News Release

Title

Mexiletine in Spinal and Bulbar Muscular Atrophy: A Randomized Controlled Trial

Key Points

- Symptomatic therapy for SBMA has not been confirmed to date.
- Patients with SBMA often experience muscular weakness under cold exposure.
- Some patients were aware of muscle weakness only under cold exposure even before they noticed daily muscle weakness.
- Cold exposure induced a prolongation in distal latency of the ulnar nerve, the magnitude of which correlated with the decrease in grip power.
- Mexiletine improved tongue pressure and grip and release test findings but did not restore the cold exposure-induced prolongation of distal latency.

Summary

A group of researchers, headed by Prof. Masahisa Katsuno, Department of Neurology, Nagoya University Graduate School of Medicine have revealed that most patients with SBMA experienced cold paresis and mexiletine improved several motor functions by supressing the abnormal Na currents present in the pathological background of SBMA. This work was published online in *Annals of Clinical and Translational Neurology* on October 8, 2022.

Spinal and bulbar muscular atrophy (SBMA), or Kennedy's disease, is a slowly progressing lower motor neuron and muscular disease characterized by bulbar and limb muscle weakness especially under cold exposure. SBMA is caused by the expansion of a CAG repeat within the first exon of the androgen receptor (*AR*) gene. The mutant AR protein harboring an extended polyglutamine tract induces degeneration of motor neurons and skeletal muscles in a testosterone-dependent manner. Muscular weakness generally manifests between 30 and 60 years of age and is preceded by prodromal symptoms such as hand tremors and muscle cramps by 10–20 years. Although leuprorelin acetate has been demonstrated to restore the bulbar function of patients at an early stage, other symptomatic therapies have yet to be established.

In our previously conducted observational study, we assessed nerve conduction and grip strength to examine the effect of cold exposure on motor function, based on which we conducted a randomized controlled trial to evaluate the efficacy and safety of mexiletine hydrochloride in SBMA (MEXPRESS). In this study, 88.0% of the patients with SBMA experienced cold paresis. Patients with SBMA exhibited greater prolongation of ulnar nerve distal latency under cold (SBMA, 5.6 ± 1.1 msec; HC, 4.3 ± 0.6 msec; $p < 0.001$); the change in the distal latencies between room temperature and cold exposure conditions correlated with the change in grip power. In the MEXPRESS trial, 20 participants took mexiletine or lactose, three times a day for 4 weeks with a crossover design. There was no difference in distal latencies at room temperature and under cold exposure between mexiletine and placebo groups as the primary endpoint. However, tongue pressure and 10-s grip and release test under cold exposure were improved in the

mexiletine group. There were no serious adverse events throughout the study period.

Our findings indicate that Cold paresis is common and associated with prolongation of distal latency in SBMA. The results of the phase II clinical trial revealed that mexiletine showed short-term safety, but it did not restore cold exposure-induced prolongation of distal latency.

Research Background

Patients with SBMA often experience muscular weakness under cold exposure that affects activities of daily living (ADLs). Cold paralysis is hypothesized to be caused by motor neuron and skeletal muscle membrane hyperexcitability in various neuromuscular disorders, due to a reduction in resting chloride conductance and/or gain-of-function in voltage-dependent sodium channels, both of which lead to excessive sodium currents. A recent study has supported a role for hyperexcitability of motor neurons and skeletal muscle fibers leading to abnormal sodium currents in SBMA pathophysiology. Mexiletine, a sodium channel blocker, is used to suppress muscle hyperexcitability in cardiac diseases as well as restore nerve activity in several neuromuscular diseases such as diabetic neuropathy, non-dystrophic myotonia, and Machado–Joseph disease. However, its effectiveness as a symptomatic therapy for SBMA has not been confirmed to date.

