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"Dysfunctional Response Syndrome"

New theories and proposals of what is now called dysautonomia

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Introduction

Socioeconomic and development differences between countries generate enormous differences in the quality of life, but none have yet managed to improve it in matters related to functional alterations that occur in organisms with a “brain at the limit” of their emotions, those who present with discomfort throughout their existence, a decrease in the quality of life and serious alterations in the beings that are related to them, where perhaps currently, the study and research on the more important quality is of greater importance than in the amount of life (1).

Functional disorders have been recognized over time in a segmental way and, therefore, in an incomplete way, from their diagnosis to their treatment. This segmentation and, therefore, the existence of partial diagnoses has been largely due to the presence of multiple medical specialties and the absence in many cases of a truly comprehensive medicine. These disorders are: migraine, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, irritable

bladder, mitral valve prolapse syndrome, orthostatic intolerance, postural orthostatic tachycardia (POTS), vasovagal syncope or, in conclusion, what is now called dysautonomia (2,3) and perhaps attention deficit disorder and sphincter of Oddi dysfunction (4) also belong to this group. These disorders are usually shared to a greater or lesser degree in all patients with dysfunction, varying both their frequency and intensity, which generates the theory of a shared cause. In this article, a theory regarding its origin is mentioned, as well as some practical proposals regarding its diagnosis and management.

General concepts

According to Dr. Joseph LeDoux, Professor at the New York University Center for Neurology, the amygdala is the site of the brain where emotional memory is housed, thus, responses are carried out from auditory or visual signals to the thalamus, the message is directed to the cortex of the brain, where it is analyzed and evaluated in search of meaning and appropriate response. However, if that response is emotional, a signal is directed to the amygdala to activate the emotional centers, where a smaller portion of the original signal is directed directly from the thalamus to the amygdala in a faster transmission, allowing an immediate response, although less precise, so the amygdala can trigger an emotional response before the cortical centers of the brain have understood what is happening. In the first thousandths of a second during which we perceive something, we not only unconsciously understand what it is about, but we decide whether or not we like it, “the cognitive unconscious” (1,5,6).

Likewise, the short-term central regulation mechanisms of blood pressure and heart rate in the cardiovascular center are characterized by acting very quickly, beginning their action in a few seconds. The intensity of the responses is strong, but it weakens in a short time; thus, sympathetic stimulation is capable of increasing blood pressure twice in 5-15 seconds and inhibition of sympathetic stimulation can decrease it by half in 40 seconds. The centers of the central nervous system that participate in this regulatory system are: the vasomotor center located in the brain stem, in the reticular formation of the lower third of the pons and the upper two thirds of the bulb. Fibers from this center project to the medulla and blood vessels. Said “controlling” center is made up of three differentiated zones: the vasoconstrictor zone (pressor), the vasodilator zone (depressor) and the sensory zone (7).

New theories and concepts regarding the syndrome

It is important to emphasize the importance of considering a more specific diagnosis through the integration of the syndrome in all patients who come to a medical consultation due to the presence of any of the symptoms, since most of the time several of them are found at the direct questioning and not just considering the presence of the syndrome in those with syncope (Table 1). The quick and imprecise responses that usually characterize the so-called dysautonomia usually have emotional experiences as a trigger, where the final, quick, abstract and primitive perception of what generates "aversion" or a "challenge" to the brain (Table 2) translates into inaccurate responses from the central regulatory centers through the sympathetic and parasympathetic systems, where the clinical manifestations to such an emotional response perhaps depend on the compensatory capacity that each organism is capable of generating in the face of it. That is, if the response is depressive, it could manifest as orthostatic or vasovagal intolerance, with chronic fatigue, dizziness when standing upright, paresthesias, with or without syncope. In this case, the absence of syncope is manifested most of the time by an adequate but exaggerated compensatory adrenergic release, which generates tachycardia, palpitations, sweating, insomnia, anxiety, tremor, vascular headache (1,6) and sometimes fibromyalgia due to the prolonged increase in muscle tone (2), or an inadequate pressure response with the classic manifestations of orthostatic postural tachycardia (8-24). That is, probably the clinical tests used, such as the tilt test, only help us to record the remote manifestations of such a response and not their origin, where, according to the present theories, it could not have great importance of the result during the same, for two reasons: 1) when the test was performed only once, it is unknown whether in all periods of discomfort the type of dysautonomic response (vasovagal, orthostatic intolerance or POTS) is the same in a given individual, since from the clinical point of view, it sometimes seems that there are manifestations of more than one type; 2) According to the present theories, the first-line treatment, identification and subsequent elimination of the “trigger” seems to be the same, regardless of the type of response in the tilt test (1).

