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Research Article

LATE DELAYED POST-RADIATION ENCEPHALOPATHY: AN UPDATED REVIEW

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ABSTRACT

Late delayed post-radiation encephalopathy mainly occurs following whole brain irradiation and is very rarely associated with focused beam irradiation. The radiation lesions consist of areas of focal necrosis and of diffuse demyelization of the deep cerebral structures. Irradiating normal tissues leads to a chronic increases in reactive oxygen/reactive nitrogen oxide species. The clinical post-radiation symptoms are consistent with a progressive multifocal leukoencephalopathy. They include seizures, hemiparesis, cranial neuropathy, headaches, blindness, dementia, and ataxia. Neuroimaging is useful to distinct radiation-induced encephalopathy from tumour recurrence, but also to show the typical post-radiation features. For small, asymptomatic lesions, an observational wait strategy can be observed. Dexamethasone is the most used drug in symptomatic patients. Other types of treatment have also been investigated.

KEYWORDS

Late radiation encephalopathy - Pathogenesis – Clinical symptoms – Neuroimaging – Treatment.

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INTRODUCTION

Direct or incidental exposure of the nervous system to therapeutic irradiation carries the risk of symptomatic neurologic injury. Central nervous system toxicity from radiation includes focal cerebral necrosis, neurocognitive deficits, and less commonly cerebrovascular disease [1]. Late delayed post-radiation encephalopathy usually occurs 4 months post radiotherapy. It is well recognised to occur following whole brain irradiation but is very rarely associated with focused beam irradiation to the brain and the pituitary fossa [2].

Late delayed radiation encephalopathy

The radiation lesions consist of areas of focal necrosis and of diffuse demyelization of the deep cerebral structures and the brain stem. Demyelization is predominantly present in cases of late appearance of the neurological symptoms while necrosis is found in cases with a short latency period. The cerebral cortex and the arcuate fibres are always the most preserved structures. The topography of the focal necrotic lesions in the cerebral hemispheres and in the brain stem correspond well to the vascular supply areas of the deep perforating arteries, while the diffuse lesions always have a predominant distribution in the periventricular arterial end- and border-zones [3].

It has been recently proposed that the radiation-induced late effects are caused, in part, by chronic oxidative stress and inflammation. Increased production of reactive oxygen species, which leads to lipid peroxidation, oxidation of DNA and proteins, as well as to activation of pro-inflammatory factors. This is observed in vitro as well as in vivo studies [4].

Irradiating late responding normal tissues leads to chronic increase in reactive oxygen/reactive nitrogen oxide species that serves as intracellular signaling species to alter cell function/phenotype, resulting in chronic inflammation, organ dysfunction, and ultimate fibrosis and/or necrosis [5]. There is a significant association between the radiation dose and the interval of the occurrence of the late radiation encephalopathy [6].

The patients develop delayed symptoms consistent with those in progressive multifocal leukoencephalopathy. The symptoms include

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seizures, hemiparesis, cranial neuropathy, headaches, blindness, dementia, and ataxia [7]. The patients who suffered from the consequences of radiation therapy have slowness of executive functions, and profound alterations of frontal functions, such as attention focusing, mentation control, analogical judgement and insight. High dose radiotherapy might result in a severely demented, bedridden patient, who "has been cured" from his brain tumour [8].

Impairment of hippocampal neurogenesis is thought to be an important mechanism underlying the cognitive decline after cranial radiation therapy, prominently the memory functions [9].

Life-threatening late delayed radiation necrosis and radiation-induced leukoencephalopathy have been assumed to be the major complications of whole brain radiation therapy. Classically, these complications are less frequent after therapeutic irradiation to the brain because in many treatment protocols of brain tumours, the radiation field is now confined to tumours and their margins and adjuvant chemotherapy is avoided as much as possible [10].

Although a causal link between chronic oxidative stress and radiation-induced late normal tissue injury remains to be established, a growing body of evidence appears to support the hypothesis that chronic oxidative stress might serve to drive the progression of radiation-induced late effects [11].

The pathophysiology of radiation-induced vasculopathy is complex and dependent on the targeted blood vessels, and upregulation of pro-inflammatory and hypoxia-related genes [12].

