News Release

Title

Elucidation of preclinical progression in a neurodegenerative disease

Key points

- The need to identify biological markers for the preclinical stages of neurodegenerative diseases has been underscored in recent years.
- Spinal and bulbar muscular atrophy (SBMA) is a neurodegenerative disease characterized by slowly progressive muscle weakness and atrophy. Patients with SBMA have a decreased level of serum creatinine due to the degeneration of motor neuron and skeletal muscle.
- In this study, we investigated the longitudinal change of serum creatinine levels in SBMA patients by analyzing the data of periodic health examinations before they noticed the disease. Our results clarified that the serum creatinine level begins approximately 15 years before the onset of subjective weakness, suggesting the pre-symptomatic progression of disease process.
- The identification of serum creatinine as a biomarker for preclinical phase in SBMA has the potential to promote preventive clinical trials for early stage of SBMA.

Summary

A group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, M.D., Ph.D.) have revealed that the disease process of SBMA begins more than a decade before the onset of subjective weakness, and that decreases in serum creatinine reflect preclinical progression of SBMA. This work was published on Friday, March 23, 2018, issue of Neurology®, the medical journal of the American Academy of Neurology.

In neurodegenerative diseases, pathological changes precede clinical onset by many years. Therefore, it is important to initiate disease-modifying interventions before neurological symptoms emerge. Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a slowly progressive neurodegenerative disease characterized by muscle weakness. In SBMA, serum creatinine levels are known to decrease with disease progression, which results from skeletal muscle degeneration and atrophy. In this study, the researchers investigated serum creatinine levels in health examinations which the patients with SBMA underwent before the subjective onset of weakness. The researchers found that serum creatinine levels start to decrease more than 10 years before the onset of SBMA. The results of this study indicate that serum creatinine level is a potential biomarker for evaluating disease progression during the preclinical stage of SBMA.

Research Background

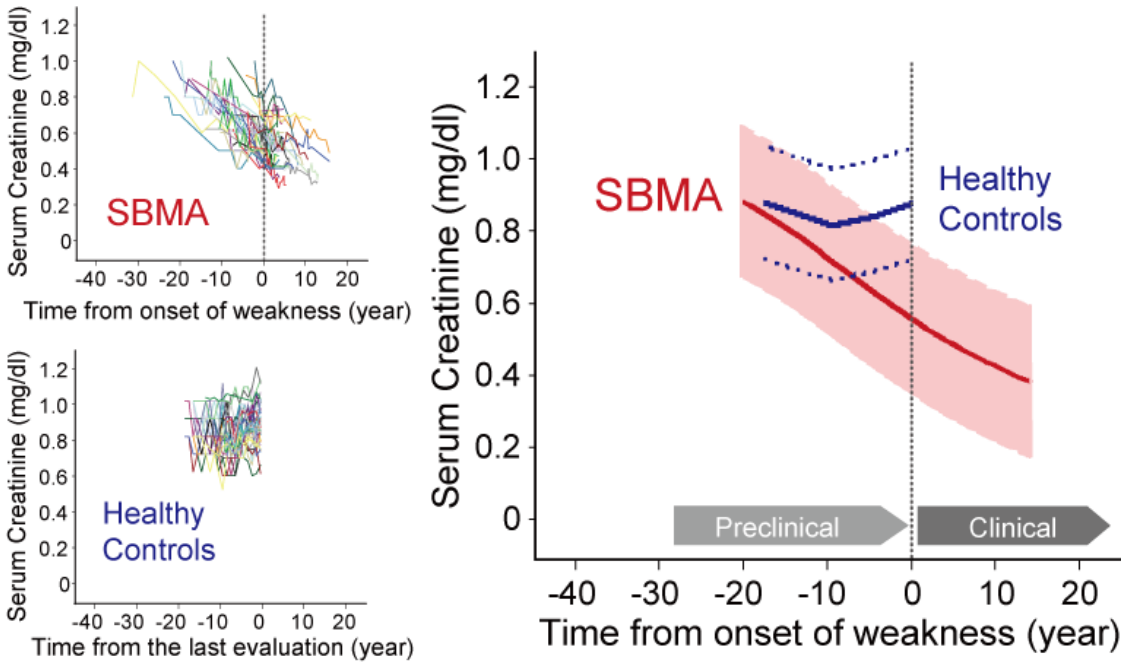
Disease-modifying therapies for neurodegenerative diseases such as Alzheimer's disease frequently exhibit poor efficacy in clinical trials. This failure indicates that early therapeutic intervention before irreversible changes in structure or function may be crucial for improving patient prognoses. Therefore, clinical studies for preclinical progression of neurodegenerative diseases have gained attention for developing preventive therapies. Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is an adult-onset, slowly progressive neurodegenerative disease characterized by bulbar and limb muscle weakness. The cause of SBMA is the expansion of CAG trinucleotide repeat in the gene encoding androgen receptor (AR). There has been no study evaluating biomarkers which reflect preclinical progression of SBMA.

Research Results

The researchers focused on the patients' health examination data before the subjective onset of weakness. The researchers enrolled 40 patients with SBMA and evaluated the patients' longitudinal health examination data including preclinical phase. The data were compared with those in healthy individuals and patients with ALS and PD. In SBMA patients, the researchers showed that the decreases in serum creatinine occurred about fifteen years before the onset. Moreover, by analysing the relationship between serum creatinine level and timing of manifestation of clinical symptoms, the onset of hand tremor and weakness were similar to the time when serum creatinine decreases below 0.8 and 0.6 mg/dl, respectively. These preclinical changes of biomarkers were not observed in either ALS or PD. The results of this study indicate that serum creatinine level is a potential biomarker for evaluating disease progression during the preclinical stage of SBMA.

Research Summary and Future Perspective

In this study, the researchers clarified that serum creatinine levels reflect the underlying progression before the onset by retrospectively analyzing the patients' health examination data. In the future, the researchers will conduct a prospective study on AR gene mutation carriers of SBMA. Moreover, the researchers are also carrying out clinical research to diagnose PD and dementia with Lewy bodies (DLB) by analyzing data of health examination in people who do not notice any neurological symptoms.



Publication

Hijikata Y, Hashizume A, Yamada S, Inagaki T, Ito D, Hirakawa A, Suzuki K, Atsuta N, Tsuboi T, Hattori M, Hori A, Banno H, Sobue G, and Katsuno M.

"Biomarker-based analysis of preclinical progression in spinal and bulbar muscular atrophy" ***Neurology***, 2018, in press.

DOI：10.1212/WNL.0000000000005360

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