chronous discharge. The lack of sufficient basal level of melatonin in patients with refractory epilepsy could thereby facilitate seizures. Alternatively, repeated seizures could alter the feedback regulatory mechanisms coordinated by the pineal gland. Thus, the low level of melatonin reflects, at least partially, a disorder in neuroendocrine regulation among these patients. The increased melatonin seen following seizures could be a protective mechanism against repetitive seizures. Increased melatonin may also contribute to tiredness following temporal lobe seizures, although seizures are known to disrupt sleep structure and particularly REM sleep.[10] Restoring melatonin to the normal level, perhaps using oral melatonin supplements, is worthy of further study. Randomized clinical trials are needed to further clarify the influence of melatonin on intractable epilepsy.

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A placebo-controlled crossover trial of creatine in mitochondrial diseases

Article abstract—To test the efficacy and safety of creatine (Cr) monohydrate in mitochondrial diseases, 16 patients with chronic progressive external ophthalmoplegia or mitochondrial myopathy were randomized in a crossover design to receive double-blind placebo or 20 g Cr/day for 4 weeks. Cr was well tolerated, but there were no significant effects with regard to exercise performance, eye movements, or activities of daily life. The power of this pilot study was limited and future multicenter trials are needed.

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Creatine (Cr) is a naturally occurring compound that plays a pivotal role in the regulation of energy metabolism. The highest Cr concentrations are found in muscle and brain, where the enzyme creatine kinase catalyzes the phosphorylation of Cr and the dephosphorylation of phosphocreatine (PCr). This acts as a high-energy phosphate-buffering system allowing the resynthesis of adenosine triphosphate (ATP). Supplemental Cr ingestion in doses of 10 to 20 g/day for 4 to 6 days is well tolerated by healthy subjects and causes an increase of approximately 20% in muscle Cr and PCr,[1,2] and may increase maximal power output in anaerobic activities up to 20%.[3]

Cr supplementation may be of particular benefit to patients with mitochondrial diseases in which depletion of ATP leads to increased dephosphorylation of PCr. MR spectroscopy (MRS) of these patients shows reduced resting PCr and delayed postexercise recovery of PCr in skeletal muscle[4] as well as a reduced PCr/ATP ratio in the brain.[5]

A recent controlled trial showed that the administration of Cr monohydrate increased the strength of anaerobic and aerobic activities in a group of seven patients with mitochondrial diseases, comprising six patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

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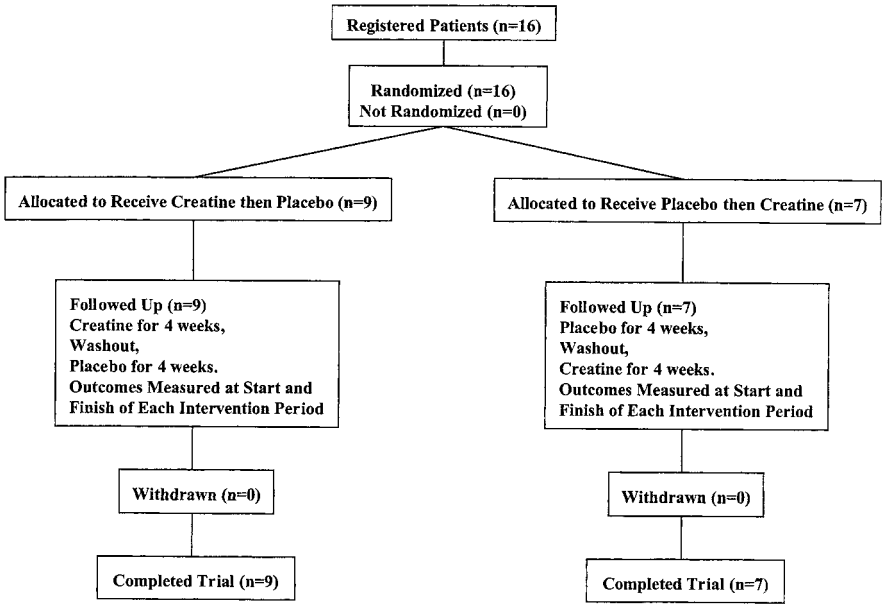

Figure. Flow diagram of the double-blind, randomized, placebo-controlled trial of creatine monohydrate in patients with chronic progressive external ophthalmoplegia or mitochondrial myopathy.

