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THE 500 YEARS STORY OF HYDROXYCHLOROQUINE AND ITS IMPLICATION ON OUR MEDICAL KNOWLEDGE: FROM MALARIA TO COVID-19

Abstract. Quinine is a famous class of drugs over the last 500 years of the history of medicine. It does not treat disease symptoms, but rather modifies the underlying mechanism of the disproportionate effect of inflammation and immunity. Thus, it is described under the rubric of DMARD (Disease-Modifying Anti-Rheumatic Drugs). The mutation of SARS-CoV-1 to SARS-CoV-2 has given the virus the advantage of bypassing many defenses, allowing the virus to spread widely, causing the current pandemic. During this progressive global crisis, the medical community began to repurpose many of the available drugs to treat SARS-CoV-2 infection. Many antiviral drugs have been proposed. Using hydroxychloroquine for the prevention and treatment of COVID-19 has received significant attention in 2020. The idea of using hydroxychloroquine came from previous experience during the initial outbreak of MERS in 2012 when physicians and other scientists conducted random observations on various approved medication to identify potential treatment for HIV, ZIKA virus-infected Ebola infected patients and MERS infection. Despite earlier encouraging findings from in vitro and early observational studies, randomised clinical trials showed the opposite. Thus, a need to reflect our interpretation of all the scientific findings at differ stages and settings.

Key words: Malaria, Quinine, hydroxychloroquine, COVID-19, pandemia.

Quinine in history

Native South American civilisation, mainly the Incas, discovered that the barks of *quinaquina* tree could treat various febrile illnesses[1,2]. . The famous taxonomist Carl Linnaeus renamed the tree in 1740 to Cinchona tree. The Spanish invaders of Peru in the 16th Century were excited with this remedy, using it to treat Malaria. They started to harvest a large amount of the barks and shipping them to Spain. They called it "Jesuit bark" or "Peruvian bark". It was a sensational drug in European folk medicine but also was a subject of arguments among physicians and intellectuals (Figure 1).

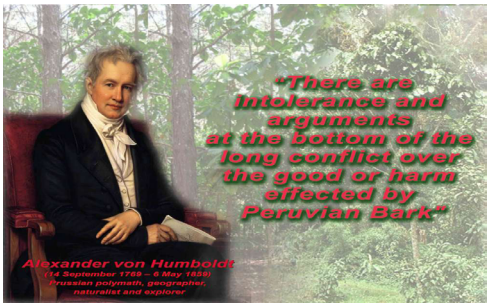


Figure 1 - A quote from a prominent 18th Century natural philosopher recognised the beneficial and toxic effects of the Barks (quinine)

This great demand caused extensive harvesting and even implantation of the tree in other subtropical areas. Today few remaining specimens of this endangered tree remain in Peru and the Andes region. By the early 19th Century French scientists isolated quinine as the effective component of the tree bark [2,3]. The quinine powder was vital and precious, for example, by the 1840s British citizens and soldiers in India were using annually 700 tons of cinchona bark for their health protection. They dissolved the powder in carbonated water, adding sugar and lemon to smoothen the bitterness of quinine, creating "Tonic Water", which when added to the Gin resulted in the cocktail of "Gin and Tonic". Winston Churchill once declared, "*The gin and tonic has saved more Englishmen's lives, and minds, than all the doctors in the Empire."*

The need for quinine uses as anti-malaria medication expanded, but there were not enough barks to cover the European colonial expansions of Asia and Africa. Accordingly, efforts were started to synthesise quinine in the laboratory by the third decade of the 20th Century (figure 2). Meanwhile, extensive use started to show some toxicity and tolerance. The demand for the protection against Malaria among the fighting troops in the Pacific during WW-II required that more/better products be synthesised. Chloroquine was synthesised circa 1945. In a few years, hydroxylation of the chloroquine moiety led to the development of hydroxychloroquine (Figure 2). These forms, chloroquine and hydroxychloroquine, are less toxic and showed better tolerance and are in use today[5].

Physicians began to experiment with the medication and, in the early 1950s, they observed their beneficial effect in the treatment of rheumatoid arthritis and lupus erythematosus using various doses. Combination with other medication(s) reduced potential toxicity and side effects. Thus, hydroxychloroquine has made its name in combination therapy today. They are relatively cheap, and it has an established clinical profile. The World Health Organization (WHO) included them in the WHO list of essential medicines.

In the last thirty years, chloroquine or hydroxychloroquine have been reported to possess potentials activities against various viruses, such as human immunodeficiency virus (HIV), hepatitis A and C virus, influenza A and B viruses, H5N1 virus, Lassa virus, Ebola virus and many others. Initial uncontrolled studies suggested it might have a utility in fighting COVID-19. This was coupled with political and media wrangling, which led to many further clinical trials which more recently showed that they are not as effective as potentially promised and with some toxicity[2][5].

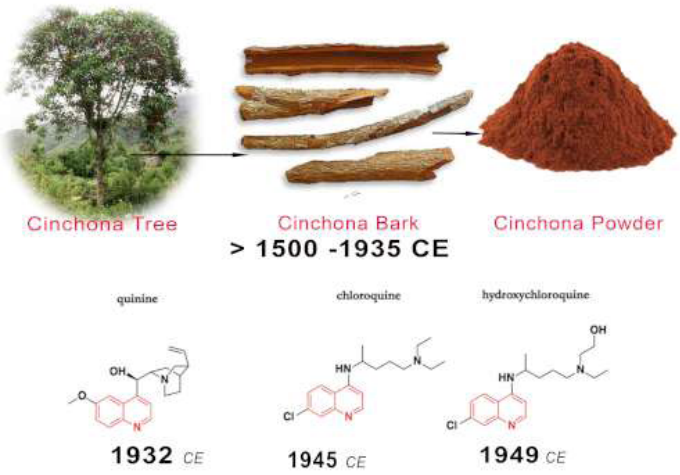


Figure 2 - For almost 400 years, nature was the source of quinine It was only in the 20th Century that synthetic forms were made and used

Mechanisms of action of hydroxychloroquine

Despite the long history and the widespread clinical use of various forms of quinine, insights into the mechanism of action is still evolving [4]. [5] Quinine interferes with the malaria parasite's ability to digest haemoglobin by inhibiting their toxic products. chloroquine or hydroxychloroquine regulate the activity and the excessive reaction of the inflammation and immune system. They neutralise the acidic lysosomal environment, thus interfering

with endocytosis or autophagy preventing the production of harmful substances. They also alter the membrane and intracellular signalling as well as transcriptional pathways, reducing the production of proinflammatory mediators and various cytokines. These mechanisms modulate and smoothen the inflammatory and immunological reaction (figure 3).

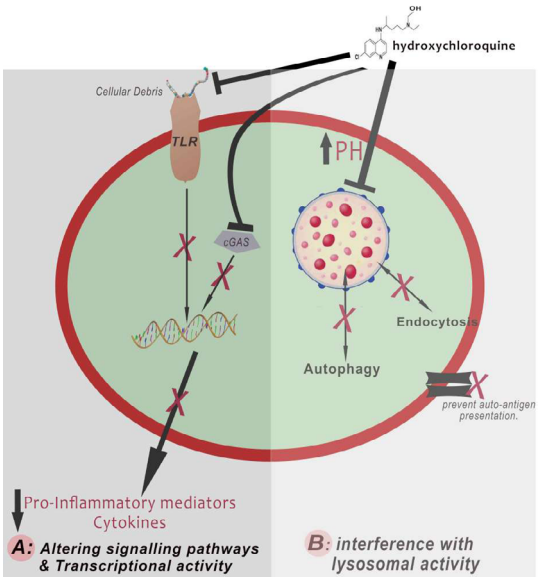


Figure 3 - Simplified schema of the potential mechanism of action of quinine, in particular hydroxychloroquine. Panel **(A)** (*the Pink box to the left*) quinines interfere with some membrane receptors, like Toll-like receptor (TLR) or ACE2, preventing binding to their ligands, and by inhibiting the intracellular nucleic acid sensor cyclic GMP-AMP synthesis (cGAS). These will alter the signalling and transcriptional pathway that produces proinflammatory cytokines, interleukins, or interferons. Panel **(B)** *(the yellow box to the right)* quinine decrease the acidic environment of the Lysosome, hindering the functionality of lysosomes as a waste disposal organelle. Thus, preventing their mechanism of endocytosis (which is essential in viral infection) or autophagy, reducing the presentation of the antigens to the immune cells

The adverse events

Since the early days of using this class of drugs, the benefits and toxic effects were recognised (Figure 1). There are some differences in the side effects between different forms and salts. Hydroxychloroquine is better tolerated and has lesser side effects than other forms of quinine, including chloroquine. The adverse events are related to the dose, plasma level and are more frequently seen with long-term use.[6-9]

The main side effects are headache, indigestion, nausea and diarrhoea, skin rashes and pigmentations, which are worse in sunlight, besides the bleaching of the hair or mild hair loss. Muscles weakening and tinnitus are also recorded [9] .

One of the significant side effects is colour vision disturbances and altered central vision because of the impact on the retina. The retinopathy may progress and is often irreversible even after stopping the medication. Therefore, ophthalmologic follow-up is a critical component when taking these medications [10-11].

The effects on the Cardiovascular system

The cardiovascular effects have been extensively discussed in scientific literature and in the media, even more so following the advocacy to use hydroxychloroquine to compact COVID-19 infection [12].

There is a dual effect on the cardiovascular system. The use of chloroquine or hydroxychloroquine reduce cardiovascular risks in patients with rheumatic diseases. This effect seems to be most relevant in patients with a thrombotic complication owing to systemic inflammation. The combination with aspirin enhances this beneficial effect. It is unknown if we can see these benefits in patients without rheumatic diseases. On the other hand, there are many reports of serious cardiotoxicity[13,14], mainly heart conduction abnormalities, cardiac arrhythmias, and cardiomyopathy, especially in patients taking high dose or in combination with other drugs. These are not frequent complications, though they are more frequent in women and with long treatment use. Fortunately, most of these adverse

events are reversible upon drug discontinuation. Reports of Cardiomyopathies were presented as left ventricular hypertrophy, hypokinesis, exacerbation of left ventricular diastolic dysfunction and heart failure. Some centres recommend investigating these complications with cardiac magnetic resonance imaging and endomyocardial biopsy to provide prognostic insights and confirm the diagnosis of hydroxychloroquine-induced cardiomyopathy[15,16].

The most morbid cardiovascular effects are the effects on ventricular repolarisation, that is prolonging the action potential of cardiac cells[17,18]. Quinine can block many cardiac ionic membrane channels which regulate the electrical properties of the cardiac cells, specifically the potassium channel known as "Inward rectifier K+ channel" causing a delay in the recovery of the cardiac cell action potential. This increases the likelihood of ventricular ectopy and ventricular arrhythmias; mostly *Torsade de pointes*, a short but disorganised ventricular arrhythmia that can degenerate to ventricular fibrillation causing sudden death. The clinical manifestation of this toxicity is by prolonging the QT interval of the electrocardiograms, an indicator of prolonging cardiac action potentials. This prolongation is often seen with electrolyte disturbances or when hydroxychloroquine is given with the other medications such as azithromycin, as used in some quarters for prophylaxis and management of COVID-19. Although *Torsade de pointes* is not common, recent uncontrolled use of these drugs leads to an increase of these arrhythmias, with more deaths. Many medical centres recommend continuous or frequent assessment of corrected QT (QTc) interval on the electrocardiogram, which should not exceed 440 milliseconds. As for all QT prolonging medicines, consider discontinuing these drugs if there are concerning increases in QTc or QTc change from baseline[19,20].

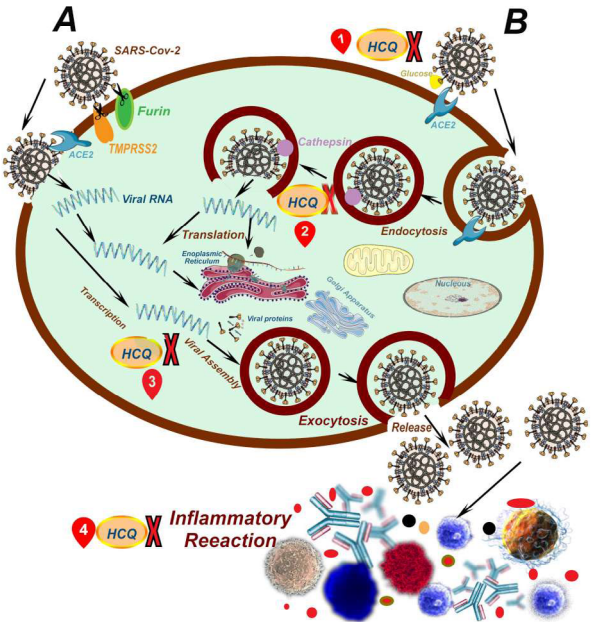
The history of hydroxychloroquine during COVID-19 Pandemic

During 2020, there were over 75 million confirmed cases and more than 1.7 million deaths worldwide because of SARS-CoV-2 infection (COVID-19). During this progressing crisis globally, the medical community started to repurpose many available drugs to manage the SARS-CoV-2 infection. Many antiviral drugs were suggested. However, quinine and its derivatives, like hydroxychloroquine, emerged as a targeted medication in the early months of the pandemic. The idea of using hydroxychloroquine came from previous experience during the initial outbreak of MERS in 2012 when physicians and other scientists conducted random observations on various approved medication to identify potential treatment for HIV, ZIKA virus-infected Ebola infected patients and MERS infection[21][22]. The uncontrolled observations suggested that in some patients chloroquine might prevent the virus from invading the human cells in vitro[22]. These observations were not confirmed with well controlled clinical trials because MERS and SARS-CoV-1 did not cause large epidemic and were under control relatively quickly, thus not enough patients in larger trials.

The interest in hydroxychloroquine emerged with the sudden rise of the cases worldwide with SARS-CoV-2 based on the above observations. It attracted disproportionate attention spurred with the endorsement from political leaders in the USA, France and India, and was amplified by news outlets and social media [23] [5]. Many regulatory agencies like the US Food and Drug Administration (FDA) and Indian regulatory agencies, out of a desperate move, provided cautious advice on its use. As a consequence many COVID-19 patients started taking hydroxychloroquine for prophylactic and treatment of symptoms[24]. The authorisations, however, were quickly revoked within a few weeks [25][26]. This unusual approach was taken with caution by many physicians and other regulators worldwide. The American College of Cardiology said in a statement that given the adverse effects of hydroxychloroquine, those taking the drug should either do so as part of a clinical trial or only after evaluating its risk and benefit [10]. The effect of the media and political pressure leads to unhealthy increase and demand hydroxychloroquine in the first half of the 2020. The uncontrolled use of this medication and some reported cases of death[27]. Furthermore, the unprecedented need for a supply of the drug lead to a real worldwide shortage and limiting dispensing quantities for patients with rheumatic diseases or lupus [1] [28] [29].

The potential role of Quinines on the pathobiology of SARS-CoV-1 (Figure 4)

The mutation of SARS-CoV-1 to SARS-CoV-2 gave the virus an advantage of bypassing many of the defence mechanisms provided opportunities for the virus to be transmitted widely, causing a current pandemic. It also enables the virus to infect cells with multiple strategies, thus provoking a challenge to manage this disease. The justification for the use of hydroxychloroquine is probably based on the experimental works on the mechanism of action (Figure 4).



The main structure of the SARS-CoV-2 virus is its envelope. It is composed of four proteins, including spike glycoprotein (commonly labelled as S protein), small envelope glycoprotein, membrane glycoprotein, and a nucleocapsid protein component. The later attaches to the core RNA, playing part in the replication process. The spike glycoprotein is one of the most critical components of the virus. It facilitates the entry to the cells. It is a trimeric glycoprotein, comprising both functional and receptor-binding domains. Structure-function studies have also shown that the spike protein of SARS-CoV-2 is highly glycosylated[30].

Much has been learned about the current knowledge of the mechanism of SARS-CoV-2 infection during 2020 pandemic [31] [32][33] [34]. The virus uses different approaches to enter the cells. The first (panel A in Figure 4) involved some membrane proteases that cleave the Spike protein, mainly transmembrane serine protease 2 (TMPRSS2) and Furin enzyme[35]. The proteolytic activities of Spike protein help in priming the virus to fuse with plasma members[36]. Some investigators believed binding to angiotensin-converting enzyme 2 (ACE2) is expected to trigger conformational changes in the spike protein facilitates cleavage by the transmembrane proteases [37]. This process results in the fusion of the viral membrane with the plasma membrane, consequently causing the cell entry of the viral RNA (the non endosomal pathway) [36].

The second entry strategy is via the process of endocytosis (Panel B of the Figure 4). The Spike glycoprotein binds to host receptor (ACE2) [38][39], serving as a medium of cell entry[40]. Proteases mentioned above and others like, a disintegrin and metalloproteinase domain 17 (ADAM17) might promote this interaction. In this process, glycosylation of the spike and ACE2 proteins support this process. Thus, hyperglycaemia might induce potential dysregulation of glycosylation of ACE2 and the spike protein of SARS-CoV-2, which possibly augment the spike protein to bind to ACE2 enhancing the viral entry into the cell. Therefore increasing severity COVID-19 in diabetic or obese patients[41]. Quinine and in particular hydroxychloroquine may prevent the virus from binding to the ACE-2 receptor by inhibiting terminal glycosylation creating a less efficient environment for the virus entry [42][43] (Pointer 1 in Figure 4). When the virus enters the cell in the endosomal vesicles forming a highly dynamic, multifunctional cellular compartment with multiple proteolytic enzymes, mainly various forms of Cathepsins which cleave the spike protein at low pH, leading to fusion of the viral envelope and membrane the endosomes. So, uncoated the viral particle releasing of viral nucleic acid (RNA) into the cytoplasm. Chloroquine and its derivatives can modulate the acidification of endosomes and partially inhibiting this process [44] [45](Pointer 2 in Figure 4).

In both strategies, the viral RNA is released. The life cycle subsequently takes place by RNA replication, transcription of the viral protein and final assembly. Some Investigator also suggested that hydroxychloroquine may interfere with some

process of replicase-transcriptase complex [46] (Pointer 3 in Figure 4).

The assembled virus will be released from the infected cell by the process of exocytosis. The new viral loads will further provoke an intense inflammatory reaction. Some investigators believe that hydrochloric acid may also contribute in modulating the inflammatory responses [47] [48] [32] (Pointer 4 in Figure 4).

The potential Clinical Benefits of hydroxychloroquine in COVID-19

During the early days of the pandemic, many are observational studies and small uncontrolled studies supported the benefits of hydroxychloroquine. These were based on the experimental findings and early observations with previous coronaviruses epidemics. In February 2020, a report of clinical trials on patients with COVID-19 in ten hospitals in China suggested that chloroquine treatment might shorten the duration of the disease[49]. French microbiologist Didier Raoult and colleagues published a randomised study of hydroxychloroquine in 20 COVID-19 patients and concluded that this group of drugs had reduced viral load in the nasal swab but didn't report clinical outcomes such as deaths[50,51]. Thought hydroxychloroquine and other quinine were recommended the former is toxic derivative[22,52]. It was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro [53].

It was estimated that hydroxychloroquine dosing regimens for COVID□19 prophylactic to maintain half-maximal effective concentration (EC_{50}) is higher than the dose needed for antimalarial management. Thus, the suggestion was to use 800 mg loading dose followed by 400 mg twice or 3 times weekly for pre□exposure prophylaxis setting and 800 mg loading dose followed in 6 hours by 600 mg, then 600 mg daily for 4 more days for post exposure prophylaxis setting[53]. The complexity of virus pathogenicity as explained above, lead many to advocate combined therapy. Hydroxychloroquine, combined with azithromycin (an antibacterial drug), was clinically noticed to be better to stop the spread of the infection than hydroxychloroquine alone, in addition to significant viral load reduction[50].

These findings fuel the media and political interest despite that many physicians and scientists start to show doubts, in particular due to the serious side effects like the one on cardiovascular that been described above.

