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Comprehensive assessment of Somnolence Syndrome in patients undergoing radiation to the brain

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ABSTRACT

Aim: The aim of this prospective study was to assess Somnolence Syndrome (SS) in patients undergoing radiation to the brain.
Background: SS is one of the sequelae of radiation to the brain, which is observed within three months of radiation. This is a self-limiting condition and a failure to diagnose leads to unnecessary investigations. This study was undertaken to objectively and subjectively analyze the occurrence, clinical presentation and severity of SS.
Materials and methods: Thirty-three patients receiving radiation to the brain were included in the study. Visual Analog Scale (VAS) was used for subjective assessment and the Littman Somnolence Syndrome (LSS) scale was used for objective assessment of SS. Sleep Latency Test (SLT) was used to quantify SS.
Results: VAS scores showed an initial fall until week 3, followed by a plateau and a sudden increase after week 10. LSS scale at week 11 and 12 showed that 13 patients (43.3%) had grade 2, 5 (16.7%) had grade 3; and 2 (6.7%) had grade 4 SS. SLT revealed a shift of predominant sleep pattern from NREM 1 to NREM 2 at 6 weeks after radiation with a p value of 0.0412.
Conclusions: An insight into SS, its features, frequency of occurrence and self limiting nature can prevent anxiety and unwarranted investigations in the immediate post radiation period.

1. Background

Radiation is the main treatment option for the management of primary brain tumors as well as for palliation in metastatic brain tumors. The sequelae of cranial irradiation have been described as early, early delayed and delayed, which are observed during, within a few months and beyond six months of radiation therapy (RT), respectively.

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Early effects are due to peri-tumoral edema and are usually detected during radiation and immediately after radiation therapy. Delayed effects mandate immediate hospital care due to their grave nature. However, an early-delayed effect, Somnolence Syndrome (SS) occurs at a time when patients are recovering after irradiation. First reported by Druckmann in 1929,[1] SS comprises non-specific symptoms like excessive sleepiness, fatigue, drowsiness and decreased appetite. It occurs at five to six weeks post-irradiation and is self-limiting, lasting for about two weeks. A number of hypotheses have been postulated to explain SS, with the strongest one attributing it to transient demyelination occurring post-radiotherapy.[2]

Various subjective and objective methods of assessing somnolence have been described. Subjective methods include Visual Analog Scales (VAS)[3] and Epworth Sleepiness Scale.[4] Objectively, a physician rated scale, the Littman Somnolence Syndrome (LSS) scale has been used.[5] Electro-Encephalographic (EEG) changes have also been studied.[6]

The timeline of occurrence of SS and failure to recognize it as a distinct radiation sequel causes undue anxiety among patients as well as healthcare providers and triggers the performance of investigations to rule out recurrence of the tumor. Awareness among healthcare personnel coupled with patient counseling during initiation of RT would go a long way in allaying patient anxiety and reducing unnecessary investigations.

There is limited data available on SS, with this entity being mainly reported in children with leukemia receiving prophylactic cranial irradiation.[5–14] There are very few reports of its occurrence in adults.[3,15,16] This study was undertaken to objectively and subjectively analyze the incidence, clinical presentation and severity of SS in adults receiving cranial irradiation for primary and metastatic brain tumors.

2. Materials and methods

This prospective study was conducted in 33 patients primary as well as metastatic brain lesions with histologically proven malignancies who were receiving RT in Radiation Oncology department of a tertiary care center from November 2012 to September 2014.

A clinical examination, including an exhaustive neurological examination was performed at initiation of RT as well as on follow-up visits. Exclusion criteria included age less than 18 years, those on benzodiazapines or any medications which could induce or modify sleep and those with pre-existing sleep disorders. Patients with Karnofsky performance status less than 30 were also excluded as their altered mental status could make the assessment difficult.

2.1. *Radiation protocol*

Patients with brain metastases were treated with palliative whole brain radiation therapy to a dose of 30 Gy in 10 fractions using a conventional technique or 3 Dimensional Conformal Radiation Therapy (3DCRT) at the physician's discretion. Those with primary tumors underwent maximal safe resection or decompression. They were treated with Adjuvant RT using 3DCRT or IMRT to a dose of 54–59.4 Gy as indicated. For Glioblastoma multiforme, gross tumor volume was considered to be gross residual disease along with the tumor bed. A 2 cm isotropic margin along with adequate coverage of peri tumoral edema was considered as the clinical target volume. Planning target volume margin was 0.5 cm as per institutional protocol. Lesser margins were used for lower grade tumors. Concurrent Temozolamide was given when indicated.

