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Substance use disorder and availability of treatment options: an overview

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Abstract: Substance use disorders are important health concern worldwide. Substance use is a chronic disorder which is associated with significant mortality and morbidity. These disorders also account for significant health care utilization and medical costs Substance use disorders occur when aperson's usage of alcohol, prescription drugs, or illegal drugs causes problems in his or her life and daily activity. Substance-use disorder comprises a wide variety of behaviors that include, but are not limited to, addiction, excessive usage, and dangerous substance-induced behavior. Diagnosis is based on criteria of behaviors that include an inability to control substance use, impairment of functioning at school, home or work, interpersonal problems caused or exacerbated by the substance use, and risky or hazardous use of the substances. The first step in managing substance use disorder is to stop using the substance. In extreme cases of physical addiction, detoxification is necessary to help with symptoms of withdrawal. For overcoming Substance use disorder, creating a supportive environment and eliminating triggers for substance abuse are essential. Treatment employed in the management may occur on an outpatient or inpatient basis depending on the severity of the problem. A doctor may suggest individual counseling with a psychologist, psychiatrist, or addiction counselor depending upon the condition of the individual. Family counseling is often important. A doctor may also recommend special rehabilitation and/or treatment programs; self-help groups for kids and families with substance problems are often quite useful. In this paper, we would briefly look at substance use disorder and treatment modalities available for its management.

Key words: Substance use disorder, Alcohol, Cannabis.

Introduction

Substance use disorders are important health concern worldwide. Substance use is a chronic disorder which is associated with significant mortality and morbidity. These disorders also account for significant health care utilisation and medical costs [1].Treatment of substance use disorder involves detoxification and prevention of relapse. The major problem in treating patients with substance use disorders is relapse. Addiction is a chronic disorder that requires long-term treatment. Anticraving agents play the key role in the prevention of relapse. These medications generally reduce drug craving and reduce the likelihood of relapse to compulsive drug use. Anticraving agents along with other psychotropic drugs are used for management of the substance use disorders [2]. In India, substance abuse has infiltrated all socio-cultural and economic strata causing loss of productivity. Mental and substance use disorders are a major public health concern everywhere, and responding to the burden they cause is a challenge for health systems in both developed and developing regions. Treatment rates for people with mental and substance use disorders remain low, with treatment gaps of over 90% in developing countries [3], [4]. Developing countries are facing an escalating burden of non-communicable disease, with mental and substance use disorders among the most significant. Many developing countries spend less than 2% of their health budgets on mental health [5]. Drug dependence produces significant and lasting changes in brain chemistry and function. Effective medications are available for treating nicotine, alcohol, and opiate dependence but not stimulant or marijuana dependence. Medication adherence and relapse rates are similar across these illnesses. Studies suggest that long-term care strategies of medication management and continued monitoring produce lasting benefits patients with substance use disorder [6]. Substance abuse causes acute and chronic physical, psychological and social effects in varying amounts along with serious social problems in the form of crime, unemployment, family dysfunction and disproportionate use of medical care. Science has not yet explained fully the psychological processes leading to drug abuse. Substance abuse affects above 50 million people worldwide. Abuse of legally prescribed drugs is also increasing rapidly [7]. In India, the abuse of alcohol, cannabis and raw opium has been traditionally known. The abuse of synthetic narcotic drugs and psychotropic substances is comparatively new. Substance abuse has affected all socio-cultural and economic classes causing loss of productivity [8]. Family stress, lack of coping skills, peer pressure, personality disorder, co-morbid psychiatric illnesses, social stress and market forces act as risk factors [9]. Survey shows that around 20-30% of adult males and 5% of adult females use alcohol while 57% of the male and 10.8% of the female drug users consume opiates in some form or other. Rapid assessment survey on substance abuse shows that the primary abused drugs are heroin (36%), other opiates (29%) and cannabis (22%); 75% of addicts start drug abuse before 20 years of age; in urban areas heroin abuse is more while in other sites cannabis abuse is more [10], [11].

Treatment of substance use disorders

Substance use disorder (SUD) has been conceptualized as a chronic relapsing medical illness with relapses and

remissions and a strong genetic component similar to diabetes type II and hypertension [6]. Risk for relapse is heightened because the neurobiological changes in brain pathways created by many years of alcohol and/or drug use do not completely revert to normal after the detoxification process. The intensity and nature of the behavioral intervention can influence the outcome of treatment for patients with SUDs. The use of medications in the treatment of SUD can also play a major role in preventing relapse and facilitating longer periods of abstinence. More effective medications have been developed over the past 30 years, and subsequently, pharmacotherapy has progressively played a more important role in the treatment of addictions. Medications are mostly used as adjuncts to psychosocial treatments and the role of pharmacotherapy in treatment depends on the specific type of SUD [12]. Pharmacological agents have three broad objectives: management of acute withdrawal syndromes through detoxification, attenuation of cravings and urges to use illicit drugs (initial recovery), and prevention of relapse to compulsive drug use [2].

Treatment of nicotine dependence

Tobacco use is highly co morbid among patients with SUDs and is the most common cause of premature death and disability among patients who are in recovery from other SUDs. Research suggests that smoking cessation may facilitate abstinence from alcohol and other drugs, and clients using tobacco should be educated about these findings as a potential motivator for reducing tobacco use. Pharmacotherapy is considered a mainstay of treatment for smoking cessation, and recommended therapies, including combinations of counseling and medication, produce abstinence rates of about 40% after 1 year. First-line therapies (treatments that are recommended by the Food and Drug Administration [FDA] as having the most evidence of effectiveness) include nicotine replacement therapies (NRT), bupropion SR (Zyban), and varenicline (Chantix). NRTs replace the nicotine obtained from smoking to prevent withdrawal symptoms and improve smoking cessation outcomes. Replacement medications are used because of the low success rate of total "cold turkey" withdrawal from nicotine. Approved formulations include the transdermal nicotine patch, nicotine gum, nicotine lozenge, nicotine vapor inhaler, and nicotine nasal spray. Behavioral therapies used in conjunction with an NRT increase quit rates [13], [14].

Treatment of alcohol dependence

Medications for Detoxification and Medical Stabilization

Chronic dependence on alcohol can result in periods of severe withdrawal syndromes marked by increased heart rate and blood pressure, anxiety, and withdrawal seizures and in severe cases delirium tremens and even death. Medications for alcohol withdrawal syndromes include benzodiazepines that act on gamma-aminobutyric acid (GABA) at the GABA receptors in the brain to stimulate release of GABA. GABA is a neurotransmitter that is responsible for decreasing activity throughout the nervous system and acts to gradually detoxify the patient from alcohol by reducing heart rate, blood pressure, sweating, and anxiety associated with alcohol withdrawal. During detoxification benzodiazepines are systematically

decreased to address the most important need, which is to prevent the occurrence of seizures and delirium. They should be avoided as a long-term strategy for controlling alcohol dependence because physical tolerance of these medications can occur rapidly and can result in dangerous interactions if patients using the medication relapse into alcohol use [15], [16]. It is important to emphasize that the detoxification process serves as only a first step to stabilize patients medically and support the transition from alcohol dependence to recovery. Patients must be engaged in active psychotherapy and behavioral treatment following detoxification to remain abstinent from alcohol [15].

Medications to Attenuate Substance Use and Reduce Relapse (Anti-craving agents)

Disulfiram (Antabuse) is the first FDA-approved medication for alcohol dependence and has been available for over 50 years. It works by inhibiting aldehyde dehydrogenase, the enzyme that converts acetaldehyde to acetate in the breakdown of alcohol. As acetaldehyde builds up the disulfiram-ethanol reaction (DER) occurs. The DER includes unpleasant and potentially dangerous symptoms such as sweating, nausea, vomiting, facial flushing, tachycardia, hyperventilation, shortness of breath, and hypotension. In severe reactions, arrhythmias and myocardial infarction, seizure, and death can occur. The DER is an aversive state that serves to extinguish an addictive behavior through negative reinforcement and behavioral counterconditioning [17].

Naltrexone (Revia) is a good example of an anti-craving medication for the long-term treatment of alcohol dependence. Naltrexone is a competitive opioid antagonist that presumably blocks the rewarding aspects of drinking by occupying opioid receptors. When naltrexone is present in the brain, alcohol cannot stimulate the release of dopamine, thereby, reducing the intoxicating effect of alcohol. Naltrexone has been shown to reduce the frequency and intensity of drinking, to reduce the risk of relapse to heavy drinking, and to increase the percentage of days abstinent. The average dose is 50 mg daily. Naltrexone is usually well tolerated, and the most frequent side effects are mild nausea and headache. A depot injection formulation of naltrexone (Vivitrol) has been developed that is administered once monthly with a slow release into the body. It has shown efficacy in reducing heavy drinking outcomes because it offers the advantage of increased medication adherence [18].

Acamprosate (Campral) was approved in 2004 by the FDA as a relapse-prevention medication for alcohol dependence. It affects various neurotransmitters and structurally resembles GABA and glutamate. Glutamate is the primary neurotransmitter for increasing neurologic activity. Acamprosate acts on gabaergic receptors but primarily it modulates glutamate receptors. It can be thought of as either a glutamate modulator or a weakly potent and partial N-methyl-D-aspartate (NMDA) antagonist. This results in its primary effect of decreasing withdrawal. It is more effective when given in the period initially after the cessation of acute withdrawal, possibly related to its effects on the NMDA receptors, and ability to diminish protracted hyperglutamatergic states that drive relapse by negative reinforcement. Specifically, acamprosate acts to decrease cravings to drink brought

on by the desire to feel relief from withdrawal symptoms [19].

Topiramate (Topamax) is a medication already approved for the treatment of epilepsy. It has been studied because of its ability to augment GABA function and inhibit glutamatergic pathways. These combined neurologic activities can decrease dopaminergic activity and, possibly, alcohol reward. Patients taking topiramate will, therefore, find it easier to drink less or become abstinent. Topiramate is started without an initial period of abstinence. In two major controlled trials, topiramate was found to be more effective than placebo for reducing heavy drinking, drinks per drinking day, and increasing percent of abstinent days. Topiramate is not FDA approved (also called "off label") prescribing to treat alcohol dependence. Further research is needed to determine which subpopulations of alcoholics would benefit most from topiramate. Topiramate has a number of side effects including mild cognitive impairment and requires a low titration (the medication must be started at a low dosage and gradually increased) over a few weeks before a fully effective dose is reached [20], [21].

Baclofen is a derivative of GABA and can activate the GABAB receptor with no known abuse potential. It has muscle relaxant and sedative properties and is primarily used to treat spasticity of neurological disorders, such as spinal cord injury, cerebral palsy and multiple sclerosis. Baclofen was first reported to be effective in inducing abstinence from alcohol and reducing alcohol craving. Subsequently, it was reported that baclofen was effective and well tolerated in alcohol-dependent patients with liver cirrhosis, and that a higher dose (20 mg three times daily) had a greater effect than the common dose (10 mg three times daily) [22], [23].

Research has been conducted using the newer antidepressants serotonin specific reuptake inhibitors (SSRI), for example, fluoxetine and citalopram, as adjuncts in the treatment of alcoholism. However, these medications have been found to be of limited utility. The overall findings suggest that SSRIs may be of some use in reducing alcohol use in sub-populations such as those with depression and alcohol dependence [24].

Treatment of opoid dependence

The most effective pharmacotherapies for opioid use disorders are the agonist therapies. As mentioned above, by occupying the sites stimulated by opioids, agonist medications essentially "turn on" the receptors. The therapeutic approach involves using medications that have similar actions to those of the abused drug but that have different pharmacokinetic profiles. Medications like methadone are longer acting and have fewer drug-like effects, and are, thereby, less reinforcing. In the case of opioids, methadone and buprenorphine are the most commonly used medications.

Once stabilized on methadone individuals who are addicted to opiates who use short-acting opioids such as heroin will no longer experience peaks of euphoria or the aversive effects of withdrawal such as anxiety, agitation, diarrhea, and insomnia. As a result, the patient is no longer preoccupied with drug-seeking behaviors. When adequate doses are used, methadone maintenance also diminishes the intensity of shorter acting opioids through cross-tolerance. This means that drug responses to a particular drug (e.g., methadone)

transfers to other drugs from the same class (e.g., heroin) and reduces their reinforcing effects, which, in turn, decreases the intensity of cravings for the drug. The combination of control of aversive effects and prevention of reinforcement makes methadone maintenance an extremely effective treatment as objectively measured with opiate-free urine drug testing [25].

In accordance to the Drug Abuse Treatment Act of 2000, in October 2002, the FDA approved the use of buprenorphine (Subutex), opioid partial agonist, as a schedule II agent to treat opiate dependence in outpatient office-based practices. Buprenorphine is a long-acting (up to 48 hours) high-affinity partial μ opioid agonist, which causes it to act as a functional antagonist blocking the effects of pure μ agonists. Because it is a partial agonist unlike methadone, a pure agonist, it is safer in overdose because it has a ceiling effect on respiratory depression. Buprenorphine is considered to cause a reduced euphoric effect compared to methadone and therefore is less likely to be diverted. To mitigate the potential for abuse of the substance and diversion, buprenorphine has been developed in a sublingual (pills or film sheets that dissolve under the tongue) with naloxone (Suboxone). Suboxone has become the treatment of choice for detoxification from opioids. The typical maintenance dose of Suboxone is 12 mg to 16 mg. Rarely doses higher than 16 mg might be useful but would necessitate a thorough reevaluation of the patient's treatment needs [26].

Naltrexone (Vivitrol) has been FDA approved for the treatment of opioid dependence, which addresses the adherence. The action of naltrexone to block dopamine makes it a potential alternative to opiate replacement treatment for opioid dependence. Patients addicted to opioids cannot get high from opioids while on naltrexone, and it has been hypothesized that they will not want to use opioids, thus improving the likelihood that they will remain abstinent [27].

Conclusion

It can be concluded that Substance use disorders are chronic, relapsing conditions, which exert deleterious consequences on subjects and society. Regrettably, despite extensive research and a continually evolving understanding of these conditions, current treatment modalities are limited and ineffective. Therefore, investigating common mechanisms that underlie addictive behavior in the search for novel therapies is of prime importance. Substance use disorders are difficult to overcome without support and treatment options. Substance use disorders can be a chronic struggle throughout a person's life but using treatment can restore emotional and physical well-being and help a person live life without substances. Thus a constant support with a properly planned treatment therapy can help a person lead a better life

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Polymorphism Of Methyltetrahydrofolate Reductase Gene Of Patients With Skin Leishmaniasis Among The Population Of Uzbekistan

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Abstract: The aim of the study was to study the genotype distribution of the methyltetrahydrofolate reductase (MTHF) gene in the development of various clinical variants of cutaneous leishmaniasis.

Material and methods: 50 patients with skin leishmaniasis were sampled. Of these, 22 (44%) were female and 28 (56%) male. The average age of the patients was 31.5 ±0.21. All patients belonged to the Uzbek ethnic group living in Bukhara province as one of the endemic regions of Uzbekistan.

Results: When genotyping the samples under study, the polymorphism of the MTHF C6777T gene revealed a healthy genotype of CC- 40%, heterozygous genotype of CT - 52% and mutant genotype of TT- 8%. The 677 C/T genotype combination is accompanied not only by a decrease in enzyme activity, but also by an increase in the concentration of homocysteine in plasma and a decrease in the folate level, as is the case with two C677T alleles. A healthy CC genotype (100%) was detected in all 16 conventionally healthy individuals.

Conclusions: In the case of cutaneous leishmaniasis, the heterozygous genotype CT- 1.3 times larger than the healthy genotype CC was detected in patients with C6777T polymorphism of the MTHF gene. It was determined that a T-allelele (mutant) was detected in 39.5% and a C-allelele was observed in 60.5%. In the group of conventionally healthy individuals, the healthy CC genotype was determined in all cases (100%).

Key words: cutaneous leishmaniasis, MTHF gene, population of Uzbekistan.

Introduction: Skin leishmaniosis (leishmaniosis cutanea, Borovskogo syndrome) - protozoic disease caused by leishmania tropica, endemic to tropical and subtropical climate, developing skin lesions with the formation of tubercles, knots, ulceration and scarring. [1]. Most often, children and young adults suffer from skin leishmaniasis. Clinically distinguish skin, skin-slime, diffuse skin and visceral forms of leishmaniasis. Most of the countries where leishmaniasis occurs are Middle Eastern countries, Brazil, Peru, India and Africa. Among the CIS countries, it is often found in Uzbekistan and Turkmenistan.

Leishmaniasis is caused by the simplest intracellular parasites, which are represented by more than 20 types of leishmaniasis. The pathogen is transmitted by female mosquitoes, in which the parasites are in a flagellate form. [2]

Mutations of the methylenetetrahydrofolate reductase (MTHF) gene encode its key enzyme of folate metabolism MTHF. Several mutation variants are known in the MTHF gene. One of the most significant polymorphisms recognized was C677T polymorphism: replacement of cytosine with thymine in the 4th exon of the gene, leading to replacement of alanine amino acid with valine in the catalytic domain of MTHF enzyme (A222V). [3]

In individuals heterozygous and homozygous under this polymorphic variant, the thermal lability of MTHF and the decrease in the catalytic activity of the enzyme in vitro are observed up to about 30% and 60%, respectively [4] This polymorphism modulates the global hypomethylation of the genome in human lymphocytes and leukocytes, but only in combination with a low level of folate intake. Such interaction of genetic predisposition and nutritional characteristics leads to an increase in homocysteine in the body. About half of the population is heterozygous carriers of the C677T allele; the frequency of homozygotes depends on the population and ethnicity and ranges from 1% (among black people on the African continent and America) to 20-35% (among residents of Italy, Spain, and Mexico). In Europe, the frequency of C677T homozygous form increases from north to south. In terms of the frequency of the mutation under consideration, the Russian population is in an intermediate position between Asian populations and most European populations. [5]. Changes in C677T in the MTHF gene structure are associated with various diseases characterized by a wide range of clinical symptoms: cardiovascular diseases, fetal development defects, colorectal adenoma and breast and ovarian cancer, mental and physical retardation, depression, and diabetes.

Objective: to study the distribution of alleles and genotypes of the methyltetrahydrofolate reductase (MTHF) gene in the development of various clinical variants of cutaneous leishmaniasis.

Materials and methods: In this study, a sample of 50 patients living in Bukhara region, one of the endemic regions of Uzbekistan, were sampled for skin leishmaniasis. All patients were in Uzbekistan and belonged to the Uzbek ethnic group. The average age of the patients was 31.5 ë0.21 (3.0-60) years. Of these, 22 (44 per cent) were female and 28 (56 per cent) were male. A group of 16 persons with no chronic microbial-inflammatory diseases were used as a

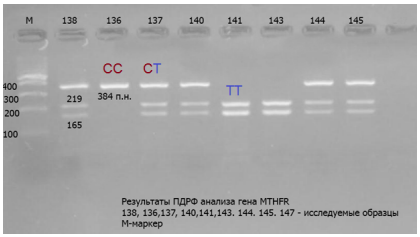
control group. The material used to study the prevalence of polymorphism variants in the gene 5,10-methylenetetetetetetetrahydrofolate reductase (C667T allele variants) was DNA samples obtained in 50 patients. Total DNA was isolated from peripheral blood lymphocytes using standard phenol-chloroform technique. The extracted DNA was frozen and stored at -20? until the genotyping was done. The quality and quantity of DNA samples were studied on the BioSpec-nano spectrophotometer (Shimadzu Biotech, Japan) and 1% in the agarose electrophoresis gel. A group of 16 conventionally healthy persons without chronic microbial-inflammatory diseases was used as a control group.

In accordance with the polymorphism of the MTHF gene (C6777T), specific primers and restriction endonuclease (HinfI) were selected. PCR parameters were optimized and restriction reactions were performed. Primers for specific MTHF gene amplification: 5I-TGACCTGAAGCACTTGAGAA -3I and 5I- GGAAGAATGTGTCAGCC-TCAAAGA -3I.

PCR-amplification of MTHF gene was performed using Isogene Gen Pak® PCR-Core reagent set. PCR was performed using the GeneAmp® PCR system 9700 with a 96-cell gold block (AppliedBiosystems). The conditions for PCR were as follows: 1 cycle at 95° C for 4 minutes, 40 cycles at 94° C for 15 seconds, 60° C for 20 seconds and 72° C for 30 seconds, then in the last cycle 4 min at 72° C. To check the presence of PCR product, 2% agarose gel electrophoresis was carried out. To determine the polymorphism of the C677T MTHF gene, PCR product was treated with HinfI enzyme at 37°C for 16 hours. The restriction product was tested in 3% agarose gel on electrophoresis.

Results and discussion: As a result of the literature review, 31 patients of the Chinese population with funicular myelosa were studied by Xin Zhang scientists and their co-authors for the polymorphism C677T of the MTHF gene. The distribution of C677T genotypes of the MTHF gene in patients with funicular myelosa (FM) was calculated according to the Hardy-Weinberg genetic balance criterion (?2 = 0.134; P = 0.935), and a significant difference between patients with FM and control group (P = 0.006) was found. The frequencies of TT, CT and CC genotypes in the control group were 27.5, 48.8 and 23.8% respectively, whereas in the FM group they were 54.8, 41.9 and 3.2% respectively. The frequency of the T allele in patients with PM was significantly higher than in the control group (75.8 vs. 51.9%), whereas the frequency of the C allele was lower in patients with PM than in the control group (24.2 vs. 48.1%) (p = 0.001).

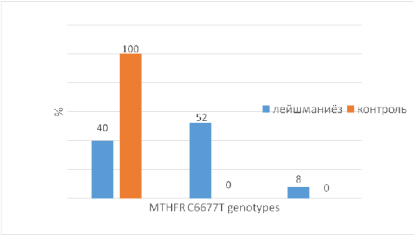
We found out that in 50 patients diagnosed with skin leishmaniasis and 16 conventionally healthy people the amplification product of PCR gene MTHF was 410 pairs of nucleotides, which corresponded to the NCBI DNA database. Restriction products are, respectively, genotype CC 384, 26 bp, ST genotype 384, 219, 165, 26 bp, TT genotype 219, 165, 26 bp (Fig. 1).



Picture 1 . Restriction analysis of polymorphism C6777T of MTHF gene

As a result of genotyping of the samples (50 samples), the polymorphism of the MTHF gene revealed a healthy genotype of CC- 40%, heterozygous genotype of CT - 52% and mutant genotype of TT- 8%.

T-allele was also found to be 30 (39.5%) (mutant), C-allele 46 (60.5%) (see Fig.2).



2 - Fig. 2 - result of polymorphism genotyping of C6777T polymorphism of MTHF gene study group

The combination of 677 C/T and 677 T/T genotypes influences the reduction of drug metabolism, which, accordingly, negatively affects the efficacy of treatment. The 677 C/T genotype combination is accompanied not only by a decrease in the enzyme activity, but also by an increase in the concentration of homocysteine in plasma and a decrease in the folate level, as is the case when carrying two 677T alleles. A healthy CC genotype (100%) was detected in all 16 conventionally healthy individuals.

Provided that the MTHF gene has a TT genotype in C677T polymorphism, the activity of the MTHF enzyme (methylenetetetetrahydrofluorolet reductase), which participates in the metabolism of folate reductase, will be 30%. At the same time, the CT-heterozygous genotype has 65% activity and the CC- 100% activity.

Conclusions. In patients with C6777T polymorphism of the MTHF gene, the heterozygous CT genotype was found to be 1.3 times larger than the healthy CC genotype. It was determined that 39.5% of the T-allele (mutant) and 60.5% of the C-allelele were heterozygous. A healthy CC genotype (100%) was found in all conventionally healthy individuals.

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Prevalence intestinal parasitic infections among primary school children in ethiopia: a systematic review and meta-analysis

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Abstract: Background: Parasitic infections are a serious public health problem because they cause anemia, growthretardation, aggression, weight loss, and other physical and mental health problems, especially in children. Numerous studies have been performed on intestinal parasiticinfections in Ethiopian school children. However, no study has gathered andanalyzed this information systematically.the aim of the present study is to systematically review the prevalence of Intestinal parasatic infection among primary school childen in Ethiopia through systematically evaluating results of studies conducted in this regard.

Materials and methods: In this systematic review study; the required data was collected using terms intestinal parasite, schoolchildern, prevalence,Ethiopia and their Persian equivalents through Google search. Out of 60 articles, 16 articles were finally considered after excluding the remaining articles which were not related to the study objectives and conducted meta-analysis using Comprehensive Meta analysis (CMA) software.

Results: Thepooled prevalence of intestinal parasatic infection among school childern in Ethiopia was53.64 %(95% CI, p-value = 0.000). the minimal value was observed in Babile town, eastern Ethiopia(13.82%) and the maximum result registered inin Chencha town, Southern Ethiopia(81%) and the relevant data ex-tractedand meta analysiswas conducted (Tables 1 and figure 1) and the Time interval of the evaluated articles varied from 2010 to 2018.

Conclusionthe overall prevalence of intestinal parasatic infection among school childern in Ethiopiais more than 50% so that Improvement of sanitation, personal hygiene, and increased awareness of people, and healtheducation can be effective in reducing parasitic infections in different communities.

Key word: Intestinal parasites, School, Children, Ethiopia, Systematic review, Meta -analysis

1. Introduction

According to a WHO report, 3.5 billion people are affected, and 450 million are sickbecause of parasitic infections, of which the majority is children. Of the total annualmortalities in developing countries, parasitic diseases accounts for 16 million deaths.

Approximately 39 million disability-adjusted life years are attributed to IPIs andthese infections represent a substantial economic burden. Preschool and schoolchildren are easily identifiable target groups. IPIs are transmitted directly amongchildren through fecal contamination of soil and water, or indirectly through poorsanitation so intestinal parasites cause considerable morbidity and mortality in the world, especially in developingcountries like Ethiopia. Both urban and rural inhabitants are vulnerable to infection with intestinal parasites indeveloping countries. (WHO, 2007)

Intestinal parasitic infections (IPIs) are a health problem in most countries, especiallyin developing countries. The infections cause iron deficiency anemia, growthretardation in children, weight loss, abdominal pain, dyspepsia, and other physical and mental health problems (WHO, 2014).

The prevalence of intestinal parasitic infectionsis very high in the school children. The high prevalence of parasitic infections in these populations of children indicates that the protozoa and helminthes concerned are very common in the environment as results of the risk factors like water, hygiene and sanitation facilities are inadequate. Water supplies are not enough to drink and use, and in the absence of environmental sanitation, when the rubbish and other wastes increased, and sewage and waste water are not properly treated (1).

Intestinal parasitic infections were the primary health problems in Ethiopia. The most possible reasons are presence of inadequate and unprotected water, limited health education access, high family illiteracy, and poor shoe wearing practices, poor hand washing habits, open defecation practices, low family income, and poor personal and environmental hygiene (2, 3, and 4).

Intestinal parasitic infections were highly prevalent health problem among school children in Dagi primary school. The risk factor of the prevalence of intestinal parasites was poor hand washing habit before meals and after defecations. In addition to this, prevalence of intestinal parasite infections was also shown a significant association among children having unclean finger nails, and did not wear shoes (2, 5, and 7).

Numerous studies have been performed on IPIs in school children from Ethiopian regions. However, there is no study to gather and systematically analyze theinformation. The aim of this study was to provide summary estimates for theavailable data on intestinal parasitic infections in Ethiopian primary school children. This study has been carried out to evaluate the prevalence of parasitic infections.

2. Objective

The aim of this study is to provide the Summery prevalence of Intestinal parasitic infection among primary school childern inEthiopia through systematically evaluating results of different studies conducted from 2010-2018.

