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CLINICAL REVIEW

Cyclic alternating pattern (CAP): The marker of sleep instability

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SUMMARY

Cyclic alternating pattern CAP is the EEG marker of unstable sleep, a concept which is poorly appreciated among the metrics of sleep physiology. Besides, duration, depth and continuity, sleep restorative properties depend on the capacity of the brain to create periods of sustained stable sleep. This issue is not confined only to the EEG activities but reverberates upon the ongoing autonomic activity and behavioral functions, which are mutually entrained in a synchronized oscillation. CAP can be identified both in adult and children sleep and therefore represents a sensitive tool for the investigation of sleep disorders across the lifespan. The present review illustrates the story of CAP in the last 25 years, the standardized scoring criteria, the basic physiological properties and how the dimension of sleep instability has provided new insight into pathophysiolology and management of sleep disorders.

Introduction

"The cyclic alternating pattern (CAP) as a physiological component of normal NREM sleep" was published in the journal Sleep in 1985.[1] Those were years of growing interest in the diagnosis and treatment of obstructive sleep apnea syndrome (OSAS) that collected most of the energy and financial resources dedicated to the field. In addition, the Rechtschaffen and Kales (R&K) manual[2] was recognized as a consistent and mandatory tool for sleep staging worldwide. Scattered contributions on electroencephalographic (EEG) phasic events had been published but an organized group of experts was still lacking. Riding the CAP wave, a number of European sleep researchers headed by Peter Halasz and Gus Declerck organized a workshop on phasic events during the May 1987 International Congress of Clinical Neurophysiology in Amsterdam. The success of the initiative allowed to include sleep microstructure as a topic of the European Concerted Action on Sleep Analysis and a new workshop was held in 1989 in Salsomaggiore (Italy). The entire set of contributions was published in the Raven Press volume Phasic Events and Dynamic Organization of Sleep edited by Terzano, Halasz and Declerck.[3] In the same year, a workshop on sleep microstructure was included in the official programme of the Founding Congress of the World Federation of Sleep Research Societies held in Cannes, France.[4] The '90s were characterized by an increasing number of papers dedicated to the clinical applications of CAP in periodic limb movements, epileptic disorders, sleep apnea syndrome and insomnia.[5] In particular, the variations of CAP in a model of disturbed sleep using continuous white noise throughout the night in normal sleepers became a standardized procedure not only to understand the pathophysiological bases of insomnia but also as a homogeneous setting for testing and comparing new and old hypnotic agents.[6] However, since 1985 most of the papers on CAP had been published by the discovering Parma group and this was both an advantageous and a limiting factor. A favorable situation because the scoring rules and cultural philosophy of CAP were well defined and established by a restricted number of persons who used the new tool daily in both research and clinical practice. The limitation was related to the fact that the procedure was applied by a restricted number of sleep clinicians. In 2000 the journal Sleep Medicine Reviews published the article "Origin and significance of the cyclic alternating pattern",[7] which has become a referential contribution on the physiological and clinical applications of CAP. In November 2000 an audit was organized in Parma involving a group of North American sleep experts (Ronald Chervin, Sudhansu Chokroverty, Christian Guilleminault, Max Hirshkowitz, Mark Mahowald, Harvey Moldofsky, Robert Thomas, Arthur Walters) to evaluate the physiological bases of CAP and discuss the modalities for a more

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Abbreviations

AASM	American Academy of Sleep Medicine
CNS	central nervous system
CPAP	continuous positive airway pressure
EEG	electroencephalographic
EMG	electromyographic
FFT	fast Fourier transform
GABA	gamma-aminobutyric acid
GH	growth hormone
IQ	intellectual quotient
NREM	normal rapid eye movement
OSAS	obstructive sleep apnea syndrome
PSG	Polysomnographic
REM	rapid eye movement
SWS	slowwave sleep
UARS	upper airway resistance syndrome
WASO	wake after sleep onset

effective diffusion of the methodology. After a lively three-day debate, full agreement was reached on the preparation of an atlas detailing the technical procedures and the scoring rules of CAP parameters in human sleep. The consensus report was published in the journal Sleep Medicine,[8] reinforcing attention on CAP and encouraging further studies based on the shared criteria. Innovative approaches were exploited, including studies on automatic analysis[9–12] and new actors were involved making CAP investigation a real international interest. After the introduction of the 2007 American Academy of Sleep Medicine (AASM) scoring rules,[13] which simplify excessively sleep staging,[14] the necessity to explore the utility of CAP has become a growing request.[15] The present review updates the physiological significance of CAP, outlines the scoring principles, revisits the clinical domains of application and offers a number of perspective studies which can further implement the use of CAP in both clinical and research frameworks.

