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ORIGINAL ARTICLE

Diagnosis and Treatment of the Primary Central Nervous System Lymphoma in the Riga Eastern Clinical University Hospital

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Summary
Introduction. Primary central nervous system lymphoma (PCNSL) is a rare tumor. It is diagnosed in 1-3% of all primary malignant tumors of the CNS. However its incidence increased over the past ten years amongst the immunesupressed and also the immunocompetent patients. PCNSL incidence amongst neurooncology patients is increasing in Latvia as well, therefore it is important to draw more attention to this problem.
Aim of the study. Research and analyse the experience of the Riga Eastern Clinical University hospital (RECUH) in the management of the patients with PCNSL over the last 11 years (from 2001 till 2012). In this research the data about the incidence of the disease, the connection between the age and sex, as well as the diagnostic and therapeutic possibilities are discussed.
Materials and methods. This is a retrospective descriptive study. In this study were included all the patients with morphologically confirmed PCNSL (n=18) that were operated in the neurosurgical clinic in the 11-year time period (from 2001 till 2012). The statistical analysis of the data was made by means of the Microsoft Excel 2010 and SPSS 20th version of the descriptive statistical methods.
Results. Over 11 years (from 2001 till 2012) PCNSL was confirmed in 18 patients, 17 (94.44%) of which were immunocompetent and in 1 patient (5.56%) HIV C1 stadium was diagnosed. Amongst immunocompetent patients 47.06% (n=8) were male and 52.94% (n=9) were female in the age between 45 and 79 years with average age of 64.41 years. Most often PCNSL was diagnosed in the age group between 65 and 69 years. 83.33% of all the PCNSL cases were diagnosed beginning with 2007. In all of the PCNSL patients a B-cell-lymphoma was morphologically confirmed. By admission the average Karnofsky Performance Scale Index was 57.78 in all patients, but after receiving a combination of therapy it was 77.78. The median survival amongst all of the patients was 515 days or 17 month, but amongst the patients, that received the full range combination therapy, the median survival achieved 867 days or 29 month.
Conclusions. The analysed data demonstrates that the incidence of PCNSL has mighty increased over the past six years and PCNSL is more often diagnosed in elderly, in which the KPS index and the median survival considerably increases after the combination therapy.
Key words: the primary central nervous system lymphoma; diagnosis; teatment.

INTRODUCTION

The primary central nervous system lymphoma (PCNSL) is classified as extranodular lymphoma, that is formed in craniospinal axis without having a systemic spreading. It generally localizes in the parenchyma of the brain, it can present itself in the eyes, leptomeninges and the spinal cord (5).

PCNSL is a rare tumor affecting the central nervous system (CNS). It is diagnosed in 1-3% of all malignant CNS tumors (10). The incidence of PCNSL amongst immunocompetent patients is about 0.28 of 100 000 people per year, but amongst AIDS patients the index equals 4.7 of 100 000 people per year (7). In spite of the small amount of patients its incidence has been increasing amongst immunosupressed and also immunocompetent patients over the past ten years (18).

PCNSL can affect patients at any age (21), most incidence is in the age range from 50 to 70 years, amongst immunocompetent patients and with mean age of 60 years (24,33). The age of the manifestatation amongst immunocompromised patients is less, for example, in patients with acquired immunodeficiency it is 10 years, after an organ transplant – 37 years and in AIDS patient – 39 years (21). The sex difference amongst immunocompetent patients is 3:2 (21), but amongst immunosupressed patients 95% are men (35). PCNSL is very rare in children and usually it associates with congenital immundeficiency, for example IgA deficiency, hyperimmunoglobulin M syndrome or Wiskott-Aldrich syndrome (14).

Up to now the origin of the malignant lymphocytes in PCNSL is not known, because there are no lymph-nodes or lymphatic tissues in the CNS. It has been proved that T-lymphocytes can cross the hematoencephalic barrier, but B-lymphocytes usually cannot be found in the structures of the CNS, even though the majority of the PCNSL cells has B-lymphocyte origin (27). Epstein–Barr virus (EBV) plays a role in the development of the PCNSL in immunosupressed patients. The genome of

the EBV can be found in 95% of the PCNSL cells and in 20% of immunocompetent patients (38). That could explain that the affected B-lymphocytes proliferate in the structures of the CNS and develop a tumor without the control of the immune system. However an assumed etiology of PCNSL hasn't been found in the immunocompetent patients (28).

