Title	Electromyographic Study on The Effects of Radiation Applied to the Spinal Cord
Author(s)	黒田, 康正
Citation	日本医学放射線学会雑誌. 1966, 26(7), p. 927-936
Version Type	VoR
URL	https://hdl.handle.net/11094/18278
rights	
Note	

ELECTROMYOGRAPHIC STUDY ON THE EFFECTS OF RADIATION APPLIED TO THE SPINAL CORD

by

Yasumasa Kuroda

Department of Radiology, Kobe Medical College

(Director: Prof. Kazuyuki Narabayashi)

脊髄に対する放射線の影響に関する筋電図学的研究

神戸医科大学放射線医学教室（主任　楢林和之教授）

黒　田　康　正

（昭和41年2月23日受付）

従来，神経組織の放射線感受性は低いとされて来たが，近年，放射線治療を受けた悪性腫瘍患者に於いて神経系の放射線障害，殊に放射線脊髄炎が注目されるようになつた．著者は脊髄に及ぼす放射線に対する筋電図検査の応用の検討を目的として本研究に着手し，次の結果を得た．

家兎を用いた実験では Co-60 γ 線の腰髄放射（Ⅴ，Ⅵ，Ⅶ，）により，被放射部位から神経支配を受ける骨格筋の筋電図に変化をみた．この変化は被検筋の弱い随意収縮時に現われた神経筋単位の放電の間隔変動であり，20,000R，30,000R 放射で放射後1週以内，10,000R 放射では放射後3週で著明となり，放射後期間の経過と共に進行した．1,000R，3,000R 放射では10,000R 以上の放射例に比して軽度であるが，放射前の筋電図との比較で有意の差が認められた．

一方，悪性腫瘍に対する放射線治療の際脊髄にも同時放射を受けた患者に，筋電図検査を行い，被放射脊髄の支配筋より明らかに神経組織の破壊によると考えられる異常筋電図を得た．

放射線による脊髄の機能障害に関しては，その発生機構や様式等更に追求すべき基礎的な問題は多いが，日常行われる筋電図検査が放射線脊髄炎の病像把握の一手段として適用し得ることは臨床上興味深い．

The relative resistance of nervous tissue to irradiation damage has long been appreciated. However, in recent years, several reports of myelopathy associated with radiotherapy for malignant tumor have appeared. Boden (1948)[1], Itabashi (1957)[5] and Dynes (1960)[2] described clinical and histologic manifestations of radiation myelitis in cervical region following radiotherapy for malignant tumor. Similar studies were reported by Greenfield (1948)[4] in lumbar region, and by Smithers (1943)[11] in dorsal, respectively. These neuronal changes in the spinal cord may be caused by prolonged survival of the patient with malignancy, according to recent progress in radiotherpeutic procedure. It is, therefore, important to established the sensibility of nervous tissue to irradiation as promptly as possible.

A considerable amount of experimental researches on this problem have also been performed for years, but still there are some differences of opinion concerning the factors which produce damages in the spinal cord. Besides, there has as yet been no report of an adequate diagnostic method for radiation pathy.myelo

In this paper an attempt was made to discuss the clinical applicability of electromyography to examine the radiation-induced myelopathy.

Experimental Series

Material and Method

The electromyographic (EMG) examination was performed in muscles which are innervated by the irradiated spinal cord.

(Animal)

Adult female rabbits weighing between 3.5 and 4.0 kg were used in this study. All animals were placed in individual cages and fed on commercial complete diet and water. And they were observed for at least 2 weeks prior to their use.

(Irradiation)

Animals were fixed in ventral decubitus under intraperitoneal nembutal anesthesia (35 mg/kg), and roentgenographic positioning of the cord segment L_5, L_6 and L_7 was performed. Single irradiation to this site, immediately after roentgenograms were taken, was given from the back with Shimazu Cobalt-60 Unit. Physical factors were shown in Table 1.

Table 1 Employed physical data in experimental cases.

Source	Cobalt-60
Dose rate	135 R/min
Source skin distance	50cm
Field size	3 X 5 cm

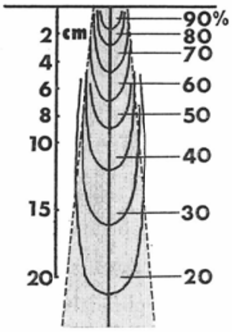

Fig. 1 Single-field isodose pattern at S.S.D. 50cm, field size 3×5cm, measured in water phantom with Shimazu Cobalt-60 Unit.

