Diffuse large B cell lymphoma presenting with hypersomnia

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Short title: DLBCL presenting with hypersomnia

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KEY CLINICAL MESSAGE:

Hypersomnia is an atypical presentation of CNS lymphoma. Involvement of the hypothalamus causing reduced orexin secretion could be the likely cause. Our case demonstrates that in patients presenting with hypersomnia, after ruling out common causes, it is essential to look for CNS malignancies before labelling it as primary narcolepsy.

INTRODUCTION:

Excessive daytime sleepiness (EDS), alternatively known as hypersomnia or hypersomnolence, is defined as the inability to maintain wakefulness and alertness during the significant waking hours of the day for at least three months (ICSD-3 definition). EDS is reported by 10-25% of the population, with equal prevalence in males and females[1]. The most common cause of EDS is insufficient sleep at night due to shift work or a medical illness like heart failure causing orthopnea. Other causes for hypersomnia are sleep disorders like obstructive sleep apnea (OSA), central disorders of hypersomnolence like narcolepsy or Kleine Levin syndrome, psychiatric conditions like depression or anxiety, medical disorders like Parkinson's disease, multiple sclerosis, hypothyroidism or intake of drugs like benzodiazepines. We present an interesting case of a middle-aged lady with no prior comorbidities who presented to us with hypersomnia but did not appear to have any symptoms or signs suggestive of the common causes of hypersomnia, and a preliminary workup for the same turned out to be negative.

CASE REPORT:

A middle-aged lady, who was a homemaker without comorbidities, presented with complaints of hypersomnia for the last three months. Her husband initially noticed that she had excessive daytime sleepiness and would fall asleep while watching television, reading newspapers, and was taking prolonged afternoon naps. Gradually, it worsened such that she would not even get up from bed in the morning and would not eat meals or communicate with family members. She did not give any history of insufficient sleep during night-time. There was no history of sleep paralysis, cataplexy, hallucinations, excessive snoring, cessation of breaths, involuntary leg movements or enactment of dreams during sleep. She did not give any history of unintentional weight gain, constipation or menorrhagia. No history of jaundice, abdominal distension or hematemesis. No history of memory loss, cognitive deficits, focal neurological deficits, hyperphagia, hypersexuality, depression, mania, trauma or any drug intake before the onset of symptoms. She was not an alcoholic or smoker and did not give any history of substance abuse.

On examination, her pulse rate was 82 beats/min, and her blood pressure and respiratory parameters were within normal limits. She was stuporous and would only open her eyes and respond to questions on giving a prolonged stimulus in the form of pain. The head-to-toe examination was within normal limits and showed no pallor, icterus, clubbing, oedema or generalised lymphadenopathy. A detailed neurological examination couldn't be done owing to her stuporous state, but her pupils were bilaterally reactive, reflexes preserved, and plantar reflexes were down-going bilaterally. Assessment of other systems was within normal limits and did not reveal hepatosplenomegaly.

Routine investigations showed normal haemoglobin (13.6g/dL), leukocyte count of 8330 cells/uL and platelet count of 1,80,000 cells/uL. Her renal function tests were normal, but liver function tests showed transaminitis (SGOT- 180U/L, SGPT- 212U/L) with normal bilirubin (1.2mg/dL). Thyroid profile, serum cortisol and ammonia levels were normal. The urine toxicology screen did not show the presence of any commonly used drugs like opioids. As the history was not suggestive of sleep-related breathing disorder or central disorder of hypersomnolence, tests like polysomnography or multiple sleep latency tests were not done. As a preliminary workup did not yield a cause for the hypersomnia, CEMRI was done. It showed an ill-defined T2/FLAIR hyper-intensity involving bilateral basifrontal white matter, anterior part of the corpus callosum, bilateral globus pallidi and hypothalami showing homogenous contrast enhancement and mild diffusion restriction with associated ventriculitis (figure 1) and the possible differentials were malignancy (?CNS lymphoma), infection like tuberculosis, or a demyelinating lesion like multiple sclerosis. CSF evaluation showed no cells, protein – 68mg/dL, and sugar 80mg /dL. CSF acid fast bacilli (AFB), geneXpert, gram stain, bacterial culture, bacterial DNA PCR, and KOH stain were negative.

Malignant cytology of the CSF was negative when repeated on three separate occasions. CECT chest and abdomen done for evaluation of other sites of involvement showed abdominal and retroperitoneal lymphadenopathy and lytic sclerotic lesions in the left femoral head, right iliac blade and L3 vertebra. Biopsy from the internal iliac lymph node suggested diffuse large b cell lymphoma(DLBCL), germinal centre type, with high ki67. Immunohistochemistry showed myc+ (figure 2). Thus, a Lugano stage IV DLBCL diagnosis was made, and the patient was transferred under the care of the medical oncology department.

