

Cognitive functions in myoclonic epilepsy with ragged red fibres – a case report

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SUMMARY

Introduction. Myoclonic epilepsy with ragged red fibers (MERRF) is a rare, progressive mitochondrial disease affecting multiple systems, including the central nervous system. Typical MERRF symptoms include: myoclonus, epileptic seizures, ataxia and cognitive decline. In mitochondrial diseases selective cognitive impairment or generalized decline, called mitochondrial dementia, is usually diagnosed.

Description of case. We present the case of an 18-year-old patient with progressive neurological symptoms such as multifocal myoclonus, cerebellar syndrome (gait impairment, intention tremor, ataxia and dysmetria). The diagnosis of MERRF was confirmed at the age of 16. Neuropsychological examination showed slowing of verbal learning and deficient spontaneous recall with improvement on recognition as well as low verbal fluency.

Discussion. The authors discuss differential diagnosis of mitochondrial diseases (MIDs) in respect to cognitive function impairment and, in particular, to dementia: MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), KSS (Kearns-Sayre syndrome), NARP syndrome (neuropathy, ataxia, and retinitis pigmentosa and ptosis). The authors emphasize importance of comprehensive neuropsychological assessment in differential diagnosis of MIDs.

Conclusion. Mild and selective cognitive impairment was identified. The type and degree of cognitive function impairment is not sufficient to diagnose dementia in this particular case of MERRF. Comprehensive neuropsychological assessment is crucial in MID in order to provide the patient with useful recommendations for education planning.

Key words: MERRF • epilepsy • myoclonus • mitochondrial diseases • cognitive impairment

INTRODUCTION

Myoclonic epilepsy with ragged red fibers (MERRF) is a rare, progressive mitochondrial disease caused by mutation within mitochondrial DNA (mtDNA). In 80% of cases the disease is caused by point mutation m.8344A>G. In the bioplate of skeletal muscle of pa-

tients with MERRF, the so-called ragged fibers, containing clusters of abnormal mitochondria under sarcolemma, are identified.

Mitochondrial diseases are multisystem genetic disorders associated with the impaired mitochondria func-

tion, failing to satisfy the energy needs of various organs. Thus, the symptoms affect mainly systems with high energy demand such as the nervous system and skeletal muscles (Zeviani and Carelli, 2007). A central nervous system involvement is identified in 30–60% of patients with mitochondrial diseases (Finsterer, 2008, 2009).

The core symptoms of MERRF are: myoclonus, generalized epilepsy, ataxia, and ragged red fibers in the muscle biopsy. Additional symptoms are: sensorineural hearing loss, myopathy, peripheral neuropathy, short stature, exercise intolerance, optic atrophy and dementia. Moreover, in some cases cardiomyopathy, pigmentary retinopathy, pyramidal signs, ophthalmoplegia or multiple lipomas, are observed (Hirano and DiMauro, 2015).

In mitochondrial diseases, selective or generalized cognitive deficits (called mitochondrial dementia) are found. The literature lacks reports on neuropsychological assessment in patients with MERRF. Most data on cognitive function in mitochondrial disease come either from studies of patients with MELAS (Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) or from mixed patient cohorts (Kartsounis et al., 1992; Turconi et al., 1999; Kaufmann et al., 2004). Slowed information processing seems to be the most prominent finding in a majority of cases (Finsterer, 2009), followed by a variety of focal cognitive deficits (visuospatial, language, memory impairment) and executive dysfunction (Kartsounis et al., 1992; Turconi et al., 1999; Sartor et al., 2002; Bosbach et al., 2003). It is unclear to what extent these findings are applicable to patients with MERRF. In this case report, the neuropsychological function of the patient with genetically confirmed MERRF is presented.

CASE REPORT

We present an 18-year-old female adolescent, born in the 38th week of pregnancy from the second pregnancy by forceps delivery, without abnormalities during pregnancy and in early childhood. The first neurological symptoms appeared at the age of 12. Upper and lower limb tremor, gait disturbances and falls were observed. The patient has suffered from brief incidents of loss of consciousness treated at first as syncope since the age of 14. A year later, gait disturbances and the hand tremor increased considerably. There was no positive family history for neurological diseases. Formal intelligence testing produced average results

