Conference Paper

Dynamics of Cognitive Functions in Patients With Parasellar Meningiomas Undergoing Radiotherapy

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Abstract

This study was focused on neuropsychological analysis of the cognitive functions in patients with parasellar meningiomas undergoing radiation therapy. In these patients, the unilateral hippocampus adjacent to the tumor was partially exposed to irradiation. A novel approach was used to assess particular memory functions including pattern separation, in subpopulations of subjects prior to the course of radiotherapy, immediately after the course, and 1–2 years after therapy. Our results show a tendency for pattern separation decline in the long-term follow-up. A possible association of these disorders with the effect of the hippocampal region irradiation and inhibition of adult neurogenesis is discussed.

Keywords: cognitive functions, radiation therapy, hippocampus, parasellar meningioma, pattern separation, adult neurogenesis

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1. Introduction

Radiation therapy is one of the principle methods of primary and metastatic brain tumors treatment. Despite the effectiveness of such treatment, ionizing radiation has neurotoxic effects on the brain. The delayed side effects of cranial irradiation include the defects in cognitive functions which may occur months and years after the course of radiotherapy. In particular, this is manifested as deterioration of verbal and spatial memory, attention, counting, and ability to solve new problems [1]. The clinical studies have shown that the cognitive impairment can be observed in 20–50% of patients with brain tumors for over a one-year period following high doses of radiation exposure. Thus, the methods of treatment aimed at prolonging patients' life and their return to daily activities, can paradoxically lead to the increased pathology of the cognitive functions.

The genesis of neurocognitive effects following brain ionizing radiation is still discussable. The pathological mechanisms include vascular abnormalities (hyalinization, decreasing of vascularization, and thickening of arteriolar walls), gliosis, demyelination, and ultimately, white matter necrosis. However, many patients show the deficits of memory without the signs of these pathological events. Since the hippocampal dysfunction in the form of depression and memory impairment is a characteristic feature of the neuropsychological effects of radiation, potential morphological changes in the hippocampus have been increasingly associated with these effects in the recent years [2, 3].

Hippocampus is a brain structure responsible for information processing and memory. On the other hand, the hippocampus is a neurogenic structure, the area with the permanent production of new neurons, astrocytes and oligodendrocytes from progenitor cells. Neural progenitors from the subgranular zone, migrate locally to granular layer of hippocampal dentate gyrus and become granular neurons [4]. The most important discovery of the recent years has provided a solid proof of constant neuronal production in human brain [5]. The ionizing radiation has one of the strongest antiproliferative effects on dividing neural precursors leading to a significant decrease in the number of new neurons in the adult hippocampus. Thus, the inhibition of adult neurogenesis induced by radiotherapy exposure may underlie some of the observed cognitive impairments in patients.

One of the key behavioral functions linked to adult neurogenesis in animals is the ability to discriminate between close, but non-identical, objects and representations – so called pattern separation. Pattern separation is a process of formation various representations in the brain for similar traces of memory [6]. Since arising as a purely computational hypothesis a decade ago, this concept received substantial experimental support from different groups, employing various behavioral models [7].

Formally, pattern separation can be defined as a process of differentiating between two similar inputs in order to reduce their overlap. This separation of the inputs should result in a decrease in the similarity of their outputs and, hence, would decrease the probability that the input patterns will interfere with each other during the memory retrieval. In other words, pattern separation is a potential mechanism for increasing the uniqueness of each input, even if they are very similar to each other.

Most of the current data on pattern separation issue has been obtained from experiments on animals. However, there is a currently increasing evidence that adult neurogenesis may be an important component of the separation patterns in humans as well. One of the obvious difficulties in human studies is the inability to experimentally manipulate human neurogenesis. However, changes in hippocampal neurogenesis may be observed as a side effect during aging, injury, disease or radiotherapy [8, 9].