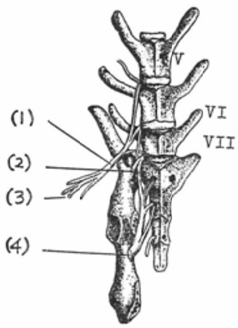

Fig. 2 Lumbar and sacral plexus of rabbit. V, VI, VII: the 5th, 6th and 7th lumbar ve rtebrae. (1) N. femoris. (2) N. obturatorius. (3) N. saphenus magnus. (4) N.ishiadicus

Dosimetry was carried out with Philips Dosimeter in water, and Fig. 1 outlins the results. This radiation field (3×5 cm) was employed in order to involve the cord segment L_5, L_6 and L_7, if settled in the center of the sixth lumbar vertebra.

(EMG examination)

The muscle investigated was M. tibialis anterior,which is innervated by N. ischiadicus emerging from the cord segment L_7, as shown in Fig. 2. Electrical discharges of neuromuscular unit (NMU) during slight voluntary efforts were observed at several spots on this muscle, paying special attention to their intervals. The electrode for conducting the action potentials was coaxial type, consisted of 24 gauge hypodermic needle with enameled copper wire of 100 micra in diameter. Action potentials, after conventional mode of amplification, were observed visually on a Braun tube oscilloscope and recorded photographically.

Results

In order to make brief differentiation of effects due to different radiation doses, four rabbits were irradiated 5,000 R, 10,000 R, 20,000 R and 30,000 R to each spinal cord respectively, and observed for a week. As in Table 2, animals irradited 20,000 R and 30,000 R had prominent weight loss with sudden anorexia, soon accompanied by urinary incontinence and paralysis of hind limbs,while the 5,000 R and 10,000 R irradiated developed no remarkable signs.

Table 2 Clinical course of rabbits after the irradiation of 5,000R, 10,000R, 20,000R, and 30,000R.

	Anorexia	Loss of weight	Incontinence of urine	Paralysis of hind limb
5,000R	(−)	(−)	(−)	(−)
10,000R	(−)	(−)	(−)	(−)
20,000R	(+)	(+)	(+) 5days after	(+) 3days after
30,000R	(#)	(#)	(+) 3days after	(+) 2days after

On the other hand, EMG changes due to irradiation were proved in rabbits irradiated 20,000 R and 30,000 R. Interval diagrams in Fig. 3 show that NMU discharge intervals after irradiation became irregular, and at the same time, mean discharge interval increased. In the 5,000 R and 10,000 R irradiated, such EMG changes were never seen.

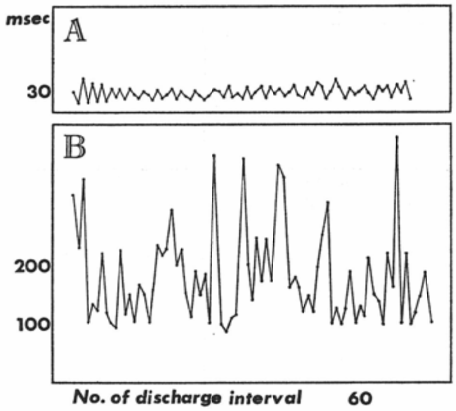

Fig. 3 Interval diagrams of NMU discharges recorded on M. tibialis anterior. (A) before and (B) 3days after the irradiation of 10,000R to the cord segments L_{5-7} in rabbit.

These results suggest that the larger radiation dose would cause the more remarkable effects on nervous system. Then, another attempt was made to know the effects due to the difference of observation periods under the definite dose. Single irradiation of 10,000 R to the spinal cord was given to each 9 rabbits, and EMG examination was performed on 1 week, 3 weeks and 6 weeks after the irradiation.

Although all animals, in early stage, failed to show the clinical signs such as seen in the 20,000 R and 30,000 R irradiated, around 2 weeks after the irradiation gradual loss of weight began, and at the period of 5th week paralysis of hind limbs had developed.

