

Pica as predictor of substance dependence in adolescence of West Siberia

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Abstract. *Pica and concomitant gustatory and olfactory deviations are factors playing predisposing role in development of substance dependence. Severity and age of onset of pica are significant for heightening the risk of dependent behavior formation. In spite of heightened frequency of family history signs of iron deficiency in addicts, to the moment of examination they more often display not iron deficiency but cytokine mediated anemia of inflammation, accompanied by increase of content of interleukin-6, ferritin, and decreased level of CD71+ lymphocytes.*

Keywords: pica, addiction, drug abuse, sensory and immune deviations

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INTRODUCTION Congenital “reward deficiency syndrome” is considered in the literature as a neurophysiologic basis of addictive behavior (Comings & Blum, 2000). Syndrome has been conditioned by dysfunction of neuro-mediator systems, and high threshold of neurophysiologic reactivity may be one of biological predictors of formation of addictive behavior and related “novelty seeking” based on need for continuous stream of sensory information, obtaining of new experience not corresponding to social norms. Probably, these regularities may reflect on need to experience severe unusual taste and olfactory sensations (Podskarbi-Fayette *et al*, 2005), including kind of pica syndrome (Nevidimova *et al*, 2005). Iron deficiency (sideropenia) is often accompanied by typical and unusual changes of olfactory and taste preferences. Such a state is known from ancient times and called “pica” (pica chlorotica), a “common but commonly missed” disorder (Rose *et al*, 2000). This often found in children and adolescents disorder is not paid necessary significance although child’s pica can form stereotype of addictive behavior and be a ground of every dependence, in particular, substance dependence. It is not excluded that basis of pica is not only pathology of mineral metabolism, but also the need to experience severe unusual taste and olfactory sensations due to change of thresholds of psychophysiological reactivity. Iron deficiency and its consequences are accompanied by also immunological disturbances, which as a whole are typical for patients with dependent behavior (Nevidimova *et al*, 2011; Vetlugina *et al*, 2008) and may be the part of pathological afferentation.

Objective of investigation: to study association of pica with clinical-immunological characteristics of formation of initial pathological craving for psychoactive substances in adolescents of West Siberia.

Tasks of investigation: 1) to study frequency and peculiarities of pica among addicts; 2) to reveal clinical-immunological correlates of pica; 3) to assess contribution of pica into onset of substance dependence.

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SUBJECTS AND METHODS Investigation has been conducted on the base of Addictive States Department and Laboratory Clinical Psychoneuroimmunology of Mental Health Research Institute SB RAMSci. We have examined more than 700 persons, of which 70% were 16-19 years old. The basic group (addicts) included 336 persons (312 males and 24 females) with disorders caused by substance use, F1 according to ICD-10. Almost a half from them had opioid dependence. The group of comparison (non-addicts) included 407 persons, among whom we have distinguished persons episodically using substances (about one forth) and practically not using substances. Patients were interviewed concerning their family history, paying special attention to age of onset and severity of pica.

Laboratory investigation included assessment of level of immunoglobulins, production of cytokines (IL-2, IL-6, TNF α) with account for number of mononuclear cells (MNC), cortisol, and ferritin with ELISA. Immunofluorescent and Flow Cytometric Analysis was conducted by applying specific monoclonal antibodies against CD2, CD3, CD4, CD8, CD16, CD20, CD71, and CD95.

For statistical processing of results we used criteria Mann-Whitney, χ^2 Pearson, Fisher, correlation analysis, rank dispersion analysis and logit regression.

RESULTS

Frequency of prevalence rate of pica in persons with initial pathological craving for psychoactive substances Pica is eating of inedible objects in infancy and childhood and, according to ICD-10, belongs to behavioral and emotional disorders, with usual onset in childhood and adolescence (F98.3). According to DSM-IV, pica belongs to eating disorders (307.52), while on opinion of some authors, to obsessive-compulsive disorders (Rose *et al*, 2000). Pica is called also *parorexia* and is referred to disturbances of instinctive drives.