Table 1 – Assessment for Somnolence Syndrome.

Pattern of assessment		
Week 1	*Week 2–11*	*Week 12*
VAS scoring	VAS scoring	VAS scoring
Littman	Littman	Littman
Somnolence scale	Somnolence scale	Somnolence scale
Sleep Latency Test		Sleep Latency Test

2.2. *Assessment of Somnolence Syndrome*

Assessment of SS was done as shown in (Table 1). Subjective assessment was made using VAS on a scale of 1–4 mm of opposing variables (alert–drowsy, strong–feeble, well-co-ordinated–clumsy, happy–sad, normal appetite–cannot face food, sleep all day–do not sleep during day, energetic–exhausted), at baseline, once a week during radiation and for six weeks after treatment was completed. The VAS score for each set of opposing variables was added to obtain a total VAS score for each week.

Objective assessment was done by the treating physician using LSS Scale (Table 2). This physician-rated scale is the most commonly used scale which grades tiredness, activity level, pyrexia appetite, hours of sleep per day on a scale of 0–4.[8] Subjects were graded at baseline, once a week during radiation and weekly thereafter for six weeks using the LSS scale.

Patients also underwent a Sleep Latency Test (SLT) for 20 min at baseline and at six weeks post RT. In the ideal context, it is known as multiple SLT, where after an overnight polysomnography (PSG) to map the patients sleep pattern, patient is given five nap opportunities, each for 20–40 min at two hour intervals.[17] An overnight PSG as well as provision of five nap opportunities was not feasible in our set-up owing to patient constraints and long waiting lists in the Sleep Laboratory. Besides, there is no data suggesting its use earlier, we gave the patient a single nap opportunity four to five hours after awakening from a self-reported good night's sleep. The conventional montage for the MSLT included central EEG

Table 2 – Littman's Somnolence Syndrome scale.

Grade	Severity	Description
0	None	No evidence of change in behavior
1	Minimal	Disturbance with some tiredness, but activity not curtailed
2	Mild	Decreased activity and increased tiredness, may have a low grade pyrexia
3	Moderate	Sleeping much of the day, decreased appetite, low grade fever, most activities curtailed.
4	Severe	Inactive, sleeping 18–20 h per day, low grade fever, markedly decreased appetite and only taking oral fluids

Table 3 – Patient demography.

Age	- Median – 45 years - Range – 26–63 years	
Gender distribution	Male:Female = 14:19	
KPS	Primary tumors	Metastatic tumors
70	4 (16%)	2 (25%)
80	6 (24%)	2 (25%)
90	15 (60%)	4 (50%)

(C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye electrooculograms (EOGs), mental/submental electromyogram (EMG), and electrocardiogram (EKG).[18]

We called it the screening-SLT. Our study is the first of its kind to have employed this assessment technique to quantify SS.

3. Statistical analysis

The statistical software IBM SPSS 20.0 was used for the analysis of the data. Wilcoxon signed rank test was used to compare the significance of VAS scores at different weeks as well as the baseline and follow up sleep latency times. The variation in LSS scores over the follow up period was analyzed using the Chi Square test. The Mc Nemar's chi square test was used to find the difference between predominant sleep patterns at follow up SLT versus baseline values. Pearson correlation coefficient and spearman's rho tests were used to correlate the results of VAS, LSS scale and SLT.

4. Results

A total of 33 patients were the subjects of the study. Twenty-five patients had primary malignancy and eight patients had diseases that had metastasized to brain. The median age was 45 years. Majority had KPS of 90. They presented with various symptoms, most common being headache. The patient demographic, tumor and treatment characteristics are as summarized in (Tables 3 and 4).

Table 5 – Comparison of VAS scores of weeks 7–12 with week 1.

	Week 1 (mean – 8.91)	
Week 7 (mean – 7.88)	0.022*	Using Wilcoxon Signed Rank test for paired samples.
Week 8 (mean – 8.0)	0.077	
Week 9 (mean – 8.19)	0.157	
Week 10 (mean – 8.72)	0.952	
Week 11 (mean – 10.6)	0.005*	
Week 12 (mean – 12.37)	<0.001*	

* Statistically significant at alpha-0.05.