In about 60% PCNSL localizes in the supratentorial space, which includes frontal (15%), temporal (8%), parietal (7%), occipital (3%) lobes, basal ganglia with the periventricular region (10%) and *corpus callosum* (5%), as well as 13% in the posterior fossa and about 1% in the spine. About 25-50% of PCNSL cases present with multiple formations (in patients with AIDS and after an organ transplant in 60-85%). Secondary PCNSL spreading to the brain layers is seen in 30-40% of the cases, but the development of a PCNSL in the leptomeninges was diagnosed only in 8% (15). Also PCNSL can be presented in the eyes because their formation is connected with CNS embryonic development and its frequency achieve 15-20% (21).

PCNSL presents mostly with focal neurological symptoms (50-80%), that depend on the localization of the tumor. That could be disorders of perception or movement, aphasia etc. Often patients have cognitive, behaviour and personality changes (20-30%), that associates with the tumor being in *corpus callosum* and in the frontal lobe. The symptoms of the increased intracranial pressure (10-30%) manifest as headache, nausea, optic disc oedema. Less often patients have seizures (5-20%) that are associated with the damage to the brain cortex. Vision problems (5-20%) manifest as monocular or binocular hazy eyesight, swimming or dashing elements in the eyesight, that can be associated with dynamic vitreoretinal traction during the posterior detachment of the vitreous body and the following vitreous hemorrhages (6,18,19,20).

In order to determine the localization and spread of a process in neuro-oncology as well as the level of damage the following methods are of most use: computer-tomography (CT), magnetic resonance imaging (MRI) and angiography. New methods of diagnostics appeared over the past 10-20 years, such as CT angiography, MRI angiography and venography, Single-photon emission computed tomography (SPECT), positron emission tomography (PET). These explorations help to early diagnose neoplasms in CNS and to apply treatment early, achieve better results in the treatment of neuro-oncological patients.

During the examination of the immunocompetent patient's, CT PCNSL appears as a periventricular or in the grey matter localized formation (18), that is hyperdense with a vasogene swelling, in MRI pictures the neoplasm is hypodense in T1 sequence (T1WI) and isointense or hyperintense in T2 sequence (T2WI). PET and SPECT are facultative methods of examination, that can help to differenciate PCNSL and others formations of the CNS in AIDS patients (12,32).

Morphological analysis is the main method to prove PCNSL diagnosis in neuro-oncological patients. During the microscopy of the PCNSL a massive lymphoid cell accumulation can be seen with the perivascular infiltrative damage and diffuse invasion of the parenchyma of the small arteria, arteriola and venules. In the periphery of the tumor a reaction of glia and infiltration of T-lymphocytes can be seen (see fig.4). Often there are isolated focuses of tumor cells near the primary tumor mass (16).

Histology shows the majority of PCNSL as typical B-cell non-Hodgkin lymphoma. The cells present with monotypical immunoglobulins, mostly IgM kappa, as well as with B-cell markers: CD19, CD20 and CD79a (28) (see fig.3). Based on Revised European-American Lymphoma (REAL) Classification and World Health Organisation (WHO) Classification 92-98% of all PCNSL are B-cell lymphomas (17). The incidence of a T-cell lymphoma is about 2-5%, but their number may be different depending on a geographical location, for example, the incidence of a T-cell lymphoma in Japan is 8-14% (21).

PCNSL are treated by combining different methods: neurosurgery, radiation, chemotherapy and corticosteroids. Corticosteroids may cause a formidable regression of PCNSL and immediate improvement of the clinical state (36). The lymphoma cells have receptors to glucocorticoids, that can cause cell apoptosis and decrease the size of the neoplasm in a few days after administration of corticosteroids and also decrease the vasogene swelling (22). Nevertheless the improvement is momentary and the tumor can retrieve its size in just a few months (12). Corticosteroids are not recommended in undiagnosed cases of PCNSL, because such therapy affects the results of biopsy and complicates diagnostics (23).

The aim of the neurosurgical manipulations is the reduction of the size of the neoplasm, that protects the brain from herniation and enhances the effect of the following chemotherapy, radiation and treatment with corticosteroids. Neurosurgical invasion can be used to acquire a biopsy that is one of the main elements of the diagnosis and planning of the following therapy (23).

There are two methods of treatment availiable in Radiation therapy of PCNSL: focal radiation and whole brain radiotherapy (WBRT). Focal radiation is applied to the constrained tumors of the brain, but its development in time is more often in comparison with WBRT (23), because PCNSL has an infiltrative growth pattern, so it is hard to define tumors borders. The results of the last researches show, that better outcomes are achieved using a focal therapy with larger area of radiation (4 cm) compared to using standard focal therapy (34). Autopsy data demonstrate that microscopical PCNSL focuses, that were not radiologically identified, are in multiple regions of the brain. So we can draw a conclusion that WBRT has more chances to control PCNSL development. The radiation dose is between 30 Gy and 50 Gy, but the optimal doses was not defined yet (4).

