Sleep Medicine 62 (2019) 29–31

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sodium oxybate (Xyrem) treatment in severely sleep-deprived child with Epstein–Barr virus encephalitis with lesion of sleep-wake regulation system: a case report

Malene Landbo Børresen [a, *], Kaare Engell Lundstrøm [a], Marianne Ifversen [a], Poul Jørgen Jennum [b]

[a] Department of Pediatric and Adolescent Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[b] Danish Center of Sleep Medicine, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 18 November 2018
Received in revised form
6 March 2019
Accepted 7 March 2019
Available online 10 April 2019

Keywords:
GHB
Gamma-hydroxybutyrate
GABA
Hemophagocytic lymphohistiocytosis
X-linked lymphoproliferative disease (XLP)
Duncan's disease

ABSTRACT

We present the effect of exogenous sodium oxybate (GHB) in a severely tormented boy unable to sleep and unable to be anesthetized due to a lesion in the sleep initiation system involving the tracks between the ventrolateral preoptic nucleus and the reticular system. We bypassed the system by using sodium oxybate's effect on the cortical GHB and $GABA_B$ receptors involved in the initiation and maintenance of sleep.

1. Introduction

We describe here a child diagnosed with X-linked lymphoproliferative disease with hemophagocytic lymphohistiocytosis secondary to Epstein–Barr virus (EBV) infection who was unable to sleep; presumably due to lesion in the sleep initiation system involving the tracks between the ventrolateral preoptic nucleus (VLPO) and the reticular system.

Encephalitis is an acute diffuse inflammation of the brain, with neurological dysfunction. It is due to infection of the brain parenchyma, for example with EBV or other pathogens [1].

Hemophagocytic lymphohistiocytosis (HLH) is a rare life-threatening condition with severe hyper-inflammation caused by uncontrolled proliferation of activated lymphocytes and macrophages that secrete high amounts of pro-inflammatory cytokines. It is characterized by fever, pancytopenia, high levels of ferritin, triglycerides, liver enzymes, and organomegaly [2]. It can be initiated by an infection with EBV in susceptible individuals, for instance in children with immune deficiencies involving degranulation of cytotoxic granules in lymphocytes.

X-linked lymphoproliferative disease (XLP, Duncan's disease) is characterized by immune deficiency involving a reduced ability to clear EBV infection, often leading to an HLH-like clinical pattern.

Gamma-hydroxybutyrate (GHB) is a naturally occurring neurotransmitter and neuromodulator. It acts on the GHB receptor, which has the highest density in the hippocampus, gray matter cerebral cortex, and the nucleus accumbens in the striatum. GHB is also a weak agonist with low affinity at the $GABA_B$ receptor, which has the highest density in the cerebellum, thalamus, followed by hippocampus, as well as at the $GABA_A$ receptor in the hippocampus [3]. GHB is the active ingredient in the prescription medication sodium oxybate (Xyrem). Sodium oxybate is used for treatment of narcolepsy because of its effect on excessive daytime somnolence (EDS) and cataplexy attacks [4]. GHB has been shown to increase slow-wave sleep and decrease the tendency for rapid eye movement (REM) sleep in modified multiple sleep latency tests, and may help sleep disruption, hypnagogic hallucinations, and sleep paralysis [5,6].

* Corresponding author. Department of Pediatric and Adolescent Medicine, University Hospital Rigshospitalet, Blegdamsvej 9, Dk-2300, Copenhagen Ø, Denmark.
E-mail address: Mboe0097@regionh.dk (M.L. Børresen).

https://doi.org/10.1016/j.sleep.2019.03.020
1389-9457/

2. Case report

A two-year-old boy was admitted to the hospital with continuous fever, signs of encephalitis with seizures, and lethargy with slowness and apathy. Laboratory tests showed an alanine aminotransferase peak value of 1940 U/L, upper limit of normal (ULN) 45 U/L; lactate dehydrogenase peak value of 5000 U/L, ULN 450 U/L; ferritin peak value 14,500 μg/L, ULN 200 μg/L; cerebrospinal fluid (CSF) leucocytes 131 cells/L, ULN 5 cells/L; CSF protein 1.65, ULN 0.45 g/L; high EBV DNA viral load peak values 113,000, 84,000, and 6,500 copies/ml in the CSF, blood and bone marrow, respectively. Magnetic resonance imaging (MRI) of the brain showed symmetric signal changes in the dorsal part of pons as well as unspecific changes in thalamus. Electroencephalography (EEG) showed slow wave activity 1.5–2 Hz, amplitude up to 370 μV, without paroxysmal activity, consistent with encephalitis. The child was diagnosed with HLH and EBV encephalitis. Further diagnostic test results were consistent with X-linked lymphoproliferative disease (XLP, Duncan's disease) with very low levels of intracellular SAP (signaling lymphocytic activation molecule–associated protein) in the natural killer (NK) cells. Multiplex ligation-dependent probe amplification (MLPA) analysis showed a deletion encountering the whole SH2D1A gene on the X chromosome; the deletion was acquired from his mother. Seizures occurred but levetiracetam was continued.