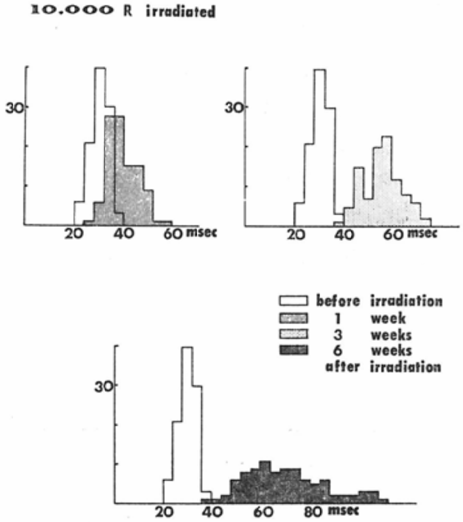

Fig. 4 Each histogram consists of 100 successive NMU discharge intervals recorded on M tibialis anterior of the 10,000R irradiated rabbit.

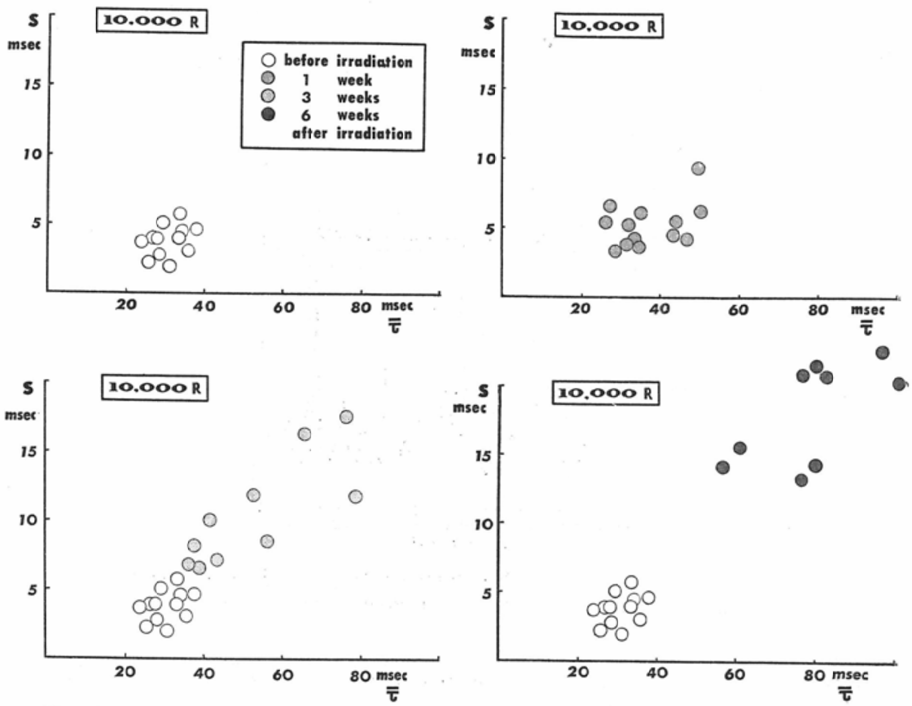

Fig. 5 The relation between $\bar{\tau}$ and S calculated from 100 successive NMU discharge intervals in the rabbit irradiated10,000R. Note remarkably increased $\bar{\tau}$ and S according to the prolonged observation period.

EMG changes were nearly parallel with the periods after the irradiation. Histograms in Fig. 4 show this trend, which consist of 100 successive discharge intervals in the same region of anterior tibial muscle. Histogram before irradiation, showing almost normal distribution around 35 msec., gradually spreads wider around the increased mean discharge interval, as time elapses. To analyse these changes, mean discharge interval ($\bar{\tau}$) and stanard deviation (S) were calculated from successive NMU discharge intervals. Fig. 5 represents the correlation between $\bar{\tau}$ and S of all tests, separately plotted according to each observation period. From these diagrams the above-mentioned EMG changes were clearly seen.

On the contrary, non-irradiated control animals which were fed for 6 weeks in the same way as the irradiated subjects showed no EMG disorders. The $\bar{\tau}$-S relation of these controls always simulates that of the animals before irradiation.

From these results it could be considered that the EMG changes might be caused even by the smaller doses in the longer observation period after the exposure. Then, twelve rabbits were divided into two groups depending on the cord dose (1,000 R and 3,000 R), and were examined electromyographically for a period of 6 and 10 weeks respectively after irradiation.

