Press Release
A sensational observation: A modified amino acid stops the onset of Parkinson's disease in its early stage

2 September 2024 - An international research group led by the Department of Neurology at the Philipps University Marburg (Prof. Wolfgang Oertel) in cooperation with the Department of Neurology at LMU Munich (Prof. Michael Strupp) today published two impressive patient cases: In both cases, therapy with the modified amino acid acetyl-DL-leucine was able to halt the progression of Parkinson's disease in the prodromal stage over a period of 22 months, and some disease markers even improved. These are early observations, and the results are preliminary, but they are so remarkable that clinical trials will soon follow.

Today, an article by scientists from Marburg, Munich, Groningen, Amsterdam and Chicago was published in the prestigious journal Nature Communications. It describes two case reports with REM Sleep Behaviour Disorder, a specific prodrome of Parkinson's disease. In both cases, the modified amino acid acetyl-DL-leucine successfully prevented the appearance of manifest Parkinson's disease. Significant markers in the prodromal stage of Parkinson's disease were reduced after administration of acetyl-DL-leucine (ADLL). "This is so unusual, I have never seen anything like this before in my entire career as a doctor and researcher," said Prof. Dr. Wolfgang Oertel, principal investigator of the study, Parkinson's expert and Hertie Senior Research Professor at Marburg University.

Two people (one female, one male) with isolated REM sleep behaviour disorder (iRBD) were treated with 5 g ADLL per day for 22 months. The dream-sleep disorder iRBD is considered a prodromal stage of Parkinson's disease. People who suffer from iRBD have a more than 85% (130 times) higher risk of developing Parkinson's disease or Lewy body dementia (a variant of Parkinson's disease) over the next 10 to 15 years. Only about 15 percent of people with iRBD do not develop these neurodegenerative diseases. Scientists therefore consider iRBD to be an early specific symptom (prodrome) of Parkinson's disease.

"We know from the preliminary examinations that the two patients were probably not among the 15 per cent of 'lucky ones' who would not have suffered this fate: The SPECT (single photon emission computerized tomography) image of the dopamine transporter clearly showed pathological findings in both of them before treatment with ADLL. "Both also suffered from a loss of sense of smell (anosmia), another early Parkinson's symptom," explains Prof. Dr. Lars Timmermann, Director of the Department of Neurology at Marburg University Hospital and co-author of the study. "What is really remarkable about these two case reports is that the neurodegenerative changes that lead to clinically manifest Parkinson's disease were not only slowed down, but the imaging signs of the disease even regressed under treatment," adds Dr Annette Janzen, co-author and consultant neurologist at the Marburg clinic. And Prof. Dr. Michael Strupp, senior author of the publication from the Department of Neurology at LMU Munich, emphasises: "No single therapeutic approach has achieved this so far. And we are talking about a simple and well-tolerated modified amino acid. It has been known for some time that acetyl-L-leucine also has a beneficial effect in other neurodegenerative diseases such as Niemann-Pick type C, a disease of the lysosomal system. We have recently been able to confirm this finding in a phase 3 trial" [2].

In the current publication, the following three criteria were analysed: 1) the severity of the REM sleep behaviour disorder (RBD-SS-3), 2) dopamine transporter single photon emission computerized tomography (DAT-SPECT) as a measure of the loss of dopaminergic fibres from the substantia nigra

to the striate body) and 3) the metabolic Parkinson's disease-related pattern (PDRP)-z-score on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET - as a measure of pathological brain activity typical of Parkinson's disease). After just three weeks of treatment, the RBD-SS-3 score fell significantly in both patients and remained reduced throughout the 18 months of ADLL treatment. In patient 1, the DAT-SPECT putaminal binding ratio (PBR) had decreased from normal (1.88) to pathological (1.22) in the five years prior to treatment, and the FDG-PET-PDRP-z score had increased from 1.72 to a pathological value of 3.28. After 22 months of ADLL treatment, the DAT-SPECT-PBR improved to 1.67, indicating recovery of the dopaminergic system, and the FDG-PET-PDRP-z score was 3.18, indicating stabilisation of brain activity. Similar results were observed in patient 2: his DAT-SPECT-PBR increased from a pre-treatment value of 1.42 to a near-normal value of 1.72, and the FDG-PET-PDRP-z score decreased from 1.02 to 0.30 after 18 months of ADLL treatment, indicating a reduction in PD-typical pathological brain activity.