The most frequent cause of pica is iron deficiency. Pica, beyond changed eating behavior proper, includes sensory shifts concerning taste and olfaction. Presence of pica was diagnosed during revealing of persistent combined eating and olfactory disturbances, observed usually for two or three age periods (before 10 years, 10-15 years, older than 15 years). Pica was called severe if eating of inedible substance of one kind and preference of one odor was observed. In case of multiple preferences pica was qualified as heavy. In the total group of examined, incidence rate of cases of pica has constituted 41.8%. We have not detected reliable differences associated with sex and drive to psychoactive substances, although maximum frequency of pica 48.3% has been documented in group of persons using intravenous substances. But pica with early onset (before 10 years) was documented more often in addicts than in group of comparison (37.5% and 22.5%, respectively, $p < 0.01$). Heavy pica with early onset also was revealed in family history of addicts more often than in group of comparison (13.3% and 7.6% of cases, respectively, $p < 0.05$). Maximum level of these indices was achieved in persons using opiates intravenously: early pica – 43.1%, heavy pica with early onset – 17.5% (in group of comparison 22.5% and 7.6%, respectively, $p < 0.01$).

Taste disturbances in male addicts were expressed in craving to eating the ice (41.2%, $p < 0.05$) and chalk (18.3%, $p > 0.05$; in group of comparison, respectively 27.1% and 14.7%). Craving to eating of tar was observed only in addicts (17.9%). Among olfactory disturbances in persons of male sex with initial pathological craving more often than in group of comparison, we noticed preferences of odor of acetone (11.2%), glue (15.1%), gasoline (38.2%; compared with 5.9%, 10.5% and 21.7% respectively, $p < 0.05$).

Women-addicts were characterized by craving to eating of tar (10.0%), chalk (30.0%), match heads (5.0%), soil (5.0%); craving to odor of gasoline (25.0%), ribbon (5.0%).

Immunological characteristics of addicts In male addicts we have revealed a significant decrease of relative content of subpopulations of CD2⁺-lymphocytes, CD71⁺-lymphocytes, increase of level of serum IgM and IgG, number of leukocytes, lymphocytes, increase of concentration of ferritin in serum of blood, tendency toward reduction of mitogen-stimulated production of TNF α and increase

of mitogen-stimulated production of IL-6 as compared with indices of persons without initial pathological craving to psychoactive substances.

As a whole, it may be concluded that formation of initial pathological craving to psychoactive substances is accompanied by accumulation of signs of inflammation with regular participation of immune mechanisms: number of leukocytes, level of immunoglobulin of class M, interleukin-6 increases, level of CD2⁺-lymphocytes decreases. Reduction of level of hemoglobin is combined with accumulation of ferritin and decreased expression of CD71-receptors, interacting with transferrin.

In period of acute inflammation a number of cytokines influence on transport of iron in the organism, decrease number of transferrin receptors on the surface of the cell, increase synthesis of ferritin for deposition of iron and thus reduce availability of the microelement for pathogens, which likely is one element of defensive reaction of the organism to an infectious process. In spite of increased frequency of family history signs of iron deficiency in persons with formed initial pathological craving to substances, to the moment of examination this deficiency does not find laboratory confirmation. Formation of substance dependence is more often accompanied by not iron deficiency but cytokine-mediated inflammation anemia.

Thus, male addicts are characterized by somatic history accompanied by clinical-laboratory signs of immune imbalance and shifts in iron metabolism. In female addicts we observe laboratory signs of inflammation, activation of humoral immune response, somatic history including inclination for frequent exacerbation of herpetic infection and diseases of gastrointestinal tract. As a whole used by us clinical-immunophysiologic parameters testify to one-directedness of changes in persons of male and female sex during formation of initial pathological craving to psychoactive substances.