3. Material and methods

3.1. Search strategy and data extraction

We searched MEDLINE via PubMed,

Science Direct, Web of Science (ISI),Google Scholar (as English databases) using the terms: intestinal parasites,,school, children,Ethiopia.

To collect precise information, a comprehensive search was carried out on all Published and unpublished articles including full texts, abstracts, and parasitologyCongress summaries.

Data were collected from articles in the English language.

Extracted data from the studies included year of the study, first author, and prevalance of

The study, total sample size, and the number of intestinal positive school childerns.

3.2. Statistical analysis

In this study, forest plots were used to estimate pool Prevalance and effect of each

Study with their confidence interval (CI) to provide a visual summary of the data.

Random effects model (DerSimonian Laird model) was used to compute overall effect andconducted meta-analysis using ComprensiveMeta Analysis software version 3,And for all statistical results were used.

3.3 Inclusion and exclusion criteria's of articles

3.3.1Inclusion criteria's of articles

- Should primary study (not review)
- Latest article
- Measurable outcome
- Relation with study objective
- No duplication of articles in the same zone

Out of 60 articles, 16 articles were finally considered.

3.3.2 Exclusion criteria's of articles

Out of 60 articles, 44 articles were excluded due to

- 2 articles dueto duplication of articles in the same zone
- 25 articles due to years of study
- 17 articles due to lack of relation with the study objectives.

4. Results

Of the 60 publications that were gathered for this systematic review, 16 wereeligible for inclusion under intestinal parasitic infections (Figure 1 and Table 1).

In this study, The results of random-effects meta-analysis showed that the highest prevalence rate of IPIs was reported From Abossie A, S.M(81%), and the lowest was reported fromTefera E, M.J(13.8%)and the pooled prevalence of IPIs among Ethiopian primary schoolChildren was 53.6% (95% CI,p.value<0.05) (Figure 1 and Table 1).

Table 1; the relevant data extraction on the prevalance of intestinal parasite on primary school childern in Ethiopia from the year 2010-2018.

S/NO	Author	Citation	Year	Number of sample taken	Numberofpostivechildern
1	Gebretsadik etal	Homesha District (Woreda) in Benishangul-Gumuz	2016	395	140
2	Gashaw et al.	Maksegnit and Enfranz Towns, northwestern Ethiopia,	2015	550	365
3	Gelaw et al.	University of Gondar Community School, Northwest Ethiopia	2013	304	104
4	Amare et al.	Northwest Ethiopia	2013	405	92
5	Haile Admasu	Gurage Zone, South Ethiopia	2017	463	195

6	Abossie and Seid	Chencha town, Southern Ethiopia	2014	400	324
7	TeferaEphrem	Babile town, eastern Ethiopia	2014	644	89
8	AbdiMerem	ZegiePeninsula,northwestern Ethiopia	2016	408	282
9	AberaAlamneh	Tilili town, northwest Ethiopia	2014	385	170
10	Tulu et al	Yadot South Eastern Ethiopia:	2014	348	89
11	MulusewAndualemAsemahagn,	Motta Town, Western Amhara, Ethiopia	2014	364	245
12	Hailegebriel	Dona Berber, Bahir Dar, Ethiopia	2017	359	235
13	MulatAlamiret al.	Dagi, Amhara, Ethiopia	2013	399	311
14	BerhanuElfuFeleke	Bahir Dar, Ethiopia	2016	2372	1464
15	*Bajiro M, Gedamu S, Hamba N, Alemu Y*	*Jimma Town, South West Ethiopia*	2018	233	118
16	Hailegebril	Bahir Dar, Ethiopia	2018	382	200

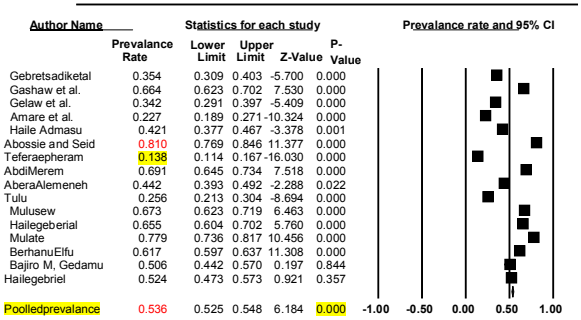

Figure 1; Meta analysis results of the study on the prevalance of Intestinal parasaitic infection of primary school childern in Ethiopia from the year 2010 to 2018.

4. Discussion

This systematic review and meta-analysis will be beneficialfor understanding thesituation of IPIs in Ethiopian primary school children. This study estimated the prevalence rate of IPIs in this group, using the documented data from the literature reviews, which havebeen gathered from different Regions of Ethiopia. According to our results, thePrevalence rate of IPIs among Ethiopian primary school children was 53.8% from 2010 to 2018.In meta-analysis has been carried out; theprevalence of IPIs differs in various Regions of Ethiopia.

Chencha town, Southern Ethiopiareported thehighest (81%) prevalence rate of IPIsdue unavailability of washing facilities constructed at home had also a contributing effect for the presence of intestinal parasitosis. And Home cleanness condition also had contribution for theexistence of IPIs. .The lowest prevalence was observed in Babile town, eastern Ethiopia (13.8%). The low rate ofIPIs in this area seems to be because general health information dissemination is suggested to be given to students on

how to protect themselves from intestinal helminthic infections with special emphasis for children. It is also suggested that the local Education Bureau as well as the local Health Bureau need to provide safe learning environment especially for students of lower grade such as school sanitation.

The prevalence of IPIsis different in other countries. For example,prevalence is 47.6% in Afghanistan (Gabrielli et al., 2005), 42.5% in Syria (Al-kafriand Harba, 2009), 31.8-37.2% in Turkey (Okyay et al., 2004), and 27% in Egypt (El-Soud et al., 2009) and my meta anaysis results varies in Region to Region and the over allprevalance of the country was 53.64%. The reasons for these differences could be socio-economicstatus,poor hygiene and sanitary facilities, weather, climate and environmental factors, aswell as inappropriate drinking water.

There were many studiesthat presented data and analysis of demographic information and risk-factors such assex, age, the literacy level of parents, etc. that were not mentioned in their articles because of the limitatation of time so It is recommended that researchers conduct and analyze demographic and risk factor information mentioned inthe respective articles.

5. Conclusions

This is the first systematic review and meta-analysis that provides a comprehensive overview of the prevalance of IPIs in Ethiopia primary school children. This studyresults showed that the prevalence of IPIismore than half percent so improved sanitation, personal hygiene, increased awareness, and healtheducation can be effective in reducing parasitic infections in different communities. Moreover, the establishment of appropriate sanitation facilities and education in hygiene schools will help make a healthy society.

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Determination Of Virulence Factors Of Diarrheal Escherichia With Pcr In Patients With Acute Intestinal Infections Complicated By Hemocolitis

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Abstract: Feces samples from 20 patients with AII in aged of 1 to 72 years with no growth of Shigella or Salmonella were examined. 19 of them were diagnosed with acute diarrhea complicated by hemocolitis and 1 patient with acute diarrhea complicated by hemolytic-uremic syndrome and acute renal failure . For genetic molecular study of diarrheal Escherichia used multiplex set RIDA GENE EHEC/EPEC, R-BiopharmAG, (Germany), designed to determine the PCR in the 3 main genes of deareasing E. coli virulence genes, stx1/stx2 (Shiga-like toxin), ipaH (gene invasiveness) and eae (gene adhesiveness or intimin). Multiplex genetic and molecular typing of fecal samples of patients with AII showed different combinations of the main genes of Escherichia virulence and confirmation of other studies that hemocolites can develop as a result of infection with different E. coli pathogens. Most often (10/50%) were recorded gene (ipaH) characteristic group enteroinvasive E.coli - EIEC/ Shigella. The gene characteristic of EPEC (eae) was determined in 5/25% of patients; combination of genes characteristic of EHEC (stx1/stx2 and eae) in 4/20% of patients. Only one sample of biological material (5%) identified a gene (stx1/stx2), which are typical for E. coli STEC(EHEC).

Key words: acute intestinal infection, E. coli,hemolytic uremic syndrome, hemocolitis, verotoxins, invasiveness, adhesiveness.

Introduction.

One of the most important problems in human infectious pathology all over the world is acute intestinal infections (AII). Though on global level mortality from diarrheal diseases has decreased considerably for the last 25 years, diarrhea in some countries rather often results in lethal outcomes, and, primarily, - at children [9]. The spectrum of AII pathogens is quite diverse - rotaviruses, noroviruses, representatives of the genus Salmonella, Yersinia, Campylobacter, Escherichia, etc. [12, 14]. More than half of the patients, the etiology of AII is not deciphered, resulting in inadequate antimicrobial treatment and inability to carry out preventive measures.

A specific place is occupied by groups of diarrheal Escherichia in etiology of acute intestinal infections, which as opposed to E.coli, being human and warm-blooded commensals, and produced by various virulence factors, that could be cause peculiarity of clinical manifestations, especially an epidemiology and pathogenesis of infection. Depending on it, several pathogens of diarrheal Escherichia [8] - enteropathogenicE.coli (EPEC), entero-hemorrhagicE.coli (EHEC), enterotoxi-genicE.coli (ETEC), enteroinvasiveE.coli (including EIEC/Shigella) and two groups that have been recently added to the list relatively - enteroaggregative (EAEC) and diffusely adhesive E.coli (DAEC) were isolated. Great attention was paid to EHEC causing outbreaks and sporadic cases of hemorrhagic colitis (HC) and hemolytic-uremic syndrome (HUS) last decade [4,6,14,16].Main representative of this group is serovar O157:H7, which is characterized by production of Shiga-like toxinStx1 and Stx2 and main factor of adhesion - an intimin. As well STEC term (Shigatoxin-producing E.coli) started to be used, including EHEC and no EHEC, not having an intimin, but is being capable to produce the Shiga-like toxin [7,11,19].

It is known, timely and reliable determination of etiology of infection is great importance both for adequate treatment and for adoption of appropriate epidemiological measures.

Determination of the etiology of AII by traditional classical methods is gradually giving way to gene-molecular methods, an advantage of which are high specificity, sensitivity and speed of obtaining the result [17,11]. In a recent publication [17], a large amount of factual material (683 children with acute intestinal infections) was showed the results of PCR by DNA / RNA indications of major bacterial enteropathogens (Salmonella, Yersinia, Campylobacter, Escherichia, etc.) in feces and compared it with the bacteriological method. DNA markers of 4 groups of enteropathogenic Escherichia were detected in feces in 169 patients, while bacterial inoculation had not given a positive result in any case.

Purpose of the study.Study goal was to determine the production of individual virulence factors of Escherichia using by PCR in the patients' feces with acute intestinal infections, complicated by hemocolitis.

Materials and methods.

From May to September 2018, we were examined 200 patients with acute intestinal infections in aged 1 to 72 years in acute intestinal infections department and intensive care unit within a clinic of Research Institute of Epidemiology, Microbiology and Infectious Diseases of the Ministry of Health of the Republic

of Uzbekistan (RIEMID MoH UZB). 145 patients of them were diagnosed with acute diarrhea gastroenteric form of moderate severity, 44th patient with acute diarrhea gastroenterocolitic form of moderate severity (AD, GEC); complication: hemocolitis (HC). 11 patients were diagnosed with AD GEC severe form complicated by HUS and acute renal failure (ARF). In bacteriological laboratory of RIEMID MoH UZB, all patients were examined for pathogenic and potentially pathogenic enterobacteria by generally accepted traditional methods. During this study period, Salmonella spp. was isolated at 3 cases from 200 patients, Shigellaflexneri at 2 patients. To identify isolated colonies of E. coli inoculation of the Endo agar were performed at several dilutions. Cultured colonies suspicious for the E.coli (red, pink with metallic sheen) after inoculation in mixed Kligler's medium were determined it physiological and biochemical properties according to Bergey's Manual of Systematic Bacteriology [1]. 20 patients with no growth of Shigella or Salmonella were selected for study of virulence genes. 19 of them were diagnosed with AD GEC, complicated by HC and one patient with AD, complicated by HUS and ARF. PCR analysis was carried out with feces samples frozen at -160C. For genetic and molecular study of diarrheal Escherichia used multiplex set RIDA GENE EHEC / EAGEC, kindly presented to us by R-BiopharmAG, (Germany). The set is designed to measure in multiplex PCR 3 main virulence genes diarrheal E. coli - stx1/stx2 (Shiga-like toxin) genes, ipaH(invasiveness gene) and eae (adhesiveness or intimin).Molecular genetic tests was occupied at reference laboratory of PCR diagnostics of Research Institute of VirologyMoH UZB (Uzbekistan, Tashkent) in full compliance with instruction of the manufacturer to the set. For DNA extraction was used AmpliSens "Ribo-prep" reagent set of Federal Budget Institution of Science "Central Research Institute of Epidemiology" of The Federal Service on Customers' Rights Protection and Human Well-being Surveillance. PCR was performed on an analyzer: Amplifier detecting DT prime, DNA Technologies Russia with hybridization-fluorescence detection in "Real time" mode. According to manufacturer's instructions for R-BiopharmAG, different combinations of virulence genes indicate different variants (groups) of diarrheal Escherichia, which is reflected in table 1.

Table 1

Interpretation of genes determination results of encoding virulence factors in PCR analysis of patients' feces samples with acute diarrhea (Manual for RIDA GENE EHEC / EPECPG 2205 LOT 14038

Virulence factors genes			Internalquality control	Interpretation results
Stx1/Stx2	eae	ipaH	ICD	
positive	positive	negative	positive	EHEC
positive	negative	negative	positive	STEC (EHEC)
negative	positive	negative	positive	EPEC
negative	negative	positive	positive	EIEC/Shigellaspp
positive	negative	positive	positive	Shigelladysenteriae Typ 1
negative	negative	negative	positive	negative (virulence genes was not detected)
negative	negative	negative	negative	not valuable

Serotyping of isolated E. coli was not carried out due to the difficulties of providing regions with Escherichia agglutinating serum.

Results and discussion.

Molecular genetic tests results of patients' feces samples with acute intestinal infections were presented in table 2

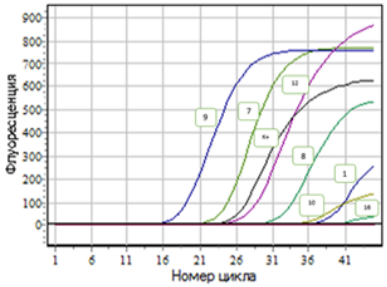
Table2

PCR results at patients' feces samplesin diarrheavariesof E. coli by RIDAGENEEHEC/EPEC

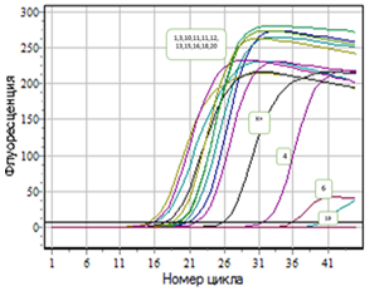
№	N.S.	Genesin PCR	PCR results
1	S.Z	stx_1, stx_2,eae	EHEC
2	M.SH	eae	EPEC
3	SH.A	ipaH, (eae)	EIEC/shigell aspp, (Entoamyoba hystolitica)
4	R.M	ipaH,	EIEC/shigell aspp,
5	V.J	eae	EPEC
6	N.A	ipaH,	EIEC/shigell aspp,
7	A.M	stx_1, stx_2,eae	EHEC
8	T.H	stx_1, stx_2,	STEC (EHEC)
9	A.A	stx_1, stx_2,eae	EHEC
10	T.A	ipaH (,eae)	EIEC/shigell aspp,

№	N.F.	Genesin PCR	PCR results
11	B.G	ipaH,	EIEC/shigella spp,
12	S.M	stx_1, stx_2,eae	EHEC
13	A.S	ipaH,	EIEC/shigella spp,
14	Dj.N	eae	EPEC
15	Kh.Dj	ipaH,	EIEC/shigella spp,
16	A.M	ipaH,	EIEC/shigella spp
17	Y.B	eae	EPEC
18	P.S	ipaH, (eae)	EIEC/shigella spp,
19	U.A.	eae	EPEC
20	A.J	ipaH,	EIEC/shigella spp,

Note: 1)N.S. - patients name and surname.2) all patients (except №19) determined diagnosis asAD, GEC of moderate severity, complication: HC. 3) №19 with diagnosis: AD, GEC severe, complications: HUS. ARF.



Picture 1. Graph of accumulation of amplification products of the stx1 / stx2 genes. Number of E.coli cultures in table 2. K - control Picture 2. Graph of accumulation of amplification products of the ipaH gene. Number of E.coli cultures in table 2. K - control



Picture 3. Graph of accumulation of amplification products of the eae gene. Number of E.coli cultures in table 2. K - control Picture 4. Graph of accumulation of amplification products of the VKO. Number of E.coli cultures in table 2. K - control

Before to discuss these results, it is to be noted following. Three from 20 cases (№3, 10, 18) combination of genes not provided in table 1 - this combination of genes ipaH and eae was revealed.Analysis of amplification graphs of these samples showed that rise of fluorescent signal of ipaH gene began from 16-21 cycles; far more late occurrence of amplification products of the eae gene was (only after 36th cycle). Therefore, during at interpretation of study results of the genes virulence genes according to Table 1, the eae gene was ignored (Table 2, it was highlighted in brackets) as well these samples were regarded as group EIEC / Shigella. It can be seen from table 2 that the ipaH invasiveness gene was detected most frequently.Besides 3 cases above, at absence of Shiga-like toxin genes stx1 / stx2 and intimine (eae), to enteroinvasive diarrheal Escherichia was related additionally 7 cases EIEC/Shigella spp. At 5 patients (25%) only intimine gene was revealed, which is characteristic of enteropathogenic E. coli - EPEC. In literature there is an assumption [7] that enteropathogenicE.coli strains(EPEC/ atypical EPEC), with the O157 antigen were originally EHEC and had the stx genes, but in due course they were lost. It is noted this group includes the only one of the examined patients diagnosed with AD, HUS and ARF.

A genetic examination of faeces at 4 patients (20%) showed a combination of genes responsible for stx1/stx2 verotoxins and intimineeae genes production; according to Table 1, the enterohemorrhagic E. coli, EHEC, were an etiological factor of diarrhea and hemocolitis at these patients. One of the 20 patients (5%), only verotoxins were detected, the lack of intimine refers to the STEC group (EHEC). Combinations of the stx1 / stx2 and ipaH genes virulence factors characteristic of Shigelladysenteriae were not found. Thus, in 10 (50%) patients with AII, an etiological factor was the group of invasive enterobacteria consisting of EIEC and representatives of the Shigella genus (except Shigelladysenteria). As noted, all patients, in parallel with the molecular gene tests were examined by traditional method for pathogenic intestinal flora and no Shigella was found in one of the 20 patients examined.

At all strains property was investigated to ferment sorbitol; however results shouldn't be regarded one-valued. As it is known, absence of sorbitol fermentation is characteristic for enterohemorragic Escherichia, in particular, for epidemic serotype O157:H7. According to our data, strain №8, related to STEC (EHEC) was sorbitol positive and similar strains serotype O157:H7 were described earlier [6, 7]. Besides E.coli №4 and №18 samples has not fermented sorbitol, though by results of genetic research allocated strains related to other pathovar, capable to ferment sorbitol - EIEC/Shigella spp. and EPEC. It is noted there are numerous messages that by activators of HC and HUS can be acted not onlyEscherichiaserovarO157:H7 or O104:H4, but also O145, O26, O111, O117, O174 etc. [6,16,18,19].

For example, serovarE.coliO101:H33 was known earlier as ETEC causing coli-infection at calf [10], but in 2015 for the first time in Russia at flare-up of food infection with HC was found out at child [16]. Up to 6% of patients with HC and HUS is allocated by strains EHEC, losing ability to form Shiga-like toxin. Instability of these genes can be caused: in vivo by

influence of factors of immunity or antibiotics and in vitro is under action of diversified factors of environment [2]. As shown in report (13) genetic determinants of the eae gene, though seldom (no more than 1%), can be met in the intestines and at healthy children. At the same time, the same publication shows a high frequency of the BFP gene (92-100%) encoding an ability of EPEC to synthesize beam-forming saws (BFP - Bundle forming pili), factor binding, which contributes to the initial attachment of E.coli to the enterocytes, and the formation of bacterial aggregations or micro colonies.

As noted [3], none of the virulence factors or combinations of these factors can accurately determine pathogenic potential of Escherichia and disease severity. Along with this, authors believe the greatest risk of developing serious infections is a combination of the genes of stx1/stx2 and token of the presence of LEE (locus enterocyte attrition) or factor labeling and erasing of the villi (A/E) epithelial cells of intestine with pedestal formation structures on their surface [3, 5].

Thus, for diagnosis of AII pathogens, the PCR method is increasingly and successfully used, especially in multiplex version. But in proposed algorithms for study of AII, phenotypic methods - ELISA, immunochromatographic analysis, latex agglutination, various variants of selective nutrient media for selection of the most epidemically dangerous Escherichia serovars also occupy an important place[3,15,16,18].

Conclusions

1. Multiplex genetic and molecular typing of feces samples of patients with AII has showed different combinations of the main genes of Escherichia virulence and confirmation of other studies that hemocolites (and HUS) can be developed as a result of infection with different E.coli pathogens.

2. Patients with AII, complicated by HC, the most frequently (50%) was detected for genes corresponding to enteroinvasive E. coli group - EIEC/ Shigella. Almost equally (25% and 20%) were determined by EPEC and EHEC; only one sample of biomaterial (5%) revealed gene STEC (EHEC).

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Haloperidol As An Antipsychotic: A Review

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Abstract: Haloperidol is a psychotropic agent. The drug has action at all levels of the central nervous system-primarily at subcortical levels-as well as on several organ systems. Haloperidol has potent neuroleptic antiadrenergic activity and weak peripheral anticholinergic activity, as well as minor ganglionic binding ability. It also possesses slight antihistaminic and anti-serotonergic activity and may also act as an anti-emetic. Haloperidol is used to treat certain mental/mood disorders (e.g., schizophrenia, schizoaffective disorders). It also reduces aggression and the desire to hurt others. It can decrease negative thoughts and hallucinations.Haloperidol can also be used to treat uncontrolled movements and outbursts of words/sounds related to Tourette's disorder. Haloperidol is also used for severe behavior problems in hyperactive children when other treatments or medications have not worked.Haloperidol is apsychiatric medication (antipsychotic-type) that works by helping to restore the balance of certain natural substances in the brain (neurotransmitters).Haloperidol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no well controlled studies with haloperidol in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy.As with other neuroleptics, the mechanism of action of haloperidol has not been entirely elucidated, but has been attributed to the inhibition of the transport mechanism of cerebral monoamines, particularly by blocking the impulse transmission in dopaminergic neurons. In this review article, we will briefly look on Haloperidol as an antipsychotic.

Key words: Haloperidol, Schizophrenia, dopaminergic neurons.

Introduction

Haloperidol is the first of the butyrophenone series of major tranquilizers.Haloperidol is indicated for use in the management of manifestations of psychotic disorders. Haloperidol is indicated for the control of tics and vocal utterances of Tourette's Disorder in children and adults. Haloperidol is effective for the treatment of severe behavior problems in children of combative, explosive hyperexcitability (which cannot be accounted for by immediate provocation). Haloperidol is also effective in the short-term treatment of hyperactive children who show excessive motor activity with accompanying conduct disorders consisting of some or all of the following symptoms: impulsivity, difficulty sustaining attention, aggressivity, mood lability, and poor frustration tolerance. Haloperidol should be reserved for these two groups of children only after failure to respond to psychotherapy or medications other than antipsychotics [1,2]. Haloperidol is a butyrophenone derivative with antipsychotic properties that has been considered particularly effective in the management of hyperactivity, agitation, and mania. Haloperidol is an effective neuroleptic and also possesses antiemetic properties; it has a marked tendency to provoke extrapyramidal effects and has relatively weak alpha-adrenolytic properties. It may also exhibit hypothermic and anorexiant effects and potentiates the action of barbiturates, general anesthetics, and other CNS depressant drugs. As with other neuroleptics, the mechanism of action of haloperidol has not been entirely elucidated, but has been attributed to the inhibition of the transport mechanism ofcerebral monoamines, particularly by blocking the impulse transmission in dopaminergic neurons [3].

Pharmacokinetics:

Peak plasma levels of haloperidol occur within 2 to 6 hours of oral dosing and about 20 minutes after I.M. administration. The mean plasma (terminal elimination) half-life has been determined as 20.7ë4.6 (SD) hours, and although excretion begins rapidly, only 24 to 60% of ingested radioactive drug is excreted (mainly as metabolites in urine, some in feces) by the end of the first week, and very small but detectable levels of radioactivity persist in the blood and are excreted for several weeks after dosing. About 1% of the ingested dose is recovered unchanged in the urine. Haloperidol is rapidly absorbed after oral administration with a bioavailability of 44-74% (mean 60%) after tablets. Variable bioavailability is likely due to inter-individual differences in gastro-intestinal absorption and extent of first-pass hepatic metabolism.

Distribution is rapid to extravascular tissue, haloperidol crosses the blood-brain barrier and is excreted in human breast milk.Metabolism is by oxidative dealkylation. The elimination half-life is approximately 20 hours, with considerable diurnal variation [4, 5].

WARNINGS AND PRECAUTIONS

Warnings

Increased Mortality in Elderly Patients with Dementia-Related Psychosis.Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Haloperidol is not approved for the treatment of patients with dementia-related psychosis.

Cardiovascular Effects

Cases of sudden death, QT-prolongation, and Torsades de Pointes

have been reported in patients receiving haloperidol. Higher than recommended doses of any formulation of haloperidol appear to be associated with a higher risk of QT-prolongation and Torsades de Pointes. Although cases have been reported even in the absence of predisposing factors, particular caution is advised in treating patients with other QT-prolonging conditions (including electrolyte imbalance [particularly hypokalemia and hypomagnesemia], drugs known to prolong QT, underlying cardiac abnormalities, hypothyroidism, and familial long QT-syndrome) [6].

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome [7].

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dyprogrammeythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extra pyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology [8-10]. The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug

therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported with haloperidol.

Usage in Pregnancy

Non-teratogenic Effects

Neonates exposed to antipsychotic drugs, during the third trimester of pregnancy are at risk for extra pyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. Haloperidol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no well controlled studies with haloperidol in pregnant women. There are reports, however, of cases of limb malformations observed following maternal use of haloperidol along with other drugs which have suspected teratogenic potential during the first trimester of pregnancy. Causal relationships were not established in these cases. Since such experience does not exclude the possibility of fetal damage due to haloperidol, this drug should be used during pregnancy or in women likely to become pregnant only if the benefit clearly justifies a potential risk to the fetus. Infants should not be nursed during drug treatment [11].

Precautions

Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, events of leukopenia/ neutropenia have been reported temporally related to antipsychotic agents, including haloperidol tablets USP. Agranulocytosis (including fatal cases) has also been reported.Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a preexisting low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue haloperidol tablets USP at the first sign of a decline in WBC in the absence of other causative factors.Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm3) should discontinue haloperidol tablets USP and have their WBC followed until recovery [12].