Randomised controlled trial with hydroxychloroquine

The interest mixed scepticisms in the use of hydroxychloroquine have necessitated more studies and proper Randomised controlled trial with more in-depth analysis. It is not surprising that by the end of 2020 there are more than 4300 studies recorded (clinicaltrials.gov) of which 265 clinical trials on hydroxychloroquine. Eighty-six of these studies were already completed and reported. Another 84 studies were terminated either early, withdrawn or suspended for various reasons such as the non-recruitment or inadequate sample size[55]. Even more studies (currently about 87 studies) which are still active. These studies were done through the various stages of COVID-19 infection such as pre-or post-exposure prophylaxis, out-patients or symptomatic hospitalised patients or an intensive care unit management [56]. Some studies included the efficacy of hydroxychloroquine in combination with other antibiotics or antiviral drugs or some minerals like zinc [57] or even using lower doses of hydroxychloroquine [58].

The two large randomised trials in hospitalised patients or in the acute intensive care period were WHO SOLIDARITY trial and RECOVERY trial Bother were launched around March 2020 to assess hydroxychloroquine and other potential COVID-19 treatment against the standard care.

Recovery Collaborative Group in the UK run The RECOVERY trial[59]. It was randomised, controlled, open-label platform trial comparing a range of possible treatments with usual care in patients hospitalised with COVID-19. Randomly assigned 1561 patients received hydroxychloroquine and 3155 to receive standard care. The primary outcome was 28-day mortality. It was completed on the 5th of June 2020[59]. The results suggested that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group (59.6% vs. 62.9%; rate ratio, 0.90; 95% CI, 0.83 to 0.98) [59]This study provided an extra finding that a moderate dose of dexamethasone (6 mg daily for 10 days) in patients with COVID-19 and respiratory failure who required therapy with supplemental oxygen or mechanical ventilation a can reduce mortality[60].

The WHO SOLIDARITY Trial was a large multicentre study involving 405 hospitals in 30 countries. It was reported recently (December 2020) [61]. The study randomly assigned 11,330 adults in patients with COVID-19. They were assigned to one of the five options (four active and the local standard of care).

1. 2750 were assigned to receive remdesivir,
2. 954 to hydroxychloroquine,
3. 1411 to lopinavir (without interferon),

4. 2063 to interferon (including 651 to interferon plus lopinavir), and

5. 4088 to no trial drug.

The major finding that neither remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalised patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay[61].

ORCHID (Outcomes Related to COVID-19 treated with Hydroxychloroquine among In-patients with symptomatic disease) trial. It was a multicentre, blinded, Randomised trial of hydroxychloroquine versus placebo for the treatment of adults hospitalised with COVID-19[62]. ORCHID trial was halted as it did not show any benefit for hydroxychloroquine based on its seven-point ordinal scale outcome [63][64].

The randomised controlled trial in China involved 16 government-designated COVID-19 treatment centres in China, in the first weeks of February 2020. It recruited 150 laboratory confirmed COVID-19 hospitalised patients. The study reported that the administration of hydroxychloroquine did not result in any benefit than the standard of care. Adverse events were higher in hydroxychloroquine recipients than in non-recipients[65].

Furthermore, few studies assessed the pre-exposure prophylaxis to COVID-19. Skipper et al. [66]reported multisite, randomised, double-blind, placebo-controlled trial enrolling 491 participants from the United States and Canada. They found hydroxychloroquine did not substantially reduce symptom, severity or prevalence over time in no hospitalised persons with early COVID-19.

The Coalition of COVID-19 Brazil Investigators used hydroxychloroquine and azithromycin to treat patients in a multicentre, randomised, open-label, three-group, controlled trial involving 504 hospitalised patients with suspected or confirmed COVID-19 who were receiving either no supplemental oxygen or a maximum of 4 litres per minute of supplemental oxygen. The study found that the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status in 15 days as compared with standard care[67].

Other clinical trials showed hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure[68] [69]. Other regional trials in many countries provided further confirmation that the use of hydroxychloroquine, whether alone or with combination with other treatment is not warranted for the treatment at any stages of COVID-19.

Lessons from the history of hydroxychloroquine.

We have learned a lot from the history of hydroxychloroquine over the past 500 years. Using hydroxychloroquine for the prevention and treatment of COVID-19 has received significant attention in 2020. Most notably, the enthusiasm for hydroxychloroquine has been one of politicisation rather than science[55], confirming that science and politics are not intertwined. By definition, science but not politics require diligence and honest assessment of the findings[70]. This public enthusiasm prompted for continuing scientific investigations and more rigorous evaluations that provide sufficient evidence to exclude any benefit for hydroxychloroquine with or without azithromycin in all stages of COVID-19 [71] [55][72].

Despite earlier encouraging findings from in vitro and early observational studies, randomised clinical trials showed the opposite. Thus, a need to reflect our interpretation of all the scientific findings at differ stages and settings. For example, is the the dosing estimate using the conventional pharmacokinetics for a drug that works at both extracellular and intracellular level appropriate? Is dosing used for one condition like rheumatoid arthritis or as antimalarial medication applied to the drug to be used as antiviral medication[73]?. Is the contradiction between our investigational and clinical findings related to dosage? Is our existing knowledge of in vitro and in vivo viral replication mechanisms the same? The experience with hydroxychloroquine also showed that using data from a similar viral infection may not be sufficient for a learned conclusion. For example, studies identify functional differences between SARS-CoV-1 and -2 entry processes and mechanistically explain the limitation of in vivo utility of hydroxychloroquine as a treatment for COVID-19[44]. Most of the early knowledge of the other coronavirus effects may not be used because of the sophisticated mutations induces by SARS-CoV-2 in the pattern that produced COVID-19 pandemics. It is a somewhat tricky questions of our future approach to research and interpreting the finding as we apply it to our medical practice. It shows us that mutations and natural selection are a powerful tool that can affect our medical management.

The other lesson we learned is that viral pathobiology can differ in different cells. Thus, using studies with cells from specific organ or species cannot be extrapolated to other organs. We have still used the concept in our modern science communities, although we have often claimed that this is not the case. For example, Hoffmann et al.

have shown that hydroxychloroquine can block the entry of coronavirus in the African green monkey kidney cells, but not human lung cells[74]. It shows that extrapolation of the mechanism from different species of the species cannot be generalised. Thus, many of the mechanism we described above in hydroxychloroquine may prove inaccurate in human-specific cells. Thus, hydroxychloroquine history was illuminating in many aspects of its early day of discovery 500 years ago. Today, the interaction of science with political and social factors and how evolution and biology work may influence our medical judgment. These lessons can help in our pursuit of knowledge and its application.

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Section 2
Original research

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INTRACELLULAR PRODUCTION OF CYTOKINES IL-1 AND IL-10 IN PATIENTS WITH THIN ENDOMETRIUM SYNDROME WITH RECURRENT IMPLANTATION FAILURE

Abstract. Evaluation of endometrial cytotoxic lymphocytes using flow cytometry for "thin endometrium" syndrome in 24 patients with recurrent implantation failure (RIF). The revealed changes in the level of immunocompetent cells indicate that the pathogenesis of recurrent unsuccessful implantation lies in a pronounced decrease in the level of CD8+ cytotoxic / suppressor lymphocytes and CD56 + lymphocytes, as well as a sharp decrease in the intracellular production of cytokines IL-1 and IL-10 by endometrial lymphocytes. Deficiency of signaling molecules and their synthesis of proteins, which occurs in the syndrome of "thin endometrium", is accompanied by disruption of peri-implantation mechanisms, including the regulatory action of sex steroid hormones. Prospects for the treatment of failed implantation attempts lie in the selective effect on the endometrium with impaired receptivity. The treatment strategy is to eliminate the microbial-infectious agent with the use of rational antibacterial and immunomodulatory therapy at the first stage, induction of intracellular regeneration: biphasic hormone therapy (low doses of estrogen and progesterone). Preference is given to micronized progesterone preparations with bioidentity to endogenous progesterone, higher bioavailability and efficiency in the intravaginal route of administration.

Key words: thin endometrial syndrome, recurrent implantation failure, endometrium, endometrial cytotoxic lymphocytes, intracellular cytokines IL1, IL10.

Introduction

The problem of repeated unsuccessful implantations is considered one of the most urgent in modern reproductology. Implantation disorders are the cause of miscarriage, infertility, ineffective in vitro fertilization (IVF) cycles and other methods of assisted reproductive technologies, since only 1/3 of IVF failures are due to the quality of the embryo and 2/3 of failures are associated with pathological changes in the endometrium [1].

The thickness, morphological structure and receptivity of the endometrium are the main signs of endometrial maturity and, at the same time, criteria for predicting a successful pregnancy, which are guided in clinical practice [2]. The preimplantation endometrium is distinguished by the presence of a developed capillary network, microcirculation, tissue oxygenation, proliferative activity of epithelial and stromal cells, active metabolism and readiness of the endometrial neuroreceptor apparatus. The period of optimal receptivity of the endometrium begins on the 6th day after ovulation and lasts 4-5 days, which corresponds to 20-24 days of the menstrual cycle, and this period is called the "implantation window".

The most frequent pathology of the endometrium, in which multiple secondary morphofunctional

changes occur, disrupting the cyclic transformation and receptivity of the mucous membrane of the uterine body, is chronic endometritis. At the same time, more and more often with this pathology, the syndrome of "thin endometrium" occurs.

The criterion for "thin endometrium" is considered to be the thickness of the endometrium less than 7 mm and the absence of a three-layer structure during the "window of implantation". The pathophysiological features of the "thin endometrium" consist in insufficient growth of the glandular epithelium, depletion of blood vessels and impaired expression of a number of regulatory cytokines, growth factors, natural killer cells, lymphocytes, which in turn reduces the implantation capacity of embryos [3].

In addition, insufficient production of progesterone can lead to suppression of progesterone receptors in the epithelial cells of the endometrium, as a result of which there is a decrease and complete loss of its receptivity by the time of implantation, no "implantation window" is formed, implantation of the ovum does not occur, which leads to infertility, and if implantation occurs, it is ineffective and miscarriage develops [4].

In recent years, endometrial dysfunction has been associated with pathological changes in the expression of numerous factors. Among new molecular research methods, the role of cytokines IL-1, IL-6, IL-10, interferon gamma, tumor necrosis factor, growth factors (leukemia inhibiting factor - LIF, granulocyte macrophage growth factor, vascular endothelial factor, transforming growth factor beta1), expression of estrogen and progesterone receptors as markers of endometrial receptivity [5, 6].

It should be noted that today the focus of scientific interest is intracellular cytokines and growth factors responsible for the receptivity of the endometrium. Intracellular production of proinflammatory cytokines by endometrial lymphocytes, in particular IL-1, are considered as biologically active factors that improve the decidualization process. At the same time, the intracellular production of anti-inflammatory cytokines, in particular IL-10, improves the receptivity of the endometrium. Integral assessment of pro- and anti-inflammatory cytokines serves as a marker of the functional state of the endometrium and a prognostic criterion for the effectiveness of therapy [7].

Thus, the aim of the present study was to study the clinical and immunological parallels in the syndrome of "thin" endometrium in patients with recurrent implantation failure.

Materials and research methods

The study included 24 patients with recurrent implantation failure and thin endometrial syndrome. The comparison group consisted of 20 patients without reproductive losses and the presence of normal endometrial thickness on days 20-24 of the cycle. For each woman, an individual observation card was drawn up, including the results of the examination with the study of complaints, somatic and obstetric-gynecological anamnesis, data of general and gynecological status, generally accepted laboratory, as well as special research methods according to indications: ultrasound of the pelvic organs, determination of the level of hormones in the blood, ELISA for infections, determination of lupus coagulant and anti-hCG in the blood, genetic consultation and karyotyping.

The criterion for "thin endometrium" was the thickness of the endometrium less than 7 mm on the 20-24 day m.c. with transvaginal echography.

The material for the immunological study was biopsy specimens of the uterine endometrium obtained by Pipel biopsy using a Goldstein catheter. Isolation of immunocompetent cells from endometrial tissue was performed using an enzyme-free method. The endometrial fragments were placed in a Medicon container (Becton Dickenson / USA), phosphate buffer was added, and ground in a Medimachine homogenizer (Becton Dickenson / USA) for several minutes. The resulting cell suspension was centrifuged for 30 min in a ficoll-verographin density gradient (d = 1.078). The content of endometrial lymphocytes CD3+, CD8+, CD16+, CD56+ (stained with phycoerythrin) and the level of intracellular production of cytokines IL-1 and IL-10 (stained with FITC after permeabilization of the cell membrane) were determined on a flow cytometer using the CELLQuest program.

Statistical analysis of the obtained results was carried out using Student's t-cryteria. Differences between the compared groups and numbers were considered significant when the probability of error was $P \leq 0.05$.

Results and discussion

In the main group, the average age of the patients was 31.3 ± 3.0 years, in the comparison group - 32.8 ± 3.6 years. The analysis of reproductive function revealed the following. All patients in the main group had a history of two or more episodes of implantation failure. Recurrences of implantation failure manifested themselves in the form of spontaneous miscarriages,

missed pregnancies, or unsuccessful IVF attempts. The history of the patients noted the presence of chronic endometritis, endometriosis / endometriotic cyst, uterine fibroids, hydro / saktosalpinx, polycystic ovary, endometrial polyp. During karyotyping, a normal karyotype was revealed in all examined patients. The study of the hemostasiogram revealed thrombophilia in 20% of cases. The examination revealed CMV, HSV, mycoureaplasma.

In the comparison group, 80% of patients had repeated pregnancies, and 60% had repeated births. In three cases, the male factor of infertility (azoospermia), the presence of STIs was the reason for contacting a reproductologist. When examining all applicants of the comparison group, the thickness of the endometrium was 19-22 m.s. was more than 8 mm.

The data characterizing the peculiarities of the subpopulation composition of endometrial cytotoxic lymphocytes in patients with recurrent implantation failure and thin endometrial syndrome are presented in the table.

Table - Cytotoxic endometrial lymphocytes in patients with recurrent implantation failure and thin endometrial syndrome

Indices, %	Comparison group, n = 20	main group, n = 24
total CD8+	8,6±1,7	0,6±0,4*
total CD16+	2,3±0,6	1,8±0,6
total CD56+	3,8±0,9	1,3±0,3*
total IL1+	8,3±3,3	0,7±0,8*
total IL10+	5,6±0,8	0,13±0,16*
IL1+/ IL10+	1,56±0,68	0,43±0,38

* Differences with comparison group are significant, P <0.05.

It was found that in patients with recurrent implantation failure and thin endometrial syndrome, a decrease in endometrial receptivity was observed, which was expressed in a significant (18-fold) decrease in the level of CD8 + cytotoxic / suppressor lymphocytes (P <0.001), as well as a 3-fold decrease in the level CD56 + cells. The level of natural killer cells with the CD16 + phenotype tended to decrease.

It should be noted that in patients with recurrent implantation failure and thin endometrial syndrome, there was a sharp decrease in intracellular cytokines by endometrial lymphocytes - interleukin-1 by 11 times and interleukin-10 by 4 times compared to the same parameters in the comparison group. The IL1 + / IL10 + index tended to decrease, but no significant differences were found, as there was a decrease in both pro-inflammatory IL-1 and anti-inflammatory IL-10 cytokines.

Thus, the revealed changes in the level of immunocompetent cells indicate that the pathogenesis of relapses of unsuccessful implantation is a pronounced decrease in the level of CD8 + cytotoxic / suppressor lymphocytes and CD56 + lymphocytes, as well as a sharp decrease in the intracellular production of cytokines - IL-1 and IL-10 by endometrial lymphocytes. It is known, the implantation process can be thought of as an inflammatory reaction that promotes attachment and invasion of the embryo into the endometrium, providing the necessary interaction with the maternal vascular system. Deficiency of signaling molecules and their synthesis of proteins, which occurs in the syndrome of «thin endometrium», is accompanied by disruption of periimplantation mechanisms, including the regulatory action of sex steroid hormones [8].

The decisive role in the effect on the endometrium is not played by the steroid hormones themselves circulating in the peripheral bloodstream, but is determined by their interaction with functionally complete receptors of the endometrial tissue for the corresponding steroid hormones. Due to the presence of receptors - «recognition molecules», the target cell is able to accurately distinguish the smallest concentration of tropic hormones in the extracellular fluid [9].

Prospects for the treatment of failed implantation attempts lie in the selective effect on the endometrium with impaired receptivity.

Considering that the leading role in the genesis of miscarriage is assigned to an infectious factor, and according to V.M. Sidelnikova [8], chronic endometritis is histologically verified in 73% of cases, and in 87% there is persistence of opportunistic microorganisms in the endometrium, and taking into account the decision of the World Congress of Obstetricians and Gynecologists (FIGO, Kuala Lumpur, 2007) that all without exception, cases of undeveloped pregnancy should be associated with the presence of chronic endometritis - an important stage in the treatment strategy is to eliminate the microbial-infectious agent and includes rational antibacterial and immunomodulatory therapy.

In addition, when studying the pathomorphogenesis of habitual miscarriage, I.O. et al. [9] demonstrated the disruption of the processes of cellular and intracellular regeneration of endometrial epithelial cells, which leads to insufficient expression of receptors for both progesterone and estrogens and underlies a decrease in the receptivity of the endometrium with a "closed window of implantation". The treatment strategy is the induction of intracellular regeneration: biphasic hormone therapy (low doses of estrogen and progesterone). For the intensification of regenerative reactions in endometrial cells, great importance is attached to both hormonal and mechanical influences with the restoration of endometrial receptivity.

Thus, the preparation of the endometrium for pregnancy should be carried out in stages. The preliminary stage includes antibiotic therapy of chronic endometritis with the use of immunomodulators, as well as other means, including physiotherapy, that can potentially restore the receptivity of the endometrium. Impaired endometrial receptivity, based on the lack of expression of receptors for both progesterone and estrogens, formed the basis for the development of a therapy strategy with the induction of intracellular regeneration: biphasic hormone therapy (low doses of estrogens and progesterone), which aims to induce the regenerative activity of endometrial epithelial cells with subsequent differentiation under the influence of progesterone [11-14]. In this case, preference is given to intravaginal routes of administration of micronized progesterone with a proven higher bioavailability and effectiveness. In addition, scientific studies of the pharmacokinetics of progesterone have shown that with the vaginal route of administration, the concentration of progesterone in the endometrium is significantly higher than with intramuscular administration [15].

From these positions, the drug of choice for hormone therapy with gestagens is Luteina - this is the latest generation of gestagen, which is completely bioidentical to endogenous progesterone: by the formula, by the mechanism of action in the body and by the effect. When using vaginal tablets Luteina, due to absorption through an extensive network of venous and lymphatic vessels of the vagina, a «first-pass effect through the uterus» is created, providing high concentrations in the endometrium and high clinical efficacy of Luteina.

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COMORBIDITY CONCEPTION OF SOMATIC DISEASES IN CARDIOLOGY PRACTICE

Abstract. The article review discusses the comorbidity of somatic diseases in cardiology practice. There are discussed the definition and formation history of comorbidity theory prevalence and options for the development of comorbidity. In the article also is analyzed the prevalence of comorbidity in the population and cohorts of individuals with various diseases. The commonality of risk factors for chronic non-inflectional diseases is an important prerequisite for the development of comorbidity. This study considers various options for the comorbidity development. We have to apply the concept in practical health care create. We also have to create the available tools to determine the prognostic of comorbidity of somatic diseases and. In the article are presented three methods for assessing the prognosis and survival in case of comorbidity of somatic diseases. There are considered unified views on the tactics of treatments, prevention of comorbidity and high risk of complications. At the moment the data is being accumulated on the benefits of poly pills tactics treatment. However, studies with firm endpoints are few in number to date. We have to combine the medicine with different mechanisms of action that have an evidence base for achieving target levels of individual indicators requires. The authors propose algorithms for managing patients with comorbid pathology, for which they have developed schemes of actions from diagnostics to monitoring the main indicators for evaluating the effectiveness of therapeutic interventions and preventive measures.

