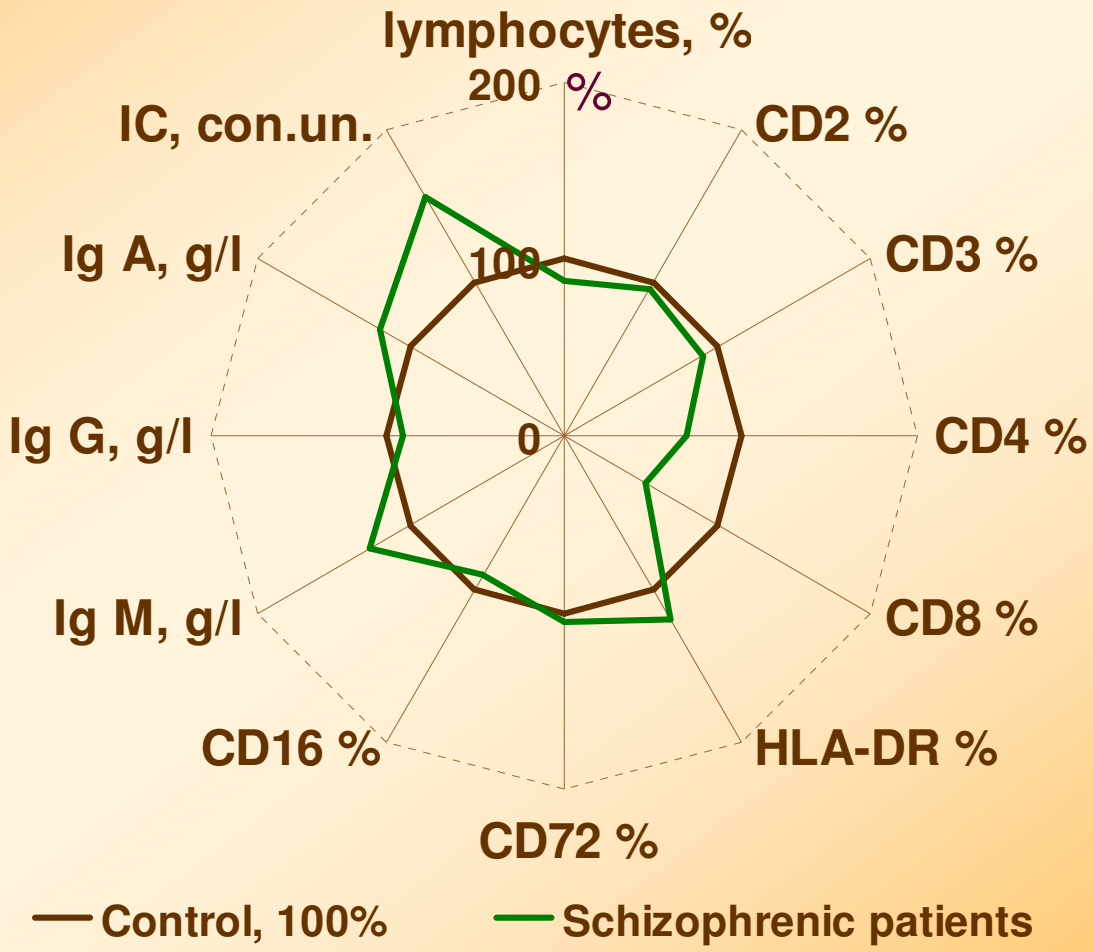
– IgM, IgG, IgA, IC

– cytokines (ILs, IFNs)