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Barriers To Reproductive Health Services Utilization Among Adolescent Street Hawkers In Ebonyi State, Nigeria

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Abstract: The aim of the study was to establish the barriers to reproductive health services utilization among adolescent street hawkers in Ebonyi State, Nigeria. A sample of 494 (male, 267, female, 227) such adolescent hawkers aged 10-19 years were studied using the cross-sectional survey. A self-developed questionnaire (r = 0.72) was used to collect data. Mean, standard deviation and t-test statistic were used to analyse data. Results show unavailability of equipment, poor quality services, inconvenient hours of operation, lack of privacy, confidentiality, long waiting hours, among others, were barriers to reproductive health services utilization among adolescent street hawkers. Data show both male and female adolescent hawkers perceive all the concepts as barriers to reproductive health services utilization, but as 'do not know about the services' ranks 1st among males, it ranks 10th among the females and 'inconvenient hours of operation' that ranks 2nd among the males also ranks 2nd among the females. t-test shows differences exist in 'do not know about the services', 'staff attitude and behavior' and 'location of the facility' among others. Results also show both 10-14 years and 15-19 years age groups adolescent hawkers perceive all the concepts as barriers to reproductive health services utilization and as 'do not know about the services' ranks 1st among the 10-14 years age group, it ranks 11th among the 15-19 years age group and 'inconvenient hours of operation' that ranks 2nd among the 10-14 years age group, ranks 1st among the 15-19 years age group. t-test indicates differences in 'do not know about the services', 'services use against my beliefs', 'preferred by parents', and 'poor referral system' among others. Further results show adolescent hawkers who reside in both urban and rural perceive all the concepts as barriers to reproductive health services utilization and as 'do not know about the services' ranks 1st among adolescent hawkers who reside in urban area, it ranks 3rd among those residing in the rural area. Mobile health clinic delivery system to reach the street hawkers is advocated.

Keywords: Barriers, Reproductive health, Reproductive health services utilization, adolescents

Introduction

Myriad sexual health problems confront adolescents all over the globe regardless of existing reproductive health services. For instance, it was reported a projected 1.3 million adolescent girls and 780,000 adolescent boys are living with HIV global and 79% fresh HIV infections among young people are in sub-Saharan Africa (World Health Organization, 2011). In Nigeria, Federal Ministry of Health reported that adolescents constitute about a fifth of the national population, 12% have first childbirth before 15 years, and most of them have become parents before age of 20 years, and suffer from sexually transmitted infections (Federal Ministry of Health, 2003). This scenario predisposes young people to sexually transmitted diseases, unwanted pregnancy, unsafe abortion and death (Iniabasi and Adindu, 2013) despite existing reproductive health services such as sexual information, pregnancy testing, treatment of sexually transmitted infections (STIs), condom use, pre-abortion counseling, safe abortion and pap screening (International Planned Parenthood Federation, 2007).

Adolescence is the period of human growth and development that occurs post-childhood and before adulthood, from ages 10 to 19 (World Health Organization, 2005) and is classified into two, namely early adolescence (10-14 years) and late adolescence (15-19 years) (Olunkunle, 2007). During this period the human starts experiencing sagacity of self-awareness and emotional independence (World Health Organization, 2002). This period is the most critical stage in human life characterized with peer pressure, mystification and pleasure which predispose the young people to sexually transmitted infection, unwanted pregnancies and unsafe abortion which may demand them to utilize available reproductive health services.

Reproductive health services are services provided to promote a state of physical, mental and emotional well-being of the individual, including the adolescent street hawker. The services, if utilized, are capable of improving the physical, social and mental or emotional health and safety of the adolescents because the services provide a comprehensive and focused approach for the promotion, prevention, early detection, and intervention of the physical, emotional and social factors affecting the health of the adolescent and even the contemporary communities (Warenius, 2006). Lloyd (2015) emphasized that reproductive health services help adolescent boys and girls stay in school, delay childbearing, have healthier children later in life, and earn better incomes. This would subsequently benefit adolescent boys and girls in the long run, as well as their families and their communities. Utilization connotes both frequency and method to which an object meant for a particular purpose is put into use (Ezeanolue, 2014). Reproductive health services utilization implies the use of health services provided for the general and sexual health of the individual, including the adolescent street hawker (Awoyemi, Obayelu & Opaluwa, 2011).

Street hawking is an act of selling retail goods directly on busy city streets (Asare, 2010). It could also be the act of displaying wares by the road side, carrying head pan or raising a sample of wares to the commuters while the vehicles are moving (Amoo, Ola-David, Ogunrinola & Fadayomi, 2012). Umar (2009)

conceptualized street hawking as the selling of things along the roads and from one place to the other. Street hawking therefore, is a small scale trade in which the seller moves around searching for prospective buyer from house to house, public offices, institutions and mainly motor parks and busy pedestals.

A street hawker is broadly defined as a person who offers goods or services for sale to the public without having a permanent built up structure, but with a temporary static structure or mobile stall (head load). Street hawkers may be stationary by occupying space on the pavement or other public or private areas or maybe mobile in the sense that they move from place to place carrying their wares on push carts or in cycles or baskets on their heads or other plastic carriers.

Factors promoting street hawking include poverty, exploitation by the adults and children's own choices as a result of ignorance, among other things. Historically, hawking appears to be part of Nigerian culture and understandably so. Nigeria being among the poorest economies in the world, with the accompanying effects of unemployment, poor infrastructural facilities, and lack of human empowerment, has seen most of her populace living in abject poverty. Due to unfavourable socio-economic conditions, children are forced to contribute to the family income by hawking various commodities on the streets to passersby and to commuters in buses and cars. They are therefore, exposed to the harsh environmental elements, physical and sexual abuse, and sexual and reproductive health disorders in form of adolescent pregnancy. Therefore, because of the low socio-economic status of most families in Nigeria and the high rate of poverty, most parents cannot help but push their adolescent children into the streets where they spend long hours, at the mercy of environmental elements, selling pure water (sachet water), fruits, confectioneries, beverages, multi-media gadgets, among other wares, so that the proceeds may contribute to family upkeep. This situation is alarming because street hawking is a form of child labour and abuse which is on the increase in Ebonyi State. Street hawking is considered a form of child abuse because it endangers the health and safety of the child. Studies (Anarfi, 1997; Ayaya & Esamai, 2001) reported some street children could not find time to visit health care centers as they struggle during the day to raise money for food and other basic necessities and are only free at night. Commuters entering Abakaliki, the capital city of Ebonyi State could attest to this situation. The present study was carried out to determine the barriers to reproductive health services utilization among adolescent street hawkers in Ebonyi State, Nigeria.

There are limited studies on the sexual health and reproductive health services utilization among street children in Africa. The few studies that were found revealed that street children reported sexual initiation from the ages of 10 to 16 years. Most of the studies from South Africa reported an initiation range from ages 8 to 14 years (Aptekar & Ciano-Federoff, 1999; Olley, 2006). The prevalence rate for gonorrhea, syphilis and genital herpes ranged from 2 to 22% among street children (Aptekar, Ciano-Federoff, 1999; Olley, 2006; Owoaje & Uchendu, 2009). No studies were found that specifically covered the issue of pregnancy and

mortality. However, unwanted pregnancy remains a significant issue with very little information regarding its prevalence among street children. These children have no steady source of income and have limited knowledge on child bearing or childrearing (Aptekar & Ciano-Federoff, 1999; Bar-on, 1997; Owoaje & Uchendu, 2009) in health care due to high hospitalization and consultation costs in health care facilities, which might be a major barrier to utilization of health services among street children who earn little or nothing on the streets.

Sexual abuse is another common occurrence that threatens the health of children involved in hawking. Although incidences have been reported among the males, it is far commoner among the females. A study (Ikechebelu, Udigwe, Ezechukwu, Ndinechi, & Joe-Ikechebelu, 2008) in Southeast Nigeria identified sexual abuse as a major hazard among female hawkers. In the study, 69.9% of the respondents had been sexually abused with approximately 17% reporting penetrative sexual intercourse. Similarly, another study (Ashimi, Amole, & Ugwa, 2015) in Northwestern Nigeria which assessed the prevalence of sexual violence presentation at a tertiary health facility found that about a third of the female children involved were street hawkers.

The most troubling, perhaps, is the fact that some are sexually exploited and forced into prostitution with the risk of unintended pregnancies and contracting sexually transmitted infections, including HIV. Some of the adolescent girls wake up as early as 4am to prepare articles for sale and proceed to hawk often without breakfast. This state of hunger makes them vulnerable to exploitation by men. An earlier study on street children in Nigeria found that more than 15.4% of female adolescent hawkers had procured abortion at least twice, had been pregnant without knowing who was responsible, had experienced rape and also contracted sexually transmitted infections (Osinowo, 1992). A more resent study (Fawole, Ajuwon, & Osungbade, 2003) showed that 30% of the violence experienced by girls on the street is sexual in nature. This is an issue of great importance because in the traditional African society, the concept of sexuality is enshrouded in secrecy.

World Health Organization (WHO, 2005) affirmed that the utilization of reproductive health services among adolescents is hindered by poor accessibility, unavailability of services and acceptability of the services, service delivery hours, cost of services, lack of confidentiality and facility organization, lack of clear directions, crowding, lack of privacy, appointment times that do not accommodate young people's work and school schedules, little or no accommodation for walk-in patients, limited services and contraceptive supplies and options calling for referral, and individual factors such as lack of knowledge and attitude of both the health worker and the individual. A study (Annear, Khim, Ir, Moscoe, Jordanwood, & Bossert, 2016) in Cambodia showed that lack of confidentiality, shyness, poor relations with health staff, illiteracy and low prioritization by parents hinder utilization of reproductive health services. In Nigeria, Awoyemi, Obayelu and Opaluwa (2011) reported inadequate staffing, lack of clear policies and guidelines on youth friendly services provision and inadequate

information education, communication, poor quality structure, long waiting hours as barriers to reproductive health (RH) services utilization among adolescents.

Some demographic variables such as gender, age and location of residence play significant roles in reproductive health services utilization among adolescents. Significant differences were reported to exist in reproductive health services utilization in relation to gender, age and location (PATH, 2001; WHO, 2011).

Federal Ministry of Health (2010) noted that in most societies in Nigeria and Africa, men are perceived as macho and women as passive. This gender role makes women and especially transgender people vulnerable in different ways to RH problems, and inhibiting access to RH services. For example, men may associate masculinity with taking risks in their sexual relations which exposes them to HIV and STIs, and may be reluctant or too embarrassed to seek out appropriate health information and care. Women who are financially, materially or socially dependent on men may have limited power to exercise control in relationships, such as negotiating the use of condoms during sex. Social expectations about how women should behave can place women in subordinate roles and increase their risk of being sexually assaulted, contracting STIs and having unwanted pregnancies. In Northern Nigeria, adolescents have to ask their parents whether to access any form of RH services like use of contraception and this might make them vulnerable to contracting STIs including HIV/AIDS. The contraceptive prevalence is very low in Northern Nigeria due to the fact that parents of these adolescents have to consent before they access any form of contraception.

WHO (2018) reported that globally, adolescents, including those on the street, between 15-19 years age group are the most vulnerable to a range of reproductive health problems, such as teenage pregnancy and childbearing, unsafe abortion and sexually transmitted infections (STIs), including HIV. In Nigeria, adolescents constitute about one fifth of the national population, 12% have first childbirth before 15 years, and most of them have become parents before age of 20 years, and suffer from sexually transmitted infections despite the existence of reproductive health services provided and made available and accessible to them (Federal Ministry of Health, 2003; WHO, 2005).

Adolescents go through physical, emotional and psychological changes which is often associated with consequences that require a public health response. This is a period of increased risk-taking and as a result, prone to behavioral problems, as well as sexual and reproductive health problems (Singh, 2004). Adolescents are often disproportionately affected by social and economic inequalities that characterize the development landscape and, as a result, suffer poor health outcomes and negative reproductive health outcomes, such as unintended and premarital pregnancies, unsafe abortions, sexually transmitted infections (STIs) including HIV/AIDS, preterm and unsafe deliveries (Lloyd, 2015).

In Algeria, Bangladesh, Ethiopia, Indonesia and Nigeria the risk of dying from complications related to reproductive health problems is two times higher for those aged 15-19 years than for those in their mid-twenties (Ancil, Gillian & Guillermo, 2014). Singh (2004) reported

the above scenario among adolescents could be as a result of high risky health behaviors together with inadequate means to protect their sexual health. Despite the International Conference on Population and Development (ICPD) Programme of Action of 1994 that encouraged governments to make reproductive health services available, accessible, acceptable and affordable to all adolescents, including those who live and hawk on streets, experience shows the reproductive health may not be utilized fully by adolescents for which the services are provided.

The study therefore was designed to determine: 1. barriers to reproductive health services utilization among adolescent street hawkers, 2. barriers to reproductive health services utilization among male and female adolescent street hawkers and 3. barriers to reproductive health services utilization among adolescent street hawkers based on age. Two hypotheses were posed with gender and age as independent variables.

Theoretical Framework

In 1950, there emerged from the United States Public Health Service a theoretical framework based on social theory to help understand behavioral patterns (Mullen, Hersey, & Iverson, 1987). This approach has been frequently applied to study health behavior, including reproductive and sexual health and is known as the Health Belief Model (HBM). From its original conceptualization, variations to the model have proliferated; usually resulting in more detailed models (Rosenstock, 1988). Theories and frameworks have also been derived from the HBM. The most important theoretical approaches used are: the Social Learning Theory (Bandura, 1977a, 1977b), later re-named as Social Cognitive Theory, the Theory of Reasoned Action (Fishbein & Ajzen, 1975), the Theory of Planned Behavior (Ajzen & Madden, 1986), and more recently, the Interactional Framework (Van Campenhoudt, Cohen, Guizzardi & Hausser, 1997; Ingham & Van Zessen, 1997). Since utilization of any service is based on the behavior of the user and the social cognition of the importance of the service, the HBM fits into the frame of the study.

According to cognitive theories, which the Health Belief Model (HBM) forms part of; the roles of subjective rationales for health-related issues are a function of the subjective values of an outcome, and of the subjective expectations that a particular action will achieve that outcome. In its original formulation, the HBM hypothesized that health related actions depend upon the simultaneous occurrence of three classes of components: 1) the existence of sufficient motivation to make health salient; 2) the belief of a perceived threat to health; and 3) the belief that following a particular health recommendation would be beneficial in reducing the perceived threat (Rosenstock, 1966; Rosenstock, 1974; Becker, 1974; Rosenstock, Stercher, & Becker, 1988).The relationship between these components and behavior is held to be mediated by demographic, structural and enabling factors.

The hypotheses in the HBM are operationalized by four explanatory factors presented in parenthesis as illustrations of factors related to the success of safer sex practices to prevent AIDS: 1. perceived susceptibility of an individual to the health risk (one's perception of the possibility that

unprotected sex would lead to AIDS), 2. perceived severity of the illness if it is contracted (if AIDS is contracted, the likelihood of dying), 3. perceived benefits of strategies for preventing the illness (condom use prevents AIDS) and perceived barriers to effective action (sex with condoms is not pleasurable, condoms are too expensive). These beliefs are likely to influence utilization of reproductive health services among adolescent hawkers.

When it has been applied the predicted power of HBM for explaining reproductive and sexual health risk has been inconsistent. The HBM has been criticized because of its inherent conceptual problems (Janz & Becker, 1984; Vanlandingham, 1993; Rosenstock, Stercher, & Becker, 1988). Some of the most serious are: the failure to consider adequately the bases of variation in an individual's ability both to evaluate the potential consequences of action and to utilize these evaluations; the cost-benefit perspectives may be ill-suited for explaining adolescent reproductive behavior, as age-related influences are ignored; one important social factor not incorporated in the model is the influence of peer groups, which may be an important factor in understanding the reproductive and sexual behavior of adolescents, including those hawking on the street.

Methods

The descriptive cross-sectional survey study was carried out to determine the barriers to reproductive health services utilization among 494 (Male 267, Female 227) adolescent street hawkers in Ebonyi state, Nigeria. All the hawkers who were encountered on the street while hawking and who agreed to provide information were interviewed during the period of the study.

Abakaliki is the capital city and the seat of government of Ebonyi State. Abakaliki is a developing urban settlement with two universities, one college of Education and many secondary schools. The inhabitants of the area are predominantly of the Igbo ethnic group and are mostly farmers and a hand full of civil servants of all cadres. Other inhabitants of the area are students and traders. The town is densely populated with poor housing and drainage system.

Based on World Health Organization's of definition of adolescent; only hawkers who were aged 19 years and below were eligible for inclusion into the study.

Self-developed semi-structured questionnaire tilted: Barrier to Reproductive Health Services Utilization Questionnaire (BRHSUQ) was used to collect data. The questionnaire consisted of 20 items meant to elicit information on the perceived barriers to reproductive health services utilization by the hawkers. The questionnaire contained two sections A and B. Section A contained three items (1-3) on the demographic data of the respondents. Section B contained 17 items meant to measure barriers to reproductive health services utilization of the hawkers. The respondents were required to indicate on a 4-point scale of Strongly Agree (SA), Agree (A), Strongly Disagree (SD), and Disagree (D) on their level of agreement or otherwise to the variables under study

The instrument was validated by five proficient academic staff in health education who are faculty members in two Universities in Southeast Nigeria. Data collected from adolescent street hawkers in Aba, Abia State were used to establish the reliability of the instrument. A reliability coefficient of 0.72 was obtained

using Cronbach alpha measure of internal consistency. The internal consistency was considered high enough for the study based on Ogbazi and Okpala's (1994) suggestion of 0.60 for good instruments.

Data were collected over a period of 8 weeks between July and September 2018 during the long vacation. The adolescent hawkers were recruited into the study while hawking on the streets between 1 and 6pm from Monday to Saturday. Semi structured questionnaire which took about 10-20 minutes to administer was used in interviewing the boys and girls. The questionnaire was administered in vernacular and/or English depending on the level of education and understanding of a given respondent.

Data were analyzed using mean, standard deviation and t-test statistic. Mean and standard deviation were used to describe the data and a criterion mean of 2.50 was set for the study. In this regard any mean up to 2.50 and above was interpreted a barrier to reproductive health services utilization and any mean below 2.50 was interpreted otherwise. The barriers were ranked in order to establish their relative strength. t-test statistic was used to test hypotheses on gender, age and location of residence. An alpha of 0.05 was set for the entire hypotheses.

Results

Table 1: Mean and Standard Deviation on Barriers to Reproductive Health Services Utilization among Adolescent Street Hawkers

Variables	$\bar{x}$	SD	R	Dec.
Do not know about the services	3.11	1.12	1	**B**
Availability of equipment	2.98	1.14	6	**B**
Poor quality of services	3.07	1.06	2	**B**
Inconvenient hours of operation	3.01	1.01	4	**B**
Lack of privacy	3.00	1.01	5	**B**
Confidentiality	3.02	0.97	3	**B**
Long waiting hours	2.98	0.96	7	**B**
Staff attitude and behavior	2.97	0.96	8	**B**
Poor facility structure	2.91	0.97	9	**B**
Services use against my values	2.76	0.04	14	**B**
Services use against my beliefs	2.81	1.05	11	**B**
Location of the facility	2.80	1.00	12	**B**
Preferred by parents	2.79	1.04	13	**B**
Embarrassment associated with use	2.84	1.02	10	**B**
Poor referral system	2.68	1.09	16	**B**
Poor follow-up system	2.67	1.12	17	**B**
Community attitudes towards service	2.69	1.11	15	**B**

R = Rank; B = Barrier

Data in Table 1 show that all the items obtained mean scores of 2.50 implying that all the concepts are barriers to reproductive health services utilization among the adolescent street hawkers. The standard deviations range from 0.04-1.14 an indication that the responses do not deviate too widely. However, 'do not know about the services' ranks 1st among the barriers followed by 'poor quality of services' and 'poor referral system' and 'poor follow-up system' rank 16th and 17th respectively.

Table 2: Mean and t-test Analysis on Barriers to Reproductive Health Services Utilization among Male and Female Adolescent Street Hawkers

Variables	Male (n = 267)		R	Female (n = 227)		R		
	$\bar{x}$	SD		$\bar{x}$	SD		t-value	p-value
Do not know about the services	3.28	1.66	1	3.01	1.18	10	2.095*	0.037
Availability of equipment	3.13	1.04	3	2.81	1.24	15	3.166*	0.002
Poor quality of services	3.06	1.08	4	3.10	1.04	7	0.431	0.666
Inconvenient hours of operation	3.14	0.99	2	3.18	1.05	2	0.195	0.846
Lack of privacy	2.89	1.03	6	3.13	0.99	5	2.635*	0.009
Confidentiality	2.90	0.97	5	3.18	0.96	3	3.139*	0.002
Long waiting hours	2.86	0.99	8	3.14	0.91	4	3.295*	0.001
Staff attitude and behavior	2.85	0.98	9	3.11	0.92	6	3.031*	0.003
Poor facility structure	2.81	1.01	10	3.04	0.93	9	2.183*	0.030
Services use against my values	2.88	2.66	7	2.85	1.26	13	0.113	0.910
Services use against my beliefs	2.81	1.02	11	2.82	1.10	14	0.023	0.981
Location of the facility	2.67	1.01	15	3.28	3.52	1	2.712*	0.007
Preferred by parents	2.72	0.99	12	2.88	1.09	12	1.752	0.078
Embarrassment associated with use	2.71	1.07	14	2.99	0.95	11	3.090*	0.002
Poor referral system	2.63	1.06	16	2.74	1.14	17	1.082	0.280
Poor follow-up system	2.72	2.60	13	2.78	1.13	16	0.346	0.730
Community attitudes towards service	2.60	1.42	17	3.06	2.15	8	2.809*	0.005

** $p < 0.05$*

Results in Table 2 indicate the means and t-test analysis on the barriers to reproductive health services utilization of male and female adolescent hawkers. The data show that both male and female adolescent hawkers perceive all the concepts as barriers to reproductive health services utilization. However, as 'do not know about the services' ranks 1st among males, it ranks 10th among the females and 'inconvenient hours of operation' the ranks 2nd among the males also ranks 2nd among the females but 'location of the facility' that ranks 15th among males ranks 1st among females. When t-test is calculated differences are observed in 'do not know about the services', 'lack of privacy', 'long waiting hours', 'staff attitude and behavior' and 'location of the facility' among others.

Table 3: Mean and t-test Analysis on Barriers to Reproductive Health Services Utilization among Adolescent Street Hawkers according to Age (Years)

Variables	10-14 (n = 288)		R	15-19 (n = 206)		R		
	$\bar{x}$	SD		$\bar{x}$	SD		t-value	p-value
Do not know about the services	3.28	1.59	**1**	2.98	1.24	**11**	2.287*	0.023
Availability of equipment	2.96	1.13	**6**	3.01	1.17	**9**	0.457	0.648
Poor quality of services	3.10	1.03	**3**	3.05	1.10	**7**	0.538	0.591
Inconvenient hours of operation	3.11	2.49	**2**	3.24	2.92	**1**	0.552	0.581
Lack of privacy	2.98	0.99	**5**	3.03	1.06	**8**	0.500	0.617
Confidentiality	3.00	0.89	**4**	3.06	1.08	**6**	0.671	0.503
Long waiting hours	2.92	0.93	**8**	3.09	0.99	**5**	1.951	0.052
Staff attitude and behavior	2.96	0.94	**6**	2.99	0.99	**10**	0.420	0.675
Poor facility structure	2.85	0.97	**10**	3.19	3.02	**3**	1.760	0.079
Services use against my values	2.64	1.09	**16**	3.18	3.02	**4**	2.783*	0.006
Services use against my beliefs	2.73	1.09	**13**	2.93	0.99	**12**	2.111*	0.035
Location of the facility	2.77	0.99	**12**	3.21	3.69	**2**	1.930	0.054
Preferred by parents	2.69	1.06	**14**	2.92	0.99	**13**	2.371*	0.018
Embarrassment associated with use	2.82	1.03	**11**	2.87	1.03	**14**	0.491	0.624
Poor referral system	2.57	1.11	**17**	2.84	1.07	**15**	2.804*	0.005
Poor follow-up system	2.68	2.54	**15**	2.83	1.08	**16**	0.777	0.438
Community attitudes towards service	2.92	2.16	**9**	2.67	1.11	**17**	1.531	0.126

Results in Table 3 indicate the means and t-test analysis on the barriers to reproductive health services utilization of 10-14 years and 15-19 years age groups adolescent street hawkers. The data show that both 10-14 years and 15-19 years age groups adolescent

hawkers perceive all the concepts as barriers to reproductive health services utilization. However, as 'do not know about the services' ranks 1st among the 10-14 years age group, it ranks 11th among the 15-19 years age group and 'inconvenient hours of operation' the ranks 2nd among the 10-14 years age group and also ranks 1st among the 15-19 years age group but 'location of the facility' that ranks 12th among 10-14 years age group, but ranks 2nd among the 15-19 years age group. When t-test is calculated differences are observed in 'do not know about the services', 'services use against my beliefs', 'preferred by parents', and 'poor referral system' among others.

Table 4: Mean and t-test Analysis on Barriers to Reproductive Health Services Utilization among Adolescent Street Hawkers according to Location of Residence

Variables	Urban (n = 280)		R	Rural (n = 214)		R		
	$\bar{x}$	SD		$\bar{x}$	SD		t-value	p-value
Do not know about it	3.23	1.05	**1**	3.05	1.87	**3**	1.291	0.197
Availability of equipment	2.95	1.14	**9**	3.02	1.15	**5**	0.704	0.482
Poor quality of services	3.09	1.00	**4**	3.06	1.14	**2**	0.333	0.759
Inconvenient hours of operation	3.02	0.99	**7**	3.35	3.91	**1**	1.354	0.176
Lack of privacy	3.04	1.01	**6**	2.95	1.02	**7**	0.930	0.353
Confidentiality	3.09	0.93	**4**	2.94	1.02	**8**	1.781	0.075
Long waiting hours	3.05	0.94	**5**	2.91	0.98	**9**	1.646	0.100
Staff attitude and behavior	3.10	0.91	**2**	2.81	0.99	**10**	3.379*	0.001
Poor facility structure	2.98	0.96	**8**	3.02	2.99	**6**	0.230	0.818
Services use against my values	2.93	2.69	**10**	2.78	1.02	**11**	0.784	0.433
Services use against my beliefs	2.87	1.06	**14**	2.74	1.05	**15**	1.302	0.194
Location of the facility	2.88	0.96	**13**	3.05	3.66	**4**	0.773	0.440
Preferred by parents	2.81	1.04	**15**	2.76	1.05	**12**	0.555	0.579
Embarrassment associated with use	2.91	0.97	**11**	2.75	1.09	**14**	1.791	0.074
Poor referral system	2.74	1.13	**16**	2.60	1.06	**17**	1.408	0.160
Poor follow-up system	2.73	1.17	**17**	2.76	2.84	**13**	0.158	0.875
Community attitudes towards service	2.89	1.18	**12**	2.71	2.39	**16**	1.144	0.253

Results in Table 4 indicate the means and t-test analysis on the barriers to reproductive health services utilization of adolescent street hawkers who reside in urban and rural areas. The data show that adolescent hawkers who reside in both urban and rural perceive all the concepts as barriers to reproductive health services utilization. However, as 'do not know about the services' ranks 1st among adolescent hawkers who reside in urban area it ranks 3rd among those residing in the rural area and 'inconvenient hours of operation' the ranks 7th among those residing in the rural area but 'location of the facility' that ranks 13th among those living in the urban ranks 4th among those living in the rural area. When t-test is calculated difference is observed in only 'staff attitude and behavior'.

Discussion

Results in Table 1 showed that adolescent street hawkers in Ebonyi State perceived all the items as barriers to reproductive health. However, they do not know about the service ranked highest among the barriers to reproductive health among adolescent street hawkers in Ebonyi State, followed by poor quality of service. This finding is in line with Federal Ministry of Health (2004) which reported that adolescents in Nigeria do not know about the existence of reproductive health services. The ministry attributed the reason for this to the fact that most of the hospitals in Nigeria where adolescent reproductive health services are sought are mere consulting clinic. The findings appeared to be in line with a study in Zambia on vulnerability and sexual and

reproductive health among Zambian secondary school students that concluded that respondents lacked adequate information about human reproduction and STIs including HIV (Warenius, 2006).