Key words: comorbidity, cardiovascular diseases, risk factors, forecasting scales.

List of abbreviations:
AH – arterial hypertension
WHO – World Health Organization
IHD – Ischemic heart disease
NID – Non-inflectional diseases
DM – Diabetes Mellitus
CVD – Cardiovascular diseases
COPD – Chronic Obstructive Pulmonary Disease

According to the documents of WHO about non-infection diseases (NID), 80% of the death are associated with four groups of NID in the developed countries in current certainly. [1] The cardiovascular diseases (CVD) at the first place. The same way the neoplastic and pulmonary diseases, there are Chronic Obstructive Pulmonary Disease (COPD) and Diabetes Mellitus (DM), are actual. [2]

The doctors encounter with more than one disease, they face with combine and mix pathology in the last years. It is called comorbidity, the Latin term means «coniunctim» and «morbus» - «together» and «disease». The comorbidity is coexistence two and more syndromes (transsyndromic comorbidity) or two and more diseases (transdiseases comorbidity) in a patient. The syndromes or diseases are interconnected or coinciding in time. [5].

The «comorbidity» term was suggested in 1970 by an American epidemiologist and researcher Alvan R. Feinstein. He considered by comorbidity the presence of a concomitant clinical picture, which manifests with main and other diseases. The

professor Feinstein showed it on the example of patient with acute rheumatic fever. The patients had a worse prognosis if they had concomitant diseases. Currently, the comorbidity is separate research direction.

The research of comorbidity is actual issue:

1. The comorbidity has pandemic condition and it has a lot of significance to prognosis. According to M. Fortin research, the prevalence of comorbidity is 69% of young patients, up to 93% of middle age patient and up to 98% of older patients group. The count of comorbidity significantly increases from 10% in the 19 ages, up to 80% in the 80 ages and it up more in elderly patients naturally. According to domestic research of pathological materials, the frequency of comorbidity is up to 94,2% [6, 7].

2. Doctors often have got the patient with comorbidity in the practice, it is two or more nosology of diseases. Sometimes the patient has got 6 or 8 diseases in isolated cases, it is up to 2,7% [8];

3. The comorbidity causes the problems to diagnosis, choice the treatment tactics, management patient tactics and prevention of associated complications diseases.

4. The comorbidity is independent state of death and it is significantly affects the prognosis of the disease and life. According to the Russian researches, if the patient with cardiovascular diseases has two or more other diseases, the risk of developing primary endpoints and deaths are 2 or 3 times more than the control group ($p<0.002$) [10].

According to the comparative cohort research, other cardiovascular diseases is founded up to 41% of the all cases and non-cardiovascular disease is founded uo to 35% of all cases in the patients with ischemic heart disease (IHD). It is 2 or 2,5 times more that in the patients who hasn`t the IHD [11].

The 80% of patient with angina pectoris has got a combination of two or more somatic diseases in reality doctors practice. It happens in spite of that the somatic diseases has got difference in frequency of the gender characteristics. The women have comorbidity of IHD, thyroid diseases and cholelithiases. The men have comorbidity of brain`s vessels atherosclerosis, nephritises, urolithiases, COPD, stomach ulcers [11]

In the several researches was shoved that comorbidity, somatic diseases and patient`s ages have got the clear correlation between each other's. It together affected the patient`s clinical condition. If one says about the compatibility of pathologies in elderly patients, the most common following combinations are atherosclerosis of the heart, brain, AH, emphysema of the lungs, neoplastic processes in the lungs, digestive system, on the skin, the gastroesophageal reflux disease, gallstone disease, gastroesophageal reflux disease, chronic pyelonephritis, prostate adenoma, DM, arthrosis, the spine osteochondritis, cataracts, glaucoma, hearing loss, osteoporosis. Recently, special attention has been paid to the combination of IHD and digestive system pathology [12].

The famous risk factors have the main role in development of the comorbidity CVD and NID [14, 15]. Obviously the universal risk factors start the cascade of several somatic disease systems. In other words, the same risk factors can simultaneously contribute to the development of CVD, respiratory diseases, oncology diseases, endocrinology diseases (table 1). Certainly, the hereditary predisposition has a significant and main role [16].

Table 1 - The general risk factors of basic non-infection diseases

Risk factors	Cardiovascular disease	Diabetes mellitus	Oncological disease	Respiratory disease
Smoking	+	+	+	+
Harmful consumption of alcohol	+		+	
Poor nutrition	+	+	+	+
Lack of physical activity	+	+	+	+
Obesity	+	+	+	+
The BP increasing	+	+		
The high level of glucose in the blood	+	+	+	
The high level of cholesterol in the blood	+	+	+	

We know several options for the development of the comorbidity of somatic diseases in cardiological practice:

• There are no etiology links between diseases (in mechanical combination)

• There has the pathology links between diseases and disorders

• There are has the causality of a disease, it can be cause another disease

It is gratifying to note, the conception of comorbidity included in modern scale for prediction the complications risk and in the fatal cases. The illustrative example of the modern scale is European scale of the cardiovascular risk complications by AH. It shows that the predicted risk can be increased several times by similar numbers of systolic or diastolic blood pressure, the presence of additional violations and associated diseases.

The predictive assessment methods of somatic disease comorbidity

The foreign researches have made enormous attempts to quantitatively assess of the clinical and prognostic significance in the comorbid pathology patients [17]. The number of indices and systems have been developed for the purpose. The main ones are the following Kaplan-Feinstein index (KFI), Index of Co-Existent Disease (ICED), Geriatric Index of Comorbidity (GIC), Total Illness Burden Index (TIBI), Chronic Disease Score (CDS), Adjusted Clinical Groups (ACG), Cumulative lllness Rating Scale (CIRS or CIR), Cumulative lllness Rating Scale for Geriatrics (CIRS-G) [1,2].

Comparative overview of a number indices (Charlson, CIRS, Kaplan-Feinstein, GIC) shows in 2010 year that the GIC is the most accurate predicting mortality index in hospitalization and the CIRS is index of the length of hospital stay. It is for predicting adverse hospitalization outcomes [3].

Another systematic review shows in 17 methods for assessing comorbidity in 2009 year, that the CDS, ACG, Charlson, CIRS and DUSOI are the most commonly used indices.

The authors concluded that the methodology needs to be developed. It has to be combination of multiple indices. The analysis of questionnaires and scales shows the correct of conclusion. Today the original tool for quantitative and predictive assessment of comorbidity hasn't been developed in the firs-line Russian doctors` practice.

Currently, the Charlson index is widely used in clinical science practice (Table 2). It is the point assessment system from 0 to 40 score, it allows to use the comorbidity diseases to predict the 10 years survive rate [18]. When counts the all points are summed up of comorbidity diseases. The one point is added every ten years of live if the patient exceeds the age of forty.

There is also an opportunity to estimate the patient`s age and deaths rate. It is 12% without comorbidity diseases and it rises to 25% with 1 or 2 points of comorbidity scale, 52% with 3 or 4 points of comorbidity scale, 85% with 5 points of comorbidity scale.

Table 2 - The score of concomitant disease with comorbidity index calculation Charlson

Concomitant diseases	Score
Acute myocardial infarction	1
Heart failure	1
The lesion of the peripheral vessels (the presence of intermittent claudication, aortic aneurism more than 6sm, acute arterial insufficiency, gangrene)	1
Transient ischemic attack	1
The stroke with minimal residual effects	1
Dementia	1
Bronchial asthma	1
Chronic nonspecific lung disease	1
Collagenases	1
Peptic ulcer and/or duodenal ulcer	1
Cirrhosis without portal vein hypertension	1

Diabetes mellitus without end-organs lesions	1
The stroke with hemiplegic or paraplegic	2
Chronic kidney disease with level of creatinine more than 3mg%	2
Diabetes mellitus with end-organs lesions	2
Malignance tumors without metastases	2
Acute and chronic lymphocytic or myeloid leukemia	2
Lymphomas	2
Hepatocirrhosis with portal vein hypertension	3
Malignance tumors with metastases	3
Acquired immunodeficiency syndrome	6

In the series of cohort researches to predict 10-years survival in patients with AH (n=110) and/or IHD (n=110) who has comorbidity of somatic diseases (COPD or DM) are shown genders difference (Table 3). The 20% patient`s survival rate is higher more among women, than men if they have AH and IHD. The proportion of people with low survival in both groups is 2 times higher than in groups of people with high 10-year survival rates in general. The patients with comorbidity of AH, IHD and DM has in low survival rate [11].

Table 3 - The Charlson index of comorbidity of 10-year survival rates in men and women with AH and IHD

Index	I group of AH n=110		II group of IHD n=110	
	Men n=56	Women n=54	Men n=80	Women n=30
More than 90%, n(%)	13(23,2)	8(14,8)	18(22,5)	5(16,7)
77%, n(%)	13(23,2)	11(20,4)	15(18,8)	4(13,3)
53%, n(%)	9(16,1)	7(13,0)	15(18,8)	6(20,0)
21%, n(%)	21(37,5)	28(51,9)	32(40,0)	15(50,0)

We have some rules to create the **clinical diagnosis formulation** for the comorbidity patient, it has to be observed in doctors practice [5, 13].

The ground rule is to highlight **the main** and **background** diseases as well as the **complications** and **concomitants** pathologies:

1. The highlight of **the main** disease is the nosological unit that determines the primary need for treatment in connection with the greatest threat to life or disability. As a rule, the disease is the reason for seeking medical help, but the situation can change if we examine the patient. The main disease can be the least prognostically favorable disease, in that case all other diseases become concomitant. Sometimes the main disease can be the several competing diseases.

2. **The competing** diseases is the other nosological unit which has the same criteria of main disease. **The background** disease causes the unfavorable course of underlying disease, contributes to the development of complications. The background disease has to be treated as well as the main disease.

3. **The complications** further in the unfavorable outcome and sharp deterioration in the patient`s condition. They are pathogenically associated with

the main disease. In some cases, the complications of main disease associated by etiology and pathology factors. It means that the main disease and complication are conjugated. The complications have to be listed in decreasing order of predictive or disability significance.

4. **The rest** of the diseases, which patient has got, have to be listed in order of importance.

5. **The concomitant** disease isn`t associated etiologically and pathogenically with the main disease

The treatment tactics and basic principles in prevention of comorbid pathologies in the cardiology practice issue

The one-time correction of the several diseases is the one of the main patients with comorbidity management aspects [19, 20]. At the same time, the main goal remains to reduce the overall risk of complications and fatalities. If you adhere to international recommendations for the treatment of comorbid patients, it is required to take at least 5-6 drugs in total. In this regard, an urgent question arises about adherence to long-term therapy. According to American expert Valentin Fuster, the factors that determine a patient's poor adherence to treatment include: complex treatment, the number of drugs taken and the number of chronic diseases [21]. Multicomponent therapy is justified by the achievement of target levels of key indicators, since individual drugs from the point of view of evidence-based medicine prevent the risk of developing global complications. However, the issues of drug interactions and the cost of treatment are serious medical and social problems. Recently, the concept of poly pills has been widely discussed, when one tablet contains drugs with several mechanisms of action. For example: antihypertensive, lipid-lowering and antiplatelet agents in the one pill. There are a number of arguments for the widespread use of poly pills treatment. These are the aging population of the world (the proportion of older and elderly people will increase by 20-30% by 2050), urbanization / sedentary lifestyle, an impending epidemic of obesity and diabetes mellitus. The factors create a prerequisite for the development of comorbidity in somatic diseases. On the other hand, low adherence to treatment and low compliance with a healthy lifestyle can be addressed with poly pills treatment. Along with the advantages, poly pills treatment has some limitations. Namely, the lack of the possibility of dose titration, since the drugs are produced with fixed doses. Also, from an evidence-based medicine perspective, the effect of poly pills treatments on endpoints is not fully understood. Also, from an evidence-based medicine perspective, the effect of poly pills treatment on endpoints isn`t fully understood. Similar clinical trials are being carried out by the pharmaceutical industry in Latin America and India. It must be emphasized that this initiative is supported by WHO. Currently, two-component drugs (antihypertensive and statins) or two-three-component antihypertensive drugs with various fixed doses are widely used in clinical practice.

When we have to choose a treatment strategy, we have to take into account the overall risk of complications and the variant of comorbidity of somatic diseases. the principle of selection of therapy may be different with different mechanisms of development of comorbidity. For example: the presence of a pathogenic connection between diseases allows the use of a drug acting on this link, which can simultaneously reduce the severity of interrelated diseases. The presence of a mechanical combination of several somatic diseases requires the use of targeted multicomponent therapy. However, it is impossible to define strict indications for the use of multiple drugs or the poly pills treatment tactics. In some cases, a combination of the principle of polypharmacy and poly pills treatment tatcis may be considered. Despite such a differentiated approach, the unifying link of all variants of the comorbidity of somatic diseases is a change in lifestyle, which is multifaceted.

When discussing the prevention of comorbidity of somatic diseases, it is necessary to emphasize the strategy of three levels [22]. Prevention at the population level is the broadest and most effective, since the impact is carried out on those lifestyle and environmental factors. It increases the risk of developing non-communicable diseases in the population and their comorbidity. High risk strategy is identifying and reducing the levels of risk factors in people at increased risk of developing NID. Finally, targeted secondary prevention is the prevention of progression and complications of the comorbidity of NID diseases.

Conclusion

The comorbidity of somatic diseases occurs often in cardiology practice, it often has the gender differences. The comorbidity increases the severity of the patient`s condition and it worsens the patient`s prognosis. It has to be considered in diagnosing and developing treatment tactics. The treatment of several diseases requires taking into account the combination of drugs. It has to be prescribed with

differentiated and selected taking into account efficiency, portability and side effects. The using of poly pills treatments have to be considered in rationalize therapy. However, clinical studies have to be assess their effectiveness from the point view of evidence-base medicine. Multicomponent therapy is one of the basic principles in reducing the goal risk of complications and fatalities.

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ROLE OF VARIOUS RISK FACTORS IN THE DEVELOPMENT OF INFANTILE CEREBRAL PALSY

Abstract. The purpose of this study was to establish the role of various risk factors in the development of cerebral palsy in children, through a retrospective study of 150 children with cerebral palsy (main group) and 150 healthy children (control group). The vast majority of children 88,0% had varying degree psychological and speech delay. 50.7% of children in the control group were found to have had respiratory infections up to 6 times a year. 95.3% of children with cerebral palsy were sick up to 6 times a year. No children were found to be incidentally ill in the main group vs. 43.3% of such children in the control group. The following factors were found to contribute to the development of infantile cerebral palsy syndrome: hyperbilirubinemia, 33.8%, head and cervical spine injuries, 15.2%, severe infections with septic condition, 11.7% of cases. The identification of risk factors is also very important in the early rehabilitation of children at high risk of developing cerebral palsy.

Key words: children's cerebral palsy, risk factors, postnatal risk factors.

Relevance

The rapidly growing disability is now one of the top challenges faced by modern society and one of the most common causes of lifelong disability [1,2].

Data from the National Genetic Registry of the Republic of Kazakhstan suggest that 2000 to 3500 children are born annually in the country with congenital and hereditary disorders, that is 20.0-24.3 per 1000 live births [6]. Infantile cerebral palsy (CP) accounts for the largest proportion in pediatric disability profile: 30% to 70%. In Kazakhstan, according to statistics, there are registered more than 44 thousand disabled children, of which number over 10 thousand are diagnosed with cerebral palsy [6].

In Kazakhstan the prevalence of cerebral palsy has increased 1.6 times from 44.6 in 2006 to 73.6 in 2015 per 100,000 population [6].

Children suffering from infantile cerebral palsy require constant care, long courses of expensive comprehensive therapy both inpatient, and outpatient [3]. Most such children are socially maladapted and dependent on others [4]. Development of adaptation, socialization and employment programs, the earliest possible introduction of new therapeutic modalities to intensify the rehabilitation activities in cerebral palsy with a decrease in the number of adverse outcomes, such as disability, are strategic focus areas for health care authorities dealing with this problem [5].

Material and methods

The study we conducted was designed as a retrospective analytical research into the risk factors for cerebral palsy development in 150 children in the city of Almaty, by reviewing the following primary medical records of recruited participants and their mothers: a record of discharge from a maternity hospital (Form No. 113/u), newborn development record (Form No. 097/u), delivery record (Form 096/u), prenatal/notification record or individual card of a pregnant woman (Form 111/u), child development record (Form 112/u), case report (Form 027/u).

The study was approved by the KazMUCE Local Ethical Committee. Informed consent was obtained from parents or guardians of the children.

A control group comprising 150 healthy children of the same age, homogenic in terms of age and gender, was set up to obtain a reliable assessment of the results.

The control group children were recruited from the catchment areas of pediatric polyclinics in Almaty, with the informed consent of parents/ guardians of the children secured.

For data input, we used the MS Access program based on DBMS (Database Management System). The materials entered into the database were processed using modern methods of variation statistics and SPSS software (version 20.0).

Continuous quantitative variables are presented as mean values with standard deviation (±SD) in case of normal data distribution or as median and quartiles. Category variables are presented as numbers and proportions.

Primary statistical processing of data was carried out to determine the prevalence (as percentage) of CP risk factors for the case group as a whole, then by clinical diagnoses and time of CP onset. Average relative values (percentages) with the value of their standard error were obtained. The Student t-criterion (for quantitative variables with normal distribution) was used to compare the data for subgroups. The differences were considered statistically significant if p values were less than 0.05. To see if there were correlation dependence between studied attributes and relationship between factorial and effective attributes we calculated Pearson's linear correlation coefficient (r).

When studying the relationship between nominal variables, in cases where the number of 'expected frequency less than 5' cells in the analyzed table exceeded 25%, the Likelihood Ratio test (LR) was used, the differences were considered statistically significant if $p < 0.05$.

Based on the results of this research, working hypotheses on statistically significant cerebral palsy risk factors have been developed using formal logic methods. These hypotheses will warrant the design of subsequent analytical studies to see if they are useful to substantiate the prospective planning of measures to prevent the cerebral palsy development.

Results and Discussion

Of 150 children with cerebral palsy aged 6 months to 18 years at the time of the study, 95 (63.3%) were boys and 55 (36.7%) were girls.

The age profile showed dominance of primary and secondary school age children, 8 to 12 years (46.2%). One third of the children were preschoolers, 3 to 7 years of age (33.1%); 17.9% were 13 to 17 years, 1.4% 6 months to 2 years and 1.4% under 6 months of age.

43.4% of children were diagnosed with cerebral palsy after the first year of life, 32.4% at 7 to 12 months, and 24.1% at 3 to 6 months of age.

In each case, the clinical type was verified against the ICD-10.

Figure 1 shows the breakdown of various clinical types of cerebral palsy in children under the study.

As seen from Fig.1, dominating among clinical types of cerebral palsy was spastic diplegia, diagnosed in 33.8% of children. 23.4% of children were diagnosed with mixed form of cerebral palsy, less frequently diagnosed were hemiplegic (15.2%), dyskinetic (14.5%) and atonic (11%) types of cerebral palsy. In 3 cases (2.1%), the outpatient records failed to indicate the type of cerebral palsy.