The patients with cavernous sinus meningiomas were prospectively included in this pilot study due to the proximity of these lesions to the hippocampus. Unlike the glial tumors of the temporal lobe, meningiomas of cavernous sinus are extracerebral, do not infiltrate brain tissue in most cases, and may cause cognitive impairments due to the direct impact. However, hippocampus receives a significant radiation dose comparable to the dose load on a tumor itself when applying photon irradiation.

The uniqueness of our research model is a limited irradiation of the hippocampus that inevitably accompanies radiation therapy of the parasellar meningiomas. This approach eliminates a number of ambiguities in the interpretation of the pattern separation results in humans observed in generalized radiation effects, damage or injury. Currently, this is the most controlled and minimally affecting approach to assess the contribution of new neurons to memory processes and separation of similar contexts in humans.

This approach allows describing the dynamics of cognitive functions in patients undergoing radiotherapy affecting the hippocampal region. This novel approach and neuropsychological analysis of memory and other cognitive functions, including the pattern separation, were carried out in subgroups of subjects prior to the course of radiotherapy, immediately after the course, and 1–2 years after therapy.

2. Methodology

Sixteen patients with parasellar meningiomas assigned to the radiation therapy at Burdenko Neurosurgery Center were enrolled in the pilot study. The first subgroup consisted of 7 patients (average age – 54 years (range 31–67 years)), which were examined twice – prior to and immediately after the course of radiotherapy. The second subgroup consisted of 9 patients (average age – 50 years (range 38–63 years)) which had received radiotherapy, on average, 21 months earlier. The subgroups did not differ in demographic characteristics and cognitive status at the time of treatment start.

Four out of seven patients in the first subgroup had experienced a partial tumor removal earlier. In two cases, operations were repeated. In the second subgroup surgical treatment was performed in 1 of 9 patients. Also, 1 patient in the second group had radiosurgical treatment previously. Meningioma WHO Grade I was verified in all cases of surgery previously performed. In all other cases, the diagnosis of 'benign meningioma' was established on the basis of a typical clinical and neuroimaging data.

Radiation therapy was performed on the 'Novalis' device (a linear accelerator (6 MeV) equipped with a micronaltech collimator) in most cases. The irradiation was carried out on the CyberKnife (linear accelerator (6 MeV), equipped with a set of replaceable conical collimators of different sizes) only in one patient. In all cases, stereotaxic conformal radiation therapy was performed with a photonic beam. The irradiation was carried out according to the standard procedure. The contouring of both the tumor and the hippocampus was done to evaluate the size and location of the tumor and degree of hippocampus compression.

Irradiation was predominantly performed in the standard fractionation mode of 29–33 (median – 30) sessions with a single focal dose of 1.8 Gy to a total dose of 52.2–59.4 (median – 54 Gy). In 2 cases, the radiation therapy was performed in a shorter hypofractization mode by 3 fractions of 7 Gy (in 1 patient of the first subgroup), and by 5 fractions of 5.5 Gy (in 1 patient of the second subgroup). All the modes used are considered to be effective in terms of the biological effect on meningiomas. The average volume of tumor irradiated was 21.3 cm^3 (5.5–28.0 cm^3) in the first subgroup and 29.1 cm^3 (13.5–54.9 cm^3) in the second.

The dosage load on the brain tissue (15 cm3) was 45.6 Gy on average (range 42.4–47.4 Gy) – in the first subgroup and 46.9 Gy (40.8–51 Gy) – in the second. In the first subgroup, 10%, 30% and 50% of ipsilateral hippocampal dose load was 46.1 Gy (range 38.5–51.1 Gy), 37.6 Gy (range 31.5–44.5 Gy) and 31.8 Gy (range 25–41.1 Gy). In the second subgroup, the dose load for 10%, 30% and 50% of the ipsilateral hippocampus volume was 39.9 Gy (range 26.4–50.3 Gy), 31.4 Gy (range 20–47.5 Gy) and 30.5 Gy (range 11.9–52.3 Gy). In the first subgroup, the compression of the ipsilateral hippocampus by tumor was observed in 6 out of 7 cases. The average volume of the ipsilateral and contralateral hippocampus was 3.0 cm^3 (range 2.9–3.1 cm^3) and 3.2 cm^3 (range 2.9–3.6 cm^3). In the second group, the compression of the ipsilateral hippocampus by tumor was observed in 8 out of 9 cases. The average volume of the ipsilateral and contralateral hippocampus was 3.4 cm^3 (range 3.1–3.9 cm^3) and 3.5 cm^3 (range 3–4.2 cm^3).

