A Case of Suspicious Encephalitis Lethargica Accompanied by Visual Acuity Decrement

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Abstract

Encephalitis lethargica (EL) is a CNS disorder presenting with pharyngitis followed by sleep disorder, basal ganglia signs (particularly parkinsonism), and neuropsychiatric sequelae. It was first described in 1916, but only sporadic cases have been described since the 1916-1927. EL is a rare disease and difficult to confirm because no diagnostic criteria have been agreed. Its additional common features include oculogryric crises and oculares features (ophthalmoplegia and ptosis). However, no case of decreasing visual acuity has been previously reported. We report a case of EL with accompanying bilateral blindness. A 31-year-old female patient visited our emergency room complaining of a headache, fever, pharyngitis, and poor oral intake. After the fever and headache subsided, the patient experienced drowsiness and bilateral decreases in visual acuity.

Brain magnetic resonance imaging (MRI) showed increased signal intensity on the hypothalamus on fluid attenuation inversion recovery (FLAIR) and T2 weighted images, which was compatible with EL. Although we critically discuss other potential etiologies, we conclude that her blindness constitutes an unusual presentation of EL.

Keywords: Encephalitis lethargica; Encephalitis, Narcolepsy; Polysomnography; Multiple sleep latency test; Von economo; Decrement of visual acuity; VEP

Introduction

Encephalitis lethargica (EL) is a neurologic complication that may result from influenza or an immune-mediated disease. Other than sleep disturbance, lethargy and extrapyramidal movements are characteristic of EL. Von Economo noted neuropsychiatric disorders (e.g., catatonia, obsessive or compulsive disorder, and mutism) were common in survivors. Other common features included oculogyric crises, ocular features (ophthalmoplegia and ptosis) and central cardiorespiratory features (particularly hiccoughs) [1]. MRI of the brain was normal in 60% but showed inflammatory changes localized to the hypothalamus in 40% of patients.1 However, no of associated loss of vision has been previously reported.

Our patient developed loss of vision progressively in a short time, which could not be explained by ocular examination or a brain lesion. This raised the possibilities of other underlying etiologies, but her clinical symptoms, polysomnography, and MRI findings suggested that the bilateral blindness was an unusual complication of EL.

Summary of Case

A 31 year-old female presented at our centre with headache and fever. She had suffered from a headache for about 3 weeks, and 2 weeks previously, her symptoms were aggravated by nausea and vomiting. She also complained of right monocular diplopia and visual dimness. She had suffered from a headache for about 3 weeks, and 2 weeks previously, her symptoms were aggravated by nausea and vomiting. She also complained of right monocular diplopia and visual dimness. Other than fever. She had suffered from a headache for about 3 weeks, and 2 weeks previously, her symptoms were aggravated by nausea and vomiting. She also complained of right monocular diplopia and visual dimness. Other than
because of the absence of any brain lesion and of any space disseminated MS lesion. Tb meningitis was viewed unlikely because acid bacillus (AFB) stain, culture, and Tb PCR of CSF (cerebrospinal fluid) were negative and CSF adenosine deaminase was not increased.

A week later, she only stayed awake for about 5 to 10 minutes at mealtimes. Sleep polysomnography was checked due to her drowsy mental state and it showed abnormal sleep architecture. Sleep latency was 1 minutes and sleep efficiency was 84.30%. Her arousal index was 23.4 /hour, wakefulness after sleep onset (WASO) was 15.59%, apnea/ hypopnea index was 0 per hour of sleep. On the same day multiple sleep latency testing (MSLT) was performed. Sleep latency shorted to 12 seconds. In addition, Sleep Onset Rapid EYE Movement (SOREM) was observed during each MSLT test (Figure 3). We started 'Modafinil' at 200 mg per day and her symptoms improved slightly (Tables 1 and 2).

Although mild improvements in mental state and other general symptoms, such as, fever and headache, were observed, she remained drowsy and her visual acuity did not improve. The patient discharged and asked to maintain her medication.

Discussion

In recent years, encephalitis lethargica, as described by Von Economo, has become a rare disease. Previously Von Economo described three main types of acute illness during the pandemic that range from 1914 to 1930, which was of the somnolent-ophthalmoplegic form, the akinetic-mute form, or the hyperkinetic form [2].

Although several case reports of sporadic encephalitis lethargica have been described in the last 30 years, details of the acute phase have often been poorly documented despite the fact that the diagnosis is reliant on its clinical features. Rail et al. [3] provided a detailed account of the acute illness, which concurred well with the original description of Von Economo, and outlined several clinical features that help to distinguish encephalitis lethargica from other encephalitides associated with extrapyramidal syndrome as, an encephalitic illness with parkinsonian features developing acutely or after a oculogyric crises or alteration in sleep cycle or ocular or pupillary changes, or involuntary movements (e.g., dystonia, myoclonus), mental changes, or corticospinal tract signs.