4.1. VAS scores

VAS scores for all variables were obtained during each week. The scores for each patient were tabulated and compared to get a pattern of the scores over the 12 weeks of study. A comparison of VAS scores at weeks 7–12 (first six weeks post radiation) with start of RT is shown in (Table 5). Graph 1 shows a representation of these VAS scores. It shows an initial fall in the VAS scores until week 3, followed by a plateau and a sudden increase after week 10.

A separate analysis was done considering all patients with primary brain tumors. The VAS scores at week 11 and 12 were higher than that at week 1 (p – 0.025 and 0.001, respectively; Wilcoxon signed rank test for paired samples).

Similarly, analysis of the sub-group of patients with metastasis was performed. The score at week eight (sixth week post RT) reached a significance value of 0.058.

4.2. Littman SS scale

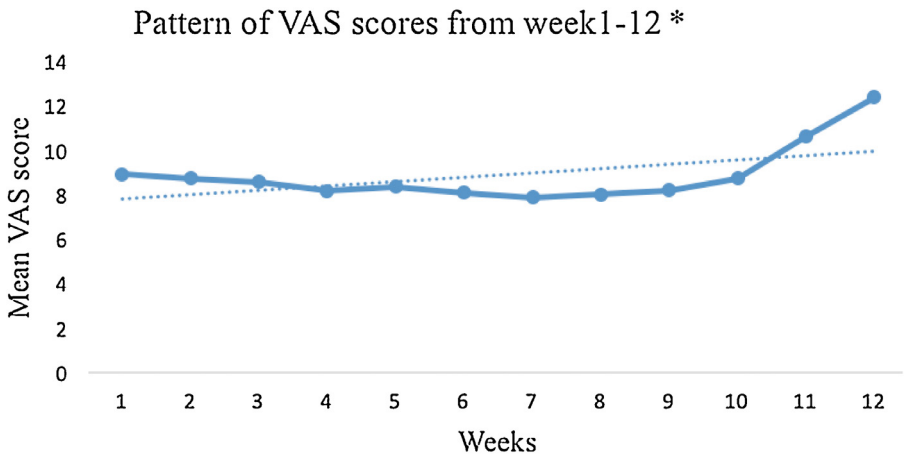
The LSS score ranged from 0 to 4. There was an increase in the number of people with a higher grade in weeks 11 and 12 (p 0.012* using the Chi square for trend analysis) (Graph 2).

4.3. Incidence based on LSS scale

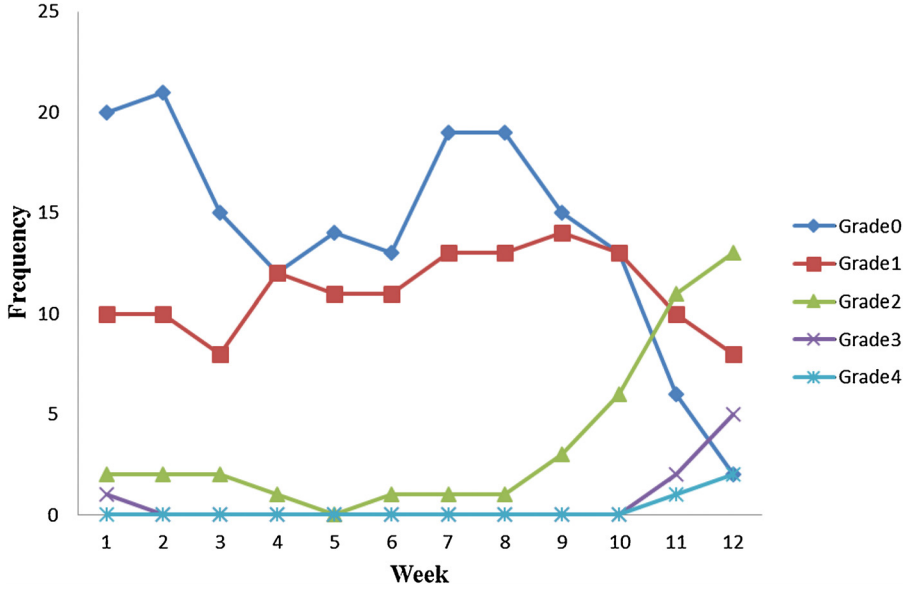
Of all the patients whose assessment was done at week 11 and 12 (30 patients), 28 patients (93.34%) had at least ≥1 i.e. at least

Table 4 – Tumor characteristics.