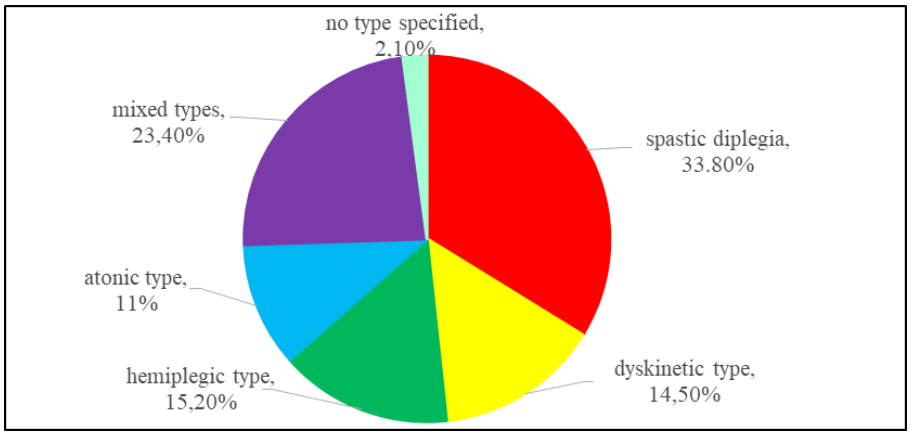

Figure 1 – Distribution of CP types in children (compiled by the author)

Table 1 - Infant feeding practices under 6 months of age

	Main group		Control group		Total	
	abs. number	% of Total, $X\pm\varsigma_X$	abs. number	% of Total, $X\pm\varsigma_X$	abs. number	% of Total, $X\pm\varsigma_X$
Breastfeeding	60	40±4.0	134	89.3±2.5*	194	64.7±2.9
Mixed	21	14.0±2.8	0	0	21	7±1.6
Artificial	34	22.7±3.4	0	0	34	11.3±2.0
No response	35	23.3±3.5	16	10.7±2.5*	51	17±2.3
Total	150	100±0.0	150	100±0.0	300	100±0.0

Note: * the differences between the main and control groups are statistically significant

Breast milk is the best diet for infants, as it provides all nutrients to a baby. Table 1 shows that only 40% of CP children were exclusively breastfed vs. 89.3% of those in the control group. In the main group, 14% were on the mixed feeding and 22.7 % of children were artificially fed. Children with cerebral palsy were found to have comorbidities (Table 2). The vast majority of children (88.%) had varying degree psychological and speech delay.

Table 2 – Comorbidities in CP children

Comorbidity	Abs.nmber	%
Psychological and speech delay	128	88,3
Visual and hearing impairments	93	64,1
Bone and joint disorders (scoliosis, deformities)	88	60,7
Encephalopathy	78	53,8
Hydrocephalus	73	50,3
Pneumonia	63	43,4
Symptomatic epilepsy	45	31,0
Pseudobulbar disorders	34	23,4
CNS birth defects	31	21,4
Microcephaly	27	18,6
Acute stroke sequelae	23	15,9
Febrile seizures	14	9,7
Sequelae of meningoencephalitis	11	7,6
Osteomyelitis	10	6,9
Down syndrome	4	2,8
Mild mental retardation (oligophrenia)	4	2,8

More than half of the children had visual and hearing abnormalities (64.1%) and bone and joint disorders (60.7%). Half of the children had encephalopathy (53.8%) and hydrocephalus (50.3%). One in three children was diagnosed with symptomatic epilepsy (31.0%), pseudobulbar

disorders (23.4%), and CNS birth defects (21.4%) (as manifested by microcephaly, 18.6%). Notably, nearly half of the children in the study group had the history of pneumonia (43.4%). Pneumonia was more frequently recorded under the age of 1 year: 2 or 3 times a year, with 10% of children having up to 7 relapses annually.

In cerebral palsy, motor and speech disorders are known to be certainly interrelated as demonstrated by the commonality of skeletal and speech musculature disorders [7]. This is due to the damage caused to the motor cortical structures regulating voluntary movements, speech and other cortical functions. To this end, we studied the level of speech development in children with cerebral palsy. Ninety-six per cent of children were found to have a speech development level below age. Speech development disorders were manifested by general underdevelopment of speech, dysarthria, speech delay, alalia.

Table 3 - Intellectual development level of children with cerebral palsy

	Main group		Control group		Total	
	abs. number	% of Total, $X\pm\varsigma_X$	abs. number	% of Total, $X\pm\varsigma_X$	abs. number	% of Total, $X\pm\varsigma_X$
Up to age	0	0	88	58.7±4.0	88	29.3±2.8
Behind age	138	92.0±2.2	62	41.3±4.0	200	66.7±2.9
No verbal contact	6	4±1.6	0	0	6	2±0.9
No response	6	4±1.6	0	0	6	2±0.9
Total	150	100±0.0	150	100±0.0	300	100±0,0

Note: * the differences between the main and control groups are statistically significant

Table 3 shows that the CP children have overwhelmingly larger percentage of delayed intellectual development compared to the control group ($p<0.05$), with no single instance of up-to-age intellectual development level in the study group. The main and control groups were studied for the incidence of acute respiratory infections (ARI).

Table 4- Incidence of common cold in children

	Main group		Control group		Total	
	abs. number	% of Total, $X\pm\varsigma_X$	abs. number	% of Total, $X\pm\varsigma_X$	abs. number	% of Total, $X\pm\varsigma_X$
< 6 times a year	143	95.3±1.7	76	50.7±4.1*	219	73±2.7
> 6 times a year	6	4±1.6	6	4±1.6	12	4±1.2
Incidentally sick children	0	0	65	43.3±4.0*	65	21.7±2.5
No response	1	0.7±0.7	0	0	0	0.3±0.3
Total	150	100±0.0	150	100±0.0	300	100±0.0

Note: * the differences between the main and control groups are statistically significant

50.7% of children in the control group were found to have had respiratory infections up to 6 times a year. 95.3% of children with cerebral palsy were sick up to 6 times a year. No children were found to

be incidentally ill in the main group vs. 43.3% of such children in the control group. Higher ARI incidence in CP children is the result of compromised adaptive capacity, primarily due to organic damage to the regulatory structures of the central nervous system, such as the hypothalamus, hippocampus, cortex.

Fig 2 shows the incidence of postnatal risk factors for cerebral palsy development in the study group.

Figure 2 - Postnatal risk factors for cerebral palsy in children (composed by the author)

Among postnatal risk factors, hyperbilirubinemia was detected in 33.8% of cases.

High bilirubin concentration can damage and even destroy the subcortical structures with resultant nuclear jaundice. Nuclear jaundice is an irreversible damage to the central nervous system [8]. In our study, nuclear jaundice occurred in 9.7% of cases.

Hemolytic disease of the newborn was found in 9.7% of cases. Cervical spine injuries are an important factor in the development of cerebral palsy. Injuries to the cervical spine in newborns were found in 15.2% of cases.

In many cases, intrauterine infection was found to have a direct damaging effect on the brain with resultant severe disability of the child. Of particular importance is the TORCH infection group: congenital rubella, cytomegalovirus, toxoplasmosis, herpes. Microorganisms in TORCH-associated intrauterine infections and in exacerbation of chronic reproductive tract infections have a high degree of affinity to nerve cells, leading to the development of intrauterine fetal malformations, and are one of the causative factors for cerebral palsy [9][10]. Severe septic infections were reported in newborns in 11.7% of cases.

We researched if there were other children with special needs in families raising children with cerebral palsy. The data is summarized in Figure 3.

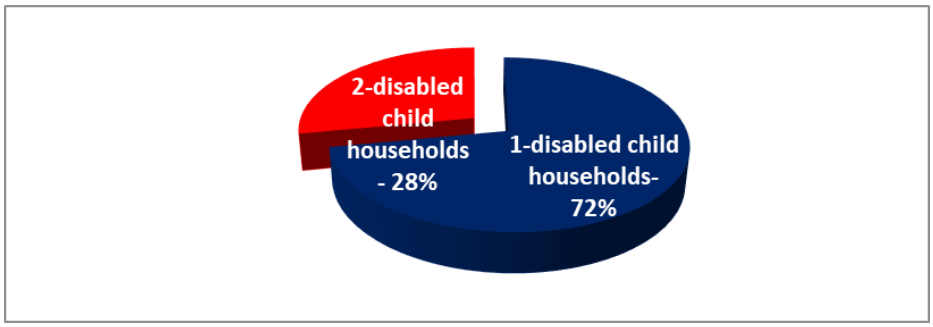

Figure 3 - Number of children with special needs in CP households (compiled by the author)

Twenty-eight per cent of families were found to bring up another child with an established disability, which apart from being an extra financial burden on the family, would have negative impact on the moral and psychological aspect of a family life[11,12,13]. We reviewed the medical records and found 33.0% of children diagnosed with CP within 6 months after vaccination, 13.2% within 7.5 to 12 months, 36.2% within 1 to 2 years and 8.8% within 2 to 3 years after vaccination.

Table 5 - Vaccine reactions in the main and control group children

	Main Group		Control group		Total	
	abs. number	% of Total	abs. number	% of Total	abs. number	% of Total
Yes	0	0	62	41.3±4.0*	62	20.7±2.5
No	144	96.0±1.6	88	58.7±4.0*	232	77.3±2.6
No response	6	4±1.6	0	0	6	2±0.9
Total	150	100±0.0	150	100±0.0	300	100±0.0

Note: * the differences between the main and control groups are statistically significant

Review of vaccination status showed that 41.3% of children in the control group had vaccine reactions manifested as fever, ailment, which resolved in 2 or 3 days. There were no vaccine reactions in the main group.

The history data collected and correlation analysis conducted between the various risk factors and the CP type, revealed the following relationships:

- statistically significant relationship between the frequency of pseudo-bulbar disorders and the CP type (likelihood ratio (LR) test, p=0.041), pseudo-bulbar disorders were more frequent in spastic diplegia);
- statistically significant relationship between epilepsy prevalence and the CP type (LR test, p=0.017), epilepsy was more frequently associated with the hemiplegic type and the unspecified type of cerebral palsy;
- statistically significant relationship between the frequency of encephalopathy and the CP type (LR test, p=0.030), encephalopathy was less frequently seen in the hemiplegic form of CP);

statistically significant association between microcephaly and the CP type (LR test, p=0.021), microcephaly was less frequently seen in the dyskinetic CP and was not observed in the hemiplegic form.

Conclusion

The array of signs and symptoms seen in infantile cerebral palsy are provoked by the following postnatal factors: hyperbilirubinemia, 33.8%; head and cervical spine injuries, 15.2%; severe infections with overt sepsis, 11.7% of cases.

In general, the prognosis of social adaptation of CP patients largely depends on how timely the medical, pedagogical and social assistance is rendered to the child and his family. Social deprivation and inaccessibility of comprehensive care may have a negative impact on the development of a child with cerebral palsy, perhaps even more pronounced than the initial structural damage to the brain[14,15].

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SUICIDE THOUGHTS PREVALENCE IN CHILDREN AND ADOLESCENTS WITH EPILEPSY

Abstract. Background/Aims: Review: Suicide is important and high prevalent problem in the world especially in adolescent. And it is one of the dangerous issue for epileptic children and adolescent. Also Epilepsy is a prevalent problem in the world, mostly among children and adolescent. It seems that epilepsy is the most common neurological disorder in children and adolescents. They suffer from seizures, traumas and with some degree of dysfunction. Due to epileptic seizures, low quality of life, social and emotional problems and maturing issues, so epileptic children and adolescents are at risk of affection. The purpose of this study was to investigate the prevalence of suicidal thoughts among epileptic children and adolescents in Herat city of Afghanistan. In addition epilepsy is a high cost disorder, because continues long time and need continuous treatment. In epilepsy treatment both pharmacotherapy & surgery is used. Many authors point to a link between epilepsy and an increased risk of suicide.

Methods and Materials: A cross-sectional study using a probability sampling process, by completing questionnaires and direct observation of the subjects during the first five months of 2020 was conducted at neurological center in Herat city.

Results: Among the 300 samples, 287 samples have completed the questionnaire (response rate was 95.6%). 92 individual with epilepsy had suicidal thoughts 32%. 56.5% of subjects was male and 43.5% was female. In this study the participants age was (7-18 year), assessment by questionnaire and direct observation was measured.

Key words: Suicide, Epilepsy, Children.

Introduction:

Epilepsy:

Epilepsy is a prevalent problem in the world, around 50-70 million people worldwide have epilepsy, mostly among children and adolescent. (WHO, 2016,2019) [1,2].

It seems epilepsy is one of the most common neurological disorder in this age [3,4,5]

The epileptic children and adolescents suffer from seizures, traumas due to seizure and this disorder is associated with some degree of dysfunction. Due to epileptic seizures, low quality of life, social and emotional problems and maturing issues, so epileptic children and adolescents are at risk of suicide. Epilepsy is a high prevalent disorder (0.7%) [1,2].

Nearly 80% of people with epilepsy live in low income countries [1,2]

The prevalence of epilepsy is more in male than female. Epilepsy is a chronic disorder that brings some limitation in person's life. In addition epilepsy is a high cost disorder, because continues long time and need continuous treatment. In epilepsy treatment both pharmacotherapy & surgery is used [1,2].

Many authors point to a link between epilepsy and an increased risk of suicide [6,7]. The frequency of suicidal events is significantly higher in patients with epilepsy than in the general population and reaches 8-12% compared to 1.1-1.2% in the general population [6].

The link between epilepsy and suicide is a complex and multifactorial problem.

The reason may be the peculiarities of the disease itself, which depends both on the form of epilepsy, the type of seizures, the localization of brain damage and social stigmatization [6]. Some of the latter associate the cause of suicide with taking antiepileptic drugs [7]

The people that think and commit suicide, 80 % of them have depressive disorders [6,7]. Suicide is currently the third leading cause of death among young people and the school-aged population [6,7,8]

These comorbidities may negatively influence the course of epilepsy and, therefore, lead to a reduced quality of life as well as increased mortality, was found in the United States [9] and suicide rate

was twofold more than in epileptic children than comparison group (in Taiwan. 2018).

In a recent study conducted in a Western country, Jones et al. found that suicidal ideation was noted in 20.3% of children with epilepsy [10].

Moreover, among adolescents in the United States who had any type of physical disability or long-term health problem, Everett-Jones and Lollar found that they had a 2.7fold higher risk of having suicide ideations and a 3.5-fold higher risk of attempting suicide than healthy students [11].

Those with epilepsy had a significantly higher rate of any self-injurious behavior and suicidal ideation (mailto:wirrell.elaine@mayo.edu).

Suicidal ideation is also more prevalent, with one study reporting a 25% lifetime risk of suicidal ideation in persons with epilepsy compared to 12.2% in controls [12].

Several factors may increase the risk of self-injurious or suicidal behavior in persons with epilepsy. Epilepsy is frequently associated with other psychiatric comorbidities, such as anxiety, depression. Some patients experience postictal depression, which may explain the increased risk of suicide in persons with temporal lobe epilepsy [13, 14].

According to Mazza M., et al (2004), the risk of suicide is 25 times higher in temporal lobe epilepsy and in complex focal seizures [13]. This is due to the existence of a link between temporal lobe epilepsy and depression [14]

Quiske A., Helmstaedter C., Lux S. and Elger C.E. (2000) Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res 39: 121-125

Quiske, A., Helmstaedter, C., Lux, S. and Elger, C.E. (2000) Depression in patients with temporal lobe epilepsy is related to mesial temporal sclerosis. Epilepsy Res 39: 121-12

Objective:

Evaluation of suicidal thoughts prevalence in children and adolescents with Epilepsy in Neurological canter – Herat – Afghanistan.

Research Method:

This was a descriptive study which was held in cross – sectional method. The subjects was randomly taken from children and adolescent who had epilepsy. Sample Size was 287, first the sample size was determined 300 person but during the process some individual didn't corporate well (regretted to participate or haven't given complete history to the interviewer), so they were excluded from the study.

This study was conducted during first 5 months of 2020 in neurological center in Herat city of Afghanistan. And epilepsy diagnosis was based on EEG (Electroencephalography) and history which was taken by specialist of neurology from patient and patient's caregivers. All children with the diagnosis of epilepsy (aged 7-18 years), regardless of the seizure type, were included to this study over period of 5 months (five month of 2020). The diagnosis of epilepsy in children was certified by all member of neurology center's board. The diagnosis of epilepsy was made after obtaining information from a history, physical examination and encephalography. After patients diagnosed epilepsy, with their caregivers both sent to a child and adolescents psychiatrist for suicidal evaluations. The child psychiatrist evaluated for suicidal thoughts, toke a history from patients by help of their caregivers with special question for suicidal thoughts and behaviors, then suicide questionnaire was given them to fill out by help of their caregivers. Patients and patients caregivers' consent was taken before including to the study.

Inclusion criteria:

- Children and adolescents who had epilepsy
- Children and adolescents who was aged 7-18 years
- Children and adolescents who didn't have high grades of mental retardation
- Children and adolescents who or whose family was interested to participate the study

Exclusion criteria:

- Children and adolescents who didn't have epilepsy
- Children and adolescents who had high grades of mental retardation
- Older than 18 years or under 7 years old
- Children and adolescents who or whose family wasn't interested to participate the study

Ethics consideration:

The research committee of neurological center approved the research proposal. All the participants' one family member (caregiver) signed an informed consent before their inclusion in this study. The participants were reassured of the confidentiality and anonymity of the study, they were told that the participation was voluntary and they could refuse to participate.

Statistics:

We used Excel and SPSS software for analysis the data.

Result:

This research was accomplished about suicide thoughts in children and adolescents with epilepsy in Neurological canter during 5 months of 2020 in Herat city of Afghanistan.

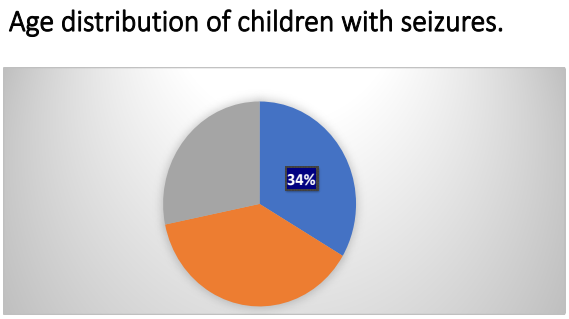


Figure 1 - Age distribution of children with seizures

Table 1 - Distribution of epileptic children by age

Age. year	frequency
7-9	96
10–15	110
16–18	81
Total:	287

This table shows that the epileptic children and adolescents were measured by age and these are the results 33.4% of them were 7-9 years old, 38.3% was within 10-15 years old and 28.2% was 16-18 years old.

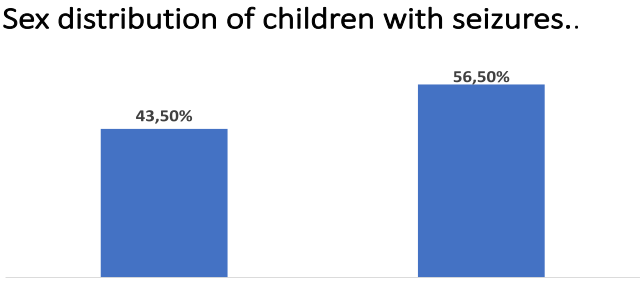


Figure 2 - Sex distribution of children with seizures

Table 2 - Epileptic cases who was student

variable	Frequency	percentage
student	210	73.2%
Not student	77	26.8%
total	287	100%

From 287 epileptic children and adolescents, who participated this study 73% was student, but 26.8% of them wasn't student.

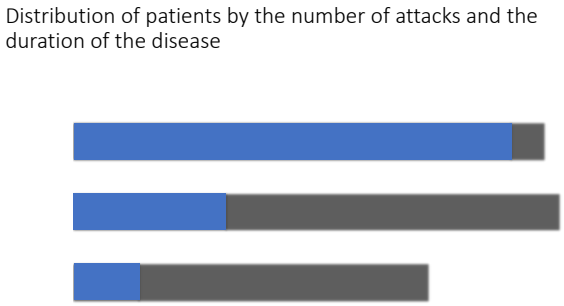


Figure 3 - Distribution of patients by the number of attacks and the duration of the disease

Table 3 - Number of seizure in children and adolescents in neurological center.

Characteristic	Frequency, n=287
Number of seizure in last year	
0-5	28
5-10	67
>10	192
Age of onset of epilepsy	
<5 year	127
5-10 year	146
>10 year	14

Number of seizures were measured in epileptic children and adolescents in one year, 67% had more than 10 seizures and 10% had 5 or less than 5 seizures in a year. The epileptic patients were studied by age of onset of epilepsy also, 51% of them reported that their seizures started between 5 - 10 years old. But 5% of subjects reported that their epilepsy started after 10 years old.

Table 4 - Suicidal thoughts in epileptic children and adolescents.