(MELAS) and one patient with a mitochondrial myopathy (MM).[6]

We report on a double-blind, placebo-controlled, crossover pilot study on the effects of Cr monohydrate in 16 patients with chronic progressive external ophthalmoplegia (CPEO) or MM.

Patients and methods. *Patients.* We examined 16 patients with mitochondrial diseases, including 11 with pure CPEO, 2 with CPEO plus, and 3 with MM (table 1). All patients had ragged red fibers in muscle biopsy specimens, indicating the mitochondrial etiology of the phenotype. Informed consent was obtained from the patients, and the trial was approved by the Ethics Committee of the Ludwig-Maximilians-University, Munich.

Design. Subjects participated in a randomized, double-blind, placebo-controlled 2 × 2 crossover trial (figure). They were asked to maintain similar dietary patterns during the study. After randomization, subjects were given Cr monohydrate in its purest form (Creapure, SKW Trostberg, Germany) or undistinguishable placebo (microcrystalline cellulose) in a dose of 5 g orally, 4 times daily for 4 weeks. They were advised to dissolve the powder in fluids, but not in hot drinks or coffee. After a washout period, subjects were given the respective other preparation for another 4 weeks. The washout period[2] was ≥29 days in all patients except two who had a washout period of 24 and 26 days. All patients were examined on the first and the final day of each of the treatment periods.

Measurements. Measurements included (as described in part previously[7]) the following: visual analog scales of subjective muscle weakness and general activity, testing of muscle strength in 32 muscles according to the Medical Research Council (MRC) scale, Hammersmith motor ability score, neuromuscular symptom score, function time test, function ranking test, and an ataxia score. Resting and postexercise lactate were determined during aerobic cycle ergometry. Maximal voluntary muscle torques of biceps muscle (arm curl) at an angle of 90° and quadriceps muscle (knee extension) at an angle of 110° were measured isometrically using the multifunctional training machine M3 (Schnell Corp., Peutenhausen, Germany). Aerobic exercise was tested by nonischemic isokinetic biceps flexion and quadriceps extension at a speed of 80 deg/sec with 15% of maximal muscle force until muscular exhaustion (two trials with a 1-minute rest). To distinguish different effects of Cr, we analyzed not only the average of these two trials,

Table 1 *Patient characteristics and results of muscle biopsy and mtDNA analysis*

No.	Diagnosis	Sex	Age, y	Age at onset, y	mtDNA
1	CPEO	M	43	31	
2	CPEO	F	63	<46	Deletion
3	CPEO	M	43	17	Deletion
4	CPEO	F	35	29	
5	CPEO	F	29	13	Deletion
6	CPEO	F	62	<40	
7	CPEO	M	26	10	
8	CPEO	M	76	60	
9	CPEO	M	32	<25	
10	CPEO	M	30	<21	
11	CPEO	F	36	<30	
12	CPEO+	M	24	15	Deletion
13	CPEO+	F	74	55	
14	MM	F	59	44	
15	MM	F	52	42	
16	MM	M	58	47	Deletion

All patients had ragged red fibers on muscle biopsy. If patients could not remember the exact age at onset, they were asked for an age when they knew they were certainly affected. This uncertainty is indicated by "<." As the mean age at onset was computed using this information, the real age at onset may be lower.

Chronic progressive external ophthalmoplegia (CPEO) = 11; CPEO+ = 2; mitochondrial myopathy (MM) = 3; M = 8; F = 8; mean age ± SD 46.4 ± 17.2 y; mean age at onset ± SD 32.8 ± 15.4 y.

