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A Review on Radiogenic Lhermitte's Sign*

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Radiation myelopathy is a rare, but extremely serious side-effect of radiotherapy. Recovery from radiation-induced motor sequelae is rare, whereas, the regeneration of sensory losses is relatively frequent. Among the sensory radiogenic injuries of the spinal cord, Lhermitte's sign (LS) is most frequent. This review describes the clinical picture and diagnostic imaging signs of radiogenic LS. There have been only a few studies on large patient groups with radiogenic LS, demonstrating a rate of occurrence of 3.6-13%, relating mainly to mantle irradiation or the radiotherapy of head and neck tumors. These cases typically manifest themselves 3 months following radiotherapy and gradually disappear within 6 months. Only 3 LS cases have been described in the English literature with extraordinarily severe symptoms lasting for more than 1 year. MRI, a sensitive tool in the detection of demyelination, failed to reveal any pathological sign accompanying radiogenic LS. However, positron emission tomography demonstrated increased [^{18}F]fluorodeoxyglucose accumulation and [^{15}O]butanol perfusion, but a negligible [^{11}C]methionine uptake in the irradiated spinal cord segments in patients with long-standing LS. These imaging data are suggestive of a close direct relationship between the regional perfusion and metabolism of the spinal cord, very much like the situation in the brain. We postulate that an altered, energy-demanding conduction along the demyelinated axons of patients with chronic radiogenic LS may explain the increased metabolism and perfusion. (Pathology Oncology Research Vol 9, No 2, 115–120, 2003)

Keywords: radiation myelopathy, permanent Lhermitte's sign, magnetic resonance imaging, positron emission tomography, [^{18}F]fluorodeoxyglucose, [^{15}O]butanol, [^{11}C]methionine

Introduction

Radiation myelopathy is a rare, but extremely serious side-effect of radiotherapy. It may involve both the white and the gray matter, white matter involvement being the common form.[27,32,49,54,57,58] It typically occurs following the irradiation or reirradiation of cancers situated close to the spinal cord that are highly likely to be controlable by irradiation (e.g. malignant lymphomas, seminomas, or thyroid, laryngeal and nasopharyngeal cancers), or on the application of modern, high-dose radiotherapeutic protocols (e.g. for pulmonary, esophageal and head and neck cancers). The disease usually exhibits a chronic, progressive and irreversible clinical course.

Recovery from radiation-induced motor sequelae is rare: only 8 well-documented cases[14,16,17,21,37,61] have been published. In contrast, the regeneration of sensory losses is relatively frequent.[58] Among the sensory radiogenic injuries of the spinal cord, Lhermitte's sign (LS) is most frequent.

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Clinical aspects of Lhermitte's sign

LS was first described in a soldier who had suffered a head injury during World War I[43]. After this, the clinical entity was characterized by Lhermitte in conjunction with injuries and multiple sclerosis.[39,40] He noted that the symptomatology was most probably secondary to damage to the cervical spinal cord resulting in demyelination. The clinical latency period corresponded to the normal survival of the myelin, since damaged oligodendrocytes are not capable of carrying out myelin synthesis. As the oligodendrocytes recover, myelin synthesis is resumed and the resolved disease does not return. Lhermitte was first used as an eponym by Read.[53]

LS is characterized by a sensation similar to an electric shock passing down the spine in the cervico-caudal direction (it may also be felt in the upper and lower limbs). It is accompanied by a sense of intense pain, which is generally symmetrical (though sometimes asymmetrical), but never corresponds in distribution to the finite territory of any spinal dermatome. LS develops following flexion (principally) or extension of the vertebral column (mainly its cervical part), demonstrating the mechanosensitivity of the damaged (demyelinated) central and peripheral sensory axons.