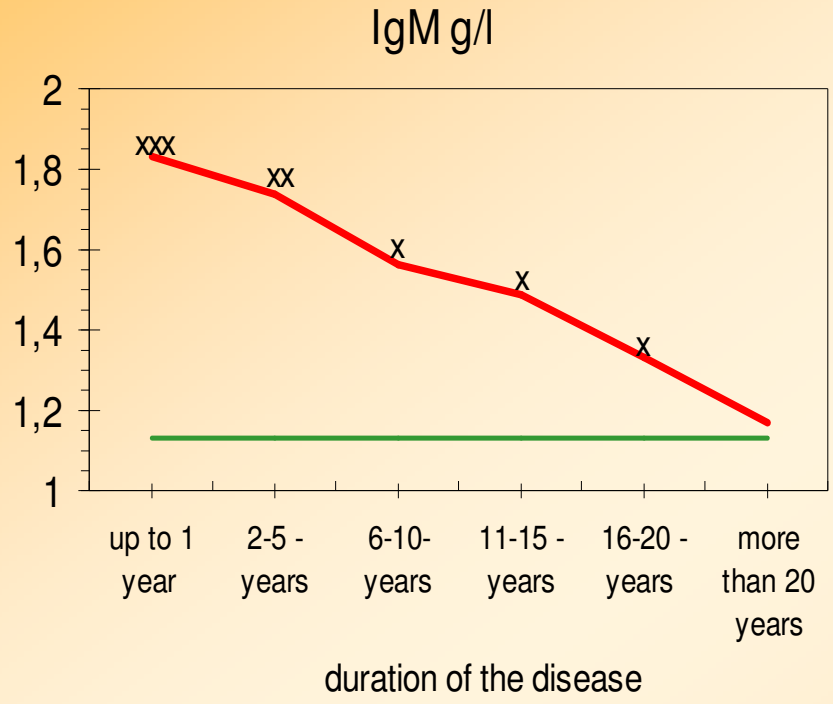
Examined groups

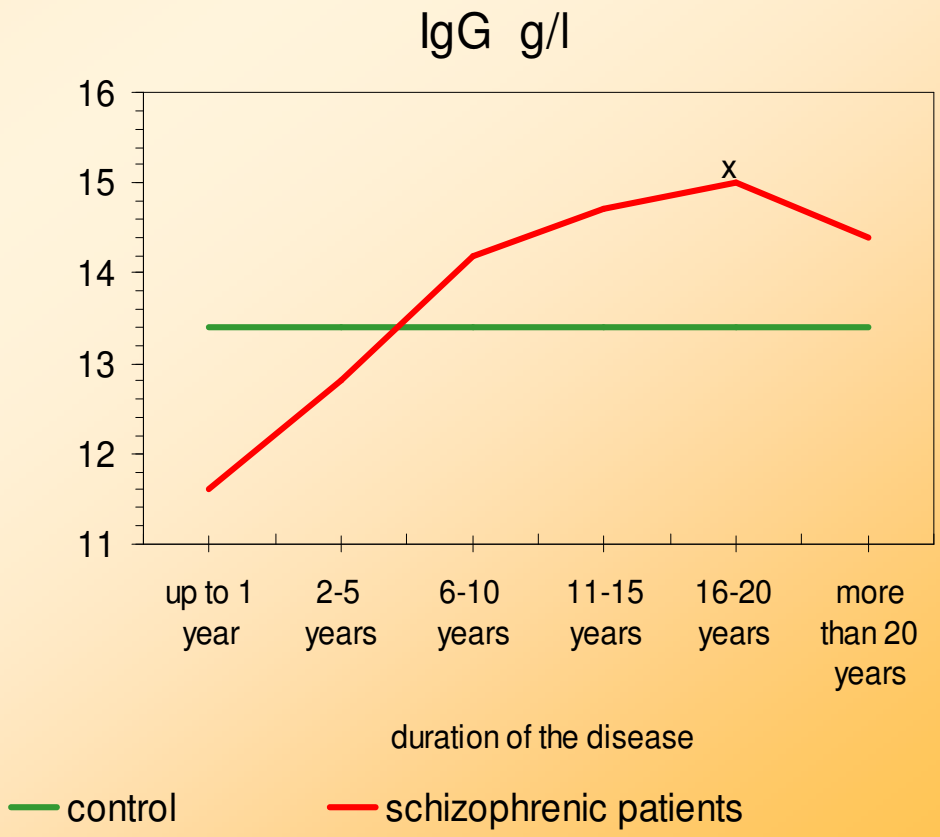
- More than 500 patients with schizophrenia
- ***For 219 patients therapy has been cancelled for 2 weeks***
- Control group for immunological investigations: 217 healthy people

