Signs of motor disorders can appear years before disease manifestation

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It is known that signs of neurological disorders such as Alzheimer's and Huntington's disease can appear years before the disease becomes manifest; these signs take the form of subtle changes in the brain and behavior of individuals affected. For the first time, an international group of researchers led by the German Center for Neurodegenerative Diseases and the Bonn University Hospital has proven the existence of such signatures for motor disorders belonging to the group of "spinocerebellar ataxias."

The scientists report these findings in the current online edition of *The Lancet Neurology*. This pan-European study could open up new possibilities of early diagnosis and smooth the way for treatments which tackle diseases before the patient's nervous system is irreparably damaged.

"Spinocerebellar ataxias" comprise a group of genetic diseases of the cerebellum and other parts of the brain. Persons affected only have limited control of their muscles. They also suffer from balance disorders and impaired speech. The symptoms originate from mutations in the patient's genetic make-up. These cause nerve cells to become damaged and to die off. Such genetic defects are comparatively rare: it is estimated that about 3,000 people in Germany are affected.

It is known that there are various subtypes of these neurodegenerative diseases. The age at which the symptoms manifest consequently fluctuates between about 30 and 50. "Our aim was to find out whether

specific signs can be recognized before a disease becomes obvious," says project leader Prof. Thomas Klockgether, Director for Clinical Research at the DZNE and Director of the Clinic for Neurology at Bonn University Hospital.

Pan-European cooperation

The study, which involved 14 research centers in all, focused on the four most common forms of spinocerebellar ataxia. These account for more than half of all cases. More than 250 siblings and children of patients throughout Europe declared their willingness to participate in appropriate tests. These individuals had no obvious symptoms of ataxia. However, about half of them had inherited the genetic defects which invariably cause the disease to manifest in the long term.

With the aid of a mathematical model that considered the genetic mutations and their effects, the scientists were able to estimate the time remaining until the disease could be expected to manifest. In the test group, this "time to onset" varied from 2 to 24 years. These and all other test results remained anonymous: the data was not known to the test subjects, neither could the researchers assign it to specific participants. The same applied to individuals whose DNA turned out to be inconspicuous. "People in families with cases of ataxia usually have not taken a genetic test and they don't want to know any results. This kind of information has to be treated very carefully for ethical reasons," emphasizes Klockgether.

Extensive tests

The study participants made themselves available for various examinations including standardized tests of muscular coordination. These included measuring the time needed by the subjects to walk a

specific distance. Another series of experiments involved inserting small pins into the holes of a board and taking them back out as quickly as possible. Yet another test measured how often the participants could repeat a certain sequence of syllables in ten seconds. "The tests were designed in such a way that they would provide significant information but still be easy to perform," says Klockgether. "Tests like these can be performed anywhere without need for special technology."

Technically complex methods were also used: all study participants were tested for the genetic defects relevant to ataxia. At some of the research centers involved in the study, it was also possible to examine the subjects with the aid of magnetic resonance imaging (MRI). This enabled researchers to measure the total brain volume as well as the dimensions of individual parts of the brain in about a third of the subjects.

Notable findings

In two of the four types of ataxia investigated, the scientists found signs of impending disease. "We found a loss in brain volume, particularly shrinkage in the area of the cerebellum and brain stem. These subjects also had subtle difficulties with coordination," Klockgether summarizes the results. "This means that manifestations of this kind can be measured years before the disease is likely to become obvious."

The findings for the other two types of ataxia were less conclusive. "I assume that there are indications also for these types of the disease. However, this subgroup of participants was relatively small. It is therefore difficult to make statistically reliable statements about these subjects," says the Bonn-based researcher.

In his view, the study results testify to the modern-day view of neurodegenerative processes: "Neurodegeneration doesn't begin when the symptoms surface. Rather, it is a stealthy disease which starts

developing years or even decades beforehand."

Klockgether believes that this gradual development offers certain opportunities: "If we intervened in this process by appropriate treatments and at a sufficiently early stage, it might be possible to slow down or even stop the disease process."

More investigations planned

The current results will be the basis for long-term investigations. A new series of tests with the same group of individuals has already started; further tests are scheduled every two years. The scientists intend to monitor the study participants for as long as possible.

More information: "Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data", Heike Jacobi, Kathrin Reetz et al, The Lancet Neurology, online publication on May 22, 2013. doi:10.1016/S1474-4422(13)70104-2

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