УДК 616.8 – 053.4 (571.56)

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Fetal alcohol syndrome

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The article represents an overview of the literature on fetal alcohol syndrome. Also here is presented diagnostics criteria, recognition of facial features, perspective of treatment.

Key words: children, fetal alcohol syndrome, facial features.

In last 10 years in the Republic of Sakha (Yakutia) growth of identification of the mental development retardation in children and behavioral infringements with social disadaptation by 30 % [2]. Fetal alcohol syndrome is the most recognizable and preventable cause of mental retardation in the world, which has a frequency 17 per 1000 live-born (in comparison with 1,3 per 1000 for a syndrome of Down) [6]. The epidemiological data indicates that prevalence of alcoholism in the Republic of Sakha (Yakutia) remains high and consist of 1,9 % of the total population (1884,7:100000). The rate of prevalence of alcoholism in the republic is higher than in Russia (1593,3:100000) by 18,3 % and lower than rate in Far East Federal district (2115: 100000) at 10,9 %.

Among women this rate is 747,0 patients per 100 thousands female population [5].

A the present time the following terms are used concerning the issue of the prenatal alcohol exposure: FAS (Fetal Alcohol Syndrome), FASD (Fetal Alcohol Spectrum Disorders), ARND (Alcohol Related Neurodevelopmental Disorders), ARBD (Alcohol Related Birth Defects).

FAS is the combination of neural and abnerval anomalies that revealed itself in pre- or postnatal lesions of the nervous system, growth deficiency, a specific facial anomalies and evidence of prenatal alteration in brain function such as congenital microcephaly, neurologic problems without postnatal antecedents or complex patterns of functional disability and occurs in infants born of women who consumed alcohol during pregnancy.

Fetal Alcohol Spectrum Disoders (FASD) is the term that describes the range of consequences that can occur in individual whose mother consumed alcohol during pregnancy. These consequences may include physical, mental, behavioral and/or learning disabilities with potenial lifelong implications. The term FASD is not intended for use as a clinical diagnosis. [12]

The first scientific mention of FAS is associated with the publication in French medical literature in 1967 by a French physician, Philip Lemoine and coauthors [17]. They examined 127 children born of alcoholic women with different anomalies and set up common features that could occur in the offspring of mothers who drank heavily during pregnancy.

Subsequently Ken Jones, David Smith [15] and associates published two articles in Lancet in 1973 concerning more detailed description of the common set of features in 11 children whose mothers were known to

be alcoholic. This combination of features was determined as the Fetal Alcohol Syndrome.

The epidemiology of FAS is quite variable. Data about prevalence FAS depends on variety of circumstances and, in particular, on medico-social features of alcohol consumption in certain group of examination, doctors and social workers awareness about diagnostic criteria of the disease [21].

FAS prevalence rates is 0,2 to 2,0 cases per 1000 live born [4]. In the US, where the issue is investigated in details the incidence of FAS is between 1 – 3 cases per 1000 live-born. The incidence of FASD is up to 190 cases per 1000 live born in families of Canadian Indian [10]. The highest rate of prevalence of FAS was recorded in South Africa: 65 cases per 1000 live born. [27]

Surveys indicate that 10% of pregnant women in the United States consume alcohol and 1,9% drink heavily. Meanwhile 20% of pregnant women in Russia consume alcohol and 2,7% drink heavily [4].

The manifestation of FAS depends on a dose, duration, frequency and time of consuming alcohol, also on genetic predisposition.

Pathogenesis

Alcohol alters the proliferation, migration, differentiation and survival of neuronal cells. Alcohol can also disrupt the development of glial cells, leading to alterations in cell signaling and myelination. Alcohol may impact on the cell membrane. For example, alcohol disturbs membrane fluidity, which can affect cell adhesion, migration and cell communication. Prenatal alcohol is also able to affect on glutamate receptors and GABA receptors [4, 28].

