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CASE REPORTS

Steroids: A Wake-Up Call in TBI Induced Hypersomnolence

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Hypersomnolence is one of the more common symptoms reported after mild traumatic brain injury (TBI) and often one of the most difficult to treat. This case series presents a cohort of patients with TBI related hypersomnolence associated with a de novo autoimmune process that successfully resolved with pulse dose corticosteroid treatment. When associated with an autoimmune inflammatory process, corticosteroids may serve to stabilize the blood brain barrier leading to the successful and sustained resolution of TBI induced sleepiness.

Keywords: autoimmune encephalitis, concussion, sleep disorders, steroids

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INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability in the United States with a significant impact on health care utilization.[1] There has been a significant interest in the pathophysiology of TBI resulting from sport related injuries, fueled by recent media exposés into the concussions of American football players. Concussions, the mildest form of TBI, are broadly categorized as closed head injuries with axonal injury. There are no objective criteria to categorize mild TBI and the spectrum of post-concussion sequelae vary greatly. Most frequently described entities are chronic traumatic encephalopathy and post-concussion syndrome. Autoimmune hypersomnolence as a result of mild TBI is not well documented in the literature. In this series we present 5 adolescents with suspected concussion related autoimmune hypersomnolence with a remarkable response to immune modulation.

CASE SERIES

Five adolescents, ages 14–17, presented to the outpatient neurology department at a tertiary care center with the chief complaint of hypersomnolence. Prior to this presentation all 5 had no medical ailments reported. All 5 patients developed progressive symptoms within 3 months after the suspected sports related concussive event and all 5 patients developed hypersomnia within 3 to 14 days after the event. Other associated symptoms included self-reported insomnia, with daytime sleepiness (Epworth Sleepiness Scale [ESS] scores of 12 or more [range 12–16]), headaches, and depression. Two of the five patients reported parasomnias in the form of confusional arousals and sleep walking.

Brain magnetic resonance imaging (MRI) was negative for any abnormalities in all 5 patients. All 5 patients had overnight attended polysomnography (PSG) with a subsequent Multiple Sleep Latency Test (MSLT) performed to help elucidate the etiology of hypersomnolence. PSG in all 5 patients revealed prolonged sleep latency and fragmented sleep. All 5 patients had a mean onset sleep latency of less than 8 minutes (range 5–7 minutes), and 2 patients had at least one sleep onset REM period observed on the MSLT. Electroencephalography (EEG) were negative in all 5 patients. All patients underwent a serologic workup which resulted in an elevated erythrocyte sedimentation rate (range 20–40). An autoimmune panel revealed 3 patients with autoantibodies to glutamic acid decarboxylase (GAD); 1 patient with autoantibodies to voltage gated potassium channels (VGKC); and 1 patient with autoantibodies to N-methyl-D-aspartate (NMDA). All patients had a negative malignancy workup. All GAD titers were greater than 0.03 nmol/L. All patients had hemoglobin A1C titers within the normal range.

Most of these patients were treated with either a stimulant for their hypersomnolence or melatonin for their insomnia prior to presenting to our center. All 5 patients were pulsed with 1 gram of solumedrol daily for 3 days at our infusion center. Three patients had a complete and sustained resolution of all concussion related symptoms, primarily hypersomnia. Two patients had a recurrence of TBI related symptoms at least 2 months after treatment with steroids and received an additional course of solumedrol at 1 gram on a monthly basis for an additional 3 months. Complete and sustained resolution was documented in these 2 patients after the additional steroid course. All 5 patients have been followed for at least 6 months after completed treatment and have not had symptom recurrence. All 5 patients had a post-treatment ESS score of 8 or lower (range 6–8). Patient characteristics are summarized in **Table 1**.

Table 1—Patient characteristics.

Patient	Age (y)	Sex	Type of TBI	Onset of TBI (mo)	Hypersomnia Onset (days after TBI)	Other Sleep Symptoms	Neurological Symptoms	Pre-TX ESS	Post-TX ESS	Mean SOL (minutes)	No. of SOREMP	Serum Auto-Antibody	Symptom Recurrence	Stimulant Therapy Prior to Steroid Therapy
1	14	F	Concussion	12	7	Insomnia, parasomnia	Headache, Depression	14	8	6	1	GAD	No	Modafinil
2	16	F	Concussion	10	3	Insomnia	Depression	15	7	5	0	VGKC	No	Modafinil, armodafinil
3	17	F	Concussion	14	5	Insomnia	Headache	15	5	7	1	GAD	Recurrence at 3 mo: treated with solumedrol (1 g/mo × 3 mo)	Armodafinil
4	15	M	Concussion	8	14	Insomnia, parasomnia	Headache	16	8	5	0	NMDA	No	Modafinil, armodafinil
5	16	F	Concussion	15	10	Insomnia	Headache, depression	12	6	7	0	GAD	Recurrence at 2 mo: treated with solumedrol (1 g/mo × 3 mo)	Modafinil

ESS = Epworth Sleepiness Scale, GAD = glutamic acid decarboxylase, NMDA = N-methyl-D-aspartate, SOL = sleep onset latency, SOREMP = sleep onset REM period, TBI = traumatic brain injury, TX = treatment, VGKC = voltage gated potassium channels.