without marked discrepancy between verbal and performance scales (Wechsler Intelligence Scale for Children-Revised-WISC-R; full scale IQ 99, verbal IQ 104, performance IQ 99). About the same time the diagnosis of developmental dyslexia was established. As she complained of progressive difficulties in writing, and her school performance was average, a psychogenic origin was suspected. Thus, she was referred to a psychiatrist. At the age of 16, the EEG evidenced numerous epileptic discharges (fig. 1), there were also seizures recorded in the form of brief loss of consciousness. The epilepsy diagnosis was established and valproic acid at a dose of 2×300 mg was introduced. An MRI brain scan performed in the same year showed a minor non-specific focus which was hyperintense in the white matter near the back outline of lateral right part of brain (fig. 2). Poor response to treatment, progressive involuntary limb movements (myoclonus) and presence of the increased paroxysmal weakness in lower limbs leading to falls, were followed by admission to the Department of Developmental Neurology, Medical University of Gdańsk. During hospitalization the patient reported increasing gait disturbances (“legs are getting wobbly”). Moreover, the intensified hand tremors was also observed, especially when performing precise movements. During neurological examination, signs of cerebellar syndrome were identified: position and intention tremor of upper and lower limbs as well as ataxia. Head tremor was also present. There were no signs of cranial nerves involvement, in particular auditory nerves. During hospitalization the short lasting absence seizures (dialeptic) were observed. The treatment with valproic acid was maintained, fluoxetine was introduced (10 mg) because of mood fluctuations. Six months later, the patient was re-admitted to the Department of Developmental Neurology because of myoclonus. The patient reported sudden jerks of head and limbs, which occurred daily, both during sleep and wakefulness. These movements caused difficulties while writing and eating. She also reported hypersensitivity to flashing lights and vivid colors. Problems with keeping balance in the standing position became more pronounced. Both cerebellar syndrome and pyramidal signs (brisk knee reflexes with patellar clonus) were identified in the neurological examination; cranial nerves were normal. Structural MRI did not show progression of structural abnormalities. EEG revealed interictally numerous changes in temporal regions both sides with tendency to generalization. The dose of val-

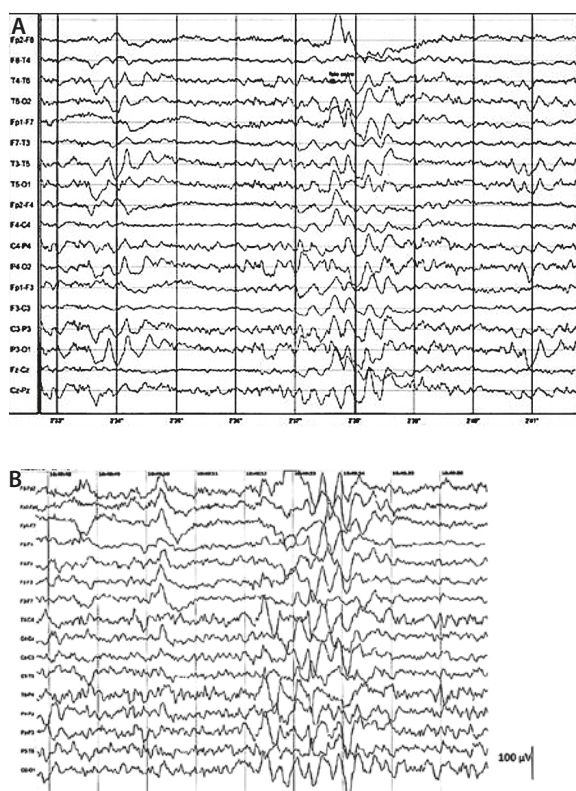


Figure 1. EEG performed at the age of 15 (**figure A**): visible numerous epileptiform discharges. **Figure B**, EEG performed at the age of 18: numerous changes in temporal regions on both sides with tendency to paroxysmal activity generalization, background activity with no proper differentiation. Vertical lines mark 1 sec.

proic acid was increased (2×500 mg), and then levetiracetam (2×1500 mg) was added resulting in a slight clinical improvement. Laboratory tests revealed a high level of creatinine in urine and a high level of lactic acid – 6.2 mg/dl, so that metabolic acidosis was suspected. The patient was hospitalized three times in the Department of Metabolic Diseases at Child's Health Memorial Hospital in Warsaw, where the analysis of organic acids in urine was performed, and then the molecular blood test (mtDNA screening) was performed in order to support the diagnosis of a mitochondrial disease. As a result of detecting the mutation m.8344A>G, the diagnosis of MERRF syndrome was established. Valproic acid was withdrawn, treatment with levetiracetam was maintained, clobazam (CLB) (2×10 mg), L-carnitine (2×250 mg), vitamin E (2×200 mg), vitamin A (2500 units/day) and creatine (3×1250 mg) were introduced. In the same year follow-up testing with WISC-R was performed, which may have suggested deterioration (full IQ decreased from 99 to 91, verbal IQ fell from 104

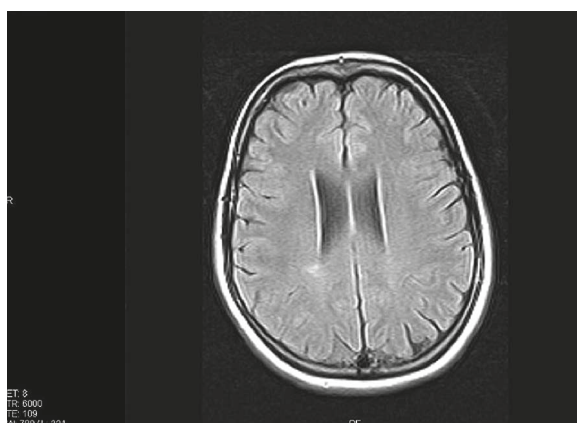


Figure 2. Magnetic Resonance Imaging (MRI) at the age of 16: a minor non-specific focus, hyperintense in the white matter near the back outline of lateral right part of brain.