It is necessary to use such chemical agents in the chemotherapy of PCNSL, that can cross the hematoencephalic barrier in order to destroy the

tumor cells, that are not only around the blood vessels, but also deep in the brain tissues (29). Drugs, that are effectively used in the treatment of a systemic lymphoma are not effective in PCNSL, because they are unable to cross the hematoencephalic barrier (24). Some of the chemical agents and their combinations are used in treatment of the PCNSL, including CHOP and CHOD (cyclophosphamide, doxorubicin, vincristine, prednisolone or dexomethasone), but they give less effect compared to radiation therapy and have more toxicity (25). During the treatment with high dosis of methotrexate (MTX) as well as intrathecal MTX there were achieved much better results, the average length of life of the patients was up to 40 months, that is an indubious improvement compared to radiation (3,8,9). It is possible to achieve much better results and control of the disease by combining chemotherapy and radiation (23). Radiation of the brain and use of MTX can cause a later leucoencephalopathy, nevertheless there is an important clinical improvement at first. The consequences of the neurotoxicity appear in patients with longer survival. Patients develop a progressing dementia, ataxia, urine incontinence and memory loss. MTX is neurotoxic itself and can cause neurological symptomes such as: seizures, cognitive deficits, motor dysfunction. Intrathecal application can cause a chemical arachnoiditis that can manifest as acute meningitis (31,37).

AIM OF THE STUDY

PCNSL incidence amongst neurooncology patients is increasing in Latvia as well, therefore it is important to draw more attention to this problem. The aim of our study is to research and analyse the experience of the Riga Eastern Clinical University hospital (RECUH) in the management of the patients with PCNSL over the last 11 years (from 2001 till 2012). In this research, the data about the incidence of the disease, the connection between the age and sex, as well as the diagnostic and therapeutic possibilities and results are discussed.

MATERIAL AND METHODS

The research took part in the hospitals of RECUH: „Gailezers", „Latvian Oncology Center", „Linezers" and „Infectology Center of Latvia". In this research there are included patients, that were operated on and have morphologically confirmed PCNSL during the last 11 years (2001-2012). The number of patients in this 11 year period is 18. This is a retrospective descriptive study. The statistical analysis of the data was made by means of the Microsoft Excel 2010 and SPSS 20th version of the descriptive statistical methodes.

RESULTS

All patients (n=18) were included in the retrospective descriptive study, 17 (94.44%) of which were immunocompetent and in 1 (5.56%) HIV C1 stadium was diagnosed. Amongst immunocompetent patients 47.06% (n=8) were male and 52.94% (n=9) were female in the age between 45 and 79 years with average age of 64.41 years. Most often PCNSL was diagnosed in the age group between 65 and 69 years (see fig.1). There was one immunosupressed patient - a 29 years old male.

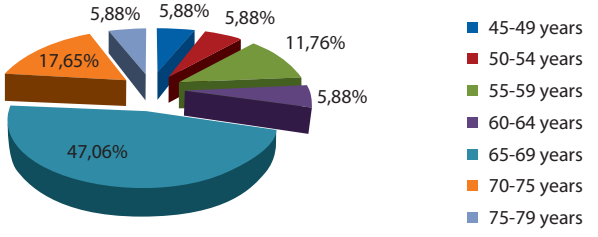

Fig. 1. PCNSL pacient`s age groups

While analysing the amount of the yearly diagnosed patients it can be seen that over the past 5 years there have been a heady increase of the number of patients along with the growth of the incidence compared to the previous years. 83.33% of all the PCNSL cases were diagnosed beginning with 2007, that is considered the begin of increase of lymphoma cases. The disease is piked in 2012 (n=4) and the incidence was 0.20 of 100 000 habitats per year (see fig.2).

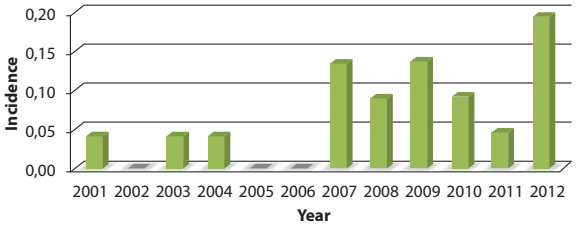

Fig. 2. PCNSL incidence of 100 000 habitats per year

In the diagnostics of all the patients (n=18) MRI was used as the imaging technique (see fig.5) and immunohistochemistry (CD5, CD20 as well as other cell markers if necessary) in order to morphologically confirm PCNSL (see fig. 3 and 4). Analysing of histological forms of PCNSL, in 100% of the cases was confirmed B-cell lymphoma (low-grade B-cell lymphoma (55.56%), diffuse large B-cell lymphoma (38.89%), intravascular B-cell lymphoma (5.56%)).

