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RABIES - AN INFECTIOUS DISEASE WITH A FATAL OUTCOME (CLINICAL CASE)

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Abstract

Actuality. Rabies is an acute, progressive, incurable infectious disease accompanied by viral encephalitis. The main reservoirs of the virus in wild nature are two genera of mammals, but the greatest danger worldwide is rabid dogs. Today, rabies is registered in 150 countries and territories of the world, on all continents except Antarctica.

Aim. To assess the current situation regarding rabies in Ukraine in general and in the Vinnytsia region in particular, we collected information on the current state of rabies cases and analyzed the medical record of a patient hospitalized with this disease.

Results. The clinical case described by us is intended to draw attention to the problem of the rabies spreading, to raise awareness of the consequences of this disease and ways of its prevention, since the problem is not only medical, but also nationwide.

Conclusions. It is necessary to review the established restrictions and bans on hunting both throughout the territory of Ukraine in general and in the Vinnytsia region in particular. It is worth paying more attention to informing the population with the help of mass media and preventive work of doctors. It is advisable to take measures to strengthen control over vaccination of domestic animals. It is extremely important to ensure that sufficient amounts of vaccine and rabies immunoglobulin are available.

The information provided will be useful to infectious disease doctors, epidemiologists, traumatologists, family doctors, and students of medical universities and colleges.

Keywords: rabies, mammals, hydrophobia, vaccine, immunoglobulin.

Резюме

БЕШЕНСТВО - ИНФЕКЦИОННОЕ ЗАБОЛЕВАНИЕ С ЛЕТАЛЬНЫМ ИСХОДОМ (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Актуальность. Бешенство — острое, прогрессирующее, неизлечимое инфекционное заболевание, сопровождающееся вирусным энцефалитом. Основными резервуарами вируса в дикой природе являются два рода млекопитающих, но наибольшую опасность во всем мире представляют бешеные собаки. Сегодня бешенство зарегистрировано в 150 странах и территориях мира, на всех континентах, кроме Антарктиды.

Цель. Для оценки текущей ситуации по бешенству в Украине в целом и в Винницкой области в частности мы собрали информацию о текущем состоянии случаев бешенства и проанализировали медицинскую карту пациента, госпитализированного с этим заболеванием.

Полученные результаты. Описанный нами клинический случай призван привлечь внимание к проблеме распространения бешенства, повысить осведомленность о последствиях этого заболевания и путях его профилактики, поскольку проблема является не только медицинской, но и общенациональной.

Выводы. Необходимо пересмотреть установленные ограничения и запреты на охоту как на всей территории Украины в целом, так и в Винницкой области в частности. Стоит уделить больше внимания информированию населения с помощью средств массовой информации и профилактической работы врачей. Целесообразно принять меры по усилению контроля за вакцинацией домашних животных. Чрезвычайно важно обеспечить наличие достаточного количества вакцины и антирабического иммуноглобулина.

Предоставленная информация будет полезна врачам-инфекционистам, эпидемиологам, травматологам, семейным врачам, студентам медицинских вузов и колледжей.

Ключевые слова: бешенство, млекопитающие, гидрофобия, вакцина, иммуноглобулин.

Түйіндеме

**ҚҰТЫРУ-ӨЛІММЕН АЯҚТАЛАТЫН ЖҰҚПАЛЫ АУРУ
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Әзектілігі. Құтыру-вирустық энцефалитпен бірге жүретін жедел, прогрессивті, емделмейтін жұқпалы ауру. Табиғаттағы вирустың негізгі резервуарлары сүтқоректілердің екі тұқымы болып табылады, бірақ бүкіл әлемде ең үлкен қауіп-құтырған иттер. Бүгінгі таңда құтыру әлемнің 150 елі мен аумағында, Антарктидадан басқа барлық континенттерде тіркелген.

Мақсаты. Жалпы Украинадағы және әсіресе Винница облысындағы құтыру ауруының қазіргі жағдайын бағалау үшін біз құтыру ауруының қазіргі жағдайы туралы ақпарат жинадық және осы аурумен ауруханаға жатқызылған науқастың медициналық картасын талдадық.

Алынған нәтижелер. Біз сипаттаған клиникалық жағдай құтырудың таралу проблемасына назар аударуға, осы аурудың салдары мен оның алдын-алу жолдары туралы хабардар болуға бағытталған, өйткені мәселе тек медициналық емес, сонымен қатар Ұлттық болып табылады.