Research Results

This study consisted of two parts. A preceding observational study prospectively collected neurological and neurophysiological data regarding cold paresis in patients with SBMA (observational study on cold exposure in SBMA). In the subsequent randomized clinical trial, which was based on the findings of the observational study, we evaluated the efficacy and safety of mexiletine in patients with SBMA (MEXPRESS trial).

Of 51 patients with SBMA, 45 (88.0%) experienced cold paresis. Approximately half of the patients with SBMA first noticed cold paresis within 5 years from disease onset, and the number of patients who experienced cold paresis gradually increased thereafter (Figure 1). Notably, 10 (22.2%) patients experienced cold paresis even before the onset of muscle weakness, indicating that cold paresis could be a prodromal symptom.

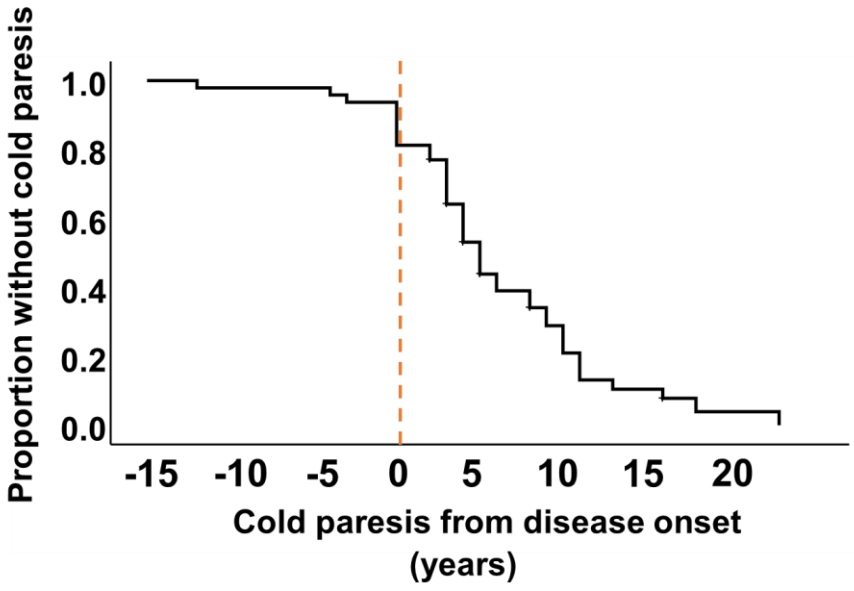


Fig. 1 Relationship between cold paresis and disease onset

Our study also demonstrated that in patients with SBMA, cold exposure induced a prolongation in distal latency of the ulnar nerve, the magnitude of which correlated with the decrease in grip power. This finding instigated us to conduct a clinical trial of mexiletine, which is a sodium channel blocker that suppresses excessive sodium current under cold conditions (Figure 2).