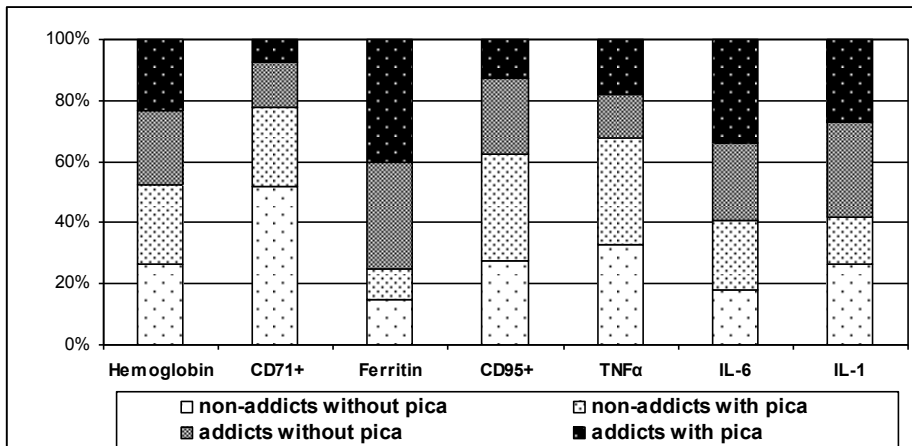
Influence of pica on immunobiochemical parameters Further analysis of association of pica with immunobiochemical indices was conducted with comparison of groups of persons with presence or absence of pica.

In male non-addicts, presence of history of signs of pica as a tendency is combined with heightening of the level of CD95⁺-lymphocytes (13.64 ± 2.08 and 11.54 ± 1.59 %, $p > 0.05$), level of CD20⁺-lymphocytes (13.50 ± 2.09 and 10.19 ± 0.70 %, $p > 0.05$), level of CD71⁺-lymphocytes (14.08 ± 3.43 and 7.25 ± 2.25 %, $p > 0.05$), lowering of concentration of ferritin (21.33 ± 7.09 and 31.69 ± 6.01 ng/ml, $p > 0.05$) in serum of blood. History of pica in non-addicts is accompanied by significant decrease of mitogen-stimulated production of IL-1 β (115.65 ± 37.76 and 198.56 ± 44.58 pg/ml/ 10^6 MNC, $p < 0.05$) and increase of production of TNF α (361.22 ± 102.8 and 338.05 ± 29.34 pg/ml/ 10^6 MNC, $p < 0.05$) as compared with non-addicts without pica in family history.

Male addicts with pica in family history differed from addicts without pica by significant decrease of mitogen-stimulated production of IL-2 (45.89 ± 34.1 and 100.32 ± 21.36 pg/ml/ 10^6 MNC, $p < 0.05$), level of CD95⁺-lymphocytes (5.71 ± 1.20 and 10.47 ± 1.65 %, $p < 0.05$), cortisol (485.85 ± 26.02 and 556.43 ± 22.09 nmol/l, $p < 0.05$), tendency to heightening of mitogen-stimulated production of TNF α (186.41 ± 67.29 and 148.46 ± 34.0 pg/ml/ 10^6 MNC, $p > 0.05$), decrease of number of CD3⁺-lymphocytes (57.35 ± 3.79 and 62.63 ± 3.99 %, $p > 0.05$), level of hemoglobin (128.89 ± 2.34 and 131.70 ± 1.93 g/l, $p > 0.05$).