She was started on triple intrathecal therapy with cytarabine 100mg, methotrexate 12mg, steroids (hydrocortisone 15mg), and systemic chemotherapy – R-HCVAD/MA regimen (Rituximab 375mg/m^2, Hyperfractionated Cyclophosphamide 300mg/m^2, Vincristine 1.4mg/m^2, Doxorubicin 50mg/m^2, Dexamethasone 40mg, alternating with Methotrexate 1g/m^2, Cytarabine 3g/m^2). There was a mild improvement in her stuporous state after the first cycle of chemotherapy. Spontaneous eye opening was present, and there was an improvement in following motor commands. The patient was discharged after the first cycle. At her last follow-up visit, after three cycles of chemotherapy, the patient has much symptomatic improvement. She has no complaints of hypersomnia at present and is in the process of returning to her regular daily routine.

DISCUSSION:

DLBCL is the most common type of non-Hodgkin's lymphoma (NHL). It is more common among males; the median age at presentation is over 60. DLBCL arises from mature B cells and can arise de novo or as a transformation of other low-grade lymphomas. It usually presents as rapidly enlarging lymphadenopathy in the neck, abdomen or mediastinum. B symptoms like fever, weight loss and night sweats are seen in 30%, and 60% of the patients have advanced disease at presentation. DLBCL invading the CNS can involve the brain, leptomeninges, eyes or spinal cord. The common presenting symptoms are focal neurological deficits, neuropsychiatric symptoms, headache, seizures, altered behaviour and ocular symptoms. Hypersomnia is an atypical and rare presentation of DLBCL.

Orexin A and B (hypocretin 1 and 2) are excitatory neurotransmitters in the lateral hypothalamus. They are secreted in the awake state and help maintain a wakefulness state. They also increase the activity of locus coeruleus, raphe nucleus and tuberomammillary nucleus, which also promote a state of wakefulness. A deficiency of orexin-secreting neurons resulting in reduced orexin levels is the proposed aetiology for narcolepsy type 1. Cerebrovascular accidents, tumours, vascular malformations, infections or inflammatory diseases affecting the posterior hypothalamus can damage the orexin-secreting neurons leading to narcolepsy, called secondary narcolepsy. Our patient did not fit the diagnostic criteria for narcolepsy as she did not have features like cataplexy, and a multiple sleep latency test couldn't be done owing to the stuporous state of the patient at presentation. The periventricular lesion encroaching upon the hypothalamus, causing reduced orexin secretion, could be the likely cause of hypersomnia in our patient.

There are some rare reports of CNS lymphomas involving the hypothalamus presenting with hypersomnia or narcolepsy[2,3]. Onofrj et al. reported the first case of a 30-year-old male who presented with narcolepsy, which was diagnosed as secondary to a temporal lobe lymphoma one year later[4]. This case was similar to ours, where narcolepsy was the only presenting complaint of the patient; however, early brain imaging helped in a prompt diagnosis and initiation of treatment of CNS lymphoma. Hamada et al. reported a case of relapsed primary intraocular lymphoma with hypersomnolence. Still, the patient also had other neurological findings, like the rigidity of lower limbs, hyperreflexia and positive Babinski sign.

Interestingly, MRI or FDG-PET scan identified no hypothalamic lesion in this patient. However, the CSF orexin levels were low and returned to normal following chemotherapy[5]. In most cases, the symptoms of hypersomnia and narcolepsy are resolved with chemotherapy directed against the primary malignancy. Our case highlights the importance of ruling out secondary causes, especially CNS malignancies, even in patients presenting with only hypersomnia and no other neurological signs or symptoms before labelling them as primary narcolepsy or hypersomnia.

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LEGENDS:

Figure 1: Axial CEMRI images show enhancement of the ependymal lining (arrow), and deep grey matter areas, including the lentiform nuclei and left caudate head (arrowheads). MR spectroscopy reveals an elevated choline peak (white arrow).

CECT abdomen reveals multiple non-necrotic mildly enhancing intraperitoneal, bilateral common iliac and left external iliac nodes (*).

Figure 2: Microphotographs showing (A) Diffuse large B-cell lymphoma (x40) and its corresponding immunohistochemistry profiles (x20), (B) CD20, (C) CD3, (D) CD10, (E) CD Bcl-6, (F) C-MYC, (G) MUM-1, (H) Ki67 proliferative index (approximately 90-95%)