LS is an early and typical sign of demyelination disorders, especially multiple sclerosis[29], but also of other diseases, e.g. radiogenic myelopathy,[2,6,10,17,18,28,38,42,45,59,62,71,75] spinal cord trauma,[1,11,36,39,43,63] epidural, subdural or intraspinal tumors[47,66] and spondylosis/discopathy.[60] It can be induced by chemotherapy, e.g. following the application of platinum and taxan compounds, cytosine arabinoside, busulfan and cyclophosphamide,[12,15,26,41,42,65,68,71] by a vitamin B_{12}[9] or thiamine deficiency,[9] low-dose pyridoxine toxicity,[50] nitrous oxide abuse,[5,35] cystinuria,[4] Behcet's disease[48] and herpes zoster.[67]

Characteristics of radiogenic Lhermitte's sign

LS was first reported as a phenomenon related to radiation myelopathy in 1948,[6] and in 1964 it was eloquently described, together with its temporal relationship to irradiation and posssible pathogenesis.[28] As opposed to multiple sclerosis, LS relating to other causes is a transient, self-limiting, benign disorder. The radiogenic cases typically manifest themselves 3 months following radiotherapy and gradually disappear within 6 months.[6,28] In 2 autopsied cases, Jones did not find any signs of pathological alterations in the cervical spinal cord by means of conventional tools.[28] Only the rare LS, manifested with a longer latency period, may forecast permanent spinal cord injury.[6,10,28] There have been only a few studies on large patient groups with LS, demonstrating a rate of occurrence of 3.6-13%, relating mainly to mantle irradiation[10,59,75] or the radiotherapy of head and neck tumors.[18,28] Only 3 LS cases have been described in the English literature with severe symptoms lasting for more than 1 year.[17,62]

Recently, we reported 2 cases of long-standing radiogenic LS[17]. During radiotherapy in these 2 nasopharyngeal cancer patients, a biologically effective dose (BED) of 103.8 Gy_2 (Case 1) or 94.8 Gy_2 (Case 2) was delivered to the cervical spinal cord. The BED was calculated according to the formula $BED = \{nd\ 1 + d/\alpha/\beta\}$, where $\underline{n}$ denotes the number of fractions, $\underline{d}$ the dose per fraction, and $\alpha/\beta = 2$ Gy presuming white matter injury in the cervical spinal cord (the parameter α/β, used in the linear-quadratic model of radiation damage, indicates a dose bringing about identical amounts of radiation-induced reparable and nonreparable damage).[20] Neurological signs relating to the irradiated spinal cord segments developed after 2 months (Case 1) or 5 years (Case 2), with radiation-induced damage equivalent to Grade 3 (Case 1) or Grade 2 (Case 2) toxicity (Common Toxicity Criteria, Version

