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## CASE STUDY

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# Advances in the Treatment of MELAS Syndrome: Could Cognitive Rehabilitation Have a Role?

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Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) is a rare inherited mitochondrial disorder, commonly due to the m.3243A>G mutation, which typically presents with seizures, headaches, and acute neurological stroke-mimicking deficits. At onset, there is often no general intellectual deterioration in these patients, although specific cognitive deficits in peculiar language domains, visual construction, attention, abstraction, or flexibility may be present. To date, there is no evidence for an effective treatment in individuals with MELAS. Herein, we describe the case of young woman affected by MELAS who underwent an intensive cognitive training by means of the following methods: (a) traditional cognitive training, (b) computerized cognitive training (CCT), and (c) CCT plus a low-intensity aerobic motor exercise. We compared her cognitive and psychological profile at baseline (T0) and at the end of each training (i.e., Time 1, Time 2, and Time 3 [T3]) using a proper psychometric battery, and we found a greater improvement at T3. Our findings support the idea that the combined CCT with motor training could represent a valuable therapeutic opportunity in MELAS.

*Key words:* aerobic exercise, computerized cognitive rehabilitation, MELAS, neuropsychological deficit

## INTRODUCTION

Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) is a rare inherited mitochondrial disorder, commonly due to the m.3243A>G mutation, which is linked to respiratory transport chain dysfunction and oxidative stress in energy-demanding organs, particularly muscles and the brain (Ciafaloni,

Ricci, Shanske, & Garcia, 1992; Goto et al., 1992). MELAS typically presents with seizures, headaches, and acute neurological stroke-mimicking deficits. However, its phenotypic expression is variable, ranging from oligosymptomatic cases to severely affected patients with multisystem involvement. Juvenile-onset forms are mainly characterized by short stature, earlier severe onset, and a rapidly deteriorating course, whereas the adult forms are characterized by cortical blindness, hearing loss, and diabetes (Yatsuga, 2012). Patients with mitochondrial disorders can show primary psychiatric symptomatology, including mood disorders, cognitive impairment, psychosis, and anxiety. There is often no general intellectual deterioration in these

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patients at onset, although specific cognitive deficits concerning peculiar language domains (production, comprehension, and repetition), visual construction, attention, abstraction, or flexibility may be present (Finsterer, 2006). Mild impairment of one or more cognitive domains, without interference with the occupational or social performances (mild cognitive impairment), may be the initial manifestation of central nervous system involvement (Finsterer, 2006). Moreover, psychotic episodes or personality changes have been also described. Nevertheless, there has been little progress in specific therapy for MELAS, despite many attempts to improve presumed oxidative enzyme deficiencies by administering various coenzymes (Penn et al., 1992; Yamamoto, Sato, Anno, Ujike, & Takemoto, 1987). None of these studies are large controlled trials, and because the results are scant, there is still no substantial evidence for an effective treatment. The phenomenon of heteroplasmy (i.e., mitochondrial DNA variability) and the observation that the proportion of normal and abnormal mitochondria within a tissue type can change over time represent the hypothetical basis for exercise training in mitochondrial diseases. The cognitive rehabilitation of neuropsychological dysfunctions in MELAS is still not considered a possible complementary treatment. Current evidence has shown that computerized cognitive training (CCT) is an effective tool in the treatment of neurophysiological deficit related to different brain disorders. The therapeutic benefits of specific programs have been reported for denomination, conversational scripts, sentence processing, comprehension, communication skills, written language, sentence construction, and spelling. Herein we sought to compare the effects of three different types of cognitive rehabilitation—(a) traditional cognitive training (TCT), (b) CCT, and (c) CCT plus a low-intensity aerobic motor exercise—in a young woman affected by MELAS.

## CASE REPORT

A 29-year-old Italian woman came to a neurology unit with a headache and speech impairment. A computed tomography scan revealed an ischemic infarction in the left temporoparietal area. Family history was unremarkable. She had been affected since 10 years of age by diabetes mellitus, treated with oral antidiabetics, and by mild renal failure. General examination showed short stature and hirsutism, whereas a mild-to-moderate left hemiparesis with expressive aphasia was detected at neurological examination. Laboratory tests, including coagulation markers, autoimmunity, and thyroid function, were within the normal range, but glycemia was (190 mg/dL) and cholesterol was 303 mg/dL. Cardiological evaluation, including transesophageal echocardiogram, was normal. Because the stroke was still of undetermined origin, the patient underwent brain magnetic resonance imaging demonstrating several areas of increased signal intensity

(flair, proton density (PD), and T2) in the left temporoparietal cortex, bilaterally in the cerebellum, and in the posterior part of the left thalamus, with loss of cortico-subcortical differentiation and reduction of signal intensity in these areas on T1 images. Brain magnetic resonance angiography showed no intracranial vascular abnormality. Because MELAS diagnosis was suspected, an acid lactic test (>460 UI/mL) and genetic test (A to G at nucleotide position 3243 of mitochondrial DNA mutation) were performed and definitively confirmed the diagnosis.

