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Long-term mood disorder antedating the diagnosis of Wilson's disease

Transtorno de humor de longa data antecedendo o diagnóstico da doença de Wilson

Dear Editor,

We evaluated a young patient with a long history of psychiatric symptoms and misdiagnosis. After nine years of receiving many ineffective symptomatic therapies, she was diagnosed with advanced Wilson's disease (WD). We would like to present this case in order to raise awareness around the wide clinical spectrum of WD as well as around the need to establishing high clinical suspicion for this diagnosis.

A 17-year-old woman, the daughter of consanguineous parents, was admitted to a university hospital with the diagnosis of cryptogenic cirrhosis. Her clinical history revealed that, since the age of nine, she had been experiencing a series of episodes of excessive fear, anxiety and depression. As her depressive symptoms grew steadily worse, she was put on antidepressants, including amytriptiline and fluoxetine. At the age of 12, she committed two suicide attempts, which were followed by an episode of frank mania with psychotic symptoms, evidenced by her attempt to bury herself up. Between the ages of 12 and 17, she remained on mood stabilizing agents, including carbamazepine and valproic acid. This course of treatment was, however, unsuccessful.

Six months before hospitalization, she experienced weight gain and diffuse abdominal pain, followed by nausea and hyporexia. Ultrasonography and computed tomography (CT) of the abdomen revealed cirrhosis and ascites. Extensive serological studies, including HIV, hepatitis B and C, anti-LKM1, anti-mitochondrial, anti-smooth muscular and anti-nuclear antibodies were unrevealing. When admitted to the hospital, her abdominal pain had worsened and she presented with severe ascites and delirium. Neurological examination showed diffuse hyperreflexia and ankle clonus. Kayser-Fleischer rings were present bilaterally. Further investigation yielded 13 points on the Child-Pugh's classification (severe ascites, stage II encephalopathy, albumin level 2.1, international normalized ratio 2.74, bilirubin levels equal to 4.2). Alpha-fetoprotein at 45.1ng/ml (normal value: < 300ng/ml) and serum ceruloplasmin at 9.0mg/dl (normal value: 15-60mg/dl). Cranial CT showed enlargement of the ventricles and caudate atrophy. She rapidly became hemodynamically unstable, thus making death seemingly inevitable. Upon immediate investigation, family members disclosed that her two brothers had been diagnosed with WD. Her mother, who used fluoxetine on an irregular basis, had been diagnosed with depression and her uncle with schizophrenia.

WD is an autosomal recessive genetic disorder related to the metabolism of copper, which accumulates in several tissues such the brain, liver and cornea. Neurological and psychiatric symptoms may occur due to the presence of such copper deposits in the brain.[1,2]

In nearly 10% of the cases, the first signs of WD may manifest in the form of psychiatric symptoms. Several psychiatric manifestations have been reported.[3] A study with 50 WD patients identified excessive talkativeness, aggressive behavior, loss of interest and abusiveness as the key behavioral changes.[4] Twelve of these patients (24%) fulfilled the diagnostic criteria for a psychiatric condition: nine patients (18%) were diagnosed with bipolar disorder, two (4%) with major depression, and one (2%) with dysthymia. In another study,[5] 11 out of 14 patients with WD had a mood disorder and three presented a schizophreniform-illness.

This case report aims at emphasizing the relevance of considering WD as a possible diagnosis in young patients with psychiatric symptoms, especially in those with a family and past history of jaundice, extrapyramidal features, neuropsychiatric disorder and premature deaths of other siblings. Awareness about the heterogeneity of WD and a high rate of suspicion may have a prognostic implication.

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Note: UFMG = Universidade Federal de Minas Gerais; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPEMIG = Fundação de Amparo à Pesquisa do Estado de Minas Gerais.
For more information, see Instructions for Authors.

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Ceiling effects in the "Effectiveness of adjunctive antidepressant treatment for bipolar depression" study: was the sky the limit?

Efeitos do teto no estudo "Eficácia do tratamento antidepressivo adjuvante para depressão bipolar": era o céu o limite?

The widely discussed study by Sachs et al., namely the *Effectiveness of adjunctive antidepressant treatment for bipolar depression* is based on a pragmatic trial that randomly assigned bipolar depression patients to receive mood stabilizer plus placebo or mood stabilizer plus antidepressant. It achieved similar results in terms of durable recovery and other secondary outcomes. Considering that the aforementioned study employed a new methodological approach, I believe that it would be worthwhile exploring its advantages and disadvantages so as to be better positioned to interpret current studies, as well as to design new ones. Based on the aspects listed below, I would like to discuss whether or not the study contains a "ceiling effect" i.e., a false negative finding resulting from performance and selection biases.

1) *Refractoriness* – In the study by Sachs et al., 60% of the patients presented more than 10 previous manic and depressive episodes,[1] thus suggesting that this group may constitute a refractory sample. Refractoriness is associated with poor treatment outcomes and, therefore, to ceiling effects.[2] For instance, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, the cumulative remission rates after one, two, three or four antidepressant trials were 33%, 57%, 63% and 67%, respectively.[3] Sachs et al. aimed at detecting an absolute difference of 15% between groups, a goal that could hardly be achieved had the subjects presented at least a moderate rate of refractoriness.

2) *Strict primary outcomes* – the primary outcome of the Sachs et al. study was "durable recovery", defined as eight consecutive weeks of euthymia, with no more than two manic *or* depression *symptoms*. This is a more orthodox criterion when compared to the criterion generally applied to most antidepressant trials, which tend to define remission as a mood score <10 points, which, in turn, can be translated as the presence of 4 to 5 mild or 2 to 3 moderate symptoms.[4] When stricter outcome criteria are adopted, both the experimental and the control interventions are more likely to yield similar response rates, thus leading to a ceiling effect.

3) *Excessive "noise"* - clinical trials are ultimately designed to detect whether treatment effects (the "signal") surpass non-specific effects (the "noise"). In the Sachs et al. study, patients were allowed to increase the dose of the mood stabilizer and enhance the use of pharmacotherapy, psychotherapy, etc. Such factors could have increased the trial "noise" by increasing non-specific effects at the expense of decreasing the "signal" of the experimental treatment.

4) *Design issues* – Sachs et al. compared mood stabilizer + placebo against mood stabilizer + antidepressant drug. In such type of design, ceiling effects are important since the effect of the combined intervention is weaker compared to the effect of each intervention tested separately.[2] For example, when two treatments whose individual remission rate is set at 50% are