Howard and Lees reinforced these criteria and defined encephalitis lethargica as an acute or subacute encephalitic illness including at least three of the following criteria, after excluding all other known causes of encephalitis: (i) signs of basal ganglia involvement, (ii) oculogyric crises, (iii) ophthalmoplegia, (iv) obsessive-compulsive behavior, (v) akinetic mutism, (vi) central respiratory irregularity, and (vii) somnolence and/or sleep inversion. In addition, he added further investigative criteria, such as abnormalities of cerebrospinal fluid (CSF; lymphocytosis, increased protein levels, oligoclonal bands), EEG changes (diffuse slow wave abnormalities), and visual evoked potential abnormalities [4].

Our case patient did not meet the diagnostic criteria but had sufficient extra symptoms and abnormal investigative findings to suspect EL. Her first symptoms were a headache and fever, disease progression, daytime sleepiness developed. She also showed ocular symptom, such as, ophthalmoplegia and decrement of visual acuity with abnormal VEP findings. Brain MRI showed increased signal intensity on the hypothalamus of FLAIR and T2W images, which is related with consciousness. CSF analysis showed pleocytosis and protein elevation. Thus, although her clinical symptoms met only two of the six essential features of EL, her distinctive somnolent and ophthalmoplegic symptom and abnormal brain MRI, CSF, and VEP findings suggested an unusual form of EL.

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Figure 3: Results for the five naps in the MSLT test. Total five sleep-onset REM periods (SOREMPs) are observed. Time in X-axis shows the clock time during the different hours of the day. Y-axis shows each stage of the sleep. Red box indicates REM sleep.

| Time               |   |
|--------------------|---|
| Total sleep time   | 341 min |
| Stage 1 sleep      | 76.5%   |
| Stage 2 sleep      | 4.8%    |
| Slow wave sleep    | 0%      |
| REM sleep          | 18.6%   |
| Total movement time| 0 min   |
| WASO               | 63 min  |
| Latency to onset   | 1 min   |
| Latency to REM sleep| 0 min  |
| Sleep efficiency   | 84.30%  |
| PLM index          | 11.8 per hour |

Abbreviation: REM: Rapid Eye Movement; WASO: Wake After Sleep Onset; PLM: Periodic Limb Movement

Sleep latency is from light out to the first epoch of sleep.

Table 1: All-night polysomnographic data obtained at the night before MSLT test. The patient shows frequent arousal, periodic limb movements in sleep, and abnormal sleep architecture in the polysomnography.

Furthermore, as compared with previously reported EL cases, our patient had previously unreported neurologic symptoms. In particular, she had distinctive ocular symptoms, that is, decrement of visual acuity, a pupillary light abnormality, and diplopia. Although several reports have described pupillary light abnormality and diplopia in EL patients, 1 damaged visual acuity has not been reported to date. The absence of left P100 waves in the VEP study indicated actual damage to the left optic nerve, the reason for which was unclear. We suppose the hypothalamic brain lesion, which was near the course of the optic nerve or infection of unknown origin affected the left optic nerve and damaged left visual acuity.

The etiology of the EL has not been resolved. For some time it was thought to be associated with influenza virus, and although an organism or virus has never been isolated, other encephalitic illnesses caused by identified organisms or viruses, such as, coxackie B2, arborvirus, Japanese B, western equine, measles, varicella, polio, and mycoplasma, are known to be associated with extrapyramidal syndromes [5-8]. On the other hand, a recent examination of archived EL brain material failed to demonstrate influenza RNA, and thus, supported the notion that EL is not an invasive influenza encephalitis [1]. By contrast, the findings of intrathecal oligoclonal bands (OCB), the causative role of Anti-NMDA-receptor (NMDAR), and the known beneficial effects of steroid treatments favor the hypothesis that EL is immune-mediated. 1,8 Our patient had a preceding viral-like infection before clinical symptoms development and had pleocytosis in CSF fluid. In addition, her symptoms did not improved on steroid. These infectious symptoms, CSF abnormality, and the ineffectiveness of steroid support the classical hypothesis of the etiology of EL. Further studies on NMDAR are needed to facilitate the diagnosis and efficient treatment of EL.