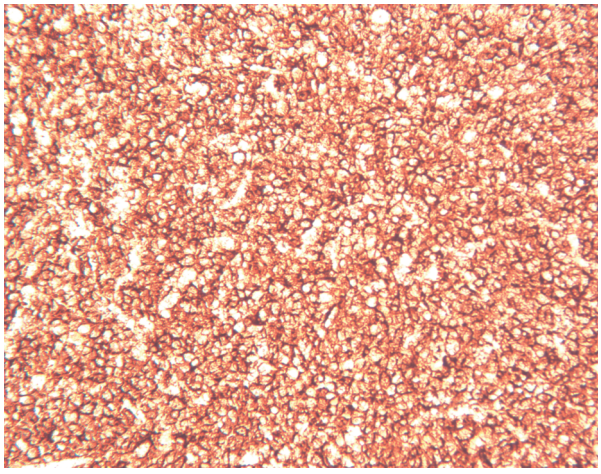

Fig. 3. Tumour cells express the pan-B-cell marker CD20. Obj. 20

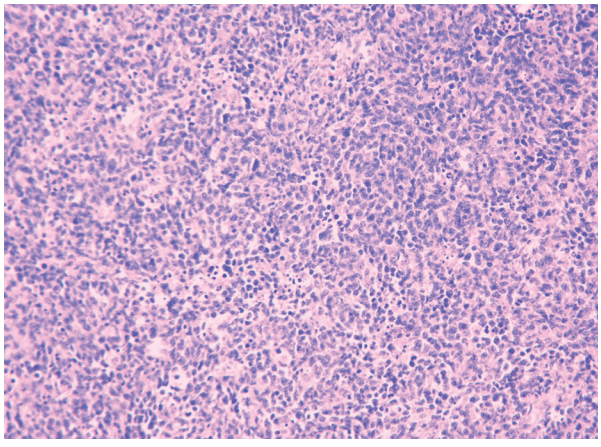

Fig. 4. Malignant, diffuse large B-cell lymphoma. Obj. 20

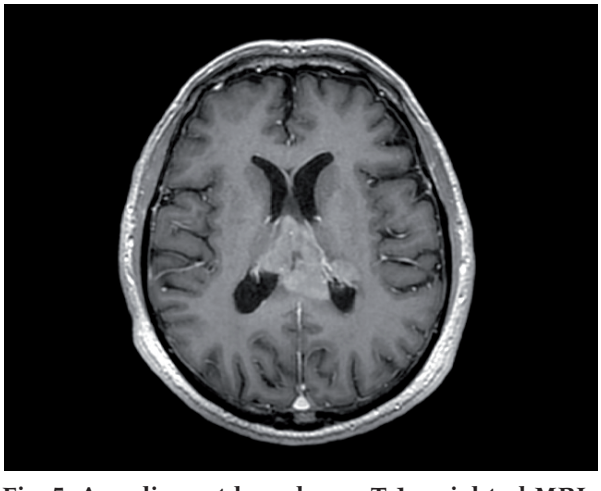

Fig. 5. A malignant lymphoma T-1 weighted MRI

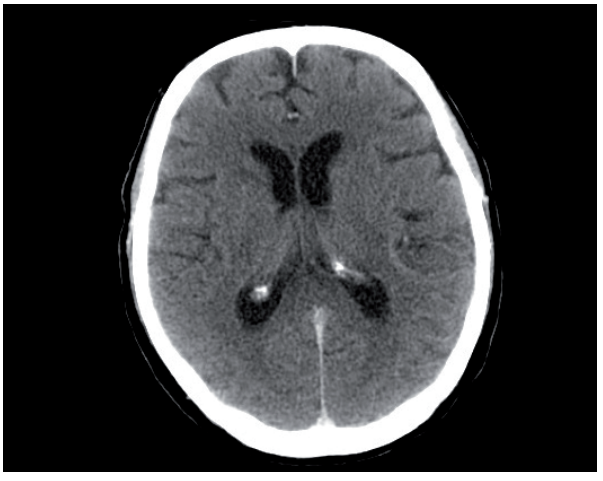

Fig. 6. Control-CT study view result after receiving a combination of therapy (the same patient)

The average Karnofsky Perfomance Scale (KPS) by admission was 57.78 amongst all the patients. 100% (n=18) of them received neurosurgical treatment, after which the KPS achieved 70. 12 patients were treated with radiation therapy, after which the KPS was by 72.50. Chemotherapy was applied to 8 patients, that achieved KPS 77.78 (see fig. 7).