Suicidal thoughts	Frequency	Percentage
yes	92	32%
No	195	68%
total	287	100%

From 287 epileptic patients (epileptic children and adolescents) 92 of them had suicidal thoughts 32% and 195 individual didn't have suicidal thoughts and ideations.

Table 5 - Distribution of epileptic children and adolescents who had suicidal thoughts, by sex.

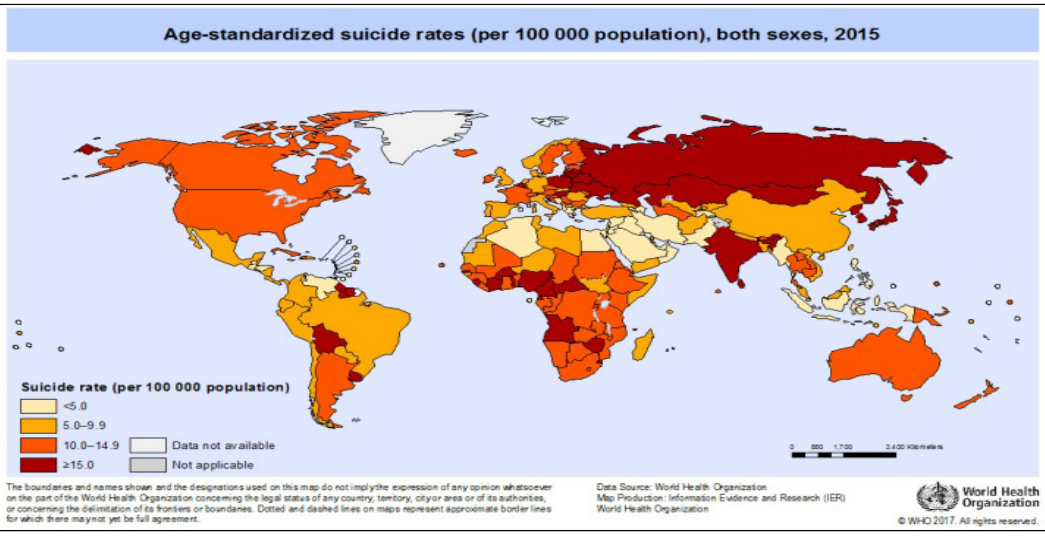
Variable	Frequency	percentage
female	40	43.5%
male	52	56.5%
Total with suicidal thought	92	100%

92 individuals of children and adolescents had suicidal thoughts that, 43.5% of them was female and 56.5% was male.

Table 6 - Diagnosis of epileptic children with suicidal thoughts.

Diagnosis	number	percentage
G. epilepsy	62	67.4%
Partial seizures	30	32.6%
total	92	100%

From 92 children and adolescents who had suicidal thoughts, 67.4% had generalized epilepsy and 32.6% had partial seizures.



Suicide Prevalence map in world [15].
WHO Figure: Age-Standardized Suicide Rates: Male: Female Ratio (Per 100,000)
[(accessed on 10 October 2017)]; Available online:
http://www.who.int/gho/mental_health/suicide_rates_male_female/en/

Desiccation

The purpose of this study is the evaluation of suicidal thoughts prevalence in children and adolescents with Epilepsy in Neurological canter – Herat – Afghanistan. In this study 287 children and adolescents were studied and some variables were discussed. They were studied by age and 38.3% of them were within 10-15 years old, 34% was within 7-9 years old and 28% of them were 16-18 years old. Also the participants were studied by sex, 56.5% was male and 43.5% of them were female. The children and adolescents were studied by number of seizure in last year and it was, 67% of patients had more than 10 seizure in last one year. But in a study which was done by Jana E. Jones, PhD and her colleagues in University of California Los Angeles, they found 55.6% of children had more than 10 seizures in one year [10]. Our percentage is higher than what they found in Los Angeles, maybe because of the compliance of our patients are low, this issue also can have many reasons that one them could be low economic situation in Afghanistan and reason could be low level of education and low information about epilepsy in our country. The participants were studied by age of onset and this percentage was found 51% of patients seizures' started in 5-10 years old. It seems that many epileptic patients' seizures appear in childhood. One third of the epileptic children and adolescents who was studied, 92 individuals from 287 epileptic patients had suicidal ideation and thoughts 32%. As in Butabika and Mulago hospitals epileptic children had suicidal thoughts, almost one

in every three adolescents with epilepsy as indicated by prevalence of 30.5% [17]. The percentage was found in Afghanistan is near with the percentage they found, maybe because both countries are poor countries.

In a Brazilian study the epileptic children under 13 were studied, the prevalence of suicidal thought was 39.6% [16]. More than the percentage in our study was found.

This result was near to the study was done in Afghanistan with a little difference. In the USA a study was done on 177 children and adolescents with epilepsy aged 5-16 years old, 20.3% reported suicidal thoughts [10].

The difference with our study lies in this fact that the children in there study were younger and were less likely to have suicidal thoughts than adolescents. Another cause is the big difference in economic situation between two countries in addition educational level differences also its effect on the percentage of suicidal thoughts and epilepsy. Also the study which was done in Mulago hospital found that suicidal thoughts and behavior was more in older adolescent aged 14-17 years [17]

And these 92 epileptic patients with suicidal thoughts was measured by sex, 43.5% were female and 56.5% were male. Also the study was done by Hillary Kuteesa and her colleagues in Uganda, they found that the participants, who had epilepsy and suicidal thoughts 55.2% was male [17], Also a study was done at University of California Los Angeles found suicide in epileptic children in male 55.5% and in female 44.4% the difference between male and female is almost the same. The epileptic patients with suicidal thoughts was studied by type of epilepsy, from 92 children and adolescents who had suicidal thoughts, 67.4% of subjects had generalized epilepsy and 32.6% had partial seizures. It means that the participants of this study in Herat city of Afghanistan most of children and adolescents' seizure was generalized epilepsy. Also the Study was done by Vladimir V. Kalinin and his colleagues, 60% of epileptic patients with suicidal thought had generalized epilepsy [18].

Conclusion

Epileptic disorders rate is high especially in children and adolescents in Afghanistan. Suicide thoughts was high in epileptic children and adolescents as in this study found. And suicide thoughts rate was found higher in male patients than in female. However we can't forget that in Afghanistan the prevalence of mental health disorders are high, maybe epilepsy is one of the precipitating factor for suicidal ideation or it is the cause of the problem for epileptic children and adolescents.

Recommendations

Prevention of problems (suicide and Epilepsy), is an important issue. One way is to Increase public information about risk factors of epilepsy and mental health disorder especially depression among epileptic children and adolescents. Another important issue is stigma about epilepsy and suicide, it should be decreased in the society. Complete treatment of epilepsy and mental disorders in epileptic children and it is needed to do more research in this area.

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CLINICAL CHARACTERISTICS OF PATIENTS WITH COVID-19

Abstract. A new virus, called acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread all over the world, became a pandemic one. Inspite of that clinical profile of patients has been reported, there is a lack of information regarding the presentation of patients with COVID-19 requiring emergency care and in particular about those who emergency medical services. We described the main clinical characteristics of patients with Covid-19. It's a single-center retrospective cohort study. All COVID-19 patients included in this study were diagnosed according to the guidelines for the diagnosis and treatment of pneumonia caused by infection with the novel coronavirus. All patients had laboratory-confirmed infection with SARS-CoV-2 (real-time RT-PCR specific for SARS-CoV-2 was positive).The value of D-dimer coagulation indices, prothrombin time, activated partial thromboplastin time, thrombin time and fibrinogen as well as C-reactive protein, procalcitonin, ferritin in predicting the severity and prognosis of COVID-19 was studied. Dysfunction of blood coagulation and procalcitonin are widely used to assess the risk of bacterial infection and C-reactive protein – an indicator of an acute inflammatory process – was found in almost everyone, more often in severe patients.

Key words: COVID-19, D-dimer, C-reactive protein.

Introduction

COVID-19 is a disease caused by the new coronavirus SARS-CoV-2. [1, 2, 3]. Most patients with COVID-19 develop symptoms of respiratory infection, some of them weigh down to a more severe systemic disease characterized by persistent fever, acute lung injury with acute respiratory distress syndrome, multiple organ failure, shock and high lethality [4, 5]. Close observation of patients with COVID-19 showed that many of them had abnormalities in the results of laboratory studies of the blood coagulation system, resembling other systemic coagulopathies, such as disseminated intravascular coagulation (ICE) and thrombotic microangiopathies [6]. In addition, COVID-19-associated coagulopathy also appears to have features that distinguish it from ICE and TMA [7].

Coagulation disorders have been reported COVID-19 patients in several descriptive studies [8, 9, 10]. Increased levels of D-dimer and fibrin degradation products (FDP), shortened or increased prothrombin time (PV), abnormal platelet count, occurrence of thrombosis or bleeding, and complications of disseminated intravascular coagulation were observed in patients with COVID-19 at different clinical stages [11.12]. These data show that impaired blood coagulation plays an important role in the clinical process of COVID-19. Impaired blood coagulation at the end stage of COVID-19 or after invasive treatment is common and valid, but with limited predictive value. Studies of patients with COVID-19 have shown that CRP levels directly correlate with disease severity and progression. A recently published study showed that low levels of CRP are common in both patients who do not require oxygen (mean 11 mg/L, interquartile range 1-20 mg/L) and patients who have developed hypoxemia (mean 66 mg/L, interquartile range 48-98 mg/L) [13]. Procalcitonin in coronavirus infection with respiratory lung lesions is within reference values [14,15]. The increase in PKT indicates the attachment of bacterial infection and correlates with the severity of the course, the prevalence of inflammatory infiltration and prognosis in bacterial complications.

Aim. To study clinical characteristics of patients with covid-19.

Materials and research methods

This study was a single-center retrospective cohort study. We included all patients with confirmed SARS-CoV-2 infection hospitalized in an infectious disease hospital from March 21 to August 12, 2020 in Bukhara. Clinical data were obtained from electronic health records, including demographic data, exposure history, signs and symptoms, and laboratory data at admission. Common blood tests: white blood cell count (WBC), lymphocyte count (LYM), mononuclear count (MONO), neutrophil count (NEU) were performed on blood samples. Blood biochemistry parameters: aspartate aminotransferase (ACT), alanine

aminotransferase (ALT), glucose (BLU), urea, creatinine and C-reactive protein (CRP) were measured using the automatic biochemical analyzer MINDRAY BC - 30 (Hitoy) Coagulation functions (D-dimer, thrombin time (TV), prothrombin time (PTV), fibrinogen (FIB), activated partial thromboplastin time (ACTV) were determined using a MINDRAY BA-88A analyzer (China). The concentration of D- dimer was determined by ELISA using immunoenzyme assay kits to determine the concentration of D- dimer in the blood plasma of D- dimer-ELISA-BEST. Patients with moderate severity and severe form used data from their first laboratory test at admission. All tests were performed by specially appointed personnel in strict accordance with the instructions for the use of reagents.

Research results and discussion.

Upon admission to the stationary ambulance department, all patients were assessed using the NEWS scale. The average score was 5.6±1.6. This made it possible to quickly sort the patients and the most serious to be sent to the intensive care unit. All COVID-19 patients included in this study were diagnosed according to the guidelines for the diagnosis and treatment of pneumonia caused by infection with the novel coronavirus. All patients had laboratory-confirmed infection with SARS-CoV-2 (real-time RT-PCR specific for SARS-CoV-2 was positive).

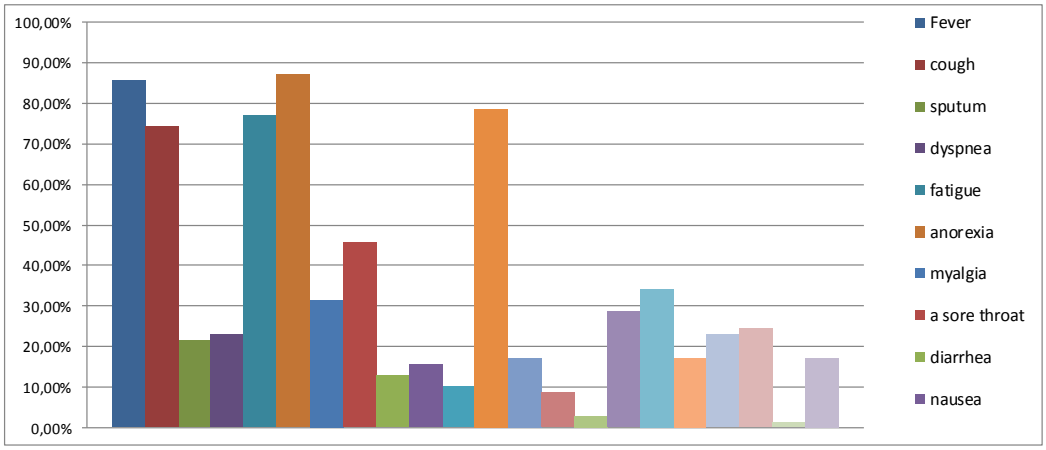
From March 21 to August 12, 2020, 70 patients were hospitalized at the Bukhara regional infectious diseases hospital. The patients were divided into severe patients (n = 32) and patients with moderate forms (n = 38). Of these, 12 (8.6%) patients were admitted to the intensive care unit.

The average age was 53 years, out of 70 patients, 56 were men. The median time from symptom onset to hospitalization was 4-5 days, and the median time to diagnosis of severe illness was 6-7 days.

The most frequent chronic diseases were: hypertension, in 6 patients; cardiovascular disease, in 5; chronic obstructive pulmonary disease, in 8 patients.

The distribution of patients by severity can be represented by the degree of lung damage. CT scan 0 was in 8.7% of patients, CT scan 1 - 14.2%, CT scan 2 - 47.1%, CT scan 3 - 30.0% of patients, mean SpO2 = 91.5%.

The most common symptoms upon admission of patients were: fever, detected in 60 patients, followed by cough in 52, sputum in 15, dyspnea in 16, fatigue in 54, anorexia in 61, myalgia in 22, sore throat - in 32, diarrhea - in 9, nausea - in 11, vomiting - in 7, headache - in 55, dizziness - in 12, abdominal pain - in 6, hemoptysis - in 2, loss of taste - in 20 , loss of smell - in 24, confusion - in 12, conjunctivitis - in 16, arthralgia - in 17, convulsions - in (picture 1)



Graph 1 - Frequency of occurrence of clinical signs in percentages (%)

According to the results of the data obtained on 70 patients, it turned out that skin manifestations were found in 12 patients. In 5 patients, they manifested themselves in conjunction with the manifestation of other symptoms, in 7 patients - after hospitalization. Among the skin manifestations prevailed: erythematous rash (in 7 patients), common urticaria (in 3 patients), also vesicles similar to rashes in chickenpox (in 2 patients).

According to the results of laboratory data, it was found that 24 patients (34.3%) had leukopenia, 12 patients (17.1%) had leukocytosis; in 58 patients

(82.9%) lymphocytopenia was revealed, in 12 patients (17.1%) - an increase in the number of lymphocytes.

Platelet count and coagulation parameters were analyzed in the present study. Of the 70 patients included in the study, thrombocytopenia was found in 9 (12.9%), thrombocytosis - in 8 (11.4%).

Indicators of hemostatic homeostasis in patients with coronavirus infection on admission are shown in the table. From this table, it follows that the concentration of D-dimer is increased in 57.9% of patients with a moderate form, and in patients with a severe form, it is detected in 75%. A similar picture was found when studying the prothrombin time, the indicators are 10.5% and 18.8%, respectively. In 50% of patients with a moderate form, the concentration of fibrinogen is increased, and patients with a severe form are 75%. Activated partial thromboplastin time was lengthened in 26.3% of patients with a moderate form of the disease, and 46.9% with a severe one.

Conclusion

Thus, such indicators of hemostatic homeostasis as D-dimer, prothrombin time, fibrinogen and Activated partial thromboplastin time, also C-reactive protein can be used as indicators of the severity of the disease in patients.

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SOCIO-DEMOGRAPHIC STUDY OF SELF-IMMOLATION IN KABUL

Abstract. Self-immolation is a dangerous method of committing suicide which is prevalent in individuals who attempt to escape a stressful situation and is considered a significant social and medical disorder in both the economically developed and developing countries.

To find out demographic characteristics (age, sex, marital state, level of education and occupation), and complication of Self-immolation cases in 2012 – 2014 in Kabul Afghanistan.

The research was designed as a descriptive-cross sectional study. The data collection were done in a census manner. Target population were all self-immolation cases that were referred to burn surgery ward of Isteqlal Hospital, the only hospital in Kabul which has burn surgery ward which were referred during 2012-2014. Data which include demographic characteristics and complication of burning obtained from hospital medical record, and data were analyzed in SPSS verion 21.

The results of the study indicate that the incidence of self-immolation in Kabul is rising and the highest incidence has been observed in young and adolescents, most of it occurred between the ages of 15-30 and mostly among married house wife women who had a low level of primary education. The number of fatalities was much higher than the number of improved cases.

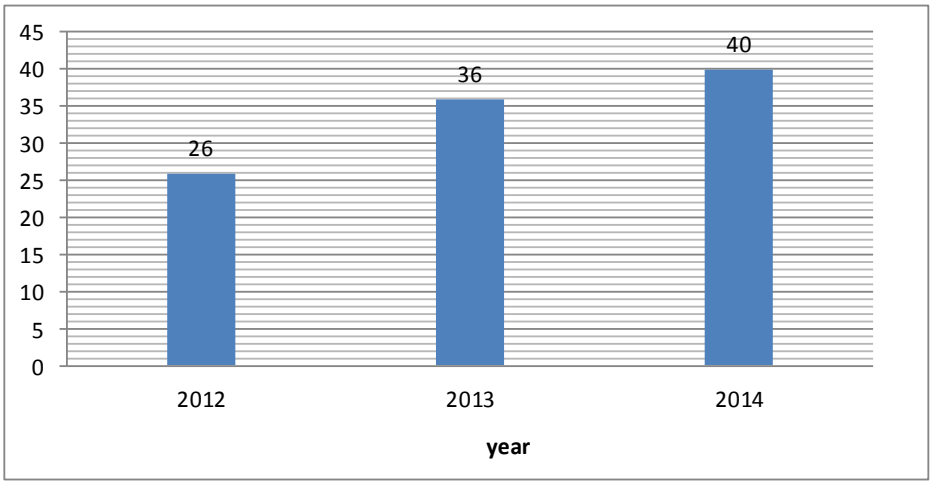
Key word: self-immolation, demographic, cross-sectional.

