

Existing drugs may improve neurological function in patients with rare genetic disorder

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New findings from Children's Hospital of Philadelphia (CHOP) show that some patients with a rare and aggressive form of leukodystrophy

may benefit from receiving treatment with a class of targeted therapy drugs that could improve their neurological function. A correspondence about these findings was published today in the *New England Journal of Medicine*.

Aicardi-Goutières syndrome (AGS) is a [rare genetic disorder](#) and type of leukodystrophy that affects the brain and [immune system](#). In patients with AGS, the body's immune system turns on itself in a destructive way, targeting the brain's [white matter](#), causing most children with the disorder to experience mild to severe intellectual or physical impairments. Most children with AGS are unable to walk or talk and have multisystemic complications, including skin inflammation.

Prior studies have linked the activation of interferons—signaling proteins that respond to various immune disruptions—to exacerbated symptoms in AGS. Researchers at CHOP wanted to explore whether a class of small molecule inhibitor drugs called janus kinase (JAK) inhibitors could be used to block interferon activation in a way that helped these patients.

"Because treatment options for AGS are limited and the symptoms that these patients experience are so severe, there is a need to explore a wide variety of options," said senior author Adeline Vanderver, MD, an attending physician in the Division of Neurology, Program Director of the Leukodystrophy Center, and Jacob A. Kamens Endowed Chair in Neurologic Disorders and Translational Neurotherapeutics at CHOP.

The study was conducted at CHOP with 35 international patients with genetically confirmed AGS. These patients received baricitinib, an oral JAK1 and JAK2 inhibitor, with doses based on each patient's renal function, age and symptoms. Patients had their developmental histories evaluated from the onset of the disease to the end of the study, which ranged from 7.4 months to 41.5 months. The study team analyzed a

variety of developmental milestones, including head control, sitting, rolling, smiling, babbling, and the use of single words and word combinations.

Before the patients in this study received treatment, 26 of the 35 had stable or declining neurologic function, and 9 of the 35 patients gained one or two of these developmental skills after disease onset. However, during the study, 20 patients met new milestones, and 12 patients gained between two to seven new skills. The improvements were typically observed within three months into the study and persisted. Children who received higher doses of the therapy appeared to achieve more of these milestones.

Some of the AGS patients who received baricitinib were at risk for developing thrombocytosis, leukopenia, and infection and therefore should be monitored closely while taking the drug.

"Measuring neurologic improvements in these patients is a complex process, but the results of this study are encouraging, especially because we observed improvements even in [patients](#) with severe and long-standing disease," Vanderver said.

More information: Vanderver et al, "Janus Kinase Inhibition in the Aicardi-Goutières Syndrome." *N Engl J Med*, online September 3, 2020. [DOI: 10.1056/NEJMc2001362](https://doi.org/10.1056/NEJMc2001362)

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