Received: 2016.07.11
Accepted: 2016.09.06
Published: 2016.12.02

ISSN 1941-5923
© Am J Case Rep, 2016; 17: 916-920
DOI: 10.12659/AJCR.900537

Three Cases of Levodopa-Resistant Parkinsonism After Radiation Therapy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 **Raja Mehanna**
BE 2 **Joohi Jimenez-Shahed**
BE 3 **Ilia Itin**

1 Department of Neurology, University of Texas Health Science Center, Houston, TX, U.S.A.
2 Department of Neurology, Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, TX, U.S.A.
3 Department of Neurology, Center for Neurological Restoration, Cleveland Clinic Foundation, Cleveland, OH, U.S.A.

Corresponding Author: Raja Mehanna, e-mail: raja.mehanna@uth.tmc.edu
Conflict of interest: None declared

Case series

Patients: Male, 77 • Female, 44 • Male, 9
Final Diagnosis: Radiation induced parkinsonism
Symptoms: Slowness
Medication: —
Clinical Procedure: —
Specialty: Neurology

Objective: Unusual or unexpected effect of treatment
Background: Unequivocal brain radiation-induced parkinsonism has so far been reported in only in two pediatric patients. However, with the rising incidence rates for brain tumors in industrialized countries and the consequential increased exposure to cranial radiotherapy, clinicians might become more exposed to this entity.
Case Report: Three patients were treated for intraparenchymal brain tumor with resection, chemotherapy, and whole brain radiation. One patient developed leukoencephalopathy and parkinsonism within one year of treatment, one developed it seven years after treatment completion, and one developed dementia, parkinsonism and cerebral infarcts 40 years after whole brain radiation. Brain MRIs and a DaTscan were obtained. All patients failed a trial of carbidopa/levodopa. We suggest that the brain radiation exposure was responsible for levodopa resistant parkinsonism, cognitive decline, and diffuse leukoencephalopathy.
Conclusions: Although rare, radiation therapy-induced parkinsonism might be responsible for levodopa-resistant parkinsonism.

MeSH Keywords: Abnormalities, Radiation-Induced • Leukoencephalopathies • Parkinsonian Disorders

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/900537>

1509 2 2 6

Background

The most frequent etiologies of non-degenerative, secondary parkinsonism include vascular disease and drugs such as metoclopramide, haloperidol, or valproic acid. Neoplasm-induced parkinsonism has been related to direct space occupying effect of the lesion, tumor-induced hydrocephalus [1], or as a complication of chemotherapy, namely amphotericin B [2].

There is very limited literature on cranial radiotherapy induced parkinsonism. However, with the rising incidence rates for brain tumors in industrialized countries [3], and the consequential increased exposure to cranial radiotherapy, clinicians might become more exposed to this entity.

We here we report on three patients who developed parkinsonism one to 40 years after cranial radiation therapy and review the available literature on the subject.

Case Report

Patient 1

A 72-year-old right-handed man was diagnosed with glioblastoma multiforme while being evaluated for new onset seizures. He was treated in 2010 by surgical resection followed by 30 sessions of whole brain radiation therapy (total dose unavailable), then by two infusions of cisplatin. Subsequently, he received temozolomide every three weeks for a total of 12 cycles. While he was undergoing radiation therapy, he developed a progressively worsening shuffling gait, motor slowness, and left-sided weakness. Because of the persistence of these symptoms, 16 months after diagnosis, five months after completing chemotherapy, and after being declared cancer free, the patient was referred to the movement disorder clinic. At that time, he was wheelchair-bound. He denied exposure to neuroleptics or metoclopramide. On examination, he was found to have generalized spasticity with superimposed rigidity, worse on the left side, as well as decreased left hand movement with bradykinesia and hyperreflexia with an upgoing toe on the left. His gait was abnormal with a stooped posture and intermittent freezing of the left leg at gait initiation and when approaching his destination. A new brain MRI was compared to MRI imaging obtained one year earlier, showing a marked increase of diffuse white matter hyperintensity, worse on the right, consistent with post radiation encephalopathy (Figure 1). A levodopa trial of 1,000 mg per day was performed without any improvement in the patient's symptoms. A DaTscan was not obtained at that time. History and examination were consistent with parkinsonism secondary to radiation therapy. The patient progressively worsened and died within a year of his first visit to our clinic.

