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Dysregulation of mood, energy, and social rhythms syndrome (DYMERS): A working hypothesis

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Abstract

A syndrome centered on the dysregulation of behavioral rhythms (DBR) is discussed. Recent pandemic brought to observe: (1) Having a DBR affecting sleep patterns, eating habits, and social interactions, before the lockdown period, was a determinant for depressive episodes during the lockdown; (2) In tighter lockdowns, DBR triggered depressive episodes in bipolar patients; (3) DBR in healthcare workers under pressure was a determinant of burnout; (4) DBR influenced the course of chronic diseases by altering immune responses. In addition, it was found that scoring positive on the Mood Disorder Questionnaire (MDQ) was closely associated with the dysregulation of sleep rhythms. MDQ is a screening tool for bipolar disorder (BD), criticized for detecting too many false positives. Studies showed that positivity to the MDQ implied a severe impairment of quality of life even in people without psychiatric diagnoses. According to this evidence, three different hyperactivation levels could be proposed (from normality to pathology): firstly, an adaptive increase in energy (e.g. athletes performing well); secondly, a DBR determined from the continuous stimulation of stress hormones, with possible positive scores on the MDQ without a diagnosis of bipolar disorder, like in burnout syndromes and, thirdly, hyperactivity during manic episodes. The Dysregulation of Mood, Energy, and Social Rhythms Syndrome (DYMERS), the second level of the scale, is proposed as a working hypothesis. DYMERS is also seen as a vulnerable condition that may evolve in other disorders (including BD) according to the individual susceptibility (including genetic predisposition) and the specific nature/level of the stressor.

Keywords

Hyperactivation, stress, social rhythm dysregulation, biological rhythm dysregulation, mood disorder, bipolar disorder

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Introduction: The emergence of clinical relevance of social rhythm dysregulation at the time of COVID-19

The perturbation of sleep and biorhythms exerts significant and adverse impacts on multiple metabolic pathways. Sleep assumes a critical role in the initiation, recurrence, dysfunction, and unfavorable health outcomes associated with various mental disorders, with a particular emphasis on bipolar disorder (BD). Many factors contributes to sleep disturbances, including external environmental elements such as road traffic noise and the influence of artificial light. These external factors profoundly affect

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immune-hormonal circadian timing mechanisms (24-h rhythms) and other inherent rhythms that have evolved to optimize human behavior when synchronized with light variations (for circadian rhythms) and other environmental factors like weather and seasons.[1,2]

A hypothesis has been put forward suggesting that alterations in sleep-wake cycle rhythms[3] could serve as a triggering factor for the onset of bipolar disorder. This might be attributed to the modern era's lifestyle changes, where staying awake at night could result in increased energy levels as an adaptation. However, this departure from the energy expenditure pattern established over millennia of evolution creates a disparity between current habits and the evolutionary perspective.[2]

During the Covid period and the related lockdowns, the clinical relevance of the dysregulation of social and behavioral rhythms came to the attention of researchers and clinicians. During that terrible "quasi-experimental condition," induced by the need to counter the pandemic, the following evidence emerged:

(1) The dysregulation of the rhythms before the lockdown was a predictor of depressive risk and of the low level of quality of life in the elderly during the lockdown (and, conversely, a good social rhythm was a factor of resilience)[4,5];
(2) The dysregulation of rhythms induced by a strict form of lockdown was a potent trigger of depressive episodes in people with bipolar disorder, when compared to people with the same disorder, but not under such a strict lockdown.[6] Even if it is probable that the same risk occurred in relation to episodes of mania, no evidence is available, in the published research as it was not possible to investigate this aspect, given the rarer occurrence of manic episodes and the consequent need for larger sample sizes to verify this hypothesis[6];
(3) The hyperactivation and burnout syndromes induced in healthcare professionals under stress and with alterations in social rhythms (i.e. not leaving the hospital for weeks for fear of infecting family members while experiencing the horror of death from Covid and the fear of getting infected)[7–11];
(4) The disruption of social rhythms influences the course of chronic diseases through the disruption of biorhythms and the modifications of the immune response.[12,13]

