REVIEW

Awakening Ptosis: A Clinical Review

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ABSTRACT

A rare condition characterized by a transient inability to open one or both eyes upon awakening from sleep was first described in 1897. Although less than a handful of papers have been written about this condition since its initial description, a well-defined clinical entity emerges from the available literature. This article reviews the history and clinical features of this unusual condition.

ARTICLE HISTORY

Received 11 October 2017
Revised 30 April 2018
Accepted 5 May 2018

KEYWORDS

Awakening ptosis; apraxia of eyelid opening; parasomnia; sleep

Introduction

Awakening ptosis (AP) (transient complete ptosis confined to awakening from sleep that resolves with mechanical elevation of the eyelids) is a rare clinical presentation. As such, few ophthalmologists and neurologists have experience managing patients with this complaint. Recent authors describing this condition have speculated that it might represent an atypical form of apraxia of eyelid opening (AEO),^{1,2} or alternatively, a focal variant of sleep paralysis (SP).² Identifying published papers about this condition can be challenging however, especially since each paper refers to it under a different name.^{1–4} Therefore, a comprehensive synthesis and review of the literature is needed, primarily to aid clinicians in managing patients with this condition, but also to identify gaps in current knowledge to direct future research.

Review method

A literature search was performed in MEDLINE, Web of Science, and EMBASE with the phrases “sleep ptosis”, “apraxia of eyelid opening,” AND “sleep.” Two published papers were found that reported transient unilateral or bilateral ptosis on awakening that resolved with mechanical elevation.^{1,2} The reference lists from these articles were checked to identify additional sources. An abstract from 1996 which reported a female patient with sleep-related ptosis was referenced by one of the papers.¹ However, this was not

included in the current review as the abstract could not be located. Articles citing the two identified papers were also examined. A single case report of a patient with sleep-related ptosis from 2013 was found.³ From the three sources identified in the literature search and three cases presented in Silas Weir Mitchell’s “Clinical lessons on Nervous Diseases,”⁴ data from 20 patients could be analysed (Table 1).

A brief history of awakening ptosis

Silas Weir Mitchell, the nineteenth-century American neurologist, may have provided the first descriptions of this condition in his book *Clinical Lessons on Nervous Diseases* published in 1897.⁴ Mitchell referred to a condition called “sleep ptosis,” in which patients awake from sleep unable to open their eyes voluntarily, yet are able to forcibly open their eyelids with their fingers, after which, volitional control of eyelid opening would be regained. He reported three cases of patients afflicted with this condition, which he considered to be a primary sleep disorder.⁴ However, one of these patients had anterior segment pathology, which some might argue could have contributed to their symptoms. Another patient had extraocular muscle abnormalities that could possibly have been reflective of an underlying neurologic condition. As such, these were not entirely “clean” cases. The condition re-emerged in 2010, when Cherian and Foroozan published a detailed case series with five patients in the

Table 1. Key demographic and clinical characteristics of patients with awakening ptosis.

References	Female: Male	Median age (age range)	Unilateral: bilateral	≥1 autoimmune disease	History of ≥ 1 ocular condition or abnormal ophthalmic examination finding	Spontaneous and complete (or near complete) resolution within 18 months
Mitchell 1897 3 patients	3:0	65 (29–67)	0:3	0/3	2/3	1/1
Cherian & Foroozan 2010 5 patients	3:2	60 (49–71)	5:0	1/3	5/5	4/5
Della Marca et al. 2013 1 patient	1:0	68	1:0	–	–	0/1
Reggie et al. 2017 11 patients	11:0	59* (35–80)	8:3	7/11	3/11	5/10
Total 20 patients	18:2	63	14:6	47%	53%	59%

* = mean value used where no median available.