Clinics and diagnostics

Nowadays the 4-Digit Diagnostic Code, CDC (Center for Disease Control and Prevention, Department of Health and Human Services, 2004) is used for diagnosis of FAS [11, 12]

According to CDC system criteria FAS diagnosis based on following procedures [CDC]:

1. Documentation of all three facial abnormalities (smooth philtrum, thin upper lip border and small palpebral fissures);
2. Documentation of growth and weight deficiencies;
3. Documentation of CNS abnormality;
4. Documentation of maternal alcohol consumption.

1. A specific craniofacial profile associated with FAS was first described by Jones and Smith in 1973 [15] and later refined by Astley, Clarren and others [11].

The facial dysmorphia criteria that is essential for FAS:

- Smooth philtrum
- Thin upper lip border
- Small palpebral fissures.

It is essential to establish standard facial anthropometric data for all ages and subpopulations. Facial phenotype is a key factor of FAS diagnostics, its specificity cannot be assumed, and moreover it should be confirmed through properly designed empirical studies [7].

Stoler and Holmes (2004) showed that the specificity of the facial score and overall accuracy was relatively high – 91,7% [23]. Among other facial features of FAS the epicantal folds, midface hypoplasia, anteverted nares, long hypoplastic philtrum should be mentioned. However some of these features, such as epicanthal folds and flat wide nasal bridge, are normal for certain ethnic groups, so it can result in overdiagnosis in these ethnic groups [23]. Cross-sectional and longitudinal studies indicate that many features can change with age or development [12].

2. Growth and weight retardation are main factors of FAS. Growth retardation begins in intrauterine life period and becomes most evident in the nearest months and years of postnatal development [4].

3. Documentation of CNS abnormality is based on structural, neurological, functional deficiencies or abnormality (CDC).

The whole IQ scores of patients with fetal alcohol syndrome varies from 20 to 120 [24]. Children with large quantity of anomalies have a significantly lower IQ than those children who has lower anomalies[20].

4. Documentation of maternal alcohol consumption during pregnancy.

A. Confirmation of prenatal alcohol exposure requires documentation of the alcohol consumption of own mother during the pregnancy based on clinical observation; self-report; reports from a reliable source, medical records confirming positive blood alcohol levels or alcohol treatment.

B. Unidentified prenatal alcohol exposure indicates that there is neither a confirmed presence nor a confirmed absence of exposure. (CDC)

All the guidelines require prenatal alcohol exposure to be confirmed but in case of exposure not identification it is assumed a diagnostics of FAS. Often the own mothers do not present at the time of the child's diagnostics. The 4-Digit Code defines that diagnosing of FAS when alcohol exposure is not identified is medically valid. [7, 8].

Among congenital development malformation concomitant to FAS following ones occur more often: the congenital heart diseases – an atrial septal deficiency, a ventricular septal deficiency, a Fallots tetrad; anomaly of eyes – ptosis, strabismus, ophtalmomycria; anomaly of urogenital system – hydronephrosis, doubling of ureters, cryptorchism и.т.д. [4, 10].

Concerning the FAS many authors often highlights the anomalies of skeleton – knitting of corpuses cervical vertebra, funnel chest, short ossa metatarsalia and short ossa metacarpalia [4, 10].

Since the FAS facial criteria is defined by short palpebral fissures, smooth philtrum and thin upper lip, it is able to be overlapped with other syndromes. Syndromes with similar combination of features are Aarskog syndrome, Williams syndrome, Noonan syndrome, De Lange syndrome, Dubowitz syndrome, toluene embriopathy, fetal anticonvulsant syndrome including fetal hydantoin and fetal valproate syndromes, maternal phenilketonuria (PKU) fetal effects. [10].

The neuroimaging method is widely used for FAS diagnostics. Magnetic resonance imaging (MRI) is applied on fetal alcohol syndrome (FAS) to detect central nervous system (CNS) anomalies. One specific feature of FAS diagnosis was revealed by MRI it is brain size decrease. Mattson considered that Pre and/or early alcohol exposure can cause decrease of cerebellum size [19]. The anomaly that is revealed by MRI is agenesis of the corpus callosum. [25]. Earlier the FAS was supposed to be the main cause of this anomaly [14].