Table 2 *Estimated treatment effects, 95% CI, and* p *values for some of the important outcome variables*

Variable	Estimated treatment effect*	95% CI	*p* Value
Nonischemic isokinetic biceps flexion, J	264.9	−130.1 to 659.9	0.1606
Nonischemic isokinetic quadriceps extension, J	68.2	−681.2 to 817.7	0.8356
Maximal biceps torque, Nm	−1.59	−7.41 to 4.23	0.5619
Maximal quadriceps torque, Nm	−11.0	−29.3 to 7.3	0.2121
Medical Research Council scale	2.20	−0.82 to 5.22	0.1359
Neuromuscular symptom score	−0.45	−1.62 to 0.72	0.4159
Hammersmith motor ability score	0.04	−0.93 to 1.01	0.9291
Function time test, s	−0.04	−2.88 to 2.80	0.9786
Ataxia score	−0.15	−1.03 to 0.73	0.7068

* Positive values indicate that creatine had a better effect than placebo, and negative values that placebo had a better effect.

but also each of the trials separately. Neuro-orthoptic examination included measurements of eye motility and eyelid drooping. Velocity, gain, and latency of visually guided, horizontal saccades were measured by an infrared reflection device.

Statistics. This was an explorative study in which a large number of measurements were investigated simultaneously. We measured the change of the above variables from the beginning to the end of each treatment period, and compared the change in the Cr period to the change in the placebo period. The four measurements for each patient (at begin and end of both periods) were analyzed using ordinary least square methods for normally distributed data.[8] The corresponding model for the post-treatment measurements included the factors patients, treatment, and period plus the covariate pretreatment measurement within each period. The treatment effect was estimated using this model, including 95% confidence intervals. A value of $p < 0.05$ was considered significant. The analyses were performed by using the SAS software package (Cary, NC).

Results. Cr was well tolerated by all patients. Except for muscle cramps in two patients during the Cr period, there were no major side effects. No significant treatment effects, however, were found in any of the measurements described above. The estimated treatment effects, the associated 95% confidence intervals, and the *p* values for some of the important outcome variables are provided in table 2.

Discussion. Cr was well tolerated by our patients. Except for muscle cramps in two patients, there were no major side effects. This is in accordance with other studies of Cr in health and disease. However, the treatment did not result in significant improvement of exercise performance, eye movements, or activities of daily life.

As pointed out in the introduction, an effect of Cr in mitochondrial diseases would be expected from a theoretical point of view. Moreover, in two recent trials[6,9] Tarnopolsky et al. reported significantly increased strength of anaerobic and aerobic type activities. In a randomized, controlled, crossover trial in seven patients with mitochondrial diseases they found significantly increased ischemic isometric handgrip strength and nonischemic isometric dorsiflexion torque, but no effects on maximal voluntary muscle torque and aerobic cycle ergometry.[6] In an open trial in 81 patients with various neuromuscular disorders, among them 17 patients with mitochondrial diseases, they again found significant improvement of ischemic isometric handgrip strength and nonischemic isometric dorsiflexion torque.[9]

How can we explain the inefficacy of Cr in this study? In the trials of Tarnopolsky et al., mitochondrial diseases encompassed mainly MELAS and Leber hereditary optic neuropathy (LHON).[6,9] CPEO and MM may respond differently to Cr, because they are chronic and long-standing conditions, and muscle weakness is often more pronounced than in MELAS and LHON. Moreover, Cr supplementation is most effective in subjects with low endogenous muscle Cr concentrations.[1,2] As these concentrations are normal in CPEO,[10] these patients may benefit less than patients with other mitochondrial diseases. Thus, Cr may be effective in certain but not all mitochondrial disorders. Conversely, as the patients in the latter trial of Tarnopolsky et al.[9] had various neuromuscular disorders, the data are difficult to interpret and may not reflect an effect of Cr in mitochondrial disease.

PCr is important for the regeneration of ATP during the initial seconds of contraction. Furthermore, PCr remains higher between repeated exercise bouts following Cr supplementation. Cr loading can increase maximal power output in anaerobic activities by 10 to 20% according to some studies in healthy individuals. In theory, Cr may be of use in endurance exercise performance by facilitating ATP shuttling from generation to sink sites in muscle, but this has not been proven. In their trials,[6,9] Tarnopolsky et al. found significant effects of Cr in ischemic isometric handgrip strength and in nonischemic isometric dorsiflexion torque, but no significant changes in maximal voluntary muscle torque or aerobic cycle ergometry. As in our study most variables measured low-intensity exercise, which may be more relevant

for daily life, we cannot exclude an effect of Cr in high-intensity exercise.

