

## Original Article

# Characteristics of radiogenic lower motor neurone disease, a possible link with a preceding viral infection

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**Objective:** To investigate the pathogenesis of the rare radiogenic lower motor neurone disease (LMND) on the basis of a meta-analysis of the published case histories.

**Materials and methods:** The authors reviewed 47 well-documented radiogenic LMND cases from the English literature.

**Results:** The disease typically occurs following the irradiation of radiosensitive cancers situated near the spinal cord. It arises predominantly (46 cases) in the lower extremities; only one case involved the upper extremities. There is a male predominance (male:female ratio 7.8:1), and the patients are characteristically young (13–40 years, with four exceptions). An overdose does not seem to be a particular risk factor for the development of the disease, as total dose, fraction size and biologically effective dose are typically below 50 Gy, 2 Gy and 128 Gy<sub>2</sub>, respectively, which are regarded as safe doses. Other risk factors (chemotherapy, operations, etc) have been identified only rarely. Radiogenic LMND is manifested in an apparently random manner, 4–312 (mean 48.7) months after the completion of radiotherapy.

**Discussion:** The complete lack of a dose–effect relationship argues strongly against a pure radiogenic nature of the pathological process. The latency period is typically several years and it varies extremely, which excludes a direct and complete causal relationship between radiotherapy and LMND. As the interaction of ionizing radiation with living tissues is highly unspecific, thus a selective motor injury due to irradiation alone, without comparable effects on the sensory and vegetative fibers, seems improbable.

**Conclusions:** On analogy with the viral motor neurone diseases, we suppose that radiogenic LMND may be preceded by viral (enterovirus/poliovirus) infection. Based on the meta-analysis, it is suggested that irradiation may be only a single component of the set of factors jointly resulting in the clinical state regarded as radiogenic LMND.

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**Keywords:** lower motor neurone disease; irradiation; chemotherapy; viral infection

## Introduction

Radiation myelopathy is a rare complication of radiotherapy that may affect both the white and the gray matter.<sup>1–7</sup> The clinical picture of the less frequently documented gray matter injury comprises radiogenic lower motor neurone disease (LMND), that is, flaccid paresis due to damage to the motor neurones situated in the anterior horn of the spinal cord. It may also accompany a predominant radiogenic white matter injury (demyelination and/or ischemic vascular injury)

with spastic motor, sensory and vegetative losses. In these cases, the gray matter injuries are manifested primarily in the arms.<sup>1–4,8,9</sup> In most cases of radiogenic LMND, however, the only clinical sign of the radiation injury<sup>10–29</sup> is the flaccid paresis. The disease involves basically the legs, exhibiting a chronic, progressive and irreversible clinical course.

## Materials and methods

The authors reviewed English literature data on the rare LMND. To exclude cases other than exclusively flaccid

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paresis, a complete neurological case history was a prerequisite for inclusion: only 47 such well-documented radiogenic LMND cases (Table 1) were found.<sup>10–29</sup> Successive publications often included previous case reports; accordingly, only the latest publications are listed.

## Results

Radiogenic LMND (Table 1) typically occurs following the irradiation of radiosensitive cancers situated near the spinal cord (eg testicular cancers or malignant lymphomas). It arises predominantly (46 cases) in the lower extremities; only one case<sup>29</sup> involved the upper extremities. There is a male predominance (male:female ratio 7.8:1), and the patients are characteristically young (13–40 years, with four exceptions). An overdose does not seem to be a particular risk factor for the development of the disease, and other risk factors (chemotherapy, operations, etc) have been identified only rarely. Radiogenic LMND is manifested in an apparently random manner, 4–312 (mean 48.7) months after the completion of radiotherapy.

Radiogenic LMND is considered an independent clinical entity, but many of its features are reminiscent of those of classical radiogenic myelopathy (CRM), acute viral (poliovirus, enterovirus 70 or 71, or coxsackievirus A7 or A9) or late viral LMNDs (postpolio syndrome (PPS)). PPS develops many years after acute, paralytic poliomyelitis, and presents as a new onset of weakness, fatigue, fasciculation and pain, with additional atrophy of muscle groups involved or not during the initial paralytic disease.<sup>30–32</sup> The two types of radiogenic myelopathy undoubtedly have a number of common features, but at the same time an appreciably higher number of dissimilarities, as will be shown below (Table 2).