The EEG records of the FAS children indicated reduced power, particularly of the alpha frequencies and the absence of significant slow activity. FAS children were more affected at the left hemisphere [16].

Prevention and treatment of FAS.

At the present time there is no specific treatment of FAS. Nevertheless development of drugs that experimentally positively affects on ethanol exposure consequences gives us the hope of its future clinical application them [9, 13, 18, 22, 26, 29].

Table 2. The experimental therapy of intrauterine alcohol exposure

Preparation	Effect
Choline	Improvement of memory and behavior, decrease of ethanol's teratogenicity;
Lithium	GSK-3 (ferment that determine ethanol's toxicity) influence prevents apoptosis
the vasoactive intestinal peptide (VIP)-related peptides, NAPVSIPQ (NAP) and SALLRSIPA (SAL),	Have effect on GAMK receptore and contribute to prevention of FAS facial anomalies
Agmatine	Effect on imidazoline and n-methyl-d-aspartate receptors (NMDAR), improve behavior
Dietary selenium plus folic acid	Effect on glutathion-reductase, catalase and protein peroxidation
Anthocyanins	Antioxidant

The important stage of preventing alcohol-exposed pregnancies is identification of women with significant risk of alcohol consumption during the pregnancy.

An early diagnosis is essential to decrease the risk of the development of subsequent "secondary disabilities" (unemployment, mental health problems, inappropriate sexual behavior) among affected people [10, 24].

1. Airapetianc M.G. Posledstviya alkogolinoi

intoksikatsii dlya potomstva / M.G. Airapetianc. - M.:Nauka,1989.- P.6-10.
2. Bazhenova O.D. Psihiatricheskaya pomosh detyam v Respublike Sakha (Yakutiya) / O.D.Bazhenova // Sostoyanie zdoroviya detei RS(Y). - Yakutsk: Ofset, 2009. - P.54-58.
3. Clinico-immunological osobennosti alcogolnogo sindroma ploda / V.A. Tabolin [et al.]// Novosti nauki i tehniki. Ser. Alkogolnaya bolezn. - VINITI, 1999.№3. P. 1-16.
4. Palchik A.B. Fetalni alkogolni cindrom: metodicheskie rekomendatsii / A.B. Palchik, L.A. Fedorova, S.V. Legonkova.- SPb., 24 p.
5. Tumusov P.S. Osnovnie pokazateli narkologicheskoi sluzhbi Respublike Sakha (Yakutiya) za 2006-2008 gg./P.S. Tumusov, M.A. Baishev, E.V. Smolenskaya // Osnovnie pokazateli narkologicheskoi sluzhbi Respublike Sakha (Yakutiya) za 2006-2008 gg. - Yakutsk,

2009. - P.3-

.

6. Abel E.L. Incidence of fetal alcohol syndrome and economic impact of FAS-related anomalies /E.L.Abel, R.J.Sokol // Drug Alcohol Depend -1987 Jan. - 19(1). – P. 51-70

7. Astley S.J. Guidelines for Fetal Alcohol Spectrum Disorders. / S.J.Astley. // Pediatrics – 2006, Vol .118 - № 4 – P. 1532 – 1545.

8. Astley S.J. Fetal alcohol syndrome (FAS) primary prevention through FAS diagnosis: II A comprehensive profile of 80 burth mothers of children with FAS / S.J.Astley [et al] // *Alcohol Alcohol.* – 2000. – 55 (5). – P.509-519

9. Chen G. Anthocyanins: are they beneficial in treating ethanol neurotoxicity? / G. Chen, J. Luo // Neurotox Res. - 2010 Jan. - 17(1). – P.91-101.

