Radiation-induced secondary narcolepsy

Sir,

Narcolepsy is a chronic neurological disorder of sleep regulation and wakefulness, characterized by excessive day time sleepiness and disturbed nocturnal sleep.[1] Idiopathic form of the disease is supposed to be due to autoimmune destruction of hypocretin producing neurons in the hypothalamus, thus inhibiting the brain's ability to regulate sleep-wake cycles normally.[2] Secondary or symptomatic form of the disorder is reported to be caused by hypothalamic involvement due to tumors, head trauma, vascular disorders, encephalopathies, degenerations, demyelinating disorders, and genetic/congenital disorders.[2] We report a case of symptomatic narcolepsy developing as a

late radiation effect following irradiation of a left parietal lobe astrocytoma.

A 26-year-old lady developed seizures in December 2007, and the magnetic resonance imaging (MRI) then showed left parietal lobe space occupying lesion. She underwent excision of the tumor and the histopathology showed Grade III Astrocytoma. Subsequently, she received radical local site radiotherapy to cover the lesion with 2 cm margin (54 Gy/28 fractions; one fraction per day, 5 fractions per week) and was asymptomatic for 3 years.

She presented to Neurology services of our institution in February 2013 with symptoms of 2-years duration. The problems included sadness often bursting into tears, temper tantrums, quarreling with family members for trivial reasons, etc. Sometimes with these emotional outbursts, she suddenly collapses, but without any loss of consciousness and gets up soon. She feels sleepy during most of the time, some times even during conversations. On positive questioning, she admitted that she occasionally gets feeling of falling to a well while sleeping and sometimes feel as if somebody is throttling her. Rarely while awake and tries to get up, she feels that she can't move. Clinical examination did not show any clinching features except that she was emotionally disturbed and was crying while narrating the story. Multiple treatments were tried previously including antidepressants and other symptomatic medications without any relief.

MRI brain showed residual cystic change at the operated site in the left parietal region with ex-vacuo dilatation of the corresponding lateral ventricle. There was no evidence of residua or recurrence of tumor or any other significant lesions in other parts of brain [Figure 1]. She underwent a nocturnal polysomnogram (PSG) with following instrumental settings. Montage - electroencephalogram (EEG): C4/A1, C3/A2, O1/A1, O2/A2 (international 10-20system); electrooculogram (EOG): EOG (R), EOG (L); EMG: Chin EMG, Leg Electromyogram (EMG); electrocardiogram (EKG): Lead I; Respiratory: Airflow, respiratory effort, snoring sensor, pulse oximetry; video monitoring and recording of the session. The PSG study showed short sleep latency and sleep onset rapid eye movement (REM) [Figure 2]. Multiple Sleep Latency Test (MSLT) was performed the next day morning and four naps were recorded, each of 20 minutes duration with 2-hours interval between each nap. Montage included EEG: C4/A1, C3/A2, O1/A1, O2/A2; EOG: EOG (R), EOG (L); EMG: Chin EMG, EKG: Lead I [Figure 3]. The result of MSLT is summarized in Table 1. Overall, the clinical and sleep study data were consistent with American Academy of Sleep Medicine (AASM) criteria for diagnosis of Narcolepsy.[3]

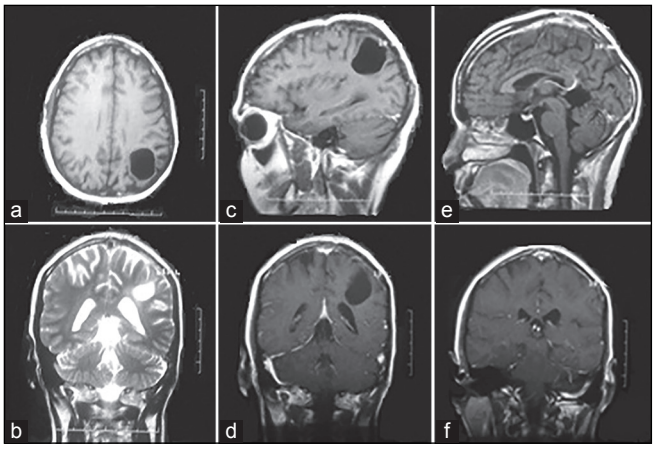

Figure 1: MRI brain plain (a and b) and contrast (c-f) showing cystic space corresponding to the removed tumour. No residual tumour identified. Note the ex-vacuo dilatation of the corresponding lateral ventricle (b and d). Hypothalamic region is not showing any identifiable abnormality

Our patient with radical local site radiotherapy following surgery of left parietal region grade III astrocytoma has presented after five years with seemingly vague symptoms of 2-years duration. Probably this vague nature of the symptoms has resulted in the delay in diagnosis by around 2 years, which is much less than the median period of 10 years delay described in literature.[1] While narcolepsy symptoms were confused with depression, co-occurrence of depression would also have been possible as it is reported in 5% to 30% cases.[1] Clinching point in the history was the dramatic collapses during emotional outbursts suggesting cataplectic attacks. This led to positive questioning about other symptoms of the classical narcolepsy tetrad[1] and hence the clinical diagnosis. Our patient exhibited all the components of the narcolepsy tetrad including cataplexy (sudden collapses with emotional outbursts), sleep paralysis (on trying to get up from sleep, can't move), hypnagogic hallucinations (feeling of falling to a well while sleeping and feeling of throttling), and excessive daytime sleepiness. Diagnosis was confirmed by the overnight PSG and MSLT done the next day. The PSG showed short sleep latency, short REM sleep latency, and poor sleep architecture.