CAP in states of reduced vigilance

In clinical practice, CAP was initially considered as an electroencephalographic (EEG) sign of cerebral disturbance associated with a reduced vigilance level. Prolonged cyclic alternation of high-voltage slow waves (phase A) and low-voltage irregular activity (phase B) can be recorded in comatose patients and correlates with the clinical outcome.[16–19] In lighter stages of coma, the A phases are closely related to hyperventilation and increased pulse rate and can be associated with greater muscle activity, restlessness and pressure variations of the cerebrospinal fluid.[20] In contrast, autonomic and muscle activities are attenuated during the B phases. This twofold behavior indicates that during CAP the comatose patient shifts repeatedly between more aroused (during phase A) and less aroused (during phase B) states that entrain also autonomic and motor functions under a common oscillatory process.[21]

As the clinical condition improves and a normal sleep structure is recovered, the cyclic EEG features are progressively replaced by periodic sequences of K-complexes indicating that CAP is the expression of a basic arousal modulator, which survives in conditions of severely impaired vigilance, but that essentially belongs to physiological sleep.[22]

According to these findings CAP appears as a well-defined marker of cerebral activity occurring under conditions of reduced vigilance (sleep, coma), translating a state of instability and involving muscle, behavioral and autonomic functions. The absence of CAP coincides with a condition of sustained arousal stability and is defined as non-CAP. CAP and non-CAP can be consistently manipulated by sensorial inputs.

Reactivity of CAP

The role of EEG reactivity in comatose patients is highly informative. In deep coma without CAP, responsiveness is abolished even under repetitive and powerful stimulation. In light coma, parts of the arousal system are still functioning and stimulation delivered during the low-voltage period of CAP elicits immediately a high-voltage slow activity, i.e., "réaction paradoxale".[23]

This behavior is observed also in non-rapid eye movement (NREM) sleep. Applying separately the same arousing stimulus during the two EEG components of CAP, phase B is the one that immediately assumes the morphology of the other component, whereas the inverse transformation never occurs when the stimulus is delivered during phase A. This stereotyped reactivity persists throughout the successive phases of CAP with lack of habituation. In contrast, when the same stimulus is presented during non-CAP, the EEG responses are generally brief, hypersynchronized and proceed toward progressive habituation.[24] However, a robust or sustained stimulus delivered during non-CAP induces the immediate appearance of repetitive CAP cycles that display the same morphology and reactive behavior of spontaneous CAP sequences. The evoked CAP sequence may herald a lightening of sleep depth or continue as a damping oscillation before the complete recovery of non-CAP.[25]

The EEG features of CAP

In natural sleep the EEG features of CAP are more complex and polymorphic compared to coma and vary in the different stages. In NREM sleep, CAP appears throughout stages 1–4,[8] where phase A is identified by transient events which clearly stand out from the background rhythm (phase B). Compared to phase B, phase A can be composed of slower higher-voltage rhythms, faster lower voltage rhythms, or by mixed patterns including both. Although EEG patterns of phase A are not strictly stereotyped, they generally include one of the phasic events,[26] which are described in Table 1.

Technical and methodological requirements for scoring a CAP sequence

The identification of CAP should be preceded by the definition of sleep stages according to the conventional criteria.[2,13]

Onset and termination of a CAP sequence

A CAP sequence is composed of a succession of CAP cycles. A CAP cycle is composed of a phase A and the following phase B. All CAP sequences begin with a phase A and end with a phase B. Each phase of CAP is 2–60 s in duration. This cut-off relies on the consideration that the great majority (about 90%) of A phases occurring during sleep are separated by an interval <60 s[24].

Non-CAP

The absence of CAP for >60 s is scored as non-CAP. An isolated phase A (that is, preceded or followed by another phase A but separated by more than 60 s), is classified as non-CAP. The phase A that terminates a CAP sequence is counted as non-CAP.

Minimal criteria for the detection of a CAP sequence

CAP sequences have no upper limits on overall duration and on the number of CAP cycles. In young adults, 2 min and 30 s is the