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ОЧНА ЛАТЕРАЛИЗАЦИЯ: ОБЗОР С ФОКУС ВЪРХУ ШИЗОФРЕНИЯТА

Катерина Акабалиева[*], Асен Бешков[**], Васил Котетаров[***]

[*]Катедра по психиатрия и медицинска психология, Медицински университет - София

[**]Катедра по психиатрия и медицинска психология, Медицински факултет, Медицински университет – Пловдив, България

[***]Клиника по психиатрия, УМБАЛ „Св.Георги", Пловдив, България

EYE LATERALIZATION: A REVIEW WITH A FOCUS ON SCHIZOPHRENIA

Katerina Akabalieva[*], Asen Beshkov[**], Vasil Kotetarov[*]

[*]Department of Psychiatry and Medical Psychology, Medical University - Sofia

[**]Department of Psychiatry and Medical Psychology, Faculty of Medicine, Medical University Plovdiv, Bulgaria

[***]Clinic of Psychiatry, UMHAT "Sv.Georgi", Plovdiv, Bulgaria

РЕЗЮМЕ:

Обзорът обхваща някои важни находки и интерпретации, свързани с очната латерализация. Първоначално започваме с представяне на явлението латерализация, неговото значение и произход и след това подетайлно описваме нормалната очна латерализация и нейните еволюционни, анатомични и функционални основи. Обръщаме внимание на някои от най-значимите проучвания върху очната латерализация, особено при голямото невропсихиатрично разстройство шизофрения. Накрая обсъждаме значимостта на установената по-често лява латерализация сред пациенти с шизофрения във връзка с невроразвитийните теории за дизонтогенеза при това заболяване.

Ключови думи: латерализация, очно доминиране, шизофрения, дисонтогенеза

ABSTRACT:

The review tries to cover some important findings and interpretations, related to eye lateralization. We first start with introducing the phenomenon of lateralization in nature, its importance and origins and then go into more details concerning normal eye lateralization, its evolutionary, anatomical and functional foundations. Attention is then more closely paid to some of the most significant research studies on eye lateralization and especially the major neuropsychiatric disorder of schizophrenia. Finally we discuss the importance of the findings of more left eye dominance among patients with schizophrenia in relation to neurodevelopmental theories about dysontogenesis in that disorder.

Keywords: lateralization, eye dominance, schizophrenia, dysontogenesis

Introduction

The word lateralization in the narrow sense means the preferred localization of a function or activity on the one side of the body. Lateralization is characterized by sexual differentiation (sexual dimorphism). It is thought that the male brain is more lateralized than the female, although more research is needed on that (30, 36, 52).

Eye dominance, just like hand and foot dominance, as well as linguistic lateralization, can be regarded as an expression of the functional asymmetry of the brain (25). Recent research shows that lateralization exists in the animal kingdom and is certainly not a human specific phenomenon (53). The asymmetry in vertebrate animals shows the evolutionary advantage of the specialization of each hemisphere (34, 42, 43). Unilateral specialization allows fast, effective processing without the need for input from, or the possibility of disruption by the other hemisphere; quick processing of multiple forms of ecologically relevant stimuli in increasing complex environment; increasing neural capacity (14).

Cerebral asymmetry is a unique feature of the human nervous system and might have been related to the development and the evolution of humans from earlier primates (10). Crow (2000) proposed that psychosis and language are linked with each other and have origin in a common genetic event (11). Hemispheric imbalance might underlie the genesis of psychosis (18). Recent work also shows that some of the genes associated with asymmetry and schizophrenia are preferentially selected in human evolution (26).

Eye lateralization – basics; research on healthy subjects

The choice of a dominant eye for vision is not the result of external influence, which makes it a strong predictor of brain lateralization. Descendants with left eye dominance have been found to be more present among the generations of ancestors with the same, proving that hereditary factors are involved in determining it (4). It is not a classical recessive or dominant Mendelian type, but a rather more complex and not completely understood genetic model of inheritance, probably involving environmental influence (41). Eye dominance is fixed approximately at the age of 2 ½ years. The concept of eye dominance relates to the tendency to prefer visual information coming through one of the eyes and the objects being thus more clearly and exactly reproduced, more stable and even larger (48). The dominant eye has priority in perceptional processing (48). The eye with the more efficient control system is probably preferred, which may be related to a motor ability such as hand dominance.

Some suggest that eye dominance is not a monolithic asymmetry, but instead includes sighting, sensory and acuity dominance (40). Of all procedures assessing eye preference (sighting dominance, sensory dominance, and acuity dominance), sighting dominance is most frequently investigated, best understood, and yields the most reliable results (40, 41).

There is indeed agreement that handedness and eyedness are associated (3, 16). Hand and eye dominance are connected in a continuous, uninterrupted way (9). Those who possess a stronger left hand are more often characterized by left eye dominance. Eye dominance is one of the first characteristics proposed as a „key" to hand dominance and other asymmetries (24). Some authors point out that the sighting dominant eye changes according to the hand used for grasping the object (7). One possibility is that human handedness actually derives from deeper perceptual (particularly visual) lateralization (53), rather than preexisting manual biases in primates. A preference for using the right eye/left hemisphere for routine activity might have driven a corresponding right-hand advantage for tool use, supported by a general left eye/right hemisphere superiority for spatial processing.

As to the cerebral dominance the relationship between the eye and the preferred hemisphere is more complex than in handedness, because fibers of any eye reach both cerebral hemispheres, and the foveal region of each retina is bilaterally represented. Though the behavioral preference of the eye is not identical with the term „ocular dominance," some of

the findings in „ocular dominance'' are remarkable with regard to hemispheric asymmetry. The preference of one eye is assumed to be associated with a certain preponderance of the contralateral hemisphere. In line with this assumption are findings by Luria (33), who considered left eye dominance as a sign of latent left-handedness, which like left-handedness results in a latent right-hemispheric dominance. Left-eyed subjects appear to have traits and preferences similar to those of left-handers, although probably to a less pronounced degree. Hence, studies investigating verbal and nonverbal abilities found that left-eyed persons, like left-handers, scored lower in verbal abilities (50), but higher in nonverbal skills (28).

Bourassa, McManus, and Bryden (1996) conducted a meta-analysis of hand eye concordance in 54,087 participants from 54 populations and 47 papers. They reported that in 54,087 participants, the rates of left-handedness and left-eyedness were 9.25% and 36.53%, respectively; and 34.43% of right-handers and 57.14% of left-handers were left-eyed. They suggested that this pattern of hand-eye association is problematic for previous genetic models of cerebral lateralisation. Sex-related factors are important for both handedness and eyedness distribution in the normal population. The incidence of left-handedness was 1.314 higher in males than in females and the incidence of left-eyedness was 1.153 higher in females than males among 9480 male and 8899 female participants in 21 studies (3).

Eye dominance may also affect intermanual coordination (IMC). In a study, 105 right-handed subjects with left or right eye dominance were compared with 105 corresponding left-handed persons. The study indicated that the left-handers scored higher in IMC than did the right handers and in addition, also left-eyed right-handers scored higher in IMC than did right-eyed right-handers (20). In healthy children those with crossed hand–eye laterality showed better performance in bimanual coordination than did children with uncrossed laterality (17).

Eye lateralization – patients with schizophrenia

Eye dominance is considered to be a neglected aspect of human lateralization [Bourassa 1996], (3). This is also true for schizophrenia research, in which most findings deal with eye dominance only in relation to crossed pattern (unequal preference of hand and eye), (13, 19).

Decreased anatomical and functional asymmetry have been demonstrated in individuals who develop psychosis. Schizophrenia patients have reversal of brain torque, reduced asymmetry of planum temporale, and sylvian fissure. There is also reduction in functional asymmetry as reflected by decreased language lateralization in a dichotic listening task (1, 2, 21). There is also reduction in functional asymmetry as reflected by decreased language lateralization (44).

Similar findings have been reported in studies examining handedness, a proxy indicator for language and cerebral lateralization; children of mixed or left-handedness have a higher risk of developing schizophrenia in later life (12), and non-righthandedness is more prevalent in schizophrenia (38). Left and mixed handedness are found to be significantly higher in patients compared with controls (49, 15).

A major investigation of the eye, foot and hand dominance of 200 patients with schizophrenia and 200 controls found more left dominance among schizophrenic patients. The authors pointed out that this can be seen in other central nervous system disorders such as epilepsy and dyslexia. However, no connection was found between eye and hand dominance with both patients with schizophrenia and controls (22).

A later study confirmed those results and left dominance was found in the three dimensions – eye, hand, food – among patients with schizophrenia in comparison with controls. Piran (1982) found that 73% of the schizophrenics are left eye dominant whereas only 23% are left-handed writers; it seems that left eye dominance is much more characteristic of adolescent schizophrenics than left handedness. The authors suggested that the excess of left-eye dominance they found in schizo-

phrenics could be considered as left-hemispheric dysfunction of this disorder. Eye dominance seemed to be the most important measure for differentiating schizophrenic from psychiatric or normal controls. Incongruence between laterality measures was also implicated for schizophrenia. Incongruence in laterality preference, in addition to increased left-sidedness, seemed to occur more typically in the schizophrenic group (39).

Another study did not confirm such a connection for neither eye, nor foot dominance. A significant difference was found between the group of patients with schizophrenia and that of the control subjects in crossed dominance (left eye and right hand dominance). The authors thus conclude that crossed dominance is a more reliable measure of sensomotor lateralization in schizophrenia. Left-eyedness was more prevalent in nonparanoid patients with younger age of onset and earlier age of hospitalization (23).

One study found both more frequent left eye dominance among schizophrenic patient in comparison to controls and more frequent crossed eye-hand dominance (19).

An excess of crossed hand-eye dominance has been reported for schizophrenics (6, 29, 31, 32, 37, 47). Among these was also the oldest such study: Oddy and Lobstein compared the handedness and eye dominance of 140 schizophrenics (age range, 18 to 65 years) with that of 497 previously tested normal subjects. They found no differences for either handedness or eye dominance. However, cross dominance (especially right-handedness and left eye dominance) was much more frequent in the schizophrenic group (37). Liu, Yang, Lin, Lee, Jeffries, Lee (2004) investigated hand preference and eye dominance in 73 schizophrenic patients. Schizophrenic patients showed a significant excess of left-eye dominance relative to controls (65.8% vs 29.6%). Female schizophrenic patients showed a higher rate of non-right (either left or inconsistent) eye dominance (80%) than male schizophrenic patients (55.8%) and controls (33.3%), (31).

Senol Dane et al. (2009) investigated the possible relationships among handedness, eye dominance, and crossed and non-congruent hand-eye dominance in 88 patients with schizophrenia. The male patients with schizophrenia had significantly increased frequencies of left eye dominance, crossed hand-eye dominance, and non-congruent hand-eye dominance compared to controls, but not the female patients. In this study patients with schizophrenia had significantly increased frequencies of the left-eye dominance compared to controls. These results are consistent with findings from previous studies. They suggest a shift from right to left for eyedness or a left occipital hemispheric dysfunction. Also, in this study the male schizophrenic patients had significantly increased frequencies of crossed hand-eye dominance and non-congruent hand-eye dominance compared to male controls. These results were again consistent with findings from previous studies (13).

Some studies have shown that crossed dominance may indicate a poorly established hemispheric specialization (5) and developmental brain impairment in various neuropsychiatric diseases (8).

Another study found a connection between the onset of the disease and crossed dominance. Patients with schizophrenia who have right hand and non-right eye dominance have an earlier onset of their disease when compared to the group characterized by right hand and right eye dominance (46). Merrin (1984) reported that left-eyedness, particularly in right-handed paranoid schizophrenics, was associated with later age of first hospitalization and a more benign course of the disease (35). Recently, Tabaris, Sanjuan, Gomez-Beneyto, and Leal (1999) found that the group of schizophrenics with increased incidence of crossed hand-eye dominance had significant earlier clinical onset and smaller brain size than the group of schizophrenics with decreased incidence of hand-eye cross dominance (51). A longitudinal study used the more frequent left or mixed foot and eye dominance, but not hand dominance, as a differential for children who would later develop disorders from the schizophrenia spectrum in comparison to those who would not develop such disorders (45).

What's more, sexual dimorphism may be implicated in eye dominance among patients

with schizophrenia. Cross-dominance is much more common in male schizophrenic patients (27). Yan, et al., 1985), reported that left eye dominance tends to be more common in female schizophrenics (33.7%) than others in a study that included only ethnic Chinese subjects (47). Leung and Chue (2000) suggested that the female brain is more symmetrically organized (less lateralized) than the male brain (30). If left hemispheric dysfunction is related to schizophrenia, then eye dominance is directly related to cerebral hemispheric dominance (27), and females with schizophrenia might have a greater chance of showing left eye dominance.

Discussion and Conclusion

The lateralization of brain functions (including eye dominance) is embedded in the fetal stages of individual development, although by still not fully clarified mechanisms. The eyes are a part of brain structure and probably the most direct indicator for hemispheric lateralization. Eyes have much in common with the development of the central nervous system, because they originate from the proencephalon. Left eye shift could indicate right hemispheric dominance and hypothetically left hemispheric disturbances or inferior left hemispheric performance. If this leftward shift is due to generalized CNS disorder or specific dysfunction in the left hemisphere is to be further investigated. Left side asymmetry is the result of the implementation of precisely guided programs of development during the embryonic period and specifically during the first three weeks of pregnancy, when the human ectoderm forms a thickened band called a neuronal disc. This means that impaired cerebral lateralization can be taken in its essence for a disorder of neuroontogenesis, which in turn underlies the development of schizophrenia. This again can make left eye dominance an indicator of neurodevelopmental deficit. Probably the inconsistent motor asymmetry or a poorly defined such is an essential pattern for neurodevelopmental disorders such as schizophrenia.