Background: in most countries Suicide is one of the large challenges and the 15th cause of death in the world by 800,000 deaths each year. More than 80% of the suicides happened in low-and-middle-income countries (WHO,2014) [1]. Suicide is an indicator of a society mental state [2{ September 10th is announced as the annual world suicide prevention day by The World Health Organization (WHO) and the International Association for Suicide Prevention (IASP) to pay more attention to such a problem and make a call for a global urgent action [3], which shows its high incidence around the world. There are many ways to commit suicide and of them is self-immolation which is mostly prevalent in people who try to run away from stressful situation and is considered as a strange and unusual method. [4]. Self-immolation is a big social and medical problem in both the economically developed and developing countries. Whereas suicide by self-immolation is incredibly rare within the developed world, [3] in developing countries suicide by Self-immolation is one of the most violent methods [5]. in keeping with statistics, Middle Eastern and East Asian countries have a high rate of self-immolation. [2]. Indeed, suicide by deliberate self-burning is quite common in countries like Tunisia, Afghanistan, Iraq, and Iran [6]. self- immolation isn't a typical style of suicide in European countries. However, it is highly prevalent in developing countries notably in Asia and Africa. [7]. in contrast to the developed countries and Western societies, self-immolation in developing countries is a common method of suicide [8]. Suicide is presently the fourth leading reason for death in individuals aged 15- 44 and also the sixth leading reason for disability worldwide. [2]and second-leading reason of death in individuals aged 10-24-years [9]. in the Eastern Mediterranean region, the Annual prevalence of self-immolation has been reported to be 2.9 to 21 per 100,000 [2]. The high rate of mortality (70-90%) and morbidity caused by self-immolation is considerable in Middle East countries in which self-immolation is a common method for suicide [10]. in 2004 Laloλ reviewed 55 studies from all countries from last 20 years; he has found that the highest rate of deliberate self-immolation was observed from Iran, Sri Lanka, India, and Egypt, [11]. People commit self-immolation mostly due to different social and economic reasons and as political protest [12]. the bulk of self-immolation attempters showed history of previous suicide attempts and psychological disorders such as personality disorders, schizophrenia, economic and social problems [4]. This is mostly happening inside a house and usually during the afternoon[10] during 2002 A statistical evaluation of self-immolation which 55 countries in 20 years and revealed 3,351 cases of immolation, 2,296 of which died. India had the highest dead rate, the high rate of self-immolation belonged to Sir Lanka, European

countries and United States have the lowest rates. In the Middle East and India women are more likely to attempte self-immolation, while in westen countries Men are more likely to commite self-immoaltion, in Europe victims are 10 years younger than Asian victims [7]. the incidence of self-immolation is considerably higher amongst the women than the men. The same gender-based differences have also been reported from Egypt, Zimbabwe, Serilanka, India, Afghanistan and Uzbekistan. In distinction, studies from Australia, North America and European countries show that men have committed suicide by self-burning more than women [3]. self-immolation in Afghanistan, where women are under the beneath of his father, brother, husband and cannot have the chance to claim economic and social independence, nor to enjoy their human rights, is increasing and kinds of violence against women in Afghanistan include Bad and Badal, along with the practice of exchanging girls for cattle or material goods. Majority of self-immolation victims had tried to kill themselves as a result of violence in the family practice of exchanging girls for cattle or material goods. Involved motives are; psychological illnesses, political protest, and ritual suicide including imitation of others' symbolic acts, Meanwhile, circumstances that can put people at increased risk of self-immolation. Following risk factor may cause or associate with self-immolation; drug addiction, smoking, alcohol consumption, age differences, lack of understanding with the spouse, lack of children or their difficulties, bigamy, lack of interest in the family affairs, lack of love, premature marriage, low socio-economic status, genetic and congenital factors and excessive sensitivity in regard to the taboo of divorce might be the case for initiation of familial tensions leading to depression and suicide attempts .Both socio-cultural and psychiatric factors have been found to be associated with self-immolation[3].

Material and method: this research was conducted as a descriptive-cross sectional study. Target population were all self-immolation cases that referred to burn surgery ward of Isteqlal Hospital which is the only hospital in Kabul which has burn surgery ward and dead body referred to forensic during 2012-2014. Data which include demographic characteristics (age, sex, marital state, occupation and level of education) and complication of burning obtained from hospital medical record and forensic report, then the data were analyzed by SPSS version 21.

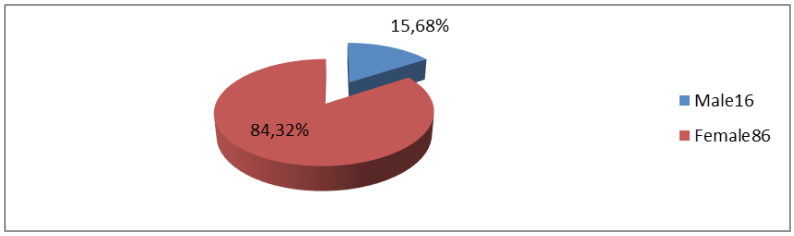
Results: According to study which was conducted over three-year period, of 102 self- immolation cases, 60% (86) of self-immolation committers were female, and 40% (16) were male (Graph1,2). Of the subjects, 26% (26) were single, 47% (48) were married,24%(24) were engaged and 3% (3) were divorced (Graph 3). As for the level of education, 36% (37) were illiterate,25%(25) had elementary education, 17%(17) high school graduate,8%(8) were Bachelor and 15%(15) were unknown (Table 2). According to duty,48%(48) were house work, 11,7%(12) were employed ,4.9%(5) were university students, 6.8%(7) were school student, 6.8%(7) simple worker, 9.8%(10) unemployed, and 12.7%(13) were unknown. Furthermore, 44.1% (45) were in the age range of 11-20 years, 33.3% (34) in the age range of 21-30 years, 14.7% (15) in the age range of 31-40 years, 5.8% (6) in the age range of 41-50 years, and above 51-60 years old there was no self-immolated case (Table1).



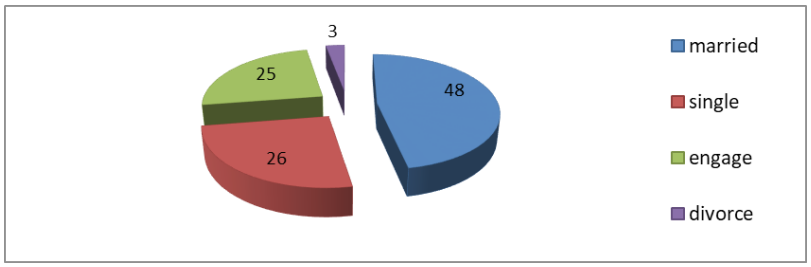
Graph 1 – Number of cases per year.

Table 1 – according to age

Age range	Number of cases	Percentage
11-20	47	46%
21-30	34	33.3%
31-40	15	14.7%
41-50	6	5.8%



Graph 2 – Number of cases according to gender



Graph 3 – incidence of self-immolation according to mariatal state

Table 2 – according the level of education

Percentage	Number of cases	Level of education
36%	37	Illiterate
25%	25	Elementary education
17%	17	High school graduate
8%	8	Bachelor
15%	15	Unkown

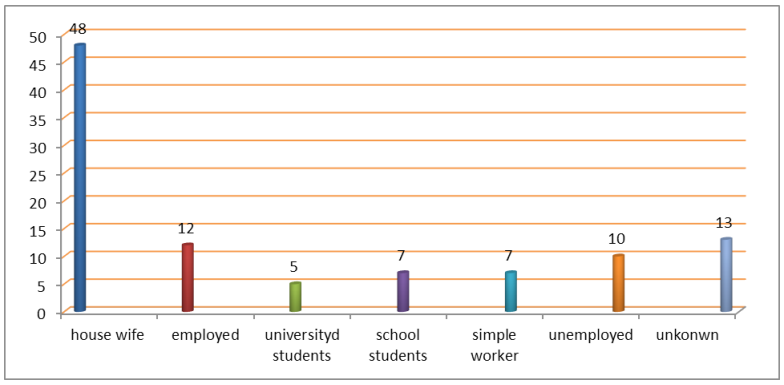


Chart 4 – according to occuption.

Most of the self-immolation were in summer and majority of them had happened inside the house with flamibal liqude (oil).

Table 3 – number of cases according to season

Percentage	Number of cases	Season
25.49%	26	spring
34.31%	35	summer
16.66%	17	fall
23.52%	24	winter

Table 4 – complication of self-immolation

Percentage	Number of cases	complication
0%	0	complete healing
8.82%	9	Healing with disability
91.18%	93	Leading to death

Discussion: the aim of this research is to determine the socio-demographic charactersitics of self-immolation cases, which was conducted over the period of three years and the total number of cases were 102, most of them were female (86 cases) which corresponds to a research conducted by Zamani SN, Bagheri M, Abbas Nejad M in Iran [4]. As the age rang in this research most cases were in age group 11-20 (46%) which is samiler to a research conducted by Ahmadi M, Ranjbaran H, Azadbakht M, Heidari Gorji M, Heidari Gorji A in the northern Iran [9]. According the level of education most of them were illiterate women (36%) which this result is same as the research conducted in Iraq by Amin PM MS, Mirlashari J PhD, Nikbakht Nasrabadi A PhD [2]. As the marital state most of the cases were recorded in married women (47%) which is in contrast with high number of cases in singles in a research conducted in one of our neighboring county (Iran), conducted by Zamani SN, Bagheri M, Abbas Nejad M in Iran [4]. Diffenitly, different aspect of self-immolation as a painful social tragedy should be explored. The majority of families conceal the truth of the case, and try to bury the bitter truths with the body. Suicide is not only condemned by Islam and laws of some developing countries, but also since long ago the majority of people around the world have considered suicide to be wrong, as in ancient Athens even the bodies of people who committed suicide were punished [16]. Therefore, serious support for women in the family and society is one of the important ways to reduce this type of suicide. In this study, most cases of self-immolation have occurred in adolescence and youth, and the results of studies show similarity in the region which conducted in some countries [14,17]. Of course, the higher incidences of self-immolation in adolescence and youth may be due to problems related to this age, such as: youthful feelings, lack of experience in life problems, their misunderstanding of ways to deal with psychological, family, environmental and economic pressures [15]. In this study, like the results of studies conducted in other countries in the region, the most common method of self-immolation is using of flammable liquids, especially oil, the possible reason for this choice was the accessibility of the victims with these materials (Table 3, Graph 4). People who self-immolated were severely burned and their chances of survival with the available facilities in the burn service of Isteqlal Hospital were very low, so in this study, the death rate due to self-immolation was about 91%. Research's results show a high incidence Comparing with other communities [13,14,17]

Conclusions: The results of the study indicate that the incidence of self-immolation in Kabul is increasing and the highest incidence has been observed in young and adolescents and mostly among married women who are at a low level of primary education and are busy with household chores. The number of fatalities was much higher than the number of improved cases.

Suggestions: To reduce the increasing incidence of self-immolation, better treatment and to prevent casualties and complications, the following suggestions are respectfully presented.

1. implementation of stratigies to reduce illiteracy.

2. Implementing educational programs to raise the level of awareness of families in order to struggle and deal with violence, and problems through media.

3. Propaganda against domestic violence by officials, clergy, and professors at schools and universities.

4. Providing of specialized burn centers and treatment programs, especially extensive equipment and facilities in hospitals.

5. Psychotherapy of patients after improvement of their condition to prevent recurrence and give them hope for continuing life.

6. Joint research by the Department of Forensic Medicine and the Department of psychiatry l and Neurology of Kabul Medical University to obtain motivations for self-immolation and determine the mental state of these patients.

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STRUCTURAL AND DYNAMIC FEATURES OF ACUTE PSYCHOSIS DUE TO THE USE OF SYNTHETIC CANNABINOIDS

Abstract. In the last 10 years, virtually all countries have faced a change in the structure of drug use due to a decrease in the number of opiate along with an increase in the number of users of the so-called "new" psychoactive substances Upon data collection from 126 patients, a dynamic clinical study of 356 psychotic states due to the use of synthetic cannabinoids was undertaken. Consecutive stages of development of psychosis along with its delirious, oneiroic, and amentive-like clinical variants were identified. The likelihood of development of psychosis and its clinical variants is determined by a complex of clinical, biological, psychopathological, and socio-psychological factors.

A complex of clinical, biological and socio-psychological factors was shown to determine the pathokinetic patterns of development of psychosis due to the use of synthetic cannabinoids. It was established that as the clinical picture of psychosis worsens, the psychopathological symptoms of a deeper level develop (hallucinations – delusions – mental automatisms – motor disorders) with a simultaneous gradual depletion of a psychopathological picture of psychosis due to a narrowing range of existing productive symptoms.

Key words: psychosis, synthetic cannabinoids, symptoms.

Introduction

In the last 10 years, virtually all countries have faced a change in the structure of drug use due to a decrease in the number of opiate users who until recently constituted the main contingent of patients at drug treatment clinics, along with an increase in the number of users of the so-called "new" psychoactive substances [1].

New psychoactive substances (NPS) are substances synthesized by making minor structural changes to the chemical formula of controlled natural or synthetic analogs [2]. According to the European Monitoring Center for Drugs and Drug Addiction (EMCDDA, 2017) [3], a significant part of the seized uncontrolled NPS refers to synthetic cannabinoids (SC) that received slang term "spice" [3]. Since September 2014, there have been periodically recorded cases of mass poisoning of persons whose urine tests revealed MDMB (N)-Bz-F tridimethylbutanoic acid of JWH group [4] in the Russian Federation.

Self-reported surveys in adolescents conducted abroad indicated a high percentage of NPS use including SC [5] in this age group [6]. There is an increase in primary treatment among adolescents regarding the use of SC in the Russian Federation [7] and in the Republic of Kazakhstan [8-9].

Mostly, the appeals for medical care in SC users are associated with the development of acute psychotic symptoms, albeit patients being mainly hospitalized in toxicology departments of general hospitals with a diagnosis of "Acute poisoning caused by unknown poison" without having a clinical diagnosis of addiction disorder established.

In connection with this, in Russian and Kazakh studies, there are no systematic descriptions of clinical dynamics of psychoses due to SC use.

Aim of study: Study of structural and dynamic features of acute psychoses due to SC use.

Materials and methods

In the period from 2014 to 2017, 126 patients with acute psychoses due to SC use were surveyed. 76 of them were in-patients of the National Scientific Center for Addiction - a branch of the FSBI "V.P. Serbskij National Medical Research Center of Psychiatry and Narcology» Ministry of Health of Russia; and 50 patients were treated at the Republican Scientific and Practical Center for Psychiatry, Psychotherapy and Narcology in Almaty.

Slavic ethnicity was represented by 89 (70.6%) patients and Kazakh by 37 (29.4%) persons.

All studied patients were divided into two groups according to clinical diagnosis: 1) patients

with harmful SC use (61; 48.4%); 2) patients with dependence from SC (65; 51.6%). Diagnostics of mental and behavioral disorders due to SC use was carried out in accordance with ICD-10 criteria. In toxicological examination of urine samples, SC (predominantly JWH, AB-PINACA and TMCP) were identified for all 126 patients.

Most of the subjects were male (114; 90.5%) of age 18-46 years old with a mean age of 26±0.3 years.

The subject of the study was 356 psychotic episodes observed in the patients during the current clinical study (126), either described in their medical records (55) or analyzed according to anamnesis (175).

Psychoses developed more often during acute SC intoxication (76, 60.3%), less often - within SC withdrawal syndrome (35; 27.8%); delayed psychotic debut (from 18 to 36 days after the last use of the SC) was registered in 15 cases (11; 9%).

Clinical-psychopathological, clinical-anamnestic, laboratory-instrumental and statistical methods were used.

Results and discussion

In clinical dynamics of the developing psychosis following the SC use, several consecutive stages were identified:

in the "prodromal period", a variety of insomnia symptoms developed in conditions of anxiety and asthenia with frequent waking up to nightmarish and / or frightening dreams; for sporadic cases, large convulsive (3) or abortive (4) epileptiform seizures were registered;

at the "affective stage", emotional lability of affect from states of emotional depression to euphoria or a hypomaniac state with heightened talkativeness, causeless fun, excessive distractibility and instability of attention, motor agitation, accelerated and inconsistent speech, uncontrollability of associations, and mental hyperesthesia were observed;

at the subsequent "illusory-hallucinatory stage", against the background of an extremely labile affect, colorful and rapidly changing multiple pareidolias developed, which were transformed into dynamic and vibrant visual hallucinations with coherent individual deception of perception, sensual delusion of persecution, mobile and changing facial expression, reflecting the content of psychopathological experiences;

at the final "stage of deep disorganization of mental activity", detachment from the surrounding world, gross disintegration of thinking, fragmentary hallucinatory-delusional symptoms, fragmentary and not connected with external factors verbal activity, as well depletion of the motor sphere were identified.

According to the clinical and dynamic analysis of psychotic states and considering the depth of obscure consciousness and its psychopathological structure, three clinical variants of psychosis were identified:

1) delirious (68; 54,0%);
2) oneiric (34; 27,0%);
3) amentative-like (24; 19,0%).

Delirious variant of psychosis (68; 54.0%) manifested by a false orientation in the surrounding, multiple, colorful and dynamic pareidolias, stage-like visual hallucinations, single tactile and auditory deception of perception. Patients watched imaginary events but were not involved in them. Fragmentary delusional ideas of an imaginative character were noted accompanied by a changeable affect with a predominance of anxiety and fear against the background of speech-motor agitation.

The clinical picture of the **oneiric variant** of psychosis (34; 27.0%) was characterized by a dreamlike obscure consciousness with an influx of dreamlike fantastic hallucinatory-delusional experiences, disorientation in place and time, a double self-orientation, and disturbed perception of time. Self-consciousness was changing and deeply disturbed. The patients perceived themselves to be participants in fantastic events, played out in their imagination, and completely immersed in the experienced images. The sense of reality was completely lost the surroundings and did not attract their attention. On their faces, there was an expression of surprise or horror, anxiety, fear related to the content of psychopathological experiences. Catatonic symptoms were observed in the form of a substupor, catalepsy, and individual short-term episodes of arousal in bed. The patients looked distracted, inhibited, sometimes wandered thoughtfully with an "enchanted smile", periodically stopped. Movements were scanty and slowed down, facial expressions were frozen/ Sometimes the patients performed "smoothly flying" movements with their hands.

The amentive-like type of psychosis (24; 19.0%) manifested with a deep degree of obscure consciousness with the depletion of all types of mental activity. Patients were deeply disoriented in place, time and self. They were confused, did not comprehend the events, did not understand the events, perceived the environment fragmentary, did not know their name, did not recognize themselves in a mirror. Individual incoherent and deprived of a certain subject visual and auditory hallucinations and elements of incoherent and fragmentary imaginative delusional ideas were observed. There was a marked

disintegration of all components of thinking and the disintegration of self-consciousness. Accelerated speech consisted of separate and disjointed words. Thinking and speaking were incoherent. Emotions inadequate, inconsistent and often changing their polarity. Their mood was unstable; the state of enthusiasm was replaced by tearfulness and / or emotional depression. Monotonous stereotypical jerking, winching and motor excitation limited to the bed. Movements were unfocused, inconsistent, and often sweeping[10]. No lucid episodes were observed; in the evening-night time, short-term episodes of delirious structure were often noted.

In all patients, withdrawal from psychosis was lytic after prolonged medical deep sleep lasting up to several hours (7±0.2 hours). After waking, the symptoms of psychosis usually completely stopped.

In rare cases (9; 7.1%), after the relief of acute psychotic symptoms for 7±1.6 days, post-psychotic asthenia was observed in the form of drowsiness, lethargy, absent-mindedness, and cognitive decline.

At the end of psychosis of the oneiric type, residual delusion was observed in some cases (8; 23.5%) for several days. Post-psychotic amnesia after the relief of psychotic symptoms of delirious and oneiric structures was not registered. After the release of the psychosys, patients reproduced the content of psychotic experiences in sufficient detail, but did not remember the real situation. After psychosis of the amentive-like structure, only isolated and fragmentary memories of psychopathological experiences were observed.

The mortality among 126 given patients was not observed.

The duration of psychosis was different: within SC intoxication, it accounted for 12-24 hours as part of a withdrawal syndrome that lasted up to 36 hours; with a delate debut – up to 72 hours. The mean duration of psychosis was 1±0.42 day.

Patients of Slavic ethnical group (89; 70.6%) more often developed psychoses of the delirious (48; 54.0%) and oneiric (31; 46.1) structures; psychoses of amentive-like type developed significantly less frequently (10; 11.2%). Patients of Kazakh ethnical group (37; 29.4%) more often developed psychoses of the oneiric (18; 48.6%) and amentive-like (12; 32.4%) structures; while delirious psychoses (7; 18.9%) were observed significantly less frequently. The prevalence of psychoses of a deeper mental disturbance (psychosis of the oneiric and amentive-like structure) among people of Kazakh versus Slavic ethnicity may indicate that the native population of the Republic of Kazakhstan has weak enzymatic mechanisms of neurobiological protection.

For a comparative clinical analysis of each of the selected clinical variants of psychoses, the parameters characterizing the specific psychotic development were extracted from all the studied data (socio-psychological, clinical-biological, clinical-psychopathological).

The delirious variant of psychosis often developed in SC intoxication (r = 0.67) and SC withdrawal (r = 0.61), in combination with other psychoactive substances (r = 0.67) with a high level of basic tolerance (r = 0.58) and relatively high actual single dose of SC (r = 0.69). Additionally, in presence of combined personal and endogenous pathology (r = 0.79), without organic mental disorder in the morbid period (r = 0.58), with organic damage to the central nervous system (r = 0.57) and somatic burdens (r = 0.78).