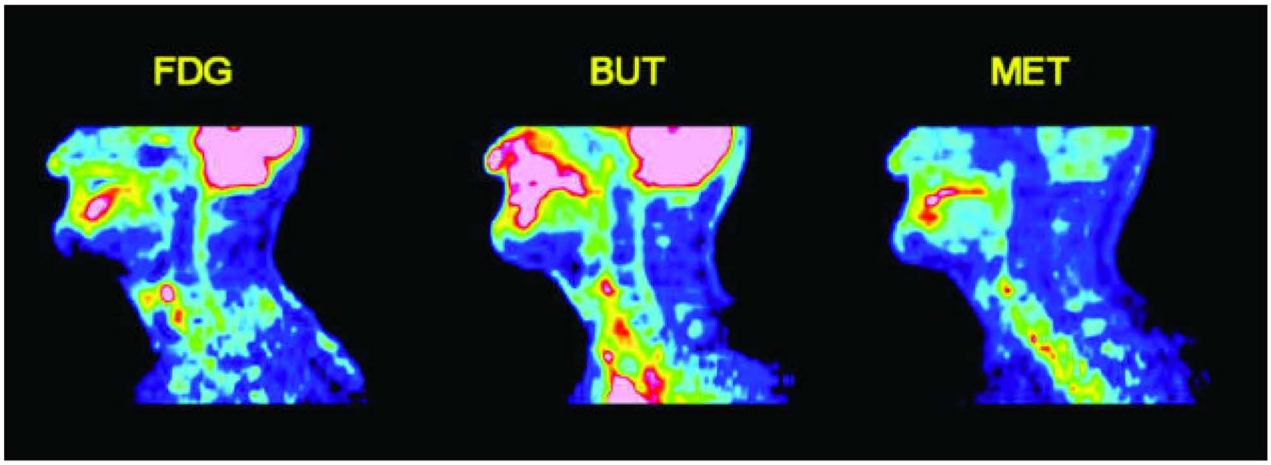

Figure 1. *PET examinations (median sagittal section of the head and neck region) of a patient with long-standing Lhermitte's sign.*

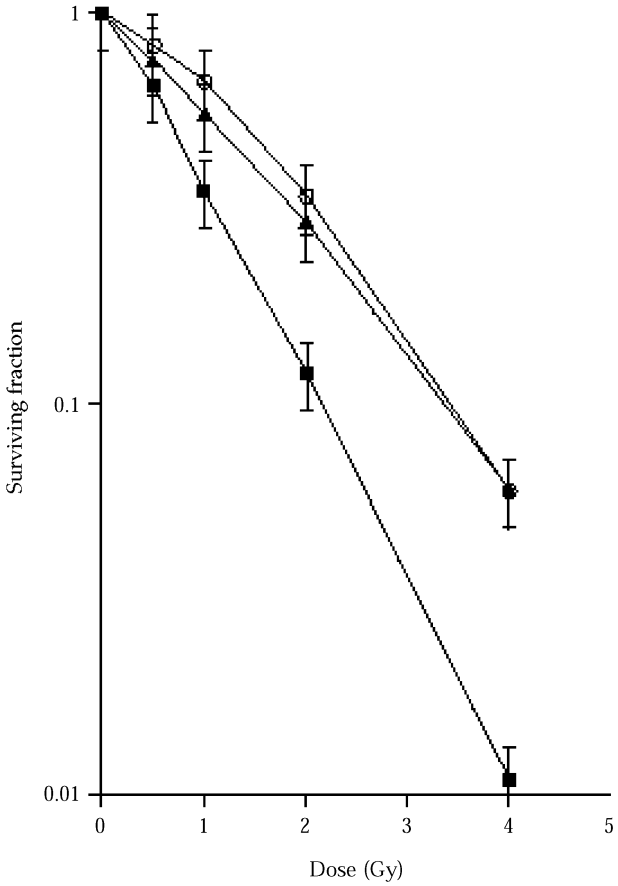

Figure 2. *Survival curves with standard deviation for primary fibroblasts cells of patients with long-standing Lhermitte's sign. Filled rectangles: fibroblasts from Case 1; filled triangles: fibroblasts from Case 2; open circles: average survival of fibroblasts from 6 healthy children.*

2.0).[46] The clinical status improved to Grade 2 (Case 1) or Grade 1 (Case 2). During the 25th and 7th postirradiation years, positron emission tomography (PET) demonstrated increased [^{18}F]fluorodeoxyglucose (FDG) accumulation and [^{15}O]butanol perfusion, but negligible [^{11}C]methionine uptake in the irradiated spinal cord segments in both patients (***Figure 1***). In clonogenic assays, fibroblasts from Case 1 displayed much higher radiation sensitivity than in healthy controls, while in Case 2 the fibroblast sensitivity was normal (***Figure 2***).

The most noteworthy features of the clinical courses of these patients were the complete clinical recovery from the motor injuries (Case 1), the incomplete regeneration of the sensory symptoms (Case 1), and the permanency of the LS (both cases). A high total physical dose and large daily fractions are known to be the most important factors promoting the development of late motor or sensory spinal cord injury.[58] Wong did not find radiation-induced white matter sequelae below a BED of 128 Gy_2[74] in his patient group; thus, the calculated BED of 103.4 and 94.8 Gy_2, respectively, for our patients[17] should not have meant a substantial risk of late motor and sensory losses.