Immunity characteristic of schizophrenic patients

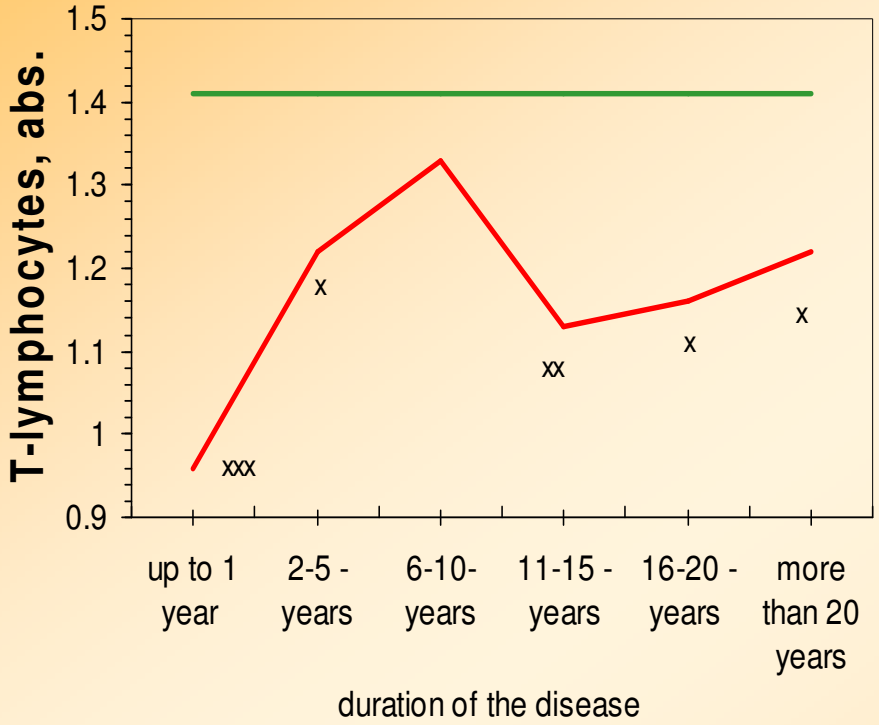


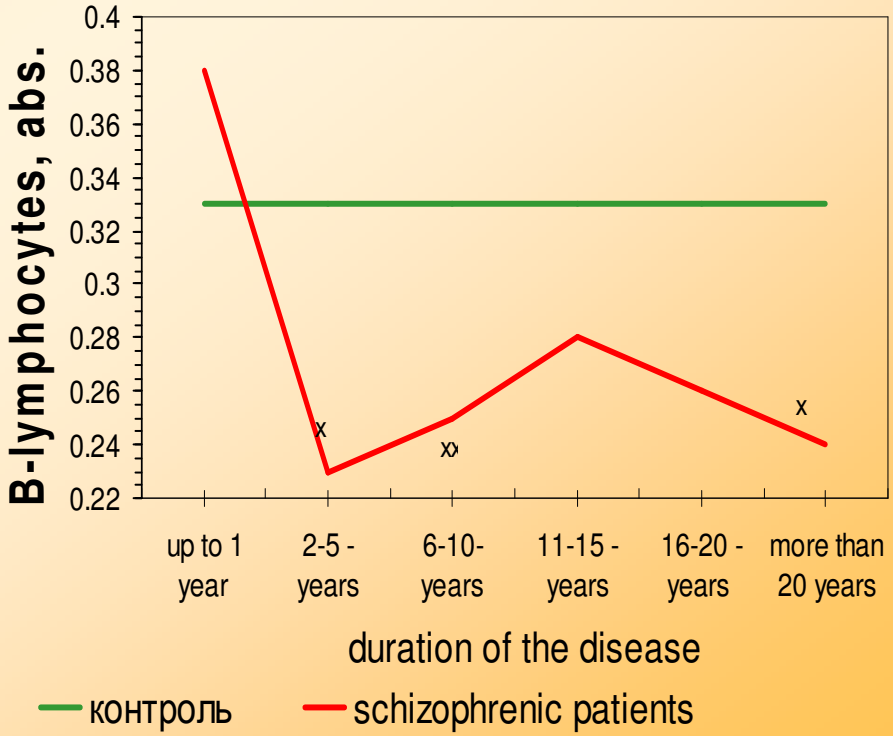
The dynamics of immune parameters among schizophrenic patients depending on the duration of the disease





The dynamics of cell immunity characteristics among schizophrenic patients depending on the duration of the disease





Correlation of immune reactivity types with the clinical forms of the disease :

Immune reactivity types (forms of the disease)	Immunity characteristic
I - hyporeactive (simple schizophrenia, hebefrenic)	N (IgM, IgG, IgA, ΣIg, T- h, Th / Ts, L) ↑ (IC); ↓ (Lph, Ts) ↓↓ - (T-Lph) ↓↓ -(PhI)
II – hyperreactive (catatonic)	N↓ - (Lph, T Lph, Th, Ts, PhI) ↑ - (IgA) ↑↑↑ (IC, IgM), ↑↑(B Lph), IgG, L, Th / Ts) ↑↑↑ - ΣIg
III –mixed (paranoid)	N - (IgG, IgA, T h) ↑ - (ΣIg, L, Th/ Ts) ↑↑ - (IC, IgM,); ↓ - (LPh, T- Lph, B- Lph, T-s, PhI)

Immune system in schizophrenia

- State of the immune system during schizophrenia is characterized as an immunological imbalance of *Th1/Th2* immune response
- The dynamics of immune parameters in the course of the disease has an oscillating pattern with changes in increase and decrease of their levels, the greatest abnormalities have been noticed during the first 5 years of the disease
- Peculiarities of the organism reactivity become evident in various types of immune response and correlate with the clinical forms of the disease

Immunological treatment options for schizophrenia

Ways based on addition of immunoactive drugs have been developed to overcome neuroleptic side effects and therapy resistance in schizophrenia patients

Patents of RF:

- № 2164799 C1
- № 2177326 C2
- № 2289137 C1
- № 2415666 C1

Overcoming resistance to pharmacotherapy

- In the absence of the expected positive effects of standard therapy for more 30 days, patients were considered resistant to therapy and assigned them Thymogen on various schemes
- With Thymogen treated more than 150 patients

- ***Тимоген*** – иммуномодулирующий низкомолекулярный синтетический дипептид α-глутамил-триптофан, оказывает влияние на реакции клеточного, гуморального иммунитета и неспецифическую резистентность организма. индуцирует экспрессию дифференцировочных рецепторов на лимфоцитах, нормализует количество Т-хелперов, Т-супрессоров и их соотношение у больных с различными иммунодефицитными состояниями

- Thymogen - low molecular weight synthetic immunomodulatory dipeptide α-glutamyl-triptophanum, affects the reaction of cellular, humoral immunity and nonspecific resistance; induces the expression of receptors on lymphocytes differentiation, normalizes the number of T-helper and T-suppressor and their ratio in patients with various immunodeficiencies

Схемы назначения тимогена

Отмена нейролептиков

- **Схема 1**: 0,01% тимоген по 1 мл внутримышечно в течение 5 дней.
- **Схема 2**: 0,01% тимоген по 1 мл интраназально в течение 5 дней.