Қорытынды. Жалпы Украинада да, Винница облысында да белгіленген шектеулер мен аң аулауға тыйым салуларды қайта қарау қажет. Бұқаралық ақпарат құралдарының көмегімен халықты ақпараттандыруға және дәрігерлердің профилактикалық жұмыстарына көп көңіл бөлген жөн. Үй жануарларын вакцинациялауды бақылауды күшейту бойынша шаралар қабылдаған жөн. Вакцинаның және антирабиялық иммуноглобулиннің жеткілікті болуын қамтамасыз ету өте маңызды.

Берілген ақпарат жұқпалы аурулар дәрігерлеріне, эпидемиологтарға, травматологтарға, отбасылық дәрігерлерге, медициналық жоғары оқу орындары мен колледж студенттеріне пайдалы болады.

Түйінді сөздер: құтыру, сүтқоректілер, гидрофобия, вакцина, иммуноглобулин.

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Introduction.

Rabies is an acute, progressive, incurable infectious disease accompanied by viral encephalitis. Its causative agents are neurotropic RNA viruses of the Rhabdoviridae family of the Lyssavirus genus. The main reservoirs of the virus in wild nature are two genera of mammals - Carnivora and the genus Chiroptera, but the greatest danger worldwide is rabid dogs [12].

Today, rabies is registered in 150 countries and territories of the world, on all continents except Antarctica.

According to WHO, rabies kills about 60,000 people every year. More than 40% of them are children and adolescents under the age of 15, 95% of deaths from rabies are recorded in Africa and Asia [12]. Economic losses from this disease exceed eight billion US dollars [11].

In Ukraine for the last 30 years, the epidemic situation regarding the incidence of rabies has been unstable. Even in the pre-war years, the problem of rabies in our country was quite acute, because more than 120,000 people sought medical help related to animal attacks every year, and more than 20,000 of them needed injections of rabies vaccine.

According to the Ukrainian Center of Public Health, several cases of rabies among people are recorded every year. The largest number (as many as seven) of them occurred in 2007 [10].

With the beginning of military actions, which caused restrictions on hunting and shooting of wild animals, in particular foxes, which are an important reservoir of this infection, the epizootic situation regarding rabies in Ukraine significantly worsened [2].

In particular, in the Vinnytsia region, the number of registered cases of rabies among animals has doubled over the past year, and 87 cases of laboratory-confirmed rabies among animals were registered in the region in 8 months. The largest percentage was cats - 50%, dogs - 35%, foxes - 5%, 2 cases of rabies in cows were recorded [5].

The key factor in virus transmission is traditionally the bite of an infected animal. After the virus passes through the entrance gate in the area of the damaged skin, its centripetal movement to the central nervous system occurs. After replication of the virus, there is a centrifugal spread to the main exit gate - the salivary glands. Although the incubation period for rabies is usually 1-3 months, occasionally the disease has been documented several days or even years after exposure [13].

Potentially, rabies should be suspected in all patients with a classic clinical picture and a concomitant history of an animal bite, and the absence of such signs significantly complicates ante-mortem diagnosis. A complete understanding of the entire complex of pathogenetic

mechanisms of rabies still remains a challenge for specialists from all over the world, and modern treatment, unfortunately, is not very effective and involves mostly only palliative measures aimed at making the patient's death less painful and tragic [14].

The attention of modern medical professionals is largely attracted by the problems of preventing the occurrence of rabies and taking measures before the onset of clinical manifestations. A set of measures aimed at preventing rabies includes careful treatment of wounds, administration of rabies vaccine and rabies immunoglobulin [1, 2].

Since rabies is a typical zoonosis by its nature, it is worth noting that the arsenal of knowledge, forces and means available today makes it possible to completely eliminate this disease among the main reservoir of this disease - wild dogs, and the use of new vaccination methods and technologies allows to significantly reduce the prevalence of the disease among individual representatives of wildlife. Nevertheless, despite the significant technological progress achieved by mankind in the last century, rabies remains a disease that is not paid enough attention, and this is an important challenge for the modern health care system [3, 15].

