Motor neuron disease

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Neuroinflammation in spinal muscular atrophy

A new study reported in *Communications Medicine* has found evidence that pro-inflammatory cytokines and neurotrophic factors are upregulated in the cerebrospinal fluid (CSF) of individuals with SMA1 — a severe form of spinal muscular atrophy (SMA). The disease-modifying drug nusinersen reduced the levels of some but not all of these molecules, and those that persisted after treatment might represent new therapeutic targets for SMA.

SMA is an inherited motor neuron disease caused by mutations in the *SMN1* gene, which encodes survival motor neuron protein (SMN). The related gene *SMN2* can partially compensate for loss of *SMN1* function, and the severity of the disease is determined, at least to some extent, by the number of copies of *SMN2* in the affected individual.

"Three therapies have recently been developed to treat SMA that are based on increasing the levels of SMN; however, these therapies do not represent a cure for the disease, and additional approaches need to be developed to increase clinical benefit in patients," explains study leader Alessandro Usiello. "Although immune system alteration represents a key factor in the onset and progression of many neurodegenerative diseases, the role of neuroinflammation in SMA has not received much attention."

Using a magnetic bead-based immunoassay, Usiello and colleagues measured cytokine and neurotrophic factor levels in CSF samples from 18 children with SMA1. Compared with individuals who had SMA2 ($n = 19$) or SMA3 ($n = 11$), which are milder forms of the disease, the participants with SMA1 showed elevated levels of the pro-inflammatory molecules eotaxin, IL-2, IL-6, IL-8, IL-12, IFNγ, MCP1, MIP1α, PDGF-BB, TNF and VEGF.

Nusinersen is an antisense oligonucleotide that increases the expression of *SMN2* and provides substantial clinical benefits in people with SMA1. Following treatment with this drug, the study participants with SMA1 showed reductions in CSF levels of a subset of the aforementioned pro-inflammatory molecules. However, levels of IL-6, IL-8, IL-12, IFNγ, MIP1α and PDGF-BB remained high, suggesting the presence of residual neuroinflammation that could be targeted with alternative therapeutic strategies.

"Our results reveal a remarkable pro-inflammatory milieu in the CSF of patients with severe SMA, although we need to confirm and expand our findings in larger cohorts," comments Usiello. "We are also interested in investigating the mechanisms driving the inflammatory response and its contribution to SMA pathology, using in vitro and in vivo model systems."

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Original article: Nuzzo, T. et al. Nusinersen mitigates neuroinflammation in severe spinal muscular atrophy patients. *Commun. Med.* **3**, 28 (2023)

Related article: Mercuri, E. et al. Spinal muscular atrophy — insights and challenges in the treatment era. *Nat. Rev. Neurol.* **16**, 706–715 (2020)