

## Bipolar disorder can be toxic to the nervous system

**Researchers analyze, based on an in vitro model developed in the Department of Biochemistry of UFRGS (Federal University of Rio Grande do Sul), the toxicity of the disease through the serum of the patients**

By Carolina Golenia

Bipolar disorder is a disease that affects the nervous system. It causes depression and excitement episodes, and cases of insomnia are usual as well. During these episodes, called mania, changes occur in the patients' brain and body. The disease is genetic and affects 2% of the population. Any person can develop the disease, but those who already have relatives with this problem may be prone to it.

In the Department of Biochemistry of UFRGS, researchers developed an *in vitro* cell model of neuroblastoma, a brain tumor that is transformed into a cell that is very similar to a human neuron. This model was used to investigate bipolar disorder, usually studied in animals. In seven days, the neuroblastoma is transformed, then the cell stops proliferating and starts emitting neurites (projections of the cell, such as axon and dendrites), producing neurotransmitters, and obtaining electric potential. In the animal model, it is only possible to mimic a mania or depression crisis, but it is not possible to mimic the bipolarity.

The coordinator of the Laboratory of Cell Biochemistry of UFRGS, Professor Fábio Klamt, explained that bipolar disorder not only affects the central nervous system in specific regions, but also causes systemic impairment. "It is possible to detect some changes in several blood components of the patients, such as peripheral diminution of neurotrophins (proteins which aid in the brain functioning), the increase of preinflammatory cytokines (molecules that indicate inflammatory processes) and the increase of oxidative stress (biological condition that increases the amount of free radicals and the inability of the antioxidant system to combat them.)"

The project is carried out in association with the Laboratory of Molecular Psychiatry of the Hospital de Clínicas and led by psychiatrist and professor Flavio Kapczinski. According to him, "when the episodes of the disease happen, these changes increase; and when the episodes cease, the changes decrease. We have observed that, when the patients are in crisis, their blood inhibits the growth of neurons, mainly the dendrites – which are ramifications of neurons."

From this data collection, researchers developed the concept of systemic toxicity. "We do not know yet whether it comes from the nervous system and leaks into the blood or is in the blood and influences the nervous system. What is important is that we can see these changes in the periphery," Klamt stated.

### Methodology

To keep the cell culture in laboratory, the researchers used fetal bovine serum, a commercially used method. "Our idea was to substitute the bovine serum with the serum of the patients," Klamt explained. In the research, we used sera of people who did not have bipolar disorder, of patients in the early stage of the disease and of patients in the advanced stage – who are assisted in the outpatient clinic of the hospital.

The researchers remove the serum (through the blood), prepare and treat the neurons in vitro with it. "When we use the serum of healthy



Study was pioneering in presenting an in vitro study model of bipolarity. Image by Rochele Zandavalli for UFRGS Archive

people, we do not detect changes in the neuron. But when we did the intervention with the serum of the patients, we noticed that the neurite density was reduced, which is a marker of toxicity," Klamt reported. This reduction damages the functioning neurons, which explains why patients lose concentration and memory. "The cell lifetime has also reduced, especially with the serum of patients in advanced stage of bipolar disorder." The results from the group of healthy people and the group of people at an early stage of the disease were similar.

### Stages of bipolar disorder

Another concept that has been studied is the disease progression. "We have observed that bipolar disorder follows stages which are not associated with the disease progress, but rather with the number of episodes of maniac or depressive crisis. The greater the number of episodes, the shorter the time between them, and the greater the severity of them. As in cancer, patients with multiple episodes tend not to respond anymore to treatment," Klamt explained.

In the early stage of the disease, patients have inflammatory alterations in the blood, but they are momentary and less intense. Only after people suffer multiple episodes or spend many years of their lives with no treatment, the changes remain. "Thus, even if the patients start the treatment, they still have these factors circulating in the blood and, in a sense, the neuronal growth inhibited." It is also possible to observe, in patients in the advanced stage of bipolar disorder, the decrease in the brain's white matter – which connects one neuron to the other.

This condition aggravates nervous system problems, which prevents them from working. "Many patients who have chronic depression or chronic bipolar disorder need to retire early because they can no longer do their jobs," Kapczinski explained.

### How to prevent Bipolar Disorder?

Bipolar Disorder initially compromises neural connections, and, throughout the disease, there is loss of cells and atrophy of specific brain regions. In neurochemistry, loss of connections is associated with degeneration. According to Klamt, "these results reinforce the idea that we cannot put all patients on a single therapy. It is important to individualize it because each patient is unique."

The best way to prevent bipolar disorder or reduce its symptoms is to seek some treatment and use appropriate medication to avoid new episodes from happening.

### Pioneering research

This was the first study to demonstrate the serum toxicity of patients with bipolar disorder in human neuronal cells, and in presenting a model of in vitro bipolarity study. The cell created by researchers from UFRGS can be used both to study pathology and to screen new drugs, as well as to serve as a basis for the development of new therapies.

### Next steps

Researchers are now working on a method to quantify neurites through an automated software. "We intend to develop a product to conduct drugs screening, "which is the identification of new medication through tests. They are also studying what is causing the degeneration or death of the cells in the serum to understand the toxicity and then to preselect the drugs that will be effective in these processes. "We are treating this cell with lithium, a drug used to modulate mood disorder," Klamt stated. "We want to see whether the lithium inhibits the reduction of neurites density when we put it in this culture of neurons," Kapczinski completed.

### Source:

Wollenhaupt-Aguiar, B. *et al.* (2016). [Reduced Neurite Density in Neuronal Cell Cultures Exposed to Serum of Patients with Bipolar Disorder](#). *International Journal of Neuropsychopharmacology*, volume 19 (issue 10). doi: pyw051.

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