One of the most interesting peculiarities of radiogenic LMND is the surprisingly low dose involved (Table 1) as compared with those leading to CRM. A majority of the former patients were treated in a single irradiation series with the total dose, fraction size and biologically effective dose typically below 50 Gy,<sup>7</sup> 2 Gy<sup>7</sup> and 128 Gy<sub>2</sub>,<sup>33</sup> respectively, which are regarded as safe doses. LMND has even been observed with a total dose as low as 24 Gy.<sup>28</sup> In the four reirradiated patients, the initial doses were 46, 36, 30 and 25 Gy, respectively, the reirradiation courses took place 2 or more years later and the cumulative doses were 80, 68.4, 55 and 55 Gy, respectively.<sup>17,20,27,28</sup> These doses are not high in light of retreatment tolerance data on the monkey spinal cord: following an initial dose of 44 Gy and an elapsed time of 3 years, the recovery is 61–100% of the initial dose with respect to a 5% probability of the occurrence of radiation injury.<sup>34</sup>

An additional striking finding of the meta-analysis of the published data is the complete lack of a dose–effect relationship in radiogenic LMND (Table 1), in marked contrast with CRM. Radiogenic LMND seems to be the only radiation-induced phenomenon without a definite

dose–effect inter-relationship. This argues strongly against a pure radiogenic nature, although irradiation definitely can promote the development of this disease.

Radiogenic LMND and the two types of virus-related LMND express exclusively motor symptoms, with flaccid paresis interpreted as a consequence of gray matter injury only (Table 2). In the four autopsied cases of radiogenic LMND,<sup>10,11,27</sup> the characteristic pathological feature was lower motor neurone degeneration. A low extent of demyelination in the anterior and posterior column<sup>10,27</sup> and cauda equina<sup>10</sup> (without consecutive clinical symptoms) was also observed. The acute and late viral LMNDs also involve injured motor neurones and subtle demyelination,<sup>30,35</sup> but the related autopsy did not reveal sensory neurone injuries. CRM expresses extensive demyelination of all axon types, but neuronal sequelae seldom occur in this disease,<sup>1–3,6,7</sup> which accords with the known lower radiosensitivity of the gray matter as compared with that of the white matter.<sup>1–3</sup>

The lack of sensory and vegetative signs in radiogenic LMND is similar to the finding in both types of viral LMND. The almost exclusive motor neurone damage requires an explanation, as the interaction of ionizing radiation with living tissues is highly unspecific, and a selective motor injury due to irradiation alone, without comparable effects on the sensory and vegetative fibers, seems improbable. Irradiation of the monkey spinal cord caused radiation-induced damage within the whole irradiated segment, as expected.<sup>34,36</sup> No radiogenic LMND cases have been published on laboratory animals and no animal model exists for radiation-induced motor signs only.

Radiogenic LMND displays a lumbar predominance (Table 1), whereas CRM is observed mainly in a cervical and/or thoracic location,<sup>1,3–7,37</sup> the latter explained by the more frequent radiotherapy indication in this location. The outlined dissimilarity suggests that factors different from the radiation dose may additionally contribute to the development of radiogenic LMND. It is worthy of interest that acute viral LMND is also characterized by a lumbar predominance, with a suggested argument that provocation by frequent and intensive muscle work plays a decisive role in the development of the disease.<sup>30</sup> It might be speculated that this too may be a factor contributing to the typical lower extremity manifestation of radiogenic LMND.

Radiogenic LMND occurs more frequently in males (Table 1), in contrast with CRM and viral LMNDs, which display a 1:1 female:male ratio. The male dominance in radiogenic LMND relates to testicular tumor being the main indication of abdominal para-aortal irradiation. Excluding testicular cancer cases, the male/female ratio for the published cases of radiogenic LMND is 1:1 (Table 1).