Patient 2

A 44-year-old left-handed woman had a WHO grade 2 left temporal glioma treated by resection, whole brain radiation, and unspecified oral chemotherapy for a month in 1986. The patient was subsequently cancer free. Around age 51, she started reporting "brain foggiess" with difficulty completing sentences followed by balance and walking difficulties (ataxia, wide based gait with some shuffling) and started falling at age 57. At age 59, she developed severe shuffling and freezing of gait, with a narrow base, and she became wheelchair bound at age 60. In addition to her gait difficulties, she developed decreased hand dexterity and dysphagia to solids at age 58. She also reported some decline in cognition, with complaints of bradyphrenia and trouble remembering dates. She presented to the movement disorders clinic at age 61. She denied any exposure to neuroleptics or metoclopramide. Her examination was remarkable for normal mental status, severe dysarthria, moderate bradykinesia worse on the right, moderate cogwheel rigidity on the right and slight rigidity on the left, and inability to walk. A brain MRI obtained at age 56 showed diffuse white matter hyperintensity consistent with post radiation leukoencephalopathy. A repeat MRI at age 61 was similar, without further radiological worsening despite clinical worsening. A DaTscan showed mildly decreased putaminal radiotracer uptake, worse on the right (Figure 2). A trial of levodopa 600 mg/day was unsuccessful and higher doses were not tolerated. The patient was diagnosed with radiation-induced parkinsonism.

Patient 3

A 9-year-old boy had a posterior fossa brain tumor and was treated with tumor resection, radiation, and unspecified intravenous and intrathecal chemotherapy in 1972. No medical records were available and the history was obtained from the patient and his family. Details regarding the type of tumor, radiation therapy, and chemotherapy were not available, but the patient's father recalled the boy had received both intravenous and intrathecal chemotherapy. Therapy was discontinued at age 16, and the patient was cancer free. At about 45 years of age, he started complaining of paroxysmal events likely of vascular origin. Five years later, the patient presented to the movement disorder clinic with decreased mobility and significant cognitive decline for the previous two years. He denied any exposure to neuroleptics or metoclopramide. His neurological examination was remarkable for mild psychomotor slowing and delayed response to questions, as well as decreased blinking and facial expression. He also had left-sided bradykinesia and mild cogwheel rigidity but no rest tremor. His gait was unsteady and wide-based. Overall, his neurological examination was consistent with parkinsonism. In addition, he was diagnosed with mixed cortical and subcortical dementia

Figure 1. Patient 1 MRI shortly after onset of the symptoms (to the left), and one year later (to the right), showing progression of the leukoencephalopathy

on formal neuropsychological testing. His brain MRI showed postoperative changes of a cerebellar resection as well as a diffuse moderate volume loss, worse than expected for age, a diffuse confluent hyperintensity in the deep white matter

compatible with microvascular ischemic or post therapeutic changes, calcifications in the left temporal lobe and a small subacute infarct in the right occipital lobe. The patient declined obtaining a DaTscan to better characterize his cerebral

Figure 2. Patient 2 DAT Scan showing mild decreased putaminal dopamine uptake, worse on the right.

dopamine function. The patient failed a trial of 400 mg/day of levodopa and was diagnosed with radiation-induced leukoencephalopathy causing parkinsonism, cognitive decline, and vascular events.

Discussion

To date, radiation therapy-induced parkinsonism has been suggested only in a total of eight patients (four children and four adults [2,4–6]), whose cases we reviewed.

Of the pediatric cases, aged 16 months to 14 years, one also had hydrocephalus and another was also exposed to amphotericin B [2,4], which are known causes of parkinsonism. The other two pediatric patients developed parkinsonism six months post adjuvant radiotherapy for intracranial tumor (Table 1). One patient was 14 years old, treated for a suprasellar tumor and developed a dopamine agonist resistant akinetic-rigid syndrome [4] while the other was 16 months old, treated for a posterior fossa tumor and developed an anticholinergic-responsive

tremor-dominant parkinsonism [5]. In both cases, the brain MRI showed no tumor recurrence but high signal intensity within the globus pallidus bilaterally on T2-weighted images. The suggested mechanism by which radiation caused parkinsonism was vasogenic edema in the older patient and interference with normal myelination in the younger patient [4].

The four previously reported adult patients with akinetic-rigid levodopa-resistant parkinsonism two to eight weeks after completion of radiation therapy for cranial tumor [6], similar to our first patient, also had infiltrative tumor growth or multiple metastases, chemotherapy and/or metoclopramide exposure, all of which are well described causes of parkinsonism. In contrast, our first patient did not have any tumor growth or metastasis on his MRI, and his chemotherapy consisted of cisplatin and temozolomide, which have not been reported as a cause of parkinsonism. However, his MRI changes were consistent with post radiation leukoencephalopathy.