Currently the most widely used instrument for assessing laterality is hand dominance. However, eye dominance is a much subtler indicator of altered hemispheric lateralization than foot and hand dominance. Handedness was under cultural pressure against using the left hand during the Communist Regime (before 1990). Social conformity determines the use of the right hand as well as the fact that the material world has been adapted for right-handed people. Such pressures are less likely to impact foot preference and do not affect eye preference at all. Eye dominance assessment provides an adequate comparability among different countries (cultures) without cultural confounding when investigating laterality and studying different neuroontogenetic disturbances such as ADHD, autism, schizothypy, psychosis, affective disorders.

Conflict of interest: The authors declare no conflict of interest in relation to this manuscript.

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Адрес за кореспонденция:

АСЕН П. БЕШКОВ

Катедра по психиатрия и медицинска психология, Медицински факултет, Медицински университет – Пловдив, България
бул. „Васил Априлов” 15А,
Пловдив 4000, България
asen.beshkov@abv.bg

Corresponding author:

ASEN P. BESHKOV

Department of Psychiatry and Medical Psychology, Faculty of Medicine, Medical University Plovdiv, Bulgaria
15A Vassil Aprilov blvd.,
4000 Plovdiv, Bulgaria
asen.beshkov@abv.bg

НЕВРОЛОГИЧНИ УСЛОЖНЕНИЯ ВСЛЕДСТВИЕ НА SARS-COV-2 ИНФЕКЦИЯ

М. Димитрова, К. Димитрова, Дж. Самуел, Н. Габровски

УМБАЛСМ „Н. И. Пирогов"

SUBSEQUENT NEUROLOGICAL COMPLICATIONS OF SARS-COV-2 INFECTION – A REVIEW

M. Dimitrova, K. Dimitrova, J. Samuel, N. Gabrovsky

UMHATEM „N. I. Pirogov"

РЕЗЮМЕ:

Заболяването COVID-19, причинено от SARS-CoV-2, се появява за първи път в провинция Ухан , Китай, през декември 2019 година и бързо се разпространи по целя свят като пандемия. Инфекцията със SARS-CoV-2 се медиира от свързването на рецептор свързващия домейн на вирусните частици и клетъчните рецептори на ангиотезин конвертиращия ензим-2 (ACE2). ACE 2 рецепторите се експресират в много тъкани (бели дробове, сърце, бъбреци, , централна нервна система, черва и тестиси).

Първите описани засягания от заболяването са респираторни и сърдечни, но впоследствие се описват и неврологични усложнения в литературата под формата на описания на клинични случаи и анализи.

Неврологичните усложнения могат да включват заболявания на централната нервна система (главоболие, световъртеж, мозъчно-съдови заболявания, нарушение на съзнанието, трансверзален миелит, енцефалопатия, енцефалит, епилепсия) и на периферната нервна система (засягане на вкуса и мириса, невралгии, синдром на Гилен-Баре, миопатия)

Първоначално се предполагаше, че неврологичните усложнения се появяват при пациенти с тежко протичане на COVID-19, но вече е ясно, че наличието и тежестта на неврологичните усложнения не е свързано

ABSTRACT:

The disease COVID-19, caused by SARS-CoV-2, appeared in Wuhan, China, in December 2019 and quickly spread to more than 200 countries as a global pandemic. Infection with SARS-CoV-2 is mediated by binding between the receptor-binding domain of viral thorns and the cellular angiotensin-converting enzyme-2 (ACE2) receptor. ACE2 receptors are expressed in many tissues (lungs, heart, kidneys, central nervous system, intestines, testicles), it is the reason for multiorgan complications.

The primary manifestations are respiratory and cardiac, but neurological complications are also reported in the literature as analyses and cases.

Symptoms can be both: from the central nervous system (headache, dizziness, cerebrovascular disease, impaired consciousness, transverse myelitis, encephalopathy and encephalitis, epilepsy) and the peripheral nervous system (hypogeusia, hyposmia, neuralgia, Guillan-Barre syndrome, myopathy).

Firstly, the suggestion was that the neurological complications are most common in patients with severe COVID-19 infection. Now it is clear that the severity of neurological complications is not dependent on the disease course. The knowledge for neurological involvement comes from the most affected world

с тежестта на заболяването. Първите знания за неврологичното въвличане при COVID-19 дойдоха от „огнищата" на заболяването в Ухан и Северна Италия, но впоследствие се потвърдиха от наличието на клинични случаи и изследвания от целия свят.

Ключови думи: коронарирус, неврологични усложнения

points Wuhan and Northern Italy, and the data confirmed with reports from all over the world.

Key words: coronavirus, neurological complications

Introduction

COVID-19 is an acute infectious disease caused by a beta-coronavirus called SARS-CoV-2, which affects the lower respiratory tract and manifests as pneumonia in humans. Most patients have an acute onset with fever, myalgia, cough, shortness of breath, and radiographic evidence of SARS. The risk of exitus letalis is 1.4% but increases significantly after the age of 60. [1] Interestingly, the relative number of symptomatic infections also increases with age, raising questions about the biological response of the host to the infection. [2]

Neurological complications

Patients with severe disease usually have neurological complications, probably due to viral invasion of the central nervous system (SARS-CoV-2 is found in the brain and cerebrospinal fluid). [3] Even at the beginning of the pandemic a study of 214 patients, neurological symptoms were observed in 36% of them and were more common in patients with severe disease. In a small retrospective study of intensive care patients, 44% of patients with neurological symptoms had abnormal MRI findings of the brain. [4] Complications include acute cerebrovascular disease, impaired consciousness, ataxia, seizures, neuralgia, corticospinal tract injury, meningitis, encephalitis, and encephalopathy. Patients may present with these signs/symptoms or may develop them during the disease. These patients have a poor prognosis.

Once the COVID-19 virus was found to use the ACE2 receptor to enter cells, targeted studies began on the expression of ACE2 in neurological tissue. ACE2 receptors have been described on glial cells and neurons, making them a potential target of COVID-19.

The research on neurological complications in COVID-19 expanded in the last year and other theories were proposed.

Mechanism of CNS involvement in SARS-CoV-2

In a review of CNS viral infections, Koyuncu et al. concluded that all viruses can reach the CNS under appropriate conditions depending on viral factors (mutations in specific virulence genes) and host factors (immunosuppression, age, and comorbidities) [6]. The spread of SARS CoV-2 into the systemic circulation or through the cryptoform plate of the ethmoid bone during the early or later phase of infection can lead to brain damage. The presence of the virus in the general circulation understandably allows it to enter the cerebral circulation. Slow blood flow within the microcirculation may be one of the factors that may facilitate the interaction of S-protein with ACE2 expressed in the capillary endothelium. [5] This was followed by the passage of viral particles through the capillary endothelium and damage to the endothelial mucosa. Once in the middle of neuronal tissues, its interaction with ACE2 receptors present in neurons can initiate a cycle of viral replication. Neuronal damage follows. However, neuroinflammation mediates secondary damage through cytokine secretion, neurotrophic factors, and protease activation to remodel the extracellular matrix. Molecules of the systemic innate immune system or directly affected neuronal populations can activate microglia in the brain and initiate neuroinflammatory events. Autopsy materials from patients who developed encephalopathy weeks after SARS-CoV-2 infection showed

edema, neuronal necrosis, and extensive glyocyte hyperplasia [7]. Immunohistochemical staining showed that SARS-CoV in the brain was associated with increased expression of the cytokine, interferon-induced monokin, and infiltration of monocytes, macrophages, and T cells. These findings are consistent with viral entry into the CNS, causing the infiltration of immune cells and the release of cytokines and chemokines, which contribute to tissue damage [8]. The T-cell response is initiated by antigen presentation by dendritic cells and macrophages. CD4 + T cells activate B cells to stimulate virus-specific antibody production, while CD8 + T cells can kill virus-infected cells [9,10]. The movement of the COVID-19 virus to the brain through the crib plate near the olfactory bulb may be an additional pathway that allows the virus to reach and affect the brain. Findings such as an altered sense of smell or hyposmia in an uncomplicated patient in the early stages of COVID-19 support this theory.

Microvascular injury

Neurological manifestations of COVID-19 have been believed to be a result of direct damage to nerve cells. But the recent studies suggest that the virus may damage the brain's small vessels [43]. The researchers presented magnetic resonance microscopy, histopathological examination, and immunohistochemical analysis in 13 patients with COVID-19. The results revealed the microvascular injury in the brain and olfactory bulb, despite no evidence of viral infection.

Mechanism of PNS involvement in SARS-CoV-2

The mechanisms of SARS- CoV 2 PNS involvement are an immune-mediated mechanism of involvement and a mechanism of molecular mimicry. While the direct effect of viruses on the nervous system occurs during the acute phase of the disease, the indirect effect is detected days, weeks, or even months after infection.

Immune-mediated mechanism

The immune-mediated mechanism is closely related to the development of a systemic inflammatory response syndrome. The mechanism of nerve damage may be by activating T cells and releasing inflammatory mediators from macrophages. Patients with COVID-19 may develop systemic hyperinflammation, referred to as a cytokine storm, also known as secondary hemophagocytic lymphohistiocytosis (sHLH). Resistance to CoV infections and their ability to infect macrophages, microglia, and astrocytes are particularly important. The neurotropic virus can activate glial cells and induce hyperinflammation [11]. Thus, due to excessive secretion of inflammatory factors such as IL-6, IL-12, IL-15, and TNF-α after infection with CoV, damage to the PNS is possible [12].

Molecular mimicry

The attachment of SARS-CoV-2 to cell surfaces is thought to be mediated by the viral spike (S) protein, which binds to the angiotensin-converting enzyme 2 receptors, as well as gangliosides containing sialic acid residues, including residue GalNAc on GM1. It has been suggested that cross-reactivity between viral protein-associated gangliosides and peripheral nerve gangliosides results from molecular mimicry.

Because the SARS-CoV-2 protein interacts with the N1-acetyl-galactosamine residue of GM1 to attach to the cell surface, an immune cross-reaction between epitopes in spike-bearing gangliosides and sugar residues from surface peripheral glycolipids is also possible. A study demonstrates that SARS-CoV-2 shares a unique amino acid sequence with human heat shock proteins (HSP). HSPs are involved in several immune-mediated clinical conditions and may be subject to an immune response, possibly as a result of molecular mimicry [13]. In molecular mimicry, an exogenous antigen has structural similarities to some host antigens. Thus, any antibody produced against this antigen can bind to host antigens and enhance the immune response. Evidence is important from a neurological point of view that autoantibodies targeting different families of HSPs are elevated in the serum and cerebrospinal fluid (CSF) of patients affected by myasthenia gravis, multiple sclerosis, and Guillain-Barre syndrome (GBS)

[14]. Sharing common sequences between virus peptides and HSPs strongly supports immune-mediated neurological damage in COVID-19. In particular, the hexapeptide shared with HSP90B and HSP90B2 is part of 5 experimentally validated epitopes of SARS-CoV. The epitope (antigenic determinant) is part of the antigen that is recognized by the immune system. Although epitopes are usually foreign proteins, sequences derived from their antigens can also be recognized as epitopes. The hexapeptide is located proximal and terminal in these epitopes, thus forming the only sequence common to all epitopes. Therefore, the shared hexapeptide is very likely to be the immunogenic determinant of all five epitopes. Thus, this hexapeptide is the ideal candidate for eliciting an autoimmune response against HS90B and H90B2 as a consequence of SARS-CoV2 infection. The second immunologically relevant motif, shared by SARS-CoV-2 and human HSP, belongs to chaperone protein 60 and is recognized by lymphomonocytes of patients affected by demyelinating CNS disease [15]. This finding necessitates further investigation of a possible association of SARS-CoV-2 infection with inflammation and demyelination not only in the PNS but also in the CNS. HSP60 is a mitochondrial protein that is distant from the plasma membrane. Nevertheless, immune responses against intracellular autoantigens are a well-known phenomenon [16,17]. Also, it has been shown that post-translational modifications (PTMs) of HSP can cause the protein to "move" across the plasma membrane [18]. Multiple concomitant mechanisms could then explain the immune responses against HSP60 in the case of autoimmunity. In summary, the present data point to the immunological targeting of HSP 90B, 90B2, and 60 as a potential pathogenetic mechanism of neuropathy after SARS-CoV-2 infection and offer special testing of sera and CSF in a patient with COVID-19 affected by GBS and possibly other peripheral neuropathies for autoantibodies to these proteins.

The neurological complications of COVID-19 can affect the central and peripheral nervous system (Table 1).

Table 1. ***Neurological complications and clinical presentation in COVID-19***

Central nervous system	Dizziness, headache, acute cerebrovascular disease, impaired consciousness, transverse myelitis, acute hemorrhagic necrotizing encephalopathy, encephalopathy, encephalitis, epilepsy, ataxia
Peripheral Nervous System	Hypogeusia, hyposmia, neuralgia, Guillian Barre syndrome, Bell's palsy

Encephalitis is an inflammation of the brain tissue, and viruses being the most common etiological factor. Recent studies have reported a possible complication of SARS-CoV-2 in human CNS, mainly encephalopathy but encephalitis as well. Cases of acute necrotizing encephalitis associated with COVID-19, acute disseminated encephalomyelitis (ADEM), and stem encephalitis have been reported.