All patients were thoroughly tested using neuropsychological methods (A. Luria, 1969), which allowed to qualify the patients' cognitive functional disorders and to suspect a locus of these violations. In order to simulate a situation of pattern separation the original author's method (EAM) was used combining the registration of eye movements (**E**yetracking), the assessment of the spatial attention distribution (**A**ttention) and memory response (**M**emory). A free verbal recall and visual recognition tests were applied in a pattern separation task [10]. Each subject was asked to 'carefully watch and remember' the 15 stimuli presented on a screen. The stimuli (colored images) were arranged in triplets on one slide separated by grey display. The exposure time to each triplet was 10 seconds. Ten minutes after watching the presentation (subject was doing other tests in a meanwhile), the subjects were asked to recall the presented images in a free manner. Fifteen minutes later a test of image recognition was done in a pattern separation task. The set of 30 images appeared one by one on a monitor, and the subject had to determine whether he saw that picture (the answer was 'I saw that image'), didn't see it (the answer was 'That is new image') or saw a similar picture (the answer was 'It is a similar image to what I have seen'). In total there were 15 previously presented pictures, 10 similar and 5 new images. A short training was done before the test, during which a complete understanding of the task was verified. The recognition errors were analyzed, including the errors associated with the difficulties of differentiation between previously presented and similar images (the pattern separation process).

3. Results

Neuropsychological study of patients conducted before and after radiation therapy, as well as in the follow-up period (of 1–2 years), showed that the dynamics of cognitive functions was complex and ambiguous. Mild neuropsychological symptoms were revealed in all patients. Both negative and positive changes in cognitive functions were observed right after the radiotherapy. There were more severe neuropsychological symptoms in the follow-up, usually qualifying as dysfunction of the frontal and tertiary temporal-parietal-occipital brain areas.

An experimental study using the EMA test showed that the number of correctly reproduced stimuli in free verbal recall did not differ in groups, but in all cases it appeared to be in the lower range of the reference values for healthy subjects. The number of stimuli recalled in EMA test at all three stages of the study was: 8.7+3.94; 8.0+2.0; 8.0+2.7. This parameter was 11.0+3.1. in the group of healthy subjects. The number of correctly recognized stimuli varied at different stages of catamnestic observation. A qualitative and quantitative analysis of recognition errors was carried out. Errors in the recognition of similar stimuli were dominant among recognition errors at all stages of the study, and their part in the total number of errors increased in the assessment right after radiotherapy and in the follow-up (33%, 54% and 51%, respectively).

4. Conclusions

The pilot study performed with the EMA test made it possible to draw conclusions about the presence of specific memory impairments manifested as the pattern separation disturbances in patients with parasellar meningiomas undergoing or underwent radiation therapy. There was a tendency for some increase in the severity of these impairments. Patients underwent radiotherapy several months/years before, tended to less often recognize similar images correctly comparing to patients tested prior to and right after the course of radiotherapy. It can be assumed that the errors of similar stimuli recognition could reflect the state of the pattern separation mechanism and be the indicator of the cognitive effects produced by radiation on the hippocampal zone.

It should be noted that these conclusions are provisional. Further research will allow relating clinical observations with the results of experimental neurogenesis depression in the hippocampus of animal models.

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