In Table 2, data indicated that both male and female adolescent street hawkers alleged all the concepts as barriers to reproductive health utilization. But 'do not know about the service' ranked 1st among the barriers to reproductive health utilization for male, but ranked 10th among the females. While 'inconvenience hours of operation' ranked 2nd among the males, 'location of facility' ranked 15th among males and 1st among females. When t-test was calculated there were significant differences in 'do not know about the services' (t-value = 2.287, p = 0.023), 'unavailability of equipment' (t-value = 3.166, p = 0.002), 'lack of privacy' (t-value = 2. 635, p = 0.009) among others. The findings were in line with Obonyo (2009) whose findings indicated significant difference in the perceived barriers to reproductive health services utilization such as do not know about the services, unavailability of the equipment, long queues at the facility, facility closure at the time of arrival at the facility, lack of money to pay for the services, staff attitude, preferred by parents, embarrassment associated with sexual reproductive health services, community attitude towards services among male and adolescents college youths in Kenya.

Results in Table 3 indicated that both 10-14 and 15-19 years age groups adolescent street hawkers perceived all the concepts as barriers to reproductive health services utilization. But, 'do not know about the service' ranked highest as a barrier to reproductive health among the adolescent street hawkers aged 10-14 years, it ranked 11th for 15-19 years age group, while 'inconvenient hours of operation' ranked 2nd among 10-14 years age group and ranked 1st among 15-19 years . When t-test was run there were significant differences in 'do not know about the service', 'services use against my beliefs', 'preferred by parents', 'poor referral system', among others. These findings are in agreement with WHO (2010) which reported that in Russian Federation, youth aged 10-14 year olds showed that they are often embarrassed to discuss difficult issues such as contraception or sexually transmitted infections (STIs) than 15-19 years and that differences existed in the reproductive health services utilization with reference to age. These findings confirmed the fact that the older youth are sexually active and have freedom to make their choices and that majority of youth aged 15-19 years made self- decisions when they needed the services and had a tendency to trust and consult their peers more than parents as compared to the younger ones (Senderowtz, 2010).

Results on Table 4 showed that adolescent street hawkers who reside in both urban and rural perceived all the concepts as barriers to reproductive health services utilization. The findings agreed with those of Olukoya (2014) that difficult in the location of the reproductive health services, poor follow-up system, services used against their values and beliefs, they do not know about the facility, poor quality of services were significant barriers to reproductive health services among adolescents. However, do not know about the services ranked 1st among adolescent street hawkers who reside in urban area, it ranked 3rd among those residing in the

rural area and inconvenient hours of operation ranked 7th among those residing in the rural area but location of the facility ranked 3rd among those living in the urban and ranked 4th among those living in the rural area. The t-test results indicated there was significant difference in only staff attitude and behavior.

Conclusion

As adolescents, including those hawking on streets, become sexually active, their access to reproductive health services must increase. Prevention and primary health care services are particularly critical for this population given that the most serious, costly, and widespread adolescent reproductive health problems, unintended pregnancy and sexually transmitted infections, are potentially preventable (Centres for Disease Control and Prevention, 1997). World Health Organization (WHO, 2004) reported that utilization of reproductive health services among adolescents is hindered by poor accessibility, unavailability of services and acceptability of the services, service delivery hours, cost of services, lack of confidentiality and facility organization, lack of clear directions, crowding, lack of privacy, appointment times that do not accommodate young people's work and school schedules, little or no accommodation for walk-in patients, limited services and contraceptive supplies and options calling for referral, and individual factors such as lack of knowledge and attitude of both the health worker and the individual.

Another study (Awoyemi, Obayelu & Opaluwa, 2011) reported inadequate staffing, lack of clear policies and guidelines on youth friendly services provision and inadequate information education, communication, poor quality structure, long waiting hours as barriers to reproductive health (RH) services utilization among adolescents.

The present study confirmed the above circumstances and therefore concluded that the adolescent street hawkers do not utilize the available reproductive health services due to the identified barriers. Mobile health clinic to reach the street hawkers is advocated and should be reintroduced in the health care delivery system. This might breach the barriers thereby improving utilization of reproductive health services among adolescents on the street.

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Conflicts of interest

No conflict of Interest

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Endotoxin Aggression In The Pathogenesis Of Preterm Birth

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Abstract: This article discusses the problem of preterm labor and the pathogenesis of the development of preterm labor. The effects of lipopolysaccharides (LPS) in pathological conditions are numerous and varied. The excessive entry of LPS into the systemic circulation against the background of absolute or relative insufficiency of endotoxin-binding systems leads to the development of toxin aggression, which can be the direct cause of the development of a wide variety of syndromes and diseases. It is possible that bacterial vaginosis is also accompanied by systemic endotoxemia, which goes beyond the physiological one. In women with vaginal dysbiosis, high concentrations of endotoxin (ET) induced the synthesis of pro-inflammatory cytokines (IL-6, etc.) in monocytes of cervical mucus

Key words: Premature delivery, pregnancy, endotoxins, lipopolysaccharides.

The purpose of this study was to determine the possible role of endotoxin aggression in the pathogenesis of preterm labor.

Endotoxin aggression is a pathological process caused by excess of LPS in the systemic blood flow and relative or absolute lack of antiendotoxin immunity (AEI), which has a clinical and laboratory manifestation and is transformed into a particular nosological form of the disease due to genetic and (or) acquired predisposition [1,5,8,].

The terms "lipopolysaccharides" (LPS) and "endotoxin" are not quite identical: the concept of "endotoxin" unites lipopolysaccharide complexes of different molecular masses, localized in the outer membrane of microbial cells, while LPS is a specific substance, thermostab-leheteropolymer with a molecular mass from 200 to 1000 kDa. In its macromolecular structure it is possible to allocate three basic parts: lipid A, central Core fragment (heterooligo-saccharide) and O-antigen. Interaction of O-antigen with antibodies leads to neutralization of endotoxin, binding of the formed complex to receptors on the surface of phagocytic cells, its phago-cytosis and degradation. At the same time it is necessary to note rather weak immunogenicity of bacterial LPS and, accordingly, weak possibility of their neutralization by antibodies [2, 7, 11, 18].

Excessive inflow of LPS into the systemic humus against the background of absolute or relative insufficiency of endotoxins binding systems leads to the development of toxin aggression, which can be a direct cause of the development of a variety of syndromes and diseases; intestinal dysbacteriosis, intestinal infections, sepsis, in-fection toxic shock, acute reactive distress syndrome of adults and children, cirrhosis of the liver, hepatitis, atopycheskogo dermatitis, atherosclerosis, myocardial infarction, chronic heart failure, acute and chronic renal failure, chronic pelvic inflammation, infertility, gestures, pre-eclampsia and eclampsia[3,4,6,12,15,19]. It is possible that bacterial vaginosis is also accompanied by systemic endotoxinemia that goes beyond physiological. In women with vaginal dysbiosis high concentrations of ET induced the synthesis of proinflammatory cytokines (IL-6, etc.) in cervical mucus monocytes [9,13,14,17].

According to M. Yu.Yakovlev [2003], the main reasons for the development of endotoxin aggression (EA) are:

- stress, which causes an additional discharge of portal blood into the shunt (bypassing the liver) into the general hemocirculation;
- insufficiency of the liver barrier, which may be a direct consequence of the metabolic, phagocytic and excretory functions of the liver;
- disturbance of the intestinal barrier, the most frequent cause of which are dysbiotic processes, as well as infection (including viral) and "irritants" that enhance motor skills;
- Immunodeficiency conditions (which, in turn, may be a direct consequence of EA), because the vector of biological action of LPS (useful or pathogenic) is determined not only by its concentration in the humus, but also by the activity of AEI;
- insufficiency of ET-excretory organs and systems (first of all, renal and liver redden).

If physiological doses of ET (less than IEU/ml) get into the bloodstream, there

is a so-called physiological systemic endotoxinemia, which, when the concentration of ET in the bloodstream increases, is transformed into endotoxin aggression, characterized by a wide range of pathogenic effects of ET. Fundamental in the mechanism of participation of intestinal and vaginal LPS in the pathogenesis of syndromes is the ability of EA to cause autoaggressiveness of polymorphonuclear leukocytes (PYAL) and cause a perverse reaction from the side of adaptive immunity directed against their own antigens, which can end up with SIR-syndrome and multiple organ failure [9,10,16,19].

The purpose of this study was to determine the possible role of EA in the pathogenesis of preterm birth.

Material and research methods

68 women between the ages of 20 and 45 (mean age 25.5ë1.3 years) and 28-32 weeks of pregnancy were examined. The comparison group consisted of 20 women with physiological course of pregnancy in the third trimester. The main group consisted of 48 re-continued pregnancies with a severe obstetric history (spontaneous abortions and PR) with intestinal dysbacteriosis and the threat of premature birth. Patients with ICN, uterine abnormalities and myomas were not included in the study. All patients complained of abdominal pain, constipation, malaise, dysuric disorders and genital discharge. The control studies were carried out on 20 conventionally healthy women of the same age.

The presence of pathogenic microflora and mixed infection was detected in 34 (86%) women in vaginal contents by PCR diagnostics. The species composition of microbiocenosis of the vagina and cervical canal of sick women was characterized by the predominance of coccobacillary flora and gardenerrellas. The diagnosis of bacterial vaginosis was established on the basis of clinical and anamnestical parameters and verified by the data of light microscopy of the posterior vaginal smear and determination of vaginal secretion reaction (pH-metry). To describe the microscopic picture of vaginal biocenosis, a light microscopy of gram-painted smears (Lumam-P8, JIOMO, St. Petersburg) was performed. The degree of vaginal dysbiosis was determined microscopically according to the criteria proposed by A.R. Mavzyutov et al. (2001). Later on, bacteriological sowings with quantitative analysis of microbiocenosis were carried out. To assess the level of endotoxinemia and the state of antiendotoxin immunity in the patients of the main and control groups before the beginning of treatment the concentration of lipopolysaccharide (LPS), antibodies of IgG class to soge-region LPS, was determined in plasma before the beginning of treatment. To determine the level of LPS chromogenic LAL-method (Limulus Amebocyte Lysate) at the end point using the test system produced by Biotechnology (Holland). Quantitative determination of human IgG to soge-region LPS in blood plasma was carried out by immunoenzyme method with the help of sets of the company "HUMAN". Quantitative indices obtained in the course of studies were processed by the methods of variation statistics. Statistical processing of the obtained data with the use of software packages "BIO-STAT". The arithmetic mean (M) of the variation series and its average error, coefficient of difference of average values according to the Student's criterion (t), level of its significance (P)

were calculated. The difference was considered reliable at $P < 0.05$.

Results of own researches and their discussion

The level of LPS in plasma of all studied groups of women did not exceed the physiological concentration (0-1 EU/ml, according to the instruction to the test system) and did not differ significantly, averaging 0.48ë0.02 EU/ml in patients with PR against 0.36+0.01 EU/ml in healthy women ($p>0.05$).

The analysis of the research results showed the influence of the intestinal and vaginal dysbiosis factor on the LPS level, where the average level of LPS (0.69+0.56 EU/ ml) was significantly higher ($p<0.05$) than in healthy patients. In pregnant women with physiological course of pregnancy, the studied indicator was on the average equal to (0,46ë0,03 EU/ml. When analyzing the changes in the level of antibodies of the class to soge-region of lipopolysaccharide it was found that their concentration in the blood of patients was significantly higher than in the control group, and strongly depended on the degree of dysbiotic process in the intestine and vagina (1.19ë0.67 EU /ml), whereas in pregnant women with physiological pregnancy it was (0.64ë0.05 EU /ml), in healthy women (0.38ë0.27 EU /ml). As can be seen from the presented results of the studies, we observe a clear dynamics to the decrease in the level of antibodies anticohesion as the dysbiotic process in the intestine and vagina progresses..

Conclusion: Thus, the study showed that bacterial endogenous intoxication from the intestine and vaginal secretion is accompanied by a pronounced endotoxinemia and a decrease in the specific immune response in pregnant women at risk of premature birth, compared with the physiological course of pregnancy and healthy women.

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Determinant Of Financial Performance And Macroeconomic Variables: Evidence From Listed Islamic Banks Pakistan

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Abstract: This study examines the macroeconomic variables of the Islamic bank's financial performance in Pakistan, using 7 years annual time series data from 2011 to 2017. In order to achieve the objectives of the study, Ordinary Least Square (OLS) is used. The test of the study signify that GDP, interest rate and the inflation rate has a positive and significant effect on Islamic banks performance and the other side, exchange rate showed the positive but statistically insignificant effect on Islamic banks performance. It can be concluded that there should be separate interest rate and exchange rate policy develop by the Central bank of Pakistan for Islamic banks so as to ensure maximum profit.

Key words: Islamic banks, Ordinary Least Square (OLS) is used.

Introduction

Globally two strategies are recommended. The first one is known as the Revolutionary strategy which Iran followed in respect of the introduction of Islamic Banking. The second one is an evolutionary strategy which Pakistan announced for introducing Islamic Banking in the country. A similar approach is being followed in Indonesia and Malaysia. State Bank of Pakistan has developed the following four-point strategies relating to the development of Islamic Banking in the country.

Islamic bank offers a wide range of products based on profit and loss according to principles of Shariah. It develops a sense of collective welfare by sharing the risk among different stakeholder. Islamic banks are primarily concerned to eliminate Riba from the economy by the promotion of risk sharing practices for economic prosperity. Islamic banks work within limits prescribed by Shariah to stimulate business and trade activities.

Galbraith (1975) reported, "The best economic system is one that supplies the most of what that most people want." It means that an ideal economic system can meet the expectations of people what they wantin a transparent manner. Islamic economic system is superior because it is based on the principles of justice, transparency, and accountability that ensure substantial economic growth. Islamic bank is beneficial due to its capability to spread risk in the economy among the concerned parities (depositor, banker, borrower, etc. According to their contribution (Siddiqui, 1973).The study suggested that Islamic banks could help to reduce risk to enhance productive activities in the economy. It is reported that different stakeholders dealing with Islamic bank are risk neutral and actively engaged in productive activities according to profit and loss based contracts (Siddiqui, 1973).

Islamic banks affect the monetary system by adjusting the demand and supply forces for money. It is found that the Islamic banking system is superior to the conventional banking system as it ensures a more stable financial sector (Khan, 1986).

Objective of the study

F To find the relationshipof financial performance indicator (NII) net interest income and macroeconomic variables of listed Islamicbanks in Pakistan.

Research Data

The sample of the data comprises on seven years annual time series data which is collected from Islamic banking bulletin published by Central bank of Pakistan along with key macro-economic variables. Time series data has been used FY 2011 to 2017 on annual frequency in this study.

Research Methodology

To find the relationship between financial performance (NII) of listed Islamic banks and Micro economic variables (GDP growth rate, inflation rate, Interest rate & exchange rate)as .The pooled regression model is used to investigate the relationship of these variable and effect on the performance of Listed Islamic banks in Pakistan.

$$NII = \alpha_0 + \alpha_1 GDP_{it} + \alpha_2 INF_{it} + \alpha_3 INT_{it} + \alpha_4 EXH_{it} + \varepsilon_{it}$$

NII= net intersest income (dependent variable)

α_0= consent

GDP= Gross domestic product (independent variable)

INF= Inflation rate (independent variable)

INT= Interest rate T-bill (independent variable)

EXH= Exchange rate (independent variable)

Net interest income (dependent variable)

Net interest income is the difference between the interest income generated by the banks and the amount of interest paid to lender.

Results

Dependent Variable: NII				
Method: Least Square				
Sample: 114				
Included observations: 14				
Variable	**Coefficient**	**Std. Error**	**t-Statistic**	**Prob.**
C	-3.333514	2.011143	-1.657522	0.1318
GDP	34.27441	17.16966	1.99622	0.077***
ER	0.015601	0.013932	1.119792	0.2918
I	0.277864	0.125011	2.222718	0.0533**
IR	13.10709	3.608009	3.632777	0.0055*
R-squared	0.719243	Mean dependent var		3.420684
Adjusted R-squared	0.594462	S.D. dependent var		0.858028
S.E. of regression	0.546408	Akaike info criterion		1.901553
Sum squared resid	2.68706	Schwarz criterion		2.129788
Log-likelihood	-8.310871	Hannan-Quinn criteria.		1.880426
F-statistic	5.764048	Durbin-Watson stat		2.738609
Prob(F-statistic)	0.013948*			

Above Table comprises the observed result of net interest income (NII) based on OLS techniques which shows that the net interest income is dependent variable and GDP, Exchange rate, Interest rate, and Inflation rate are independent variables. The result displays that GDP is significant at 10% level, the Interest rate at 5% level and the Inflation rate is 1% level while the exchange rate is insignificant. The values of coefficient of all macroeconomic variables are positive which shows the positive relationships between dependent and independent variables. The value of F-statistics is significant at 10% level which is mean the model is a good fit.

Conclusion

Banks performance has a measured feature of financial performance in this changing environment. This study has a focus to examine the Islamic bank's financial performance with key macroeconomic variables. The sample of the data comprises on seven years annual time series data which is collected from Islamic banking bulletin published by Central bank of Pakistan along with key macro-economic variables. Time series data has been used FY 2011 to 2017 on annual frequency in this study. OLS method is used to test the long run determinants. Based on empirical findings, we found that Inflation has a positive and significant impact on Islamic banks financial performance. This positive relation reported that Islamic banks in Pakistan are managing their cost well under the increase in inflation increment and obtaining higher financial performance.

The Islamic financial banks are using interest rate only as a benchmark in Pakistan as (Ali 2016). So the impact in our findings is statistically significant, and this relationship is exerting a positive impact on financial performance. As Islamic banks do not offer cash in terms of the loan so when interest rate goes up, Islamic financial institutions raise their profit by increasing their bank charges to their customers. The contribution of the exchange rate in our study is positive and insignificant on Islamic banks financial performance. Increase in exchange rate depreciates the local currency and this change in exchange rate usually gave a negative impact on the banking side. But we have taken Islamic financial environment where they deal foreign exchange trade according to sharia laws. On the other side, Islamic banks have a very small portion of foreign exchange trade along with risk-free transactions and sharia scholars are engaged to develop a model for the arrangement of foreign exchange transactions.

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JOURNAL OF RESEARCH IN HEALTH SCIENCE

Role Of Globalization In Small Industries: Evidence From Talib Engineering Works, Pakistan

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Abstract: This paper has enlightened the importance of globalization for capital companies. Modern technologies and strategies should have to adopt for survival of the companies.Talib Engineering Works have a strong position in market due to its minor monopoly. It maintain its positioning with better strategies and adoption of modernism but it also have a need to adopt the quick processing and high quality mechanisms for production it's not only make a mark for the company but also create a strong hold monopoly in this area.

Key words: Talib Engineering Works, Ratio Analysis, Competency of Product

Introduction to Talib Engineering Works

We want to introduce ourselves as a leading manufacturer and exporter of textile weaving machinery and its parts, The Company was established in the 1974 and since then it has become a brand name in the local market as well as in the markets of Bangladesh, Nepal, Sri Lanka, South Korea and South Africa. Our three thousand looms are running just in Bangladesh.We believe in long lasting buyer seller relationship.

TBEW manufacture Rapier, Auto, Fixed/loose Reed, Towel/Cloth looms, Sectional Warping Machines, Dobie's, pirn winders and cone winders in different sizes along with all types of other textile machinery and allied accessories. The infrastructure of the unit is also fully capable and equipped to opt and execute any kind of engineering project apart from its routine projects.

Under the dynamic leadership of Mr.TalibHussain, a team of dedicated and professional management, qualified, innovative and devoted engineering staff and highly skilled workers and working day and night for the organization.

In due recognition of development of textile machinery locally and producing first Pakistani Automatic cop-change loom, Towel Manufactures Association of Pakistan given us a cash prize of Rs. 200,000/- and commendation certificate. The successful operational trials of automatic cop-change loom was conducted by textile & Research center of Pakistan at Cotton committee building, Karachi.

With the grace of Almighty Allah we are also pioneer of first Rapier shuttle less loom in Pakistan. In this field we have developed shuttle less (rapier) loom for Terry Towel, silk and Grey cloth with the provision of jacquard driving system in different sizes.

Talib Brothers Engineering Works is situated at an area of 66000 square feet. Besides our management team; more than one hundred qualified engineers, technicians and supporting staff are working round the clock to achieve excellence in the textile engineering.

Company introduction

Talib Engineering Works is one of the leading engineering manufacturing groups in Pakistan. It is a vertically integrated group with operations in all sectors of the engineering works from melting of cast iron to a loom. The annual turnover of the group is around 300 million Pakistani rupees. Talib Engineering Works provide employment opportunities to about 200 families. It has a capital product and market portfolio. Talib Engineering works hold a special position in the engineering industry in the sense that it provides the variety of looms to its customers under one roof.

The manufacturing processes are certified on ISO 9001:2000 standards. Talib Engineering works is a quality conscious company; it has a well define policy towards quality. This policy is the driving force behind achieving the quality of the products produced in Talib Engineering.

Talib Engineering Works is only one Association of its own nature, no competitor of the association is available in the domestic market. 4 top engineering companies also worked in Pakistan but these companies produce different product related to National Engineering Services Pakistan (broadcasting services), DESCON Engineering (fertilizer, chemical, power, cement, textile and

manufacturing etc.), Zishan Engineering Private Limited (oil, gas, petrochemicals, water, power, generation and various other industrial sector), Batala Engineering Company (rolled products, electric products, pump, turbines and foundry product etc.). But Talib Engineering works produced towel looms which not produced by any other engineering company so company face rare threats of competition.

Our philosophy is to create a single channel for satisfying diverse and high class needs of our valued partners. We are highly flexible in responding to dynamic needs of our customers. We have a set of truly devoted professionals who focus on their areas of specialties to produce highly valued products. We believe in partnership not only with our customers but also with our employees who have proved to be a key in maintaining the highest level of excellence in our outputs.

Opportunities:

Global demand of engineering products for established a new set up. Current and Future Thrust of the engineering industry:

- Up-gradation of quality of products
- Switch over to value addition
- Use of quality raw materials
- Balancing modernization and replacement of obsolete plant and equipment
- Professional & Business Ethics
- Meeting schedules and reducing delivery times
- Maintaining price competitiveness
- Promoting economic blocs and international joint ventures

Pakistan is currently implementation an ambitious strategic plan for the engineering industries which contributed 5% of total Gross Domestic Product (GDP) till 2005 to upgrade its operating facilities to effectively meet the present and future challenges of global marketTalib Engineering Works is also one of them.

- Switch over to value addition
- Use of quality raw materials
- Balancing modernization and replacement of obsolete plant and equipment
- Professional & Business Ethics
- Meeting schedules and reducing delivery times

Investment policy and incentives:

- Whole of engineering sector is included in the list of value added industries.
- 5% customs duty on imported machinery if not manufactured locally.
- Tex relief: initial Depreciation Allowance (IDA) @50% of machinery & equipment cost.

Above incentive are also available if 50% of annual production is exported.

2.3 VISION AND MISSION STATEMENT

2.3.1 VISION STATEMENT: Our vision is to provide our customers' capital product for a new set up so that country and nation earn a lot of foreign exchange.

2.3.2 MISSION STATEMENT: Our mission is to become the buyer's first choice all around the world and to achieve this target we make sure that we stay true to the highest standards of excellence and customer's satisfactions.

Organizational hierarchy chart

4.1 PRODUCTS

4.1.1Terry Towel Rapier Loom

Shedding

DTM-900T series can be fitted with the dobby machine (up to 24levers). For the dobby shedding, 18 levers are available for heald frames and 6 levers for control functions of higher or lower pile section, weft selection and take-up stop motion.

Warp Stop Motion

Electric warp stop motion has been used for pile and ground so that loom stops when warp threat is broken.

Selvedge

Independent leno motion can be employed.

Weft Insertion

The head of rapier is designed to be adjustable in the gripping strength of the weft yarn according to its type, which ensures safe insertion of the weft yarn. The tape guide on the sley is also ideally engineered for holding the clearance from the top and bottom faces of the tapes at the optimum state, which prevents the tapes from breaking the warp yarns due to touching on their driving.

Let-off For Pile Beam

As the letting-off from the pile beam, operated by the electronic pile sensor, is automatically controlled by a separate brake motor and the electronic clutch, the over-tension has the loom stopped safely.

Let-off For Ground Beam

The letting-off brake wheel, driven by can be connected with the main shaft of the loom, is controlled by the brake lining. The tension lever controlling the warp tension ensures proper letting-off of the ground beam through automatic stop of the loom in the event of abnormal tension by controlling the revolutions of brake lining.

Rapier Drive

The special gear designed for the most stable insertion and high speed drive enable the precise movements of the rapier for weft insertion by means of the minimized rotating clearance of the rapier wheel s. this is due to the forward and reverse drive by the lever of high tension which are featuring the latest mechanism in structure of its kind. As a result, the noise and vibration and the transfer of the weft at a high speed is affected without errors and the weft tension gets evenly maintained.

Jacquard Rapier Loom

Shedding

DTM-900J series can be fitted with the jacquard machine.

Warp Stop Motion

Electric warp stop motion has been

used so that loom stops when warp thread is broken.

Selvedge

Independent leno motion can be employed.

Weft Insertion

The head of the rapier is designed to be adjustable in the gripping strength of the weft yarn according to its type, which ensures safe insertion of the weft yarn. The tape guide on the sely is also ideally engineered for holding the clearance from the top and bottom faces of the tapes at the optimum state, which prevents the tapes from breaking the warp yarn due to touching on their driving(Jordan, Kemper et al. 2018).

Let-off For Ground Beam

The letting-off brake wheel, driven by can be connected with the main shaft of the loom, is controlled by the brake lining. The tension lever controlling the warp tension ensure proper letting-off the beam through automatic stop of the loom in the event of abnormal tension by controlling the revolution of brake lining.

Rapier Drive

The special gear designed for the most stable insertion and high speed drive enable the prices movements of the rapier for weft insertion by means of minimize rotating clearance of the rapier wheels. This is due to the forward and reverse drive by the lever high tension which is featuring the latest mechanism in structure of its kind. As a result, the noise and vibration are reduced and the transfer of the weft at a high speed is affected without errors and the weft tension gets evenly maintained(Zefrehyee, Tehran et al. 2015).

Automatic Cop-Change Grey Cloth Loom

There are different models of automatic cop-change grey cloth loom and every machine has its own working time according to per minute. Cop-change system is rotary type hopper magazine and hopper capacity is 24 cops (Pourdeyhimi and Jackson 1968). Left hand handling position and loose reed system of wrap protection is major feature of this loom. Shuttle size and power to drive are varying from machine to machine in respect of the size of machines.

Some other local product of association is also given below:

- TERRY TOWEL DROP BOX LOOM
- SECTIONAL WARPING MACHINE
- VERTICAL WEFT PIRN WINDER
- HORIZONTAL WEFT PIRN WINDER
- HANKS TO CONE AND CONE TO CONE WINDER etc.

Division

The major company products are power loom and rapier loom. As the other products machinery also goes through a process, machinery process a bit complex other than textile products and so many other products which produced the basic need products.

The raw material used for production consists of two basic head major raw material and minor raw material. Firstly major material consists on cast iron, sand and Ms' product (angle channel, MS Patti, MS round bar, tooling of shafts, iron molding (pure iron) electronic ferns)

Secondly, minor components are bars, plastics, wood, electronic components, Motors, electronic panels etc. This purchased from within Faisalabad and some product of MS steeling labor and Karachi. There are four major steps of product process.

