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Original Article

A PET study on the characterization of partially reversible radiogenic lower motor neurone disease

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Objective: To investigate the pathomechanism of the rare radiogenic lower motor neurone disease (LMND) on the basis of a case history involving a partial functional recovery.
Patient: A 31-year-old seminoma patient received postoperative para-aortic and para-iliac telecobalt irradiation with a biologically effective dose of 88 Gy_2 (44 Gy in 2 Gy fractions/day, with an estimated α/β of 2 Gy) delivered to the spinal cord following a single cycle of chemotherapy. LMND developed 4 months after the completion of radiotherapy. The patient exhibited flaccid paraparesis of the lower extremities (without sensory or vegetative signs), followed by a worsening after further chemotherapy, due to pulmonary metastatization. A gradual spontaneous functional improvement commenced and led several years later to a stabilized state involving moderately severe symptoms.
Methods: In the 15th year of the clinical course, magnetic resonance imaging (MRI) and positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG) and [^{11}C]methionine were conducted. Four lines of experiments (clonogenic assay using fibroblasts isolated from a skin biopsy sample of the patient, comet assay, micronucleus assay, and the testing of chromosome aberrations after *in vitro* irradiation of peripheral blood samples) were performed in a search for an increased individual radiosensitivity.
Results: MRI investigations failed to reveal any pathological change. PET demonstrated an increased FDG accumulation, but a negligible [^{11}C]methionine uptake in the irradiated spinal cord segments. The radiobiological investigations did not indicate any sign of an increased individual radiosensitivity.
Conclusions: We suggest that the observed partial functional recovery and stabilization of the symptoms of radiogenic LMND may be explained by the higher than normal density of sodium channels expressed along the demyelinated axons of the restored conduction. The increased energy demands of this type of conduction are proved by a higher metabolic rate (increased FDG uptake) of the irradiated spinal cord segments without a substantial regenerative process (lack of detectable protein synthesis).
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Keywords: lower motor neurone disease; irradiation; chemotherapy; functional recovery of conduction; positron emission tomography; sodium channels

Introduction

Radiation myelopathy is a rare, but most feared complication of radiotherapy. It may affect both the white and the grey matter, white matter involvement being the more common.[1–7] The clinical picture of the rare grey matter injury involves radiogenic lower motor neurone disease (LMND), ie flaccid paresis due to the motor neurones situated in the anterior horn of the spinal cord. It may accompany a predominant radiogenic white matter injury (demyelination and/or ischaemic vascular injury) with spastic motor, sensory and vegetative losses. In these cases, the grey matter injuries are manifested primarily in the

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upper limbs.[1–4,8,9] Radiogenic LMND, however, is mainly reported as the only sign of the radiation injury[10–28] and in these situations it involves basically the lower extremities of young, testicular cancer patients exhibiting a chronic, progressive and irreversible clinical course.

In this communication, we report on the 16-year history of a patient who displayed a partial, but significant functional recovery from radiogenic LMND, including results of positron emission tomography (PET) and radiosensitivity examinations.

Case report

The case history of the 31-year-old man involves previous pleural tuberculosis (medication with streptomycin, isoniazid and pyrazinamide between 1974 and 1976) and a motocycle accident (1977, concussion). He was hemicastrated for left-sided classical seminoma in stage pT2 N0 M0 in 1985. Postoperative lymphography revealed no lymph node metastases below the diaphragm. During the first postoperative month, the patient received one cycle of chemotherapy (Vincristine 4 mg, Adriamycin 80 mg, Cyclophosphamide 2400 mg, Cis-platinum 80 mg and Bleomycin 60 mg, subdivided into four identical weekly doses). Adjuvant telecobalt irradiation was initiated on the penultimate day of chemotherapy, with the intention of treating the abdominal para-aortic and left para-iliac lymphatic regions with a maximum midplane dose of 44 Gy, using anterior and posterior portals daily (2 Gy/day, five times a week). A biologically effective dose (BED) of 88 Gy_2 was calculated for our patient according to Fowler[29] as $BED = nd\,[1 + d/\alpha/\beta]$, where n denotes the number of fractions, d is the dose per fraction and α/β was estimated as 2 Gy (parameter α/β, used in the linear-quadratic model of radiation damage, indicates a dose bringing about identical amounts of radiation-induced reparable and non-reparable damage).