DISCUSSION

The case series presented is the first, to our knowledge, that describes complete resolution of concussion related autoimmune hypersomnolence with steroids. Sleep disturbances after TBI are reported in 30% to 70% of the adult population, and in 10% to 38% of children.[2] The link between TBI and autoimmune processes, such as encephalitis, has been infrequently reported. EEG, MRI, and histopathology confirmed Rasmussen's encephalitis has been reported to occur after TBI, was treated with immunosuppressants, yet developed refractory partial epilepsy needing surgical resection.[3] Secondary NMDA encephalitis has been associated with an immune mediated relapse of primary herpes simplex virus encephalitis, with successful resolution after immunotherapy.[4] Similarly, our cohort presented with autoimmune hypersomnolence temporally related to mild brain injury.

The spectrum of TBI related sleep disorders is wide and depends on the intracranial structures damaged during the injury.[5] Coup-countercoup brain injury occurs in the skull base with damage to the inferior frontal and anterior temporal regions which includes the basal forebrain, the site of sleep initiation. This results in insomnia. TBI related hypersomnolence, also known as posttraumatic hypersomnia, may be seen when areas involved in the maintenance of wakefulness are damaged. These may include the brainstem reticular formation, posterior hypothalamus, and suprachiasmatic nucleus and its projections. Any form of brain injury can lead to damage to these wakefulness centers and result in hypersomnolence. High cervical spine damage such as often occurs in car and motorcycle accidents can lead to posttraumatic hypersomnolence as well. In general, the degree of hypersomnolence correlates with the severity of TBI. In children, sleep disorders caused by moderate or severe TBI can lead to worse functional outcomes, and may lead to academic, social, and psychological sequelae.

Brain injury of any type may also lead to circadian dysregulation and subsequent sleep disturbances such as initiation and maintenance insomnia as well as hypersomnia. To objectively determine a circadian rhythm change dim light melatonin onset should be measured. This measurement was not done in our cohort given the observational nature of our study. The mechanisms for circadian disruption as a result of TBI are not well understood, but suspect injury to the suprachiasmatic nucleus is one possible etiology.

The diagnosis of TBI related hypersomnolence follows standard practice guidelines, and includes attended PSG followed by the MSLT. A diagnosis of posttraumatic hypersomnia is made when symptoms are present for at least 3 months, the mean onset sleep latency is less than 8 minutes, and there are less than two sleep onset REM periods. PSG results show prolonged sleep onset latencies and reduced sleep efficiency, as reported in this case series. Initial treatment is often aimed at symptom control and includes stimulant use as well behavioral modifications. The success of this treatment varies with some studies reporting modafinil use to result in a lower ESS score, and others reporting no improvement in sleepiness.[6,7] In our case series, our patients did not have any significant improvement in symptoms with stimulant use.

Acute brain injury leads to secondary injury that involves inflammation, astrogliosis, oxidative stress, and alters the dynamics of the blood brain barrier (BBB). Under steady state conditions the BBB acts as a boundary between the systemic blood supply and that of the brain itself. Appropriate metabolic proteins, nutrients, and cells are allowed to cross from the blood into the brain through the "guardians" of the BBB, the tight-junction endothelial cells. A secondary surveillance system, the glymphatic system, that is astrocytic aquaporin-4 mediated, may contribute to the clearance of harmful proteins from the cerebrospinal fluid. Like the endothelial barrier, the glymphatic barrier is susceptible to breakdown as a result of TBI. If the BBB is altered, the system of checks and balances no longer exists and all substances, both harmful and beneficial, are free to flow down their concentration gradients from the blood to the cerebrospinal fluid, and vice versa. The

activation of the peripheral immune system as a result of TBI may lead to the generation of autoantibodies against brain antigens that may be detrimental to the brain once the BBB is compromised. Additionally, non-TBI related diseases such as stroke, seizures, and dementia may be affected by the presence of these autoantibodies as well.[8]