The age of the patients varies appreciably but those with CRM are generally older (probably because of the increasing incidence of malignant tumors with age), whereas for radiogenic (Table 1) and viral LMNDs young and middle-aged subjects predominate. The time

**Table 1** Reported cases of radiogenic lower motor neurone disease

Author	No. of cases/ gender	Age	Diagnosis	Estimated radiation dose to the spinal cord (Gy)	Daily dose/ fraction (Gy)	Additional risk factors	Latency (months) from completion of radiotherapy
<i>Lower limbs (following lumbar radiotherapy)</i>							
Berlit <i>et al</i> <sup>10</sup>	1 F	47	Breast carcinoma Lumbar metastasis	38	2	None	9
Bowen <i>et al</i> <sup>11</sup>	1 M	21	Seminoma	40	1.7	None	48
	2 M	22	Nonseminoma	44.6	7.4	None	168
	3 M	23	Nonseminoma	46	1.8	Chemotherapy	36
	4 M	50	Seminoma	49.6	2.2	None	132
	5 M	37	Nonseminoma	44	1.8	None	120
	6 M	26	Nonseminoma	48.5	2.0	None	312
de Carolis <i>et al</i> <sup>12</sup>	1 M	64	Pheochromocytoma	<58	NS	Abd.operation	7
de Greve <i>et al</i> <sup>13</sup>	1 M	57	Hodgkin's disease	40	2	None	21
Ésik <i>et al</i> <sup>14</sup>	1 M	31	Seminoma	44	2	Chemotherapy	4
Feistner <i>et al</i> <sup>15</sup>	1 M	34	Testicular tumor	48	2	RLA	36
	2 M	39	Seminoma	45	2.5	None	30
	3 M	NS	Testicular tumor	46	1.7	None	108
Gallégo <i>et al</i> <sup>17</sup>	1 M	34	Primary Lumbar bone NHL	46+ 34	2 2.5	Two irradi. series (6 years)	13
	1 M	26	Nonseminoma	49.2	1.4	Hypertension	276
Grünwald <i>et al</i> <sup>19</sup>	1 M	33	Seminoma	25+	NS	Two irradi. series (2 years)	
Horowitz and Stewart <sup>20</sup>				30		RLA, 9 g CTX	9
Katirji <sup>21</sup>	1 F	40	Kidney tumor	~36	~1.5	None	120
Kristensen <i>et al</i> <sup>22</sup>	4 M	19	Nonseminoma	53.2	2	None	4
Lamy <i>et al</i> <sup>23</sup>	1 M	32	Hodgkin's disease	40	NS	Chemotherapy	108
	2 M	30	Seminoma	30	NS	None	120
	3 F	26	Hodgkin's disease	40	NS	Chemotherapy	16
Maier <i>et al</i> <sup>24</sup>	1 M	21	Testicular tumor	43	≤2	For the group: one field/ day irradiation	64
	2 M	31	Testicular tumor	35.1	≤2	For 14 patients:RLA	27
	3 M	38	Testicular tumor	48.1	≤2		15
	4 M	25	Testicular tumor	41.5	≤2		7
	5 M	33	Testicular tumor	45.9	≤2		156
	6 M	35	Testicular tumor	42.5	≤2		12
	7 M	29	Testicular tumor	35.7	≤2		12
	8 M	28	Testicular tumor	48.5	≤2		13
	9 M	22	Testicular tumor	44.2	≤2		12
	10 M	24	Testicular tumor	35.2	≤2		12
	11 M	20	Testicular tumor	48	≤2		6
	12 M	27	Testicular tumor	56.8	≤2		12
	13 M	19	Testicular tumor	36.5	≤2		9
	14 M	24	Testicular tumor	53.1	≤2		4
	15 M	25	Testicular tumor	54	≤2		12
Sadowsky <i>et al</i> <sup>25</sup>	1 F	15	Medulloblastoma	38	<1.8	None	11
Schiødt and Kristensen <sup>26</sup>	8 M	31	Nonseminoma	57 <sup>a</sup>	2	None	23

Table 1 (continued)

Author	No. of cases/ gender	Age	Diagnosis	Estimated radiation dose to the spinal cord (Gy)	Daily dose/ fraction (Gy)	Additional risk factors	Latency (months) from completion of radiotherapy
	9 M	35	Nonseminoma	57 <sup>a</sup>	2	None	26
	10 M	33	Nonseminoma	57 <sup>a</sup>	2	None	12
	11 M	24	Nonseminoma	57 <sup>a</sup>	2	None	10
	12 M	25	Nonseminoma	55 <sup>a</sup>	2	None	14
Schild <i>et al</i> <sup>27</sup>	6 F	23	Hodgkin's disease	35	NS	None	36
	7 M	38	Hodgkin's disease	44	NS	None	12
	8 M	33	Hodgkin's disease	30+	NS	Two irradi. series (4 years) Chemotherapy	24
Tallaksen <i>et al</i> <sup>28</sup>	1 M	26	Seminoma	36+	2	Two irradi. series (3 years)	10
Upper limbs (following cervical radiotherapy) Tan and Pye <sup>29</sup>	1 F	13	T-cell ALL whole brain and C 1-3	32.4	2 × 0.9	Chemotherapy	42

+, refers to two irradiation series; ALL, acute lymphoid leukemia; C, cervical; CTX, cyclophosphamide; NHL, non-Hodgkin's lymphoma; NS, not stated; RLA, retroperitoneal lymph node dissection.