However, a few days after admission, the boy developed neurological symptoms comprising severe encephalopathy with motor agitation, as well as severe fear and inability to sleep. He had difficulties initiating sleep, and after falling asleep he woke up very quickly. Multiple sedatives including midazolam, barbiturates (phenobarbital and thiopental), ketamine, clonidine, risperidone, haloperidol, levomepromazine, and promethazine, as well as morphine, were used to induce sleep and to calm him down; these were either without any long-lasting effect or were withdrawn because of unacceptable side effects as extra pyramidal side effects and agitation. After 14 days with a minimum of sleep, the boy was intubated with the purpose of inducing deep sedation and sleep. Despite high doses of propofol, fentanyl, midazolam, clonidine, and risperidone the child was intermittent agitated and severely tormented, trying to extubate himself.

Intubated at the intensive care unit, the boy was treated with a test dose of 2 g sodium oxybate (Xyrem) during continuous EEG monitoring. A short-lasting stage 3 sleep was induced, followed by an alternating stage 2 (N2) and 3 (N3), pattern with longer- and longer-lasting periods of slow waves. During the monitoring, the child woke up with withdrawal symptoms; he therefore also received 5 mg of midazolam intravenously. The boy slept in total 1.5 h, including 1 h with slow-wave sleep, much longer than had been observed the previous 14 days. An algorithm of 2 g of sodium oxybate at 20:00 and at midnight, as well as an optional additional dose in the early morning, was initiated. To avoid withdrawal symptoms, baseline lorazepam and clonidine were continued. The boy was extubated and transferred to the intermediate care pediatric ward.

Over the next few weeks, his sleep pattern improved considerably, and the boy was less tormented during day. The other sedatives were tapered off. One month after initiation of sodium oxybate, PSG showed a normal sleep pattern and a classic effect of sodium oxybate with induction of low frequency delta sleep. A lumbar puncture was performed to rule out secondary narcolepsy. A normal hypocretin level in the CSF (364 ng/L, normal value > 200 ng/L) was observed, along with normal proteins and no cells.

Sodium oxybate was tapered off over the next weeks, and the boy maintained a good sleep pattern.

Concurrent treatment for the hyper-inflammatory condition with intravenous rituximab initially biweekly (375 mg/m^2) was initiated, as well as HLH therapy according to HLH2004 protocol with daily dexamethasone (10 mg/m^2) plus weekly etoposide (150 mg/m^2) as well as a series of four intrathecal methotrexate and methylprednisolone administrations weekly, with good clinical response. The sleep pattern was unaffected by his HLH and EBV treatment. Three months after admission, he was successfully treated with an allogeneic bone marrow transplantation with a matched sibling donor (sister). At follow-up six months post-transplantation, his sleep pattern was normalized, and no major neurological deficits were observed. The child remains full donor chimera, is off immune suppression with no graft-versus-host disease 15 months after transplantation, and is developing age appropriately.

Written consent to publish the case report was obtained from the parents.

3. Discussion

Sleep–wake regulation is a complex interaction between excitatory and inhibitory neurotransmitters. There is a complicated and not yet fully understood interaction between the neurons in the median preoptic nucleus (MnPn) and the ventrolateral preoptic nucleus (VLPO) in the onset and maintenance of sleep by means of inhibiting the reticular activating system. The MnPn plays an important but not exclusive role in promoting the onset of sleep and non–rapid eye movement (NREM) sleep, whereas neurons in the VLPO play a role in the maintenance of sleep. Initiation of sleep is based mainly on the activation of neurons in the sleep-promoting nuclei MnPn and VLPO as well as in the brainstem, hypothalamus, and the basal forehead. It is caused by inhibitory GABAergic activity on the wakefulness-promoting area (ie, the reticular activation system in the brainstem) as well as on the histaminergic tuberomammillary nucleus in the hypothalamus. This leads to the inhibition of cholinergic, noradrenergic, and serotonergic activity in these areas. Hence, it is an increased inhibitory mechanism that initiates but also withholds sleep.