1 Muolding/Foundry
2 Cooling
3 Assembling
4 Paint line

Moulding/ Foundry

First of all, the cast iron melts in the electronic ferns at high degree. When cast iron completely melted and changed into liquid form than by using the Kupla oven melted cast iron and moasis mixed completely in shake form. Liquid form material poured in the different patterns as you need for the completion of product(Prasad and Ratna 2018) and (Salonitis, Zeng et al. 2016).

Cooling

In the second step of the patterns are still remain at room temperature almost 4-5 hours. After the specific time the components are pick out from the patterns. Iron not take more cooling pouter for shopping, at the room temperature iron changed itself in solid form(Pourdeyhimi and Jackson 1968).

Assembling

Finishing product of cooling process used as the raw material for assembling process. Now all the components although major or minor aggregate for assembling.

According to the need the products components collected and minor molding process repeated but it is not similar to foundry/molding process. Some special tools are used to molding or shaping so that components joined properly in form of a machine(Greenwood and Vaughan 1956). A lot of tooling machines are used but the intensively used "Khraad" and "Shaper" machine which are used for dug holes and create a proper shape of component. According to blue print or sample components that prepared within the company or imported from outside of company fixed such as sample(Greenwood and Vaughan 1956).

Paint Line

After completion of product use a specific spray which painted inner side of machine so that the internal components shun form the rust and make sure smooth working of machine. After internal paint, it paint properly again in second coat internal or external, stumped on the company logo(Zefrehyee, Tehran et al. 2015).

Power loom is totally local product but rapier loom is completed after using some imported components like Dobby etc. from china.

SWOT ANALYSIS

Association has no competitor in the market within country boundary, Talib Engineering Works a monopolistic company. Its monopoly is the strength of company if any association or engineering company tries to compete the Talib Engineering Works so, the association's SWOT analysis is may give below:

Strengths

- ISO 9001 certification.
- WRAP certified.
- Vertically integrated
- Highly qualified products.
- Adequate financial resources.
- Competitive advantage.
- Adopting information technology.
- Recruitment on merit.
- Loyal customers.
- Skilled labor.
- Broad and motivational vision.
- Back track system.

Weaknesses

- Increased employee turnover.
- Centralized management system.
- High cost of production.
- Low production capacity
- De-motivated staff

- Less promotion activities
- Non cooperative culture
- Insufficient benefits for the employees.
- Stereotype machinery for processing

Opportunities

- Can expand its divisions
- Can introduce its own label in domestic and international market
- Can capture new market segment
- Full potential of entering the local market
- Can reduce the cost by proper utilization of resources
- End of quota restrictions
- Can hire well educated and experienced staff
- Globalization
- Communicational gap among different departments

Threats

- Entry of new competitors just like china
- Buyer needs and demand change
- political instability
- Changing geopolitical situation
- Change of Govt. policies
- Low price offered by competitors& Globalization

Financial statement
Talib Brothers Engineering Works
BALANCE SHEET
AS ON JUNE 30, 2014

Current assets:	**2012**	**2013**	**2014**
Stock in trade	1975640	2556412	3756437
Trade debt	000	21524	91460
Deposit and prepayment	6561930	508603	2670165
Cash&bank balance	26222822	10253746	6863315
Total current assets	**34760392**	**13340285**	**13381377**
Fixed assets:			
Property and equipment	2,331,00.00	2,331,00.00	2,331,00.00
Building	3,276,500.00	3276500.00	7278331.00
Plant & Machinery	4,662,875.00	4662875.00	4662875.00
Furniture & Fixture	55,440.00	554400.00	196310.00
Electric Installation	17,318,50.00	2981850.00	3100160
Tools and Equipment	45,245.00	45245.00	45245.00
Less: Accumulated Dep. (relevant year)	4,691,307.00	5254052.00	5712069.00
Total fixed assets	**5313703.00**	**6000958.00**	**9803952.00**
Long-term Deposits & Securities	512274.00	727459.00	740518
Total other assets	**512274.00**	**727459.00**	**740518.00**
Total assets	**40586369.00**	**20068702.00**	**23925847.00**

Balance Sheet (Liabilities)
Talib Brothers Engineering Works
BALANCE SHEET
AS ON JUNE 30, 2014

EAQUITY&LIABILITIES	2012	2013	2014
Share Capital& Reserved			
Owner's Equity	17000000.00	17000000.00	17000000.00
Accumulated Profit	997293.00	484096.00	1482100
	17997293.00	17484096.00	18482100.00
CUIRRENT LIABILITIES			
Trade Creditors	1075600.00	900600.00	725366.00
Advance from Buyers	8531080.00	1148400.00	2672416.00
Accrued Charges	2532396.00	235606.00	1645965.00
Provision For Taxation	450000.00	300000.00	400000.00
Total Current LIABALITIES	12589076.00	2584606.00	5443747.00
Total Liabilities	**40586369.00**	**20068702.00**	**23925847.00**

Income Statement
Talib Brothers Engineering Works
INCOME STATEMENT
AS ON JUNE 30, 2014

Particulars	2012	2013	2014
Sales	36543360.00	19299403.00	31364363.00
Cost Of Sales	(29349223.00)	(15462216.00)	(25650145.00)
Gross Profit	**7194137.00**	**3837187.00**	**5714218.00**
Administration, Selling & Distribution Expenses	4478067.00	2490481.00	3692690.00
Financial Charges	254813.00	112064.00	5066.00
Selling Expenses Relating to the Export	1000584.00	536190.00	0000.00
Operating Profit (Before Tax and Interest)	1460673.00	698452.00	2016462.00
Other Operating Expense (W.W.F)	(15763.00)	(4269.00)	(40329.00)
Provision for Taxation	(447616.00)	(210087.00)	(494033.00)
Net Profit	997293.00	484096.00	14820100.00

VERTICAL ANALYSIS

(Also known as common-size analysis) is a popular method of financial statement analysis that shows each item on a statement as a percentage of a base figure within the statement. To conduct a vertical analysis of balance sheet, the total of assets and the total of liabilities and stockholders' equity are generally used as base figures. All individual assets (or groups of assets if condensed form balance sheet is used) are shown as a percentage of total assets. The current liabilities, long term debts and equities are shown as a percentage of the total liabilities and stockholders' equity. To conduct a vertical analysis of income statement, sales figure is generally used as the base and all other components of income statement like cost of sales, gross profit, operating expenses, income tax, and net income etc. are shown as a percentage of sales.

In a vertical analysis the percentage is computed by using the following formula:

Percentage of base=amount of individual item/amount of base *100

A basic vertical analysis needs an individual statement for a reporting period but comparative statements may be prepared to increase the usefulness of the analysis

Vertical analysis

BALANCE SHEET (ASSETS)
Talib Brothers Engineering Works
BALANCE SHEET
AS ON JUNE 30, 2014

Current assets:	**2012**	**2013**	**2014**
Stock in trade	4.8	13.00	133818716
Trade debt	0	0.11	0.4
Deposit and prepayment	16.17	3.0	11.2
Cash & bank balance	64.61	51.09	29
Total current assets	**86**	**67**	**56**
Fixed assets:			
Property and equipment	0.11	0.23	0.189
Building	8.07	16.32	30
Plant & Machinery	11.48	23.23	20
Furniture & Fixture	0.137	0.28	0.22
Electric Installation	4.27	15	13
Office Equipment	0.57	1.20	0.97
Less: Accumulated Dep. (relevant year)	11.55	26.18	23.87
Total fixed assets	**13**	**30**	**41**
Long-term Deposits & Securities	1.262	3.62	3.09
Total assets	**100%**	**100%**	**100%**

Vertical analysis
Balance Sheet (Liabilities)
Talib Brothers Engineering Works
BALANCE SHEET
AS ON JUNE 30, 2014

EAQUITY&LIABILITIES	2012 %	2013 %	2014 %
Owner's Equity	42	85	71
Accumulated Profit	2.45	2.41	6.19
	44	87.41	77.19
CUIRRENT LIABILITIES			
Trade Creditors	2.65	4.49	3.03
Advance from Buyers	21	6	11.16
Accrued Charges	30.87	1.17	7
Provision For Taxation	1.11	1.50	1.67
Total Current LIABALITIES	56	13.16	22.86
Total Liabilities	**100%**	**100%**	**100%**

Vertical analysis
Income Statement
Talib Brothers Engineering Works
INCOME STATEMENT
AS ON JUNE 30, 2014

Particulars	2012 %	2013 %	2014 %
Sales	100	100	100
Cost Of Sales	(80.31)	(80.12)	(82)
Gross Profit	**19.69**	**19.88**	**18**
Administrative, Selling & Distribution Expenses	(12.25)	(12.90)	(11.78)
Financial Charges	(0.697)	(0.58)	(0.020)
Selling Expense Relating to Export	(2.74)	(2.77)	-
Operating Profit	**3.997**	**3.63**	**6.20**
Other Operating Expense W.W.F	(0.043)	(0.022)	(0.129)
Provision For Taxation	(1)	(1)	(7)
Net Profit For The Year After Taxation	(1.225)	(1.088)	(1.575)
Net Profit	**2.73**	**2.52**	**4.75**

HORIZONTAL ANALYSIS

Horizontal analysis (also known as trend analysis) is a financial statement analysis technique that shows changes in the amounts of corresponding financial statement items over a period of time. It is a useful tool to evaluate the trend situations.

The statements for two or more periods are used in horizontal analysis. The earliest period is usually used as the base period and the items on the statements for all later periods are compared with items on the statements of the base period. The changes are generally shown both in dollars and percentage.

Dollar and percentage changes are computed by using the following formulas:

Dollar change=amount of item in comparison year-amount of item in base year

Percentage change=dollar change/amount of the item in base year *

Horizontal analysis may be conducted for balance sheet, income statement, schedules of current and fixed assets and statement of retained earnings.

HORIZONTAL ANALYSIS
Balance Sheet (Assets)
Talib Brothers Engineering Works
Balance Sheet
As On June 30,2014

Assets	**2014-13%**	**2013-2012%**
Current assets:		
Stock in trade	46.94	29.39
Trade debt	324.92	0
Deposit and prepayment	425	-0.922
Cash & bank balance	-33.07	-60.89
Total current assets	**0.31**	**-61.62**
Fixed assets:		
Property and equipment	0	0
Building	122.13	0
Plant & Machinery	0	0
Furniture & Fixture	254	0
Electric Installation	3.96	72.17
Office Equipment	3.96	0
Less: Accumulated Dep.(relevant year)	8.717	11.995
Total fixed assets		
Long-term Deposits & Securities	1.795	42
Total assets	**-50.55**	**19.22**

HORIZONTAL ANALYSIS
Balance Sheet (Liabilities)
Talib Brothers Engineering Works
BALANCE SHEET
AS ON JUNE 30, 2014

EAQUITY&LIABILITIES	2013-2014 %	2012-2013 %
Owner's Equity	0	0
Accumulated Profit	-51.45	206.160
CUIRRENT LIABILITIES		
Trade Creditors	752.84	-19.45
Advance from Buyers	-86.54	132.71
Accrued Charges	-90.70	598.61
Provision For Taxation	-33.33	33.33
Total Liabilities	-50.55	19.22

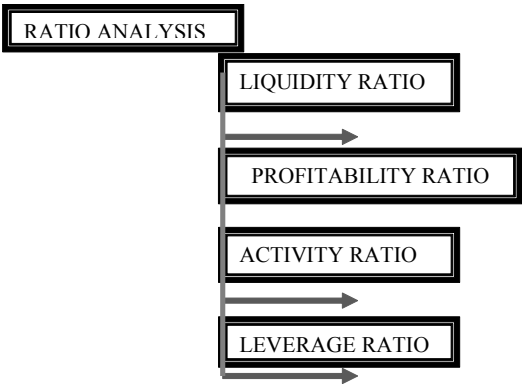
HORIZONTAL ANALISIS

Income Statement
Talib Brothers Engineering Works
INCOME STATEMENT
AS ON JUNE 30, 2014

Particulars	2014-13	2013-12
Sale	62.51	-47.19
Cost Of Sale	65.89	-47.32
Gross Profit	**48.92**	**-46.66**
Operating Expenses		
Administrative, Selling & Distribution Expenses	48.27	-44.38
Financial Charges	-95.48	-56.02
Selling Expense Relating to Export		**-46.41**
Operating Profit	**188.70**	**-52.18**
Other Operating Expense W.W.F	844.69	-72.92
Provision For Taxation	135.16	-53.07
Net Profit For The Year After Taxation	206.16	-51.46

RATIO ANALYSIS

Ratio Analysis Is One Of The Techniques Of Financial Analyst Where Ratio Are Used As A Yardstick For Evaluation The Financial Condition And Performance Of A Firm. Analysis And Interpretation Of Various Accounting Ratio Gives Skilled And Experience Analyst A Better Understanding Of The Financial Condition And Performance Of The Firm Than What He Could Have Obtained Only Through A Perusal Of Financial Statement



LIQUIDITY RATIO

Liquidity Ratio may refer to: Liquidity ratio, expresses a company's ability to repay short-term creditors out of its total cash. The liquidity ratio is the result of dividing the total cash by short-term borrowings. It shows the number of times short-term liabilities are covered by cash. If the value is greater than 1.00, it means fully covered. Common liquidity ratios include the current ratio, the quick ratio and the operating cash flow ratio. Different analysts consider different assets to be relevant in calculating liquidity. Some analysts will calculate only the sum of cash and equivalents divided by current liabilities because they feel that they are the most liquid assets, and would be the most likely to be used to cover short-term debts in an emergency.

A company's ability to turn short-term assets into cash to cover debts is of the utmost importance when creditors are seeking payment. Bankruptcy analysts and mortgage originators frequently use the liquidity ratios to determine whether a company will be able to continue as a going concern:

1. Current ratio

2. Quick ratio

CURRENT RATIO

From Wikipedia, the free encyclopedia

The current ratio is a financial ratio that measures whether or not a firm has enough resources to pay its debts over the next 12 months. It compares a firm's current assets to its current liabilities. It is expressed as follows:

Current ratio=current Assets/ current liabilities

The current ratio is an indication of a firm's market liquidity and ability to meet creditor's demands. Acceptable current ratios vary from industry to industry and are generally between 1.5 and 3 for healthy businesses. If a company's current ratio is in this range, then it generallyindicates good short-term financial strength. If current liabilities exceed current assets (the current ratio is below 1), then the company may have problems meeting its short-term obligations. If the current ratio is too high, then the company may not be efficiently using its current assets or its short-term financing facilities(Awasthi et al). This may also indicate problems in working capitalmanagement. Low values for the current or quick ratios (values less than 1) indicate that a firm may have difficulty meeting current obligations. Low values, however, do not indicate a critical problem. If an organization has good long-term prospects, it may be able to borrow against those prospects to meet current obligations. Some types of businesses usually operate with a current ratio less than one. For example, if inventory turns over much more rapidly than the accounts payable become due, then the current ratio will be less than one. This can allow a firm to operate with a low current ratio (Allen and Henshaw, 1990).

If all other things were equal, a creditor, who is expecting to be paid in the next 12 months, would consider a high current ratio to be better than a low current ratio, because a high current ratio means that the company is more likely to meet its liabilities which fall due in the next 12 months. You should view the relation between the operation cycle period and the current ratio.

Current assets:	**2012**	**2013**	**2014**
Stock in trade	1975640	2556412	3756437
Trade debt	000	21524	91460
Deposit and prepayment	6561930	508603	2670165
Cash & bank balance	26222822	10253746	6863315
Total current assets	**34760392**	**13340285**	**13381377**

CUIRRENT LIABILITIES			
Trade Creditors	1075600.00	900600.00	725366.00
Advance from Buyers	8531080.00	1148400.00	2672416.00
Accrued Charges	2532396.00	235606.00	1645965.00
Total Current LIABALITIES	**5043747**	**2284606**	**2213076**

Particulars	**2014 Rs**	**2013 Rs**	**2012 Rs**
Current Assets	34760392	13340285	13381377
Current Liabilities	5043747	2284606	2213076
Ratio	**2.653**	**5.838**	**1.571**

Current Ratio interpretation

Current ratio gives an idea of company's operating efficiency. A high ratio indicates "safe" liquidity, but also it can be a signal that the company has problems getting paid on its receivable or have long inventory turnover, both symptoms that the company may not be efficiently using its current assets

Quick ratio

In finance, the Acid-test or quick ratio or liquid ratio measures the ability of a company to use its near cash or quick assets to extinguish or retire its current liabilities immediately. Quick assets include those current assets that presumably can be quickly converted to cash at close to their book values. A company with a Quick Ratio of less than 1 cannot currently fully pay back its current liabilities.

Quick ratio=cash and cash equivalent+ Marketable securities+ Accounts receivable/ current liabilities

Note that Inventory is excluded from the sum of assets in the Quick Ratio, but included in the Current Ratio. Ratios are tests of viability for business entities but do not give a complete picture of the business' health. If a business has large amounts in Accounts Receivable which are due for payment after a long period (say 120 days), and essential business expenses and Accounts Payable due for immediate payment, the Quick Ratio may look healthy when the business is actually about to run out of cash. In contrast, if the business has negotiated fast payment or cash from customers, and long terms from suppliers, it may have a very low Quick Ratio and yet be very healthy. Generally, the acid test ratio should be 1:1 or higher; however this varies widely by industry. In general, the higher liquid ratio shows the greater the company's liquidity (i.e., the better able to meet current obligations using liquid assets).

Notice that very often "Acid test" refers to Cash ratio, instead of Quick ratio:

Acid test ratio= (current Assets- Inventory)/current liabilities

Current assets:	**2012**	**2013**	**2014**
Stock in trade	1975640	2556412	3756437
Trade debt	000	21524	91460
Deposit and prepayment	6561930	508603	2670165
Cash & bank balance	26222822	10253746	6863315
Total current assets	**34760392**	**13340285**	**13381377**
Less inventory	1975640	2556412	3756437
Liquid Assets	32784752	10783873	9624940

Particulars	**2014 Rs**	**2013 Rs**	**2012 Rs**
Quick Assets	32784752	10783873	9624940
Current Liabilities	5043747	2284606	2213076
Ratio	**6.50**	**4.72**	**4.349**

Quick Ratio interpretation

Quick Ratio is an indicator of company's short-term liquidity. It measures the ability to use its quick assets (cash and cash equivalents, marketable securities and accounts receivable) to pay its current liabilities.

Quick ratio specifies whether the assets that can be quickly converted into cash are sufficient to cover current liabilities. Ideally, quick ratio should be 1:1.

If quick ratio is higher, company may keep too much cash on hand or have a problem collecting its accounts receivable. Higher quick ratio is needed when the company has difficulty borrowing on short-term notes. A quick ratio higher than 1:1 indicates that the business can meet its current financial obligations with the available quick funds on hand. A lower quick ratio than 1:1 may indicate that the company relies too much on inventory or other assets to pay its short-term liabilities. Many lenders are interested in this ratio because it does not include inventory, which may or may not be easily converted into cash.

Activity Ratios

Activity ratios are used to measure the relative efficiency of a firm based on its use of its assets, leverage or other such balance sheet items. These ratios are important in determining whether a company's management is doing a good enough job of generating revenues, cash, etc. from its resources. Companies will typically try to turn their production into cash or sales as fast as possible because this will generally lead to higher revenues. Such ratios are frequently used when performing fundamental analysis on different companies. The total assets turnover ratio and inventory turnover ratio are two popular examples of activity ratios used widely across most industries

Leverage Ratio

1. Any Ratio Used To Calculate The Financial Leverage Of A Company To Get An Idea Of The Company's Methods Of Financing Or To Measure Its Ability To Meet Financial Obligations. There Are Several Different Ratios, But the Main Factors Looked At Include Debt, Equity, Assets and Interest Expenses.

2. A Ratio Used To Measure A Company's Mix Of Operating Costs, Giving An Idea Of How Changes In Output Will Affect Operating Income. Fixed And Variable Costs Are The Two Types Of Operating Costs; Depending On The Company And The Industry, The Mix Will Differ.

Debt And Debt-To-Equity Ratios

Two Of The Most Popular Calculations, The DebtRatioAnd Debt-To-Equity Ratio, Rely On Information Readily Available On The Company's Balance Sheet. To Determine The Debt Ratio, Simply Divide The Firm's Total Liabilities By Its Total Assets:

Debt Ratio = Total Liabilities / Total Assets

A Figure Of 0.5 Or Less Is Ideal. In Other Words, No More Than Half of the Company's Assets Should Be Financed By Debt. In Reality, Many Investors Tolerate Significantly Higher Ratios. Capital-Intensive Industries Like Heavy Manufacturing Depend More On Debt Than Service-Based Firms, For Example, And Debt Ratios In Excess Of 0.7 Are Common.

As Its Name Implies, the Debt-To-Equity Ratio Instead Compares The Company's Debt To Its Stockholder Equity. It's Calculated As Follows:

Debt-To-Equity Ratio = Total Liabilities / Stockholders' Equity

If You Consider The Basic Accounting Equation (Assets - Liabilities = Equity), You May Realize That These Two Equations Are Really Looking At The Same Thing. In Other Words, A Debt Ratio Of 0.5 Will Necessarily Mean A Debt-To-Equity Ratio Of 1. In Both Cases, A Lower Number Indicates A Company Less Dependent On Borrowing For Its Operations.

While Both These Ratios Can Be Useful Tools, They're Not without Shortcomings. For Example, Both Calculations Include Short-Term Liabilities In The Numerator. Most Investors, However, Are More Interested In Long-Term Debt. For This Reason, Some Traders Will Substitute "Total Liabilities" With "Long-Term Liabilities" When Crunching The Numbers.

Definition of 'Debt Ratio'

A Financial Ratio That measures The Extent of A Company's Or Consumer's Leverage. The Debt Ratio Is Defined As The Ratio Of Total Debt To Total Assets, Expressed In Percentage, And Can Be Interpreted As The Proportion Of A Company's Assets That Are financed by Debt.

$$\text{Debt Ratio} = \frac{\text{Total Debt}}{\text{Total Assets}}$$

The Higher This Ratio, the More Leveraged the Company andthe Greater Its Financial Risk. Debt Ratios Vary Widely Across Industries, With Capital-Intensive Businesses Such As Utilities And Pipelines Having Much Higher Debt Ratios Than Other Industries Like Technology. In The Consumer Lending And Mortgage Businesses, Debt Ratio Is Defined As The Ratio Of Total Debt Service Obligations To Gross Annual Income.

Debt Ratio			
Particulars	**2014 RS**	**2013 RS**	**2012 RS**
Total Debt(Long)	0	0	0
Total Debt(Short)	5043747	2284606	22139076
Total Assets	23925847	20068702	40586369
Ratio	0.211	0.411	0.545

Analysis

Debt Ratio ranges from 0.00 to 1.00. Lower Value Of Debt Ratio Is Favorable And A Higher Value Indicates That Higher Portion Of Company's Assets Are Claimed By It Creditors Which Means Higher Risk In Operation Since The Business Would Find It Difficult To Obtain Loans For New Projects. Debt Ratio of 0.5 means that half ofthe Company's Assets Are Financed through Debts.

Definition of 'Debt/Equity Ratio'

A Measure ofA Company's Financial Leverage Calculated By Dividing Its Total Liabilities By Stockholders' Equity. It Indicates What Proportion Of Equity And Debt The Company Is Using To Finance Its Assets.

Note: Sometimes Only Interest-Bearing, Long-Term Debt Is Used Instead Of Total Liabilities In The Calculation.

Also Known As The Personal Debt/Equity Ratio, This Ratio Can Be Applied To Personal Financial Statements As Well As Corporate Ones.

Long Term Debt To Share Holder Equity Ratio			
Particulars	2014 RS	2013 RS	2012 RS
Total Liabilities	23925847	20068702	40586369
Equity	17000000	17000000	17000000
Ratio	**1.41**	**1.18**	**2.39**

Interpretation:

A High Value Of This Ratio Is Bad News For A Company As It Cuts Into The Profits And Weighs Heavily On The Overall Finances. On The Other Hand, A Low Debt-To-Equity Ratio Indicates That The Company Is In Overall Good Health And Is A Comparatively Better Stock Investment Option, As Debts Are Not Cutting Into Its Profits To A Large Extent. A Ratio Of 1 Or 1: 1 Means That Creditors And Stockholders Equally Contribute To The Assets Of The Business.

A Less Than 1 Ratio Indicates That The Portion Of Assets Provided By Stockholders Is Greater Than The Portion Of Assets Provided By Creditors And A Greater Than 1 Ratio Indicates That The Portion Of Assets Provided By Creditors Is Greater Than The Portion Of Assets Provided By Stockholders.

Creditors Usually Like A Low Debt To Equity Ratio Because A Low Ratio (Less Than 1) Is The Indication Of Greater Protection To Their Money. But Stockholders Like To Get Benefit From The Funds Provided By The Creditors Therefore They Would Like A High Debt To Equity Ratio.

Debt Equity Ratio Vary From Industry To Industry. Different Norms Have Been Developed For Different Industries. A Ratio That Is Ideal For One Industry May Be Worrisome For Another Industry. A Ratio Of 1: 1 Is Normally Considered Satisfactory For Most Of The Companies.

Profitability Ratios

A profitability ratio is a measure of profitability, which is a way to measure a company's performance. Profitability is simply the capacity to make a profit, and a profit is what is left over from income earned after you have deducted all costs and expenses related to earning the income. The formulas you are about to learn can be used to judge a company's performance and to compare its performance against other similarly situated companies.

Profitability ratios show how much profit the company takes in for every dollar of sales or revenues. They are used to assess a business's ability to generate earnings as compared to expenses over a specified time period

- Profitability ratios are used to compare companies in the same industry, since profit margins will vary widely from industry to industry.

- Taxes should not be included in these ratios, since tax rates will vary from company to company.

- the profit margin shows the relationship between profit and sales and is mostly used for internal comparison.

Types of Profitability Ratios

Common profitability ratios used in analyzing a company's performance include gross profit margin (GPM), operating margin (OM), return on assets (ROA) ,return on equity (ROE), return on sales (ROS), and return on investment (ROI). Let's take a look at these in some detail.

Gross Margin

Gross margin tells you about the profitability of your goods and services. It tells you how much it costs you to produce the product. It is calculated by dividing your gross profit (GP) by your net sales (NS) and multiplying the quotient by 100:

Gross Margin = Gross Profit/Net Sales x 100

Gross Profit Margin Ratio			
Particulars	**2014 Rs**	**2013 Rs**	**2012 Rs**
Gross Profit Margin Ratio	5714218	3837187	7194137
Sale	31364363	19299403	36543360
Ratio	18.21%	19.88%	19.69%

Operating Margin

Operating margin takes into account the costs of producing the product or services that are unrelated to the direct production of the product or services, such as overhead and administrative expenses. It is calculated by dividing your operating profit (OP) by your net sales (NS) and multiplying the quotient by 100:

Operating Margin = Operating Profit/Net Sales x 100

Operating Margin			
Particulars	**2014 Rs**	**2013 Rs**	**2012 Rs**
Operating Income	1460673	698452	2016462
Sale	31364363	19299403	36543360
Ratio	4.65%	3.61%	5.52%

Return on Assets/assets

This metric measures how effectively the company produces income from its assets. You calculate it by dividing net income (NI) for the current year by the value of all the company's assets (A) and multiplying the quotient by 100:

Return on Assets = Net Income/Assets x 100

Return On Investment/Assets			
Particulars	**2014 Rs**	**2013 Rs**	**2012 Rs**
Net Profit	1482100	484096	997293
Total Assets	23925847	20068702	40586369
Ratio	6.195%	2.41%	2.45%

Return on Equity

Return on equity measures how much a company makes for each dollar that investors put into it. You calculate it by taking the net income earned (NI) by the amount of money invested by shareholders (SI) and multiplying the quotient by 100:

Return on Equity = Net Income/Shareholder Investment x 100

Return On Equity			
Particulars	**2014 RS**	**2013 Rs**	**2012 RS**
Net Profit	1482100	484096	997293
Equity	17000000	17000000	17000000
Ratio	8.72%	6.91%	5.86%

Net Profit Margin/return on sale

The profit margin ratio, also called the return on sales ratio or gross profit ratio, is a profitability ratio that measures the amount of net income earned with each dollar of sales generated by comparing the net income and net sales of a company. In other words, the profit margin ratio shows what percentage of sales are left over after all expenses are paid by the business.