The patient came to our neurorehabilitation research center after about 6 months after stroke onset. Because the patient was in the poststroke chronic phase, we decided to treat her by using an intensive cognitive rehabilitation protocol, including three different kinds of training. The patient underwent 2-month TCT, based on a face-to-face approach between therapist and patient, using paper-and-pencil tools. We then used the Italian platform ERICA (“Esercizi Riabilitativi Cognitivi per Adulti,” i.e., Adult Cognitive Rehabilitation Exercises) characterized by specific computerized task-oriented exercises with a progressive and modularity difficulty, regarding five peculiar cognitive domains: attention, spatial cognition, memory, and verbal and no verbal executive function. Finally, we performed the CCT combined with a low-intensity aerobic motor exercise (20 min of cyclette at low frequency; CCT<sub>plus</sub>). Two-week intervals separated each training session, which consisted of 3 sessions weekly for 2 months (for a total of 24 rehabilitative sessions). The patient underwent a neuropsychological and clinical evaluation before (T0) and after each rehabilitative cycle (Time 1 [T1], Time 2 [T2], Time 3 [T3]). Neuropsychological status was assessed by a skilled neuropsychologist through a proper battery to investigate cognitive domains such as language, attention abilities, memory, learning, executive functioning, and depression pathology. The battery included: the Mini Mental State Examination (MMSE) to test general cognitive functioning; the Aachen Aphasia (AAT) to assess spontaneous speech and comprehension and communication skills; the attentive matrices to evaluate the selective attention process; the Rey Auditory Verbal Learning Test Immediate and Recall (RAVLI; RAVLR) to estimate verbal memory abilities; the Hamilton Rating Scale for Depression (HRS-D) to detect the presence of depression symptoms; and the Coping Orientation to Problem Experienced-New Italian Version to evaluate copying styles in five large, essentially independent dimensions including: social support (ss), voidance strategies (vs), positive attitude, problem solving, and turning to religion. An assessment in balance and walking was also performed by means of the Tinetti scale.

Raw neuropsychological data (see Table 1) were transformed to interval-level data (logits) and rescaled on a scale from 0 to 100. Hence, the Wilcoxon signed-rank test was used to examine neurobehavioral changes after each rehabilitative cycle.

TABLE 1  
Comparison of Language and Psychometric Measures at T0, T1, T2, and T3

Test	Cognitive Domain	T0	T1	T2	T3
MMSE	Global cognitive status	23.07	26	30	30
AAT Token Subtest	Language	27 (50)	26 (53)	11 (60)	11 (60)
AAT Understanding Subtest	Language	118 (76)	118 (76)	118 (76)	118 (76)
AAT Written Language Subtest	Language	55 (52)	60 (55)	82 (64)	90 (70)
AAT Denomination Subtest	Language	109 (76)	115 (78)	120 (80)	120(80)
AAT Repetition Subtest	Language	130 (57)	136 (62)	145 (66)	147 (68)
RAVLI	Memory	36.5	37.5	46.5	48.5
RAVLR	Memory	8.8	8.8	9.8	10.8
AM	Attention process	38	39	49	52
Hamilton Rating Scale for Depression	Depression symptoms	27	22	11	11
	Social support	15	17	17	20
	Avoidance strategies	26	25	23	21
	Positive attitude	20	20	20	22
	Problem Solving	20	23	23	25
COPE-NIV	Turning to religion	24	24	24	24
	Balance	7	8	12	12
Tinetti scale	Walking	4	6	9	9

Note. Mean raw data are reported. T0 = baseline; T1 = Time 1; T2 = Time 2; T3 = Time 3; MMSE = Mini Mental State Examination; AAT = Aachen Aphasia; RAVLI = Rey Auditory Verbal Learning Test Immediate; RAVLR = Rey Auditory Verbal Learning Test Recall; AM = attentive matrices; COPE-NIV = Coping Orientation to Problem Experienced-New Italian Version.

At baseline (T0), AAT showed slurred and slow speech, with a delayed response after stimuli presentation. Alterations in the Token subtest (27/0 NS = 50), understanding (118/120; NS = 76), written language (55/90; NS = 52), denomination (109/120; NS = 76), and repetition (130/150; NS = 57) were also evident. Moreover, the patient showed an overall moderate cognitive alteration (i.e., MMSE = 23.07/30), with inadequate and dysfunctional coping strategies (ss = 15; vs = 26). The Tinetti scales indicated a severe imbalance in stance (p.7/16) and walk (p.4/16). Moreover, the patient showed severe depression (HRS-D = 27).