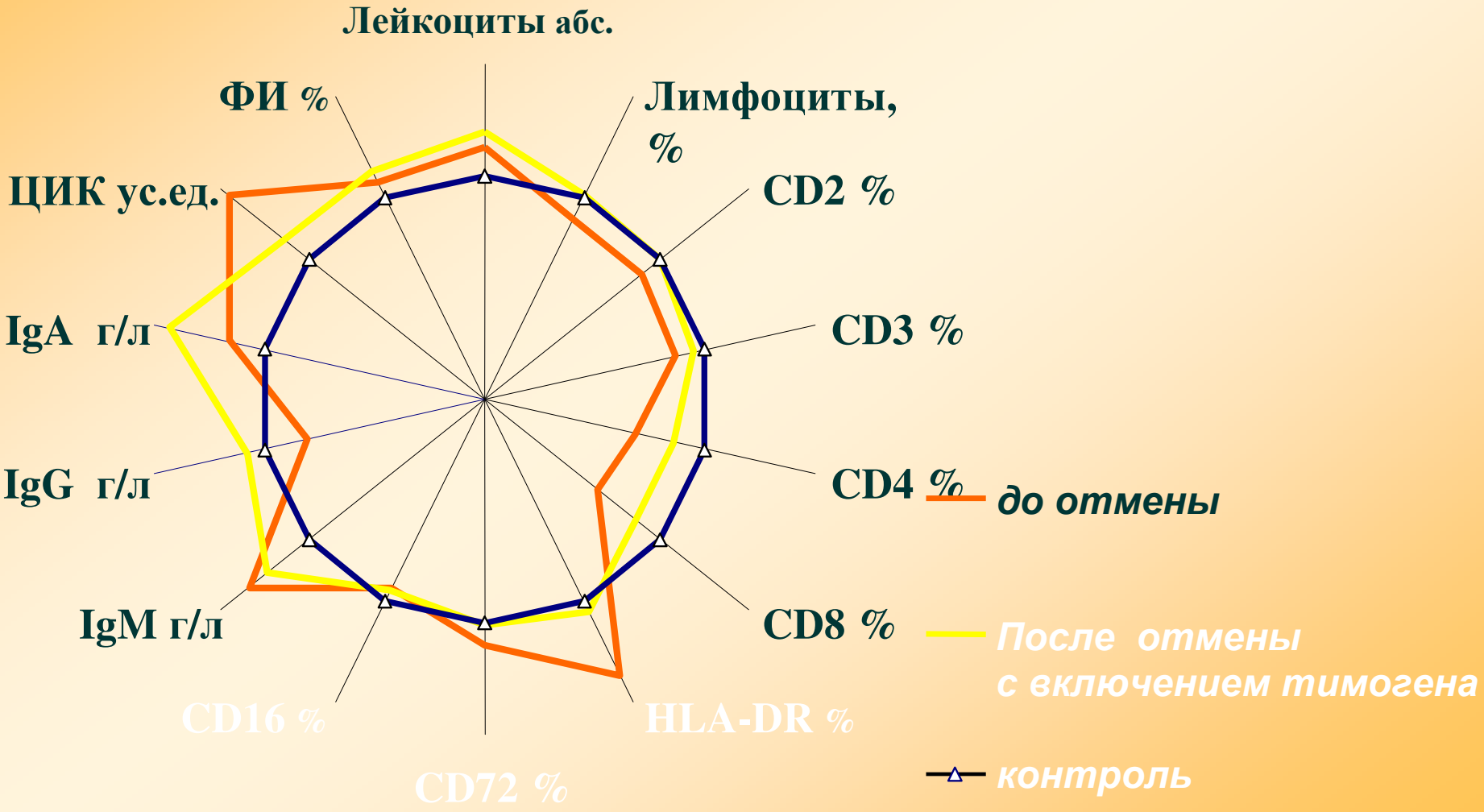
На фоне нейролептической терапии

- **Схема 3**: 0,01% раствор тимогена по 1 мл 1 раз в день интраназально ежедневно в течение 5 дней.

Assignment scheme of thymogen

- ***Cancel neuroleptics***
  Scheme 1: 0.01% Thymogen in 1 ml intramuscularly for 5 days
  Scheme 2: 0.01% Thymogen in 1 ml intranasally for 5 days
- ***On the background of neuroleptic therapy***
  Scheme 3: Thymogen 0.01% solution 1 ml of 1 intranasally once a day every day for 5 days

ДИНАМИКА ПОКАЗАТЕЛЕЙ ИММУННОГО СТАТУСА ТРУДНОКУРАБЕЛЬНЫХ БОЛЬНЫХ ШИЗОФРЕНИЕЙ НА ФОНЕ ПСИХОФАРМАКОТЕРАПИИ И ОДНОМОМЕНТНОЙ ОТМЕНЫ ПСИХОТРОПНЫХ СРЕДСТВ С ВКЛЮЧЕНИЕМ ТИМОГЕНА