Creditors and investors use this ratio to measure how effectively a company can convert sales into net income. Investors want to make sure profits are high enough to distribute dividends while creditors want to make sure the company has enough profits to pay back its loans. In other words, outside users want to know that the company is running efficiently. An extremely low profit margin would indicate the expenses are too high and the management needs to budget and cut expenses.

The return on sales ratio is often used by internal management to set performance goals for the future.

Net profit /return on sale			
Particulars	**2014 Rs**	**2013 Rs**	**2012 Rs**
Net profit	1482100	484096	997293
Sale	31364363	19299403	36543360
Ratio	4.73%	2.50%	2.73%

Net Profit Margin interpretation

Net profit margin is a key financial indicator used to assess the profitability of a company.

Net profit margin formula is:

$$\text{Net Profit Margin} = \frac{\text{Net profit (after taxes)}}{\text{Net Sales}} \times 100$$

Net profit margin measures how much of each dollar earned by the company is translated into profits. A low profit margin indicates a low margin of safety: higher risk that a decline in sales will erase profits and result in a net loss.

Net profit margin provides clues to the company's pricing policies, cost structure and production efficiency. Different strategies and product mix cause the net profit margin to vary among different companies.

Net profit margin is an indicator of how efficient a company is and how well it controls its costs. The higher the margin is, the more effective the company is in converting revenue into actual profit.

Net profit margin is mostly used to compare company's results over time. To compare net profit margin, even between companies in the same industry, might have little meaning. For example, if a company recently took a long-term loan to increase its production capacity, the net profit margin will significantly be reduced. That does not mean, necessarily, that the company is less efficient than other competitors.

Trend Analysis

Trend Analysis Is Also Called Time-Series Analysis. Trend Analysis Helps A Firm's Financial Manager Determine How The Firm Is Likely To Perform Over Time. Trend Analysis Is Based On Historical Data From The Firm's Financial Statements And Forecasted Data From The Firm's Pro Forma, Or Forward-Looking, Financial Statements. One Popular Way Of Doing Trend Analysis Is By Using Financial Ratio Analysis. If You Calculate Financial Ratios For A Business Firm, You Have To Calculate At Least Two Years Of Ratios In Order For Them To Mean Anything. Ratios Are Meaningless Unless You Have Something To Compare those To, In This Case Other Years Of Data. Trend Analysis Is Even More Powerful If You Have and Use Several Years of Financial Ratios

Sales Trend

2014-13	2013-12
79.43%	-15.12%

Sale in 2013 Decrease 15% According 2012 And In 2014 Sale Increase 79.43% Rather Than 2013 So It Is Beneficial For Organization Indication

PROFITABILITY RATIOS

Gross Margin

Gross Profit Margin Ratio			
Particulars	**2014 Rs**	**2013 Rs**	**2012 Rs**
Gross Profit Margin Ratio	5714218	3837187	7194137
Sale	31364363	19299403	36543360
Ratio	18.219%	19.882%	19.687%

Gross Profit Margin Interpretation

It shows that gross profit margin decreasedcontinuously.

Return on Assets/Assets

This Metric Measures shows that The Company Produces Income from Its Assets efficiently which was 2.45% in 2012 and increase to 6.19% in 2014 this result shows the better performance.

Return on Equity

Return on Equity Measures shows A Company Makes for Each rupees That Investors Put into it.It increase 8.718% in 2014 according to2012 it shows that shareholder more earn from their equity with the passage of time

Net Profit Margin/Return on Sale

Net Profit Margin Interpretation

Net Profit Margin Is A Key Financial Indicator Used To Assess The Profitability Of A Company.

Net Profit Margin Measures How Much of Each Rupees Earned By the Company Is Translated Into Profits. If we see in 2012 it was 2.73% and increase 2.50% in 2013 but in 2014 it increased reach at 4.725% so profit margin on each rupees increase sufficiently.

Balance sheet

Total Assets	2014-13	2013-12
Ratio	19.22%	-50.55%

Assets of Talib Brothers Engineering Worksfirstly Decrease In 2013 But In 2014 It Increase 32%

Total Liabilities	2014-13	2013-12
Ratio	19.22%	-50.55%

Liabilities of Talib Brothers Engineering WorksContinuously TrendtoIncrease Which Reached 19% in2014 andIncrease Rapidly

Current Ratio

Current Ratio Interpretation

Current Ratio Gives An Idea Of Company's Operating Efficiency. Current ratio decrease it shows that unsafe liquidity but it also shows that company has not face any problem in paid on its receivable because its assets more than its liabilities.

CONCLUSION

It's Period of Globalization, Any Organization Or institute who Ignore the Element of Globalization Automatically Kick Out From the Market(Zefrehyee, Tehran et al. 2015) .Only Those Can Be Survive Who Compete This Global Market Perfectly.Talib Brothers Engineering Works has a strong position in the overall textile industry. Due to the good quality of cotton in Pakistan, there is a high opportunity of making creativity in textile sector, hence of high margin of profit the Talib Brothers Engineering Works is striving its best to avail this opportunity.

RECOMMENDATIONS

So as HR manager I recommend a solution for the Talib Brothers Engineering Works That if they want to compete in this global village and take edge over their competitors than they must focus on their human resources which is very important and precious for any organization because if the employee of the company are satisfied than they become more productive for the organization: and organization gain more and move from its business. So for the satisfaction of Talib Brothers Engineering Works Employees the management should take the following steps immediately:

- Increment in basic pay
- Annual increment from 5% to 8% according to their job responsibilities

- Annual Bonus ,and Double pay for over time
- Give some relaxation in timing
- Provide the medical facility and SSC to every employee after1 years rather than 3
- Working condition must be good
- Provide transportation facility free of cost to the employee

SUGGESTIONS

- Employees should be empowered
- To decentralize the management system
- To strive for high quality with minimum cost
- Employees should be motivated with different means
- Promotional activities should be made more effective
- Employees should be given sufficient benefit
- Create competitors edge
- IT and other technological system should be helpful to tackle buyer needs and demand
- Products should be of international standard

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Pharmacovigilance: A Program In Practice

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Abstract: An organized Adverse Drug Reaction monitoring program is one mechanism to more actively detect ADRs, and consequently positively affect the quality of patient care. To prevent or lessen harm to patients and improving public health, the various mechanisms for evaluating and monitoring the safety of medicines in clinical use are important. In Clinical practice this implies having in place a well-organized Pharmacovigilance system.Pharmacovigilance is an important exercise for monitoring of drug related issues after marketed in "real world setting". Pharmacovigilance and all drug related issues are important for everyone whose life is being impacted any way by medical interventions. The evolution of Pharmacovigilance in recent years has growing importance as a science critical to effective clinical practice and public health science. The national Pharmacovigilance centers have become a significant influence on the drug regulatory authorities, at a time when drug safety concerns have become increasingly important in public health and clinical practice. In this paper, we will briefly explain the role of Pharmacovigilance in health care.

Key words: Pharmacovigilance, Adverse drug reactions, Quality of life

What is Pharmacovigilance?

Drug Post-marketing surveillance programs are essential in every country for monitoring the occurrence of ADRs, as the data derived from within the country may encourage national regulatory decision making. These programs may contribute to decrease in morbidity, mortality, hospitalization and healthcare costs, and liability associated with ADRs. Majority ADRs often go unrecognized or unreported. An organized ADR monitoring program is one mechanism to more actively detect ADRs, and consequently positively affect the quality of patient care [1]. To prevent or lessen harm to patients and improving public health, the various mechanisms for evaluating and monitoring the safety of medicines in clinical use are important. In Clinical practice this implies having in place a well-organized Pharmacovigilance system. Pharmacovigilance in the early 1990s was entirely about monitoring adverse drug reactions and hence was defined as "The detection in the community of drug effects, usually adverse. Pharmacovigilance maybe passive (the collection of spontaneous reports) or active (structured) where patients and prescribers are recruited and surveyed"'[2-3].The WHO defines Pharmacovigilance as the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism andtraditional medicines with a view to identifying new information about hazards associated with medicines and preventing harm to patients [4].Pharmacovigilance has been elucidatedas: "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem[5]. Pharmacovigilance is an important exercise for monitoring of drug related issues after marketed in "real world setting". Pharmacovigilance and all drug related issues are important for everyone whose life is being impacted any way by medical interventions. The evolution of Pharmacovigilance in recent years has growing importance as a science critical to effective clinical practice and public health science. The national Pharmacovigilance centers have become a significant influence on the drug regulatory authorities, at a time when drug safety concerns have become increasingly important in public health and clinical practice. Pharmacovigilance is now firmly based on strong scientific principles and is basis to effective clinical practice. The discipline needs to develop further to meet public expectations and the demands of modern public health [6-7].

Pharmacovigilance is aimed at:

- Improving patient care and safety in relation to the use of medicines and all medical and paramedical interventions,
- Improving public health and safety in relation to the use of medicines,
- Contributing to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including costeffective) use, and
- Promotion of understanding, education and clinical training in pharmacovigilance and its effective communication to the public [8].

Need for Pharmacovigilance:

Not everything is known about a medicine when it receives its license for marketing. The merits of a new drug, balancing its beneficial and its untoward

effects become established only after sufficient experience has been gained from its use in real practice [9].The reasons for the necessity of Pharmacovigilance are:

- Information on drug safety collected during drug development is incomplete as preclinical drug development processes involve the evaluation of drug safety and efficacy in animal experiments and often it may not be appropriate to extrapolate the results of animal experiments to human
- Clinical trials are evaluated for limited duration and limited numbers of carefully selected patients in carefully selected settings and so it is extremely difficult to accurately determine actual efficacy, adverse effects and total risk-benefit ratio under actual clinical setting
- information is often incomplete or not available on
- Rare but serious reactions
- Use of drugs in vulnerable groups (pregnant women, children, geriatric)
- Risks of long term, repeated use and drug-drug, drug-food, drug-nutritional supplement interactions
- At the time of licensing, the drug is exposed to less than 5,000 human subjects. This allows only the most common ADRs to be detected

F At least 30,000 people are required to be treated with a drug to be sure not to miss at least one patient with an ADR which has an incidence of 1 in 10,000 exposed individuals [9].

REGULATORY PHARMACOVIGILANCE

Various stakeholders have been integral to the development of Pharmacovigilance. The authorities, both at the national and increasingly at the international level, have initially helped fostered the field. Labelled as regulatory Pharmacovigilance by Waller et al., they define pharmacovigilance as 'the process of evaluating and improving the safety of marketed medicines'[10]. They underlined the responsibilities the various governments have in the monitoring of drug safety, which task many national governments took firmly in hand following the thalidomide tragedy.The contributionof the WHO stands out here. The flagshipprogramme was launched under the auspices of the WHO by 10 countries in 1968, resulting in the WHO International Drug Monitoring Programme [11-14].Strong regulatory arrangements provide the base for a national ethos of medicine safety, and for public confidence in medicines. To be effective, the scope of drug regulatory authorities needs to go further than the approval of new medicines, to encompass a wider range of issues relating to the safety of medicines, such as; Clinical trials , safe use of complementary and traditional medicines, vaccines and biological medicines and arrangement of communication between all parties which have an interest in safety of medicines, ensuring that they are able to function efficiently and ethically, particularly at times of crisis.

To achieve their respective objectives, Pharmacovigilanceprogrammes and drug regulatory authorities must be mutually supporting of each other. On one hand, Pharmacovigilanceprogrammes need to maintain strong links with the drug regulatory authorities to ensure that the latter are well briefed on safety related problems in everyday clinical practice, whether these problems and issues are related to future regulatory action .On the other, regulators need to understand the

specialized and pivotal role that Pharmacovigilance plays in ensuring the ongoing safety of medicines[6].

PHARMACOVIGILANCE IN DRUG REGULATION [15]

Pharmacovigilance programs have been made powerful by collaborating with regulators. As per Regulators, Pharmacovigilance could play a specialized and crucial role in ensuring ongoing safety of medicines[15].

Pharmacovigilance in Clinical trial regulation: There has been a tremendous enhancement in the number of clinical trials in developed and developing countries in these years. During the approval of these trials, regulatory bodies ensure safety and efficacy of new medicinal products under investigation. Assessment of Safety of medicines in common use should be a crucial part of clinical practice. A regular flow of knowledge and exchange of ideas in this way means that national pharmacovigilanceprogrammes are ideally placed to identify challenges in our understanding of ADRs[16].

Pharmacovigilance in Post marketing safety drug monitoring: It encompasses assessment of drug interactions, measuring the burden of medicines used in large masses after they have been marketed, assessing the contribution of 'inactive' constituents to the safety profile, systems for comparing safety of identical medicines, observation of the adverse effects on human health of drug residues in animals[17].

Pharmacovigilance in national drug Policy: Providing good quality, safe and effective medicinal products and their proper use is the responsibility of national governments.Interdisciplinary association is of prime importance in particular; collaboration needs to be done between different authorities of the ministry of health and also with other partners, such as the pharmaceutical industry, universities, NGOs and those professional associations having important role in ensuring safe and rational use of medicinal products.

Pharmacovigilance in Disease Control Public Health Programmes: Monitoring safety of medicines in nations where there is no regulatory or safety monitoring system in usage, or in remotest areas having little accessibility to health care or infrastructure, has been identified as a challenge. The issues are especially visible in cases that involve the use of medicines in specific communities viz for the treatment of tropical diseases such as malaria etc., and for the treatment of HIV/AIDS and tuberculosis. Pharmacovigilance should be a matter of utmost priority for every nation with a public health disease control programs[15-17].

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Markers Of Nonspecific Inflammation in Prediction The Patients With Acute Coronary Syndrome

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Abstract: Methods of study and evaluation of nonspecific inflammation markers in prediction the patients with acute coronary syndrome (ACS) have been observed in this research.

During the experiment, diagnosis of ACS was established on the base of ESH/SSC (2015) classification criteria. All patients have been undergone clinical, laboratory, instrumental and special investigation. Interconnected findings enable the prediction of risk of ACS↑ST/AMI with Q, ACS↑ST/AMI without Q and ACS ACStrNS development, clinical prediction, early diagnostics and prompt urgent medical aid.

Keywords: prediction, acute coronary syndrome, nonspecific inflammation markers, early diagnostics.

The high frequency of acute coronary syndromes (ACS) indicates a lack of knowledge of the pathogenetic and prognostic role of various factors in the development of this disease. One of the most important factors in the pathogenesis of ACS is the cardiovascular risk markers play a special role. The most significant (key) among them are immune responses, nonspecific inflammation markers, markers of myocardial damage and markers of cardiovascular diseases adverse outcomes [1; 2; 3; 4]. However, the role of primary inflammation mediators and their relation to impaired catecholamine metabolism (CM) in the development of ACS or adverse outcomes in patients with this pathology has not yet been fully evaluated. The study and/or development of these issues can provide up-to-date information for the diagnosis, assessment, severity of ACS [5; 6; 7]. Literature data suggests that the pathogenetic mechanisms underlying cytokin-induced disorders in ACS are not quite clear. To date, issues of pathogenesis, clinical and diagnostic features and therapeutic and rehabilitation aspects for improving the effectiveness of treatment that considers cytokines, non-specific markers of inflammation, predictors of early myocardial damage of unfavorable prognosis

(PAPP-A NT-proBNP)

are insufficiently studied. Studies aimed at solving these issues seem to be a relevant issue. The aim of the study was the analysis and comparative assessment of nonspecific inflammation markers and some predictive factors in patients with acute coronary syndrome.

Materials and methods

149 patients with ACS admitted to the Andijan State Medical Institute clinic and Republican Scientific Center of Emergency Medical Care participated in the study. ACS diagnosis was established using ESH/ESC (2015) classification. The criteria for participation in the study were: characteristic anamnestic and clinical signs in men and women aged 25–75 years who signed an informed consent to participate in the study. The exclusion criteria for the patients were: acute inflammatory and infectious diseases, exacerbation of chronic inflammatory diseases, symptomatic hypertension, acute disorders of cerebral circulation, acquired and congenital heart defects, rheumatism, cardiomyopathy, pericarditis, myocarditis, endocarditis, oncological and hematological diseases. The control group consisted of 20 healthy individuals. Urine sampling to determine the daily catecholamines (CA) excretion and blood sampling was performed on the 1 day of admission to the hospital. On day 1, all patients underwent clinical laboratory and instrumental examination as a basic procedure: determination of CA in daily urine and serum, lipid factors, nonspecific inflammation markers (interleukins IL-6, IL-10, tumor necrosis factor TN-α, C-reactive protein hsCRP), matrix metalloproteinase (PAPP-A) and brain natriuretic peptide (NT-proBNP) in serum. The comparison of the studied values was carried out between the main groups of patients (control, ACS) and between subgroups of the main group: ACS↑ST/AMI with Q(acute coronary syndrome/myocardial infarction with ST elevation with Q wave); ACS↑ST/AMI without Q (acute coronary syndrome/myocardial infarction with ST elevation without Q wave); ACSTUA (acute coronary syndrome with transformation to unstable angina).

All studies were performed in accordance with Good Clinical Practice standards and Microsoft Excel 2010 statistical processing principles. Arithmetic and relative values (M), mean error and relative values (M), Student's coefficient (t), Student's t-test statistical differences significance (P), as well as the correlation coefficient (r) were calculated. Differences in values between means are significant at $p < 0.05$. Significance of differences between groups was found using the Mann-Whitney test.

Results and discussion

Elevated levels of IL-6 and IL-10 were determined in all three groups of patients with ACS (48.9%, 16.7%, 38.2%, respectively). An increased concentration of cytokines with a relatively high frequency is determined in patients with ACS↑ST/AMI with Q (I-group), which exceeds the valuesof patients with ACS↑ST/AMI without Q (II-group) and ACSTUA (III-group) from 6.5 up to 1.2 times ($p<0.001$). Comparison of nonspecific inflammation markers in patients with ACS, depending on age, also showed some interesting data. The obtained data as a whole correspond in general with the data present in the world literature and confirm the existence of a relation with age and hypercytokinemia. For example, IL-6 and IL-10 values in patients with ACS ST/AMI with Q increase with age and this process looks like this: if in the age group of 30–39 years old IL-6 and IL-10 averaged–162±66.8 and 7.9±4.8 pg/ml, in the patients group aged 40–49 years its levels are 166.1± 10.9 and 8.0±0.6 pg/ml respectively (with an increase of 1.2 and 0.9 times; $p>0.05$), in 50–59–183.9 ± ± 20.8 and 10.1±0.7 pg/ml (with an increase of 1.2 and 1.4 times; $p_2<0.05$) in 60–69–200.0 ± 16.0 and 110.0 ± ± 0.6 pg/ml (with an increase of 1.2 and 1.5 times; $p_1<0.05$, $p_2< 0.05$), in>70 years – 229.8±8.3 and 12.8±0.4 pg/ml (with an increase of 1.4 and 1.8 times; $p_1<0.05$, $p_2<0.01$). The increase in cytokine indices was also observed in the group of patients with ACS ST/AMI without Q: the detectability of elevated levels of IL-6 and IL-10 increases from 3.4 times ($p < 0.001$) to 1.8 times ($p < 0.01$) with an increase in age. The lowest mean value of cytokines was determined in patients with ACSTUA from 8.5±1.1 to 29.2±1.6 pg/ml and from 4.2 to 8.3 pg/ml, IL-6 and IL-10 respectively.

However, there is a significant increase in the mean IL-6 values with age by 3.4 times ($p < 0.01$) and a statistically significant increase in the mean level and IL-10 by 1.9 times in patients with ACSTUA. Significant differences in groups of women and men by ACS categories were identified. The serum cytokines in patients with ACS were characterized by relatively higher levels in women than in men.

Comparative assessment of TNFα and hsCRP in serum in healthy and patients with ACS showed that in patients with ACS↑ST/AMI with Q, the levels of TNFα and CRP were 115.4 ± 3.2pg/ml and 6.7 ± 0.1 pg/ml, which is respectively 15.4 times ($p < 0.001$) and 6.1 times ($p < 0.001$) more than control values. The lesser trends were endured in the group of patients with ACS↑ST/AMI without Q. For example, the mean level of TNFα in patients was 29.5 ± 1.8 pg/ml, which is 4.1 times higher ($p < 0.001$) than control values, and the mean value of hsCRP was 4.8 0.1 mg/ml, which is 4.4 times higher ($p < 0.001$) than control values.

We noted a statistically significant, compared with groups of patients with ACS↑ST/AMI without Q, but a less significant increase in TNFα and hsCRP in patients with ACSTUA: TNFαin the blood was 19.7 ± 1.0 pg/ml, what is 2.7 times

higher than the control, and the mean level of hsCRP was 6.7 + 0.1 mg / ml, which is more than 6.2 times higher than the control ($p < 0.001$).

We noted that the mean values of TNFα, hsCRP in patients with ACS significantly increase with age statistically, which is most pronounced in groups I and II of patients with ACS. It would not be an exaggeration to note that according to our data, TNFα and hsCRP have a special place among clinical and laboratory tests in patients with ACS. This is primarily due to their special properties, such as acute phase reactants.

The obtained data correspond to the results of other researchers, confirming the existence of a relation between TNFα, hsCRP, ACS. The findings also confirmed that the rates of both TNFα and hsCRP are characterized by higher levels among women with ACS than men. In general, the relation between a combination of ACS↑ST/AMI without Q and ACSTUA with the main nonspecific inflammation values was found, which have rational specific features and require

research and analysis in population data.

It is known that the hyper-PAPP-A state (>10 mm E/l) is a sensitive marker of atherosclerotic plaque inflammation, which may be the cause of ACS and therefore the determination of this value significance can be used to diagnose acute coronary events.

We have studied and assessed the PAPP-A value in the serum of patients with ACS. The results of the study showed that the mean PAPP-A value in patients with ACS↑ST/AMI with Q was significantly increased and amounted to 9.8 ± 0.2 μg/l, which is 49 times more than the control values ($p < 0.001$). The content of PAPP-A in patients with ACS↑ST/AMI without Q and ACSTUA was also significantly increased: thus, the level of PAPP-A in patients with ACS↑ST/AMI without Q was 5.1 ± 0.2 μg/l, which is 25 times higher than the value of the control group ($p < 0.001$). Lower rates of PAPP-A were observed in patients with ACSTUA, averaging 1.9 + 0.1 μg/l, which is 9.5 times higher than the control group ($p < 0.001$). The data obtained by us makes it obvious that age is quite a powerful factor in the development of ACS against the background of pronounced changes in the concentration of PAPPA in the blood toward a sharp increase. This trend is observed in all groups of patients with ACS. In all groups of patients, PAPP-A in the blood is higher in women than in men. For example, the average PAPP-A level in the group of men and women with ACS↑ST/AMI with Q was 9.4 ± 0.3 and 11.3 ± 0.2 μg/ml, respectively ($p < 0.05$), which statistically significantly higher than the control (0.2±0.04 and 0.2 ± 0.03) by 47.0 and 57.0 times ($p < 0.001$).

The average level of PAPPA in male and female patients with ACS↑ST/AMI without Q was –5.0 ± 0.0 and 45.6 ± 0.1 μg/ml ($p < 0.05$), which is 25.0 and 58.0 times the control level ($p < 0.001$). In general, groups of men and women with ACS were characterized by a pronounced increase in blood readings of PAPP-A At the same time, in the group of female patients with ACS↑ST/AMI with Q, ACS↑ST/AMI without Q and ACSTUA, significantly higher levels of PAPP-A were observed.

Among the important factors in the pathogenesis of ACS, a special role is played by the brain sodium-uretic peptide (NT-proBNP). At the same time, the participation

of this factor in the development of ACS has not been studied enough. Therefore, the next task of our work was the study of NTproBNP values in the serum of patients with ACS. It should be noted that our version of the role of NTproBNP in ACS initially to a certain extent receives its statistically reliable confirmation. For example, the mean value of NT-proBNP in patients with ACS↑ST/AMI with Q was 87.0 ± 3.1 pg/ml, which is 5.6 times more than the control ($p < 0.001$).

In patients with ACS↑ST/AMI without Q, the average content of NT-proBNP was also significantly higher (55.0 ⊥ ⊥ 2.8 pg/ml) than in the control group (15.6 ⊥ 2.8 pg/ml) by 3.5 times ($p < 0.001$). In the group of patients with ACSTUA, it is also obvious that the average content of NT-proBNP is significantly higher, amounting to 30.6 ± 1.6 pg/ml, which is 23.0 times higher than the control ($p < 0.01$).

It should also be noted that the version confirms the diagnostic value of NT-proBNP, in both men and women with ACS. In patients with ACS↑ST/AMI with Q, the highest increase in the level of NT-proBNP was observed in women than in men (105.7 ± 4.0 pg/ml versus 82.0 ± 3.5 pg/ml) ($p < 0.01$).

In patients with ACS↑ST/AMI without Q, the highest increase in the level of NT-proBNP in women was also 966.2 ± ± 2.2 pg/ml versus 51.1±3.3 pg/ml ($p< 0.05$).

Table 1. -NT-proBNP values in in the serum of patients with ACS by age

Age (years)	NT-proBNP		
	ACS↑ST/AMI with Q (n=67)	**ACS↑ST/AMI without Q** (n=25)	**ACSTUA** (n=57)
30–39	75.4 ± 32.7	25.5 ± 14.1***	8.7 ± 2.1°°°
40–49	66.9 ± 4.4	25.5 ± 1.4***	27.8 ± 3.5°°
50–59	86.5 ± 7.6	55.6 ± 3.8***	31.3 ± 2.2°°°
60–69	93.6 ± 5/7	61.7 ± 4.0***	32.1 ± 5.3°°°
>70	106.6 ± 2.9	64.2 ± 1.8***	38.6 ± 1.8°°°

* significance of $p < 0.05$ between ACS↑ST/AMI groups with and without Q;

** significance of $p < 0.01$ between ACS↑ST/AMI groups with and without Q;

*** significance of $p < 0.001$ between ACS↑ST/AMI groups with and without Q;

° significance of $p < 0.05$ between ACS↑ST/AMI without Q and ACSTUA groups;

°° significance of $p < 0.01$ between ACS↑ST/AMI without Q and ACSTUA groups;

°°° significance of $p < 0.001$ between ACS↑ST/AMI without Q and ACSTUA groups.

The data in the table show that the NT-proBNP in patients with ACS↑ST/AMI with Q, depends on the age of patients: it increases from 75.4 ± 32.7 pg/ml (30–39 years) to 106.6 2.9 pg/ml (>70 years), which is 1.4 times higher ($p<0.01$). The patients group with ACS↑ST/AMI without Q, the level of NT-proBNP also increases with age from 25.5 + + 14.1 pg/ml (30–39 years old to 64.2+1.8 pg/ml (>70 years),

which is 2.5 times higher ($p< 0.001$). In patients with ACSTUA, lower values were observed in the patients group of 30–39 years old (8.7 ± 2.1 pg/ml) and 40–49 years old (27.8 ± ± 3.5 pg/ml), higher levels of NT-proBNP were observed in the groups of patients with ACSTUA – 50–59 years (31.3 ⊥ ⊥ 2.2 pg/ml), 60–69 years (32.1 ⊥ 5.3 pg/ml) and >70 years (38.6 ± 1.8 pg/ml). Total increase of the NT-proBNP in patients with ACSTUA is 4.4 times ($p < 0.001$).

