New drug candidate slows the progression of adrenoleukodystrophy

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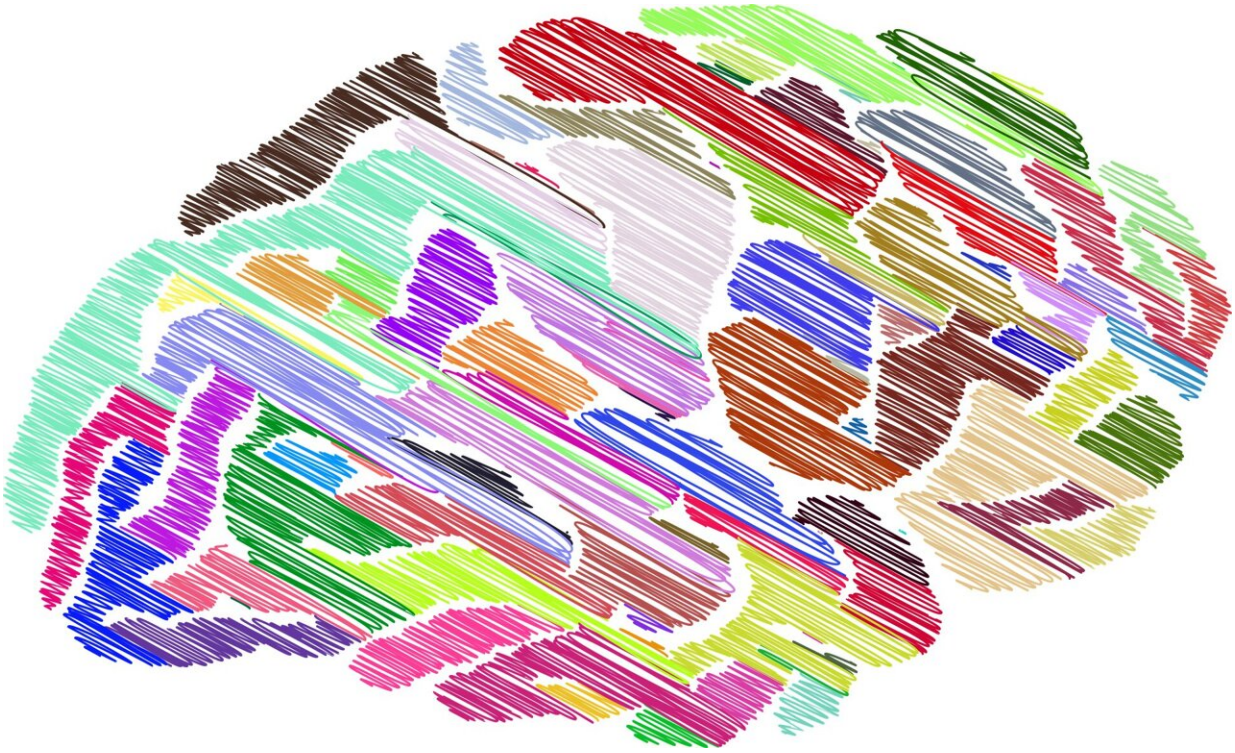

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The work of Professor Fanny Mochel (AP-HP, Sorbonne University) at Paris Brain Institute, in collaboration with clinical research teams in eight countries and Spanish biotech Minoryx Therapeutics, has demonstrated the protective effects of leriglitazone in the progression of adrenoleukodystrophy—a rare genetic disease in which the white matter

of the central nervous system is damaged. The results are published in *The Lancet Neurology*.

Most rare neurodegenerative diseases suffer from a lack of effective treatments. This is also the case for X-linked adrenoleukodystrophy (or X-ALD), an inherited condition that affects 6 to 8 out of every 100,000 births. It is characterized by an excessive accumulation of very-long-chain fatty acids in various tissues, particularly in the brain, spinal cord, and adrenal glands.

By the time they reach adulthood, these patients present with degeneration of the spinal cord. As a result, they often develop adrenomyeloneuropathy (AMN), which causes chronic debilitating symptoms such as stiffness of the lower limbs and balance problems that increase the risk of falls. In addition, urinary symptoms are frequently present.

Changing the trajectory of the prognosis

The disease is progressive, and because it is linked to a mutation on the X sex chromosome, its most severe forms affect mostly males. It is estimated that one-third of boys and more than half of adult men affected by AMN also develop aggressive inflammation of the brain, called cerebral adrenoleukodystrophy (cALD), in which the myelin sheaths that surround the extensions of neurons are attacked. The flow of the nerve impulse is disrupted and leads to rapid cognitive and motor decline, which can be fatal within a few years.

Controlling the inflammation appears to be an avenue to slow down the evolution of the disease and reduce symptoms, since no pharmacological treatment exists at present. This is the path taken by Professor Fanny Mochel at Paris Brain Institute, in collaboration with European and American teams.

In ADVANCE, a randomized, double-blind, placebo-controlled study, researchers studied 116 adult male patients with clinical signs of adrenomyeloneuropathy for two years, in order to test the effectiveness of a new drug developed by the Spanish biotech Minoryx Therapeutics: leriglitazone. This molecule, a PPAR gamma agonist capable of penetrating the brain, regulates the expression of genes that contribute to the neuroinflammation and neurodegeneration related to the disease.

Promising results

At the end of ADVANCE phase II/III, the researchers found that taking leriglitazone daily reduced the progression of certain key symptoms—such as gait imbalance—and, remarkably, decreased the risk of cALD, the acute cerebral form of the disease associated with premature death. Only subjects in the placebo group developed cALD, suggesting a protective effect of the drug.

Furthermore, daily use of leriglitazone only caused moderate side effects—mainly weight gain and superficial edema. This safety profile is therefore likely to promote adherence to treatment.

The study is now in an extension phase to confirm the ability of the molecule to delay the evolution of the disease. In addition, Professor Mochel's team is treating a dozen adults with cALD on a compassionate basis and has observed a stabilization, sometimes even a regression, of brain lesions in these patients.

In view of these very encouraging results, a marketing authorization application for leriglitazone has been filed with the European Medicines Agency for the treatment of adult male patients with X-linked adrenoleukodystrophy.

Better monitoring for better treatment

There is a pressing need for an effective, minimally invasive treatment for the disease: currently, only hematopoietic stem cell transplantation (HSCT) has potential to treat cALD. HSCT is a cumbersome procedure which includes chemotherapy; it also requires finding a donor, which proves to be difficult: close relatives may carry the genetic anomaly present in X-linked adrenoleukodystrophy.

Today, the greatest challenge is to identify patients with X-linked adrenoleukodystrophy as early as possible and to follow them throughout their lives, notably via MRI imaging. To this end, Professor Fanny Mochel now coordinates a national surveillance network within the Reference Center for Leukodystrophies and Leukoencephalopathies based at the Pitié-Salpêtrière Hospital, in Paris.

Following the results of the ADVANCE study, leriglitazone will be evaluated for other indications in which it is likely to act on neuroinflammation, such as other forms of leukodystrophies.

More information: Wolfgang Köhler et al, Safety and efficacy of leriglitazone for preventing disease progression in men with adrenomyeloneuropathy (ADVANCE): a randomised, double-blind, multi-centre, placebo-controlled phase 2–3 trial, *The Lancet Neurology* (2023). DOI: 10.1016/S1474-4422(22)00495-1

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