Our patient had daytime sleepiness, which is a core symptom of EL, and seems similar to secondary narcolepsy. The diagnosis of narcolepsy is essentially clinical and its estimated incidence varies across countries and ethnic groups from 168 to 799 per 100,000 in most studies, although Japanese studies have indicated a prevalence as high as 1600 per 100,000 [9,10]. The incidence of secondary narcolepsy in EL has not been reported but is likely to be scarce. We found some reports of secondary narcolepsy related to the infection but unfortunately sleep has rarely been analyzed in infectious patients, due to the emergency aspects of diseases like meningitis or severe viral infection. In previous studies sleep modifications associated with bacterial or viral diseases have been linked with immune reactions. The nature of the uncoupling between the acute phase of the immune reaction in sleeping sickness and sleep-wake patterns has not been determined [11].

Nocturnal polysomnography followed by a Multiple Sleep Latency Test (MSLT) is a useful tool for diagnosing narcolepsy. The diagnostic criterion of narcolepsy is a mean sleep latency of less than eight minutes with at least two sleep onset REM periods (SOREMPs). Our polysomnography study showed frequent arousal, periodic limb movements in sleep, and an abnormal sleep architecture that increased in stage I and decreased in stage II, SWS, and REM sleep. Also in the MSLT study, sleep latency was shortened to 12 seconds and SOREMPs were observed all five trials. Accordingly, her MSLT results were compatible with narcolepsy.
defined cell groups with identified neurotransmitters. This pathway findings aid the understanding of the pathophysiology of EL and aid showed profound and long-lasting arousal impairment [13].

The brain lesion depicted by MRI in our patient may explain her hypersomnia. In 1916 Von Economo first described hypersomnia patients with a brain lesion in the posterolateral hypothalamic region of the brain, which regulates sleep and wakefulness [12]. The ascending arousal system largely originates from a series of well-defined cell groups with identified neurotransmitters. This pathway has two major branches. The first branch is an ascending pathway to the thalamus that activates the thalamic relay neurons crucial for transmission of information to the cerebral cortex, whereas the second branch bypasses the thalamus and instead activates neurons in the lateral hypothalamic area, basal forebrain (BF), and throughout the cerebral cortex. Lesions along this second pathway, particularly in the lateral hypothalamus (LHA) or rostral midbrain, produce the most profound and long-lasting forms of sleepiness or even coma [12].

Recently, several symptomatic narcoleptic cases were described with unique bilateral symmetric hypothalamic lesions associated with significant hypocretin ligand deficiency [10]. Accordingly, given reported cases and the anatomy and functions of these systems, it is not surprising that our patient, who had a lesion on the hypothalamus, showed profound and long-lasting arousal impairment [13].

We report a rare case of EL with accompanying bilateral blindness. No definitive diagnostic criteria have been agreed for EL, but some effort has been expended to determine its pathophysiology. EL is an extremely rare disease and few cases have been reported. Although our patient was without extrapyramidal symptoms and a definite neuropsychiatric symptom, its distinctive somnolent-ophthalmoplegic form, which is a common presentation, and abnormal brain MRI findings, which are compatible with a previous report of Von Economo, and abnormal CSF study supports a diagnosis of an unusual form of EL. Furthermore, we report two new findings not previously associated with EL. First, our patient exhibited decrement of visual acuity, which we believe may be new symptom of EL. Second, we performed polysomnography to obtain some information about the sleeping pattern of EL, and as far as we know this is the first polysomnography report in EL and hope the information provided aids the characterization of its sleep pattern.

Table 2: MSLT results for the patient. Sleep latency was reduced to 12 seconds and SOREMPs were observed in all five MSLT trials.

| Session | TST (minutes) | NREM (minutes) | REM (minutes) | Sleep latency (seconds) | REM Sleep (seconds) |
|---------|---------------|----------------|--------------|-------------------------|-------------------|
| 1.      | 15.0          | 0.0            | 15.0         | 0.4                     | 0.4               |
| 2.      | 17.5          | 0.0            | 17.5         | 0.5                     | 0.5               |
| 3.      | 8.0           | 0.0            | 8.0          | 0.3                     | 0.3               |
| 4.      | 12.5          | 0.0            | 12.5         | 0.0                     | 0.1               |
| 5.      | 21.0          | 0.0            | 18.0         | 0.5                     | 3.5               |

Abbreviation: TST: Total Sleep Time; NREM: Non Rapid Eye Movement; REM: Rapid Eye Movement Sleep latency is from light out to the first epoch of sleep.

As far as we know this is the first polysomnography study of an EL patient, and consider it provides a basis for the identification of the sleep patterns of EL and secondary narcolepsy related to infection. We assume that the sleep pattern of EL shares the features of that of narcolepsy, as exhibited by our patient. Because somnolence is distinctive feature of EL and polysomnography is easily accessible and provides a non-invasive way of diagnosing narcolepsy, we hope our findings aid the understanding of the pathophysiology of EL and aid future diagnoses (Tables 1 and 2).

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