10. Chudley A.E. Fetal alcohol spectrum disorder: Canadian guidelines for diagnosis / A.E.Chudley [et al] // CMAJ – 2005. - Vol.172, (suppl.5) – S.1-21.

11. Diagnostic Guide for Fetal Alcohol Syndrome and Related Conditions. The 4-Digit Diagnostic Code. 2nd Edition – Seattle. – 1999. – 111p.

12. Fetal Alcohol Syndrome: Guidelines for Refferal and Diagnosis – Atlanta, CDC – 2004. – 48 p.

13. Incerti M. Prevention of the alcohol-induced changes in brain-derived neurotrophic factor expression using neuroprotective peptides in a model of fetal alcohol syndrome. / M.Incerti [et al] // Am J Obstet Gynecol. - 2010 May. - 202(5). 457.e1-4.

14. Jeret J.S., Frequency of agenesis of the corpus callosum in the developmentally disabled population as determined by computerized tomography / J.S.Jeret [et al] // Pediatr. Neurosci. – 1986. – Vol.12. –

P.101–103.

15. Jones K.L. Pattern of malformation in offspring of chronic alcoholic mothers / K.L.Jones [et al] // Lancet. – 1973. - Vol 1. – P.1267 – 1271/

16. Kaneko W.M. EEG findings in fetal alcohol syndrome and Down syndrome children / W.M.Kaneko et al] // Electroencephalogr. Clin. Neurophysiol. – 1996. – Vol. 98, № 1. – P. 20-28.

17. Lemoine P. Les enfants de parent alcoolique: Anomalie observes a propos de 127 cas / P.Lemoin [et al] // Ouest Med. – 1968. - Vol.21 – P.476 – 482

18. Luo J. Lithium-mediated protection against ethanol neurotoxicity. / J.Luo // Front Neurosci. - 2010 Jun 28; 4:41.

19. Mattson S.N. MRI and prenatal alcohol exposure. / S.N.Mattson, T.L.Jernigan, & E.P.Riley. // Alcohol Health & Research World – 1994 - 18(1) - P 49-52.

20. Mattson S.N, Riley EP. A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. / S.N.Mattson, E.P.Riley //Alcohol Clin Exp Res. - 1998 Apr - 22(2) - 279-94. .

21. May P.A. Estimating the prevalence of fetal alcohol syndrome. A summary. / P.A.May, J.P.Gossage. // Alcohol Res Health.- 2001 - 25(3):159-67. Review.

23. Stoler J. M. Recognition of Facial Features of Fetal Alcohol Syndrome in the Newborn / J.M.Stoler, L.B.Holmes. // American Journal of Medical Genetics Part C (Semin.Med.Genet.) – 2004 – 127C – P.21 – 27.

24. Streissguth A.P. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. / A.P. Streissguth [et al] // J. Dev. Behav. Pediatr. – 2004. – Vol. 25 - P.228 –238.

25. Swayze V.W. Magnetic resonance imaging of brain anomalies in fetal alcohol syndrome. / V.W.Swayze [et al] // Pediatrics. – 1997. – Vol. 99. – P. 232–240.

26. Thomas J.D. Prenatal choline supplementation mitigates behavioral alterations associated with prenatal alcohol exposure in rats. / J.D. Thomas [et al] // Birth Defects Res A Clin. Mol.Teratol. - 2010 Oct. - 88 (10); 827-837.

27. Viljoen, D. L. Fetal alcohol syndrome epidemiology in a South African community: A second study of a very high prevalence area. / D.L.Viljoen. // Journal of Studies on Alcohol – 2005 - 66 P.593-604.

28. Volpe J.J. Neurology of Newborn. / J.J.Volpe. // 4th Edition – Philadelphia, Saunders -2001 – 911p.

29.. Wellman K. Agmatine reduces ultrasonic vocalization deficits in female rat pups exposed neonatally to ethanol. / K. Wellman. et al // Neurotoxicol Teratol 2010 Mar-Apr; 32(2):158-63