<sup>a</sup>Doses taken from the publication by Kristensen *et al.*<sup>26</sup>

between irradiation and CRM onset is around 12 months (range 3–48 months).<sup>1,3,5-7,37</sup> The latency period in radiogenic LMND is typically several years (mean 48.7 months), and it varies extremely (Table 1), which excludes a direct and complete causal relation between radiotherapy and LMND.

The central and peripheral motor conduction velocities (Table 2), as measured within the involved regions, may be normal in different phases of radiogenic LMNDs,<sup>11,13,15,17,19,20,21,23,25,27-29</sup> acute poliomyelitis<sup>30</sup> and PPS.<sup>38</sup> In contrast, the central and peripheral conduction velocities are both diminished in CRM.<sup>39,40</sup> The functional deficit in the latter disease is always assigned to the irradiated segment. In radiogenic LMND<sup>11,23,29</sup> and PPS,<sup>31,35,38</sup> however, special functional deficits may also develop, which relate to asymptomatic regions previously.

CRM is very different from the other three diseases in often being fatal, whereas radiogenic and viral LMNDs usually display a benign, stable character (Table 2). Steroid therapy (Table 2) is contraindicated in acute poliomyelitis,<sup>8</sup> and ineffective in radiogenic LMND<sup>10,20,22,27</sup> and PPS,<sup>41</sup> but it may have a favorable effect in the acute phase of CRM.<sup>7</sup> These findings accord with immunosuppression by the steroids (a significant handicap during an acute viral infection), and the lack of acute inflammation in radiogenic LMND<sup>10,11,27</sup> and PPS.<sup>30,35</sup> The three LMNDs all behave similarly in not displaying any ischemic vascular lesion<sup>10,27,30,35</sup> (Bowen observed extensive vasculopathy in an autopsied radiogenic LMND case, but this was probably related to the widespread arteriosclerosis<sup>11</sup>), whereas CRM often exhibits these pathological features.<sup>1,2,3,6,7</sup>

### Discussion

Although PPS is thought to be related to the progressive dysfunction and loss of motor neurones,<sup>38</sup> but the role of a histopathologically proven persisting virus<sup>32,42-45</sup> or an immune-mediated phenomenon<sup>32</sup> within the spinal cord are also possibilities. Interplay of these possible mechanisms cannot be discounted, as enterovirus/poliovirus RNA sequences have been identified by PCR in muscle biopsy<sup>42</sup> and CSF samples<sup>42-45</sup> from PPS patients, and immune reaction products too have been detected.<sup>32</sup>

On analogy with these assumed mechanisms, we suppose that radiogenic LMND may be preceded by viral infection. We suggest that special conditions comprising persisting enterovirus/poliovirus and additional disturbing/provocative factors may lead to the development of the disease. This suggestion may be supported by the following arguments. Similar to irradiation, chemotherapy can conduce to a clinical picture identical to that of radiogenic LMND. It has been described in Hodgkin's disease patients after chemotherapeutic regimens,<sup>27,46-48</sup> and in a non-Hodgkin's lymphoma patient vaccinated with poliovirus just before chemotherapy.<sup>49</sup>