Table 1: Multiple sleep latency test (MSLT) naps showing sleep latency and sleep onset rapid eye movements (SOREMs)

Lights off time	Sleep onset latency	Slow wave sleep latency	REM sleep latency	SOREM
9.51 am	0 min	0 min	0 min	yes
11.47 am	0 min	11 min	0 min	yes
1.32 pm	1 min	11 min	Nil	Nil
3.37 pm	0 min	20 min	0 min	yes

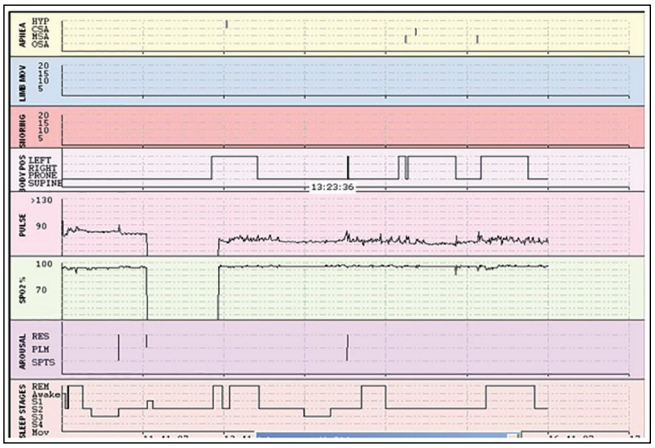

Figure 2: PSG showing short sleep latency (<10 m), short REM sleep latency (<20 m) and poor sleep architecture

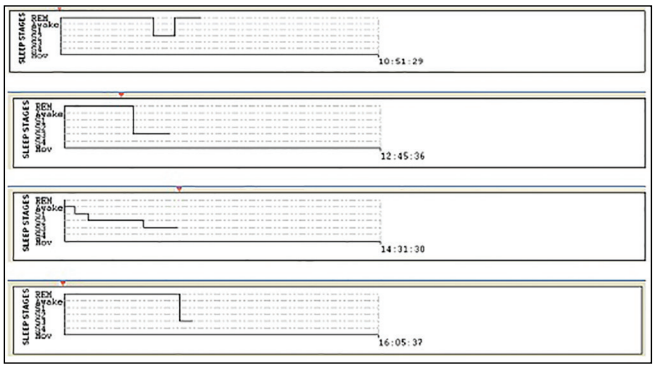

Figure 3: MSLT showing SOREMs (3/4) and short mean sleep latency (<5 m)

Three out of the four MSLT naps showed sleep onset REM periods and short mean sleep latency. Altogether, she qualified for the AASM criteria of Narcolepsy.[3]

What caused narcolepsy in our patient? While autoimmunity against hypocretin neurons in hypothalamus is the most supported current theory of causation of narcolepsy,[2] a complex interplay of autoimmunity with genetic factors is probably important. Abnormalities of the hypothalamus based hypocretin system due to tumors, head trauma, vascular disorders, encephalopathies, degenerations, demyelinating disorders, and genetic/congenital disorders are well-known to produce symptomatic narcolepsy.[2] Moderate decrease in cerebrospinal fluid (CSF) hypocretin levels were seen in a large majority of these cases. Is there a link between the radiation given for astrocytoma and the narcolepsy which developed subsequently? While radiation-induced narcolepsy is proposed following irradiation of pituitary adenoma, there are no reports of narcolepsy developing as a late effect following radiation of a non-contiguous site. Our patient received a total radiation dose of 54 Gy, and the calculated dose received at the hypothalamic region (in the beam of radiation) is around 25 Gy. The tolerance limit (TD5/5, i.e., 5% of irradiated patients developing symptoms over 5ea) is 40 Gy. Still we think the possible cause of narcolepsy in our patient is late radiation effect (and not idiopathic narcolepsy), since the age of onset is neither in the primary peak (second decade) nor in the secondary peak (around 35 years) of idiopathic narcolepsy.[4] Further, development of the disorder time locked at 3 years (time of peaking of the late radiation effect) from the radiation exposure was also suggestive. However, the MRI brain didn't show any lesion in the hypothalamic region, which strictly speaking is not against a late radiation effect, since the mechanism may be chronic vascular change and not radiation necrosis. In a sequential MRI study of malignant gliomas, radiation-induced MRI changes were reported in only two-third of patients undergoing radiation.[5] This was in spite of additional chemotherapy, which is well-known to enhance the radiation effect in MRI. Whether the radiation has changed the autoimmune milieu so that the narcolepsy has manifested also needs to be debated. Despite all these, the possibility of narcolepsy in our patient being purely idiopathic could not be excluded.

We didn't do a CSF hypocretin level in our patient, since it was not freely available or standardized in India and the patient was not keen to send sample abroad. However, we feel the CSF hypocretin level would not have been useful since it is well described to be low even in secondary narcolepsy. We haven't done a human leukocyte antigen (HLA) typing also since its main role is to exclude a diagnosis of narcolepsy. Further, genetic predilection may be a factor even in secondary narcolepsy and so HLA typing may not help to differentiate primary versus secondary narcolepsy.

To conclude, we reported a case of narcolepsy with an unusual age of presentation developing after three years of radiation treatment of an astrocytoma. Late radiation effect in the small vessels of the hypothalamic region is proposed to be the mechanism of development of narcolepsy in our patient. Though we were not able to unequivocally establish the causative role of late radiation reaction in the development of narcolepsy, this is probably the first ever report of such an association in literature and a vigilant watch for such an association in future is recommended.

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