Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Neurosciences

Journal homepage: https://www.ijnonline.org/

Case Report

FLUORO-DOPA pattern in Kleine Levin syndrome

Shrikant V Solav[1,*], Shailendra V Savale[1], Aman Shrikant Solav[1], Suresh Lajpatrai Balani[1]

[1] *SPECTLAB, Nuclear Medicine Services, Bavdhan, Pune, Maharashtra, India*

ARTICLE INFO

Article history:
Received 06-08-2022
Accepted 23-08-2022
Available online 03-09-2022

Keywords:
KLS
FDGPET CT
Ga68 DOPA

ABSTRACT

Kleine Levin syndrome (KLS) is a rare neurological disorder characterized by excessive sleep with or without associated symptoms such as hyperphagia, abnormal behavior, cognitive dysfunction. Symptoms are cyclical and usually affect adolescents. Onset of symptoms is usually rapid and may last for days or weeks. The exact cause of KLS is unknown though it shows features of affection of hypothalamus that controls sleep, appetite and body temperature. There have been reports of viral infections preceding KLS raising a possibility of autoimmune response. Presented here is a six years old patient who had features of KLS. The FDG PET CT scan revealed hypometabolism in the thalami quite characteristic of the entity. F-DOPA scan revealed physiologic expression of dopaminergic activity in the neostriatum. However, the over-expression of dopaminergic activity in the right basi-frontal cortex and medial temporal lobe was also noted. The nigrostriatal, mesocortical, mesolimbic, tuberomammillary pathways are known dopamine transmitters. This case report attempts to explain the reason for dopaminergic expression in these regions in KLS.

1. Introduction

Klein Levin syndrome (KLS) was initially described "periodic sleep disorder" in a series of five patients in 1925 by Willi Klein in Frankfurt.[1] Four years later Max Levin in New York described a case of narcolepsy with hyperphagia.[2] It differs from narcolepsy in that there are extremely long sleep periods. Narcolepsy on the other hand is characterized by excessive day time sleepiness and cataplexy i.e. sudden muscle weakness that may be initiated by positive emotion such as laughter.[3] The sleep duration in KLS may last from one to two weeks. KLS is a relapsing disorder that may last for as long as 14 years. Behavioral changes (hypersexuality, hyperphagia), and cognitive dysfunction (memory, language disturbances) are known associates of KLS. Functional imaging has been reported to show hypometabolism in thalamus and hypothalamus. Earlier studies using SPECT during the symptomatic and asymptomatic phase have shown thalamic- hypothalamic hypoperfusion during the symptomatic phase.[3] Studies have also demonstrated hypoperfusion in the cortex (frontal- parietal- temporal lobes) during the symptomatic phase.[4]

2. Case Report

A six years old child had recurrent episodes of intermittent ataxia, aggressive behavior, prolonged sleepiness lasting 18 to 20 hours for 2 years. He remained confused in the post sleep period. He was born of non-consanguineous marriage and had no obvious neurological deficit. Interictal and awake electroencephalograph (EEG) showed normal waveform and intermittent generalized epileptiform discharge. MRI of the brain was normal. An F-18-

* *Corresponding author*.
E-mail address: drsolav1@gmail.com (S. V. Solav).

https://doi.org/10.18231/j.ijn.2022.042

FDG (fluoro-deoxyglucose) PET CT (positron emission tomography computed tomography) was performed during the partial recovery phase. There was symmetric hypometabolism seen in bilateral thalami. To further map the neurotransmission F18- DOPA (dihydroxy phenylanaline) PET CT was performed after 48 hours. The child had recovered from the sleep cycle during this scan. The basal ganglia showed symmetric uptake of dopaminergic activity. However, there was evidence of localization of DOPA in the right basi-frontal region as well. The uptake was in close proximity of amygdala. The uptake was asymmetric and has not been described previously.