Although the final diagnosis of viral encephalitis largely depends on the isolation of the virus, this is difficult for COVID-19 because the prevalence of SARS-CoV-2 is transient and its titer in CSF can be extremely low. Therefore, the diagnosis is based primarily on neurological status and anamnestic data. Except two cases of positive PCR in CSF for SARS-Cov2 in two meningitis/encephalitis users [19, 20], all other studies in which CSF was developed could not detect SARS-Cov2 by PCR [21, 22, 23, 24]. This failure to detect traces of SARS-Cov2 can occur in the absence of optimal CSF testing techniques for this virus [25]. The pathophysiological characteristics of SARS-CoV-2-associated encephalitis are not fully understood. The SARS-CoV-2-induced immune response can cause inflammation and swelling of the brain, leading to changes in consciousness.

Ye Mingxiang et al. reported a case of a Wuhan man positive for SARS-CoV-2 who developed a complication of encephalitis. It is one of the first reported cases. The initial symptoms were fever, shortness of breath, and myalgia, and 10 days later progressive blurring of consciousness was added. The neurological status revealed neck rigidity, positive Kernig, and Brudzinski. The laboratory test showed a low number of WBC (3.3x109 / L) and lymphopenia (0.8x109 / L). Chest CT reveals multiple subpleural "frosted glass" shadows, and brain imaging is normal. A lumbar puncture was performed and an increased CSF pressure (220 mmHg) was found, while the other laboratory parameters of the CSF remained within normal limits. CSF was further tested for SARS-CoV-2, but negative. Treatment in this patient is mainly supportive, including infusion of mannitol. The patient's consciousness gradually improved and after two negative PCRs for SARS-CoV-2 the patient was discharged. [26]

A series of cases with encephalitis starting with seizures were reported. Sandeep Sohal et al. reported a case of a 72-year-old man with a history of hypertension, coronary heart disease, permanent patient stent, type 2 diabetes, CKD in the final stage of hemodialysis. The patient complains of weakness and dizziness after a hypoglycemic episode. After the admission, the patient deteriorates for a short time and develops respiratory failure, accompanied by quantitative impairment of consciousness and hemodynamic instability. PCR for SARS COV-2 was positive. CT of the head showed chronic microvascular ischemic changes, but there was no evidence of the acute cerebrovascular accident. Chest CT shows shading of both lung bases with the consolidation of the right lower lobe. On the 3rd day of admission, numerous episodes of generalized tonic-clonic seizures had been observed. A 24-hour EEG shows epileptogenic areas in the left temporal region. Before admission, the patient had no history of seizures. Blood glucose levels recorded before and after episodes of seizures did not indicate hypoglycemia. Over the next two days, tonic movements of the upper limbs had been observed, 2-3 times a day. Despite intensive care and antiepileptic therapy exitus letalis occurred on the 5th day of admission to the hospital. The patient was persistently febrile during hospitalization, possibly associated with the cytokine storm caused by COVID-19. Imaging and lumbar puncture were not performed due to the constantly unstable condition of the patient. [27]

Gary N. McAbee et al. reported a case of an 11-year-old child who had status epilepticus and CSF data for encephalitis. The nasopharyngeal swab was positive for COVID-19. The patient had a two-day history of generalized weakness and fever without respiratory symptoms. CT of the head was normal, but the EEG shows frontal intermittent delta activity. [28]

Po Fung Wong et al. described a case of a 40-year-old man with stem encephalitis associated with SARS-CoV-2 infection. [26] The patient developed acute brainstem dysfunction three days after hospitalization with symptoms of COVID-19. The initial complaints had been unstable gait, and in the next 24 hours developed diplopia, oscillopsia, ataxia of the limbs, sensory disturbances in the right hand, hiccups, and disorders of swallowing function. MRI showed changes consistent with inflammation of the brainstem and upper cervical spine, leading to a diagnosis of rhombencephalitis. PCR for SARS-CoV-2 was not possible. The patient had a good response to conservative treatment.

Acute necrotizing encephalopathy (ANE) is a rare complication of viral infections associated with an intracranial cytokine storm that results in disruption of the blood-brain barrier without direct viral invasion or parainfectious demyelination. To date, no direct association of ANE with COVID-19 infection has been demonstrated. However, a recent report in the Lancet suggests that a subset of patients with severe COVID-19 may develop cytokine storm syndrome. [29] In support of this, it was present a case of a 58-year-old woman positive for COVID-19 and diagnose with ANE [29]. The patient's initial symptoms are associated with the typical manifestations of COVID-19 - fever, cough, and muscle aches. A few days later, however, the patient became confused, lethargic, suggesting CNS involvement. CSF analysis was negative for

HSV type 1 and HSV type 2, HZS, and West Nile virus. A test for the presence of SARS-CoV-2 in CSF has not been performed. Imaging examinations of the brain revealed symmetrical hemorrhagic lesions in the thalamus, medial temporal lobes, and subinsular.

Acute transverse myelitis Kang Zhao et al. described a case of acute myelitis in a 66-year-old man from Wuhan. The patient's initial symptoms were fever and body aches. During admission, he developed acute paralysis in the lower extremities, with a sensory disturbance - hypoesthesia from Tx-10 down, with incontinence of the pelvic reservoirs. Chest CT confirmed pneumonia and PCR of nasopharyngeal swab was positive for COVID-19. He was treated empirically with IVIG, steroids, antibiotics, and antiviral therapy, with gradual improvement. The presence of acute myelitis is due to cytokine storm and overactive inflammatory response. [30]

Maike Munz et al reported a 60-year-old patient with typical respiratory symptoms of COVID-19 infection without neurological symptoms. He recovered quickly from COVID-19 pneumonia and was discharged home 5 days later without any symptoms. Three days after the discharge, he developed bladder dysfunction and progressive weakness of the lower extremities. When re-administered two days later, clinical examination revealed hypoaesthesia below Th9 levels and moderate spastic paraparesis. Babinski's sign was positive on both sides. Paraclinical studies were unobstructed, and repeated nasopharyngeal swabs showed negative PCR for SARS-CoV2. MRI of the spine revealed hyperintense levels from Th2 to Th9, suggesting acute transverse myelitis. MRI of the brain showed no inflammatory changes. CSF analysis revealed protein-cell dissociation. SARS-CoV2-PCR in CSF and oligoclonal bands are negative. Numerous additional CSF tests have been performed, such as PCR for herpes viruses, antineuronal antibody panel, Aquaporin-4, and myelin oligodendrocyte glycoprotein antibodies. Follow-up MRI on day 6 further showed uneven hyperintensity of thoracic myelon at Th9-10 and at level Th3-5, suggesting transverse myelitis. Methylprednisolone treatment was started. The patient was discharged at home on day 13 with mild spastic paraparesis and hypoaesthesia below the Th9 level, but normal bladder function. [31] [32]

Cerebrovascular disease Wu et al. suggest that virus-mediated cytokine storm and coagulation disorders, evidenced by elevated D-dimer and platelet counts, increase the chance of acute CVA in patients infected with SARS-CoV-2. [33]

Sharifi et al. describe a case from Iran with intracerebral hemorrhage, in a 79-year-old man with COVID-19 positive. He was hospitalized with severe impairment of consciousness (Glasgow coma scale 7/15) and a history of fever and cough. PCR for nasopharyngeal secretion was positive for COVID-19. A CT scan of the chest confirmed pneumonia, and a CT scan of the brain revealed a massive hemorrhage in the right cerebral hemisphere, with a rupture in the ventricles and subarachnoid space. The patient had no history of hypertension and was not on anticoagulant treatment. The coagulogram on admission to the hospital was normal. The authors postulate that dysregulation at ACE2 receptors is likely to lead to disturbances in cerebral autoregulation, the sympatho-adrenal system, and cerebral blood flow, leading to bleeding. [34]

Mao et al. reported 6 cases of cerebrovascular accidents, 5 with ischemic and 1 with hemorrhagic stroke. A French cohort reported three cases of ischemic stroke from imaging studies. Patients were free of focal neurological deficits. [35]

The cerebrovascular complications are confirmed with series of cases from different countries and it is clear they are the most common neurological disorder after COVID-19.

Parkinsonism The occurrence of transient or permanent parkinsonism following a viral infection is well known. In these cases, parkinsonism might occur through different mechanisms: 1) structural and functional basal ganglia damage mainly involving the substantia nigra pars compacta and nigrostriatal dopaminergic projection; 2) extensive inflammation or even hypoxic brain injury within the context of an encephalopathy; 3) unmasking of underlying but still non-symptomatic Parkinson's disease; or 4) the hypothetical

possibility that a viral infection might trigger a series of processes that result in the development of Parkinson's disease over the long term in individuals with genetic susceptibility. Marcelo Merello et al. analyze three cases with parkinsonism after SARS-CoV-2 infection. Onset had been acute in the three cases (10–32 days after COVID-19 diagnosis); one patient (the 58-year-old male) had developed akinetic rigid syndrome in the context of a complex neurological presentation compatible with encephalopathy, including myoclonus and opsoclonus, while the other two patients had had pure asymmetric akinetic-rigid features, with tremor, and mild respiratory disease. The spontaneous improvement had been reported in one of the patients Functional nigrostriatal neuroimaging was abnormal in all three cases, which implies dopaminergic nigrostriatal impairment, but is not diagnostic of Parkinson's disease [44].

Headache and dizziness Headache and dizziness are non-specific symptoms of many diseases. They have been reported as minor symptoms associated with the presentation of COVID-19.

Anosmia and taste disturbances The disturbance in taste and smell is shown to be pronounced in COVID-19 positive patients. Most of these patients had mild symptoms and were outpatients. They theorize that the virus is likely to spread through the nasal passages to outpatients with COVID-19 compared to severely ill patients with the most likely pulmonary spread. Bagheri et al. reported that the results of a large Iranian cohort with anosmia were reported in 48.23% of patients, while 83.38% also had a decreased sense of taste. [36]

Guillain Barre syndrome (GBS): Zhao et al. reported the first case of GBS in a 61-year-old woman traveling to Wuhan, China. The patient was admitted with acute weakness in the lower extremities and severe fatigue, progressing within a day. Nerve conduction studies (NCS) and electromyography (EMG) have demonstrated demyelinating polyneuropathy. Treatment with IVIG was started, but later respiratory symptoms developed. The COVID-19 test was positive. The authors conclude that based on travel history, lymphopenia and thrombocytopenia at the time of admission are consistent with the GBS parainfectious model due to COVID-19. Their patient achieved good motor recovery after isolation and application of antiviral drugs. [1]

Sedaghat et al. also reported a case of GBS in a 61-year-old man and the patient was treated with IVIG. [37] Virani et al. described a case of GBS in a 54-year-old man from the United States who was hospitalized with progressive ascending paresis that led to a respiratory disorder. The COVID-19 test was positive. The patient was treated with IVIG as well. [38]

A study of GBS patients diagnosed during an outbreak of SARS-CoV-2 infection in 12 hospitals in seven cities (Bergamo, Brescia, Cremona, Milan, Padua, Pavia, and Verona) in Northern Italy was included between March and April 2020. They are divided into COVID-19-positive and COVID-19-negative patients. A total of 34 GBS patients with symptoms between 1 March and 30 April 2020 were collected. Thirty (88.2%) patients were diagnosed with confirmed SARS-CoV-2 infection with a nasopharyngeal swab and/or serum-specific antibodies against SARS-CoV-2 and designated as COVID-19-positive GBS. The other four patients were negative for SARS-CoV-2 infection. The interval between the onset of COVID-19 and neuropathic symptoms was 24.2 ± 11.6 days. In five patients, GBS symptoms appeared within 20 days of the clinical remission of COVID-19 symptoms. In the remaining patients, GBS began when the symptoms of COVID-19 were still present. The clinical presentation of GBS is the classic form in 27 (90%) patients. One patient (3.3%) had facial diplegia with mild distal weakness, one (3.3%) pharyngeal-cervical-brachial weakness, and one pure sensory form (3.3%). Both COVID-19-positive and COVID-19-negative patients with GBS received similar treatment (intravenous immunoglobulin or plasmapheresis) and no significant difference in response was observed. This study found a significantly higher than expected number of GBS cases during the COVID-19 outbreak in Northern Italy and a high incidence of GBS in patients with COVID-19. [39].

In another analysis, a total of 50 cases of GBS with COVID-19 from 39 studies worldwide were identified and examined through different series of cases and reports. This examination was from a total cohort of 50 patients, of whom 49 patients (98%) underwent nasopharyngeal RT-PCR testing. A positive test was obtained in 45 patients (91%), and the remaining 4 (9%) had a negative result. The remaining 5 cases (10%) were diagnosed with COVID-19 with a confirmatory serum antibody test against SARS-CoV-2 IgG. Interestingly, none of the reported patients had a positive PCR for SARS-CoV-2 in the CSF. Although intravenous immunoglobulins have some association with thromboembolic adverse events and SARS-COV-2 is associated with a prothrombotic condition [40], none of the SARS-COV-2 GBS patients treated with intravenous immunoglobulin developed thrombotic complications. [41]

Myopathy Mao et al. reported myopathy in 19% of COVID-19 patients in severe condition, and 5% of patients with the mild clinic. Complaints of myalgia with elevated creatinine kinase levels serum above 200 U / L confirmed myogenic damage. It is not clear whether the myogenic damage is due to the direct effect of the virus on the muscles. Another possible mechanism of the immune response, mediated by infection, is suggested, which causes elevated proinflammatory cytokines in the serum and leads to skeletal muscle damage. No NCS / EMG or muscle biopsy was performed in these patients. It is therefore difficult to rule out that these patients may also have critical disease myopathy and neuropathy in addition to skeletal muscle damage. [42]

Conclusion

SARS-CoV-2 was discovered only at the end of 2019. At the beginning of the pandemic, changes in the respiratory system predominated, but later there were descriptions of cases with neurological complications, and data and research in this direction began to accumulate. We have presented the possible pathogenetic mechanisms known so far to involve the nervous system. We also presented some of the first descriptions of cases with neurological complications of COVID-19. Our knowledge of the neurological symptoms of COVID-19 is to be supplemented.