Subsequent to initial leg pain, a moderately severe flaccid paraparesis (with a distal and right-sided predominance) due to the injuries to spinal cord segments Th 12–S 2 (equivalent to vertebral bodies Th 10–12 and L 1) started gradually to develop 4 months following the completion of radiotherapy. The most marked signs were those relating to spinal cord segments L 4–5 and S 1, which resulted in muscle atrophy in 6 weeks. Electroneuronography (ENG) revealed no obvious sign of diminished peripheral motor conduction velocity, as the mean conduction velocity was 42.2 m/s on the right, and 45 m/s on the left peroneal nerve (normal value 45 m/s). Electromyography was performed on the right and left quadriceps muscles, the anterior tibial muscle and the triceps muscle on the calf and resulted in diffuse peripheral neurogenic lesions with fibrillation. The motor symptoms were not accompanied by vegetative or sensory signs (the patient had only a mild paretico-atactic gait for several weeks). Lumbar CT and myelography during the initial phase of the neurological symptoms did not demonstrate any pathological alteration. The CSF findings were insignificant: 24/3 mL leucocytes and a total protein content of 0.5 g/L. No sign of acute viral infection was observed.

Pulmonary dissemination (two foci measuring about 2 cm) developed 6 months after irradiation, and a new cycle of chemotherapy was started (Vepesid 750 mg, Cis-platinum 175 mg and Adriamycin 60 mg). Following the first cycle, the signs of flaccid paraparesis worsened, and the patient experienced difficulties in locomotion: he had to use two canes. With regard to the life-threatening consequences of the metastatization, four more cytostatic cycles were applied. During this period, the patient received vitamins B_1 and B_6, and high-dose steroids (without any objective signs of improvement). Following termination of the chemotherapy, a gradual spontaneous improvement was observed within several months and continued over a period of years, leading finally to stabilized symptoms.

The patient is currently ambulatory (without any aid) and has a job, but he experiences moderately severe flaccid paraparesis and muscle atrophy of the legs. In the 16th year of the clinical course (April, 2002), ENG revealed obvious signs of a diminished peripheral motor conduction velocity: zero in the right and left peroneal nerves and diminished in the right (41.5 m/s) and left (37.7 m/s) posterior tibial nerves, with decreased amplitudes (4.3 mV and 3.5 mV, respectively). At the same time, normal sensory conduction velocities were found bilaterally in the peroneal nerves. The sensory and motor conduction proved to be normal in the right and left median and ulnar nerve.

Methods

Diagnostic imaging of the whole spinal cord was performed in the 15th year following the completion of radiotherapy. Magnetic resonance imaging (MRI) was carried out with a 1.5 Tesla equipment (SYMPHONY; Siemens Medical Solutions, Erlangen, Germany). PET examinations were conducted with a GE 4096 Plus camera (General Electric, Uppsala, Sweden). Following a transmission scan, metabolic maps of the tracers [^{18}F]fluorodeoxyglucose (FDG), [^{11}C]methionine and [^{15}O]butanol (flow tracer) were detected.

Four lines of experiments were performed in order to check whether individual radiosensitivity played a role in the development of the myelopathy. Fibroblasts isolated from a skin biopsy sample of the patient were irradiated in a clonogenic assay[30] with different doses of radiation and the survival was followed. The corresponding clonogenic survival of six primary fibroblast cultures isolated from foreskin samples from healthy children served as controls.

In the second set of experiments, a single-cell electrophoresis (comet) assay was used to estimate the individual radiosensitivity.[31] Whole blood was irradiated with a 2 Gy γ-radiation dose, and comet

analysis was performed either directly after irradiation to measure the initial DNA damage or 4 h later to allow time for DNA repair and to determine the residual damage. Comet moments were compared with the corresponding patterns for 20 samples collected from healthy individuals (Komet Analysis System software package, Kinetic Imaging Ltd., Liverpool, UK).

The spontaneous and the 2 Gy γ-irradiation-induced micronucleus frequencies were measured in a micronucleus assay[32] and compared with controls.[33,34] Finally, the presence of chromosome aberrations was studied after *in vitro* irradiation of peripheral blood samples[35] and compared with controls.