Hyperactivation and stress: The risk of short-circuit

Having to face a serious prolonged difficulty leads to the activation of the chronic stress response.[14,15] It is well known that, at times when greater efforts are required by the body, cortisol causes an increase in blood sugar and fat in the blood.[16] In this way, the body has more energy available for a prompt response. The combination of cortisol and catecholamines raises blood pressure to improve physical performance and alertness. Tension leads to less sleep and sleep restriction, with the consequent light hyperstimulation, induces, through melatonin, an imbalance of stimulating sex hormones (estradiol and testosterone) toward the stabilizing ones (progesterone and derivatives).[17] This recruitment of additional energy can have an adaptive effect, that is, it can allow unusual difficulties to be overcome. However, even in people without a predisposition to pathological mood cyclicity, continuous stimulation by stress, especially when the issues producing stress are not solved and persist, can cause hyperactivity, irritability, sleep disturbances, and disruption of social and behavioral rhythms.[18] In people with specific predispositions, activation of cortisol and neuro-stimulating steroids (summarizing the effect of the decrease in sleep and the consequent light pollution that leads to melatonin dysregulation) is associated with the risk of mania.[19,20] In fact, people with bipolar disorders showed higher levels of testosterone and estradiol during manic episodes.[18,21]

Dysregulation of mood, energy, and social rhythms syndrome a common stress-related disorder?

It is possible to suppose that the dysregulation of social and behavioral rhythms could be a basis of common vulnerability from which different pathological pictures could develop according to the specific individual vulnerability.

The Mood Disorder Questionnaire (MDQ) is an instrument that was initially conceived as a screening test for hypomania and that consists of 13 questions, which aim to detect a state of hyperarousal and hyper-energy.[22–24] However, people that did not receive a diagnosis of bipolar disorder during clinical investigations, and people with psychiatric diagnoses other than bipolar disorder, frequently scored positive on this tool, thus its accuracy was debated.[25,26]

Some researchers interpreted these high numbers of "false positives" as the fact that the diagnoses of bipolar disorder did not cover the whole "spectrum" of disorders, but only the tip of the iceberg and therefore only the most serious cases.[27] In fact, there was a strong evidence of comorbidity between bipolar disorders and almost all the pathologies highlighted in the "false positives." It is also well known that when another mental health condition shows comorbidity with bipolar disorder, frequently the onset of bipolar disorder has followed the onset of the other disorder ever by years.[28,29] The false positives could, therefore, be subthreshold cases that would have eventually led to a diagnosis of bipolar disorder several years after the evaluation.

However, new data has ascertained that:

(1) Positive scores on the MDQ are closely associated with the dysregulation of sleep rhythms.[30] The rhythm of sleep is, in turn, closely linked with the rhythms of eating and socializing.[31] Positive scores on the MDQ, therefore, reveal a syndrome characterized by hyperactivity (which is not always sufficient to identify an episode of hypomania) with dysregulation of social and behavioral rhythms.
(2) Positive scores on the MDQ are associated with a serious impairment of the quality of life, similar, in terms of importance, to that highlighted in serious chronic diseases, but independent of the presence of mood disorders[8] or other psychiatric diagnoses.[32] This impairment in quality of life in MDQ-positive people is independent of comorbidity and comes evident even at an old age, when a late onset of another psychiatric diagnosis is possible, but unlikely.[33]

This new data, therefore, suggests that the "false positives" at the MDQ could reveal a "sui generis" spectrum of mental suffering, characterized by the hyperactivation and the dysregulation of social and personal rhythms, independent of other psychiatric disorders. However, it may be considered a common risk that would develop in different ways based on the different individual vulnerabilities (including genetic ones) and the specificity of the stress that triggered the dysregulation.