How does acetyl-leucine work?
The mechanisms of action of acetyl-DL-leucine include two effects: 1) on the lysosomal system and 2) on 'cellular respiration', i.e. the energy metabolism of cells. In every cell, adenosine triphosphate (ATP), the cell's main energy carrier, is produced in the presence of oxygen in the mitchondria (the cell''s 'power stations') from glucose, which is supplied with food. Without sufficient amounts of ATP, cellular functions cannot be maintained. A biochemical study shows that acetyl-L-leucine increases the production of ATP [3]. Disorders of the lysosomal system in the brain have been described in Parkinson's disease, and recent findings by the co-authors of the present article, Dr. Geibl and Dr. Henrich [4] in a mouse model of the prodromal stage of Parkinson's disease show that in the early stages both energy balance and lysosomal function are severely impaired in damaged dopaminergic neurons. This is all the more reason to use acetyl-DL-leucine, with its dual mechanism of action, in patients with isolated REM sleep behaviour disorder.

The drug acetyl-DL-leucine was used in the two iRBD patients. Chemically, acetyl-leucine exists in two forms: acetyl-D-leucine (D stands for 'turn the light to the right') and acetyl-L-leucine (L stands for 'turn the light to the left'). The mixture of the two forms acetyl-D-leucine and acetyl-L-leucine is called acetyl-DL-leucine (ADLL). Only ADLL was available as a drug for individual OFF-label use (compassionate use) in the two patients with iRBD described above. Current evidence from basic research in animal models suggests that only the L-form of ADLL, i.e. acetyl-L-leucine, is effective. Future studies will therefore use acetyl-L-leucine [2].

What are the conclusions? "We see evidence that acetyl-DL-leucine can prevent the progression of the disease. The typical Parkinson's imaging patterns are even reversible - and it seems that the better the baseline values or the milder the disease at the start of treatment, the more effective the therapy can be. We have to stress that these are only two patient reports so far, with all the limitations such as non-blinding, lack of a placebo group, etc. Randomised, placebo-controlled, long-term trials are planned. What makes us optimistic and what is particularly intriguing is the imaging data, because the improvement in brain pathology cannot be explained by a placebo effect," explains Prof. Oertel.

Many achievements in medicine, such as the discovery of penicillin, can be traced back to chance observations. If large clinical trials confirm what has been observed here in two patients, namely that acetyl-DL-leucine can halt the onset of Parkinson's disease, this discovery will be a major milestone in the history of medicine. "However, there is still a long way to go and, despite the euphoria, we must

remain cautious and set up controlled studies that will provide evidence as quickly as possible," emphasizes Prof. Dr. Peter Berlit, Secretary General of the German Neurological Sociey.

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[1] Oertel WH, Janzen A, Henrich MT, Geibl FF, Sittig E, Meles SK, Carli G, Leenders K, Booij J, Surmeier DJ, Timmermann L, Strupp M. Acetyl-DL-leucine in two individuals with REM sleep behaviour disorder improves symptoms, reverses loss of striatal dopamine transporter binding and stabilises pathological metabolic brain patterns - case reports. Nat Commun 15, 7619 (2024). https://doi.org/10.1038/s41467-024-51502-7
[2] Bremova-Ertl T, Ramaswami U, Brands M, Foltan T, Gautschi M, Gissen P, Gowing F, Hahn A, Jones S, Kay R, Kolnikova M, Arash-Kaps L, Marquardt T, Mengel E, Park JH, Reichmannova S, Schneider SA, Sivananthan S, Walterfang M, Wibawa P, Strupp M, Martakis K. Trial of N-acetyl-l-leucine in Niemann-Pick disease type C. N Engl J Med. 2024;390(5):421-43 https://www.nejm.org/doi/10.1056/NEJMoa2310151
[3] Kaya E, Smith DA, Smith C, Morris L, Bremova-Ertl T, Cortina-Borja M, Fineran P, Morten KJ, Poulton J, Boland B, Spencer J, Strupp M, Platt FM. Acetyl-leucine slows disease progression in lysosomal storage disorders. Brain Commun. 2020 Dec 20;3(1):fcaa148. doi: 10.1093/braincomms/fcaa148. PMID: 33738443; PMCID: PMC7954382.
[4] Geibl FF, Henrich MT, Xie Z, E, Tkatch T, Wokosin DL, Nasiri E, Grotmann CA, Dawson VL, Dawson TM, Chandel NS, Oertel WH, Surmeier DJ. α-Synuclein pathology disrupts mitochondrial function in dopaminergic and cholinergic neurons at-risk in Parkinson's disease. bioRxiv [preprint]. 2023 Dec 11:2023.12.11.571045. doi: 10.1101/2023.12.11.571045. PMID: 38168401

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