Effectiveness of treatment with Thymogen addition for patients with schizophrenia (in %)

Assignment scheme	the effectiveness of therapy	
	main group	comparison group
Cancel neuroleptics **Intramuscularly** **intranasally** comparison group - *Cancel neuroleptics*	**72,7 #** **66,7 #**	**33,3**
On the background of neuroleptic therapy **Intramuscularly** comparison group - *neuroleptic therapy* **intranasally** comparison group - placebo	**68,6 #** **60,6 #**	**32,1** **40,0**

Inflammation plays a key role in the pathogenesis of schizophrenia

- Leonard BE, 2007
- Myint AM, Schwarz MJ, Steinbusch HW, Leonard BE, 2009
- Leonard BE, Schwarz M, Myint AM, 2012
- Müller N, Myint AM, Krause D, Weidinger E, Schwarz MJ, 2012
- Fillman SG, Cloonan N, Miller LC, Weickert CS, 2013
- Fineberg AM, Ellman LM, 2013
- Al-Asmari AK, Khan MW, 2013
- Al-Amin MM, Nasir Uddin MM, Mahmud Reza H, 2014
- Müller N, 2014
- Müller N, Krause D, Weidinger E, Schwarz M, 2014
- de Witte L, Tomasik J, Schwarz E, Guest PC, Rahmoune H, Kahn RS, Bahn S, 2014
- Debnath M, Berk M, 2014

Cytokines production by MNC of schizophrenic patients

Cytokines	Controls	mediana (LQ–UQ)	
		Schisophrenic patients	p
IL-1 proinflammatory	387,37 (123,85-705,91)	580,65 (432,90-967,74)	0,4839
IL-2 (Th1) proinflammatory	24,00 (13,22-117,50)	***11,14 (6,85-17,01)***	0,0293
IFN-γ (Th1) proinflammatory	2304,38 (1887,9-3248,6)	***1484,55 (1128,2-1756,3)***	0,0001
TNFα proinflammatory	358,57 (231,96-458,97)	***507,76 (280,51-520,27)***	0,0455
IL-4 (Th2) anti-inflammatory	17,54 (3,31-35,76)	***40,00 (20,18-66,17)***	0,0001

Anaferon, which contains ultra-high dilutions of affinity purified antibodies to human interferon gamma

- In this double-blind, placebo-controlled randomized trial in parallel-group, 40 patients (age 22-54 years) were enrolled. Patients from the main group (n=20) received anaferon as a part of complex therapy; patients from the comparative group (n=20) – placebo.

Assignment scheme of anaferon

- **Along with antipsychotic therapy adequate for the main disease schizophrenia, patients received anaferon or placebo under medical observation using the following scheme: 2 tablets per intake 4 times a day with equal intervals, usually at hours 8, 12, 16, and 20. Duration of the combined therapy was 30±5 days.**
- **Use of any immunomodulating drugs including interferons was not allowed.**

- Registration of clinical symptoms based on PANSS scores in the groups demonstrated that complex therapy exerted significant clinical effect. By the end of the treatment both groups showed significant reduction of mean values of the total score for positive, negative, general symptoms and the total PANSS score.