Unusual late-onset complication, characterized by reversible neurologic focal signs, seizures, and magnetic resonance imaging (MRI) alterations, is recently reported and classified as stroke-like migraine attacks after radiation therapy (SMART) and peri-ictal pseudoprogression [13].

Neuroimaging is useful to distinct radiation-induced encephalopathy from tumour recurrence. The radiation related lesions observed on computed tomography (CT) of the brain can show uni- or bilateral involvement, mainly of the white matter and subsequently of the gray matter of the lower portion of the brain included within the portals of irradiation and its vicinity. The lesions are oedematous and

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hypodense and show post-contrast enhancement in 50% of the cases [14].

On magnetic resonance imaging (MRI) the white matter lesions are predominantly hyperintense on T2-weighted images, but in 65% of the cases foci with heterogeneous signal intensity consistent with necrosis are detected. Gray matter lesions are detected in 88% of the patients. Blood-brain barrier disruption characterized parenchymal contrast enhancement is observed 89% and haemosiderin deposits, in 53%. There is a significant correlation between white matter necrosis, gray matter lesions, and blood-brain barrier disruption, in the regions that have received the highest radiation dose [15].

A combination of tension imaging and proton magnetic resonance spectroscopy can be used to detect radiation-induced brain injury. Patients can be divided into three groups acording to the time after completion of radiotherapy: group 1, less than 6 months; group 2, 6–12 months; group 3, more than 12 months. Mean fractional spectroscopy in group 1 is significantly lower compared to group 3. Group-wise comparisons of apparent diffusion coefficient values among all the groups are not significantly different [16].

MRI demonstrates typical cortical swelling and contrast enhancement, primarily in the parieto-occipital regions of brains with SMART syndromes after radiation therapy. On follow-up both clinical and MRI features improve spontaneously [17].

Serial MRIs of the brain at different stages of the disease of single case of radiation encephalopathy and Kluver-Bucy syndrome shows a pontine infarct, enlarged temporal lobes with serpentine hyperintense signal at cortical gyri on T2-weighted and proton density MRI, and progressive brain calcification which appears hyperintense on T1-weighted images and hypointense on T2-weighted images [18].

For patients with delayed radiation encephalopathy confirmed by clinical symptoms and imaging findings, positron emission tomography (PET) of the brain maintains a 100% coincidence rate with CT. PET reveals obvious hypometabolic changes whereas CT display normal density. The incidence of brain stem metabolic reductions is 24.5% . Delayed radiation encephalopathy patients exhibit significant hypometabolic changes in the inferior temporal lobe, captured by PET much earlier than by CT [19].

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For small, asymptomatic lesions, an observational wait strategy, with continuous clinical follow-up can be adopted, wherein this is supplemented with continuous diagnostic imaging. [20].

Dexamethasone is the most used drug and usually assists in quickly relieving the clinical symptoms caused by focal necrosis in late onset radiation encephalopathy. However this effect is temporary [21].

Because radiation injury to the brain can be mainly caused by ischemia due to vascular injury anticoagulant therapy has been proposed to prevent the progression of the disease [22].

Bevacizumab is a humanized monoclonal antibody that blocks the vascular endothelial growth factor. It reduces vascular permeability and normalize the blood-brain barrier in late radiation injury [23].

A recent phase II study shows that the use of nerve growth factor (NGF) in the treatment of brain radiation necrosis is more effective than corticosteroids with little side effects. NGF has also a longer duration in controlling the necrosis related symptoms than corticosteroids [24].

Hyperbaric oxygen therapy weekly can reduce brain radiation necrosis from 20% to 11%. However, the evidence is limited to case reports and no randomised controlled trial articles have been published until now [25-28].

CONCLUSIONS

Although the incidence of radiation-induced encephalopathy remains low, it affects the quality of life of patients. Close monitoring of functional imaging of the brain after radiotherapy remains essential. There is currently no unified treatment plan for radiation induced necrosis, but alternative treatments are increasing, and certain positive results have been achieved.

Clinically, much attention should be paid to reduce the incidence of radiation brain necrosis and improve the symptoms of the patients. Radiotherapy is extensively used in the treatment of malignant tumors of the central nervous system, but may itself be the cause of considerable morbidity and mortality, probably through damage to the remarkably vulnerable vascular system [29].

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