Results

MRI failed to show any pathological signs. The FDG PET examination indicated an increased uptake within the lower thoracic and lumbar spinal cord (Figure 1), while [^{11}C]methionine PET investigation resulted in no tracer uptake in either the irradiated or the non-irradiated segments of the spinal cord. No methionine uptake was found in the location of Th 10–12 and the lumbar vertebral bodies, in accordance with the boundaries of the radiation portal (Figure 2). [^{15}O]Butanol PET examination did not furnish interpretable results because of the increased renal blood flow.

The radiation sensitivity of the fibroblasts of the LMND patient was in the same range as for the controls (about 80, 60, 28 and 5% clonogenic survival after irradiation with 0.5, 1.0, 2.0 and 4.0 Gy ^{60}Co-γ radiation, respectively). In the comet assay, no essential differences in the initial damage were detected and the DNA repair was complete after 4 h. In the micronucleus assay, the spontaneous micronucleus frequency was slightly higher in the LMND patient (39 micronuclei *versus* 16 ± 8 in 1000 binucleated cells) than in historical controls.[33] After irradiation with 2 Gy γ-radiation, the micronucleus frequency was elevated to 236 per 1000 cells, which was in the same range as for the controls.[34]

In the chromosome aberration studies after *in vitro* irradiation of peripheral blood samples, the mitotic index was very poor after phytohaemagglutinin induction and colcemid arrest. In two separate experiments, we scored only 41 and 100 metaphases, respectively in the unirradiated samples of the patient. Nevertheless, the number of chromosome aberrations was very high (4 and 7% aberrations, respectively) relative to that for controls (3%) in our laboratory. In the first experiment, one acentric fragment, one minute chromosome, one deletion and one translocation were detected. In the second experiment, one cell contained dicentric and corresponding acentric fragments. In separate cells, we also scored two acentric fragments and four deletions. Unfortunately, we did not receive a sufficient number of metaphasic cells after the 2 Gy irradiation.

Discussion

Our male patient had a case history that was very similar to those published in the literature. He was 31 years old at the time of the diagnosis of his testicular cancer, and only flaccid paralysis developed in his lower extremities, without sensory or vegetative signs. To date, he is the only testicular cancer patient diagnosed with radiogenic LMND at the National Institute of Oncology (NIO), Budapest, although the NIO has been the centre for the treatment of Hungarian testicular cancer patients since the early 1980s. During this period, about 7000 seminoma and non-seminoma patients (95% of all such cases in Hungary) have been treated here. All these patients have been actively followed up, and thus we can reinforce that this disease really is a rare entity.

The noteworthy feature in the clinical course of this patient was the partial recovery from the LMND. Recovery from grey or white matter motor injuries is a rare event: only eight[11,13,21,25,26] and seven[8,36–38] well-documented cases, respectively, have been published. MRI does not seem to be an effective tool for the characterization of radiogenic LMNDs, as MRI yields anatomical data on this disease that are similar to those on healthy subjects.[11,12,14,22,27]

Results of ENG measurements unequivocally refer to residual damage of the spinal cord still existing in the partially recovered state. While the values of the measured functional parameters of the sensory neurones and axons were identical to those characteristic for the physiological state, nerve conduction studies disclosed a decreased conduction velocity of the motor action potential, together with a diminished amplitude of the action potential. The simultaneous decreased values of these parameters clearly indicate that the number of functioning axons is reduced and segmental demyelination has occurred. For a deeper insight into the underlying process and possible mechanism, we decided to apply a functional imaging modality, and to use PET to explore differences in the tissue biochemistry of the sequeled spinal cord.