The most commonly described autoantibody induced by TBI is against S100B which is expressed primarily by astrocytes and Schwann cells, and functions in the cell cycle, and has been proposed as a marker of brain injury severity in the setting of concussion.[8] In our case series, we have identified 3 autoantibodies: VGKC, NMDA, and GAD that were induced by TBI. These autoantibodies are traditionally associated with encephalitis which was excluded in our patient cohort with negative brain imaging and EEG, with the limitation of not being able to perform confirmatory lumbar punctures in this age group in an outpatient setting. In general, NMDA and VGKC autoantibodies are directed against cell surface antigens, while GAD autoantibodies are directed against intracellular neuronal proteins. Serum autoantibodies against GAD may be seen in 1% of healthy individuals as well as in about 80% of individuals with type 1 diabetes mellitus.[9] Diabetes mellitus was excluded in all 3 patients who tested positive for the GAD autoantibody. All three autoantibodies are known to affect the limbic system which is home to the suprachiasmatic and ventrolateral preoptic nuclei as well as to the orexinergic neurons (lateral hypothalamic area) of the hypothalamus. The suprachiasmatic nucleus and ventrolateral preoptic control the circadian rhythm and act as a "flip-flop" switch between sleep and wakefulness, respectively. The lateral hypothalamic area area is responsible for wakefulness. Our patients primarily complained of hypersomnolence which is expected based on the autoantibodies generated, but interestingly there were no recognizable symptom syndromes commonly associated with these autoantibodies as are described in classic forms of infectious, neoplastic, and paraneoplastic forms of limbic encephalitis.

The exact mechanism of induction of these autoantibodies in our patients is unknown but it can be postulated that the inflammatory process resulting from TBI led to their generation. Theoretically, the use of pulse dose corticosteroids stabilized the BBB and served as an immunomodulator to prevent further downstream sequela of a chronically induced inflammatory process. It is important to note that in individuals over 16 years of age corticosteroids are no longer recommended in moderate to severe TBI because of increased 6-month mortality, but the increase in mortality was not substantiated in mild TBI.[10] It is also unknown if the use of corticosteroids would have the same effect on hypersomnolence as a result of mild TBI without an autoantibody response.

Immunosuppression is a novel approach to the treatment of hypersomnolence after TBI especially when few cases successfully resolve spontaneously. In our cohort, it may be postulated that it is the auto reactivity induced by TBI, and that manifests clinically as hypersomnolence, that is treated by corticosteroids. Immunomodulation effectively stops the chronic inflammatory processes that lead to the generation of auto antibodies. Further prospective monitoring of our patient cohort is underway to assess the duration of remission of hypersomnolence. Our case series opens up a possible therapeutic pathway for TBI related hypersomnolence, both autoimmune related and not, and should guide future observational and therapeutic studies in the field.

ABBREVIATIONS

BBB, blood brain barrier
EEG, electroencephalography
ESS, Epworth Sleepiness Scale
GAD, glutamic acid decarboxylase
MRI, magnetic resonance imaging
MSLT, Multiple Sleep Latency Test
NMDA, N-methyl-D-aspartate
PSG, polysomnography
REM, rapid eye movement
TBI, traumatic brain injury
VGKC, voltage gated potassium channels

REFERENCES

1. Casson IR, Viano DC, Powell JW, Pellman EJ. Twelve years of National Football League concussion data. *Sports Health*. 2010;2(6):471–483.
2. Oullet MC, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury, frequency, characteristics, and risk factors. *J Head Trauma Rehabil.* 2006;21(3):199–212.
3. Soh D, Cordato DJ, Bleasel AF, Brimage P, Beran RG. Can head trauma trigger adult-onset Rasmussen's encephalitis? *Epilepsy Behav.* 2017;74:119–123.
4. Nosadini M, Mohammad SS, Corazza F, et al. Herpes simplex virus-induced anti-N-methyl-D-aspartate receptor encephalitis: a systematic literature review with analysis of 43 cases. *Deve Med Child Neurol.* 2017;59(8):796–805.
5. Singh K, Morse AM, Tkachenko N, Kothare SV. Sleep disorders associated with traumatic brain injury-a review. *Pediatr Neurol.* 2016;60:30–36.
6. Kaiser PR, Valko PO, Werth E, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. *Neurology.* 2010;75(20):1780–1785.
7. Jha A, Weintraub A, Allshouse A, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil.* 2008;23(1):52–63.
8. Dadas A, Janigro D. The role and diagnostic significance of cellular barriers after concussive head trauma. *Concussion*. 2018;3(1):CNC53.
9. Finelli PF. Autoimmune limbic encephalitis with GAD antibodies. *Neurohospitalist.* 2011;1(4)178–181.
10. Edwards P, Arango M, Balica L, et al. Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet*. 2005;365(9475):1957–1959.

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DISCLOSURE STATEMENT

Work for this study was performed at Cohen Children's Medical Center and Lenox Hill Hospital, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell. The authors report no conflicts of interest.