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Адрес за кореспонденция:
Д-р МАРИЯ ДИМИТРОВА, д.м
dr.m.i.dimitrova@gmail.com

Corresponding author:
Dr. MARIA DIMITROVA, MD
dr.m.i.dimitrova@gmail.com

ПРЕГЛЕД И ЛЕЧЕНИЕ НА СИНДРОМА НА НЕУТРОПЕНИЧНА ФЕБРИЛНОСТ ПРИ ВЪЗРАСТНИ СЪС ЗЛОКАЧЕСТВЕНИ ХЕМАТОЛОГИЧНИ ЗАБОЛЯВАНИЯ И РЕЦИПИЕНТИ НА ХЕМАТОПОЕТНИ КЛЕТКИ

Д-р Иван Киндеков[1], д-р Галина Рачева[2]

[1]Военномедицинска академия, Катедра по хематология и онкология

[2]Военномедицинска академия, Катедра по радиобиология и радиационна защита

OVERVIEW AND TREATMENT OF NEUTROPENIC FEVER SYNDROMES IN ADULTS WITH HEMATOLOGIC MALIGNANCIES AND HEMATOPOIETIC CELL TRANSPLANT RECIPIENTS

Ivan Kindekov, MD, PhD[1], Galina Racheva, PhD[2]

[1]Military Medical Academy, Department of Haematology and Oncology

[2]Military Medical Academy, Department of Radiobiology and Radiation protection

РЕЗЮМЕ:

Антинеопластичната цитотоксична терапия използвана за лечение на онкоболни пациенти, води до тежка миелосупресия и нарушава интегритета на гастроинтестиналната мукоза, което води до тежка инвазивна инфекция причинена от нормалната бактериална и гъбична флора обитаваща гастроинтестиналния тракт. Пациенти с продължителна неутропения са високорискови по отношение на тежко протичащи бактериални инфекции, такава продължителната неутропения може да настъпи в подготвителната фаза на трансплантацията или по време на индукционната фаза на терапиятана острата левкемия. Сериозна животозастрашаваща инфекция може да настъпи с минимални признаци, често температурата е единствения знак за инфек-

ABSTRACT:

Cancer patients receiving cytotoxic antineoplastic therapy sufficient to adversely affect myelopoiesis and the integrity of the gastrointestinal mucosa are at risk for invasive infection due to colonizing bacteria or fungi that translocate across intestinal mucosal surfaces. Patients with profound neutropenia are at particularly high risk for serious infections; prolonged neutropenia is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation (HCT; particularly allogeneic) and in patients undergoing induction chemotherapy for acute leukemia. Serious infection can occur with minimal symptoms and signs, fever is often the only sign of infection. Infections in neutropenic patients can progress rapidly, leading to hypotension and/or other life-threatening

циозното усложнение. Инфекцията при неутропенични пациенти протича бързо, води до хипотензия или друго животозастрашаващо усложнение. От съществено значение, е да се разпознае неутропеничната треска рано и да се започне емпирична антибактериална терапия рано, за да се избегне тежко септично състояние и възможен смъртен изход.

Ключови думи: невропатична треска, неутропения, инфекция, антинеопластична терапия, антибиотична терапия, бактериални патогени, вирусни патогени, гъбични патогени

complications. It is critical to recognize neutropenic fever early and to initiate empiric systemic antibacterial therapy promptly in order to avoid progression to a sepsis syndrome and possibly death.

Key words: neutropenic fever, neutropenia, infection, antineoplastic therapy, antibiotic therapy, bacterial pathogens, viral pathogens, fungal pathogens

INTRODUCTION

Cancer patients receiving cytotoxic antineoplastic therapy sufficient to adversely affect myelopoiesis and the developmental integrity of the gastrointestinal mucosa are at risk for invasive infection due to colonizing bacteria and/or fungi that translocate across intestinal mucosal surfaces. Since the magnitude of the neutrophil-mediated component of the inflammatory response may be muted in neutropenic patients [1], a fever may be the earliest and only sign of infection.

The definition of fever as an indicator of infection in neutropenic patients has varied. In 1868, Carl Wunderlich proposed that the mean normal body temperature was 37°C with an upper limit of normal of 38°C (100.4°F), above which fever was defined [3-5]. The British Society for Haematology regarding their institutional definitions of fever identified 10 definitions of fever, ranging from a single temperature >37.5°C to either a single temperature >39°C or two successive temperatures >38.4°C [6]. These beliefs notwithstanding, the empirically observed mean oral temperature of 148 healthy adults between the ages 18 and 40 years was reported as 36.8±0.4°C (98.2±0.7°F) with a range of 35.6°C (96.0°F) to 38.2°C (100.8°F), the latter defining the upper limit of normal [4].

The Infectious Diseases Society of America defines fever in neutropenic patients as a single oral temperature of ≥38.3°C (101°F) or a temperature of ≥38.0°C (100.4°F) sustained over a one-hour period [2]. Similar definitions have been provided from South America, Europe, and Asia [7-9].

It is known from animal models that glucocorticoids may have a mitigating effect on the development of fever due to bacterial or endogenous pyrogens [10]. The antipyretic effect of concomitant use of glucocorticoids in neutropenic patients may confound the recognition of an infection [10]. The presence of signs of systemic inflammatory response syndrome (SIRS), including tachycardia, tachypnea, or hypotension in an afebrile neutropenic patient who is receiving concomitant glucocorticoids, should raise the suspicion of infection.

Neutropenia is usually defined as an absolute neutrophil count (ANC) <1500 or 1000 cells/microL, severe neutropenia as an ANC <500 cells/microL or an ANC that is expected to decrease to <500 cells/microL over the next 48 hours, and profound neutropenia as an ANC <100 cells/microL [2, 11]. The risk of clinically important infection rises as the neutrophil count falls below 500 cells/microL and is higher in those with a prolonged duration of neutropenia (>7 days). Further, the risk for bacteremic infection increases as the ANC decreases below 100 cells/microL.

1. Neutropenic fever syndromes

A number of neutropenic fever syndromes have been described [12, 13]. The International Immunocompromised Host Society has classified initial neutropenic fever syndromes into the following three categories [12]:

• Microbiologically documented infection – Neutropenic fever with a clinical focus of infection and an associated pathogen

• Clinically documented infection – Neutropenic fever with a clinical focus (eg, cellulitis, pneumonia) but without the isolation of an

associated pathogen

• Unexplained fever – Neutropenic fever with neither a clinical focus of infection nor an identified pathogen

The first neutropenic fever is the first febrile episode occurring during a given period of chemotherapy - induced neutropenia. A persistent neutropenic fever syndrome is a febrile episode without defervescence after at least five days of initial empiric broad-spectrum antibacterial therapy in high-risk neutropenic patients or after at least two days in low-risk neutropenic patients. A recrudescent neutropenic fever syndrome is a febrile episode that recurs following initial defervescence during a course of broad-spectrum antibacterial therapy. The myeloid reconstitution syndrome is defined by fever and a new inflammatory focus or progression of a preexisting inflammatory focus in temporal relationship to neutrophil recovery from aplasia.

The initial clinical evaluation focuses on assessing the risk for serious complications. This risk assessment dictates the approach to therapy, including the need for inpatient admission, intravenous antibiotics, and prolonged hospitalization.

Validated scoring systems used to estimate the risk for medical complications include the Talcott rules [14], the Multinational Association for Supportive Care in Cancer (MASCC) score [15], and the Clinical Index of Stable Febrile Neutropenia (CISNE) score [16]. These scoring systems assume the states of neutropenia and fever for a given patient and do not focus upon either the degree or duration of neutropenia as predictors of the likelihood of medical complications that require or prolong hospitalization. Only the CISNE score considers the absolute monocyte count in the estimate of complication risk. Further, the CISNE score predicts three levels of risk of serious complications: low (score = 0), intermediate (score = 1 to 2), and high (score ≥3).

• Low-risk patients are those who are expected to be severely neutropenic (absolute neutrophil count [ANC] <500 cells/microL) for ≤7 days, have an MASCC score ≥21 or a CISNE score of 0 at the time of assessment, and who have no comorbidities or evidence of significant hepatic or renal dysfunction. This group of patients has been well studied in randomized trials and has been shown to be at low risk for serious complications [2]. Most patients receiving chemotherapy for solid tumors are considered to be low risk for complications requiring hospitalization or prolonging hospitalization.

• High-risk patients are those who are expected to be severely neutropenic (ANC <500 cells/microL) for >7 days and who have an MASCC score <21 or a CISNE score of ≥3 at the time of assessment. Intermediate CISNE scores (1 or 2) may require clinicians to judge the relative safety of outpatient oral therapy versus hospitalization for parenteral antibacterial therapy. Patients with neutropenic fever who have ongoing comorbidities or evidence of significant hepatic or renal dysfunction are also considered to be high risk for medical complications, regardless of the duration of neutropenia.

Some experts have defined high-risk patients as those expected to have profound neutropenia (ANC ≤100 cells/microL) for >7 days based on experience that such patients are the most likely to have life-threatening complications [2, 3]. However, formal studies to clearly differentiate between patients with an ANC <500 cells/microL and ≤100 cells/microL are lacking. Profound prolonged neutropenia (ie, ANC ≤100 cells/microL expected to last >7 days) is most likely to occur in the pre-engraftment phase of hematopoietic cell transplantation (particularly allogeneic) and in patients undergoing induction chemotherapy for acute leukemia.

In general, neutropenic fevers develop in approximately 5 to 10 percent of solid tumor patients receiving cytotoxic therapy and who are at low risk for medical complications [17], compared with 20 to 25 percent of non-leukemic hematologic malignancy patients and 85 to 95 percent of acute leukemia patients [18].

2. Therapeutic approaches

Approaches to the management of infection in patients at risk for neutropenic fever include primary prophylaxis, secondary prophylaxis, empiric therapy, and preemptive therapy.

Primary prophylaxis involves the administration of an antimicrobial drug to prevent infection in patients at increased risk.

Secondary prophylaxis involves the administration of prophylactic doses of an antimicrobial drug to prevent recurrent infection.

In patients with chemotherapy-induced neutropenia, empiric therapy involves the initiation of therapy at the time of the onset of neutropenic fever but before a firm diagnosis of infection has

been established. Empiric antimicrobial therapy is a standard part of the management of neutropenic fever.

Preemptive therapy involves the initiation of therapy based upon screening with a sensitive microbiology assay (eg, antigen detection or molecular assays) in an attempt to detect the presence of a putative pathogen or early subclinical infection. Patients whose infections are detected using a preemptive approach are treated to avoid progression to invasive disease. A preemptive approach is sometimes used for antifungal therapy.

An elevated body temperature is the trigger for initiating an aggressive protocol of neutropenic fever management.

Since the decision of whether to initiate the neutropenic fever management pathway may be based upon the difference of half a degree Celsius [19], the reliability of the procedure used to measure body temperature is extremely important. The risk of serious complications in high-risk patients who are not treated promptly is substantial. A potential toxicity of antimicrobial agents, the impact of antimicrobial use, and the costs of hospitalization and antimicrobial therapy are significant factors. It is therefore critical to accurately assess body temperature in order to aggressively treat patients with neutropenic fever and to avoid the overtreatment of stable neutropenic patients who do not have a fever.

Oral thermometry in patients without oral mucositis, and tympanic membrane thermometry or axillary thermometry in patients with oral mucositis [5]. Peripheral methods of monitoring temperature (temporal artery, axillary, and oral thermometry) do not accurately reflect core body temperature as measured by central methods (pulmonary artery catheter, urinary bladder, esophageal, and rectal thermometry) and are less sensitive [20]; however, central methods are not practical or safe in neutropenic patients.

Rectal thermometry is not recommended in neutropenic or thrombocytopenic patients because it may increase the risk for local mucosal trauma-induced bacteremia and bleeding.

Contributory factors to the pathogenesis of neutropenic fever include [2]:

• The direct effects of chemotherapy on mucosal barriers and the immune system

• Breeches in host defenses related to the underlying malignancy

Chemotherapy-induced mucositis occurs throughout the alimentary system, and seeding of the bloodstream from endogenous flora in the gastrointestinal tract is believed to cause the majority of episodes of neutropenic fever. Obstruction of lymphatic channels, the biliary tract, and/or bronchial, gastrointestinal, or urinary systems by tumor(s) or as a result of surgical procedures are also common causes of infection.

Immune defects related to underlying hematologic disorders, in addition to the immunosuppressive effects of chemotherapy, also place patients at higher risk for infection [21].

The risk for specific types of infections is influenced by the nature of the underlying malignancy and its associated humoral or cellular immune deficits:

• Abnormal antibody production or clearing of immune complexes in multiple myeloma, chronic lymphocytic leukemia, and splenectomized (including functional asplenia) patients results in an increased risk of sepsis from encapsulated organisms, including *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria meningitidis, Capnocytophaga canimorsus and Babesia* spp.

• The T cell defects associated with lymphoma result in an increased risk of infection with intracellular pathogens, such as Listeria *monocytogenes, Salmonella* spp, *Cryptococcus neoformans,* and *Mycobacterium tuberculosis.* Patients with acute lymphocytic leukemia, central nervous system tumors, and other cancer patients receiving high-dose glucocorticoids are at increased risk for *Pneumocystis jirovecii* pneumonia [18].