Only a few reports have been published on PET investigations of the spinal cord;[8,39–41] this might be connected in part with the low spatial resolution of PET cameras. The spinal cord normally displays a very low FDG accumulation, because of the considerable proportion of white matter with a low FDG uptake as compared with the small bulk of the grey matter,[8,39,40] and a rather low methionine uptake, in consequence of the slow cell turnover and protein synthesis.[8,41]

In a set of previous investigations,[8] we applied the PET method to study a case of reversible radiation myelopathy with initial prominent white matter injuries (spastic paraplegia in the legs, and spastic paresis in the left arm) and mild grey matter sequelae (muscle atrophy in the left hand). In that study, which to the best of our knowledge is the only one to date on the regional tissue perfusion of the spinal cord, we

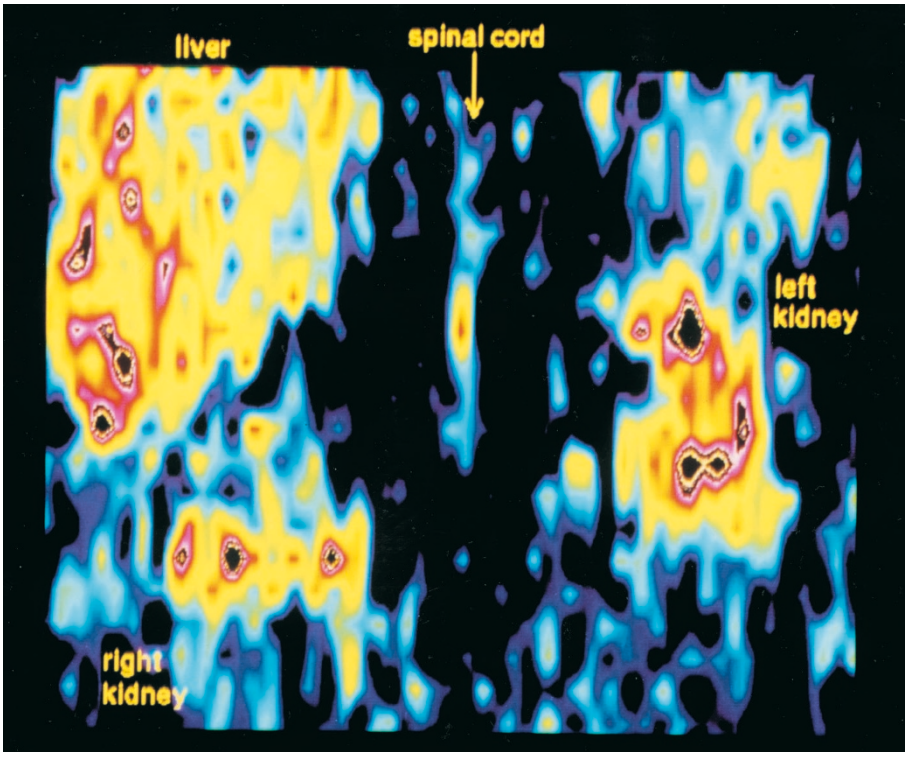

Figure 1 FDG PET examination (coronal section of the upper abdomen) reveals an increased FDG uptake within the irradiated lower thoracic and upper lumbar spinal cord segments

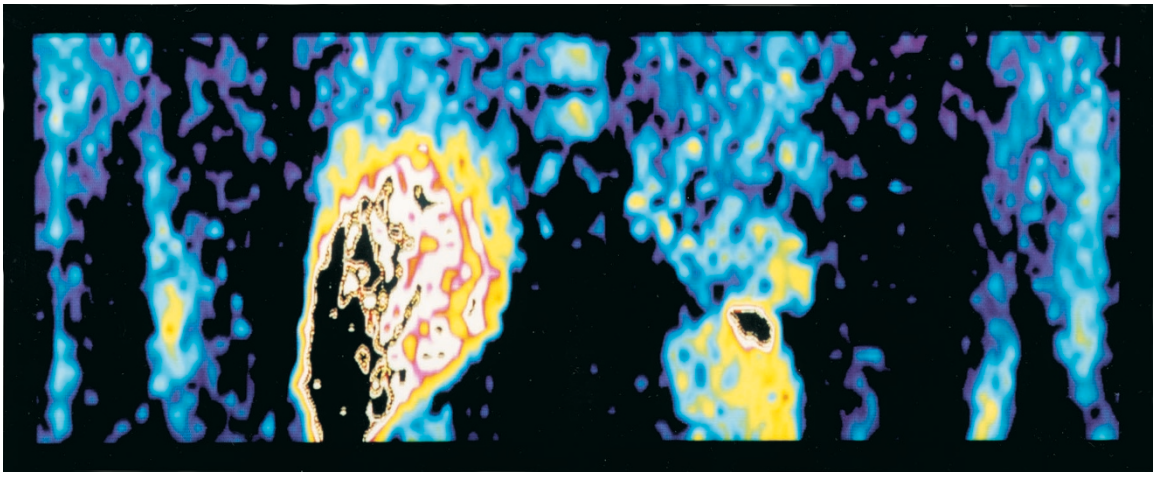

Figure 2 Methionine PET examination (coronal section of the upper abdomen) reveals no tracer uptake in the bone marrow of Th 10–12 and the lumbar vertebral bodies