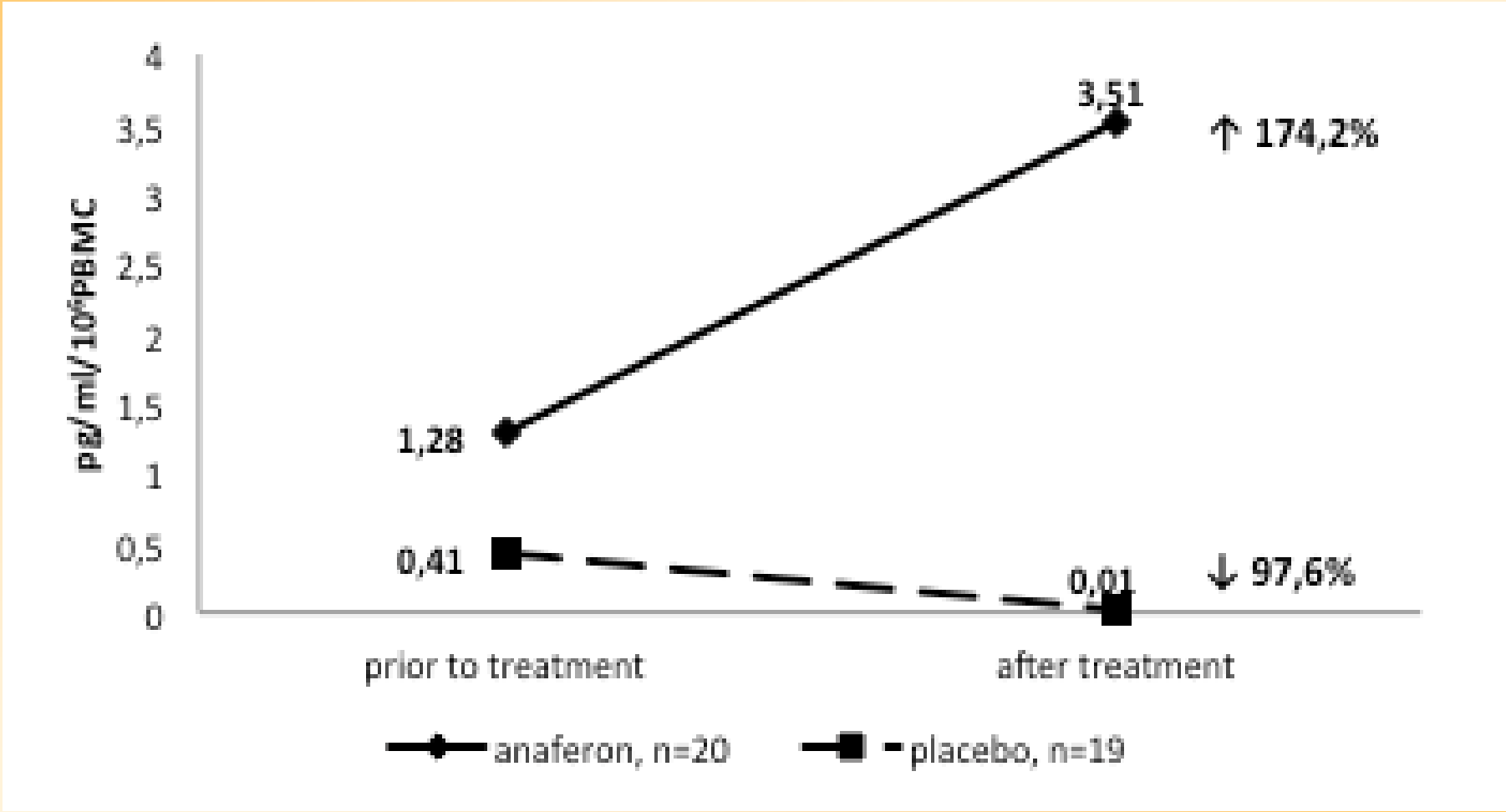
Efficacy of combined therapy of schizophrenia according to clinical general impression scale CGI-C

Criteria	Number of subjects	
	Main group (Anaferon); n=20	*Comparative group (placebo); n=19*
Significant improvement (1)	2	3
Expressed improvement (2)	15	9
Insignificant improvement and no changes (3+4)	3	7
Total: significant and expressed	***17***	***12***

Level of IFN-γ production by PBMC in general group of subjects with schizophrenia and healthy subjects

Parameters	Median value (LQ–UQ)		p
	Healthy (n=15)	Schizophrenia (n=40)	
Mitogen-induced production of IFN-γ (pg/mL/10^6PBMC)	2569,79 (2482,6-2569,8)	1484,55 (1128,2-1756,3)	0,00001
Spontaneous production of IFN-γ (pg/mL/10^6PBMC)	9,68 (0,00-21,70)	0,41 (0,00-26,01)	0,233

Changes in spontaneous IFN-γ production during combined therapy including Anaferon and placebo



Correlation has also been established between spontaneous production of IFN-γ by ICC in subjects taking anaferon with positive changes during combined therapy of negative symptoms, general symptoms and total score of psychopathological symptoms assessed using PANSS scale

Spontaneous IFN-γ production	Total negative symptom score	Total general symptom score	Total score
Main group (n=20)	r = - 0,453 p = 0,045	r = - 0,578 p = 0,008	r = - 0,544 p = 0,013
Placebo group (n=19)	r = 0,256 p = 0,290	r = 0,148 p = 0,545	r = 0,182 p = 0,456