Symptoms		*Primary tumors*	*Metastatic tumors*
Headache		18 (72%)	6 (75%)
Seizures		8 (32%)	2 (25%)
Motor deficits		8 (32%)	5 (62.5%)
Tumors		*Patient no (%)*	
Primary		25 (62.5%)	
Metastatic		8 (24.24%)	
Histopathology-primary	*Patient no (%)*	*Metastasis from primary*	*Patient no (%)*
Astrocytoma	11 (44%)	Breast	4 (50%)
Oligodendroglioma	6 (24%)	Lung	2 (25%)
Mixed Oligoastrocytoma	5 (20.8%)	Kidney	1 (12.5%)
Primary CNS Melanoma	1 (4%)	Testis	1 (12.5%)
Ependymoma	1 (4%)		
PPTR	1 (4%)		
Radiation details		*Dose/fractions (no of patients)*	
Adjuvant RT (25)		5400 cGy/30 Fr (3)	
		5940 cGy/33 Fr(22)	
Palliative RT (8)		3000 cGy/10 Fr (8)	
Concurrent Temozolamide		19/25 (76%)	



Graph 1 – Pattern of VAS scores from week 1 to 12. *Radiation therapy given from weeks 1 to 6; weeks 7 to 12 represent weekly follow up for 6 weeks post completion of irradiation.



Graph 2 – Trends of Littman grades over the 12 weeks*. *In the initial stages, Grade 0 predominated while higher grades (2–4) started rising toward the end.

minimal Somnolence Syndrome. 13 patients (43.3%) at week 12 had Littman's grade 2, 5 (16.7%) had grade three and 4 (6.7%) had grade 4.

4.4. *Sleep latency testing*

The SLT was performed for all 33 patients at baseline. 22 of 33 patients underwent follow-up Sleep Latency Test at six weeks post irradiation. The reasons for lesser follow up tests were mainly because of death (two patients), inability to return for follow-up on account of hospice care (one patient) and patient preference against undergoing a follow-up SLT (eight patients).

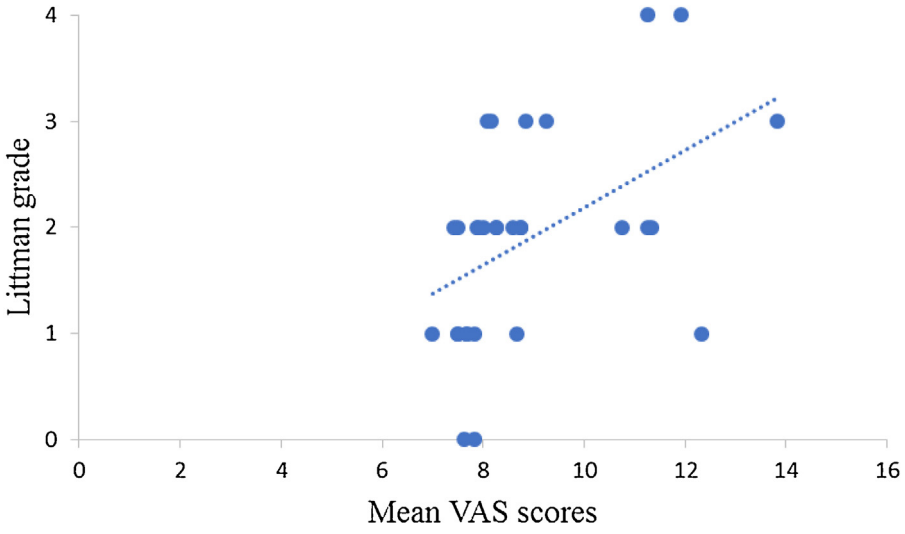
Thus, data from 22 patients whose baseline and follow up SLT readings were as shown in (Table 6). The baseline and follow up sleep latency times were compared using Wilcoxon signed rank test, and the difference was not statistically significant (p value = 0.456).

Table 6 – Mean, standard deviation and range of baseline and follow up sleep latency times/correlation between SLT at baseline and at follow up.