The oneiric variant of psychosis correlated with delayed debut (r = 0.67), the presence of combined personal and endogenous pathology (r = 0.68), without drug abuse history or only a single and non-systemic SC and other drugs' use in the past (r = 0.73). As well as that, with a low level of basic tolerance to SC (r = 0.63) and in the absence of a combined clinically significant somatic and neurological pathology (r = 0.78).

Amentative-like variant of psychosis developed more frequently during the withdrawal period (r = 0.57), correlated with SC dependence (r = 0.78), combined somatic (r = 0.69) and neurological pathology (r = 0.72), organic mental disorder (r = 0.68), and low level of basic tolerance (r = 0.73).

Conclusions

Psychoses due to the use of SC develop either in the framework of SC dependence or after single episodes of SC abuse. They manifest in all phases of SC use: intoxication, withdrawal syndrome or period of up to 20 days after the last SC intake with delayed debut.

The likelihood of development of psychosis and its clinical variants is determined by a complex of clinical, biological, psychopathological, and socio-psychological factors.

A comparative analysis of the psychopathological structure of the identified SC psychotic variants came to the following conclusions. As the clinical picture of psychosis worsened and the state of confusion intensified, psychopathological disturbance of an ever deeper level developed (affective symptoms – illusions and pareidolias – hallucinations – delusions – mental automatisms – motor disturbances) with a simultaneous gradual depletion of a psychopathological picture of psychosis in the context of a narrowed range of existing symptoms.

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Section 3
Clinical case

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ACUTE VIRAL HEPATITIS CAUSED BY SARS-COV-2

Abstract. Background Liver damage during SARS-CoV-2 is more often manifested as part of a cytokine storm and is a predictor of a more severe course of the disease. However, there is scant information on spontaneous liver damage during coronavirus infection. Aims To report on the acute coronaviral hepatitis manifestations. Methods In our study, we analyzed two clinical cases with SARS-CoV-2 debuted with acute hepatitis. Results Patients who tested positive for coronavirus had symptoms of acute viral hepatitis, elevated transaminases titles and minimal lung involvement. Moreover, one of the patients developed diabetes for the first time. Steroid treatment resulted in improved liver function tests, clinical findings, but not diabetes. Conclusion These cases indicate that acute hepatitis can be an independent manifestation of SARS-CoV-2 and that liver damage can be combined with damage to the pancreas, causing diabetes. Timely therapy with an adequate dose of glucocorticosteroids helped to stop the progression of the disease and avoid complications.

Key words: SARS-CoV-2, Acute Viral Hepatitis, Coronaviral Hepatitis.

Background

Coronavirus-2 Severe Acute Respiratory Syndrome (SARS-CoV-2) caused by the RNA beta coronavirus spread in December 2019 from Wuhan, China and became a worldwide pandemic [1]. The main organ-specific manifestations are the lungs and the cardiovascular system, which lead to complications such as acute respiratory distress syndrome (ARDS) and thromboembolism [2]. It is known that due to the tropism of the coronavirus to the Angiotensin Converting Enzyme-2 receptor (ACE2) of the gastrointestinal tract (GIT), coronavirus can cause symptoms such as nausea and diarrhea appearing from, moreover it may be detected in gastrointestinal secret and stool and increase liver enzymes in 20-30% cases [3,4]. Using single-cell RNA sequencing, scientists have proven that ACE2 is present mainly in cholangiocytes and 20 times less in hepatocytes, and such a number of receptors cannot cause coronavirus-associated hepatitis [5]. Elevated transaminases occurs in patients during a cytokine storm, hypoxaemia caused by pneumonia and/or the toxic effect of drugs used for treatment [6,7]. In this report we showed that liver involvement can be an independent manifestation of SARS-CoV-2.

#1 Case presentation

Previously healthy 40-year-old male doctor, on day 10 after contact with a SARS-CoV-2 infected patient was admitted to the hospital with a dry paroxysmal cough, fever up to 39 degrees, nausea, slight malaise in the right hypochondrium, general weakness. Two days after contact with a patient who tested positive for coronavirus by PCR, he developed the above symptoms. CT scan revealed: mild focal pneumonia of viral etiology. PCR for SARS-CoV-2 was positive, patient was negative for viral hepatitis B and C. There were no any signs of chronic liver disease, no peritoneal irritation, ascites or hepatic encephalopathy was observed on physical examination. In the lungs, hard breathing with fine bubbly hips on the left and weakening of breathing in the lower sections was detected. Abdominal percussion revealed dullness on the right. The general condition was severe due to liver damage.

On admission blood test showed an increase in transaminases, bilirubin and glucose (table1). The lymphocyte count in this patient was the highest with an absolute number of 3.6 checked by FACS analysis.

Table 1 - Laboratory results

Timing	Before hospitalisation	During hospitalisation		At discharge	*Normal values*
ALT (U/I)	579	361	218	132.5	*(0–45 U/L)*
AST (U/I)	224	110	53.7	37.5	*(0-35 U/L)*
Total bilirubin (mg/dL)	9.9		6.9	8.2	*(5.1–9.0 mg/dL)*
Direct bilirubin (mg/dL)	3.2				*(<0.3 mg/dL)*
Glucose (mmol/L)	6.3	6.37	6.76	7.4	*(3.89 – 5.83 mmol/L)*
Amylase (U/L)		32	55	54	*(30-110 U/L)*
CRP (mg/L)	15.3		4.9	3.1	*(<5 mg/L)*
Ferritin (ng/mL)	>1000				*(20-250 ng/mL)*
D-dimer (mg/L)	1.06	1.26	1.07	0.61	*(<500 mg/L)*
ESR (mm/h)	36				*(<10 mm/h)*
Leukocytes	11.5	12,3	13,18	13,44	*(4-9 x10^9/L)*
Lymphocytes	5.29	7,9	7,68	9,78	*(1.2-3.0 x10^9/L)*
Platelets	196	246	256	320	*(180-320 x10^9/L)*

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate.

Treatment

The patient was regularly tested to assess the condition of the liver and was treated with methylprednisolone 250 mg/day 1 day and ademetionine 500 mg/day 10 days, metformin 1500 mg/day daily.

Outcome and follow-up

During the hospital stay transaminases markedly improved (table 1) all clinical symptoms regressed, however, the patient had a persistent increase in blood glucose, fasting 9 mmol/L. In this case, a healthy person, after being infected with a coronavirus, developed type 2 diabetes. After discharge from the hospital, the patient took metformin protractedly.

#2 Case presentation

A 50-year-old man from another hospital 7 days after exposure to a SARS-CoV-2 infected person complained of severe dyspeptic symptoms: heaviness and pain in the epigastric region, bloating, absence of stool and gas, nausea, weakness, decreased appetite and sweating. The patient has a history of type 2 diabetes. Objectively, the liver is enlarged by 1 cm. His blood tests showed elevated amylase, transaminase and glucose levels (table 2). PCR for SARS-CoV-2 was positive. There were minimal changes in the lungs with signs of chronic bronchitis. An abdominal ultrasound revealed pancreatitis. During palpation, the abdomen was sensitive in the upper part, intestinal motility was sluggish.

Table 2 - Laboratory results

Timing	Before hospitalisation	During hospitalisation		At discharge	*Normal values*
Amylase (U/I)	3455	3451	3600	35	*(30-110 U/L)*
ALT (U/I)	554		184	60.2	*(0–45 U/L)*

AST (U/I)	368.9		34	39	*(0-35 U/L)*
Total bilirubin (mg/dL)	67.6			31.55	*(5.1–9.0 mg/dL)*
Glucose (mmol/l)	7.66	9.2	4.5	5.04	*(3.89 - 5.83 mmol/l)*
CRP (mg/L)	215.55	35.34	4.9	3.1	*(<5 mg/L)*
Ferritin (ng/mL)	1147.5			740.1	*(20-250 ng/mL)*
D-dimer (mg/L)	0.80			0.29	*(<500 mg/L)*
ESR (mm/h)	20			45	*(<10 mm/h)*
Leukocytes	12,3			15,3	*(4-9 x10^9/L)*
Lymphocytes	1,1			1,21	*(1.2-3.0 x10^9/L)*
Platelets	318			216	*(180-320 x10^9/L)*

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C reactive protein, ESR: Erythrocyte sedimentation rate.

Treatment

The patient was treated with octreotide 0.1mAcute coronavirus hepatitis has been associated with minimal lung damage.

Patients did not have lymphopenia.

After steroid therapy for at least 250 mg/day was a quick positive dynamics.

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THE RARE CASE OF RETROCAVAL URETER IN UROLOGY SERVICE OF ALIABAD TEACHING HOSPITAL

Abstract. Retrocaval ureter is an uncommon congenital abnormality in which the Inferior Vena Cava locates anterior to the ureter and causes its obstruction and hydronephrosis, as a result, and it is also considered one of the rare causes of hydronephrosis. The abnormality almost always occurs on the right because of the physiological position of the Inferior Vena Cava. It is a congenital abnormality, but the patients usually attend to the hospital due to hydronephrosis and right flank pain in the third and fourth decade of live. The abnormality needs surgical intervention and anastomosis of the ureter anterior to the Inferior Vena Cava.

A 40-year-old woman complaining from right flank pain and occasional nausea, vomiting and dysuria, was hospitalized in urology service of Aliabad Teaching Hospital on May 18, 2019. Renal ultrasonography and Intravenous Urography showed moderate hydronephrosis on the right, which was mistakenly diagnosed as uretero-pelvic junction obstruction. Consequently, after further exploration, retrocaval ureter was diagnosed and the retrocaval segment of the ureter was removed followed by end-to-end anastomosis of ureter on ureteral catheter.

The case implies that, clinically, retrocaval ureter seldom causes pain in the right flank and/or hydronephrosis, which can be mistaken for uretero-pelvic junction obstruction in IVU.

Key words: Inferior retrocaval ureter, Hydronephrosis, Pain in the flan.

Introduction

Retrocaval ureter is a rare congenital urologic anomaly. The incidence is reported about one in every 5000-10000 cases [1,3]. Since the Inferior Vena Cava is located on the right side; the abnormality usually occurs on the right. However, its occurrence on the left has also been reported in the literatures in the presence of duplicated Inferior Vena Cava or, situs-inversus [2,7].

Inferior retrocaval ureter is also referred to as Circumcaval Ureter and/or Pre ureteral IVC, in which the ureter passes first medial and then posterior to the IVC. It, then, passes anteriorly, lateral to the IVC after orbiting around it. Eventually, it enters the bladder. The abnormality used to be considered a genetic defect which occurred during the development of the ureter. Nonetheless, now it is found out that the defect occurs in the development of IVC [3,7].

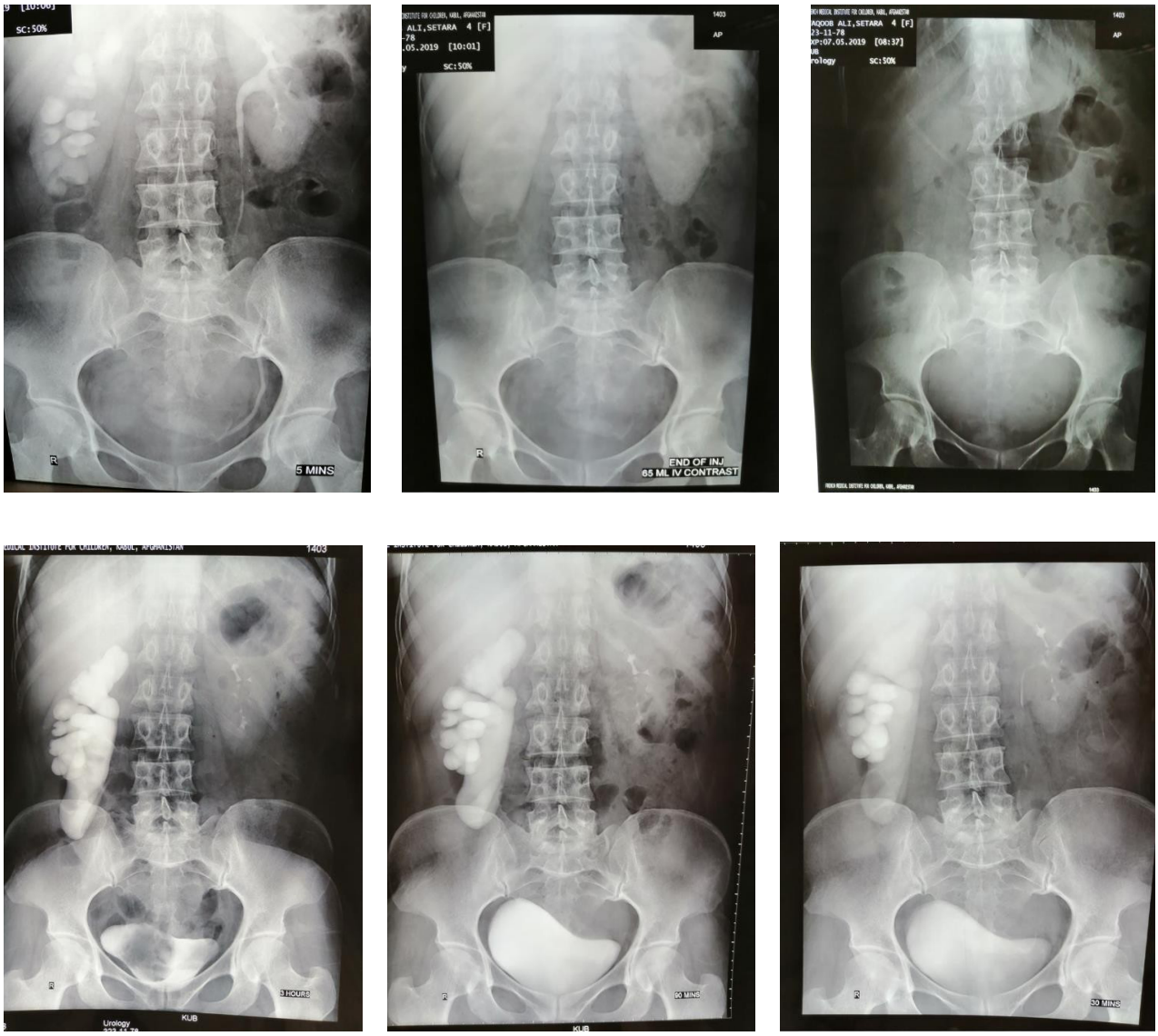
Despite the fact that it is a congenital abnormality, signs and symptoms of the disease appear in the third or fourth decade of life. The patients refer to hospital due to pain in the right flank and hydronephrosis, which is caused by immobilization of a segment of ureter and the pressure of IVC and psoas muscle on the ureter, and the ureter is trapped between IVC and psoas muscle. It is a congenital anomaly which causes hydronephrosis, so other causes of hydronephrosis specifically uretero-pelvic junction obstruction should be considered in differential diagnosis. This specific case indicates that not all hydronephrosis cases are caused by uretero-pelvic junction obstruction.

To make the case more prominent, we want to present the report of the scarce case of inferior retrocaval ureter causing right flank pain and hydronephrosis, and mistakenly diagnosed as uretero-pelvic junction obstruction in IVU.

Case Report

A 40-year-old woman was complaining from right flank pain and occasional nausea, vomiting and dysuria, was hospitalized in urology service of Aliabad Teaching Hospital on October 18, 2019. Based on her explanation, the patient had been suffering from it for three years. According to the patient's explanation, she had suffered from the condition for three years, and pain had always been present and was described as cricks in the right flank. The patient added that the pain sometimes had deteriorated to colic, accompanied with nausea and vomiting. During the three years, the patient had

also suffered from dysuria, which had disappeared after taking a lot of liquid or over-the-counter antibiotics. Medicines like alpha blocker have been taken for the treatment of hydronephrosis, which hadn't resulted in full recovery from the disease. Both right and left flanks were found normal in inspection. However, right flank was palpated tender in bimanual examination. Murphy's punch sign (tenderness at the costovertebral angle due to percussion) was positive on the right in percussion. Ultrasonography revealed moderate hydronephrosis on the right. KUB was normal, but IVU showed distended pelvis and calices in the right side. (shape 1)



Shape 1 – Scout film is normal no stone, nephrogram shows normal distribution of contrast bilaterally, but 5 minute, 30 minute, 90 minute and 3 hour films show right side calyceal and pelvis distention clearly.

shape 1: scout film is normal no stone, nephrogram shows normal distribution of contrast bilaterally, but 5 minute, 30 minute, 90 minute and 3 hour films show right side calyceal and pelvis distention clearly.

Laboratory examination result of urine was as below: Glucose… nil

pH 5
Albumin trace
RBC… 7-8
WBC… 12-14
Epithelial cell many

Laboratory examination result of blood was as below: Monocyte… 2%

Lymphocyte… 31%
Neutrophil 65%
WBC… 7000
Hb 12.2
Urea… 30
Creatinine… 0.8
FBS… 108
HBS… negative
HCV negative

The patient, diagnosed with right moderate hydronephrosis due to right uretero- pelvic junction obstruction, was nominated for open pyeloplasty. The operation, then, was carried out on October 22.2019. Under general anesthesia, a lumbotomy incision was done on the right side. All the layers were incised one by one and the peritoneum was pushed medially. Consequently, the ureter was found posterior to the peritoneum. Unexpectedly, it was found out that the ureter, in the middle part, passed from medial to posterior and subsequently from lateral to anterior side of the Inferior Vena Cava. The distended superior ureter was dissected up to pelvis, which was also distended. The ureter was cut in the superior part and the retrocaval segment of the ureter, which was collapsed and stenotic, was removed. Then, an ureteral stent was inserted into the ureter through the pelvis and an end-to- end anastomosis of the ureter using vicryl 4.0 sutures was performed . Drainage tube was inserted and the layers were repaired one by one. Finally, sterile dressing was applied and the patient was transferred to recovery room. Ureterostomy and drainage tube were removed on tenth and twelfth day of the operation respectively. The patient was discharged from the hospital on October 30.2019 after she got full recovery. The intraoperative stent was removed cystoscopically 4 weeks after the surgery and intravenous urography of patient was normal, no hydronephrosis was observed 8 months after surgery.

Discussion

Retrocaval ureter is an uncommon congenital abnormality the occurrence of which is 1 in every 1500 cases. Moreover, it is 3-4 times more common in men then in women. The first retrocaval ureter case was reported by Hoschstter in 1893[1,3,7,8]. This is the first retrocaval ureter case being reported in a female patient in Urology Service of Aliabad Teaching Hospital.

First it was thought the abnormality is related to the ureter but embryologic studies revealed that it is related to Inferior Vena Cava [3,7]. Therefore, the term Pre Ureteral IVC is a more appropriated one for the abnormality.

It almost always occurs on the right side, as in the mentioned patient. However, if in some cases it occurs on the left, it will be accompanied by partial or complete situs inversus or duplicated IVC [2,7].

The ureter crosses the IVC medial to posterior. Then, it rotates around IVC following its way posterior and lateral to it and eventually turns medially and locates anterior to IVC. It, then, follows its normal route and leads to the urinary bladder, as it is seen in this specific case. Pelvis and the superior segment of ureter, prior to moving posteriorly, are dilated and tortuous forming a J or Fish hook shape [2,7]. Although it is a congenital abnormality, clinical manifestations appear in the third or fourth decade of life, and most of the patients refer with flank or abdominal pain [1,3,7,8]. It is mostly a vague pain or aching which is due to hydronephrosis and occurs intermittently.

Hydronephrosis is caused by immobility of a segment of the ureter and compression of ureter between IVC and Psoas muscle [5,9]. Nonetheless, some patients refer to hospital due to repeated urinary infection, hematuria, kidney stone and pyonephrosis, and the retrocaval ureter is sometimes diagnosed accidentally via radiographic examination carried out to find out other conditions. In this specific case, a 40-year-old woman is reported to have complained about right flank pain, whereas hematuria, repeated urinary infections and pyonephrosis were not found.