In summary, a strong relation between the levels of NTproBNP and the formation of ACS was discovered. NTproBNP is an important pathogenetic link in the development of all clinical forms of ACS.

Conclusion

In summary, it was shown that the following correlated hyper states are seen in ACS patients as leading risk factors: hypercytokinemia (IL-6, IL-10), hyper-CRP-nemia, hyper-PAPP-A-nemia, and hyper-NT-proBNP-nemia. They are in a strong direct (in patients with ACS↑ST/AMI with Q), moderate (in patients with ACS↑ST/AMI with Q), and weak (ACSTUA) correlation dependance on the level of other risk factors for patients with ACS. The nature of these relations is complex and cannot be viewed as definite proof of cause and effect relations, since these issues are the subject of long-term epidemiological and randomized studies. Consequently, our results can serve as objects of further research at the population Level in different regions of the country. However, following the detected logic of the ACS development, we can assume that the correlative values of these studied factors can predict the risk of the development of ACS. The results of the study can be used to identify high-risk groups for the development of ACS↑ST/AMI with Q, ACS↑ST/AMI without Q and ACSTUA, optimizing the strategy of clinical prognosis of early diagnosis and therapeutic and preventive interventions.

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Diagnosis And Differential Diagnosis Of Pandas Syndrome

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Abstract: In order to develop a differential diagnostic algorithm, a comparative analysis of clinical manifestations, laboratory and neuroimaging features of PANDAS syndrome, "small" chorea and CNS intoxication was carried out on the example of examination of 89 children aged 6 to 16 years with tickosehypercinesis. Availability of BGSGA against the background of normative parameters of leukocytes, SDS and RF determine the development of neuropsychiatric disorders in the patient group "PANDAS". Morphometric differences of the "PANDAS" group are characterized by the presence of changes in the form of convulsive readiness at EEG.

Keywords: PANDAS, SDS and RF.

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) is a chronic condition associated with the sudden onset of obsessive-compulsive disorders, ticks and other related diseases in children.

PANDAS syndrome is often mistaken for neuropsychiatric disorders, and many authors view it as a stand-alone condition. However, patients with diagnosed PANDAS often did not respond well to standard tick therapy or obsessive-compulsive syndrome, but showed rapid improvement with penicillin, plasmapheresis, corticosteroids, or immunoglobulin treatment [2, 3].

Currently, scientific research on this problem is devoted to the study of the causal relationship between streptococcal infection and PANDAS. However, the existence of PANDAS is not yet considered proven, and the sensitivity and specificity of its criteria require special research.

Thus, the contradictory views on the etiology and pathogenesis of the disease, the variability of clinical manifestations, similarity with other neurological manifestations dictate the need for a detailed and comprehensive study of this issue from a neurological standpoint.

Objective of the study: to develop a differential diagnostic algorithm for PANDAS syndrome, "small" chorea and CNS intoxication.

Materials and methods of investigation: in order to develop a differential diagnostic algorithm, a comparative analysis of clinical manifestations, laboratory and neuroimaging features of PANDAS syndrome, "small" chorea and CNS intoxication was carried out on the example of examination of 89 children aged 6 to 16 years with tick-borne hypercinesis.

The studied clinical groups included 37 children suffering from PANDAS syndrome, 27 children with CNS intoxication and 25 children with small chorea. The control group consisted of 20 healthy children, comparable to patients by sex and age. These children underwent targeted clinical and neurological, laboratory and instrumental examinations.

The diagnosis was based on the results of clinical and neurophysiological (EEG, computerized and magnetic resonance imaging), biochemical and microbiological studies.

The main group included patients with simple and complex motor and vocal tickerkinesis. Among them there were 61 boys (68,5%) and 28 girls (31,5%), the average age was 9,9±0,34 years.

Based on the current understanding of the nature of hyperkinetic syndromes in childhood and adolescence, as well as the existing and previously voiced syndromes - PANDAS [9], PITANDAS [4] and the recently proposed term PANS [5, 8], we selected the following patients.

In terms of gender participation, the first group consisted of 22 male and 15 female patients (50.5% and 40.5%, respectively), which may indicate that this syndrome prevailed in boys almost 2.5 times more frequently; the average age of the patients was 10.0±0.5 years.

The second group consisted of 19 boys and 6 girls (76% and 24% respectively); the average age of the patients was 11.0±0.5 years. The 1st and 2nd groups did not differ in terms of the mean age indicator. The third group consisted of 27 sick children, 20 boys (75%) and 7 girls (25.9%); the average age of the patients was 8.8±0.7 years.

The control group "relatively healthy faces" was 20 people; 14 boys and 6 girls were in this group; the average age was 8.1±0.7 years.

Results of the study: among 37 patients of the "PANDAS" group 15 patients with Tourette-type tickoses (40.5%), 11 patients with chronic simple motor tics (29.7%), 7 patients with chronic simple and complex motor or vocal ticks (18.9%), 3 patients with chronic simple motor and vocal ticks (8.1%) and 1 patient with transient ticks (2.7%) were observed.

Almost all patients of the "PANDAS" group were diagnosed with chronic infection. As a result of questionnaires and information collection, 36 of them (97.3%) were traced to chronic upper respiratory tract and ENT diseases.

Among the patients of the SC group there were 8 patients with chronic simple motor tics (32%), 6 patients with chronic simple motor and vocal tics (24%), 5 patients with chronic simple and complex motor or vocal tics (20%), 4 patients - Tourette type (16%) and 2 patients with transient tics (8%).

In 63% (17 children) of children with CNS intoxication there were chronic simple motor cases and in 37.0% of children there were chronic simple motor and vocal ticks (10 children).

Proceeding from the abovementioned, among the group "PANDAS" patients with hyperkinesis of Tourette's type prevailed (40,5%), in their turn, among children with SCpatientspatients with chronic simple motor tics prevailed (32%), whereas during intoxication of CNS chronic simple motor tics (63%) and chronic simple motor and vocal tics (37%).

Obsessive-compulsive disorders (OCD) were found in all PANDAS patients (100%). The severity of obsessive-compulsive disorders ranged from 22 (moderately severe) to 37 (extremely severe obsessive-compulsive disorder); the average Y-BOCS overall severity score was 32.4±0.67, which corresponds to severe "obsessive-compulsive" disorder (Table 1).

Table 1

Frequency of "obsessive-compulsive" disorders

Parameters	«PANDAS» (n=37)	MX (n=25)	IntoxicationCNS (n=27)
Average point	32,4±0,67 22-37 score	8,4±2,1* 8-12 score	0,56±0,22*^ 0-3 score
Subclinicalstate	0 (0,0%)	8 (36,0%)	0 (0,0%)
mild OCD	0 (0,0%)	17 (68%)	0 (0,0%)
Mid-range OCD	12 (32,4)	0 (0,0%)	0 (0,0%)
Heavy OCD	25 (67,9%)	0 (0,0%)	0 (0,0%)

*Note: * - reliability of data to indicators at "PANDAS"; ^ - reliability of data to indicators at SC (P<0.05)*

Among the patients of the MCH group, 36% of patients (8 children) had RCDs. The severity of obsessive-compulsive disorders ranged from 4 (subclinical course of development work) to 12 points (obsessive-compulsive disorder of a mild degree of severity); the average points of the overall assessment of the severity of obsessive-compulsive disorders on the Y-BOCS scale were 8.4±2.1 points, which corresponds to "obsessive-compulsive disorder of a mild degree of severity".

In children with CNS intoxication there were no OCDs, the average index for the group was 0.56±0.22, the variation series was from 0 to 3 points (no symptoms).

Thus, a reliable difference in the relative values of OCD occurrence in the groups "PANDAS" and children with SC, CNS intoxication (confidence coefficient t=4.5, i.e. t>2, which corresponds to the probability of error-free prognosis of more than 68.3% and has significant differences; P<0.001) was established.

According to the data of the study, the severity of obsessive-compulsive disorders could affect the severity of tickose hypercinesis in the patient group "PANDAS" (r=0.578, p 0.001, which corresponds to a moderate correlation), and, on the contrary, there was no correlation between the severity of ticks and the severity of OKR in patients of the SC group and intoxication of the CNS (r=0.201 and r=0.178, respectively).

All children with PANDAS and SC showed an increase in the indices of ASL-O from 400 to 800 ME/L, children with CNS intoxication had normal ASL-O indices (up to 200 ME/L) (Table 2).

Table 2

ASL-O indicators among the surveyed groups

	«PANDAS» (n=37)	MX (n=25)	IntoxicationCNS (n=27)
ASL-O, ME/l	610±10,8 400-800	716,7±20,1 600-800	199,3±0,7 180-200

β-hemolytic streptococcus was sown in 11 patients (29.7%) with "PANDAS"; in 3 patients (12%) with SC, in patients with CNS intoxication, sowing of β-hemolytic streptococcus was not observed (Fig. 1)

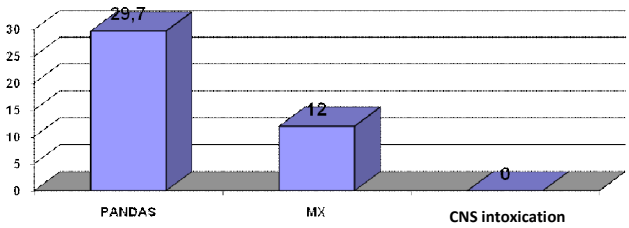

Fig. 1. Seeding frequency of β-hemolytic streptococcus

Children with PANDAS showed a 3-fold increase in the indicators of ASL-O against the background of the normative indicators of leukocytes, SDS, DRR and

the Russian Federation. In children with SC, along with 3-fold increased SL-ASL-O values, there is a significant increase in SLE, DRR and RF. Children with CNS intoxication are characterized by a two-fold increase in leukocytes, SDS, SDS, however, the indicators of ASL-O and RF are within normal limits.

Morphometric differences of the "PANDAS" group are characterized by the presence of changes in the form of convulsive readiness at EEG.

Thus, on the basis of the received clinical, laboratory and instrumental data the algorithm of differential diagnostics of "PANDAS" syndrome was developed:

Algorithm of differential diagnostics of "PANDAS" syndrome, "small chorea" syndrome and CNS intoxication

Expressions	«PANDAS» syndrome	"Little chorea."	Intoxication CNS
Debut of the disease	from 5 to 12 years old	from 3 to 5 years old	Doesn't depend on age.
Anamnesis.	there is a clear connection with the sore throat caused by beta hemolytic streptococcus group A	Possible connection with an angina-induced beta hemolytic streptococcus group A	No connection to an angina-induced beta hemolytic streptococcus group A
Nerve-psychological changes	Presence of mild to moderate obsessive-compulsive disorders ADHD withpredominanthyperactivity	Presence of mild to moderate obsessive-compulsive disorders, presence of ADHD with predominance of hyperactivity	No ADHD obsessive-compulsive disorder
Tics	Hypercinesis like Tourette	Chronic simple motor tics	Chronic simple motor and vocal ticks
Clinic	It's going on with a certain periodicity. The time of the so-called attack is from 10 to 15 weeks. There are no rheumatic nodules, ring erythema, polyarthritis or carditis.	No rheumatic nodules, ring erythema, polyarthritis, carditis	
Laboratory data	Increase of ASL-O indicators against the background of standard indicators of leukocytes, JWPs, DRR and the Russian Federation.	Increase of ASL-O, SOE, DRR and RF.	Increase of leukocytes, JWPs, RBCs, ASL-O and RF within normal limits.
EEG	Presence of changes in the form of convulsive readiness at EEG	No changes	Sometimes it is possible to have changes in the form of EEG seizure preparedness in the presence of comorbidity
MRI	Without organic lesions of basal ganglia and cortical structures	Possible organic lesions of basal ganglia and cortical structures	Without organic lesions of basal ganglia and cortical structures
Treatment dynamics	The prescription of antibiotic therapy (penicillin antibiotics) is marked by the leveling of clinical symptoms of the disease, which takes place almost without a trace	Requires long-term treatment and supervision	Etiopathogenic therapy is effective

Proceeding from the laboratory data of the compared groups, it can be assumed that the presence of BGSA carriers against the background of the normative parameters of leukocytes, SCE, DRR and RF determine the development of psychoneurological disorders in the patient group "PANDAS". Morphometric differences of the "PANDAS" group are characterized by the presence of changes in the form of convulsive readiness in EEG.

Conclusion: Based on the results obtained, it was established that the complex of clinical and laboratory and clinical and morphometric studies can serve as objective diagnostic criteria for the characterization of patients with "PANS". The developed differential-diagnostic criteria will make it possible to diagnose and conduct a differentiated approach to the management of patients with tickosehypercinesis of different nature.

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Modern notions of peripheral neuropathy in children (literature review)

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Abstract: This article considers the main forms of peripheral polynervopathy in children. The etiopathogenetic mechanism of different types of polyneuropathies is described considering modern concepts of disease occurrence.Much attention is paid to the diagnostics of peripheral polyneuropathies, among which the gold standard is still electroneuromyography (ENMG), which allows to determine the speed of nerve impulse conduction and to determine the latency of M- and F-wave, which is a great advantage in comparison with other research methods.

Keywords: peripheral polyneuropathy, electron neuromyography, children.

Relevance.

Chronic inflammatory polyneuropathy (CHIPN) is an acquired autoaggressive immunogenic disease of the peripheral nervous system with gradual onset and progressive course.

The prevalence of CHIPN is 1.0-1.9 in adults and 0.48 in children per 100,000 inhabitants. The onset of the disease is associated with intercurrency infections or immunization (preventive vaccination): 33-57% of children developed the disease within 1 month after the infection or vaccination.

Previously, it was believed that the carriers of certain HLA genes (A1, B8, DRW3) associated with a high risk of developing the disease were more common among patients with CHIPN, but this hypothesis was not confirmed later. Nevertheless, it is believed that the most likely cause of the disease is its immunosuppressive nature, involving both cellular and humoral immunity. It is also thought that auto-aggressive t cells play a leading role in the pathogenesis of the disease, triggering an inflammatory response at sensory and motor nerve level at myelin level.

As you know, each axon is either covered with a shell of a Schwannese cell - in this case the fiber is called non-myelinated, or surrounded by concentrically lying membranes of Schwannese cells - in this case the fiber is called myelinated. The nerve contains both myelinated and non-myelinated fibers. Only non-myelinated fibers contain autonomous efferent and some sensitive afferent fibers.

Thick myelinated fibers carry out vibration and proprioception. Thin myelinated and non-myelinated fibers are responsible for pain, touch and temperature. The main function of nerve fibers is to carry out impulses.

Alternative way of glucose oxidation in hypoxia - polyol (glucose under the influence of the enzyme aldosoreduktaza formed sorbitol, from it - fructose). Sorbitol and fructose do not pass through the membrane and remain inside the cell, which leads to increased osmolarity, hyperhydration, further swelling and death. There is also a deficit of HAED, followed by a decrease in the production of glutathione antioxidant. In addition, the activity of protein kinase C increases and reduces the activity of myoinositol, which regulates the activity of Na+/K+ATPhase, disrupts the activity of ion pump and conductivity of the cell, there is the accumulation of intracellular sodium, which further increases intracellular osmolarity. Disturbance of fatty acids synthesis, especially arachidonic and gamma-linolenic acids, as a result of polyol pathway activation leads to a decrease in prostaglandin endothelial synthesis and disturbance of endoneural blood flow [3].

Protein glycosylation [1, 3, 4] can be both enzymatic and nonenzymatic. In chronic hyperglycemia, hyperglycosylated end products (advanced glycosylation end products, AGE) are formed, which are deposited in the basal membrane of vessels. Vascular endothelium is an insulin-independent tissue, and the damaging effect of glucose and AGE is especially pronounced in it. The pathological process involves proteins of the nerve cell membrane (protein part of myelin), cytoskeleton (tubulin), etc. Hyperglycosylated myelin loses the ability to conduct nerve impulses.

Later it degenerates and dies.

Oxidative stress and mitochondrial dysfunction.

Oxidative stress is a cascade of pathological reactions, the main result of which is accumulation of free radicals and parallel decrease of antioxidant protection [1, 4]. "Attack" of free-radical particles and lipid peroxidation (LPO) products is an additional factor of cell membrane damage. Especially high is the energetic metabolism in peripheral nerves: the farther from the nerve center the nerve fiber is located, the greater is its energy needs [9].

The cycle of tricarboxylic acids (CTA) gives 38 molecules of the main energy source - adenosine triphosphate (ATP). Lack of ATP production during the activation of polyol pathway leads to "energy hunger", activates the decomposition of structural components, in particular proteins, and the accumulation of toxic ammonia that destroys nervous tissue.

As aresult of peripheral nerve damage, polyneuropathy develops, the most common form of which is distal motor-sensory neuropathy, characterized by sensory and motor function disorders. Nerve ischemia ends with the development of focal, multifocal, fascicular or sectorial degeneration of nerve fibers of peripheral and intramuscular nerves.The development of ischemia primarily affects small vessels that feed the vascular wall (epineural arteries, vasa vasorum), which develop occlusion due to thickening of the intima and the formation of wall clots. These abnormalities lead to gradual degeneration of the nerve fibre. The nerve fibre reveals a paradoxical contrast between its physiological resistance to ischemia and increased susceptibility to morphological ischemia (Nukada H., 2014). Even with marked nerve damage, regeneration is possible if neuronal viability is maintained. The recovery rate is about 2-4 mm/day.

Signs of demyelination can be observed at any segment of the peripheral nerve, from the spinal roots to its distal areas. In addition to demyelination, inflammatory infiltrates and subclinical edema have been found in calf biopsy. The chronic course of the disease may be accompanied by the formation of a "bulbous head", which is associated with the proliferation of Schwann's cells in the repetitive processes of de - and remyelination [5]. It should also be noted that morphological changes in CVDP resemble those in experimental autoimmune neuritis [6].

CDPC has four main flow variants [3,4]:

- Chronic monophasic - symptoms gradually reach their maximum severity, and then undergo full or partial regression, and then the disease does not progress and does not recur;
- chronic recurrent-remitting - clearly delineated episodes of increased symptomatology with subsequent reverse development - relapses, followed by periods of stabilization, during which the disease does not progress - remission;
- Gradual - progressive - progressive - gradual gradual increase of symptoms;
- steadily progressive - slow continuous increase of symptoms.

Complaints and anamnesis

When collecting anamnesis and complaints, attention should be paid to the presence of anamnesis and complaints:

- normal physical and motor development before the disease begins;
- gait changes;
- frequent falls;
- weakness of the lower and upper limbs muscles;
- Paresthesia and dysesthesia;
- A number of patients may have complaints of tremor and ataxia;

- gradual development of symptoms, but increased motor disorders may be rapid in 16% of patients [1,2,3,8,10])

In its debut, the disease may be asymptomatic for several months, or, conversely, the development of symptoms may be rapid, with repeated acute episodes [7, 8]. The most common complaints from children with CDPD are gait disorders and frequent falls [9]. This is associated with disorders of predominantly motorized innervation of the proximal and distal lower limb muscles. Weakness of upper limb muscles, tremor, ataxia are also observed in a number of patients. Tendinous reflexes are always reduced or absent [3, 4]. At least 1/3 of children with CDPD have sensitivity disorders: couple and dysesthesia, deep sensitivity disorders, etc. [3, 10]. Lesions of cranial nerves, weak respiratory muscles, and dysfunction of the autonomic nervous system are not typical signs of CVDP in children, but in 20-40% of cases the disease's debut may show signs of cranial nerve involvement [11, 12].

It is generally accepted that the course of CVDP in children has the following features [11, 13-15]:

- the initial symptoms of the disease are more pronounced and develop more rapidly;
- the disease is most often characterized by a gait disorder;
- The first neurological signs of the disease are more pronounced;
- is characterized by a remissionary course of the disease;
- the prognosis of the disease is more favorable. In 16% of children, as well as in adults, the disease may be characterized by acute onset (the so-called acute onset CVDP), indistinguishable from Guillain-Barrett syndrome. The distinction between CVDP and Guillain-Barrett syndrome in this situation is difficult to distinguish; only dynamic observation of patients for more than 2 months allows for an unmistakable diagnosis [12, 16].

In addition to chronic inflammatory polyneuropathy (CHIPN), peripheral neuropathy also includes hereditary motor-sensory neuropathy (Sharko Marie-Tuta).

Charco-Marie-Tut's disease - or Sharco-Marie-Marie's neural amniotrophy known as hereditary motor-sensory neuropathy (MMSN) - is an extensive group of genetically heterogeneous diseases of peripheral nerves, characterized by symptoms of progressive polyneuropathy with a predominant lesion of the muscles of the distal parts of the extremities. NSMN is not only the most common hereditary disease of the peripheral nervous system, but also one of the most frequent hereditary diseases in humans.

Clinical-genetic heterogeneity of Sharko-Mari neural amyotrophy was the basis for the search for loci linked to these diseases. To date, 40 loci responsible for hereditary motor-sensory neuropathies have been identified, more than 20 genes have been identified, mutations in which lead to the development of the clinical phenotype of NMSS, all types of inheritance of NMSS are described: autosomal dominant, autosomal recessive, X-linked. Autosomal dominant inheritance is the most common.

Primary nerve damage leads to secondary muscle weakness and atrophy. The most affected are the thick "fast" nerve fibers covered with myelin sheath - these fibers are used to innervate skeletal muscles. Longer fibers are more damaged

because they are the most stressed muscles in the feet, shins, hands, arms and forearms.

The first symptoms are weakness in the legs, a change in gait (cock's gait), and tibia twisting. Later on, muscle weakness progresses, shin muscle atrophy occurs, legs take the form of "inverted bottles".

In addition to hereditary neuropathy to peripheral neuropathy include tunneling neuropathy of the upper limbs. The most common of which is carpal tunnel syndrome (CTS). The frequency of morbidity in the United States is 1-3 per 1,000 cases per year (Bickel K.D., 2017).

Elbow nerve neuropathy (cubic canal syndrome) is the second most common type of upper limb tunnel syndrome.

The pathophysiological mechanism of tunnel syndromes is based on the compression of surrounding tissues, which triggers a cascade of mechanical damage to nerve fibers: compression - ischemia - nerve edema - compression - ischemia. Peripheral neuropathies may be caused by repeated or double compression of the nerve. Upton and McComas (2015) have suggested that compression of the nerve at the proximal site makes distal areas sensitive to compression. Noting also the high frequency of SPE and SCC with cervical root damage, they concluded that compression of the nerve in the proximal and distal regions would lead to changes in axoplasmic flow and the occurrence of pathology, and therefore symptoms. Because of the compression in the distal section, the proximal one becomes more susceptible to secondary compression, and the term "double-compression reversibility" has been proposed.

The "criterion standard" of the study of the functional state of nerve fibers is electron neuromyography (ENMG), which allows us to assess the degree of damage to peripheral nerves, diagnose subclinical pathology, track the condition of nerve fibers in the dynamics. The main indicators evaluated in the course of ENMG are excitation rate (ERV), M-response amplitude and residual latency (RL).

A valid diagnosis corresponds to at least one of the following characteristics.

a) Increased latency of M-response when performing electromyography with distal point stimulation by 50% or more from the upper limit of normal values in the two nerves (it is necessary to exclude median nerve neuropathy on the wrist due to carpal tunnel syndrome).

b) Reduced rate of excitation propagation through motor fibers by 30% or more from the lower limit of normal values in the two nerves.

c) An increase in latency of F-wave by 20% or more from the upper limit of normal values in the two nerves (or by 50% or more from the upper limit of normal values if the amplitude of the negative peak of distal M-response is less than 80% of the lower limit of normal values).

d) Absence of F-waves in two nerves if the amplitudes of the negative peak of distal M-response when stimulated by these nerves are 20% or more of the lower limit of normal values + one other demyelination parameter (in any nerve) satisfying any of the criteria (a-r) in one or more other nerves.

e) Local motor nerve conduction block: reduction of the amplitude of the negative peak of the proximal M-response relative to the distal one by 50% or more if the negative peak of the distal M-response is 20% or more of the lower

limit of normal values in two nerves or in one nerve + one other demyelination parameter (in any nerve) satisfying any of the criteria (ah)

f) in one or more other nerves.

g) Local motor nerve conduction block: reduction of the amplitude of the negative peak of the proximal M-response relative to the distal one by 50% or more if the negative peak of the distal M-response is 20% or more of the lower limit of normal values in two nerves or in one nerve + one other demyelination parameter (in any nerve) satisfying any of the criteria (ah) in one or more other nerves.

h) Presence of temporary dispersion (increase in duration of negative peak M-responses obtained by stimulation at distal and more proximal points by more than 30% in two or more nerves.

Increased duration of distal M-response (the interval between the beginning of the first negative peak and the return to the isolation of the last negative peak) in one or more nerves (in the median one - > 6.6 ms, in the ulnar one - > 6.7 ms, in the peroneal one - > 7.6 ms, in the tibial one - > 8.8 ms) + one other parameter of demyelination (in any nerve), satisfying any of the criteria (a-j) in one or more other nerves.

2) Probable diagnosis: A decrease in the amplitude of the negative peak of the proximal M-response relative to the distal one by 30% or more, with the exception of the tibial nerve, if the negative peak of the distal M-response is 20% or more of the lower limit of normal values, in two nerves or in one nerve + one other demyelination parameter (in any nerve) satisfying any of the criteria (a-j) in one or more other nerves.

3) Possible diagnosis: Any of the characteristics (a-j) of a valid diagnosis found in only one nerve.

Supporting criteria for CDPC (according to EFNS/PNS 2010) [17]:

- increased protein content in cerebrospinal fluid at leukocyte count < 10/mm3 ;
- in magnetic resonance imaging - accumulation of gadolinium and/or hypertrophy of the horse's tail, lumbosacral or cervical spinal cord roots, or shoulder or lumbosacral plexus;
- disruption of electrophysiology of sensory responses in at least one nerve:
- the amplitude of the sensory action potential of the calf nerve is normal, while the amplitude of the sensory action potential of the median nerve (but it is necessary to exclude the neuropathy of the median nerve on the wrist due to carpal tunnel syndrome) or the radial nerve is impaired;
- excitation velocity - < 80% of the lower limit of the normative values (< 70% if the amplitude of the sensory potential of action < 80% of the lower limit of normal values);
- increased latency of somatosensory evoked potentials without the presence of central nervous system pathology;
- objective clinical improvement as a result of immunomodulatory treatment;
- Electronic microscopy of nerve biopsies or the analysis of combed nerve fibers (teased fiber analysis) reveals signs of de and/or remyelination.

In considering the supporting criteria, the increasing role of neuroradiological methods in the diagnosis of CVDP in general and in children in particular should be noted. It has been shown that intracortical edema and spinal cord root thickening do not correlate with the

degree of severity of initial manifestations of the disease and the severity of symptoms, but in repeated studies, there is a clear dependence of positive changes on the efficacy of therapy [18]. A nerve biopsy in children should be recommended as a diagnostic procedure in exceptional cases where all other research methods have proven to be uninformative.

Axonal degeneration - pathological changes (disruption of axonal transport), clinically manifested insensitivity and muscle atrophy. Signs of axonopathy according to electron neuromyography (ENMG) data: decrease in M-response amplitude (muscle response), increase in F-wave amplitude (late muscle response), decrease in the number of motor units [6].

