Neurophysiologie Clinique/Clinical Neurophysiology (2009) **39**, 27—30

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE/ARTICLE ORIGINAL

Low-frequency rTMS of the premotor cortex reduces complex movement patterns in a patient with pantothenate kinase-associated neurodegenerative disease (PKAN)

La stimulation magnétique répétitive à basse fréquence du cortex prémoteur diminue les mouvements complexes chez un patient atteint de neurodégénérescence associée à un déficit en pantothénate-kinase (PKAN)

V. Mylius[a,*], A. Gerstner[a], M. Peters[b], H. Prokisch[c], A. Leonhardt[b], D. Hellwig[d], F. Rosenow[a]

[a] *Department of Neurology, Philipps-Universität Marburg, Rudolf-Bultmann Street 8, 35033 Marburg, Germany*
[b] *Department of Paediatrics, Philipps University of Marburg, Marburg, Germany*
[c] *Institute of Human Genetics, TU-München and GSF National Research, Center, Marburg, Germany*
[d] *Department of Neurosurgery, Philipps University of Marburg, Marburg, Germany*

Received 11 March 2008; accepted 15 December 2008
Available online 15 January 2009

KEYWORDS
PKAN;
NBIA;
Dystonia;
Repetitive transcranial magnetic stimulation;

Summary
Introduction. — Pantothenate kinase-associated neurodegenerative disease (PKAN) is a secondary generalized dystonia associated with an accumulation of iron in the basal ganglia and increased motor cortex excitability. A pilot study in three patients with secondary generalized dystonia had reported a reduced frequency of painful axial spasms following inhibitory 1-Hz repetitive transcranial magnetic stimulation (rTMS) applied over the premotor cortex.
Patient and methods. — We compared the effects of real versus sham rTMS on the frequency of the complex movement pattern and the need for additional benzodiazepine medication

* Corresponding author.
E-mail address: mylius@med.uni-marburg.de (V. Mylius).

0987-7053/$ - see front matter
doi:10.1016/j.neucli.2008.12.003

rTMS

in a 6-year-old male patient with PKAN. A 20-minute session of left premotor 1-Hz rTMS was performed daily on 5 consecutive days.
Results. — The occurrence of the complex movement pattern was gradually reduced from three to two attacks daily to one attack daily by real rTMS while sham rTMS had no effect. This reduction was obtained concomitantly with a similar reduction of additional benzodiazepines for both real and sham rTMS sessions.
Conclusion. — Inhibitory rTMS of the premotor cortex may be used to temporarily control motor symptoms in PKAN.

MOTS CLÉS
PKAN ;
NBIA ;
Dystonie ;
Stimulation magnétique transcrânienne répétitive

Résumé
Introduction. — La neurodégénérescence associée à un déficit en pantothénate-kinase (PKAN) est une dystonie secondaire avec accumulation de fer dans les ganglions de la base associée à une hyperexcitabilité du cortex moteur. Une étude pilote avait montré une diminution des spasmes dystoniques par stimulation magnétique répétitive (SMTr) à basse fréquence du cortex prémoteur chez trois patients atteints de dystonie secondaire généralisée.
Patient et méthodes. — Nous comparons les effets de séances quotidiennes de 20 minutes, réelles ou simulées, de SMTr à 1 Hz du cortex prémoteur administrées durant cinq jours sur les spasmes dystoniques et le supplément de médication à administrer chez un enfant de six ans atteint de PKAN.
Résultats. — Les mouvements complexes diminuent pendant la SMTr mais pas dans la stimulation simulée. Lors des deux stimulations, la médication supplémentaire a été réduite dans les mêmes proportions.
Conclusions. — La diminution de l'excitabilité du cortex moteur primaire par SMTr à basse fréquence du cortex prémoteur peut avoir des effets sur les symptômes moteurs dans la dystonie secondaire.

Introduction

Pantothenate kinase-associated neurodegenerative disease (PKAN) is an autosomal recessive disorder that can present with secondary generalized dystonia of early onset and rapid progression [5,6]. It is caused by a mutation of the *PANK2* gene encoding a mitochondrial pantothenate kinase, a key regulatory enzyme required for the biosynthesis of coenzyme A [7]. The mutation leads to accumulation of iron in the basal ganglia with severe extrapyramidal and pyramidal symptoms. The diagnosis can be based on both genetic testing and finding of a pallidal hypointensity with or without central hyperintensity ''eye-of-the-tiger sign'' on the T2 images of brain MRI. Besides partially effective pharmacological treatment, neurosurgical interventions using pallidothalamotomy or stimulation of the *globus pallidus internus* (GPI) were performed with a promising outcome [2,4]. In particular, bilateral GPI stimulation has been found to provide long-lasting improvement of painful spasms and dystonia for at least 24 months up to 5 years [4,10].

Reduced inhibition of the thalamus induced by pathophysiological changes within the basal ganglia in dystonia, for example in writer's cramp (WC), results in an increased cortical excitability with an enhanced corticospinal output [15]. Based on this, inhibitory repetitive transcranial magnetic stimulation (rTMS) has been used to modulate cortical excitability. In patients with WC, therapeutic effects of inhibitory 0.2-Hz premotor rTMS have been described [13]. RTMS was performed over the premotor cortex since the excitability of the primary motor cortex is more reduced after low-frequency rTMS over the premotor cortex than over the primary motor cortex itself [12]. A modulation of spinal excitability by 1-Hz premotor rTMS has been reported also in early-onset primary generalized dystonia associated with the *DYT1* gene [8]. Recently, three cases of secondary generalized dystonia of different origin (viral encephalitis, neonatal brain injury, and disulfiram intoxication) were reported to experience a reduced frequency of painful axial spasms following inhibitory 1-Hz rTMS applied over the premotor cortex [11]. Therefore, we tested the hypothesis that inhibitory 1-Hz rTMS of the premotor cortex would partially reduce motor symptoms in PKAN.

Patient and methods

The procedure was performed in a 6-year-old male Caucasian patient presenting with the clinical features of PKAN and an ''eye-of-the-tiger'' sign in brain MRI. Mutation screening of *PANK2* revealed a homozygote deletion of 6.2 kb covering exons 3 and 4. According to Hartig et al. [5], patients with two losses of function alleles display symptoms at an early developmental stage of live. The first symptoms occurred at the age of 2 years. On admission in 2006, the patient presented with right-predominating dyskinetic (mostly choreic) movements of the upper extremities, spasticity of the lower extremities, slight head dystonia and reduced axial tone at rest, presumably due to intrathecal baclofen. These symptoms were occasionally triggered and/or enhanced by emotion. Dystonia at rest was scored by the Burke-Fahn-Marsden's Dystonia (BFMD) movement and disability score [3]. The movement score was 82/120 (maximal scores for the provoking factors, extremities, speech and swallowing, slight neck dystonia and no dystonia in the