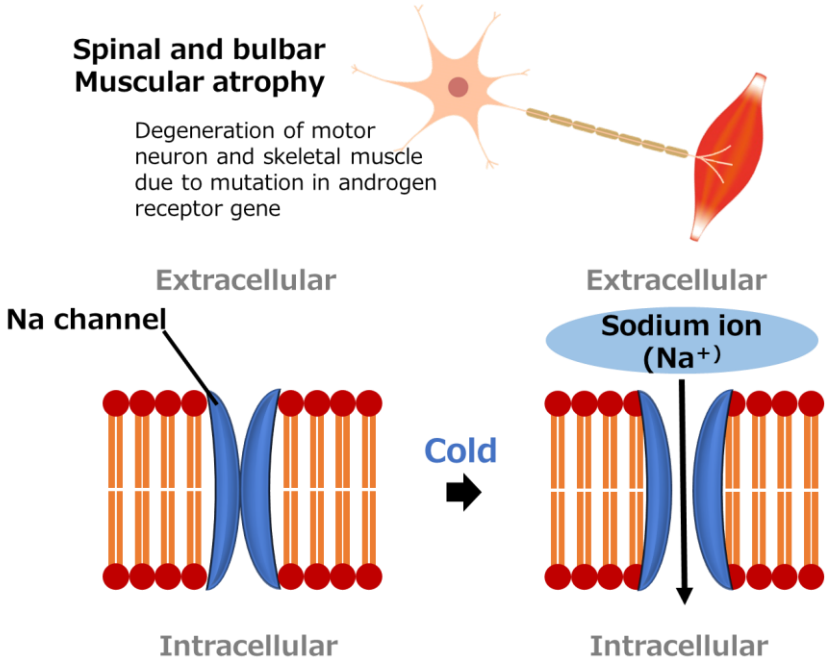
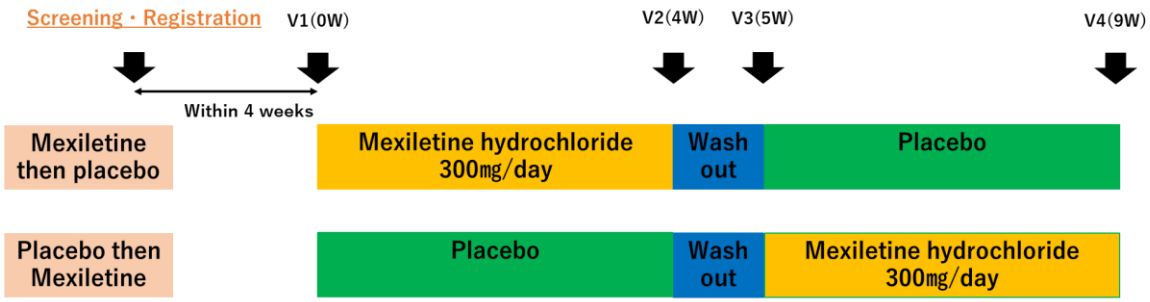


Fig. 2 Abnormal Na current in skeletal muscles and motor neurons of SBMA patients

The results of the phase II clinical trial revealed that mexiletine improved tongue pressure and grip and release test findings but did not restore the cold exposure-induced prolongation of distal latency (Figure 3).



Outcome measure	Treatment Effect Estimate (95% CI)	p-value
Distal latencies between room temperature and cold exposure conditions, m/s	-0.02 (-0.26 to 0.21)	0.843
ALSFRS-R	0.51 (-0.10 to 1.12)	0.094
Tongue pressure, kPa	1.33 (0.20 to 2.45)	0.023
Grip and release test, times	1.37 (0.10 to 2.65)	0.037
Grip power, kg	0.25 (-0.28 to 0.79)	0.331
Timed walk test, second	-0.17 (-0.63 to 0.30)	0.464
Patient reported outcome	-0.53 (-1.02 to -0.04)	0.035

Fig. 3 Study design and results of MEXPRESS

Research Summary and Future Perspective

Our findings indicate the most patients with SBMA experienced cold paresis, which was characterized by prolongation of distal latency in nerve conduction study. Prolongation of distal latency was correlated with a decrease in grip power. Mexiletine improved tongue pressure and the grip and release test, although it did not restore the cold exposure-induced prolongation of distal latency in patients with SBMA. This study showed the short-term safety of mexiletine in patients with SBMA. Further parallel-group validation trials are warranted to verify the effects of mexiletine on motor function in patients with SBMA.

Publication

Shinichiro Yamada, Atsushi Hashizume, Yasuhiro Hijikata, Tomonori Inagaki, Daisuke Ito, Yoshiyuki Kishimoto, Fumie Kinoshita, Akihiro Hirakawa, Shinobu Shimizu, Tomohiko Nakamura and Masahisa Katsuno

"Mexiletine in Spinal and Bulbar Muscular Atrophy: A Randomized Controlled Trial"

Annals of Clinical and Translational Neurology, October 8, 2022.

Japanese ver.

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Ann_221011.pdf