Sense of smell holds the key to diagnosis and treatment in early stage Parkinson's disease

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A fast, simple and non invasive test of the ability to smell may be an important tool to screen people who are likely to develop Parkinson's disease (PD), in which motor symptoms only become evident at a later stage of the disease, a German scientist will tell the annual conference of the European Society of Human Genetics today. Dr. Silke Nuber, from the Department of Medical Genetics, University of Tubingen, Germany, will say that her team's research could help in the development of treatments for the early stages of the disease.

Dr. Nuber and colleagues from Germany, Switzerland, and the UK, decided to study transgenic mice with high levels of human alpha-synuclein, a protein known to be crucial in the development of PD. Alpha-synuclein can be turned off in these animals by administration of an antibiotic, allowing scientists to look at the reversibility of neuropathological alterations.

"The mice expressed alpha-synuclein primarily in neurons of the olfactory bulb", said Dr. Nuber, "and we therefore expected to find alterations in smell-related behaviour in these animals. Since one of the earliest symptoms in PD patients is a reduction in the sense of smell, we felt that these mice could mimic the early stages of the disease."

Parkinson's disease is a degenerative disorder of the central nervous system that affects the control of motor skills, speech, mood and behavioural problems, and cognitive functions. It is characterized by muscle rigidity, tremor, and slowing or loss of physical movement. It is a

chronic, progressive condition and there is currently no cure.

The scientists tested the sense of smell of the transgenic mice by analysing their behaviour when exposed to a new scent, for example the male mice were exposed to the scent of female mice. They then looked at neurotransmitter activity in different areas of the brain and found a malfunction of dopamine regulation.

When expression was blocked in middle-aged mice, the dopamine level was comparable to those of wild-type (normal) animals, implying both direct influence of transgenic expression on dopamine levels, and the reversibility of symptoms. Dopamine receptors are involved in a number of neurological processes, and abnormal dopamine receptor signalling is known to be implicated in PD. "We believe that we have developed one of the first models to show this olfactorial dopamine deficit without additional abnormalities in the nigrostriatal pathway", said Dr. Nuber.

The nigrostriatal pathway is one of the major dopamine pathways in the brain, and is particularly involved in the control of movements. Loss of dopaminergic neurons in the substantia nigra, a structure located in the midbrain, is one of the main features of PD, but the motor symptoms of the disease do not show themselves until more than half of the dopamine function has been lost. Being able to identify the early stages of dopaminergic dysfunction is therefore particular important both for diagnosis and treatment of PD.

The scientists also carried out a fear-related smell test, in which the animals would normally have been expected to remain motionless because they sensed the presence of a predator. However, the mice showed reduced anxiety in this test. "In animals with olfactory bulbectomy - a suppression of the sense of smell - hyperactivity and increased exploratory behaviour are strong markers of behavioural alterations", said Dr. Nuber. "These animals model depression and anti-

depressive drugs can ameliorate their depressive symptoms."

Increased exploratory behaviour may diminish the anxiety and depressive signs in new surroundings that would be normal for mice lacking any sense of smell. The researchers therefore surmised that this behaviour might also exist in mice with a reduced dopamine transmission in the olfactory bulb. "It would be interesting to study whether early treatment with anti-depressive drugs might increase odour sensitivity in PD patients", said Dr. Nuber. At present, diagnosis of PD is based entirely on the motor symptoms which appear at a later stage, and all drug treatments have been approved for use only at this stage.

The researchers say that it would be worthwhile to develop some standardised tests for testing smell function. "We don't know whether the existing drugs used at a later stage in PD would be effective in the earlier phases of the disease, but having an early biomarker would enable us to try to develop different treatment strategies", said Dr. Nuber. "Based on what we know now, the clinical definition for the diagnosis of PD should not rely solely on the diagnosis of motor symptoms. It would be helpful to test the ability of olfactory detection and learning. Even if we cannot preserve olfactory structures and functioning, it will enable us to diagnose the disease earlier on and also help with the development of treatment strategies to halt or even reverse the underlying disease process in PD.

"We believe that detailed functional imaging analyses paralleled by behavioural studies in the mouse model could lead to the development of an efficient preclinical therapy that can be used to halt the massive dopaminergic neurodegeneration that takes place in human PD patients", she concluded.

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