There was no evidence of objective signs all over the period in both groups, but slight EMG changes were noted. In consequence of 3,000 R or 1,000 R irradiated to the lumbar segments, when 6 or 10 weeks elapsed, some increases of $\bar{\tau}$ and S of NMU discharge intervals were observed. However, most of them remained nearer the values in the pre-irradiation than those in the cases irradiated 10,000 R. There is no significant difference in the degree to which these irregular fluctuations took place, both in different cord doses (1,000 R and 3,000 R) and observation periods (6 and 10 weeks). This phenomenon is indi-

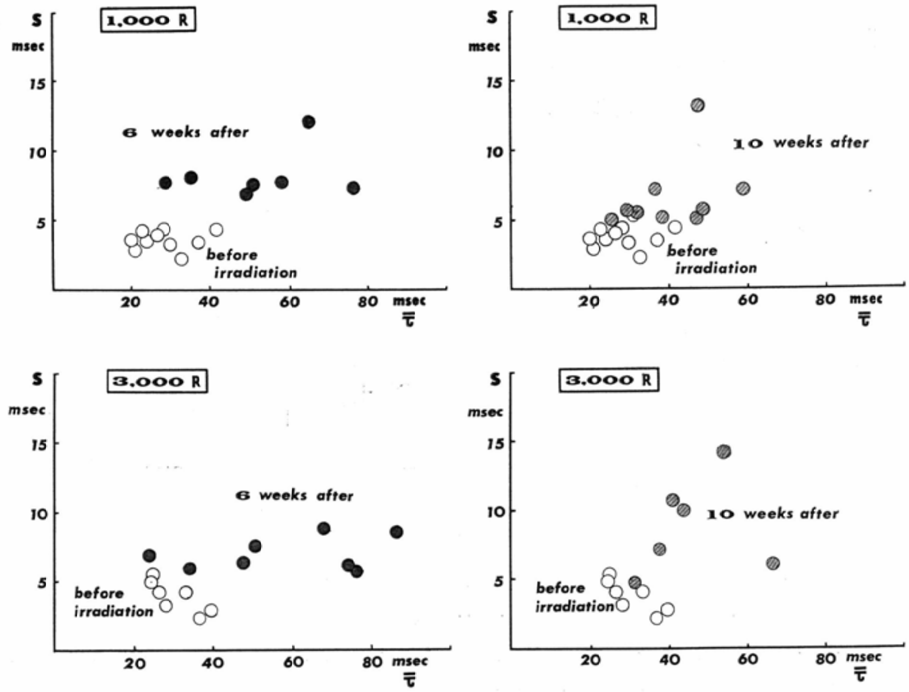

Fig. 6 The relation between $\bar{\tau}$ and S calculated from 100 successive NMU discharge intervals in rabbits irradiated 1,000R and 3,000R. Both $\bar{\tau}$ and S increased apparently as compared with those of the pre-irradiation.

cated in the $\bar{\tau}$-S plot (Fig. 6).

Histologic studies on the muscles which had formerly been tested for EMG revealed no degenerative findings, even in the case with hind lumb paralysis following large dose irradiation, as in Fig. 7.

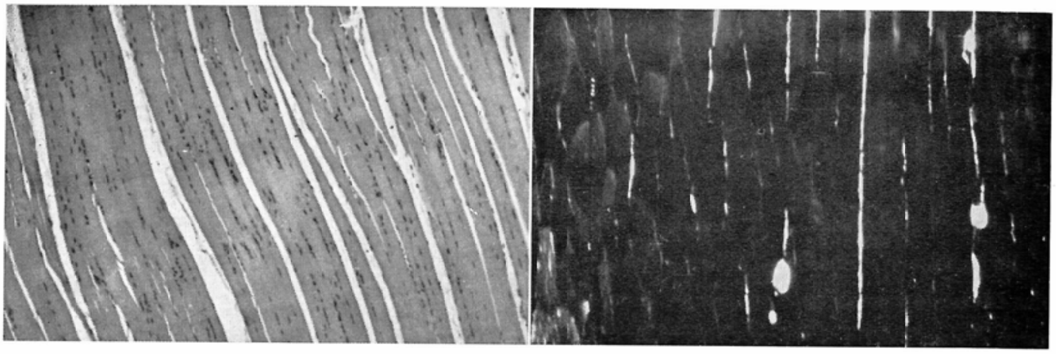

Fig. 7 No degenerative findings in the paralysed anterior tibial muscles after the irradiation of 20,000R to the cord segments L_{5}-$_{7}$ Left: Hematoxylin-eosin stain (10×10). Right: Azan Mallory's stain (10×10).