– = information not ascertainable.

journal *Ophthalmology*.¹ Noticing the similarity with the neuro-ophthalmological disorder AEO, and the fact that most of their patients had exclusively unilateral ptosis, they suggested that this represented a benign form of AEO, which they called benign unilateral apraxia of eyelid opening (BUAEO). Unfortunately, they had not been aware of Mitchell's earlier description, which led them to believe that they had been the first to describe the condition. In 2013, Della Marca et al. presented a single case report of a patient with transient unilateral ptosis confined to awakening from sleep in the journal *Neurology*.³ They suggested that this condition is not a true apraxia and proposed that the most likely cause is the persistence of sleep-related muscular atonia into wakefulness. They recommended "unilateral hypnopompic eyelid palsy" and "awakening ptosis" as alternative names for the condition. Most recently, in 2017, Reggie et al. published a case series of 11 patients with "sleep-induced apraxia of eyelid opening," in *Journal of Neuro-Ophthalmology*.² However, given that this condition may not in fact be an apraxia, and it can be either unilateral or bilateral, BUAEO, unilateral hypnopompic eyelid palsy, and sleep-induced AEO may all be inappropriate names. Sleep ptosis, as originally suggested by Mitchell, would give the impression that ptosis during sleep is abnormal, yet ptosis during rapid eye movement (REM) sleep is indeed

normal. The abnormality is the persistence of ptosis on awakening from sleep. As such, for the purpose of this review, AP will be the preferred name to refer to this condition.

Symptomatology

AP is usually unilateral rather than bilateral (70% unilateral, 30% bilateral). In the papers that recorded lateralization of unilateral ptosis, three patients had ptosis in the right eye and three patients had ptosis in the left.^{1,3} When it is unilateral, it usually occurs in the same eye each time. However, two patients initially presenting with unilateral ptosis eventually developed bilateral ptosis.² In one patient that initially had bilateral ptosis, the ptosis of the left eye remitted after several months, whilst the ptosis of the right eyelid persisted.² Patients with AP are able to regain volitional control of eye opening by elevating their eyelids with their fingers.^{1–4} When the ptosis is not interrupted by mechanical elevation, it typically lasts between 1 and 6 minutes,^{1–4} although in rare instances it can last for half an hour or longer.^{1,4} In 13 cases in which the frequency of AP occurrences could be ascertained, 12/13 patients reported episodes of AP occurring every morning.^{2–4} In one patient, it occurred just once a week.² Five patients stated that AP also occurred after daytime naps, alongside awakening in the

morning.¹⁻³ Two of these patients volunteered that they only awoke with ptosis if they had been asleep for at least a certain amount of time (30 minutes and 3 hours).^{1,2} This suggests that there may be a critical duration of sleep required to elicit an episode of AP. The only paper that included details about sleep fragmentation showed that 3/3 patients had multiple awakenings during the night and these were also associated with ptosis.⁴ However, the sample is too small to conclude that sleep fragmentation is specifically linked with AP.

Prevalence

No study has specifically investigated the prevalence of AP. However, the fact that many neurologists and ophthalmologists are unfamiliar with this condition might allow us to infer that AP is rare. Over a 6-year period in a single neuro-ophthalmology practice, just 5 of 208 patients presenting with ptosis had ptosis that was confined to awakening from sleep that also resolved with mechanical elevation.¹ Further, only 11 patients with features consistent with AP were found in the records of three different neuro-ophthalmology practices over a 1-year period.² However, systematic studies into the prevalence of AP from neurology, ophthalmology and sleep medicine practices are also needed. It is also possible that the apparent rarity of AP may be explained by patients remaining undiagnosed. In a single thread on an online patient forum between the years of 2007 and 2016, 24 individuals described symptoms consistent with AP.⁵

Risk factors

Female gender, white Caucasian ethnicity, age, concurrent autoimmune diseases, and previous ocular pathology are key risk factors for AP (Table 1). Ninety percent of the patients with AP in the literature are female. In one paper that included ethnicity data, 11/11 patients were white Caucasian.² The condition typically affects patients in their 60s (medians ranged from 59 to 68). A significant number of patients also had an autoimmune disease (47%) such as hypothyroidism, and/or a benign ocular condition, such as cataracts (53%).

