Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Alpha coma in COVID encephalopathy

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Alpha coma is an EEG pattern often considered a rare finding carrying a poor prognosis. Koutroumanidis et al. (2021) report in this issue of *Clinical Neurophysiology* finding alpha coma in certain patients who had an encephalopathy during a COVID-19 infection. That report reviewed the clinical circumstances, and reminded the reader about the brainstem encephalitis found affecting some patients with an active COVID infection.

Alpha coma is a term used in different ways. It has come to imply a poor prognosis for neurologic recovery. That is true for patients after a cardiac arrest whose EEG shows a prominent generalized, often frontally predominant, non-reactive alpha frequency activity. In those circumstances, prognosis for recovery is poor. The most important factor is the lack of EEG reactivity to verbal or noxious stimulation, for which noxious stimulation may be deep nail bed pressure or tracheal suctioning by the nurse or respiratory therapist.

Alpha rhythm appears also in other clinical circumstances. The original description of persistent, non-reactive alpha rhythm (Loeb and Poggio, 1953) was due to a pontine hemorrhage. Westmoreland et al. (1975) named such a persistent frontal nonreactive alpha frequency rhythm as "alpha coma". For years, our epitype for alpha coma has been a prominent bifrontal non-reactive alpha on EEG. Such an EEG finding was a sign of serious brainstem injury, a sign very useful in the days before modern neuroimaging. The patient's prognosis was very poor. The clinical community soon recognized that prominent bifrontal non-reactive alpha was seen more commonly after a cardiac arrest that caused a significant diffuse brain anoxic injury. Post-arrest coma became the most common clinical circumstance for alpha coma. The patient's prognosis was very poor, as it was for the original brainstem injury pathologic cause. The generally accepted clinical significance was that alpha coma carried a poor prognosis.

Over time, different versions of alpha coma have been recognized. Westmoreland et al. (1975) noted that alpha can be seen in coma when a patient is in the locked-in state. In that circumstance, the alpha is posterior, reactive, has sleep-wake cycles, and is a sign of consciousness. It is a sign of regular awake alpha activity, just seen in a different setting. The prognosis was that of the locked-in state.

Deleu and Ebinger (1989) noted how generalized or bifrontal alpha frequency activity sometimes is seen in a coma after a sedative overdose. In overdose patients the alpha often was reactive, which helped to differentiate it from the nonreactive alpha of the post-anoxic state or brainstem injury. Drug overdose patients usually recover well despite that alpha-coma EEG finding. EEG reactivity is the key for prognosis in such clinical circumstances as brainstem disorders, stroke, head injury, or hypoxia without cardiac arrest. Preservation of EEG reactivity was the strongest predictor of outcome (Kaplan et al., 1999).

Spindle coma is another fast EEG rhythm encountered in some coma patients, one which should be differentiated from alpha coma. Seconds-long spindles, vertex waves, and sensory evoked K-complexes are seen in some coma patients (Chatrian et al., 1963; Kaplan et al., 2000). These spindles are slightly faster than the alpha frequency range. As with alpha coma, EEG reactivity is the most important factor for prognosis.

The COVID-19 pandemic has placed neurologists into a health care system challenged to provide care for large numbers of patients with this emerging disease (Josephson and Kamel, 2020). ACE2 receptors, the favored target of COVID-19, are found on capillary endothelium and on neurons (Baig et al., 2020). As a consequence, COVID-19 infections are associated with certain neurologic and vascular disorders. More than one-third of patients with severe COVID-19 respiratory illness experience a variety of neurologic manifestations, including altered mental status and acute cerebrovascular diseases (Mao et al., 2020). Delirium occurs among hospitalized patients with COVID-19, and the multifactorial basis for this includes direct infection by the virus. Corona virus can spread across synapses from lung mechanoreceptors and chemoreceptors into the medullary cardiorespiratory centers (Li et al., 2020; Benameur et al., 2020). Koutroumanidis et al. (2021) suggest that the relatively high incidence of the alpha coma pattern in COVID infections may reflect direct viral neurotropism affecting the brainstem ascending reticular system. Direct neuronal damage can ensue from viral infection as well as immune-mediated tissue damage associated with markedly elevated interleukins (Benameur et al., 2020). Other central nervous system injury can occur due to vascular-related injuries such as thromboses.

These brainstem COVID-19 processes provide a pathophysiologic basis for some brainstem-related EEG phenomena. Both alpha coma and spindle coma have a brainstem site of injury seen for many case reports. It seems reasonable to believe that these various EEG phenomena are signs of brainstem injury from the virus, thromboses, or immune-mediated regional dysfunction. The cases reported by Koutroumanidis et al. (2021) likely fall into that set of

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circumstances. As with the original descriptions of alpha and spindle coma, EEG reactivity may be the strongest sign of favorable prognosis. Non-reactive persistent alpha likely is associated with a poor prognosis. Whether those prognosis rules hold for COVID-19 patients is still not well validated, but likely will hold up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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