The results of all experiments may be summarized as follows:

1) The larger irradiation dose to the spinal cord gives rise to the more remarkable EMG disorders even in early stage.

2) Such radiation-induced disorders have a tendency to develop much more remarkably according to the prolonged observation period.

3) Neurological symptoms are severely noted in the animals 10,000 R, 20,000 R and 30,000 R irradiated, but fail to develop in the other.

Table 3 shows the results of EMG examinations.

Table 3 Summarized EMG changes in rabbits.

Cord dose (R)	Period of observation				
	3 days	1 week	3 weeks	6 weeks	10 weeks
1,000				±	±
3,000				±	±
5,000	−	−			
10,000	−	±	+	++	
20,000	+	++			
30,000	+	++			

(−) negative, (±) slight, (+) remarkable, (++) very remarkable

Clinical Series

The present series consists of ten cases of malignant tumors treated with gamma-rays of cobalt-60 (Table 4). The spinal cords of these patients were irradiated unavoidably for the sake of the sites of tumors. Most of the cords received exposures at the level of dorsal region and cord doses varied from 1,051 R to 6,208 R. All these patients at periods varying from 2/3 to 41 months after the beginning of radiotherapy, were examined with EMG on the muscles innervated through the effected region of the cord.

One of them was shown to have radiation myelopathy on the basis of abnormal EMG which suggest-

Table 4 Summary of cases

Case No.	Sex and age	Disease	Irradiated cord segments	Cord doses (R)	Periods from the beginning of radiotherapy to EMG (months)	EMG findings
1	M. 28	Seminoma with metastases of retroperitoneal lymph nodes	D_{12}-L_2	1,128	6	(−)
2	M. 52	Malignant mediastsnal tumor	D_2-$_5$	6,208	12	(+)
3	M. 60	Stomach cancer (resected)	D_{12}-L_2	3,947	41	(−)
4	M. 67	Gullet cancer	D_5-$_7$	2,994	1	(−)
5	F. 60	Gullet cancer	D_9-$_{11}$	2,686	3	(−)
6	M. 58	Pulmonary cancer	D_4-$_7$	2,450	8	(−)
7	F. 66	Malignant mediastinal tumor	D_5-$_8$	1,051	2/3	(−)
8	M. 60	Malignant mediastinal tumor	D_2-$_6$	1,409	21	(−)
9	F. 61	Pulmonary cancer with cervical lymph nodes metastases	C_5-$_7$	5,421	3	(−)
10	M. 73	Gullet cancer	D_5-$_7$	3,724	6	(−)

(+) in EMG findings: abnormal EMG

ed the neuronal degenerations in the irradiated cord segments.

The clinical course of this case is described as follows:

(Case 2) In March 1962, a man of 52, during the treatment of amebic dysentery at another hospital, complained of gradually increasing substernal oppression. Chest roentgenograms revealed tumor-like widening of the superior mediastinum bilaterally. Surgical removal of this lesion failed because of tight adhesion with superior vena cava. Histologic examination of the specimen proved to be teratoma with malignant changes. Then, cobalt-60 teletherapy was carried out using the radiation field of 8×10 cm at 75 cm S.S.D. A tumor dosage of 6,000 R was administered in 35 days, and the tumor shadow regressed considerably. Thereafter the patient remained well untill December 1962, when he developed edema in the face and neck accompanied by substernal oppression and dyspnea.

In February 1963, he was admitted to our clinic for the second course of radiotherapy. X-ray films of the chest showed relapsed feature: vena caval compression by tumor in angiocardiogram and adhesion around the tumor in pneumomediastinogram. The palliative radiotherapy with cobalt-60 gamma-rays was performed from the 29th of February to the 27th of April 1963, using the field of 8×10 cm, 6,600 R were given altogether. The dorsal segments 2–5 were irradiated 6,208 R as a total through radiotherapy. Afterwards the patient's course went gradually downhill and expired on June, 15.

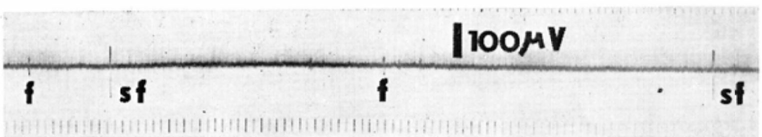

Fig. 8 Abnormal EMG recorded on right external intercostal muscle in case No. 2. f: fibrillation voltage, sf: simple fasciculation voltage, time scale: 20msec.