Clinical consequences

The majority of cases spontaneously resolved without treatment (Table 1). In 10 out of 17 patients in which the time taken for symptom resolution could be ascertained, the condition had resolved spontaneously and completely (or near completely) within 18 months.¹⁻⁴ However, the duration of AP ranged from just a few weeks to several years.² Follow-up telephone reports after 2 to 6 years, with five patients from Cherian and Foroozan's study, revealed that none of the patients developed a serious neurologic disease that would be associated with ptosis.¹ Prospective longitudinal studies are needed to confirm whether or not harmful consequences ensue long after the onset of the symptoms and also to clarify the likelihood of AP reoccurring.

Aetiology

Some ophthalmologists would attribute AP to the overnight effects of dry eye.² It could be argued that when the eyes dry out, mucus seals the lid margins shut, and air and fluid between the eyelids form a suction effect which leads to a mechanical inability to open the eyes on awakening from sleep. However, only 2 of 11 patients in Reggie et al.'s case series had symptoms consistent with dry eye syndrome.² Furthermore, lubricating ointment did not lead to resolution of symptoms in any of the five patients to whom it had been administered.² Given that dry eye syndrome is not uncommon, it would also be expected that AP would be encountered much more frequently in ophthalmology clinics. A final weakness of the dry eye theory would be its inability to account for the frequent unilaterality of AP.

The most popular aetiological theory is that AP is caused by the intrusion of focal sleep-related muscular atonia into wakefulness.¹⁻³ Sleep and wakefulness are coordinated by a balance of excitatory and inhibitory neurotransmitters that are released from the hypothalamus.⁶ Neurotransmitters such as orexin (hypocretin) provide excitatory stimulation for motor neurons to the levator palpebrae superioris (LPS) during wakefulness.⁷ This increases eyelid muscle tone and allows the eyes to remain open.⁷ During the transition from wakefulness to sleep, motor neurons to the LPS are inhibited by a powerful GABAergic and glycinergic drive,⁸ which leads to

hypotonia of the eyelids during non-rapid eye movement (NREM) sleep, and complete atonia during REM sleep, thus facilitating eyelid closure. On awakening, excitatory neurotransmitters will once again predominate.⁶ This initiates a reversal of the inhibition of motor neurons to the LPS, which would consequently enable eye opening. It has been proposed that a delay to reverse this inhibition leads to the intrusion of sleep-related muscle atonia into wakefulness, and thus the occurrence of AP.^{1,2} In theory, it should be possible to perform an EMG study to definitively demonstrate eyelid atonia in AP⁹; however, given the transient nature of the symptoms and the technical difficulty of obtaining EMG recordings from the LPS,^{10,11} especially during sleep, such evidence may be difficult to come by. Nevertheless, if the intrusion of sleep-related muscle atonia into wakefulness is indeed the cause of AP, this would make AP analogous to the parasomnia SP, or “sleep paralysis of the eyes.”² One paper which reported polysomnography of a patient with AP partially supports this theory.³ Overnight polysomnography of spontaneous sleep of a patient with AP demonstrated that ptosis occurred on spontaneous awakening after a period of REM sleep (one awakening), but not on spontaneous awakening after periods of NREM sleep (two awakenings). This is consistent with studies that have shown that SP occurs only on awakening from REM sleep.^{12,13} The paper also reported polysomnography from a second night, in which the researchers awakened the patient several times during episodes of REM and NREM sleep. AP could be elicited with forced awakenings from both REM sleep and NREM sleep, thus demonstrating that AP is not exclusively a REM sleep phenomenon, unlike SP.

It has also been suggested that AP may represent a benign variant of AEO.^{1,2} AEO was first described in 1965 as “a nonparalytic motor abnormality characterized by the patient’s difficulty in initiating the act of lid elevation.”¹⁴ However, despite the fact that the aetiology of AEO still remains unknown, it is now widely considered that AEO is not a true apraxia. Instead, it is commonly attributed to involuntary LPS inhibition,¹⁵ and/or the abnormal persistence of orbicularis oculi activity.¹⁶ Likewise, it is probable that AP is not a true apraxia either. Given that an apraxia is defined as an inability to perform a voluntary motor movement despite normal muscle

function,¹⁷ the suggestion that AP is caused by prolonged inhibition of motor neurons to the LPS would by definition exclude AP from being an apraxia.