Clinical manifestations: decrease/ decrease of tendon reflexes, disturbance of deep sensitivity. At ENMG there is a decrease or blocks of conduction (correlated with the severity of the demyelinating process), an increase in the duration of M-response at normal amplitude and an increase in the residual latency (time of nerve impulse passing through the axonal terminals), "scattering" of F-waves [6].

Conclusions:

1. Summarizing the above, peripheral neuropathy is quite common in children. Among the etiological factors of origin are autoaggressive T-cells, the state of cellular and germoral immunity. The pathogenetic mechanism is associated with immunological instability of the main histocompatibility cells (HLA) to the action of infectious, traumatic, viral factors, which predetermines the outcome of the disease.

2. Electroneuromyography (ENMG) remains the gold standard in the diagnosis of peripheral polyneuropathy, which is universal, as it allows us to assess the rate of impulse passing through the nerve fiber in the dynamics of the study, which is an advantage over other methods of study.

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Maternal Health: An important issue

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Abstract: Maternal health problems are an important public health issue in most of the developing countries. India accounts for over a one-fifth of maternal and about a fourth of under-five deaths in the world. Promotion of maternal and child health has been one of the most important objectives of the Family Welfare Programme in India. The National Population Policy has also stressed on lowering down the maternal mortality rate and to improve maternal health in general. Despite significant changes in the health system, maternal and child mortality levels remain unacceptably high which continue to hinder national potential to improve life expectancy at a faster rate. The maternal and child healthcare (MCH) outcomes in India are poorer than many developing nations with similar or even lower income per head. India has made extensive efforts to reduce maternal mortality and to increase access to reproductive health care and in some regions much progress has been achieved.During pregnancy, additional energy is required for the growth and maintenance of the fetus, the placenta, and maternal tissues. Maternal micronutrient deficiency predisposes a mother to poor health, including infection, preeclampsia/eclampsia, and adverse pregnancy outcomes such as premature birth and intrauterine growth retardation. In this article, we will briefly have an overview of the maternal health issues.

Key words: Maternal Health, Gestational Diabetes, Anaemia.

Introduction

The concept of reproductive health has long been discussed and there is a need to focus on reproductive morbidity as a measure of reproductive health has evolved. There is poor reproductive health with neglect of women's health. Compounded with socio-cultural factors the result is poor treatment seeking and hence the poor quality of life. Similarly, it is a fervent hope of all mothers-to-be to have a safe and healthy pregnancy. While most pregnancies and births are uneventful, all pregnancies are at risk. Around 15 percent of all pregnant women develop potentially life-threatening complications that call for skilled care and some will require a major obstetrical intervention to survive [1,2]. Maternal mortality is the most extreme consequence of poor maternal health. Millions of women in developing countries experience life threatening and other serious health problems related to pregnancy or childbirth. Complications of pregnancy and childbirth cause more deaths and disability than any other reproductive health problems and are the leading cause of disability and death among women between the ages of 15-49. Globally, about 8 million women having pregnancy-related complications and more than half a million die from those complications. In developing countries, one woman in 16 may die due to pregnancy-related complications [3].

There are various pregnancy related complications and risk factors among the women before or after the delivery and also among the outcomes. About 500,000 women die every year because of complications related to pregnancy and childbirth, and maximum number of deaths occur in developing countries [4]. According to the report (Indian Express, 2010) only six countries are contributing 50 percent of the maternal deaths worldwide, and India is one among them. As per Sample Registration System (2007-09) maternal mortality ratio in India is 212 per hundred thousand live births. Prevailing high maternal morbidity and mortality has always been a source of concern, and antenatal and intrapartum care aimed at reducing maternal morbidity and mortality have been components of the family Welfare Programme since inception [5].

National Rural Health Mission (NRHM) offers institutional mechanism and strategic options to reduce high MMR. 'JananiSurakshaYojna,' strengthening of CHCs (as per Indian Public Health standards) to offer 24 hours quality services including that of anaesthetists and Accredited Social Health Activist (ASHA) are important proposals in this regard. District Health Mission can play an important role in monitoring maternal deaths occurring in hospitals or community and thus create a social thrust to prevent and reduce maternal deaths [6]. It is unfortunate that large number of maternal deaths occur due to haemorrhage, obstructed labor and unsafe abortions while safe and affordable technologies to prevent such deaths to exist. One of the studies shows that the Maternal Mortality Rate (MMR) is an indicator of the quality of health care available during pregnancy, childbirth and in the postpartum period. Of all maternal deaths, 80% can be potentially avoided by interventions during pregnancy, childbirth and the postpartum period that are feasible in most countries. The common causes of maternal death include haemorrhage, hypertension, infection,

obstructed labour and unsafe abortion [7]. Despite the international recognition, gynaecological morbidity remains largely neglected and poorly understood at the community level. Public health programs around the world have created an illusion of promoting women's health while devoting resources towards other interests. Health care initiatives have failed to address women's health concerns and issues as interests worthy of investment in their right. Consequently, the status of women and their access to appropriate services have not improved in many parts of the world [8].

In public health discourse, three constituencies demography, maternal and child health, and women's health have articulated women's health concerns in different ways. The community of population scientists has tended to equate reproductive health with family planning. Concerned primarily with reducing birth rates, family planning programs have focused on numbers rather than the quality and responsiveness of services to women's health needs. As a result, family planning programs in developing nations have neglected women as a distinct group with specific health care needs. This has resulted in a failure to address the issue of gynaecological health [9]. Advocates of the maternal and child health (MCH) programs promote the health needs of women during pregnancy and childbirth, and their skills for child care, without attending to their broader reproductive health needs. This program has targeted women, although its true beneficiaries are children and the objective has been to improve child survival [9]. In fact, efforts to improve child survival have achieved wide-scale recognition while the maternal health component of the program has lagged behind. Morbidity leading to poor pregnancy outcomes exists long before and after pregnancy. Essentially, women's health outside the realm of pregnancy has been largely ignored [9]. One of the studies reveals that, in each year over 50 million women experience pregnancy-related complications. Fifteen million of which lead to long-term illness or disability often because they have no access to medical care, because pregnancyhas exacerbated already existing malnourishment or illness, or because the medical care that they do manage to access is substandard [10]. It has also been ascertained that pregnancy-related problems have far-reaching consequences on the overall reproductive health of women, in addition to their contribution to maternal mortality [11]. It has seen that "a growing community of women activists, NGOs and researchers, is concerned with broader women's issues and has drawn attention to the importance of women's empowerment and reproductive rights for improving reproductive health" [9]. Women's health advocates view current programs as failures for women's reproductive health and criticize the exclusion of women from research and policy development. The fact that women have not had the opportunities to articulate their own health care needs that contributes to the failure of public health programmes [9]. In the developing world, constrained by limited knowledge and resources, faces a more difficult challenges and a stronger need to address the issue of reproductive health. Prevalence of reproductive health complications in the developing world is known to be high, but accurate numbers remain elusive. Statistics is mostly extrapolated from community-based data derived from

inconsistent clinical criteria and unreliable diagnostic techniques. Without solid documentation of reproductive morbidity, researchers have had little opportunity to explore socioeconomic and cultural factors [12]. The impact of reproductive health morbidity on women's reproductive health is particularly serious in developing countries like India where weak or non-existent systems of health care make the diagnosis and treatment of these conditions difficult [9]. On the other hand health policy in India has floundered in its management of both the demand and supply sides [8]. As late as 1992-93, half of all pregnant women in India did not receive a single antenatal check-up. "Initiatives over the last half-century have not effected a significant change in the situation of women. Poverty alleviation programs are structurally biased against women and welfare programs for women and children are limited in scope and resources" [8]. Addressing women's needs as a distinctive group among the disadvantaged populations of India continues to be a challenge. Indian studies on women's reproductive health problems are scanty, and there large gaps in knowledge about women's perceptions of morbidity and health seeking behaviour (Oomman, 2000). Obstetric complications that lead to maternal morbidity and mortality cannot be predicted; therefore, receiving care from a skilled provider (doctor, nurse, or midwife) has been identified as the single most important intervention in safe motherhood programs [13].Women in developing countries face a high risk of severe complications during pregnancy and delivery. These can lead to adverse consequences for their own health and that of their offspring [14]. There are five most important direct causes of maternal mortality in developing countries. Those are haemorrhage, sepsis, unsafe abortion, eclampsia, and obstructed labor. Together these causes account for more than two-thirds of maternal mortality in the world. Indirect causes of maternal death, which are responsible for approximately 20 percent of maternal mortality worldwide, include pre existing conditions such as malaria and viral hepatitis that are exacerbated by pregnancy or its management (WHO, 1999). Health indicators document Indian women's disadvantaged position in society. "The adverse sex ratio, lower life expectancy among women and higher infant mortality among girl children are evidence of bias against women" (Rishyasringa 2000). India has not seen the global level of improvement in female mortality rates since World War II. Moreover, the actual risk of an Indian woman dying from causes related to pregnancy and childbirth is over 20 times greater. Highermaternal mortality is a reflection of poor nutrition, early marriage and inadequate quality of health care [8].

Conclusion

Chronic disease prevalence during pregnancy has found as the most important determinant of poor birth outcome such as, preterm delivery, low birth weight,premature delivery, stillbirths and child with any health complications. So, early detection and treatment for chronic diseases are very much essential to reduce the disease burden and to improve birth outcome. In most of the cases, it has seen that if the women have any chronic disease during pregnancy opt for institutional delivery and the health of the new-born is found very much poor among them. Therefore, women must be encouraged to make use of the services

and go to health providers not only when they feel sick. But counseling to follow a good and healthy dietary routine, birth preparedness, proper examination for any chronic disease prevalence during pregnancy should also give to the pregnant women. Similarly, proper supply of IFA tablet to the pregnant women is also equally important to combat with the iron deficiency during pregnancy. But they go through all the check-ups during pregnancy. Follow up of patients is equally important to know the health status and also to give awareness regarding the consequences related to chronic disease prevalence mainly during pregnancy. Women who remain uneducated about chronic ill health will never be able to make wise decisions in seeking the services that has been provided.

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Hemodynamics and functional state of kidneys in patients with coronary heart disease on the background of type II diabetes mellitus

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Abstract: The close relationship between the cardiovascular system and the kidneys attracts alot of attention to the functional state of the kidneys in various cardiovascular diseases.

Keywords: coronary heart disease, diabetes mellitus, renal hemodynamics.

Cardiovascular disease (CVD) remains one of the most common causes of disability and mortality in industrialized countries today. Among them, coronary heart disease (CHD) is one of the most common causes of disability and mortality in industrialized countries. IHD and diabetes mellitus (diabetes mellitus) are two interlinked pathologies that have powerful, mutually reinforcing damaging effects directed at several target organs: heart, kidneys, brain vessels and retina. Decreased renal function has a negative effect on cardiovascular disease (CVD) prognosis. A decrease in the rate of glomerular filtration (GFB) below 60 ml/min/1.73m2 is associated with a 50% increase in cardiovascular mortality (Wannamethee S.G. etal, 2006).

The problem of heart to kidney relationship is relevant in modern cardiology due to the high prevalence of chronic kidney disease (CDP) in the population, on the one hand, and the epidemic of CVD - on the other hand [5]. The results of the studies indicate that the reduction of SCF is an independent risk factor for the development of CVD [1, 4, 6], the cause of accelerated development of pathological changes in CVD and increases the risk of mortality, and is considered as a marker of unfavorable prognosis of common CVDs [2, 3].

Kidneys are part of the body's microcirculatory system and affect the formation of AH, especially in combination with diabetes mellitus, heart failure and kidney disease [1, 4, 6]. As the severity of CPP increases, left ventricular hypertrophy progresses, systolic and/or diastolic dysfunction develops, and atherosclerosis "accelerates",

Calcification of the vascular system [5]. In the Fremingham study, left ventricular myocardial hypertrophy is 3-4 times more common in patients with renal dysfunction than in AH patients with preserved renal function [7].

Early diagnosis of ischemic kidney disease predetermines the success of treatment of such patients, allowing not only to reduce the number of cases of terminal CSF, but also to reduce the number of complicated forms of CHD (Mukhin, N.A., 2009).

Purpose of the study: To study changes in hemodynamics, renal function and renal blood flow in patients with coronary heart disease (CHD) with or without type 2 diabetes mellitus (diabetes mellitus 2).

Materials and methods:The study included 55 patients with CHD, including 25 patients with diabetes mellitus 2 and 30 without diabetes mellitus. The parameters of carbohydrate and lipid metabolism, renal blood flow were determined.

The criteria for inclusion in the study were the presence of stable CHD in patients who were diagnosed according to the recommendations. Patients with an endocrinologist's diagnosis of diabetes mellitus 2 (according to WHO criteria) or patients undergoing treatment with sugar-reducing drugs for the previously diagnosed diabetes mellitus 2 were included in the group of diabetes mellitus 2. The comparison group (without diabetes mellitus) included patients who did not have a carbohydrate metabolism disorder according to the data of oral glucose tolerance test (75 g) (according to WHO criteria, 2006).

Creatinine clearance was calculated using the Cocroft-Golt formula:

Creatinine clearance (ml/min) = [88 x [140 - age (years)] x body weight (kg)] / [72 x serum creatinine (xmol/l)] for women was multiplied by 0.85.

Cystatin C (CKFz) was calculated using the Macisaac R.J. et al. (2006):

SKFz (ml/min/1.73 m2) = (84.6 - 3.2)/cystatin C

Determination of microalbuminuria (MAU) in a single urine dose was performed using test kits. In accordance with the International Diabetes Federation regulations, ULVA was considered to be the ratio of albumin to creatinine greater than 2.5 mg/mmol of creatinine in men and more than 3.5 mg/ mmol of creatinine in women [8].

All patients underwent conventional methods of investigation (clinical and biochemical blood tests, general urine analysis, coagulogram, sugar and blood lipid spectrum, electrocardiogram, EchoKG, internal ultrasound, duplex scanning of renal arteries, concentration of cystatin C in blood serum).

All patients signed an informed consent to participate in the study.

Results of the study:Clinical characteristics of patients. The study included 55 patients with CHD, including 25 patients with diabetes mellitus 2 and 30 patients without diabetes mellitus.

The groups of patients did not differ significantly by age, sex and blood pressure (Table 1). In the 1st group of diabetes mellitus 2 as compared to the 2nd group without diabetes mellitus, a higher heart rate was observed: 74(60-90) oud/min vs. 69(56-87) oud/min ($p<0.01$).

The groups of patients differed significantly in glucose content in fasting venous plasma and HbA1c, which in the group of patients with diabetes mellitus 2 was 7.3% (6.9-8.0), and in the group without diabetes mellitus type 2 - 4.9% (4.7-6.1) ($p<0.001$) (Table 1). Contenttriacylcerides (TAG) and median body mass index (BMI) were significantly higher in the group of patients with diabetes mellitus 2 (Table 1).

In 45 (81,8%) patients, stable stress angina functional class (FK) III was diagnosed, in 10 (18,2%) patients of FC IV

Among the 25 patients with diabetes mellitus with diabetes mellitus 2, 18 (72%) with revealed diabetic nephropathy, there was a high rate of BP and FC of stable angina of tension.

Table 1

Clinical characteristics of patients in comparison groups

Index	Patients with diabetes mellitus 2 (n=25)	Patients without diabetes mellitus (n=30)	p
Age, years.	63(56-69)	63(56-69)	ND
Sex, male/female	15/10	20/10	нд
САД, мм.рт.ст.	160(130-170)	130(125-145)	p<0,01
ДАД, мм.рт.ст.	90(80-100)	80(75-85)	нд
Heart rate/min	74(60-90)	69(56-87)	p<0,01

Body mass index, kg/m^2	31,6(27,8-35,5)	29,4(27,6-31,6)	p<0,05
Glucose of venous blood on an empty stomach, mmole/l	8,5(6,7-9,6)	5,4(5,0-5,8)	p<0,001
Glycatedhemoglabin, %	7,3(6,9-8,0)	5,9(5,7-6,1)	p<0,001
OHS, mmole/l	4,7(4,0-6,1)	4,2(4,0-5,2)	нд
ХС ЛПНП, ммоль/л	2,7(2,3-4,1)	2,8(2,3-3,4)	нд
ХС ЛПВП, ммоль/л	1,1 (1,0-1,2)	1,1 (1,0-1,3)	нд
ТАГ, ммоль/л	1,7 (1,4-2,5)	1,4(1,1-1,6)	p<0,001

Note. SAD-DAD-systolic and diastolic blood pressure, respectively; BMI body mass index; GC - total cholesterol; LDL cholesterol - low-density lipoprotein cholesterol; HDL cholesterol - high-density lipoprotein cholesterol; TAG - triacylcerides.

Table 2

Functional state of kidneys and renal blood flow in patients

Index	Patients with diabetes mellitus 2 (n=25)	Patients without diabetes mellitus (n=30)	p
Kidneyfunctionlabindicators			
Creatinine, мкмолμmol/l ь/л	78,2 (69,0–85,6)	74,2 (69,6–83,4)	нд
Creatinineclearance, ml/min	110,5 (90,9–137,7)	101,9 (88,7–125,9)	нд
Albumin/Creatinine ratio, mg/mol Cr	0,5 (0,01–1,7)	0,1 (0–0,6)	p<0,05
Cystatin C, mg/l	1,34 (1,25–1,53)	1,34 (1,27–1,49)	нд
SKFZ, ml/min/1.73m2	60 (52–64,7)	59,5 (52,2–63,5)	нд
Ultrasound data - renal blood flow studies			
РИ	0,8 (0,7–0,8)	0,7 (0,7–0,8)	p<0,01
ПИ	1,7 (1,4–1,9)	1,4 (1,2–1,5)	p<0,001

Note: n - number of patients. SCFz - ballast filtration rate calculated by cystatin-C; PI - pulsation index; PI - resistive index.

The groups of patients did not differ in terms of the filtration function of the kidneys: concentration of creatinine and cystatin C in blood serum, creatinine clearance and SCF value calculated by cystatin C (SCFz) (Table 2). In both groups, negative correlation correlation between creatinine clearance and age of patients was observed ($rs=-0.65$; $p<0.001$ and $rs=-0.56$; $p<0.001$, respectively). In addition, in the group of patients with diabetes mellitus 2 a negative correlation of creatinineclearance with the duration of diabetes mellitus disease was observed: $rs=-0.27$; $p<0.05$.

The LSA value in the group of patients with diabetes mellitus 2 was 5 times higher than in patients without diabetes mellitus.

Conclusions:

1. The obtained results testify to the commonality and interrelation of pathogenetic mechanisms underlying the development of renal dysfunction in patients with diabetes mellitus 2.

2. Presence of risk factors such as high AH, age, male sex, duration of CHD, dyslipidemia, increase of glucose in venous blood increases the risk of development of blood flow disturbances and hemodynamics in kidneys.

3. Patients with CHD have a more malignant nature, which can lead to the development of severe complications that threaten the life of the patient. Several hypotensive drugs are required to reduce blood pressure to the target level.

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Distribution of alleles of LEPR (Arg223Gln) gene polymorphism under overweight and obesity in women of fertile age

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Abstract: Leptin functions are performed by binding to the leptin receptor (LEPR), the genetic variants of which are associated with awide range of phenotypes, including obesity, hyperlipidemia, type 2 diabetes, etc.One of the main and most frequent polymorphisms of the LEPR gene is Gln223Arg.The aim of this research was to study the LEPR Gln223Arg gene polymorphism in women of fertile age in the Uzbek population with alimentary obesity.In women of fertile age of Uzbek nationality with alimentary obesity, women with GA-genotype prevail in the distribution of Gln223Arg polymorphism of the LEPR gene.While in overweight women and in the control group with normal body weight, the homozygous Arg223Arg polymorphism of the LEPR gene prevails.

Key words: obesity, leptin, leptin receptor gene.

Relevance. Today, the problem of overweight and obesity is becoming more and more acute for all mankind and for our republic in particular. Obesity is a serious health problem in all countries because of its spread and development of significant health consequences associated with high morbidity and mortality. Some experts say that there is an epidemic of obesity, as about 1.5 billion adults suffer from obesity in the modern world [1, 3-8].

The increase in the proportion of overweight and obese people is widespread and affects women of reproductive age. About 30% of women of childbearing age suffer from obesity and another 25% of women in this group are overweight. According to WHO, by 2025, the incidence of obesity among the female population is expected to increase to 50% [1, 3-8].

Fatty tissue produces a wide variety of peptide products. Some are synthesized in adipocytes, while others are synthesized in stromal fat cells or in macrophages that migrate to fatty tissue when obese. A special role in the regulation of reproductive function is played by leptin, adiponectin, resistin, and tumor necrosis factor-? [7, 457-478].

The level of leptin in the blood increases as the weight of fat tissue increases (its production in subcutaneous fat is higher than in visceral fat depots). The concentration of leptin, however, varies widely in people with the same body mass index, confirming the involvement of both genetic and environmental factors in the regulation of this hormone. The action of leptin is based on the activation of a specific leptin receptor represented by long and numerous short isoforms. Such receptors are located in different areas of the brain - hypothalamus, cerebellum, cortex, hippocampus, thalamus, vascular plexus, and endothelium of brain capillaries [2, 250-251].

The secretion of the mellitus hormone depends on the weight of fatty tissue in the body and plays a key role in the regulation of appetite, body weight and energy metabolism [6, 5-7]. Acting on the mechanism of negative feedback, leptin transmits to the hypothalamus information about the amount of energy reserves on the periphery, which is necessary for the regulation of energy consumption and food intake [1, 3-8].

However, despite the high level of hormone, obesity is a condition that "promotes the development of cellular processes that disturb the pathways of signal transduction of leptin" [2, 250-251] and leads to leptin resistance, leading, in turn, to the risk of deactivation of the hypothalamic-pituitary-ovarian system, menstrual cycle disruption and anovulation. Hyperleptinemia, in turn, disrupts the processes of steroidogenesis in granular and teca-cell ovaries. In addition, high concentration of leptin may disturb folliculogenesis and oocyte maturation in the ovary [9, 565-576].

As one of the components of the metabolic syndrome, obesity is a topical medical and genetic problem, since the change in diet and physical activity is realized only with the participation of genetic factors, in particular polymorphisms or so-called single nucleotide replacements (SNP) of genes [3, 81-82].

The role of the leptin receptor (LEPR) in the obesity genesis is conditioned by the binding of leptin, a hormone of subcutaneous fatty tissue adipocytes, which blocks the production of neuropeptide Y that causes hunger. Polymorphisms that determine the leptin-binding functions of the receptor can be associated with body mass index (BMI) and contribute to obesity [3, 81-82].

To date, doctors have been conducting genetic studies to assess a particular pathology and to select the best treatment option. Determining the cause of the disease at the molecular level allows us to draw a correct conclusion in case of ambiguous symptomatology.

Analysis of the literature data on LEPR gene polymorphism, as well as our own observations of women with reproductive dysfunction and obesity with an ambiguous clinical picture and sometimes unsuccessful therapy, has led us to conduct a molecular genetic study.

The aim of the study was to determine the polymorphism of the gene of the leptin receptor Gln223Arg associated with excess body weight and obesity in women of fertile age.

Materials and methods of research. Genotyping of 149 women of fertile age of Uzbek nationality with excess weight and obesity, as well as 33 women of reproductive age with normal body weight, who applied for consultation to the Republican Center for Reproductive Health, endocrinological department and the consulting clinic of Clinic No. 3 of TMA was carried out.

The criteria for inclusion in the main group were: age of women from 18 to 40 years of age (average age was 29.8ë0.79 years), absence of pregnancy, body mass index over 25 kg/m2.

Criteria for exclusion from the main group: diabetes mellitus type 1 and type 2, pituitary tumors, hypogonadotropic hypogonadism, VDKN, hypothyroidism, severe somatic pathology.

Genotyping was performed from whole blood, by polymorphism of the gene of the Leptin receptor Gln223Arg.

DNA was extracted from whole blood with the help of "DiatomTMDNAPrep 200" set according to the standard protocol of the manufacturer (IsoGen RF laboratory).

The analysis of the obtained parameters was carried out with the help of the software package "SPSS forWindows" and "STATISTICA" MicrosoftExcel with the processing of the material using the methods of variation statistics. The reliability of the obtained results was assessed by the paired method using the Student's t-criterion. Differences were considered reliable at $p<0.05$.

Results and discussion. The distribution of genotypes by the polymorphism of Gln223Arg LEPR gene among women with excess body weight, obesity of different degrees and control group was as follows.

In overweight and obese women, the predominant genotype was G/A, which was 55%, A/A, which was 31.5%, and G/G, which was 13.5%. A/A genotype prevailed in the control group - 54.6%, G/G genotype - 24.2% and G/A genotype - 21.2%. The distribution by alleles was as follows: A-allelelicle - 59%, G-allelicle - 41% in overweight and obese women. A-allelele - 65.2%, G-allelele - 34.8% in the control group.

This distribution of Gln223Arg polymorphism of LEPR gene in patients and healthy individuals corresponds to the theoretical calculation of genotype and allele frequencies by Hardy-Weinberg.

Among all the women of fertile age of Uzbek nationality studied, the analysis of the obtained results indicates the predominance of G/A-heterozygous polymorphism Gn223Arg gene LEPR.

There are available data on the results of studies on the association Gln223Arg of polymorphisms of LEPR gene with different components of metabolic syndrome (MS). Some authors note that the carriers of the Arg223Arg homozygous genotype are less active physically, consume less energy, and have larger abdominal adipocytes than the carriers of the Gln223Gln genotype [8, 233-236].

However, there are also contradictory data, for example, in the study of Gottlieb M.G. and its co-authors (2009), the 223Gln allele in the homozygous and heterozygous state (genotypes Gln223Gln and Gln223Arg) cause an increase in fat, leptin, and, consequently, a predisposition to MS [5, 341-348].

Further, in our study, women in the main group were subdivided into the following subgroups:

1. Overweight women (BMI=27.7ë0.61) - 33.5%
2. Women with obesity of the 1st degree (BMI = 32.5ë0.85) - 45%
3 2-3 degree obese women (BMI=38.7ë1.25) - 21.5%

The distribution of genotypes by group showed the following results.

Group 1:

A/A-genotype - in 32 women,
G/A-genotype - 13 women,
G/G-genotype - 5 women.

In the first group, a reliable predominance of A/A genotype in comparison with G/G genotype was observed.

Group 2:

G/A-genotype in 42 women out of 67,
A/A-genotype in 13 women
G/G genotype in 11 women

In the second group, a significant predominance of the G/A-genotype over the G/G-genotype was found.

Group 3:

G/A-genotype in 26 women out of 32,
G/G genotype in 4 women
A/A-genotype in 2 women

In the third group of women with pronounced alimentary obesity, a significant predominance of the G/A-genotype over the G/G and A/A genotypes was revealed.

The analysis of the obtained genetic results in comparison with the data of Quinton N.D.et al.of 2001, where the relationship between the 223Arg allele and abdominal obesity was shown in the study in Caucasian women [8, 233-236.], in contrast to the Uzbek population, where a reliable predominance of this allele was observed in the control group in women with normal body weight. However, our data are similar to another study conducted in 2010 by Furusawa T. et al. in the Pacific Islands, where the 223Arg allele prevailed in the control group, and is likely to have a "protective" effect, reducing the risk of obesity [4, 287-294.]

Conclusions:

1. For Uzbek women of fertile age with alimentary obesity, the distribution of the LEPR gene polymorphism Gln223Arg is dominated by women with a GA-genotype.

2. In women with excess weight and in the control group with normal body weight, the homozygous type of polymorphism Arg223Arg of the LEPR gene prevails.

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