As of today, in the world, and in Ukraine in particular, there are proven and effective measures for the prevention of rabies. These include: control of the wild animals' population density, trapping of stray cats and dogs, control of compliance with pet care rules (timely registration, use of muzzles), annual mandatory vaccination against rabies of pets, especially dogs, control of the domestic animals' transportation.

According to the Ukrainian rabies prevention protocol for the prevention of rabies in people who are professionally associated with the risk of rabies infection (workers of veterinary diagnostic laboratories, hunters, etc.), it is advisable to use a course of preventive immunization, which consists of three intramuscular injections of the vaccine. One year later and every three years thereafter, a single re-vaccination is required if the person continues to be in a high-risk area.

Domestic animals, in which an episode of human bites was recorded, must be urgently delivered by the owner or a special team for catching stray animals to the nearest veterinary medical institution for examination and keeping under the supervision of specialists for 10 days. In some cases, in the presence of a protected yard or an outdoor room that can be securely closed, after the permission of the veterinary medical institution, as an exception, such an animal can be left under a receipt from the owner, who undertakes to keep it on a reliable leash in an isolated room for 10 days and submit for a veterinary examination within the time specified by the veterinarian supervising the animal. All medical institutions, when addressing persons bitten, scratched, mauled by any animal, as well as people who were injured during the processing of carcasses, during the autopsy of the corpses of animals that died of rabies, or during the autopsy of the corpses of people who died of rabies, are obliged immediately provide first aid to such person and send him to the trauma center (department), and in its absence - to the surgical department for prescribing and conducting a course of rabies vaccinations [4].

Thus, in Ukraine, there is an approved, workable and effective, at least on paper, rabies prevention and control scheme. However, unfortunately, cases of this dangerous disease are still registered not only among animals, but also among people.

We would like to bring to your attention an extract from the medical record of an inpatient.

Clinical case.

Patient B, 60 years old, was brought to the infectious disease department of the Mogiliv-Podilskyi Medical Center by the medical team at 10:00 p.m. with complaints of pronounced general weakness, hyperkinetic movements, orthostatic instability, and subfebrile body temperature.

From the medical history, it was established that for the first time the patient felt sick two days ago, when he first developed a headache, hydrophobia, and the body temperature began to increase. In addition, it was possible to learn from the patient about an episode of being bitten on the lower third of the right hand by his own domestic cat, which had been absent for one week, which had occurred two months before the onset of the first symptoms. After the bite, the patient treated the wound with a solution of brilliant green, did not seek medical help, although the healing of the wound was extremely poor. A few days after the bite, the cat died.

Life history: the patient lives in a rural area, was retired, periodically worked on his own homestead. Suffers from CHD, atherosclerotic myocardiosclerosis.

The results of the objective examination: height 164 cm, body weight 62 kg, at the time of hospitalization, the patient's condition was of moderate severity. Consciousness is clear, the position in bed is active, Ps 71/min, BP 140/90 mmHg, RR 16/min, SaO₂ 98%. On the skin of the inner surface of the wrist closer to the main phalanx of the first finger - a bluish scar, 2.5-3 cm long. The abdomen is sensitive in the epigastrium. Urination and defecation without significant changes.

Results of additional research methods:

CBC: Hb 175 g/l, erythrocytes $5.38 \times 10^{12}/l$, platelets $177 \times 10^9/l$, leukocytes $15.2 \times 10^9/l$, ESR 7 mm/h, band neutrophils 2%, segmented neutrophils 88%, eosinophils 1%, lymphocytes 8%, monocytes 1%.

MSCT of the brain without intravenous enhancement. Conclusion: cystic-gliotic changes at the level of the basal nuclei on the right. At the time of examination, no fresh focal changes were detected. Cyst of the right maxillary sinus.

The rest of the laboratory parameters were within normal limits.

Considering the above, the patient was given a diagnosis: Rabies, typical form, stage of excitement.

Prescribed treatment: in order to sedate the patient, from the first hours of his stay in the hospital, the patient was prescribed an intramuscular injection of 2.0 ml Sibazone solution.

Dynamics of the patient's condition: from the morning of the next day, the patient's condition began to progressively deteriorate, although he still continued to be accessible to contact, complained of severe general weakness, anxiety, unreasonable fear, sleep disturbances, increased sweating, palpitations, headache, dryness in the mouth, thirst, attacks of painful convulsions, difficulty in breathing and swallowing,

spasm of the muscles of the pharynx and pain at the sight of water, the mention of it, or an attempt to drink it.