With regard to the observation that mechanical eyelid elevation facilitates the resolution of AP,¹⁻⁴ it has been suggested that mechanical elevation of the lids represents a “geste antagoniste,” as seen in blepharospasm and hemifacial spasm.¹ However, given that geste antagonistes typically occur due to a sensory signal distant from the dystonic muscle,¹⁸ it may therefore be inappropriate to label mechanical elevation of the LPS itself as a “geste.” Alternatively, it could be the case that mechanically elevating the LPS gives a signal back to the oculomotor nucleus to get going when the patient awakens in the morning (via a light signal to the superior colliculus). Irrespective of which theory may be correct, it is interesting to note that the resolution of AP by mechanically elevating the eyelids is not too dissimilar from the observation from SP patients, who report episodes of SP being terminated by being touched by their bed partners.¹⁹

Differential diagnosis

AP is a very distinctive condition. There are no other known causes of ptosis confined to awakening from sleep. As such, it should not be difficult to distinguish these patients from those with myasthenia gravis, Horner’s syndrome, and oculomotor nerve palsy.

An unresolved question, however, is whether AP is a variant of AEO, or whether it is a distinct clinical entity. Although AP and AEO are both unique in the sense that a transient inability to open the eyes is their sole symptom, they do however have a number of differences. One significant difference is that AP is confined to awakening from sleep, whereas AEO occurs following voluntary or involuntary eye closure during the day. Additionally, AEO is bilateral, whereas AP is predominantly unilateral. AEO typically co-occurs with benign essential blepharospasm, neurodegenerative disease, or hemispheric lesions (i.e. stroke)^{11,20,21}; however, AP has no association with neurologic disease. AP on the other hand appears to be associated with autoimmune disease and a history of ocular pathology. As has already been mentioned, the ptosis of AP resolves when the

patients mechanically elevate their eyelids, whereas AEO patients may try manoeuvres such as lightly touching their temple regions, using their frontalis muscle to elevate their eyebrows or engaging in backward thrusting of their head, in attempts to open their eyes.^{22,23} AP frequently resolves within 18 months of symptom onset; on the contrary, a review of patients with isolated AEO reported an average disease duration of more than 4 years, with a range between 1 and 8 years.²⁴ Thus, given these vast array of dissimilarities, it is likely that AP and AEO represent separate clinical entities.

Conclusions

AP is a well-defined clinical entity with a benign nature. It is predominantly unilateral, typically affects white Caucasian women around 60 years of age with a history of autoimmune and/or ocular conditions, and usually resolves spontaneously within 18 months. AP has distinct differences to AEO, and it may represent a rare and currently unrecognized sleep disorder. I propose for the first time the essential criteria for the diagnosis of AP: (a) recurrent transient ptosis (unilateral or bilateral) confined to awakening from sleep; (b) spontaneous eyelid opening after a few minutes or upon mechanical elevation, after which complete volitional control is regained; and (c) not associated with known neurological or ophthalmological causes of ptosis. Clinicians encountering patients with AP can reassure their patients that their condition is likely to be benign, and that it will probably resolve in a number of months without any intervention. However, identification of a treatment would be particularly beneficial for those patients whose symptoms persist for several years. Clinicians should also be aware that laboratory testing and neuroimaging are not indicated in these patients, as patients with AP that have been investigated with neuroimaging and laboratory tests have all shown normal findings.^{1–3}

There is still much that is not known about AP. For example, accurate prevalence data are lacking. Even though the small number of patients in the studies by Cherian and Foroozan and Reggie et al. might indicate that AP is very rare, it would nevertheless be useful to establish the relative prevalence of AP in neuro-ophthalmology practices outside of North America. With respect to the pathophysiology

of AP, detailed investigations of patients using polysomnography would help to confirm sleep-related muscular atonia as the cause of transient ptosis confined to awakening from sleep, as well as to identify any additional changes in sleep architecture, such as sleep fragmentation. Interestingly, AP has not received a mention in current sleep medicine classification systems or textbooks.^{25,26} Given that AP may represent a novel parasomnia, sleep physicians ought to be aware of this condition, alongside neurologists and ophthalmologists.

Declaration of interest

The author reports no conflicts of interest.

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