**Table 2** Comparisons of radiogenic LMND, viral (acute and late) LMNDs and classical radiogenic myelopathy

	<i>Radiogenic lower motor neurone disease</i>	<i>Post-polio syndrome</i>	<i>Acute poliomyelitis-like viral infection (with paralysis)</i>	<i>Classical radiogenic myelopathy</i>
Irradiation dose dependence	Not observed	Not relevant	Not relevant	Yes
Onset	Insidious	Insidious	Acute	Insidious
Clinical signs	Exclusively motor (flaccid paresis)	Exclusively motor (flaccid paresis)	Exclusively motor (flaccid paresis)	Motor (spastic, plus rarely flaccid) sensory, vegetative
<b>Pathology</b>				
Anterior horn motor neurone injury	Always	Always	Always	Sometimes
Demyelination	Yes	Yes	Yes	Pronounced
Ischemic vasc. injury	No	No	No	Yes
Inflammatory cells	Chronic	Chronic	Acute	Chronic
Animal model	No	No	Yes	Yes
Typical spinal cord location	Mainly lumbar	Uniform	Slight lumbar predominance	Cervical and thoracic
Female:male ratio	Male predominance	1:1	1:1	1:1
Age of patients	13–40 years	Middle-aged or older	Young or middle-aged	Older
Typical time elapsed after irradiation	Very variable (4 months–26 years)	Not relevant	Not relevant	12 months (3–48 months)
Peripheral motor conduction velocity	May be normal	May be normal	May be normal	Diminished
Spinal cord motor conduction velocity	May be normal	May be normal	May be normal	Diminished
Consistency to the originally injured segments	Not always	Not always	Consistent	Consistent
Lethality	Exceptional	Exceptional	Rare	High
Steroid therapy	Without effect	Not indicated	Contraindicated	Moderate effect
Chemotherapy	Provokes identical clinical picture	No data available	May provoke viral disease	Enhances existing symptoms
No. of published cases	Decreasing	Decreasing	Close to zero	Increasing

The number of publications on radiogenic LMND has been decreasing for some time, and no newly diagnosed case has been communicated for 10 years. From this aspect, the dose reduction of the para-aortal radiotherapy during the past decade, the recent substitution of irradiation by chemotherapy or a ‘watch-and-wait’ protocol in seminoma does not seem a convincing explanation. However, it is of great significance that the incidence of acute poliomyelitis (and consequently that of PPS) has also fallen dramatically since the early 1960s (paralysis due to the wild-type poliovirus was last documented in the Western Hemisphere in 1991), and its eradication is planned by the WHO by 2005.<sup>30</sup> A similar decreasing trend cannot be observed with CMR, which appears with low frequency, but regularly, in large-scale clinical studies on the radiotherapy of lung, head and neck or esophageal cancer. Indeed, the clinical data indicate an increasing incidence of CRM, explained by the less effective radiation protection by the bone at the higher energies of the modern photon sources than at the lower energies of the earlier widely used orthovoltage irradiation, resulting in higher radiation dose absorption by the spinal cord.<sup>4</sup>

In susceptible mice, Theiler’s murine encephalomyelitis virus (TMEV) infection causes immune-mediated demyelination similar to that in human demyelinating disorders.<sup>50,51</sup> The disease has an unusual biphasic character, with early viral replication in the neurones, followed by chronic demyelination. The virus persists within the central nervous system throughout the chronic demyelinating disease. Experimental data support the hypothesis that the specificity of the primary white matter destruction in the TMEV model depends on immune-sensitized cells. Immunosuppression with  $\gamma$ -irradiation renders normally resistant mice susceptible to TMEV-induced demyelination and allows increased viral replication.<sup>52</sup> In contrast, immunosuppression of normally susceptible mice results in acute disease and a high mortality, accompanied by large-scale neurone destruction. This study indicates an important active role of the immune system in limiting the viral infection during disease induction in nonimmunosuppressed mice.

The hypothesis of the viral origin of radiogenic LMND may be consistent with the lack of proven viral infection in the related case histories, as infections may be subclinical, but they nevertheless serve as viral prehistory. PPS can also develop without clinical

manifestations of preceding acute paralytic poliomyelitis<sup>53</sup> or in individuals exposed to children with acute poliomyelitis or children who have recently received the trivalent poliovaccine.<sup>32,38</sup> A viral hypothesis likewise accords with epidemiological observations: the first epidemic aggregation<sup>18</sup> was detected among soldiers exhibiting case cluster formations in the worst poliomyelitis epidemic years (1945–1946) in the USA.<sup>53</sup>

The comparisons indicate the possibility that radiogenic LMND is related to a previous viral infection, as its second stage. Its manifestation is triggered by the development of immunosuppression, brought about essentially by exposure of the lower motor neurones (in which the virus persists many years after the primary stage of the infection) to ionizing radiation. Verification of this suggestion requires further clinical investigations.

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