Patient 2 and Patient 3 in our series developed levodopa-resistant akinetic-rigid parkinsonism and cognitive decline seven

Table 1. Unequivocal radiation-induced parkinsonism in the literature.

Author, year	Age of patient at onset	Latency after radiation	Type of parkinsonism	Treatment and response
Voermans et al., 2006 [3]	14 years old	6 months	Akinetic rigid	DA resistant
Skimming et al., 2003 [4]	16 months old	6 months	Tremor dominant	Anticholinergic responsive

DA – dopamine agonist.

Table 2. Summary of the findings in our three patients.

	Age of patient at onset	Latency after radiation	Type of parkinsonism	Treatment and response
Patient 1	72 years old	0 (during radiation)	Akinetic rigid	C/L resistant
Patient 2	51 years old	7 years	Akinetic rigid	C/L resistant
Patient 3	48 years old	39 years	Akinetic rigid	C/L resistant

C/L – carbidopa/levodopa.

and 40 years after completion of radiation therapy, without any evidence of tumor recurrence (Table 2). Our second patient's MRI showed extensive leukoencephalopathy while our third patient's MRI revealed extensive leukoencephalopathy, as well as calcifications, atrophy, and focal infarct, all consistent with ischemia due to radiation-induced obliterating vasculopathy, a phenomenon that is well-recognized to occur after a prolonged latency [4].

Although two patients were exposed to unspecified chemotherapy, it is unlikely that this would contribute to their symptoms seven to 40 years later. Indeed, neurological complications of chemotherapy typically develop within a few months of the completion of the course [5]. On the other hand, radiation therapy-induced atrophy, calcification, leukoencephalopathy, and necrosis are known to occur years later [5,6]. The co-existence of idiopathic Parkinson's disease in our three patients was very unlikely as they did not respond to 1,000 mg/day, 400 mg/day, or 600 mg/day of levodopa respectively. Vascular parkinsonism was also unlikely as parkinsonism was not lower-body predominant, and the patients did not demonstrate other features suggestive of degenerative forms of atypical parkinsonism such as progressive supranuclear palsy or multiple systems atrophy.

The absence of response to levodopa as well as the changes observed on MRI suggests a post synaptic mechanism to the parkinsonism. This in turn brings the focus of pathophysiology away from the substantia nigra and toward the basal ganglia. While comparative studies are lacking, the current report might suggest avoiding radiation to the basal ganglia whenever possible, using targeted rather than whole brain radiation for example. Meanwhile, a higher awareness about cranial radiotherapy induced parkinsonism should be promoted, especially between radiation oncologists and neurologists.

Conclusions

Radiation therapy-induced parkinsonism should be considered in a patient presenting with parkinsonism following a history of cranial radiation therapy and with leukoencephalopathy on brain imaging. The latency to onset of this clinical manifestation after radiation exposure may vary from one to 40 years. More reports and studies are necessary to better characterize it and understand its pathophysiology. This might in turn help to develop strategies to prevent this treatment resistant complication.

References:

- Dolendo MC, Lin TP, Tat OH et al: Parkinsonism as an unusual presenting symptom of pineal gland teratoma. *Pediatr Neurol*, 2003; 28: 310–12
- Pranzatelli MR, Mott SH, Pavlakis SG et al: Clinical spectrum of secondary parkinsonism in childhood: A reversible disorder. *Pediatr Neurol*, 1994; 10: 131–40
- Ries LAG, Eisner MP, Kosary CL et al: (eds.): SEER Cancer Statistics Review, 1975–2001, National Cancer Institute. Bethesda, MD
- Voermans NC, Bloem BR, Janssens G et al: Secondary parkinsonism in childhood: A rare complication after radiotherapy. *Pediatr Neurol*, 2006; 34: 495–98
- Skimming JA, McDowell HP, Wright N, May P: Secondary parkinsonism: An unusual late complication of craniocervical radiotherapy given to a 16-month child. *Med Pediatr Oncol*, 2003; 40: 132–34
- Wick W, Hochberg F, O'Sullivan J et al: L-dopa-resistant parkinsonism syndrome following cerebral radiation therapy for neoplasm. *Oncol Rep*, 2000; 7: 1367–70