found that recovery from radiogenic myelopathy was manifested in increased FDG and [^{15}O]butanol uptakes, but a negligible [^{11}C]methionine uptake within the irradiated (cervical) spinal cord segment. Our data were suggestive of a close direct relationship between the regional spinal cord blood flow and the regional spinal cord metabolism, very much like the situation in the brain.[42] In the irradiated lower thoracic and lumbar spinal cord segments of our seminoma patient with LMND who exhibited a partial functional recovery, we also observed an increased FDG uptake, but a negligible [^{11}C]methionine uptake (the [^{15}O]butanol study could not be interpreted).

An elevated glucose metabolic rate can be a concomitant sign with cell division or inflammatory processes. The irradiated part of the spinal cord, however, did not have a higher than background methionine accumulation, which was strong evidence

against a significant cell proliferation (eg tumorous process, regenerative cell division, etc.). This is consistent with expectations, as it is not to be anticipated that a 15-year uninterrupted improvement and stabilization of the clinical state would be followed by a restoration process accompanied by intensive cell proliferation.

Inflammation is an energy-demanding process, and could therefore be a reason for an increased glucose consumption. However, we do not believe that inflammation makes a substantial contribution, if any, to the increase in metabolic activity detected 15 years after the occurrence of the lesion. First of all, the results of pathological studies[10,11,26] argue against a substantial inflammatory reaction in LMND. Secondly, a decreased FDG uptake[43] of the brain following high-dose irradiation 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 involve other phenomena with augmented energy requirements.

Radiation damage brings about alterations in the molecular structure of the axon membrane, demyelination being one of the most pronounced changes.[1–3,6,7] 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. Having lost the myelin sheath, the axons display action potential conduction at a reduced speed. Conduction can be restored in some chronically demyelinated axons that acquire a higher than normal density of sodium channels.[44,45] The modified molecular structure and conducting mechanism of these internodal segments give rise to an extra energy requirement, as a larger number of sodium channels allows a larger displacement of intraaxonal ion concentrations during the propagation of the action potential. The pumping-out of extra amounts of intracellular sodium against a concentration gradient will demand an increased amount of energy.

During the radiotherapy of our patient, the total dose (44 Gy), the daily dose (2 Gy) and the BED (88 Gy_2) were below the usual threshold doses for radiation injury,[7] and we were not able to demonstrate any further obvious radiotherapeutic circumstances potentiating the development of a radiogenic complication.

Chemotherapy applied before radiotherapy may be an exciting agent of a potential contribution to the development of radiation injury.[7] It is well documented, however, that intensive chemotherapy for a year is needed to diminish the threshold dose of radiogenic myelopathy in a combined therapy to 40.3 Gy.[46] Our patient received only one conventional cycle of chemotherapy, and it therefore seems unlikely that this was a crucial factor. The worsening of the LMND following the second course of chemotherapy, however, indicates the role of cytostatics in the progression of the neurological sequelae. Interestingly, we detected an increased number of chromosome aberrations in this patient after 15 years. The persistence of these aberrations might be a consequence of the combined radio- and chemotherapy, but the possibility of more recent genotoxic damage cannot be ruled out.

The road accident and isoniazid-related peripheral neuropathy cannot be regarded as additional risk factors, as they occurred in the distant past (about 10 years previously). The possibility of an increased individual radiosensitivity was ruled out by means of different radiobiological investigations. Thus, without evident promoting factors for the development of radiogenic LMND in our case, we hypothetize that it may be related to additional precipitating factors, eg a subclinical viral infection or other unknown causes. The outlined interpretation should be regarded as speculative and its validation requires additional evidence.

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