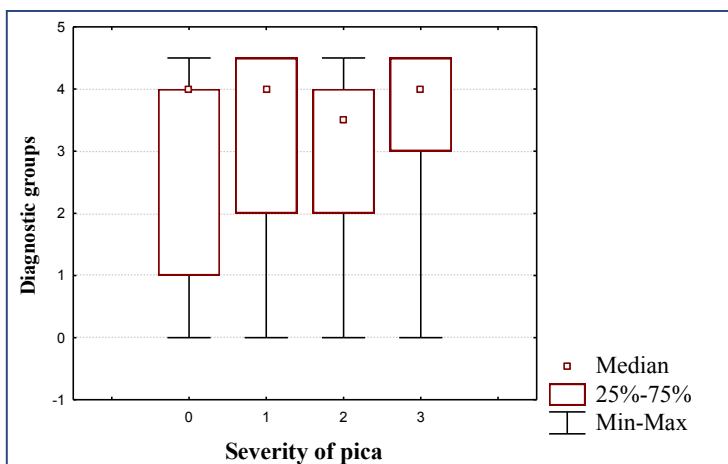
Thus, in non-addicts, history of pica is little reflected on laboratory indices, except regular for latent sideropenia lowering of supply of iron (ferritin on lower limit of norm) and heightening of expression of receptors to transferrin (CD71⁺-lymphocytes on upper limit of norm). It is typical that in addicts we observe a contrast effect: history pica is accompanied by maximum content of ferritin (84.63 ± 22.64 ng/ml) and minimum level of CD71⁺-lymphocytes (2.31 ± 0.62 %), that as mentioned above testifies to inflammatory redistribution of iron (**Figure 1**).

Figure 1 Immunobiochemical characteristic of history of pica in males in groups of comparison



Predisposing value of pica In group of non-addicts family history of pica is associated with predictable clinical consequences: heightened risk of worm infestation and poisonings, diagnosing of iron deficiency anemia. Family history of pica in addicts is associated to major extent with inclination to formation of pathological behavioral stereotypes although it influences very little on motivation of substance use. In male addicts with pica in family history, the basic motivation of first use of psychoactive substances was novelty seeking (74.8%), hedonistic motive characterized 11.2% persons (without pica 66.1% and 15.7%, respectively, $p > 0.05$). Male addicts with signs of pica in family history had some earlier age of first use of substances as compared with persons without pica (11.7 ± 0.2 and 12.4 ± 0.2 years, respectively, $p > 0.05$) and higher score of initial pathological craving to psychoactive substances (12.2 ± 0.7 and 7.4 ± 0.7 scores, respectively, $p < 0.05$). Earlier pica increases risk of formation of dependent behavior as much as 1.5-2 times (according to results of regression analysis). Use of rank disperse analysis has allowed to identify that pica exerts significant influence on formation of dependence on psychoactive substances ($H = 10.86$; $p < 0.05$). In addition, increase of severity of pica leads to lessening of number of cases with absence of initial pathological craving to psychoactive substances, what is indicated by interquartile intervals for level of consumption of substances in groups ranked according to severity of pica (**Figure 2**).

Figure 2 Values of median and interquartile intervals for level of substance use in groups with different severity of pica. Diagnostic groups: 0, 1 – practically without substance use; 2 – episodic substance use; 3 – substance abuse with harmful consequences; 4 – substance dependence syndrome; 5 – dependence syndrome, use of substances intravenously. Severity of pica: 0 – absence of symptoms of pica, 1 – episodic disturbances, 2 – severe pica, 3 – heavy pica.



CONCLUSIONS

1. In persons with primary pathological craving to psychoactive substances in 37.5% of cases early pica is revealed with onset at the age up to 10 years, heavy pica with early onset has been detected in 13.3% of cases. Maximum level of these indices is achieved in persons with intravenous substance use: early pica – 43.1%, heavy pica with early onset – 17.5% (in group of comparison 22.5% and 7.6% respectively, $p < 0.01$).
2. Clinical-immunological examination of addicts reveals signs of inflammation and anemia with participation of immune mechanisms: erythrocyte sedimentation rate, level of immunoglobulin of class M, interleukin-6 increases, level of CD2⁺-lymphocytes decreases. Decrease of level of hemoglobin is combined with accumulation of ferritin and decreased expression of CD71-receptors, interacting with transferrin. Addicts with signs of pica additionally are characterized by decrease of mitogen-stimulated production of interleukin-2, decrease of level of CD95⁺-lymphocytes, maximum content of ferritin and minimum level of CD71⁺-lymphocytes, reversely correlating with level of interleukin-6.
3. Pica is a factor playing predisposing role in formation of dependence on psychoactive substances. For increase of risk of formation of dependent behavior, severity and age of onset of pica are significant.

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