During the examination: the body temperature is 37.3°C, the patient is sitting alone in bed, agitated, chaotic twitches of the muscles of the limbs are observed, the voice is hoarse, muscle spasms of the pharynx and difficulty breathing are noted. RR 23/min, SaO₂ 98%. At 11:30 the patient was transferred to the intensive care unit. For the purpose of sedation and analgesia, morphine hydrochloride 1% solution 1 ml, sodium thiopental 1.0 g were added to the 2.0 ml sibazone solution, which was prescribed to the patient the day before and 5% ketamine solution 2 ml.

In the morning of the next day, despite the treatment, the patient's condition became difficult: breathing became increasingly difficult, became shallow, saturation decreased to SaO₂ 90%, in connection with which the patient was transferred to a ventilator with 60% oxygen supply, BP 115/65 mm Hg, PS 100/min.

Despite intensive therapy, the patient's cardiac activity stopped and clinical death was diagnosed at 2:05 PM. Resuscitation measures were immediately started, but they proved to be ineffective, cardiac activity did not recover and biological death was declared at 2:25 p.m.

Comment: as of today, several rabies treatment protocols have been developed and applied in the world, the most famous of which is, of course, the so-called Milwaukee protocol, which was first developed and implemented by a doctor from the United States - Rodney Willoughby. The protocol involves putting the person into a chemically induced coma and using antiviral drugs. It was first used in 2003. Since then, 39 cases of using the protocol have been described in the literature, 11 of which were successful. Unfortunately, the results of the treatment of many cases of rabies, especially those that ended fatally, were not published in the literature, even when the Milwaukee protocol was used. This significantly complicates an accurate assessment of its effectiveness. The modern medical community does not have an unequivocal attitude to the assessment of the protocol use, but the vast majority of scientists and doctors consider its use impractical due to the high cost of implementation and ethical difficulties associated with its use [18].

Pathological-anatomical epicrisis: in the cytoplasm of the patient's neurons, the presence of inclusions typical for rabies - Negri bodies, signs of meningoencephalomyelitis, dystrophic-neurotic changes in neurons, proliferation of glia with its replacement of dead nerve cells ("rabies nodules", "Babesh nodules"), accumulation of hyaline layers, perivascular infiltrates in the form of clutches of lymphoid and plasma cells, as well as inflammatory foci in the brain tissue itself, perivascular and paracellular edema, drainage state of glia, droplet hemorrhages).

Pathological and anatomical diagnosis: Rabies, typical form. Rabies meningoencephalitis. Swelling and dislocation of the brain with wedging of the cerebellar tonsils in the large occipital foramen. Dystelectases and focal hemorrhages in the lungs (histologically). Waxy muscle necrosis. Dystrophy of parenchymal organs. Necrotic nephrosis. Atherosclerosis in the stage of atheromatosis and sclerosis with the predominant affection of the coronary arteries and aorta. Atherosclerotic myocardiosclerosis.

Comment: in this case, we were dealing with a typical version of the course of rabies, which developed after exposure to the virus, as a result of the bite of one's own domestic cat, which occurred two months before the appearance of the first manifestations of the disease.

Unfortunately, no measures were taken by the patient to prevent this terrible, deadly disease. It is quite obvious that under such circumstances, as well as in view of epizootological data, regarding animal rabies in the territory of Vinnytsya region, the patient needed immediate first medical aid, in accordance with the order of the Ministry of Health of Ukraine dated 04.15.2004 No. 205 "On improving measures for the prevention of human diseases in rabies" with changes introduced in accordance with the order of the Ministry of Health of Ukraine No. 757 dated 29.11.2007 [6, 7, 8] and "Instructions for the use of rabies concentrated purified inactivated dry vaccine (KoKAV)", approved by the Ministry of Health of Ukraine on 11.16.2004 [9], which involve thorough washing of the wound, scratches, sores, swollen areas with soap and water, treatment of the edges of the wound with 70% ethyl alcohol or 5% iodine solution, application of a sterile bandage. The edges of the wound are not excised or sutured for 3 days, with the exception of injuries that require special surgical interventions based on vital signs.