CONCLUSIONS

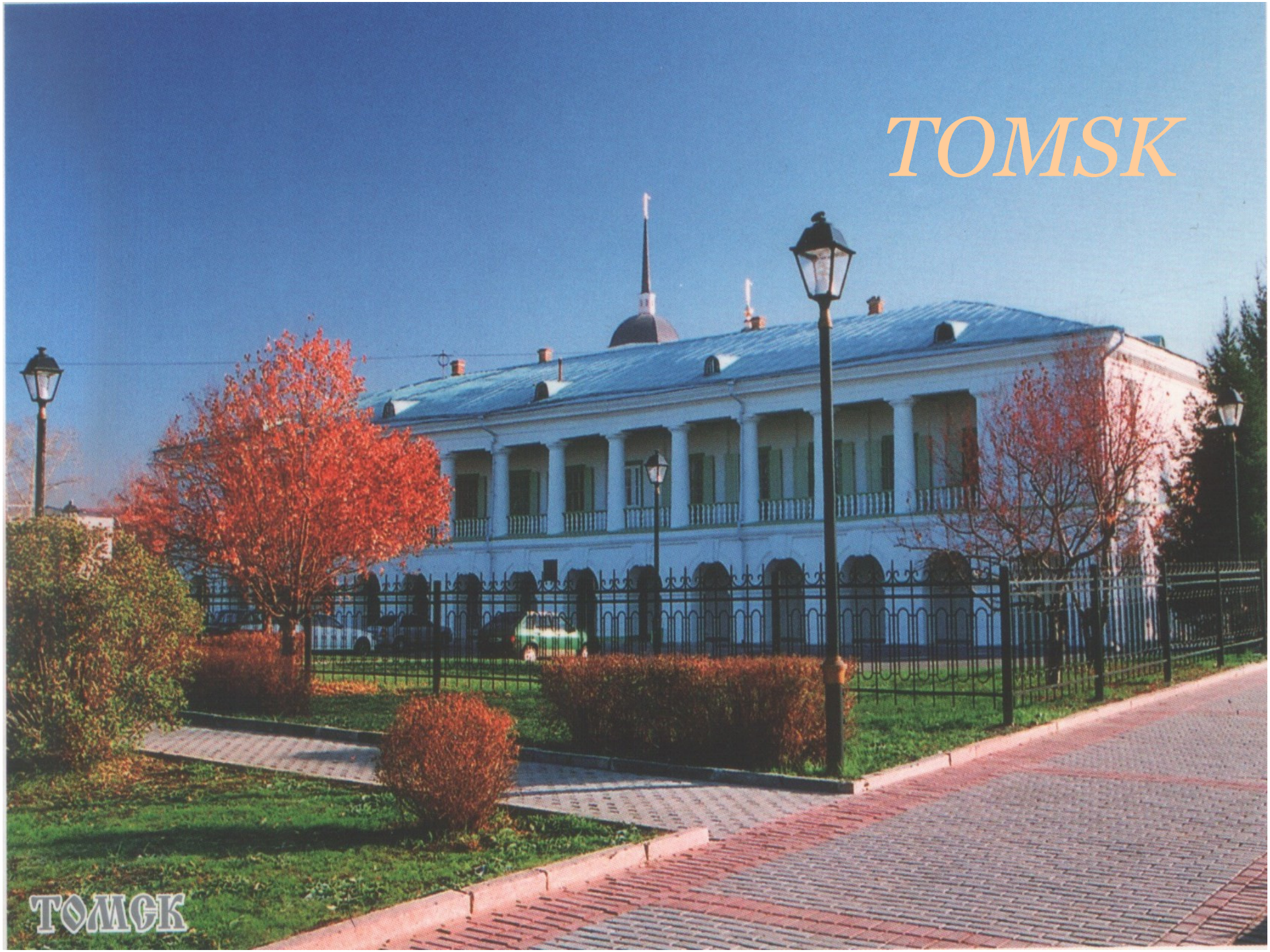
- Observed alterations of the immune parameters among schizophrenic patients depending on the clinical peculiarities of the pathological process (form, tempo of progression, stage and duration of the disease, influence of pharmacological drugs) reflect the modulation of psychoneuroimmune interrelations during schizophrenia
- Neuroimmune disturbances, Th1/Th2 imbalance towards activation Th2, immune inflammation have been involved into pathophysiology of schizophrenia

✓ The addition of immunoactive drugs into therapeutic programs of schizophrenic patients has been pathogenically proved and aimed at the optimization of disturbed neuroimmune interaction

- В докладе представлены материалы исследований, полученные в лаборатории клинической психонейроиммунологии и отделении эндогенных расстройств