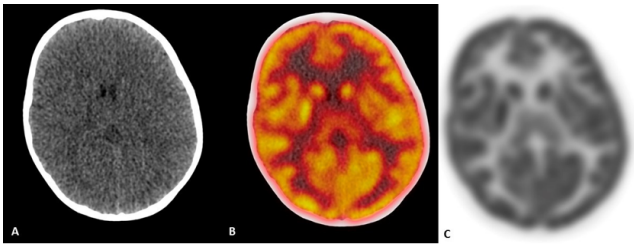

Fig. 1: FDG PET CT, Plain CT; **A:** Fusion PET CT showing bilateral thalamic hypometabolism; **B:** Dedicated FDG Brain PET; **C:** Image showing bilateral thalamic hypometabolism.

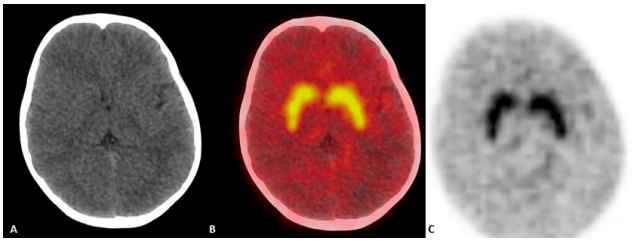

Fig. 2: F-DOPA PET CT, Plain CT showing striatal structures; **A:** Fusion PET CT showing normal dopaminergic activity in striatum; **B:** Dedicated DOPA Brain PET image; **C:** showing normal dopaminergic activity in striatum.

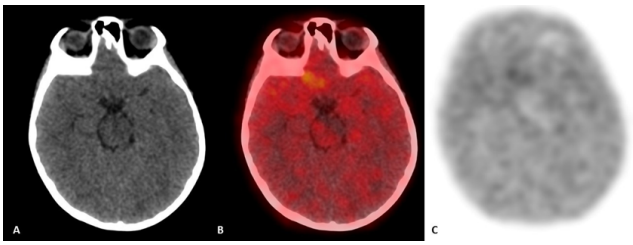

Fig. 3: F-DOPA PET CT, Plain CT; **A:** Fusion PET CT; **C:** showing increased dopaminergic activity in right basi-frontal region; **B:** Dedicated DOPA Brain PET image showing increased dopaminergic activity in right basi-frontal region.

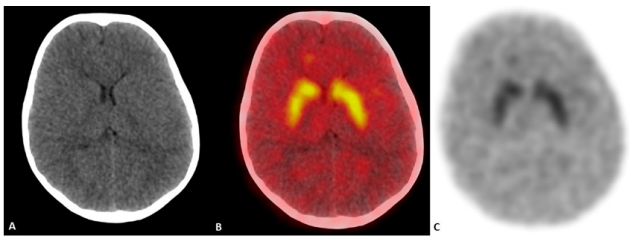

Fig. 4: F-DOPA PET CT, Plain CT; **A:** Fusion PET CT; **C:** showing increased dopaminergic activity in right mesocortical tract; **B:** Dedicated DOPA Brain PET image; **C:** showing increased dopaminergic activity in right mesocortical tract.

3. Discussion

It is believed that the sleep-wake cycle is governed by neurotransmitters in a complex circuitry that connects hypothalamus- thalamus and various other parts of the brain.[5] The exact etiology of KLS is unknown however, autopsy studies have demonstrated involvement of thalamus.[6] Reduced pontine and thalamic connectivity has also been demonstrated in a case of congenital nystagmus with KLS using blood oxygen level dependence (BOLD) on functional MRI.[7]