Table 1

Symptoms in the "REDIS"

Heart rate variability

Tachycardia when standing up

Variability in blood pressure

Low blood pressure with symptoms

Dizziness

Syncope

Dyspnea

Paresthesia

Fatigue

Loss of spatial orientation

Headache

Palpitations

Fibromyalgia

Dysuria

Sweating

Dyspareunia

Premenstrual syndrome

Irritable bowel syndrome

Sleep disorders

Emotional disorders

Table 2

Common triggers of functional disorders

Warm environment, hot baths. Exercise. Physical or emotional stress. Standing without movement for a long time. When getting up. Unravel. Depression, anxiety. Valsalva maneuver. Volume depletion. Get up after a long bed rest. Rapid postural change. Alcohol consumption. Certain medications. Tilt test.

In a study that we carried out in Mexico City in 2012, called *"REDIS-1"*, after analyzing 1647 tilt tests, we found that 71.5% were performed in women, 39% of the tests corresponded to the subtype of orthostatic intolerance, 44% to vasovagal reaction, while only 4% were POTS, and the rest were negative. The average age of the tests was between 27 and 33 years, with a female: male ratio by subtype of: 3: 1 orthostatic intolerance, 2: 1 vasovagal reaction and 5: 1 POTS, data very similar to those reported in a study conducted in Cleveland, USA (25). Subsequently, a subanalysis (*"REDIS-2"*) was performed to try to relate the symptoms with the result of the tilt test (26), and in other publications we have proposed what could be the new indications to perform the tilt test, based on the present theories and concepts (1).

In the *"REDIS-1"* study, 93% of the tests analyzed concluded during the *"active phase"* (after administration of a vasodilator), which may correspond to the theories expressed in this article and which are mentioned below in relation to the tilt test. According to what has been cited throughout this writing, it could be the phenomena of emotional "aversion or challenge", the origin of the *"REDIS"*, which could be related to the important predominance of positivity of the tilt test during the *"phase active "*, in which, as already mentioned, a drug is administered that requires the brain to do a lot of work to compensate for the effect it exerts on the body, thus perhaps the effect that the *"active phase"* of the tilt test could be caused by any other phenomenon in patients with a "brain at the limit". Therefore, perhaps and it does not seem very important to perform the tilt test, at least initially, to know the response subtype, since, as we have mentioned, it seems to only measure the effects that are produced "at a distance". Therefore, current treatments would only act as palliative (4, 25).

Therefore, the following points could be considered: the now called dysautonomia in these cases, although it reduces the quality of life of a large number of people around the world, is considered a benign condition, so it can sometimes lead to diagnostic errors in cases of secondary dysautonomia, such as multiple systemic atrophy syndrome, storage disease such as amyloidosis, Parkinson's disease or other degenerative diseases of the central nervous system (1,2), so it might be prudent to call these benign functional disorders as "dysfunctional response syndrome" (REDIS; from its acronym: dysfunctional response in Spanish) (1). According to the foregoing, perhaps the origin of these dysfunctional responses is secondary to factors of education of the individual, in relation to rapid and inappropriate responses of the emotional system, but not for this reason, it does not cease to constitute a clear relationship between the psyche and the organism, where, even, mood disorders such as depression and / or anxiety constitute in many cases a "trigger" of these responses (1,6).

In other words, the *"REDIS"* could be the representation of an educated emotional system with little tolerance for frustration, which keeps the rest of the brain and consequently its subordinate organism, always at the limit of its demands, where it only wants to stay on stimuli and excessive daily demands within his limited area of "comfort", "easy to irritate and difficult to please" (4).

The foregoing would not only describe the organic response profile that people with a "borderline brain" seem to have, but also, most likely, certain personality profiles that the management and characteristics of their emotional brain confers on them, where and perhaps the so-called borderline personality disorder defined as "instability in self-image, personal goals, interpersonal relationships, and affections, accompanied by impulsivity, risk-taking and hostility" according to the DSM-V, could be then frequent in people with *"REDIS"*. Perhaps they are individuals with an emotional brain capable of generating immediate, impulsive and disorderly responses both at the level of their organism (*"REDIS"*) and their behavior, exerting on the latter a certain prolonged period of irritability due to the action of the consequent exaggerated release of adrenaline, secondary to *"REDIS"*, followed by a feeling of "guilt" regarding the behavioral errors committed, once the stimulus is finally rationalized in the cerebral cortex, and thus, they are usually maintained throughout life, which reduces the quality of life in the people who are related to them (1).