After the end of the TCT (T1), depression symptoms improved (-18%) and a mild improvement in balance (+14%) and walk (+50%) were detected. Nevertheless, we did not observe a significant improvement in nearly all the psychometric tests (p = .2). After training with ERICA (CCT; T2), we found a mild improvement, but it was still nonsignificant in comparison to T0 (p = .1) or T1 (p = .1), in other specific cognitive abilities, with regard to the selective attention process (+29%) and immediate and delayed recall on the RAVLI (+27%) and RAVLR (+11%). We also observed an improvement in some language abilities (i.e., in the Token subtest = 11/0, NS = 60), in particular in understanding (118/120; NS = 76), written language (82/90; NS = 64), denomination (120/120; NS = 80), and repetition (145/150; NS = 66).

Interestingly, the patient showed the best improvement in cognitive function, with regard to written language (+64% vs. +10%), denomination (+10% vs. unchanged), and attention (+37% vs. +6%) after the CCT<sub>plus</sub> session (T3) in comparison to T2 (Z = -1.8, p = .04) and T0 (Z = -2.2, p = .02). An improvement in coping style (+10%

vs. +6%) and a significant reduction in the patient's vs (-19% vs. -9%) and depression symptomatology (-59% vs. unchanged) were also noted.

## DISCUSSION

The novelty of our data is the evidence of the possibility to improve cognitive deficit in a patient affected by MELAS. Comparing the TCT to the CCT, we obtained a greater improvement after CCT and a more evident amelioration when we added the aerobic motor activity (CCT<sub>plus</sub>) either in comparison to baseline or to CCT.

Recovery from a stroke event is a complex process, likely due to a combination of spontaneous and learning mediated processes, mainly occurring within the first 6 months after disease onset. It is unlikely that in our patient other factors than the intensive rehabilitative training have played a role in cognitive improvement because stroke was in the chronic phase and MELAS is per se a potentially progressive disease.

General cognitive dysfunction or focal deficits are detected in 61% of patients affected by MELAS (Finsterer, 2008), with short-term memory deficits attributed to frontal- or temporal-lobe dysfunction. Visuo-perceptual organization and drawing abilities may be also affected. Cognitive functions and intellectual abilities may decline from initially focal cognitive impairment to dementia, with no strong correlation to stroke events. The mechanism by which mitochondrial dysfunction results in cognitive decline or dementia remains speculative. Possible mechanisms could be: (a) Depletion of energy causes dysfunction

of cortical neurons; (b) increased oxidative stress impairs functions of cortical neurons and glial cells; (c) mitochondrial defect results in apoptosis of cortical neurons; or (d) focal paroxysmal discharges inhibit physiologic membrane functions. The impairment of verbal and nonverbal short-term memory and executive function is probably attributed to dysfunction of the basal ganglia and the related frontal structures (Finsterer, 2008). Only a small number of studies systematically applied a detailed neuropsychological battery to assess cognitive functions in patients with MELAS. Neuropsychological deficits in MELAS were first described by Suzuki, Nagao, and Suzuki (2011) and Lang et al. (1995), but without providing a detailed assessment of memory, attention, executive functions, or visuoconstructive abilities. More extensive neuropsychological testing has been recently carried out. There is actually no effective treatment of mitochondrial dementia, except for coenzyme-Q in patients with dementia from primary coenzyme-Q deficiency.

The increasing availability of computers, the Internet, wireless connections, and other electronic devices opens a wide range of possibilities to incorporate these technologies into CCT, thus representing a promising tool in the treatment of neuropsychological deficit related to different brain disorders (Cappa et al., 2005).

Moreover, recent research in rehabilitation indicates that aerobic exercise may increase brain activation in the frontal lobe and improve cognitive function, especially executive function (Colcombe et al., 2004).

An increasing number of randomized intervention studies examined the relationship between fitness training, cognition, and dementia.

In particular, exercise training in patients with muscle-specific mitochondrial mutations has been shown to increase the proportion of mitochondria with normal wild-type genomes and improve the metabolic function of muscle. The treatment of dementia related to mitochondrial diseases includes general measures and specific therapy. However, only a small number of studies systematically applied detailed neuropsychological testing to assess cognitive functions in patients with MELAS (Finsterer, 2008).

Our data showed that cognitive rehabilitation and psychological counseling should be considered rehabilitative tools in MELAS. Thus, we may speculate that the best response of our patient to CCT<sub>plus</sub> may be related to the capacity of exercise training to improve the metabolic function of brain and

muscle (Taivassalo et al., 1999). Further and larger prospective studies are needed to confirm our promising findings.

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