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Neuro*Images*

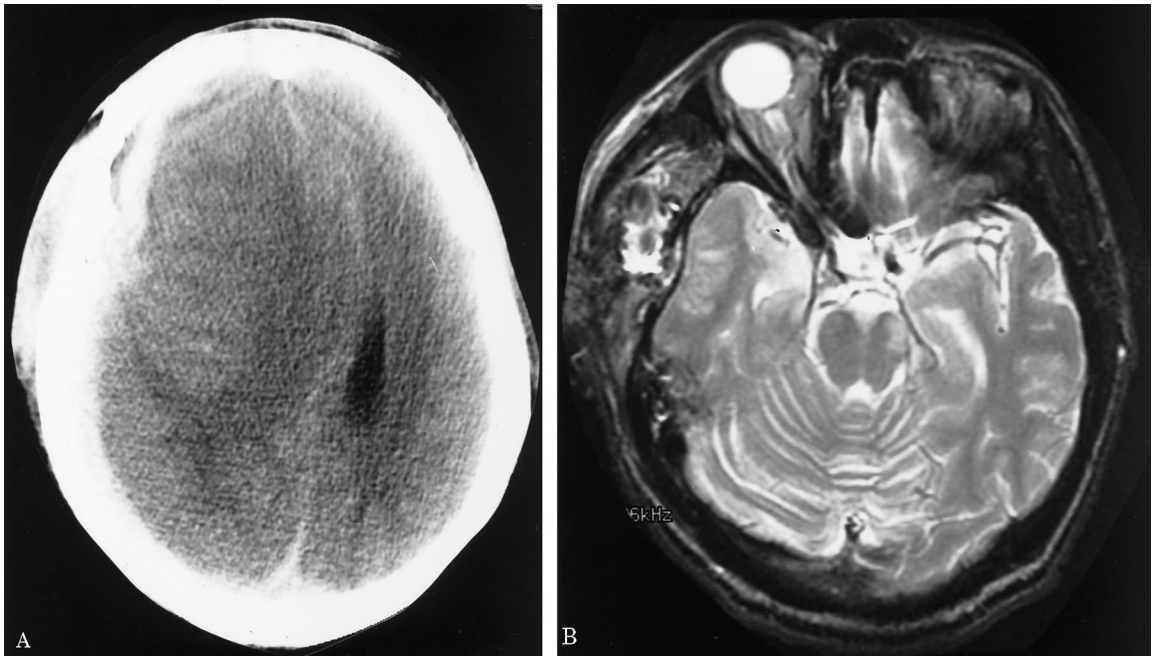

Figure. (A) Axial noncontrast head CT demonstrates an acute right-sided subdural hematoma with midline shift. (B) Kernohan's notch is shown on T2-weighted axial MRI. A hyperintense region is located in the contralateral left cerebral peduncle, giving rise to the ipsilateral hemiparesis.

MRI correlate of Kernohan's notch

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A 29-year-old professional boxer was found unconscious in the shower after a sparring match. He presented to the emergency room with a Glasgow Coma Scale of three and a right fixed and dilated pupil. A CT scan verified the presence of an acute, right-sided subdural hematoma with mass effect (figure, A). A right frontotemporal craniotomy was performed emergently to remove the hematoma. Postoperatively, he had a right hemiparesis.

In 1925, Kernohan and Woltman[1] described the compression of the contralateral cerebral peduncle against the tentorial edge by a supratentorial mass. MRI confirmed injury to the left cerebral peduncle, which was responsible for the false localizing ipsilateral hemiparesis (see figure, B). This finding was not evident on the initial CT scan. Subsequently, the patient recovered partially. He is independent with his activities of daily living, but is no longer boxing.

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