	Baseline sleep latency (min)	Follow up sleep latency (min)
Mean	6.25	6.91
Standard deviation	8.02	7.93
Range	0–20	0–20

4.5. *Predominant sleep pattern*

Pattern of predominant sleep pattern was analyzed. Of the 11 patients who had NREM 1 as the predominant sleep pattern in the baseline study, six had predominant NREM 2 in the follow up study. Two patients had NREM 2 pre dominance in both baseline and follow up study. One patient had REM predominance in baseline study. His pattern shifted to NREM 2 during



Graph 3 – Correlation between VAS scores and Littman Somnolence Syndrome scores (r – 0.477, p – 0.008)/correlation between scales – Littman Somnolence Syndrome scale and VAS.

follow up. This shift of predominant sleep pattern from NREM 1 to NREM 2 at 6 weeks follow up was statistically significant with a p value of 0.0412*; analyzed using the Mc Nemar's Chi square test.

4.5.1. *Correlation of VAS scores with LSS scale*

This will be follwed by correlation between other assessment methods Correlations between different assessment methods VAS and Littman Somnolence syndrome scale- A direct correlation was observed between VAS and Littman SS scale,and it was statistically significant as shown in Graph 3.

4.6. *Correlation of VAS with SLT*

The mean VAS score negatively correlated with the follow-up sleep latency time (minutes) done at six weeks post irradiation. It implies that patients who had higher VAS scores had a faster sleep onset. (Pearson's correlation = −0.444, p value = 0.03). VAS scores did not correlate with sleep latency time done at baseline.

4.7. *Correlation of LSS scale with sleep latency time*

The LSS score did not correlate with the baseline or follow up sleep latency time (p = 0.063, 0.71, respectively; Spearman's Rho correlation).

4.8. *VAS and LSS scale with predominant sleep pattern*

There was no significant correlation with LSS scores as well as the VAS scores with the predominant sleep pattern observed at baseline and follow up SLT.

5. Discussion

This is a first of its kind prospective study that used a VAS to characterize symptomatology of SS, objectively graded its severity using the LSS scale[5] and quantified it using a screening SLT.

Several authors have studied SS in pediatric population.[7–14] However, only two studies have been done in adult population prior to the present study. While Faithfull and Brada[15] have also used VAS and LSS scale, Cerri Powell et al.,[3] have used Fatigue and Quality of life scales in addition.

All our patients with primary brain tumors had been treated with radiation using conventional fractionation. In the study by Faithfull et al.,[15] majority (15/19) of the patients received accelerated fractionation. They noted that although the incidence remained the same, the severity increased in those treated with accelerated fractionation.

5.1. *Assessment for Somnolence – VAS*

A VAS of opposing variables incorporating the common symptoms of SS was used. We used a 4 mm scale in contrast to a 10 mm scale used by other studies. This was based on an observation that patients found it easier to respond on a scale of one to four rather than 1–10.

VAS scores increased in the fifth and sixth week post RT implying the development of SS. It was also noted that scores in the first week post RT were lower than those at baseline, which means there was improvement at the first week post completion of RT compared to the start of radiation. This could be because many patients had weakness, lack of strength, increased sleepiness, loss of appetite and sadness during the initial one to two weeks of radiation, which could be due to the overlap in time frames of post-operative recovery and start of adjuvant radiation. They improved over two to three weeks, which is in concordance with the decrease in post-operative edema with start of steroids. This observation is exemplified

by noting the maximum value of VAS score in week one and two of 19, which drops to 13 in the third week. Hence, the comparison of all weeks post RT with week three or four along with week one of the start of RT was considered significant and carried out as an additional test. The subjective nature of this scale should be remembered while interpreting these results.

When the same analysis was conducted in primary brain tumors, Somnolence Syndrome developed in the fifth and sixth week post irradiation. A similar difference was noted in the first week post RT; however, it was not statistically significant. Understanding the pattern of improvement during the first two weeks of RT, we compared all follow up weeks with the third week of treatment. The trend that was noted in week 7 (first week following RT) disappeared, and the level of significance for the 11th and 12th week (meaning increase in VAS scores) was higher when compared with week three rather than week one.

These symptoms developed in the fifth week post completion of RT and continued into the sixth week, which is partly consistent with Faithfull et al.,[15] where symptoms peaked in the fifth week. A striking difference was that in their study, symptoms arose in the second week, lasted from day 11 to day 21, improved to further appear in the fifth week, lasting for five days. Our results did not reveal this biphasic nature. Also, our symptoms continued into week 12 (sixth week of follow-up) and further follow up was not done. The exact duration for which these symptoms would have persisted could not be appreciated. The study by Cerri Powell et al.,[3] also showed that SS peaked six to eight weeks following irradiation and resolved four to six weeks later.

