Chemotherapy and cognitive dysfunction: hope for a new treatment

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Translated from Le Journal de Montréal, March 11th, 2019

Over half of all patients who receive chemotherapy for the treatment of cancer develop cognitive problems. According to a recent study, this cognitive dysfunction is linked to a perturbation of three types of glial cells present in the white matter of the brain, suggesting that medications which target these cells could diminish the undesirable effects of chemotherapy on cognition.

A large number of patients undergoing chemotherapy treatment for cancer must deal with a deterioration in their cognitive functions following this treatment.

These problems generally take the form of loss of memory, problems with attention and concentration and an inability to perform several tasks simultaneously as well as marked modifications in the sense of humor. This phenomenon, familiarly known as "chemobrain", is particularly frequent in survivors of breast cancer, can sometimes last for several years and can have serious effects on the quality of life for the affected patients.

With improved effectiveness in cancer treatments and a significant increase in the number of people who survive this disease, the cognitive dysfunction which results from chemotherapy thus represents a very serious side-effect, and it is important to understand how to improve the quality of life for patients affected by cancer.

SIGNIFICANT DAMAGE

A very important discovery in this area was recently made by a team of scientists at Stanford University (Palo Alto, California)[1].

While the majority of studies to date on chemobrain have focused on neurons, these researchers were instead interested in the effects of chemotherapy on the glial cells, a class of support cells which participate in the proper functioning of the neurons. There are 3 principal types of glial cells:

1. The oligodendrocytes, which produce the myelin i.e. the fatty layer which isolates the nerve fibres and thus permits the transmission of nervous impulses.
2. The astrocytes, which supply essential nutrients to neurons.
3. The microglia, a class of immune cells responsible for the defense against pathogens.

The first evidence of a role for these cells in post-chemotherapy cognitive dysfunction came from post-mortem examination of frontal lobe samples taken from children who had, or had not, received anti-cancer chemotherapy before their deaths. There was a drastic decrease in the quantity of oligodendrocytes producing myelin in the brains of children treated by chemotherapy, suggesting that these cells might play an important role in the perturbation of neuronal functions.

To better understand this phenomenon, the researchers next treated mice with methotrexate, a commonly-used chemotherapeutic agent which is known to cause cognitive dysfunction. They were able to show that this medication caused significant damage to the oligodendrocytes, leading to a thinning of the myelin sheath and the appearance of motor and cognitive problems similar to those observed in humans (jerky movements, increase in anxiety level and decreased short-term memory).

Further studies have shown that these phenomena are caused by an over-activation of the microglia, which leads to an inflammation that disturbs the normal functioning of the astrocytes and compromises the transmission of nervous impulses by the neurons. In other words, chemotherapy affects the function of the three types of glial cells, with dramatic repercussions on neuronal function.

DECREASING THE EFFECTS

The discovery that over-activation of the microglia is responsible for the cognitive dysfunction caused by chemotherapy is very interesting because some medications which are able to eliminate the hyperactivity of the microglia have been developed in recent years and could thus allow us to halt, or to at least decrease, these secondary effects of chemotherapy on cognition.

This possibility is nicely illustrated by the observation that administration of one of these medications (PLX5633, a molecule which blocks CSF1R, an essential receptor for the survival of microglia) reverses the effect of methotrexate on the oligodendrocytes and astrocytes and eliminates some of the cognitive problems caused by the chemotherapy. This type of medication could thus help in diminishing the cognitive dysfunction in cancer survivors and thereby considerably improve their quality of life.

While we await the day that these treatments become available, it is worthwhile to note that certain aspects of lifestyle can reduce post-chemotherapy inflammation and decrease its effect on cognition.

For example, regular physical exercise and a quality diet (rich in plants and avoiding industrially processed foods which are rich in sugar and bad fats) both have powerful anti-inflammatory effects which can contribute to diminishing the negative effects on neuronal function.

These aspects of lifestyle are all the more important because a number of studies have clearly shown that they are associated with a significant diminution in risk for the recurrence of several types of cancers, as well as with longer survival for the patients.

(1) Gibson EM et al. Methotrexate chemotherapy induces persistent tri-glial dysregulation that underlies chemotherapy-related cognitive impairment. Cell 2019; 176: 43-55.

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