Considering the fact that after the bite, the patient was able to observe the animal, and also taking into account the fact that a week after the bite, the cat died, it can be confidently stated that in this case it was worth using the indications for vaccination, which are prescribed in the mentioned above regulatory documents and start a course of rabies vaccination according to a special scheme: 1.0 ml of KoKAV on the 0th (the day of the first dose of vaccine), 3rd, 7th, 14th, 30th days, which would give it is possible to 100% ensure the production of specific antibodies by the body above the necessary protective titer (1:80) up to 45 days after the start of immunization.

After that, it was necessary to perform a booster administration of another dose of KoKAV on the 90th day to maintain the antibody titer for a year [9].

At the same time, it is worth noting that in the described case there was a dangerous localization of the bite. This conclusion is due to the fact that the area of the palm is strongly innervated, so it was possible to assume a reduction of the incubation period to 7 days. This term is shorter than the time of production of post-vaccination immunity, so it is unconditional that the patient needed passive immunization by administering human rabies immunoglobulin at a dose of 20 IU per 1 kg of body weight (heterologous 40 IU/kg).

It is appropriate to remind that the Ukrainian standards of aiding persons who have been bitten or licked by rabid or suspicious animals differ somewhat from world practices. In particular, the medical care protocol approved by the WHO, in a situation similar to ours, provides for intradermal injection of 0.1 ml of rabies vaccine in two different injection sites on days 0, 3 and 7, or two doses intramuscularly at two different injection sites on day 0 followed by an additional dose on days 7 and 21. In practice, the advantage is mostly given to the intradermal scheme, because it allows to spend less vaccine, which is more economical, and also requires less time [16].

Of note is the protocol proposed by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) of the United States. It involves administration of the vaccine on days 0, 3, 7, and 14, and one additional injection on day 28 in immunocompromised patients.

Regarding the administration of immunoglobulin, there are also certain differences in protocols. In particular, the CDC advises to give preference to the introduction of rabies homologous immunoglobulin directly into the wound, without primary closure, and in case of impossibility, the entire dose should be administered intramuscularly, although WHO recommendations no longer support this method [16, 17].

The same recommendations emphasize that the site for intramuscular administration of immunoglobulin should not be located near the site of vaccine administration, and the use of rabies immunoglobulin can be delayed for up to 7 days after the first dose of the vaccine, if necessary (for example, in the absence of).

Heterologous rabies immunoglobulin is recommended for use only in developing countries and only in the absence of human immunoglobulin. Although both types of immunoglobulin have shown similar clinical results in the prevention of rabies, the heterologous variant is less expensive. In addition, the latest recommendations allow the introduction of heterologous immunoglobulin without initial skin testing [16].

It is worth noting that since 2007, September 28 has been celebrated worldwide as Rabies Day. It was on this day in 1895 that Louis Pasteur died, who invented a vaccine against rabies for mankind, thereby saving millions of people bitten by rabid animals from inevitable death. Ukraine is one of the countries in Europe that are disadvantaged in terms of rabies. This issue became even more urgent because of the war, as there were many conditions for the spread of this dangerous disease.

The clinical case described by us is intended to draw attention to the problem of the spread of rabies, to raise awareness of the consequences of this disease and ways of its prevention, since the problem is not only medical, but also nationwide.

Conclusions:

1. Taking into account the significant increase in the number of cases of rabies among animals on the territory of Ukraine, as well as the occurrence of deaths caused by this disease among citizens, it is advisable to review the restrictions and prohibitions established on hunting both throughout the territory of Ukraine in general and in the Vinnytsia region in particular.

2. It is worth paying more attention to informing the population with the help of mass media and the preventive work of family doctors, regarding issues of the danger of rabies and possible ways of preventing this disease.

3. It is appropriate to take measures to strengthen control over the vaccination of domestic animals by their owners.

4. It should be mandatory to ensure the availability of a sufficient amount of vaccine for the prevention of this dangerous disease among humans and animals and to create a sufficient supply of rabies immunoglobulin.

The author(s) hereby confirm(s) that:

- The above-mentioned work has not previously been published and that it has not been submitted to the Publishers of any other journal;

Contribution of authors. All the co-authors named have agreed to its publication: **Palii D.V.** - Personal contribution - systematization of the material and its direct presentation;

Mohniy G.O. - Personal contribution - collection of material, design of the article; **Voinalovych O.O.** - Personal contribution - collection and analysis of literature sources, design of the article.

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