Retrocaval ureter is divided to two clinical types. Type 1, which is more common and forms 50% the cases, results in severe ureter obstruction and moderate to severe hydronephrosis. Type 1 includes the middle third or ureter, in which severe deviation of ureter is seen posterior to IVC. Type 2, which occurs in 10% of the cases, includes mild deflection of the ureter posterior to IVC. Furthermore, it either causes mild hydronephrosis or doesn't cause it at all [1,2,7,10,15]. Surgical operation (robotic, laparoscopic or open payeloplasty) is indicated to reform Type 1 because it is symptomatic. In the mentioned patient existed Type 1 which involved middle third of the right ureter, and resulted in moderate hydronephrosis. Thus, surgical open operation was carried out for the purpose of treatment.

Kidney ultrasonography revealed hydronephrosis and proximal hydroureter, in addition pelvis and proximal ureter distension are seen in IVU, whereas middle and inferior ureter is not usually seen. Hence, retrograde ureteropyelography is necessary for diagnosis, which was not carried out in this specific

case. Retrograde ureteropyelography is important to carry out even though a CT-Scan has been done. MRI indicates the pathway of ureter and provides more details than CT-Scan about the abnormality. In spite of not being invasive, it exposes smaller amount of radiation to the patient than CT-IVU [3,7,10]. In this case, ultrasonography and IVU were carried out, while retrograde pyelography and CT-Scan were not performed because the patient already had an IVU.

The treatment for Type 1 retrocaval ureter is surgery, which can be done either robotically, laparoscopically or open. The retrocaval segment of the ureter, which is immobile, is either removed or saved. Then, an end-to-end anastomosis is performed on ureteral JJ Stent between the two ends of ureter or between pelvis and ureter [1,2,3,7]. The retrocaval segment of ureter was removed, but anastomosis was performed on ureteral JJ Stent.

The abnormality should be differentiated from retroperitoneal fibrosis and retroperitoneal tumors both of which push the ureter and displace it. Retrograde pyelography, CT-Scan and MRI can help differentiate the two conditions. The abnormality was mistakenly diagnosed as uretero-pelvic junction obstruction in this patient. Moreover, retrograde pyelography, CT-Scan and MRI were not carried out for diagnosis.

Conclusion

Retrocaval ureter is an uncommon congenital abnormality which is mostly ignored due to its uncommonness. The patients usually refer to hospital complaining about right flank pain in third or fourth decade of life. In IVC, the abnormality can easily be misdiagnosed as all the other conditions causing external pressure on the ureter such as uretero-pelvic junction obstruction, retroperitoneal fibrosis and tumors, so not all hydronephroses are caused by uretero-pelvic junction obstruction, which should be seriously considered. Some additional radiographic examinations such as retrograde pyelography, CT-IVU and MRI are required in order to make sure that the condition is accurately diagnosed. If the abnormality is symptomatic, robotic, laparoscopic or open surgery is indicated for treatment.

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THE RARE CASE OF NON-METASTATIC PENILE CANCER IN UROLOGY SERVICE OF ALIABAD TEACHING HOSPITAL

Abstract. Penile cancer is a very rare cancer of urogenital system of males which occurs in one in every 100000 individuals annually. Senescence, poor personal hygiene, and existence of prepuce are the contributing risk factors. About 95% of the cases are of squamous cell carcinoma type. Metastasis to the nearby lymph nodes indicates poor prognosis. Hence, physical examination, especially palpation of the inguinal region is vital to diagnose the disease and predict the prognosis. The best treatment choice is surgery, and, in case of lymphatic metastasis to the inguinal region, dissection of the lymph nodes.

An 80-year-old man, complaining about a painless ulcer in his penis, was hospitalized on July 14, 2019 in the urology service of Aliabad Teaching Hospital. The patient had been suffering from the ulcer for three years. The ulcer had been small in size for the first two years. It, then, had enlarged and caused urinary retention for one year. Thus, cystostomy had been performed. The ulcer was inspected red which was occupying the distal half of the penis. Moreover, the glans was completely destroyed. However, the inguinal lymph nodes were found normal in size in palpation. Biopsy indicated a squamous cell carcinoma. A partial penectomy was consequently carried out.

This particular case implies that penile ulcers especially in the glans could be the primary sign of a penile cancer. Therefore, the patient had better be consulted regarding biopsy, pathological examinations and early diagnosis and treatment.

Key words: Penile cancer, squamous cell cancer, penectomy.

Introduction

Penile cancer is the most rare tumor of male genitourinary system, the annual occurrence of which is 1/100000 individuals in the world [2,3,11,12,13,14]. It occurs a lot less frequently in the Jewish and Islamic societies due to early customary circumcision, suggesting that circumcision decreases the likelihood of a penile cancer to a great extent [13].

Common risk factors of the disease include chronic inflammatory diseases such as phimosis, balanoposthitis, balanitis xerotica obliterans, phototherapy with ultraviolet radiation, multiple sexual partners, and history of condyloma, cigarette smoking, and Human Papilloma Virus types 6, 11, 16 and 18 which can be transmitted from the infected partner during sexual intercourse. Smegma is thought to be carcinogenic, so circumcision decreases chances of developing the disease.

In terms of microscopic classification, more than 95% of the cases are squamous cell carcinoma. It is believed that SCC originates from penile intraepithelial neoplasia, or novo.

Pathogenesis of the disease includes transcription of viral oncogenes E6 and E7 by cells which are infected with Human Papilloma Virus types 16 and 18. The E6 oncogene targets P53 gene, but the E7 oncogene targets RB1 gene. P53 and RB1 are tumor suppressor genes, which prevent overgrowth of body cells. Transformation of these genes by E6 and E7 results in uncontrollable growth of cells and formation of cancers, as a result, Glans penis is involved in around 48% of the cases.

Clinical manifestations of the disease varies a lot, the beginning sign of which could range from a small area of erythema and skin induration to a deep ulcer or lesion. As the disease develops, pain, prickling, secretions, bleeding, and mephitis would likely appear. Clinical symptoms might be delayed due to psychological factors and the patient would not want to see a doctor in the early stages of the disease.

Size, location, and other characteristics of the lesion and the meatus should thoroughly be assessed in physical examination of the patient. Furthermore, palpation of the inguinal lymph nodes is vitally important because the tumor's initial lymphatic metastasis targets the superficial and deep inguinal lymph nodes and then the pelvic and periaortic lymph nodes. Metastasis to distant organs, which is seen only in the late stages of the disease, is not usual and occurs in only 1-10 percent of the cases.

Surgical intervention approach is chosen according to the location and size of the lesion, and patient's demand in order not to remove the penis so as to have sexual intercourse. Treatment of Penile Intraepithelial Neoplasia (PIN) includes topical.

Imiquimod or 5-Fluorouracil, circumcision, local excision, and laser ablation therapy. If the tumor is well-differentiated, a penile sparing surgery, which includes removing of the lesion and maintaining the penis, is carried out. In case the inguinal lymph nodes are involved, dissection and removal of the lymph nodes is recommended.

It is considered one of the rarest cases of male genitourinary system, especially in societies where boys are circumcised. In Afghanistan, where majority of male population are circumcised, it is very rare. Nonetheless, the pathology can occur. As a result, all penile lesions should be assessed thoroughly in terms of being malignant and treated accordingly. On the other hand, penile cancers usually suggest penile amputation, which is unacceptable to the patient. For instance, in the case being presented, the patient, is spite of being very elderly, had not agreed with penile amputation for three years. Amputation of penis could cause psychological problems in the patient, so the treatment of the condition is also somewhat challenging.

Case Report

On August 14, 2019, an 83-year-old man was referred to and hospitalized in Aliabad Teaching Hospital, Urology Service. His chief complaints included an ulcer with prickling and mild pain in the distal end of his penis. According to his explanation, the problem had begun as erythema and induration in the glans three years ago. The erythema and induration had then increased and enlarged gradually over time and had ultimately developed to an ulcer. The ulcer had, subsequently, increased in size, and besides destroying the glans, it had developed toward the shaft of the penis. As the ulcer had been enlarging, mild pain, prickling, secretions, and nasty smell had appeared. Consequently, since one year before his referral to hospital, he had been suffering from dysuria and then urinary retention. The patient was first taken to a primary clinic, where he was fitted with a suprapubic catheter. As the patient explained, he had first used topical over- the-counter medicine. Then, he had just agreed with dressing of the wound. The doctors he had referred to had recommended biopsy and amputation of the penis, which he had rejected.

The patient was not complaining about any sexually transmitted diseases. Similarly, he was not a smoker and had only one sexual partner. Nobody else in his family had had the same problem and all his other organs and systems had normal function.

In physical examination of the external genitourinary organs, a big ulcer was inspected. The ulcer had completely occupied glans penis and shaft up to the base of the penis. Moreover, the ulcer was red in color with some white spots of fibrin on it. Some black and necrotic ulcers were visible on the edges of the lesion. In addition, necrotic points were noticed in the tip of penis, whereas meatus was not visible (figure 1). Scrotum was normal in inspection, while the suprapubic catheter was visible in the suprapubic region. Inguinal region was symmetrical and no prominence was found in the area. The patient was slim and cachexic. Palpation of the inguinal region revealed no abnormality and no sign of enlargement of the lymph nodes was found.

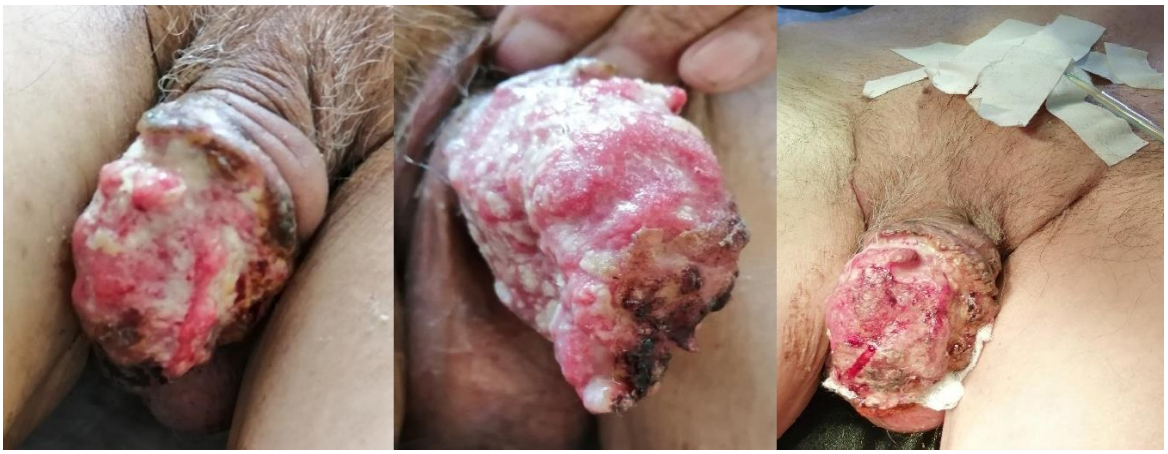

Figure1 - Showing large penile lesion involving glans and penile shaft

Laboratory examination of urine read as below:

Glucose nil
pH… 6
Albumin… (+)
RBC… 0-1
WBC 30-32
Epithelial cells… 2-3

Laboratory examination of blood was reported as following… Monocytes… 2%
Eosinophils… 2%
Lymphocytes… 35%
Neutrophils… 61%
WBC 6000
Hb… 12.6
Urea 37mg/dl
Creatinine 0.97mg/dl
Glycaemia… 126mg/dl
HBS Negative
HCV Negative
HIV Negative

In addition to the mentioned laboratory examinations, a chest x-ray was carried out, in which the lungs looked normal and no sign of metastasis was seen.

A biopsy of the ulceration was performed which indicated squamous cell carcinoma with moderate differentiation. Before the surgical operation was carried out, abdominopelvic and inguinal ultrasonography had been ordered to assess lymph nodes which was reported as normal.

The patient, with the diagnosis of moderately differentiated squamous cell carcinoma, was prepared for a partial penectomy. After using spinal anesthetics in supine position and draping, a circular incision was made 1cm proximal to the tumor. All superficial vessels identified and ligated. The corpus spongiosum was dissected and separated from corpora cavernosa. The corpora cavernosa were transected and the corpus spongiosum was transected then, all bleeding points controlled. The urethra was then spotted and brought out on the ventral surface of penile stump. Corpora cavernosa were repaired in tow layers. The meatus was inverted and implanted into the skin of the base of the penis afterwards. A Foley catheter was inserted and the patient, whose vital signs were normal, was transferred to recovery room (figure 2).

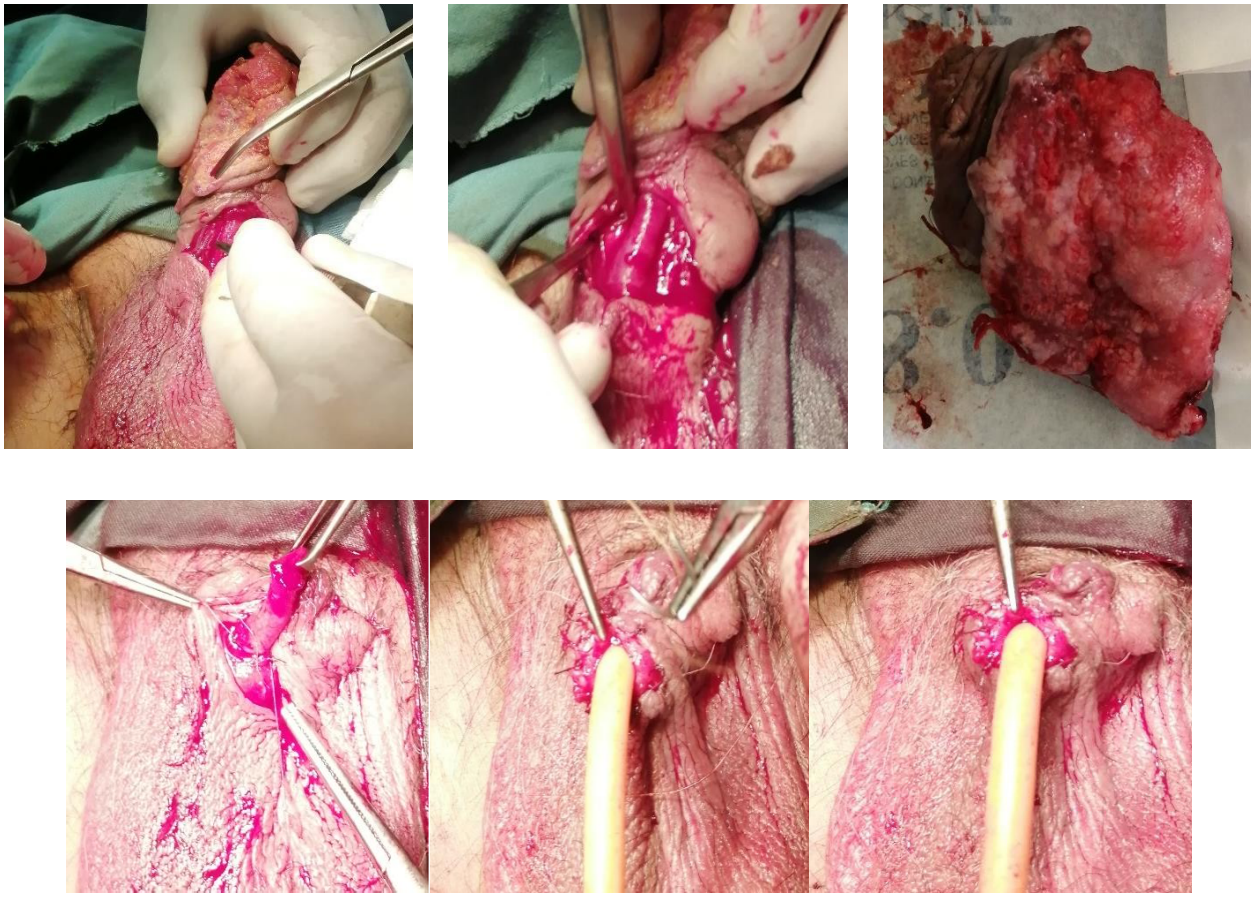

Figure 2 - Showing steps of operation with excised tumor and final appearance of urethral opening with foley catheter applied to it

Discussion

Penile cancer is the most uncommon malignant tumor of male genitourinary system, which is reported in 1/100000 people every year [1, 2, 3, 7, 11, 14]. Similarly, this was the first penile cancer case ever recorded in urology service of Aliabad Teaching Hospital.

The most common type of primary penile cancer is squamous cell carcinoma which constitutes more than 95% of the cases [1, 7, 11, 12, 13, 14], as was the reported case.

The risk factors which are thought to contribute to the occurrence of the condition include old age, chronic inflammatory diseases of glans and prepuce such as phimosis, smoking, multiple sexual partners, Human Papilloma Virus, which is transmitted from the infected individuals, poor hygiene of genital organs, positive history of condyloma, and radiotherapy with ultraviolet radiation [2, 8, 12, 13, 14]. The patient discussed in this case was elderly, 80 years old. However, he didn't complain about any chronic inflammatory disease of glans and prepuce, was not a smoker, had only one sexual partner, and didn't explain positive history of condyloma. The patient had not carried out any laboratory exams to detect HPV, which might have contributed to the disease, besides old age.

Circumcision, which is a cultural and religious matter in Jewish and Muslim societies, is considered to decrease the likelihood of the disease to as many as 5 times because smegma, which located underneath the prepuce, is carcinogenic [8, 12, 13, 14]. The mentioned patient had been circumcised in his childhood.

Primary penile cancers metastasize via lymphatic vessels to superficial and deep inguinal, and pelvic lymph nodes [3, 9, 10, 11, 14]. Moreover, they can metastasize via veins to the liver, the lungs, bones, the brain, the heart, the skin, and even to the breasts [7, 9,

11]. Lymphatic metastasis of the cancer implies poor prognosis. Therefore, palpation of the inguinal lymph nodes in physical examination of the patients is deadly essential [14]. Nonetheless, in spite of normal lymph nodes, there is a possibility of 20% micro metastasis [3]. CT-Scan, MRI, and PET could be used in order to better detect lymphadenopathy in the inguinal and pelvic regions [9,12]. The inguinal lymph nodes were palpated normal in physical examination. Furthermore, pelvic, inguinal and abdominal ultrasonography were found normal. The chest x-ray, ordered to find out metastasis to the lungs, were normal. On the other hand, CT-Scan, MRI, and PET, to further investigate inguinal lymph nodes, and bone scanning, to assess metastasis to the bones, were not carried out.

Treatment of penile cancers include partial or total penectomy. However, total penectomy is not very common contemporarily. Partial penectomy is carried out with or without inguinal lymph nodes dissection [10, 11]. In addition, a 2cm margin is used in partial penectomy [8], but studies have shown that dissecting a few millimeters of margin is safe in terms of malignant cells [10]. In this case, partial penectomy was carried out without intervention to the inguinal lymph nodes and 1cm of margin was dissected. The marginal cells were reported normal according to pathology.

Conclusion

Primary or secondary penile cancer, which appears as erythema, induration and ulcer in penis, is a rare pathology of the male genitourinary system. Due to its uncommonness, it could be treated as a benign or precancerous lesion. Thus, it requires more attention and precision to differentiate it from benign ulcers[12-14].

The patients may not represent any of the risk factors and only complain about penile ulcer. Nevertheless, physicians should not neglect the likelihood of a penile cancer, which can a potential threat to the patients' lives. Thus, they had better accomplish thorough examination and investigations to find out whether the patients or their partners are infected with HPV or not.

Early diagnosis and treatment are vitally necessary for the patients because the problem can be eliminated by merely a penile sparing surgery, in which the patient's sexual productivity is preserved. In case the patient refers to the doctor very late, it is better to carry out CT-Scan of the pelvis, abdomen and even the thorax, bone scan and

Fine Needle Aspiration Biopsy of the inguinal lymph nodes, and merely ultrasonography and a simple chest x-ray are not sufficient[15].

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CONTENTS

Section 1
Reviews, lectures

Section 2
Original research

Section 3
Clinical case