As far as bipolar disorder is concerned, it must be considered that studies have recently shown that positive scores on the MDQ are not associated, "per se," with a genetic risk for this disorder.[30] On the other hand, one of the genetic variants found to be associated with bipolar disorder, CACNA1C rs1006737, was highly frequent in hyperactive, socially well adapted old adults without BD, to an equal extent as old adults with a diagnosis of BD, while non-hyperactive old adults without bipolar disorder had a strong lower frequency of this genetic variant.[34–36] A recent study showed that both a genetic test aimed to evaluate the presence of the genetic variant CACNA1C rs1006737, and the MDQ, could be quite accurate in screening bipolar disorder, but with unreliable and strongly specular results.[37] In fact, the genetic test showed a quite good sensitivity (a positive result was associated with a high probability of having bipolar disorder), whereas the MDQ was strongly specific (a negative result was associated with a high probability of not having bipolar disorder).[37] The unreliability of the two screening tests suggested that they do not measure the same underlying dimension of BD. This study, thus, seems to suggest the hypothesis that a condition of hyperactivation common to a stress condition, identified by a positive score on the MDQ, can trigger BD in people with a predisposition to hyperactivity (i.e. people with a specific genetic predisposition).

Adaptive and non-adaptive hyperactivation

Based on what has been previously illustrated, three levels of hyperactivation can be highlighted, ranging from an adaptive response to a mental distress (a trigger condition for several mental disorders) and then to a frank mental disorder:

(1) Adaptive increase in energy, which can be typical of any person preparing to face a difficult task, but which can lead to success. In highly trained people, the increase in adaptive energy can be marked such as in some sports stars, who report performing excellently even if they do not sleep the day before the race or the exercise due to hyper-activation.[38]
(2) Increase in energy linked to the dis-stress and associated with the dysregulation of social rhythms (sleep, eating, and relational),[39] typical of conditions in which the stress is strong and persists for a long time. In these cases, the increase in energy is still focused on the goal/issue producing the stress, but it is ineffective in resolving it, such as in occupational burnout syndromes, when some people report feeling "like a car that has its wheels spinning in the sand." The fact that stress syndromes result in false positives at the MDQ[30,40,41] may be the consequence of the activation symptoms that accompany stress syndromes.[42] In fact, the more the hyperactivation increases, the more it negatively reverberates on the physical and mental state and the situation seems unsolvable[43] and it may impair the health-related quality of life.[43] Burnout/occupational syndromes[43] and adjustment disorders,[44] in fact, severely impair the health-related quality of life.
(3) Hyperactivity and increased energy in the picture of an episode of hypomania or mania. In mania or hypomania, hyperactivation is out of control and loses relationships with adaptive goals (on the other hand, the hyperactivation due to stress and burnout, as described in point 2, is always focused on overcoming the issues even if it fails in its intent). In mania and hypomania, hyperactivity often rebounds into depression. For this condition to occur, stress and environmental factors need to be, possibly, associated with a specific and additional genetic risk. As indicated above, some genetic risks for bipolar disorder and a positive score on the MDQ could be independent components of BD.[37] A predisposition to hyperactivity could be the substrate of the disorder if trigged by great stress.

Future perspectives and tasks

At present, the diagnostic concept of "Dysregulation of Mood, Energy, and Social Rhythms Syndrome (DYMERS)" is to be considered a heuristic hypothesis, although based on different evidence sources that, together, represent stimulating clues.

It is therefore essential to verify these indications through:

(1) Studies on large samples, including non-clinical ones, which would allow us to verify the links between hyperactivation, dysregulation of rhythms, and stress.
(2) Research that clarifies how different expressions of genetic vulnerability can respond differently if subjected to dysregulation of biological rhythms and stress.
(3) Studies investigating how different personological characteristics and different genetic profiles related to personality can approach/research for stressful tasks.

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