3. Pathogens

An infectious source is identified in approximately 20 - 30 % of febrile neutropenic episodes [2, 21]. Often the only evidence of infection is bacteremia, which is documented in 10 to 25 percent of patients [2]. Approximately 80 percent of identified infections are believed to arise from the patient's endogenous flora [21].

3.1. Bacterial pathogens — Gram-negative bacilli, particularly Pseudomonas aeruginosa, were the most commonly identified pathogens in neutropenic patients until the 1980s [22]. Subsequently, gram-positive bacteria have become the most common pathogens [23, 24]. Common gram-positive cocci include

Staphylococcus epidermidis (by far the most common), Staphylococcus aureus, and streptococci; gram-positive organisms include Corynebacterium jeikeium, Bacillus spp, Leuconostoc spp, Lactobacillus spp, Cutibacterium acnes, and Rhodococcus spp [25].

A number of changes in practice likely accounted for the trend toward gram-positive infections, including the introduction of long-term indwelling central venous catheters [26], the use of empiric antibiotic regimens for neutropenic fever designed to cover P. aeruginosa.

However, the ratio of gram-positive to gram-negative bacteria as the cause of bacteremia in cancer patients remains at approximately 60:40 [27, 28].

In a study from the Multinational Association for the Supportive Care in Cancer (MASCC) of 2142 high- and low-risk patients with chemotherapy-related neutropenic fever, there were 499 bacteremias (23 percent) [29]. Gram-positive organisms accounted for 57 percent of cases, gram-negative organisms for 34 percent, and polymicrobial bacteremia for 10 percent.

The following observations have been made about bacterial infections in neutropenic patients:

• Bacteria are the most frequent infectious causes of neutropenic fever [30].

• Gram-negative bacteria (eg, *P. aeruginosa*) are generally associated with the most serious infections.

• *S. epidermidis* is the most common gram-positive pathogen, accounting for approximately one-half of all infections due to gram-positive infections [28].

• Among gram-positive bacteria, *S. aureus* (particularly methicillin-resistant strains), some viridans streptococci, and enterococci (particularly vancomycin-resistant strains) can cause serious infections [24].

• Although anaerobic bacteria are abundant in the alimentary tract, they are infrequent pathogens isolated from patients with neutropenic fever. However, they can contribute to the pathogenesis of necrotizing mucositis, sinusitis, periodontal cellulitis, perirectal cellulitis, intra-abdominal or pelvic infection, and neutropenic enterocolitis (typhlitis) and can cause anaerobic bacteremia.

• Polymicrobial infections are infrequent, but their frequency appears to be rising [30].

3.2. Fungal pathogens are common in high-risk patients with neutropenic fever, but are uncommon in low-risk patients. The risk for invasive fungal infections increases with the duration and severity of neutropenia, prolonged antibiotic use, and number of chemotherapy cycles. Fungi are rarely the cause of the first febrile episode in neutropenic patients [31, 32]. The following observations have been made about fungal infections in general and about specific fungal pathogens:

• Fungi are rarely identified as the cause of initial fever during neutropenia. More commonly, they are identified as causes of persistent or recurrent fever beyond the first week of neutropenia.

• *Candida* spp and *Aspergillus* spp account for most invasive fungal infections during neutropenia. The former are acquired through gastrointestinal tract colonization and translocation across damaged intestinal epithelial surface.

• Fever is often the sole manifestation of candidemia. Erythematous macronodular skin nodules may occur in some patients with candidemia. The reported median time of candidemia following standard remission-induction therapy for acute myelogenous leukemia (AML) has been 16 days (range 13 to 25 days) from the first day of the cytotoxic regimen, coincident with the time of maximum cytotoxic therapy-induced intestinal epithelial damage [33]. Among patients who develop disseminated candidiasis following chemotherapy, hepatosplenic involvement is common; signs and symptoms are often not present until the neutropenia resolves. The reported median time to a diagnosis of hepatosplenic involvement after AML induction therapy has been 26 days (range 19 to 31 days) from the first day of the cytotoxic regimen [33].

• *Candida albicans* accounts for the majority of candidemias; *C. glabrata, C. tropicalis,* and other *Candida* spp account for the remainder. A higher proportion of candidemias are due to non-albicans *Candida* species when fluconazole prophylaxis has been administered.

• *Candida* spp are common fungal causes of central venous catheter-associated infections and can cause disseminated candidiasis.

• *Aspergillus* spp is a common fungal pathogen in immunocompromised hosts.

• *Fusarium* spp have been increasingly repor-

ted to cause invasive fungal infections in patients with hematologic malignancies with prolonged severe neutropenia or significant glucocorticoid exposure.

• New infection or reactivation infection with endemic fungi (*Histoplasma capsulatum, Blastomyces dermatitidis, and Coccidioides* spp) should also be considered in patients who have lived in or traveled to endemic areas, particularly in the setting of prolonged glucocorticoid use or other immunosuppression.

3.3. Viral infections, especially human herpesviruses, are common in high-risk patients with chemotherapy-induced neutropenia and are effectively prevented with antiviral prophylaxis. Most herpes simplex virus (HSV)-1 and -2 infections in adults are due to reactivation of latent infections in seropositive patients. The likelihood of reactivation is influenced by the intensity of the chemotherapy regimen and by the relative impact upon virus-specific cytotoxic T-lymphocyte-mediated host defenses. Reactivation occurs in two-thirds of seropositive patients undergoing induction chemotherapy for AML and those undergoing hematopoietic cell transplantation (HCT) in the absence of antiviral prophylaxis [34, 35]. Ulcerations of the oral or esophageal mucosa are the most common manifestations. HSV can cause a wide variety of syndromes, including encephalitis, meningitis, myelitis, esophagitis, pneumonia, hepatitis, erythema multiforme, and ocular disease.

The reported median time to reactivation of herpes zoster in lymphoma patients has been approximately five months following initiation of chemotherapy (range 0.4 to 51.3 months) [36]. Immunocompromised patients with disseminated varicella-zoster virus infection can have pulmonary involvement and should be placed on respiratory precautions to prevent aerosolized transmission to susceptible individuals.

Reactivation or, less commonly, primary acquisition of other human herpesviruses (Epstein-Barr virus, cytomegalovirus, or human herpesvirus 6 A or B) can also occur in this patient population as a result of immunosuppression or receipt of blood products or stem cells, respectively. Allogeneic HCT recipients are at particularly high risk for these infections.

Infections caused by community-acquired respiratory viruses (CARVs) are a significant threat to patients with hematologic malignancies and stem cell transplantation [37-39]. CARVs include influenza virus, respiratory syncytial virus, parainfluenza viruses types I to IV, human adenovirus, human rhinoviruses, human coronaviruses, and human metapneumovirus. The risk for infection by these organisms tends to coincide with respiratory virus outbreaks in the general population. Although information on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), in cancer patients and organ transplant recipients is limited, reports suggest that the severity of the infection may be greater, particularly among those with active comorbidities [40, 41]. SARS-CoV-2 is also potential cause of neutropenic fever.

Reactivation of tuberculosis should be considered in patients with epidemiologic risk factors, especially in those with prolonged glucocorticoid use or other forms of immunosuppression that increase the risk (eg, a tumor necrosis factor-alpha inhibitor). Babesia microti or B. divergens infection can cause overwhelming sepsis in patients with compromised splenic function.

4. RECOMMENDATION:

Antibiotics should be given as early as possible. The guidelines recommend that empiric broad-spectrum antibacterial therapy be initiated immediately after blood cultures have been obtained and before any other investigations have been completed in all patients with neutropenic fever [8, 42]. International guidelines recommend the administration of empiric antibacterial therapy within **60 minutes** of presentation in all patients presenting with a neutropenic fever [18, 42-44]. In a retrospective cohort study of 2731 patients with septic shock (only 7 percent of whom were neutropenic), each hour delay in initiating effective antimicrobials decreased survival by approximately 8 percent [46]. The in-hospital mortality among adult patients with severe sepsis or septic shock decreased from 33 to 20 percent (odds ratio 0.30, 95% CI 0.11-0.83) when the time from triage to appropriate antimicrobial therapy was one hour or less compared with more than one hour [45, 47].

The successful management of neutropenic fever and sepsis syndromes is a time-dependent process analogous to acute stroke or ST-segment elevation myocardial infarction syndromes [42]. There is a spectrum of the severity of the illness. In one multicenter observa-

tional French study using standard definitions, 55 percent of febrile neutropenic cancer patients presenting to emergency departments had a defined sepsis syndrome and almost one-half (45 percent) had evidence of a severe sepsis syndrome or septic shock [49]. Approximately 2 to 5 percent of febrile neutropenic patients seeking medical care from the emergency department require critical care services [49-51].

The reported median times from assessment of febrile neutropenic cancer patients in an emergency department setting to the initiation of empiric antibacterial therapy have ranged widely from 15 minutes to over 9 hours [6, 48, 49-57].

The aim of empiric therapy is to cover the most likely and most virulent pathogens that may rapidly cause serious or life-threatening infection in neutropenic patients [2]. Although antimicrobial agents are usually administered empirically, they should always include appropriate coverage for suspected or known infections. Even when the pathogen is known, the regimen should provide broad-spectrum empiric coverage for the possibility of other pathogens, unlike the treatment strategy adopted in many immunocompetent hosts [58]. Consideration of the risk of resistant organisms has emerged as a factor that impacts the choice of empiric therapy and targeted therapy once a pathogen has been identified, as well as outcomes.

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Адрес за кореспонденция:

Д-р ИВАН КИНДЕКОВ

Бул. Георги Софийски 3
Военномедицинска Академия
Клиника по хематология и онкология
ivankindekov@gmail.com

Corresponding author:

Dr. IVAN KINDEKOV

Bul. Georgi Sofiyski 3
Military Medical Academy
Clinic of Hematology
and Oncology
ivankindekov@gmail.com

ДИАГНОСТИЧНИ ПРОУЧВАНИЯ ПРИ БОЛНИ С ХИПОФАРИНГЕАЛЕН КАРЦИНОМ

Ст. Стоянов[1], Н. Ананощев[2]

[1]Университетска Специализирана болница за активно бечение по онкология /УСБАЛО/ гр.София;

[2]Университетска многопрофилна болница за активно лечение „Свети Георги" ЕАД гр.Пловдив

PATIENTS WITH HYPOPHARYNGEAL CARCINOMA - DIAGNOSTIC EVALUATIONS

St. Stoyanov[1], N. Ananoshtev[2]

[1]University Specialised Hospital for Oncological Diseases Treatment – Sofia;

[2]University Multiprofile Hospital for Active Treatment „St.George" – Plovdiv

РЕЗЮМЕ:

Извършено е ретроспективно и проспективно проучване на общо 135 пациента с хипофарингеален плоскоклетъчен карцином, диагностицирани и регистрирани в КОЦ-Пловдив през периода 2000-2019 г. Пациентите са на възраст от 45 до 70 години, от които мъже 119 случая / 88.5%/ и жени 16 случая /11.5%/. Хипофарингеалният плоскоклетъчен карцином много трудно се диагностицира в ранен стадий на заболяване. Многовариантният анализ показа, че възрастта, TNM-стадия на диагностициране и вида на лечение, всички те заедно имат корелативна връзка за лошата прогноза от изхода на заболяването. Едногодишна преживаемост имаха 74.9% от случаите, 3-годишна преживяемост имаха 39.8% от случаите и едва 15.7% от случаите имаха 5-годишна преживяемост.Ключът към подобряване на преживяемостта е:- оперативно лечение, селективна или радикална шийна дисекция и интензитет- модулирана радиотерапия (IMRT).

ABSTRACT:

There has been done retrospective ,prospective evaluation of 135 patients , all with diagnosted hypopharyngeal carcinoma – at the Complex Oncological Centre – Plovdiv , Bulgaria during the period – 2000-2019. All of them are at an age between 45-70 , among them 119 are men (88.5 %) , the rest 16 (11.5 %) – women. The hypopharyngeal carcinoma is still rather difficult to be early diagnosted. The multivariant analysis shows that the age , TNM- stage of the illness ,as well as the treatment – all taken together influence a lot over the bad prognosis of the illness itself. As a matter of fact – just 74.9% of the patients survive 1 year , 39.8% -do live a bit more than 3 years , and only 15.7% of these patients are happy for 5 years whole survival period of time. So the key for making better life and longer survival is : operative treatment , neck dissection – both types , intensity-modulated radiotherapy (IMRT).

Ключови думи: хипофарингеален плоскоклетъчен карцином, TNM-стадий, преживяемост, интензитет-модулирана радиотерапия (IMRT), шийна дисекция

Key words: Hypopharyngeal squamous cell carcinoma ,TNM-stage , survival , IMRT-intensity -modulated radiotherapy , neck-dissection

INTRODUCTION:

The hypopharyngeal squamous cell carcinoma is an almost rarely to be found illness, but still with extremely bad prognosis. Nevertheless its" rare occasion, and on the other hand – diagnostic and theurapetic forwarding processes, it has a high mortality index. Most of the patients are usually in advanced – 3rd, or 4th stage – even rather advanced, low index of survival and bad prognosis as a whole – concerning generally the carcinoma. The mean period of time for a recurrence – from the beginning of the treatment is 10.4 months (3.3-55 months). Non-activity survival time in patients, treated by operatively and radiochemo-therapy is 79% - regarding 1 and 3 years period of life. Radiochemo-therapy alone is not enough, we do not declare such 3 years survival among patients with operative treatment, only.