We suspected a lesion in the sleep initiation system involving the tracks between the VLPO in the anterior part of hypothalamus to the reticular system in the upper part of the brainstem, which

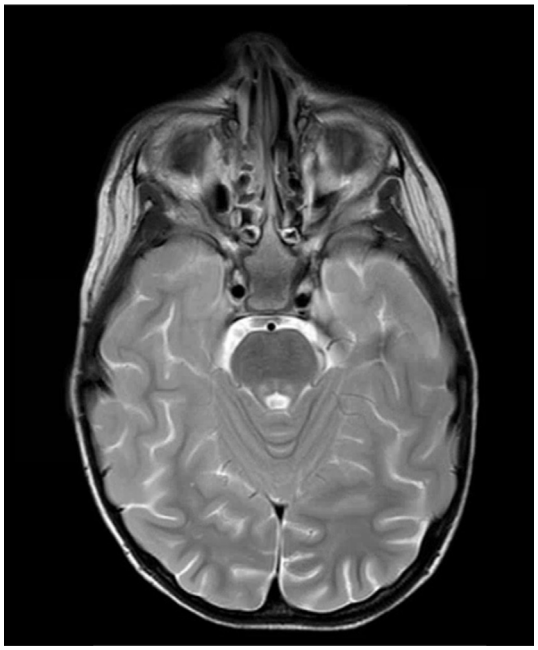

Fig. 1. MRI of brain, T2W_TSI image. Symmetrical changes in the dorsal part of pons with inhibition of diffusion at colliculus facialis.

corresponded to the changes found on MRI (Fig. 1). VLPO is active during sleep and releases GABA, which inhibits the reticular system. A lesion in the VLPO–reticular tract results in no effect of $GABA_A$-agonistic/positive allosteric modulators (PAM), which could explain agitation and sleeplessness despite unusually high doses of benzodiazepines, barbiturates, and propofol, which act mainly on the $GABA_A$-receptor. We aimed to use sodium oxybate for its effect on the $GABA_B$ receptors in the thalamus that induce deep stage 3 NREM sleep with slow waves (ie, delta-waves) [7].

We speculated as to whether baclofen would have the same effect on the $GABA_B$ receptors in the thalamus and would induce sleep. Baclofen is a selective $GABA_B$ receptor agonist used for treating spasticity. Its mechanistic action is not yet fully understood, but it has a muscle tone–regulating effect on the brainstem. However, recently, Niewenhuijzen et al., showed in rats that several brain regions, including the supra-optic and paraventricular nuclei of the hypothalamus and the central nucleus of the amygdala, were activated by both GHB and baclofen, indicating activation of $GABA_B$-receptors, GHB receptors, or both [8]. However, GHB but not baclofen induced c-Fos expression in the median raphe nucleus and the dentate gyrus of the hippocampus, as well as in several brain regions involved in sleep physiology. Furthermore, because baclofen has a respiratory depression effect, we do not believe that baclofen in a tolerated dose could have been used therapeutically to induce sleep via cortical $GABA_B$ receptors.

4. Conclusion

In conclusion, this case history reports, for the first time to our knowledge, the effect of exogenous sodium oxybate (GHB) in a severely tormented boy unable to sleep, presumably due to a lesion in the system involving the tracks between the ventrolateral preoptic nucleus and the reticular system. We bypassed the system by using sodium oxybate's effect on the cortical GHB and $GABA_B$ receptors involved in the initiation and maintenance of sleep.

Conflict of interest

All authors declared that they have no competing interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.03.020.

References

[1] Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013;57:1114–28.
[2] Ramachandran S, Zaidi F, Aggarwal A, et al. Recent advances in diagnostic and therapeutic guidelines for primary and secondary hemophagocytic lymphohistiocytosis. Blood Cells Mol Dis 2017;64:53–7.
[3] Kamal RM, Van Noorden MS, Franzek E, et al. The neurobiological mechanisms of gamma-hydroxybutyrate dependence and withdrawal and their clinical relevance: a review. Neuropsychobiology 2016;73(2):65–80.
[4] Kornum BR, Knudsen S, Ollila HM, et al. Narcolepsy. Nat Rev Dis Prim. 2017 Feb 9;3:16100.
[5] Walsh JK, Hall-Porter JM, Griffin KS, et al. Enhancing slow wave sleep with sodium oxybate reduces the behavioral and physiological impact of sleep loss. Sleep 2010 Sep;33(9):1217–25.
[6] Moghadam KK, Pizza F, Primavera A, et al. Sodium oxybate for idiopathic REM sleep behavior disorder: a report on two patients. Sleep Med 2017 Apr;32:16–21.
[7] Scammell TE, Arrigoni E, Lipton JO. Neural circuitry of wakefulness and sleep. Neuron 2017 Feb 22;93(4):747–65.
[8] van Nieuwenhuijzen PS, McGregor IS, Hunt GE. The distribution of γ-hydroxybutyrate-induced Fos expression in rat brain: comparison with baclofen. Neuroscience 2009 Jan 23;158(2):441–55.