НИИ психического здоровья

Thank you for attention!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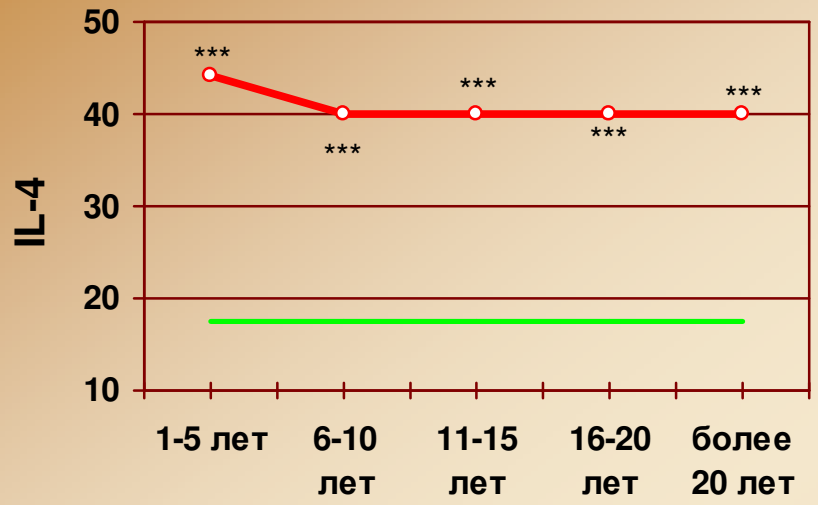
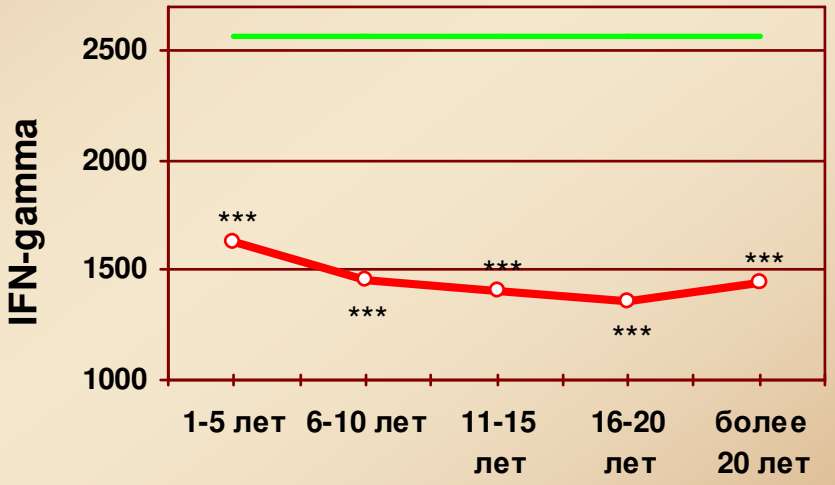
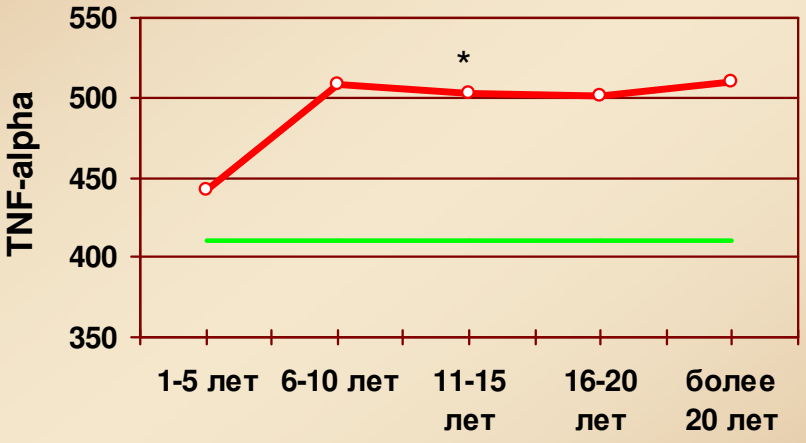
The dynamics of cytokines among schizophrenic patients depending on the duration of the disease (pg/ml/10^6 MNC)







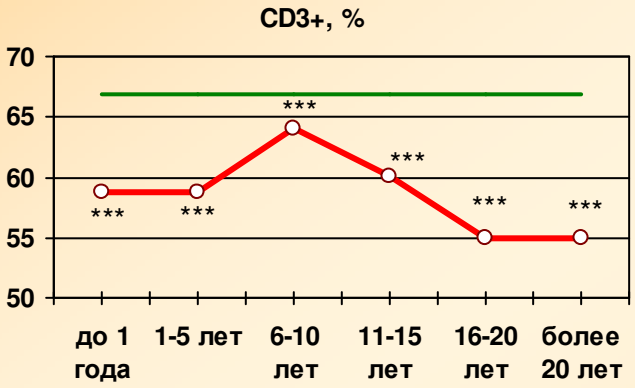
больные шизофренией;

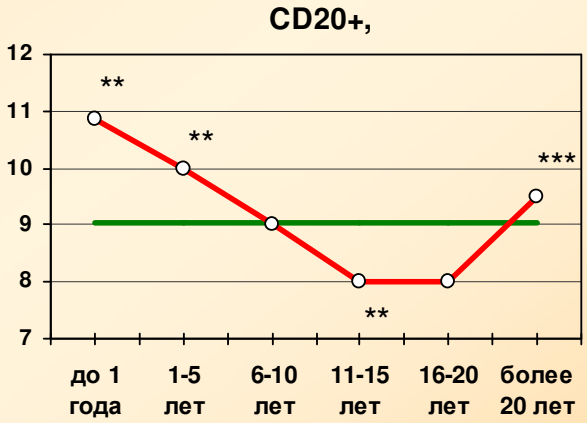
контроль

* - достоверность по отношению к контролю, p<0,05

*** - достоверность по отношению к контролю, p<0,001

Lobacheva O.A., 2011


CD3+, %
70
65
60
55
50
***
до 1 года
1-5 лет
6-10 лет
11-15 лет
16-20 лет
более 20 лет


CD20+,
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11
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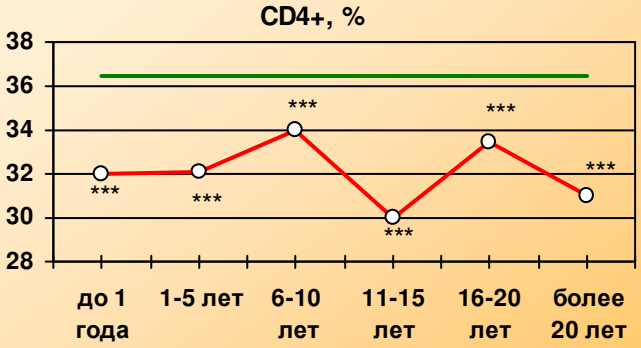
7
**
***
до 1 года
1-5 лет
6-10 лет
11-15 лет
16-20 лет
более 20 лет


CD4+, %
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36
34
32
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28
***
до 1 года
1-5 лет
6-10 лет
11-15 лет
16-20 лет
более 20 лет