AIM of the study:

The aim is to analyse the disease - rate, treatment and survival of people, suffering from hypopharyngeal carcinoma, being patients for the Complex Oncological Centre in Plovdiv – during the period 2000-2019, as well as to analyse the results in the different ways of treatment and thus- survival rates.

The analysis includes : number of patients, age, sex, localization of the primary tumour, clinical estimation of the status of lymph nodes. Then the results were statistically checked.

MATERIALS AND METHODS :

There has been done retrospective and prospective investigation of 135 patients with hypopharyngeal squamous cell carcinoma, diagnosted, treated and registered in Complex Oncological Centre – Plovdiv, during the period 2000-2019. The investigation is thoroughly done. All 135 patients with hypopharyngeal carcinoma have been checked, among them- 119 men (88.5%) and 16 women (11.5%). Age-between 45 – 70 years of age. The analysis is performed under Kaplan- Meier way of analysis, as well as – the multivariate Koch regressive one.

RESULTS:

The density -rate of the hypopharyngeal carcinoma during the period 2000-2019 - do increases by a mean 1.8% change, annually. Table 1 shows the distribution of the hypopharyngeal carcinoma due to the primary localization.

So, the tumour itself comes out from :

- sinus pyriformis -101 cases (74.8%);
- posterior pharyngeal wall – 25 cases (18.5 %);
- posterior cricoid region- 9 cases (6.7%).

Among all 135 patients, 95 of them have been treated operatively – as it follows: (table 2).

97 from all these 135 patients have been treated in a operative way, so the different operative methods are :

- Partial hypopharyngeal resection – in 21 cases (15.5%);
- Partial laryngectomy with partial hypopharyngeal resection – in 7 cases (7.2%);
- Total laryngectomy with partial hypopharyngeal resection – in 53 cases (39.1%);
- Total laryngectomy with total hypopharyngeal resection and gastro-pharyngeal anastomosis – in 12 cases (8.7%);
- Total laryngectomy with hypopharyngeal resection and entero-pharyngeal anastomosis – in 4 cases (2.9%);
- Non-operated patients -36 (28.7%).

The most common way- laryngo-pharyngectomy dicreases by 2.5%, while the radiotherapy lonely treatment increases. We declare that the common cases, treated by operative and radio-therapy ways,do increase during that period of time. There is a trend of increasing the 5-years whole survival. The multivariant analysis shows that there is a

TABLE 1. ***Distribution of the hypopharyngeal squamous cell carcinoma – due to the primary localization in hypopharynx – both, in men and women:***

№	Primary localization	men	women	total
1	Sinus pyriformis	87	14	101
2	Posterior pharyngeal wall	24	1	25
3	Posterior cricoid region	8	1	9
	Total	119	16	135

TABLE 2. ***Different ways of operative treatment for hypopharyngeal carcinoma:***

№	Type of an operative treatment	Number of cases	percentage
1	Partial hypopharyngeal resection	21	15.5
2	Partial laryngectomy , with partial hypopharyngeal resection	7	5.1
3	Total laryngectomy with partial hypopharyngeal resection	53	39.1
4	Total laryngectomy with total hypopharyngeal resection and gastro-pharyngeal anastomosis	12	8.7
5	Total laryngectomy with hypopharyngeal resection and entero-pharyngeal anastomosis	4	2.9
6	Non-operated patients from the total number of cases	36	28.7
7	Total	135	100

correlation between the factors – age, TNM-stage, way of treatment,concerning the bad prognosis of the disease.

Many of the patients are already in a rather advanced period -3rd, 4th stage, so the survival rate is low,bad prognosis – in general.

The follow - up of these patients reveals :

- 1 year survival – 74.9% of the cases;
- 3 years survival – 39.8% of the cases;
- 5 years survival – 15.7% of the cases.

CONCLUSIONS:

1. The hypopharyngeal squamous cell carcinoma comes to be very difficult for a diagnosis on an early stage of the disease;

2. The cancer itself has tendencies for recurrency and metastasis – soon after an operation;

3. We declare the main healing strategy, i.e. :

- Strictly and carefully chosen operative method;
- Neck dissection;
- Adjuvant postoperative radiotherapy;

4. The hypopharyngeal carcinoma of the posterior pharyngeal wall has greater ability and tendency for metastasis and recurrency, in comparision to the other 2 types, concerning the localization-sinus pyriformis and posterior cricoid region;

5. The so-called "KEY" for a better survival is :

- operative treatment, neck dissection – both types-radical or selective, intensity-modulated radiotherapy (IMRT);

6. The multimodal non-surgical treatment could be a helpful option for non-operative patients,but being generally potential-activated, without main or serious other complaints;

7. Another important moment in the prognosis of the hypopharyngeal carcinomas" situation is the lymph node status, especially after chemo-radio-therapy;

8. Basically regarding – the operative treatment is one of the main standart ways for solving the problem, called „Hypopharyngeal carcinoma", nevermind whether it is combined with postoperative radio-therapy, or not. Then comes the reconstructive way of thinking – with, or without preserving the larynx.

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Адрес за кореспонденция:

Акад. проф. д-р
НИКОЛА АНАНОЩЕВ, дмн

e-mail: nikola_ananoshtev@abv.bg

Corresponding author:

Acad. Prof. Dr.
NIKOLA ANANOSHCHEV, MD

e-mail:
nikola_ananoshtev@abv.bg

ЕПИДЕМИОЛОГИЯ, ДИАГНОСТИКА И ЛЕЧЕНИЕ НА ЗЛОКАЧЕСТВЕНИТЕ ТУМОРИ НА ХИПОФАРИНКСА

Ст. Стоянов[1], Н. Ананощев[2]

[1]Университетска Специализирана болница за активно лечение по онкология /УСБАЛО/ гр.София;

[2]Комплексен онкологичен център гр.Пловдив

EPIDEMIOLOGY, DIAGNOSTIC AND TREATMENT PROCESSES OVER MALIGNANT TUMOURS OF THE HYPOPHARYNX

St. Stoyanov[1], N. Ananoshtev[2]

[1]University Specialised Hospital for an Active Treatment of Oncological Diseases, Sofia;

[2]Oncological Diseases Treatment Centre , Plovdiv , Bulgaria

РЕЗЮМЕ:

Изследвани са епидемиологично ретроспективно историите на заболяванията с рак на хипофаринкса общо 957 случая за периода 2000-2013г. и новорегистрирани в Република България по области. Извършихме клинико-епиде-миологично кумулативното време на преживяемост на 102 болни с рак на хипофаринска, регистрирани в КОЦ-Пловдив от Областите Пловдив, Пазарджик и Смолян за периода 2000-2013г.Установяваме почти двойно нарастване на фактическата заболеваемост от рак на хипофаринска за изследвания период от 0.72 случая на 100 000 население през 2000 г. на 1.20 случая на 100 000 население през 2013 г. При мъжете спрямо жените рака на хипофаринска се среща почти 9 пъти по-често. Най-често заболеваемостта се среща във възрастовата група на 55-64 години.От нашето клинико-епидемиологично изслед-ване на регистрираните и диспансеризирани болни

ABSTRACT:

There has been done retrospective and prospective epidemiological investigation of 957 cases of diagnosted primary hypopharyngeal cancers in Bulgaria for the period of 2000-2013. The investigation is thoroughly done. Thus, we checked almost twice increasing of the real morbididty-i.e.,0.72 cases during 2000 – to 1.20 cases per 100 000 citizens in 2013.The other index- the standartised morbidity rises up from 0.47 cases in 2000, to 0.66 cases in 2013. Among men the real morbidity rises from 1.28 cases in 2000 – to 2.23 cases in 2013. In comparison to the women, men suffer 9 times more often (9.4 :1). 87 % from all primary diagnosted hypopharyngeal cancers belong to third and fourth clinical stage, which enables such patient to live longer. We have investgated in clinical and epidemiological way 102 patients, living in the following 3 districts in Southern Bulgaria – Plovdiv, Pazardjhik and Smolyan, declaring, that 1 year survival have 14.46 %

с рак на хипофаринска в КОЦ-Пловдив за Областите Пловдив, Пазарджик и Смолян за периода 2000-2013 г., установяваме, че 1-годишна преживяемост достигат 14.46% от случаите, а 5-годишна преживяемост достигат едва 2.41% от случаите. Предлагаме проект за утвърждаване на алгоритъм за съвременен подход за ранна диагноза и комплексно лечение на рака на хирофаринска.

Ключови думи: рак на хипофаринска, лъчелечение, хирургично лечение, химиотерапия, TNM– класификация десета ревизия, 2003 г., преживяемост, заболеваемост.

of these cases, while 5 years survival have only 2.42 % of them. So, we suggest a project for a controlled algorithm for a comprehensive behaviour – both – for early diagnostic processes, and then- a complex treatment of the hypopharyngeal cancers.

Key words: hypopharyngeal cancer, radiological treatment, polychemotherapy, TNM – classification- 10-th revision, 2003

INTRODUCTION :

The malignant tumours of the hypopharynx are extremely interesting for us, because of the discreet symptomatic behaviour, as well as the difficulties, an ENT- doctor meets with, while making a certain diagnostic process. They rank 3-rd among all the pharyngeal tumours, mainly during the 5-th and first half of 6-th decade. The cancer rate is 0.4-0.6 per 100 000 citizens. Among all the ENT – malignant tumours, those of the hypopharynx exceed to 10.7 % (1,2). As far as the ethyological factors are concerned, that – like tobacco smoking, alcohol drinking, some professional activities do play a harmfull effect. Usually these tumours are primary, coming out from the structures, forming the pharynx itself – epithelium, mesenchimal tissues, as well as such, emerging from local tissues around by, or being connected with them-respectively. Among epithelium tumours most often is the squamous cell carcinoma – both differentiated and non- differentiated. According to the level of differentiation thew are – well -, moderately – differentiated, not-well developed and finally-non-differentiated. Adenocarcinoma as a histological evidence is very rarely to be found. Among these, already mentioned above forms, extremely rarely is to fell upon a case, connected with the lymphoid system – non Hodjhkin – type malignant lymphoma. Finally – males suffer 9 times more than the females – 9.4 : 1 is the ratio.

MATERIAL AND METHODS :

There have been checked retrospectively 957 human being cases during the period 2000-2013 as well as the new-registered cases. Annually there are approximately 70 such patients in Bulgaria.

We examined thoroughly 102 patients with diagnosted hypopharyngeal cancer, registerd in the Oncological Diseases Treatment Centre in Plovdiv during the period-2000-2013.

The morbidity and death rates are registered per 100 000 citizens, both men and women.

The standarization process is along with the World Classical Standard – Segi 1960 . We used the international Classification of the diseases, revision 10 - 2003.Finally we used the software product SPSS for the sake of completing the data.

RESULTS :

We have made a thorough epidemiological retrospective investigation for 957 cases of hypopharyngeal cancer – being diagnosted as primary such, in Bulgaria during the period 2000-2013.

Nowadays this report reveals the medical history of 102 hypopharyngeal cancer"s patients, among them – 90 men (88.23%) and 12 women 11.77%) –all between 45-70 years of age.

We discovered that the real morbidity for that disease has increased almost twice – from 0.72 cases per 100 000 citizen in 2000, to 1.20 cases in 2013 (table 1).

Table 1: ***Morbidity of hypopharyngeal cancer in Bulgaria during the period 2000-2013.***

Year	Absolutely new ill patients			Real morbidity ratio per 100 000			Standard morbididty ratio per 100 000		
	men	women	total	men	women	total	Men	Women	total
2000	51	8	59	1.28	0.19	0.72	0.86	0.12	0.47
2001	56	6	62	1.45	0.15	0.72	1.06	0.08	0.55
2002	63	8	71	1.65	0.19	0.90	1.13	0.12	0.60
2003	64	3	67	1.68	0.07	0.85	1.08	0.06	0.53
2004	51	8	59	1.35	0.20	0.76	0.92	0.12	0.49
2005	64	10	74	1.70	0.25	0.96	1.11	0.17	0.61
2006	60	4	64	1.61	0.10	0.83	1.01	0.05	0.55
2007	56	10	66	1.51	0.25	0.86	0.95	0.14	0.52
2008	48	7	55	1.30	0.18	0.72	0.81	0.11	0.44
2009	68	7	75	1.85	0.18	0.99	1.19	0.11	0.61
2010	63	6	69	1.73	0.15	0.92	1.10	0.10	0.56
2011	58	8	66	1.62	0.21	0.90	1.05	0.12	0.57
2012	77	6	83	2.12	0.16	1.14	1.27	0.13	0.66
2013	79	8	87	2.24	0.21	1.20	1.28	0.11	0.66

It is obvious that :

- The standard morbidity increases from 0.47 cases per 100 000 citizens in 2000, to 0.66 cases for the same population during 2013 ;
- The male population is much more ill – real morbidity goes up from 1.28 cases per 100 000 citizens in 2000,to 2.24 cases in 2013 ;
- The female population almost stays unchanged as far the real morbidity is concerned – 0.19 cases per 100 000 in 2000, to 0.21 in 2013;
- The standard morbidity in men goes up from 0.86 cases per 100 000 citizens in 2000, to 1.28 such cases in 2013, while in women this ratio is 0.12 in 2000, to 0.11 in 2013, i.e., no increasing tendations. Temporally higher morbidity ratio in female patients is to be seen during 2005 (0.17 cases per 100 000), and 2007 (0.14 cases);
- Republic of Bulgaria is devided administratively into 28 regions, so the highest ratio for a standard morbidity in males is as follows :
- -on the „first place" is Dobrich region with 3.7 cases per 100 000;
- „second place" goes to Silistra region-3.7 cases per 100 000, they are „neighbours" geographically, also;
- Then comes on the 3-rd place Haskovo region with 3.1 cases per 100 000;
- Finally, on the 4-th place goes Gabrovo region with 3.0 cases per 100 000 citizens. Let us discuss now the same situation - highest standard morbidity in females among all the regions in Bulgaria.
- The highest ratio is 1.5 cases per 100 000 people - in Smolyan region;
- Then comes 0.6 cases - in Vratza region;
- Third place goes to Veliko Tarnovo region with 0.33 cases;
- Finally - 0.2 cases per 100 000 are to be found in Pleven and Stara Zagora regions.