Although LS belongs among the late spinal cord complications of radiotherapy, it exhibits a substantially different dose-effect curve from the motor or other sensory sequelae. The development of this symptom starts at around 30 Gy[6,28], and the most important risk factors for its manifestation[18,38] are a total dose of ≥50 Gy and a daily dose of ≥2 Gy (equivalent to a calculated critical BED of 100 Gy_2). The probability of occurrence of LS displays a shallow dose-effect curve,[18] as this probability is 3.3% or 8% with a total dose of <50 Gy or ≥50 Gy, respectively, while that with a fraction dose of <2 Gy or ≥2 Gy is 3.4% or 10%, respectively. These doses were exceeded in our published cases,[17] and the risk of the development of LS was therefore real.

Diagnostic imaging in chronic Lhermitte's sign cases

MRI, a sensitive tool in the detection of demyelination, earlier revealed signs of demyelination of the posterior cervical column only in multiple sclerosis[22] and in a single case of intraspinal tumor-related LS.[47] It failed to show any pathological sign accompanying LS caused by other disorders,[42,63,65] and we presume that these normal MRI findings may be related to the transient nature of the LS. We did not detect any pathologic MRI sign in our patients with long-standing LS either,[17] and thus we looked for another method to characterize this infrequent clinical picture. Since PET is a very sensitive tool with which to establish the functional status of different organs,[16,17,33,34,37,51,52,70] we thought that it might be of help in diagnosing permanent radiation myelopathic signs.

Few studies have been published on PET investigations of the spinal cord; this may be due in part to the low spatial resolution of PET cameras. The spinal cord normally has a very low FDG accumulation and a low [^{15}O]butanol uptake (***Figure 3***), because of the considerable proportion of white matter (with a low glucose consumption and perfusion) relative to the small bulk of the gray matter.[13,30,44,72,73] The spinal cord usually exhibits a rather low methionine uptake (***Figure 3***), in consequence of the slow cell turnover.[25,56,72]

Irreversible sequelae of radiation of the spinal cord have never been studied by using PET. Problems include the difficulty in the transportation of these patients and the low likelihood of useful consequences of the findings. In our partially reversible radiation myelopathic patients (including the 2 long-standing LS cases),[16,17,37] we described that recovery from radiogenic myelopathy was manifested in increased FDG and [^{15}O]butanol uptakes, but a negligible [^{11}C]methionine accumulation.

An elevated glucose metabolic rate can be a concomitant sign with cell division or inflammatory processes. The