Theory of pathophysiology in the "REDIS"

1- Exposure to the emotional trigger on its way to the amygdala, which responds immediately in search of "flight" (avoids experiencing the aversion situation) to the central cardiovascular center, **2-** which generates a dysfunctional response (*"REDIS"*) in the body, by way of orthostatic intolerance, vasovagal reaction or POTS (dysautonomia) **3-** with secondary and exaggerated release of adrenaline, which, if sufficient, prevents syncope, **4-** but generates its effects both in the body and in the brain, which exacerbates the impulsivity of the emotion, subtracting the rationality effect that the cerebral cortex should have, which can sometimes generate errors in behavior, **5-** once the adrenaline levels decrease or the person recovers from syncope, the stimuli are rationalized and the feeling of "guilt" may come, if, in their case, there were behavioral errors (1).

Theories about the frequency of symptoms in the "REDIS"

1- *The behavior of a person without "REDIS":* he lives far from the limit and only approaches it in the face of emotional "triggers", with an adequate response and control to them, without reaching syncope.

2- *The behavior of those who suffer from the syndrome, but with adequate control:* it consists in that the symptoms always appear after the exposure of a “trigger” but they return to their baseline of well-being as long as they are not exposed to another “trigger”. However, your baseline state is always near your limit (“brain at the limit”).

3- *The behavior in those who suffer from the syndrome with fluctuations, but most of the time with discomfort:* it may correspond to the presence of a hidden and constant "trigger", being frequent the presence of mood disorders such as chronic depression.

4- *What probably constitutes a subgroup of patients with “REDIS”:* those who, in addition, suffer from the so-called “Biliary dyskinesia syndrome” (BDS), tend to present intermittently more discomfort, but hardly reach their baseline of well-being, that is, they present intermittent periods of greater discomfort, but they never manage to feel without discomfort (1).

"Biliary dyskinesia syndrome" (BDS)

Biliary dyskinesia constitutes a disorder in the mobility of the gallbladder, which was only limited to abdominal discomfort, such as nausea, vomiting or both, and pain in the upper right part of the abdomen, however, we have recently postulated to call it as “Biliary dyskinesia syndrome” (BDS) since we have observed the frequent association of said vesicular alteration with mood symptoms resistant to psychiatric treatments (mainly depression and / or anxiety disorders) and symptoms of the so-called dysautonomia with positive tilt test inclusive, (which will probably cause the modification of the Rome III criteria in the future) in which case, the predominant symptoms of the alteration in the adequate contraction of the gallbladder (gallbladder ejection fraction less than 35% by nuclear medicine scintigraphy), they are usually frequent episodes of abdominal distension, which is often misdiagnosed as irritable bowel in these patients. This could perhaps be explained by the constant vasovagal stimulus that the gallbladder with dyskinesia seems to exert, in which case, the dysautonomic representations will depend on the adrenergic compensatory capacity of each individual as

explained above. On the other hand, "BDS" may also be involved in excessive postprandial sleep, perhaps due to a dual effect, both by vasovagal stimulation and by the action of cholecystokinin at the brain level. So maybe this syndrome constitutes a subgroup of patients with the syndrome called dysautonomia, which perhaps exacerbates the symptoms, so it seems important to keep this alteration in mind, since I consider it may be part of a previously unrecognized “trigger”, as it probably sphincter of Oddi dysfunction represents a manifestation of the so-called functional disorders, which should be suspected in those patients with persistent symptoms once the gallbladder dyskinesia has been resolved through cholecystectomy. In other words, “BDS” can be a “hidden trigger” in patients with *“REDIS”* (with a “borderline brain”) wrongly diagnosed with irritable bowel, and this constitute a cause of dysfunctional symptoms, usually intermittent but constant (1, 4).

Conclusions

Probably, a “brain at the limit” and its organic manifestation that could perhaps be called more appropriately as *“REDIS”*, represent from an integral point of view of the human being, the first entity with a clear relationship between what one feels, emotions, the brain, behavior and physical discomfort, a syndrome perhaps much broader to understand than the still so limited entity called dysautonomia today. Perhaps and it will be necessary to select the patients who require the tilt test, since the diagnosis can be made clinically, where through the adequate identification of the "triggers" and an adequate control of them, it can be achieved an improvement in the increasingly frequent patients with dysfunctional syndrome, where in many cases behavioral therapy will be required and perhaps in a still distant future the emotional reeducation of the individual will become possible.

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