More common symptoms were lack of strength, exhaustion and increased sleepiness; which were different from those identified by Faithfull et al.[15] The most common symptoms in their study were drowsiness, clumsiness, lethargy and slow mental processes. This can be attributed to the differences in the populations studied. It was noted that although 'SS' is considered a symptom complex, it can also manifest as a single symptom.

While analyzing only patients with brain metastases, VAS scores were higher in the fifth and sixth week post radiation, however it showed only a trend toward significance (p value = 0.058). This is the first study where VAS scores have been used for patients with brain metastases. However, one study by Chow et al.[17] has used Edmonton Symptom Assessment Scale (ESAS) which is similar to the VAS scales. With improvement in technologies, increasing overall survival, it is worthwhile to compile more data on this symptom complex in patients with brain metastases.

There are limitations in using VAS, it is subjective and, hence, can be affected by the time of questionnaire, family support and many other factors.

5.2. *LSS scale*[6]

SS was classically observed during 11 and 12 weeks and it was mostly Grade I–III. Out of two patients who had grade III SS at 12 weeks, one had progressive disease. It is difficult to predict Somnolence versus progression on the basis of grade alone. A clinical judgment is required.

A strong correlation was noted between VAS and LSS scores ($p = 0.008$). These two parameters also strongly correlated in the study by Cerri Powell et al.[3]

5.3. *Sleep Latency Test*

We subjected the patients to baseline and follow-up sleep latency tests. This is the first study to have tried this to quantify Somnolence Syndrome.

We did not find a significant difference in the sleep latency times at baseline versus six weeks post RT follow up. However, what we observed was a statistically significant shift from NREM 1 to NREM 2 sleep at follow up SLT compared to baseline. This implies that although the amount of time it took the patients to fall asleep was not significantly different, they went into deeper sleep over 20 min at 6 weeks follow up as compared to baseline.

A back ground slowing in the alpha rhythm was noted both in pre and post irradiation studies. This was not quantified, but could be an important finding that should be studied. Although a SLT has not been done before, similar EEG changes have been described by Ch'ien et al.[6] They performed EEG examination in leukemic children receiving PCI, immediately before and after cranial irradiation, thereafter at six to seven weeks, three months, six months, one year, and then yearly along with clinical assessment. All children with clinical evidence of Somnolence Syndrome had electro encephalographic changes. For children in whom the syndrome developed, alpha frequencies were slow at the time ALL was diagnosed. They gradually became faster until the onset of Somnolence Syndrome. At its onset, the background frequencies declined more than three standard deviations below the normal mean. Although the EEG slowing during somnolence became less pronounced within the next three weeks, the background frequencies remained below normal for at least four years after the diagnosis of ALL. Even patients who did not develop clinically Somnolence Syndrome had electro-encephalographic changes. We performed only two SLTs unlike multiple ones done by them.[4]

An issue requiring notice was that during performing SLT, several patients started with NREM 2 sleep in our analysis which is unlikely to be true. We attribute it to be due to a combined effect of SS and the hook up time which has not been considered in the calculated sleep latency time. Also, it was subject to inter-observer variability, especially because overnight polysomnographic sleep pattern was not available.

We studied correlation patterns of SLT findings with VAS and Littman scores. Increase in VAS scores correlated with lower sleep latency times which mean that patients with higher Littman scores fell asleep faster. Other correlations were not significant which can be attributed to a number of confounding factors like anti-epileptic medications and lack of overnight polysomnography. Again, these are our unique findings with minimal literature. Hence, we have no comparison to present with other data.

A mention about steroids is necessary as they have shown to decrease the incidence of Somnolence Syndrome. Our patients have received steroids at the discretion of the treating physician. Their use has not been quantified.

The strength of our study is that it is prospective in nature and is the first study to quantify objectively the use of a SLT. The limitations include a small sample size and limited period of follow-up.

6. Future directions

A study with longer follow up will shed more light on the exact duration of SS. Daily diaries can be used to get a more detailed pattern. SLT with more nap opportunities, following an overnight PSG can be attempted.

7. Conclusion

SS is a common side effect that is seen around the 11th–12th week of radiation but there is little awareness of it. An insight into its features, tune of occurrence and self limiting nature can prevent anxiety and unwarranted investigations in the immediate post radiation period.

Conflict of interest

None declared.

Financial disclosure

None declared.

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