From the neurological aspect, he complained of a peculiar sensation in the right forearm and "pins and needles" in both sides of scapular regions in April, 1963. Abnormal EMG such as in Fig. 8 were observed in May 1963, after the beginning of the first course of radiotherapy, on the right external intercostal muscle in a state of muscular rest.

Discussien and Conclusion

In EMG tests it was possible to observe the electrical silence, if the rabbit was kept in a state of complete muscular rest. However, incomplete fixation of the animal was sometimes required so as to obtain action potentials at voluntary efforts. In such a condition, the animal non-anesthetized often acted violently, especially on the stimulus of electrode insertion. So it was difficult to record successive discharges on a muscle under the various designated contractions.

Recording was limited in a state of slight voluntary efforts in which the same strength of contraction was relatively maintained. Most of the present animals showed characteristic mean discharge interval depending upon the exposed dose or the observed period. Mean discharge interval in the pre-irradiation state was usually found to be low in value, and to increase following the spinal cord irradiation. The $\bar{\tau}$-S relation of each rabbit, therefore, was presented merely as a distribution without showing a curve.

It is well-known that in the voluntary activity smooth and constant muscle tension is maintained with srevo-mechanism of the closed circuit which consists of efferent fiber, muscle spindle and afferent fiber. And this circuit is thought to keep discharge interval constantly more regular as possible. Irregular fluctuation of discharge intervals following the spinal cord irradiation, in the present work, must be due to dysfunction of this mechaism. To explain the origin of functional disorders in the spinal cord, some considerations should be taken into the radiation effects of all elements which concern this circuit.

Recently, Sato et al[9]. investigated the synaptic activity following local X-ray exposure of lumbar segments in cats. In the acute studies they noted the increase of both mono- and polysnaptic excitatory postsynaptic potentials (EPSP), when the X-ray irradiation of 600 R was made. On the other hand, monosynaptic inhibitory postsynaptic potentials (IPSP) were never affected by 1,200 R, and polysynaptic IPSP showed only some increase with large dose of 16,800 R. The same authors[10] have testified that IPSP induced by Renshaw's neuron remained normal against 18,000 R.

From these results it is difficult to explain that radiation effects of synaptic activity have caused EMG changes in the present work such as the increased values of mean and standard deviation of successive discharge intervals. The enhanced EPSP may sometimes cause irregular discharge intervals on the innervating muscle, but it is not necessary to bring about the decreased muscle tension at which $\bar{\tau}$ usually ranks high in value. IPSP showing strong resistance to irradiation are also likely to be compatible with these EMG changes.

It is generally known that gamma motoneuron takes part in the before-mentioned servo-mechanism, innervating muscle spindles directly. There is no immediate connection between alpha and gamma motoneurons in the anterior horn, but impulses travel from the latter to the former via 'gamma loop'.

According to Gerstner (1956)[3], among the alpha, beta and gamma fibers of the isolated sciatic nerve of the frog, gamma fiber showed the most remarkable functional changes following X-ray irradiation of 75–200 kR. There exists a considerable amount of literatures that the chemical agents such as procaine can block gamma fiber selectively. Kubota and Oshima (1959)[7] demonstrated, by means of gamma blocking of N. fibularis produndus with procaine, irregular fluctuation of NMU discharge intervals strikingly increased. These reaction of peripheral nerves are noteworthy to be considered in relation to the present experiment, because the spinal nerve roots were also exposed inevitably at the cord irradiation. From these facts it is of interest to speculate whether EMG changes in this work were due to radiation effects of the gamma motoneurons.

Radiation-induced damages in nerve cells of the cord are never excluded to discuss the origin of EMG disorders. Some histologic studies on the spinal cord have revealed apparent neuronal changes. Stevenson et al. (1945)[12], in their clinical series of radiation myelitis, pointed out the three main histologic findings: in (1) nerve cell, (2) vascular system and (3) glia cell. Warren (1943)[13] stressed that vascular changes were more dominant than neuronal. Boden (1948)[1] suggested that the large doses produced the destruction of nerve tissue primarily while the small doses brought about vascular changes. Otsuka et al. (1964)[8] reported, in the clinical cases, the remarkable neuronal degeneration in the spinal cord of the patient who survived for 31 months after the radiotheray for lung cancer. They also noted, in rabbits, the neuronal degeneration both in gray and white matter which received the irradiation of 10,000R and 20,000 R. These histologic manifestations would suggest the occurrence of the EMG changes.