The ascending arousal system in brain follows two pathways. A ventral pathway passing via the hypothalamus and a dorsal pathway passing via the thalamus. The ventral pathway of ascending arousal system activates the neurons in the lateral hypothalamic area, basal forebrain and cerebral cortex. The origin of the ventral pathway is in the upper brainstem (monoaminergic), locus coeruleus (noradrenergic), dorsal and median raphe nuclei (serotoninergic), ventral periaqueductal grey matter (dopaminergic), tuberomammillary neurons (histaminergic).[8] This pathway also receives signals from peptidergic neurons in lateral hypothalamus that contains orexin or melanocyte concentrating hormone and also from basal forebrain neurons that contain gamma-aminobutyric acid and acetylcholine. The dorsal ascending pathway that activate the thalamic relay neurons and the cortex receive signals from pedunculopontine and laterodorsal tegmental nuclei (both acetylcholine producing excitatory cell groups). These neurons are active during wakefulness and rapid eye movement (REM) sleep. They are dormant during the non-REM sleep.[9,10] Relay to cerebral cortex is by lateral hypothalamic peptidergic neurons (mediated by orexin or melanin concentrating hormone) and basal forebrain neurons (acetylcholine or GABA). Orexin (hypocretin) is produced exclusively in posterior half of lateral hypothalamus. Lack of orexin has been shown to cause narcolepsy in experimental animals.[11] Orexin neurons are active during wakefulness and have ascending projections to the cerebral cortex and descending projections to monoaminergic and cholinergic cell group of

arousal system. There are to and fro neuronal projections between the orexin producing neurons and ventrolateral preoptic (VLPO) cells. However, there are no orexin receptors in VLPO cells and hence they cannot inhibit VLPO cells. Lesions in rostral midbrain, thalamus, lateral hypothalamus produce profound sleep.[12] There is a mutual inhibition between the sleep and arousal system the so called "switch" in which the VLPO nucleus appears to play a key role mediated by galanin and GABA.[13] The VLPO cells send output to all the major cells in hypothalamus and brainstem that participate in arousal.[14] The VLPO neurons are primarily active during sleep.[15] Hence damage to VLPO nucleus causes insomnia. Noradrenaline, serotonin, GABA, galanin and endomorphin are inhibitory neurotransmitters on VMPO nucleus.[16] These hormones are released by neurons arising from locus coeruleus and tuberomammillary neurons.

Acetylcholine activates cortical neurons and is released at high rate during waking and rapid eye movement sleep. Neurons involved in sleep wake control that release acetylcholine are located in basal frontal and mesopontine tegmentum of brainstem.[17]

Dopamine neurons in ventral tegmental area show high impulses during waking and REM sleep. This results in increased of dopamine in target regions such as nucleus accumbens and prefrontal cortex.[18]

Keeping in view the preceding background an attempt is made to explain the findings in our patient with KLS. The FDG PET CT revealed hypometabolism during the terminal phase of sleep. Diminished activity of thalamus is known to induce sleep as described earlier. The F-DOPA PET CT scan was done while the child was recovering from his sleep cycle i.e. at 48 hours after the sleep cycle. The scan showed increased dopaminergic activity in the basal forebrain and adjoining medial temporal region. This can be attributed to stimulation of basal forebrain by dopaminergic pathway that is known to evoke waking. Within the ascending arousal system, the thalamus receives inputs from pedunculopontine pathway and laterodorsal tegmental nuclei. These facilitate the thalamocortical pathway. The mediators for secondary pathway include histamine, dopamine, serotonin, noradrenaline. Thus, the dopaminergic activity seen in the basal forebrain and medial temporal cortex n our patient explains the ascending arousal pathway.

There is a complex neurotransmitter circuitry involved in sleep wake cycle. Most of the studies are done on animal models to explain various pathways of neurotransmission to explain the sleep wake mechanism. However, other than FDG PET CT we did not come across any publication related to F DOPA pattern in KLS. As this molecule plays critical role in various neurologic functions, further studies may help to identify its role in sleep wake cycle in greater detail.

4. Source of Funding

No funding or grant support.

5. Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Kleine W. Periodische Schlafsucht. *Monatsschr Psychiatr Neurol*. 1925;57:285–304. doi:10.1159/000190426.
2. Levin M. Periodic somnolence and morbid hunger: A new syndrome. *Brain*. 1936;59(4):494–504. doi:10.1093/brain/59.4.494.
3. Hong SB, Joo EY, Tae WS, Lee J, Han SJ, Lee HW, et al. Episodic diencephalic hypoperfusion in Kleine-Levin syndrome. *Sleep*. 2006;29(8):1091–93. doi:10.1093/sleep/29.8.1091.
4. Landtblom AM. Temporal lobe dysfunction in Kleine–Levin syndrome. *Acta Neurol Scand*. 2003;107(4):306. doi:10.1034/j.1600-0404.2003.00091.x.
5. Saper C, Scammell T, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437(7063):1257–63. doi:10.1038/nature04284.
6. Carpenter S, Yassa R, Ochs R. A pathologic basis for Kleine-Levin syndrome. *Arch Neurol*. 1982;39(1):25–8. doi:10.1001/archneur.1982.00510130027005.
7. Engström M, Karlsson T, Landtblom AM. Reduced thalamic and pontine connectivity in Kleine-Levin syndrome. *Front Neurol*. 2014;5:42. doi:10.3389/fneur.2014.00042.
8. Sapers CB, Chou TC, Schemmel TE. The sleep switch hypothalamic control of sleep and wakefulness. *Trends Neurosci*. 2001;24(12):726–31. doi:10.1016/s0166-2236(00)02002-6.
9. Strecker RE, Morairty S, Thakkar MM, Porkka-Heiskanen T, Basheer R, Dauphin LJ, et al. Adenosinergic modulation of basal forebrain and pre optic/ anterior hypothalamic neuronal activity in the control of behavioural state. *Behav Brain Res*. 2000;115(2):183–204. doi:10.1016/s0166-4328(00)00258-8.
10. Hallanger AE, Levey AI, Lee HJ, Rye DB, Wainer BH. The origins of cholinergic and other subcortical afferents to the thalamus in the rat. *J Comp Neurol*. 1987;262(1):105–24. doi:10.1002/cne.902620109.
11. Chemelli RM. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell*. 1999;98(4):437–51. doi:10.1016/s0092-8674(00)81973-x.
12. Ranson SW. Somnolence caused by hypothalamic lesions in monkey. *Arch Neurol Psychiatr*. 1939;41(1):1–23. doi:10.1001/archneurpsyc.1939.02270130011001.
13. Gaus SE, Strecker RE, Tate BA, Parkar RA, Saper CB. Ventrolateral preoptic nucleus contains sleep active, galaninergic neurons in multiple mammalian species. *Neuroscience*. 2002;115(1):285–94. doi:10.1016/s0306-4522(02)00308-1.
14. Sherin JE, Shiromani PI, Mccarley RW, Saper CB. Activation of ventrolateral preoptic neurons during sleep. *Science*. 1996;271(5246):216–9. doi:10.1126/science.271.5246.216.
15. Szymusiak R, Alam N, Steininger TL, Mcginty D. Sleep waking discharge patterns of ventrolateral preoptic/anterior hypothalamic neurons in rats. *Brain Res*. 1998;803(1-2):178–88. doi:10.1016/s0006-8993(98)00631-3.
16. Chou TC. Afferents to the ventrolateral preoptic nucleus. *JNeurosci*. 2002;22(3):977–90. doi:10.1523/JNEUROSCI.22-03-00977.2002.
17. Mesulam MM, Mufson EJ, Wainer BH, Levey AI. Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1-Ch6). *Neuroscience*. 1983;10(4):1185–201. doi:10.1016/0306-4522(83)90108-2.
18. Dahan L, Astier B, Vautrelle N, Urbain N, Kocsis B, Chouvet G, et al. Prominent burst firing of dopaminergic neurons in the ventral tegmental area during paradoxical sleep. *Neuropsychopharmacology*. 2007;32(6):1232–41. doi:10.1038/sj.npp.1301251.

Author biography

Shrikant V Solav, Incharge Consultant https://orcid.org/0000-0002-4653-9912

Shailendra V Savale, Consultant https://orcid.org/0000-0002-2124-8254

Aman Shrikant Solav, Incharege Consultant

Suresh Lajpatrai Balani, NM Physicist

Cite this article: Solav SV, Savale SV, Solav AS, Balani SL. FLUORO-DOPA pattern in Kleine Levin syndrome. *IP Indian J Neurosci* 2022;8(3):208-211.