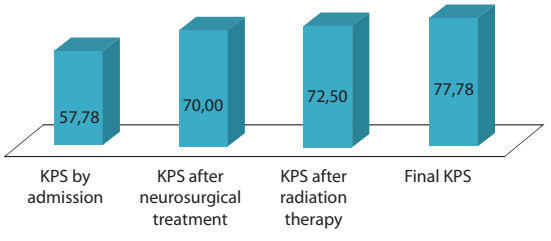

Fig. 7. KPS after receiving combined therapy stage

The prolonged development of the PCNSL was diagnosed in 22.22% (n=4) of the cases. Complications after neurosurgery were seen in 11.11% (n=2) as large ischemic stroke, but after radiation the complications reached 16.67% (n=2) – the patients had toxic-allergic reaction to radiation. The median survival amongst all the PCNSL patients was 515 days or 17 month, but patients that received combined therapy lived up to 867 days or 29 month (see fig.6).

DISCUSSION

Our study demonstrated that PCNSL is most often diagnosed in patients 65-69 years of age amongst immunocompentent patients and with mean age of 64.41 years (see fig.1), that agrees with the internationally published data, that says the most incidence occurs between 50-70 years of age with mean age of 60 years (24,33).

Our research demonstrated that the amount of PCNSL

patients has increased over the past 5 years, considering the yearly decrease of the country inhabitants, the incidence of PCNSL seems to be greater with the greatest index in 2012, when the incidence was 0.20 of 100 000 habitants (see fig.2). However, in comparison with the data described in the foreign literature, the incidence is less, that could be explained by the fact that not all PCNSL patients treated RECUH, some of them probably received necessary treatment in other medical institutions and so we do not reflect the incidence of the overall situation in society.

B-cell-lymphoma was morphologically confirmed in all the PCNSL patients, that is near to the results described in literature (92-98%), the discrepancy can be explained with our small amount of patients.

The PCNSL patients treated in RECUH received combined therapy consisting of neurosurgery, radiation and chemotherapy, after which the KPS index was 77.78 and the mean lifespan was 867 days or 29 month. Considering the starting KPS index (57.78) and the mean age of the patient (64.41 years) we think that the achieved results are good. The patients can take care of themselves and their quality of life is close to the normal level, as well as in the foreign literature describe the results of which PCNSL patients survival after received combination therapy ranges from 15 to 60 months (1,2,11,13,26,30), we can conclude that PCNSL patients treated RECUH survival approaching the average level of the world.

After the received therapy in the 22.22% (n=4) of the PCNSL patients the prolonged development of the tumor was stated, that is a large enough number and for that reason it is necessary to analyse the tactic of treatment in each stage, to find possible reasons and prevent them in the treatment of the following PCNSL patients. It is also necessary to analyse the reasons of the complications in order to possibly reduce its number. For example, it is sometimes better to take a larger biopsy during the neurosurgery than performing a subtotal evacuation.

In conclusion we want to add that even though PCNSL is a rare disease, its incidence and significance grows with every year in the modern society. In the risk group are the elderly and immunosupressed people, the number of which constantly grows in our country, that is why it is necessary to draw attention to this problem and find solutions. RECUH offers all the necessary methods of diagnosis and treatment in order to help the PCNSL patients to accept this diagnosis, improve the prognosis and the quality of life, but in order to achieve better results more detailed and extensive studies are needed as well as education of the medical attendants and the patients about PCNSL.

CONCLUSIONS

Most commonly PCNSL is diagnosed in the age range between 65 and 69 years, the mean age being 64.41 years and with sex proportion of 47.06% male and 52.94% females. Over the past five years the increase of the incidence appeared: 83.33% of all the PCNSL cases being diagnosed beginning with 2007, with greatest number of sick in 2012 (n=4), that is considered as an increase of lymphoma. The starting KPS index amongst all the PCNSL patients was 57.78, but after the combined treatment it increased up to 77.78, that shows considerable improvement. In all patients MRI was used as the imaging method, immunhistochemistry for morphological diagnosis of PCNSL and combined therapy, that consisted of: neurosurgery, radiation and chemotherapy, as a method of treatment and the median survival was 867 days or 29 months.

Conflict of interest: None

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