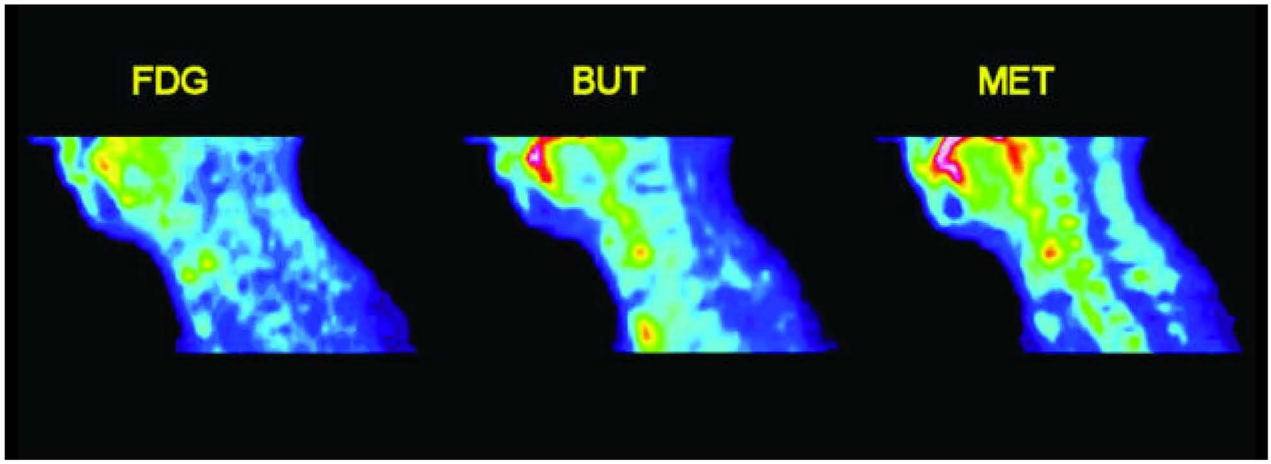

Figure. 3. *PET examinations of a reference subject not exposed to irradiation (median sagittal section of the head and neck region) reveal low FDG, [^{15}O]butanol and [^{11}C]methionine accumulation within the cervical spinal cord segments.*

irradiated parts of the spinal cord, however, did not exhibit a higher than background methionine accumulation, which was strong evidence against a significant cell proliferation. This is consistent with expectations: it would not be anticipated that the stabilization in the clinical state after the improvement during many years would still be accompanied by a restoration process involving intensive cell proliferation.

Inflammation is an energy-demanding process, and could therefore be a reason for an increased glucose consumption. We are inclined to assume, however, that years after the occurrence of the radiogenic lesions, inflammation would not make a substantial contribution, if any, to the increase in metabolic activity. The results of pathological studies[27,37,49,57,58] also argue against a substantial chronic inflammatory reaction in radiation myelopathy. A decreased FDG uptake[64] of the brain following high-dose radiation may support the argument that inflammatory reactions of glial and astrocytic elements of the spinal cord would probably not cause a considerable increase in FDG accumulation. Thus, the explanation of the increased glucose consumption may be based on other phenomena involving an augmented energy requirement.

Radiation damage brings about alterations in the molecular structure of the axon membrane, demyelination being one of the most pronounced changes.[27,32,37,49,54,57,58] After loss of the myelin sheath, the segments between the nodes of Ranvier, expressing sodium channels in low density, are exposed to the interstitial fluid. Demyelination of the axons results in a reduced speed of the action potential conduction. It is documented that a higher than normal density of sodium channels may restore conduction in some chronically demyelinated axons.[19,69] The modified molecular structure and conducting mechanism of these internodal segments give rise to an extra energy requirement. This is related to a larger displacement of intraaxonal ion concentrations during the propagation of the action potential as a consequence of the larger number of sodium channels involved in the conduction mechanism. The pumping-out of extra amounts of intracellular sodium against a concentration gradient can be accomplished only at the cost of extra energy consumption.

The assumption of a close coupling of the glucose utilization to the tissue perfusion in the spinal cord with its restored conduction could provide a full explanation for the observed increased blood flow in the radiation-damaged segments with their reconstituted function and increased glucose metabolism. Such an interrelationship would be very much the same as that already proved for the brain.[55]

Significance of radiobiological investigations

A common feature of the history of our LS patients was that their radiation-induced symptoms have persisted for many years, instead of their recovering within 6 months as usual. It is known that about 15% of the population have an increased radiosensitivity,[8] potentiating radiation sequelae. Thus, the question arises of whether an increased radiosensitivity might have contributed to the rare phenomena observed.

There is evidence that individual radiosensitivity can contribute to the development of radiation-induced toxic reactions.[3,23,24] A strong correlation has been found, for instance, between the clonogenic survival of cultured fibroblasts and also the radiation-induced DNA double-strand breaks in cultured fibroblasts and the late radiotherapy reactions of breast cancer patients[7,31]. The measured fibroblast radiosensitivity of our Case 1 was higher than that of Case 2, suggesting that this fact may have con-

tributed (besides the higher BED) to the differences between the two cases (more severe sequelae and the longer case history of Case 1). This seems probable, even if we are aware that the radiosensitivity of the fibroblasts may be used only as an estimate of that of oligodendrocytes or endothelial cells, as targets of radiation damage to the CNS.[23]

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