Most often the hypopharyngeal cancer is to be found during the 5-th decade-50-54 and 55-59 years of age. There are extremely rare occasions in people up to 29 years of age in the years 2000, 2003, 2005, 2007.

Table 2: ***Density of hypopharyngeal cancer in Bulgaria ,according to the age ,during the period 2000-2013.***

Year	Real morbidity of hypopharyngeal cancer in ages for 2000-2013								
	0 - 29	30 - 39	40 - 44	45 - 49	50 - 54	55 - 59	60 - 64	65 +	total
2000	1	1	1	4	13	16	5	18	59
2001	2	2	4	11	11	10	11	11	62
2002	0	1	5	8	16	15	11	15	71
2003	1	0	1	6	11	10	15	23	67
2004	0	0	2	10	8	12	12	15	59
2005	1	1	3	8	14	16	12	19	74
2006	0	1	3	13	11	13	13	10	64
2007	1	2	1	2	13	14	13	20	66
2008	0	1	1	6	8	15	7	17	55
2009	0	0	4	7	11	20	9	24	75
2010	0	1	1	9	9	18	11	20	69
2011	0	2	4	8	14	12	10	16	66
2012	0	3	2	7	12	15	18	26	83
2013	0	0	1	9	11	12	16	38	87

And now let us discuss the hystological type of the hypopharyngeal cancer in Bulgaria during that mentioned period -2000-2013.There are:

- most of all - sqamous cell (carcinoma spinocellularis) carcinoma - in 61.01 % from all the cases to be seen;
- second- keratinised (the same spinocellularis carcinoma) - 27.27 %;
- non-keratinised, big cells spinocellularis carcinoma - 9.09 %;
- 4-th place- adenocarcinoma (glandular form) - in 2.60 %.

We investigated the real and standard death rates during that period, thus calculated the epidemiological indexes for the effectiveness of the treatment.

Table 3: ***Real and standard death rates in males and females - from hypopharyngeal cancer during the period 2000-2013 in Bulgaria:***

Year	Number of cases			Real death rate ratio per 100 000			Standard death rate ratio per 100 000		
	Men	women	total	Men	women	total	men	women	total
2000	39	9	48	0.98	0.22	0.59	0.71	0.14	0.41
2001	51	6	57	1.32	0.15	0.72	0.90	0.07	0.47
2002	33	6	39	0.86	0.15	0.50	0.60	0.08	0.33
2003	52	9	61	1.34	0.22	0.78	0.89	0.11	0.48
2004	56	6	62	1.49	0.15	0.80	0.96	0.08	0.49
2005	35	13	48	0.93	0.33	0.62	0.59	0.14	0.36
2006	53	14	67	1.42	0.35	0.87	0.95	0.18	0.55
2007	44	14	58	1.19	0.35	0.77	0.75	0.22	0.46
2008	34	9	43	0.92	0.23	0.56	0.58	0.14	0.34
2009	40	10	50	1.09	0.26	0.66	0.72	0.13	0.41
2010	38	7	45	1.04	0.18	0.60	0.65	0.11	0.36
2011	47	10	57	1.31	0.27	0.78	0.77	0.15	0.44
2012	62	6	68	1.74	0.16	0.93	1.05	0.12	0.56
2013	48	3	51	1.36	0.08	0.70	0.75	0.04	0.37

Results:

Among men the real death rate increases from 0.98 cases per 100 000 in Bulgaria for the period 2000-2013.

Among female population - there is a trend of dicreasing the real death rate - from a ratio 0.22 cases in 2000, to 0.08 cases in 2013, but a slowly trend of increasing with a ratio 0.35 cases in 2006 and 2007, as well as a ratio of 0.33 cases in 2005.

And now- let us discuss the standard death rates :

-among men it increases from 0.71 cases per 100 000 in 2000-to 0.75 cases per 100 000 in 2013.

-among women it dicreases from 0.14 case per 100 000 in 2000-to 0.04 cases in 100 000 in 2013.

So, the letality index shows good clinical effect, a result of some complex theurapetical behaviour, performed everywhere in Oncological - Active Health Care Centres, I.e., hypopharyngeal cancer treatment.

The certain results, showing the distribution of the hypopharyngeal cancer due to the precise localisation in all these 102 patients in Oncological Centre - Plovdiv is as follows:

Table 4: ***102 cases with hypopharyngeal cancer - due to the primary localisation - men ,women ,during the period 2000-2013 inOncological Centre - Plovdiv.***

number	Primary localisation in 102 cases in Plovdiv"s Oncological Centre	Men	Women	Total
1	Hypopharynx	90	12	102
2	Retrocrycoid region	4	-	4 = 3.9 %
3	Reccessus piriformis	16	-	16 = 15.68 %
4	Plica aryepiglotica towards hypopharynx	8	2	10 =9.80 %
5	Posterior wall of hypopharynx	24	2	26 = 25.49 %
6	Not dedicated area ,unspecified	48	8	56 = 54.90 %
7	Total	90	12	102 = 100 %

There is an extreme high percentage of the so-called „not dedicated area", unspecified – 54.90 % from all the cases. Such a data is a result, because of the emerge difficulties ENT-doctors meet with, while diagnostic process is going on. The hypopharyngeal cancer is registered usually still too late, thus comes the low rate of survival among such patients.

Then we checked the cumulated survival period of time for everybody among all these 102 patients – for the sake of reaching a direct epidemiological index for the effectiveness of the local treatment during that period (Table 5).

Table 5: ***Cumulative survival of 102 patients with hypopharyngeal cancer ,treated in Oncological Centre – Plovdiv , Bulgaria ,for a period 2000-2013.***

Group	Ratio for a cumulative survival in %						Intermediate survival	P
Hypopharyngeal cancer	3 months %	6 months %	9 months %	1 year %	over 1 year %	5 years %		
C 13.9	36,36	31.82	11.37	9.09	6.84	4.54	23.00	0.16
Hypopharyngeal cancer								
C 13.2	35.89	20.52	15.38	20.52	7,69	0	25.0	0.16
Total survival	36.14	26.51	13.25	14.46	7.22	2.42	21.00	0.06

The cumulative survival index comes to be a direct epidemiological criteria for declaring the clinical effect of the treatment in hypopharyngeal cancer patients in the Oncological Centre – Plovdiv, covering a territory of 3 major regions – Plovdiv, Pazardhik and Smolyan, with a total population of over 1 mln people, approximately.

The index itself shows the possibility for every patient to survive 5 years –period of active treatment and observerness in accordance to the localization and time.

Finally, the result of our investigation is that only 2.42 % of all these 102 cases survive 5 years and more, 14.46 % -do live - up to 1 year. Extremely bad data!

CONCLUSIONS:

1. There have been checked 957 primary cases of hypopharyngeal cancer in Bulgaria during the period 2000-2013, or about 70 people annually.
2. We discovered almost twice increasing of the morbidity for that same period – from 0.72 cases per 100 000 citizens in 2000, to 1.20 cases per 100 000 in 2013.
3. The standard morbidity index in 2000 is 0.47 cases, while 13 years later it goes up to 0.66 cases .
4. The cancer itself is much more often to be seen in men, 9 times more, than in women. (9.4 : 1)
5. The real morbidity index in men rises from 1.28 cases per 100 000 men in 2000 – to 2.24 cases per 100 000 in 2013.
6. The same index among the female population shows the following : it stays almost steady during the years -0,19 cases in 2000, to 0,21 cases in 2013.
7. Our experience shows, that the highest peak of morbidity is to be seen during the 5-th decade, mainly-55-59, as well as 60-64 years of age.
8. There are extremely rare occasions of such patients bellow 45 and just a case for a person at 29.
9. The real morbidity index rises from 0.59 cases per 100 000 in 2000, to 0.70 cases per 100 000 in 2013.
10. The real death rate index in men shows increasing from 0.98 cases per 100 000 men in 2000, to 1.36 cases per 100 000 men in 2013.
11. The same one index in women, however dicreases from 0.22 cases per 100 000 women in 2000, to 0.08 cases per 100 000 women in 2013.
12. The standard death rate index goes down from 0.41 cases per 100 000 citizens in 2000, to 0.37 cases per 100 000 citizens in 2013, because of the lower standard death rate index in women .
13. As far as the patients with hypopharyngeal cancer from Plovdiv, Pazardjhik and Smolyan regions are concerned, we established, that only 14.46 % of them survive 1-year period, 5-years survival have just 2.42 %
14. We discovered also a high percentage (54.90%) cases with so-called „not-dedicated, unspecified" area, as an anatomic localization of the disease.
15. So, we suggest a modern and up-to date project for early diagnostic and complex treatment of the hypopharyngeal cancer.

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Адрес за кореспонденция:

Акад. проф. д-р
НИКОЛА АНАНОЩЕВ, дмн

e-mail: nikola_ananoshtev@abv.bg

Corresponding author:

Acad. Prof. Dr.
NIKOLA ANANOSHCHEV, MD

e-mail:
nikola_ananoshtev@abv.bg

ДИФЕРЕНЦИАЛНО ДИАГНОСТИЧЕН СПЕКТЪР ПРИ ОСТРА ДОЛНА ПАРАПАРЕЗА. КЛИНИЧЕН СЛУЧАЙ НА ПАЦИЕНТ С ВТОРИЧНА ХИПЕРКАЛИЕМИЧНА ПАРАЛИЗА

Кристина Димитрова, Николай Симеонов, Мария Димитрова

УМБАЛСМ „Н.И.Пирогов", Отделение по нервни болести

THE DIFFERENTIAL-DIAGNOSTIC SPECTRUM OF ACUTE LOWER PARAPARESIS. CLINICAL CASE OF A PATIENT WITH SECONDARY HYPERKALEMIC PARALYSIS

Kristina Dimitrova, Nikolay Simeonov, Mariya Dimitrova

UMHATEM "N.I. Pirogov", Department of Neurological Diseases

РЕЗЮМЕ:

Въведение: Остро появилата се слабост в долни крайници представлява предизвикателство и налага разглеждане на широк диференциално диагностичен спектър от заболявания. Вторичната хиперкалемична парализа се характеризира с неясна мускулна болка с последваща мускулна слабост, която обикновено се проявява във възходящ модел, като в крайния си етап засяга лицевите и дихателните мускули.

Цел: Целта на представянето на този случай е да покаже широкият обхват в диференциалната диагностика на внезапна долна парапареза и важността на рутинните параклинични тестове за бързата диагноза и навременно лечение.

Клиничен случай: Представяме кли-

ABSTRACT:

Introduction: Acute weakness in the lower extremities is a challenge and requires consideration of a wide range of differential diagnoses. Secondary hyperkalemic paralysis is characterized by muscle pain with subsequent muscle weakness, which usually manifests itself in an ascending pattern, ultimately affecting the facial and respiratory muscles.

Aim: The purpose of presenting this case is to show the wide range in the differential diagnosis of sudden lower paraparesis and the importance of routine paraclinical tests for early diagnosis and treatment.

Case report: We present a case of a female patient with sudden weakness in the lower extremities, which progresses to the impossibility of independent gait. The patient has a history of chronic kidney disease (CKD)

ничен случай на жена с внезапна слабост в долни крайници, която прогресира до невъзможна самостоятелна походка. Пациентката е с анамнеза за хронична бъбречна недостатъчност (ХБН) – IV степен, на хемодиализа. Обективно се установи умерена към тежка долна парапареза. Въз основа на параклиниката и проведените образни изследвания решихме, че се касае за преходна хиперкалиемична миоплегия.

Заключение: Вторичната хиперкалиемична парализа е животозастрашаващо състояние, но потенциално може да се предотврати и с ранно разпознаване да се лекува без тежки последици.

Ключови думи: парапареза, ХБН, хиперкалиемия

- IV degree on chronic hemodialysis. The neurological examination revealed lower paraparesis, moderate to severe. Diagnostic tests, laboratory, and imaging tests led us to the diagnosis of transient hyperkalemic myoplegia.

Conclusion: Secondary hyperkalemic paralysis is uncommon but potentially life-threatening. However, rapid differential diagnosis and treatment usually lead to a complete reversal of symptoms.

Key words: paraparesis, CKD, hyperkalemia

Introduction

Secondary hyperkalemic paralysis is characterized by vague muscle pain with subsequent muscle weakness, which usually manifests itself in an ascending pattern, ultimately affecting the facial and respiratory muscles. Patients usually experience areflexia, motor paralysis, preserved muscle tone, and sphincter sensory dysfunction. The onset is usually progressive over a few days but maybe more sudden. These non-specific symptoms complicate the diagnosis, but elevated serum potassium and possible changes in the ECG help to immediately distinguish the diagnosis [1].