In the present clinical cases, abnormal EMG were obtained on the patient who had radictherapy for malignant teratoma of the lung. Fibrillation voltage and simple fasiculation voltage of this case signify neuronal degeneration in anterior horn of the spinal cord. These abnormal EMG might have appeared on account of partial exposure of the cord at radiotherapy, because there was no evidence of neoplastic invasion to the posterior mediastinum according to possible diagnostic examintions. It can be considered that dyspnea was partly due to paralysis of intercostal muscles. Kozuka et al. (1963)[6] mentioned the same symptom in a case report of cervical radiation myelitis.

Recent advancement in high energy radiotherapy for malignant disease has become to provide the damage to nervous system much frequently. The primary purpose of this paper is to discuss the clinical applidability of EMG to radiation myelopathy. In this study EMG examination could reveal an aspect of its feature as a diagnostic method, but fundamental importance is to prevent from these damages minimizing the partial exposure of the spinal cord. EMG may be utilized to establish the clinical course of radiation myelopathy in cooperation with the other examinations.

Summary

EMG investigations were attempted to the radiation-induced myelopathy both in clinical and experimental subjects, and clinical value of EMG tests for these cases have been discussed.

1) In the rabbits irradiated more than 10,000 R, EMG changes were noticeable.

2) These changes developed increasingly as time passed, during the observation period.

3) EMG findings in the 3,000 R or 1,000 R irradiated animals were less prominent than the 10,000 R or more irradiated.

4) Abnormal pattern of EMG was noted in a patient whose spinal cord received the exposure, suggesting the radiation-induced mylopathy.

Acknoledgments

The author's grateful thanks are due to Profs. K. Narabayashi and I. Suda for their constant advice and guidance in this investigation, and to Drs. S. Hayashi, R. Otsuka and M. Nishida for their generous assistance throughout the experiment. The author is also indebted to Mr. Y. Inoue, B. Ph. for providing physical data. This work was supported by a grant in aid for Fundamental Scientific Research from the Education Ministry.

References

1) Boden, G.: Radiation myelitis of the cervical spinal cord. Brti. J. Radiol. 21 (1948), 464.
2) Dynes, J.B. and Smedal, F.M.: Radiation myelitis. Amer. J. Roentgenol. 83 (1960), 78.

3) Gerstner, H.B., Orth, I.S. and Richey, E.O.: Effect of high intensity X-irradiation on velocity of nerve conduction. Amer. J. Physiol. 180 (1) (1955), 232.
4) Greenfield, M.M. and Stark, F.M.: Post-irradiation neuropathy. Amer. J. Roentgenol. 60 (1948), 617.
5) Itabashi, H.H., Bebin, J. and DeJong, R.N.: Postirradiation cervical myelopathy. Neurology 7 (1957), 844.
6) Kozuka, T., Kawamura, J. and Terashita, H.: Rabiation myelitis. a case report. No to Shinkei 16 (11) (1964), 81. (Japanese with English abstracts)
7) Kubota, K. and Oshima, T.: Effects of gamma blocking on muscular activity and their relation to myasthenic state. Neurologia medico chirurgica 1 (1959), 171.
8) Otsuka, R., Kuroda, Y. and Nishida, M.: Diagnosis of radiation injury of the spinal cord by cobalt-60. Proceeding of the 5th Annual Meeting of the Neuro-Radiological Association of Japan 5 (1964), 23.
9) Sato, M., Stahl, W. and Austin, G.: Acute radiation effects on synaptic activity in the mammalian spinal cord. Radiation research 18 (1963), 307.
10) Sato, M.: Hoshano to shinkeikei (Radiation and nervous system). Seitai no Kagaku 15 (1) (1964), 33. (Japanese)
11) Smithers, D.W., Clarkson, J.R. and Strong, J.A.: The roentgen treatment of cancer of the esophagus. Amer. J. Roentgenol. 49 (1943) 606.
12) Stevenson, L.D. and Eckhardt, R.E.: Myelomalacia of the cervical portion of the cord, probably the results of roentgen therapy. Arch. Pathol. 39 (1945), 109.
13) Warren, S.: Effects of radiation of normal tissues. IX. Effects on nervous system. Arch. Pathol. 35 (1943), 127.