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PRESS RELEASE

Friedreich Ataxia
First results in the treatment of neurological disorders

A team of researchers from the "Medical Genetic Clinic and Research Unit" Inserm Unit 781 directed by Arnold Munnich (Necker-Sick Children's Hospital, Paris) in collaboration with Ioav Cabantchik (Hebrew University, Jerusalem) have just obtained promising results for the treatment of neurological damage from Friedreich Ataxia, the most frequent of hereditary ataxias. Movement coordination, speech as well as certain sensory disorders were improved under the effect of deferiprone, a molecule which traps the iron accumulated abnormally in certain regions of the brain.
These positive results, obtained right from phase I/II of the trail, offer short term therapeutic prospects for this severely disabling disease.

This work was carried out at Inserm Unit 781 and financed by the AFM thanks to Téléthon donations. It can be consulted on the Internet site of the review "Blood."

Friedrich Ataxia is the most frequent of the hereditary ataxias, and affects 1 person in 50 000 in Europe. One European in 120 is a carrier of the genetic anomaly at the origin of this recessively transmitted disease. The anomaly was identified in 1996 – it concerns a large expansion of the triplet GAA (100 to 2 000 repeats) in a gene situated on chromosome 9 coding for a protein named "frataxin."

This neurodegenerative disease is due to damage to certain cells of the nervous system. It manifests itself mainly in problems of balance and in the coordination of voluntary movements (ataxia). Cardiac damage (cardiomyopathy), osteoarticular disorders (scoliosis, high-arched foot) and diabetes are sometimes associated.

In 1997 Arnold Munnich's team highlighted the mechanism of the disease – protein deficiency leading to an abnormal accumulation of iron in the mitochondria, seats of cellular respiration and energy production. This excess of iron results in the formation of oxygen-free radicals, which are toxic for the cell. In 1999 this team carried out a first clinical trial based on the administration of idebenone[1], which led to some early encouraging results by reducing cardiomyopathy. However, this treatment had no effect on the neurological damage. The researchers therefore tried to reduce it by using a molecule which eliminates iron excess – an iron chelator.

Using a sequence of magnetic resonance imaging (MRI) developed to measure the quantity of iron at any precise point, the researchers were able to highlight the abnormal

[1] This molecule acts as an antioxidant by neutralising the free radicals liberated by the mitochondria.

accumulation of iron at the cerebellum, the regulating nervous centre of the motor function. Using this information, they opted for an iron chelator which crosses the barrier separating the brain from the blood circulation, deferiprone.

For 6 months each patient absorbed two doses of deferiprone daily. By the end of the trial the neurological disorders had improved for 8 of the 9 patients, due to the decrease in the quantity of iron in the cerebellum. These improvements first concerned the sensorial or sphincterian problems such as incontinence or constipation, then the execution of movements and speech and finally movement and balance.
Such positive results were not expected at such an early stage of the clinical trial.

Soon an international double-blind randomised multi-centric trial will be launched in cooperation with the Canadian firm ApoPharma.

Thanks to its capacity to redirect excess iron to iron-deficient zones of the body, in the future deferiprone could be used in the treatment of other more common pathologies such as anemias due to chronic inflammatory diseases.

For further information:
Selective iron chelation in Friedreich Ataxia. Biological and clinical implications. Nathalie Boddaert[1], Kim Hanh Le Quan Sang[2], Agnès Rötig[2], Anne Leroy-Willig[3], Serge Gallet[4], Francis Brunelle[1], Daniel Sidi[5], Jean-Christophe Thalabard[2], Arnold Munnich[2,] Z. Ioav Cabantchik[6]. ***Blood (on line)*.**

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