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Interferon-beta aids balance and movement in mice with spinocerebellar ataxia 7

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The group of genetic conditions known as spinocerebellar ataxias currently have no treatment or cure and are always fatal, in the case of affected children at an early age. Symptoms include a progressive lack of co-ordination of gait, and poor co-ordination of hands, speech and eye movements, due to a failure of co-ordination of muscle movements. Now researchers from France and the US have found a new way of controlling the symptoms and significantly improving the physical condition of animal models of the disease, the annual conference of the European Society of Human Genetics will hear on Monday, June 10.

Dr. Annie Sittler, from the Centre National de la Recherche Scientifique (CNRS), working in the team of Professor Alexis Brice at the research centre Brain and Spinal Cord Institute (CR-ICM), Paris, France described the team's work in the field of polyglutamine disease, a group of neurodegenerative conditions involving abnormal protein conformation. "Accumulation of a polyglutamine-containing protein known as mutant ataxin -7 is responsible for neurotoxicity, neuronal dysfunction, and eventually neuronal death", she explains. "We had previously shown in cells that mutant ataxin-7 was degraded in nuclear bodies, structures found in the nucleus of cells, by a protein known as promyeloctyic leukaemia protein or PML, and that interferon-beta could help with this process and protect against disease."

The researchers used a mouse model of a particular form of spinocerebellar ataxia known as SCA7. The genetically-modified 'knock-in' mice develop the severe type of the disease, similar to the infantile

human version, and have a very short lifespan of around 14 weeks. They were injected with mouse interferon-beta three times a week, starting at five weeks of age, just before their first symptoms of disease were due to appear. Investigation of their brains post-mortem showed that the mice who had received the interferon-beta, as opposed to those in the control group, had a reduced load of mutant ataxin-7.

On the physical level, substantial improvements in the interferon-beta treated mice were noticed. "At twelve weeks of age the physical performance of the mice that received the active substance was significantly improved compared to the control group. We gave them a locotronic test, where they have to cross a kind of ladder. This test is used to check motor co-ordination when walking. We also put them through a beam-walking test, which enables us to measure their balance and limb co-ordination. The treated mice did much better in both of these tests", Dr. Sittler will say.

Further proof of the positive effects of interferon-beta came from analysis of the PML nuclear bodies, involved in many cellular processes such as transcriptional regulation and apoptosis. A subset of these nuclear bodies is responsible for regulating the degradation of accumulated misfolded proteins in the cell nucleus. The treated mice had more, and very much larger, PML bodies, and they were present in the Purkinje cells, responsible for motor co-ordination emanating from the cerebellum The researchers further found that these PML bodies were clastosomes, the specialised nuclear bodies involved in the degradation of mutant ataxin-7 and other polyglutamine-containing proteins. "This, together with the physical improvements we saw in the interferon-beta treated mice, was the proof we needed that our findings in the cell could be successfully transferred to living animals", says Dr. Sittler.

"Now that we have found that interferon-beta can slow progression of disease in SCA7 mice, we believe that, after confirmation in another

mouse model, it would be merited to test its effects on humans in a clinical trial,", she will say. "Such trials are difficult in rare diseases, since a special design is needed to test a hypothesis on a small number of patients. However, there are a number of other polyglutamine diseases, for example Huntington's, where patient numbers are larger, and the effects of the condition just as devastating. We hope that our results will encourage others to collaborate with us in order that we may be able to pursue our research to the benefit of all those afflicted with spinocerebellar disorders."

Provided by European Society of Human Genetics