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LETTERS TO THE EDITOR

Speculating on Kleine-Levin Syndrome mechanisms

Response to Ortega-Albás JJ, López R, Martínez A, Carratalá S, Echeverria I, Ortega P. Kleine-Levin Syndrome, GABA, and glutamate. *J Clin Sleep Med*. 2021;17(3):609–610. doi:10.5664/jcsm.9058

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We read with interest the recent letter by Ortega-Albas et al, hypothesizing that the Kleine-Levin Syndrome (KLS) results from an instability between γ-aminobutyric acid (GABA) and glutamate transmissions during neurodevelopment.[1] Although interesting, this hypothesis is speculative, as it can hardly be tested, neglects some opposed evidence, and may seem too holistic for such a rare disorder. Indeed, GABA and glutamate represent 80% of synaptic brain transmission. Consequently, they are not restricted to the functions (sleep, behavior, cognition, mood) specifically altered during KLS episodes but are involved in hundreds of different functions, including for example synaptic stability (resulting in seizures, which are notably absent in KLS, when affected). Plus, it may seem oversimplistic to attribute the "positive" (hypersexuality, megaphagia, hallucinations, or end-episode insomnia) KLS symptoms to increased glutamate stimulation (or impaired GABA inhibition) and the "negative" (apathy, derealization, hypersomnia, cognitive impairment) symptoms to increased GABA inhibition (or decreased glutamate inhibition), as two successive GABA inhibitions result for example into stimulation. Eventually, benzodiazepines, which stimulate the GABA system have no efficacy in KLS.[2]

The KLS mechanisms are still unknown, although genetics, inflammatory, and autoimmune origins have been suspected.[2] Because KLS shares the remitting-relapsing course of multiple sclerosis and may possibly be inflammatory (at least in neuropathological cases, although inflammatory markers are absent in the cerebrospinal fluid), we tested lithium therapy (a potent anti-inflammatory drug) and intravenous steroids and found partial benefits in controlled observational cohorts. On the other hand, several complex neurologic and psychiatric syndromes are now recognized as autoimmune encephalitis caused by newly identified autoantibodies. Anti- *N*-methyl-D-aspartic acid (NMDA) receptor autoantibodies are interesting in the context of KLS, as they cause sleep and behavioral symptoms[3] and have been found (with enzyme-linked immunosorbent assay but not cell-based assay) in a recent KLS case.[1] Unfortunately, this research field on autoimmunity has been disappointing in our experience, despite following 300 patients with KLS. Indeed, we could not find any association with human leukocyte antigen genotypes in 228 patients with KLS,[2] and any positive cerebrospinal fluid anti-NMDA autoantibodies in 5 symptomatic KLS patients. We found normal serum levels of anti-IA-2 (islet tyrosine phosphatase 2), antiglutamate acid decarboxylase (GAD65), and antiaquaporin 4 autoantibodies in more than 100 KLS sera tested (personal communication), despite a single KLS case with anti-GAD65 autoantibodies having been reported.

KLS is a remitting-relapsing disorder, as diagnostic criteria stipulate that sleep, cognition, mood, and behavior are normal between episodes. However, many other remitting-relapsing disorders (eg, bipolar disorder, multiple sclerosis, chronic obstructive pulmonary disease) comprise mild interepisode symptoms and signs, interrupted by sudden exacerbations, often triggered by an identified external agent. Eventually, this "iceberg model" also applies to KLS, as several recent studies indicate that a mild, attenuated symptomatology may persist or emerge during "asymptomatic" periods in 20–25% patients, including memory and attention difficulties,[4] as well as mood and anxiety disorders,[5] whereas brain functional imaging often shows hypoperfusion and hypometabolism in associative and subcortical brain areas during asymptomatic periods.[2]

The mechanisms of KLS still remain to be determined in the future, thanks to large, national and international cohorts.

CITATION

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DISCLOSURE STATEMENT

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