Sudden lower paraparesis Lower paraparesis is a loss of motor power in both legs. It can be partial (-paresis) or complete (-plegia). The most common cause of lower paraparesis is spinal cord injury. Non-traumatic causes are significantly rarer. [2]

In the case of a sudden onset of symptoms, the anterior spinal artery syndrome should be ruled out first. This syndrome is manifested by acute flaccid paraparesis, which gradually progresses to spasticity and loss of exteroceptive sensation. The etiology of the syndrome can be divided into two major groups: primary (atherosclerosis, lupus, Sjögren's syndrome) and secondary (tumor compression or disc prolapse, aortic dissection). [2,3]

The differential diagnosis may also include space-occupying inflammatory processes - an epidural abscess or spondylodiscitis caused by various skin infections, LP, back injuries, vertebral osteomyelitis, or hematogenesis (IV drug abuse, DM). The symptoms are chills, back pain, headache, and malaise; rapidly progressing paraparesis; sensory disturbances; loss of control of pelvic reservoirs.

Space-occupying non-inflammatory lesions include slowly progressing or rapidly growing tumors (metastases or secondary fracture of the spine). They lead to acute or subacute secondary ischemia of the spinal cord or compression of spinal vessels. The same result can give a medial prolapse of the disc. Clinically, they present with local back pain, followed by acute flaccid paraparesis, impaired sensory function, and loss of bladder/rectum control. [2.4]

Another cause of acute lower paraparesis can be various spinal hemorrhages - spinal hematoma; subarachnoid hemorrhage; intramedullary hemorrhage. Clinically, they manifest with a sudden onset, and motor and sensory symptoms are eliminated. Vascular malformations, such as spinal fistula or intramedullary AVM, may also be considered, but they have slowly progressive symptoms and are less common. [2,3]

Acute inflammatory disorders of the spinal cord are also included in the differential diagnosis of lower paraparesis. These include tro-

pical spastic paraparesis caused by HTLV-1; herpes radiculomyelopathies; polio (asymmetric weakness); West Nile virus (asymmetric or ascending), syphilis (meningo-vasculitis), AIDS (vascular progression), and tuberculosis. Guillain-Barré syndrome onset is acute, with ascending symmetrical flaccid paresis. Impaired sensitivity and areflexia are also observed. [4]

Acute transverse myelitis may be due to acute segmental trauma to the spinal cord or may manifest as a post-infectious process (immunologically mediated (NMO) or after viral infection and after vaccination (ADEM)). The initial symptoms are paresthesia, back pain, and weakness in the legs.

Acute inflammatory demyelinating disorders of the spinal cord also include neuromyelitisoptica-Devic's disease (simultaneous inflammation and demyelination of the optic nerve and spinal cord) manifested with optic neuritis and acute myelitis (severe spastic weakness of the legs).

Lower paraparesis is accompanied by chronic demyelinating inflammatory disorders of the CNS, such as multiple sclerosis (in which spastic paraparesis may be acute or gradually progressive); diseases of motor neurons, such as amyotrophic lateral sclerosis (ALS); systemic diseases, such as Behçet's disease (usually flaccid paralysis or incomplete paraplegic symptoms).

Hereditary spastic paraplegia (HSP) is a group of clinically and genetically diverse disorders. They are manifested by weakness and spasticity of the lower extremities. They are due to defects in the mechanisms that transport proteins and other substances across the cell membrane. [3.5]

Acquired hypo / hyperkalaemic paralysis is acute or subacute, with flaccid paraparesis and areflexia. No sensory impairment was detected.

Action potential Potassium (K +) is a very tightly regulated cation, ubiquitous inside and outside all living cells. It is responsible for maintaining the potential of the cell membrane needed for physiological functioning. Because there is a significant gradient of K + between inside and outside the cells, even a slight change in the extracellular level of K + has a significant physiological effect. In addition, the magnitude of the electrical membrane potential of muscle and nerve tissue is determined by the ratio of intra- and extracellular potassium. [6]

Under normal conditions, approximately 90% of potassium excretion is excreted in the urine, with less than 10% excreted in sweat or faeces. 90% of the filtered K + is reabsorbed in the proximal tubule and the Henle loop, and only 10% reaches the distal tubule. There, however, a significant amount of K + is secreted under the influence of aldosterone. In turn, aldosterone production and secretion are stimulated by both angiotensin II and serum K + concentrations. [6,7,8]

In the case of above-threshold stimulation, changes in the membrane potential and the ion currents occur, determining the action potential. First, a transient increase in sodium permeability is observed. When the membrane depolarizes above the critical potential, the number of active sodium channels is so large that the passive current cannot compensate. This results in an avalanche-like increase in sodium permeability and a shift of the membrane potential to the equilibrium potential for sodium ions. This process is called regenerative depolarization. Due to the existence of a small passive current directed outwards, the value of the equilibrium potential of sodium ions is not fully reached. At this point, some of the sodium channels begin to deactivate, and at the same time, the potassium permeability increases due to the activation of potential-dependent potassium channels. This is the process of repolarization. In most cases, trace potentials are observed after rapid repolarization. [9]

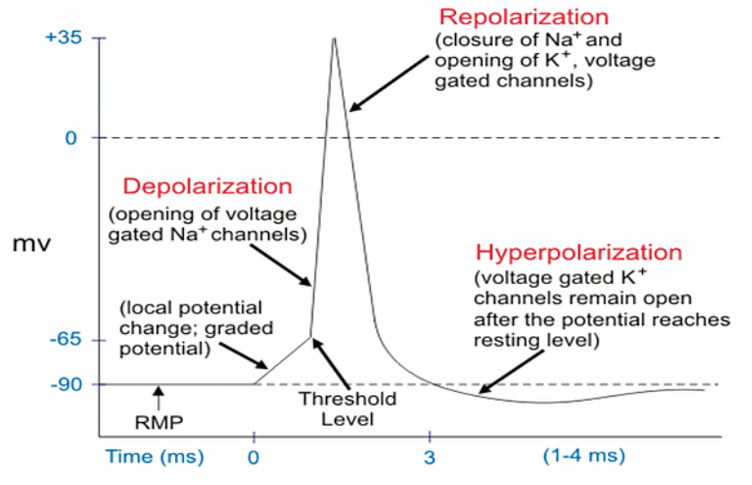

Fig. 1 ***Action potential***

Chronic kidney disease Patients with chronic kidney disease are particularly vulnerable during conditions of dehydration and acute kidney damage. Proximal tubular sodium reabsorption increases secondary to bulk shrinkage and compromised glomerular filtration rate. Reduced sodium delivery to the distal ducts reduces urinary potassium excretion, increasing serum potassium concentrations [10].

The mechanism of muscle weakness and paralysis is probably due to abnormal depolarization of the nerve membrane, secondary to changes in the potassium gradient and resting membrane potentials [11]. As the ratio of intercellular to extracellular potassium decreases, the magnitude of the resting membrane potentials will also decrease. The sodium channels of the cell membrane can be inactivated by this prolonged and permanent depolarization, which leads to reduced excitability of the membrane, which is manifested by muscle weakness or paralysis. These symptoms can occur in the heart and/or skeletal muscle [8, 11,12].

The appearance of symptoms and signs of hyperkalemia depends on the chronicity of the disorder. The changes caused by hyperkalemia are limited to abnormal cardiac conduction and muscle weakness, which can lead to potentially fatal arrhythmias and paralysis. An ECG can give us an idea of the severity of hyperkalemia. Common findings are high T waves, extended QRS, prolonged PR interval, and P wave loss. These changes can progress rapidly to fatal arrhythmias. Neurological manifestations are less commonly reported. Muscle weakness associated with hyperkalemia occurs as a result of changes in neuromuscular conduction. Increasing the plasma K concentration decreases the value of the ratio of intracellular K + concentration / extracellular K + concentration, which leads to a decrease in the magnitude of the resting membrane potential. Although this should increase the excitability of the membrane, the effect observed in patients is different. Depolarization inactivates sodium channels in the cell membrane, thus creating a net reduction in membrane excitability, which may manifest clinically through muscle weakness or paralysis. The process that causes hyperkalemic paralysis focuses on the level of the nerve, not the muscle. Muscle weakness does not usually develop until the plasma K + concentration exceeds 8 mEq / L. This is followed by muscle weakness. It is usually seen in the legs, then in the torso and arms. The facial and respiratory muscles are the last to be affected. [12]

Case report We present a case of a 65-year-old woman admitted as a matter of urgency due to sudden weakness in the lower extremities, which progressed to the impossibility of independent gait. Reports trembling in the upper extremities. The complaints are less than 24 hours old. The patient has concomitant diseases: arterial hypertension (III degree), diabetes mellitus (IBD), chronic kidney

disease (IV degree), performing chronic dialysis, secondary anemic syndrome. The patient's systemic therapy is Insulatard 10E / evening; Actrapid 3x3E; Norvask 1 tablet/morning; Moxogamma 1-0-1; Betalok ZOK 1tablet.

The neurological examination revealed muscular hypotension for the lower extremities and lower paraparesis, moderate to severe. Tendon-periosteal reflexes were preserved for the four limbs, and no pathological reflexes were detected. Unconvincing sensory disturbances were found with the presence of h1 hyperalgesia distally bilaterally. The postural tremor was reported bilaterally.

Native computed tomography of the head, thoracic and lumbar departments, performed as a matter of urgency, showed an extensive hypodense zone of ischemic changes with right frontal and initial degenerative changes along the spine, without stenosis in the departments affected by the study.

Paraclinical tests revealed exacerbation on the background of CKD (creatinine = 885mmol / l and urea = 35.5mmol / l). Potassium was worth 9.1 mmol / l. An emergency ECG was performed, which bore the hallmarks of hyperkalemia (high and acute T-waves; prolonged PR-interval; extended QRS-complex; decreased P-wave amplitude).

Other changes from the laboratory results showed evidence of mild leukocytosis (12.9G / l), ESR (23mm / h), and CRP (6.64mg / dL), a blood culture was taken that was positive with isolated Escherichia colli.

A few hours after taking it, the patient also complained of pain in the lower quadrant of the abdomen. On this occasion, review radiography of the abdomen was performed - without pathological abnormalities. Ultrasound examination of parenchymal abdominal organs and retroperitoneum was also performed without abnormalities.

Treatment included a regimen of intravenous calcium administered to antagonize the effects of potassium on cardiomyocytes and reduce membrane excitability. Insulin is administered to displace potassium intracellularly by stimulating sodium-potassium ATPase. Due to the registered high values of creatinine, urea, and potassium, and the ECG changes, emergency hemodialysis was performed to normalize the values. During hospital treatment, the patient continued to undergo systematic hemodialysis at the discretion of the nephrologist, and according to the paraclinical. An antibiotic following the CKD dose (Axetin 1.5 g) was added to the therapy due to a single fever (up to 38.8 ° C) and paraclinical evidence of inflammation.

As early as the 24th hour after hospitalization, there was an improvement in the neurological deficit and a week later the patient was discharged with restored gait and without sensory disturbances.

Discussion Secondary hyperkalemic paralysis is a life-threatening condition, but can potentially be prevented and treated with early recognition without serious consequences. The identification of risk factors for hyperkalemia is necessary to prevent such an event. Clinicians should routinely monitor serum potassium and creatinine levels. The symptoms outlined in this case should be recognized early with secondary hyperkalemic paralysis as part of the differential diagnosis. Routine therapies for hyperkalemia (insulin dextrose, sodium bicarbonate, beta-2 agonists, calcium) should be administered imme-

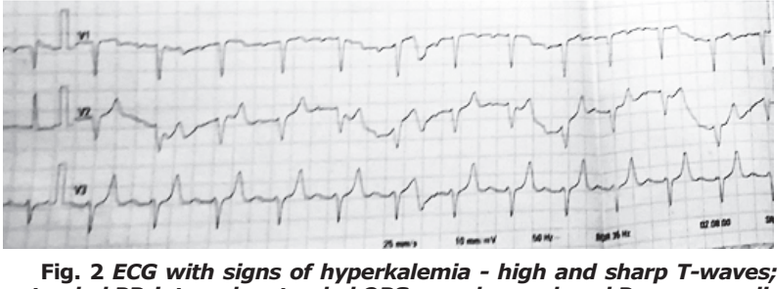

Fig. 2 ***ECG with signs of hyperkalemia - high and sharp T-waves; extended PR-interval; extended QRS complex; reduced P-wave amplitude.***

diately with follow-up doses within 2 hours. If hyperkalemia, ECG changes, and muscle weakness persist, immediate hemodialysis is required.

Upon admission of the patient to the emergency neurological office and after the initial examination, a very broad differential diagnosis was revealed. Due to the sudden onset of lower paraparesis in the foreground, the question arose whether it was a spinal stroke. The symmetry of symptoms, as well as the presence of sensory disorders, included in the differential diagnostic plan and ascending paralysis of Landry. Discordance syndrome required additional brain imaging. We also included compression myelopathy in the differential diagnostic plan. Considered the possibility of transverse myelitis, especially in the presence of evidence of an inflammatory process.

After the paraclinical tests, the diagnostic and treatment approach changed. High levels of urea and creatinine, life-threatening serum potassium, and ECG changes required immediate hemodialysis. Within a week, the patient underwent regular hemodialysis, remaining under the active supervision of nephrologists. Even after the first course of hemodialysis treatment, enslavement to paraparesis was reported. Gradually, within the week, the sensory disturbances disappeared. The patient was discharged with serum K levels of 5.8 mmol / l and regained independent gait. She was referred for regular follow-up by a GP and a nephrologist. The importance of control and regular monitoring of urea, creatinine, and potassium in an outpatient setting was also emphasized.

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Адрес за кореспонденция:

МАРИЯ ДИМИТРОВА

УМБАЛСМ „Н.И.Пирогов",
Отделение по нервни болести
dr.m.i.dimitrova@gmail.com

Corresponding author:

MARIYA DIMITROVA

UMHATEM „N.I. Pirogov",
Department of Neurological Diseases
dr.m.i.dimitrova@gmail.com