to 94, performance IQ declined from 93 to 82). A significant decrease was noted especially in subtests assessing information processing with time limits (Arithmetic: decrease of 4 points in scaled scores) and Coding (difference of 5 points in scaled scores). When aged 18 the patient was referred for further care to the Movement Disorders Outpatient Clinic at the St. Adalbert Hospital in Gdańsk. Follow-up EEG showed a stable pattern. The severity of cerebellar signs and myoclonus increased. There were no signs of hearing loss or optic atrophy at that time. The dose of levetiracetam was increased (2×1500 mg), L-arginine (3×2 g) and clonazepam (3×0.5 mg) were administered leading to a decrease of myoclonus and the reduced frequency of epilepsy seizures. The patient was wheelchair-bound and dependent on her mother's assistance in many activities of daily living. However, due to her stamina and perseverance she managed to graduate from High School and pass her final exams.

Neuropsychological examination

Neuropsychological examination was performed at the age of 18. The patient showed significant fatigability, so the testing was administered during 3 sessions. Due to severity of motor symptoms, methods involving manual dexterity were avoided. The patient did not report lowered mood. However, marked irritability and moderate anxiety were noted. Within language functions slight anomia was observed (Boston Naming Test 53/60, improvement after phonemic cues and in multiple choice condition) and lowed verbal fluency, both semantic (animals 14, fruit and vegetables 19) and phonemic ("K" 9, "P" 10). Object perception was

preserved (Visual Object and Space Perception Battery, VOSP – Incomplete letters 20/20), as well as visual search (Schenkenberg line bisection and Letter Cancellation from Behavioral Inattention Test). Satisfactory performance was also noted on most space perception tasks (VOSP – Dot Counting 10/10, Position discrimination 18/20, Number Location 10/10, Cube Analysis 10/10). Deficient performance was noted only in tasks requiring good eye fixation (Benton Judgement of Line Orientation 17/30).

Immediate spatial and verbal span was preserved (Corsi Block Tapping task forward: max. 5, Benton Visual Retention Test, recognition format, version G: 15/15, Digit span forward: max. 6), as well as working memory (Digit Span backwards max. 4, SS=12, Corsi sequences backwards max. 4). Verbal learning was slowed and spontaneous delayed recall was deficient. As delayed recognition was well preserved, the impaired spontaneous recall may have been due to language or executive failure (raw scores on Auditory Verbal Learning Test: learning curve 5-7-10-11-13, recognition 12, delayed recall 7, delayed recognition 13). Visual memory was well-preserved (Continuous Visual Memory Test: total score: 84, 92.8 percentile, delayed recognition 7, 100 percentile). Cognitive flexibility and planning were preserved (The Brixton Spatial Anticipation Test SS=6; Tower of London – version 4 with no time limits and enlarged beads so as to minimize motor demands – within average range).

Mild and selective cognitive impairment was identified. The severity of cognitive impairment was not sufficient to diagnose mitochondrial dementia. The results were discussed in terms of education requirements and adaptations to be made while studying: short studying sessions and frequent breaks to limit the effect of mental fatigue, using audiobooks (to compensate for reading problems) and using visual mnemonics to compensate for verbal memory problems.

DISCUSSION

Our patient presented with mild and selective cognitive impairment and managed to complete her high school education. Diagnosis of mitochondrial dementia (Finsterer, 2009) was excluded. Mild and/or focal cognitive deficits were also described in previous reports of patients with mitochondrial disease (Kartsounis et al., 1992; Turconi et al., 1999; Sartor et al., 2002; Bosbach et al., 2003) and only in few reported cases mitochondrial dementia was diagnosed (Lang et al., 1995).

MELAS patients are often described in the literature as those most cognitively impaired, but often they were not always diagnosed with mitochondrial dementia as they presented with focal cognitive impairments (Lang et al., 1995; Sartor et al., 2002; Kaufmann et al., 2004). Although there are publications describing cognitive impairment among patients with mitochondrial diseases (MIDs) such as for example MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) and KSS (Kearns-Sayre syndrome), NARP syndrome (neuropathy, ataxia, retinitis pigmentosa and ptosis), it is hard to find publications on MERRF cases only. It is very uncommon disease among all other MIDs where mental deterioration was diagnosed. According to this fact, we present status of cognitive functioning in MERRF in reference to current findings about all mitochondrial diseases.

In many studies of MIDs, Wechsler Intelligence Scales (WISC or WAIS) were used to assess cognition (Karsounis et al., 1992; Turconi et al., 1999; Sartor et al., 2002; Bosbach et al., 2003). However, Wechsler intelligence scales do not evaluate important areas of cognition, such as episodic memory or executive functions (Lezak, 1988; Ardila, 1999). Furthermore, many Wechsler subtests have time limits and are motor-dependent (e.g. Coding or Symbol Digit). Thus, many subtest scores and in consequence the overall score is invalid in MID patients and prone to misinterpretation, as such scales were validated for the population of neurologically-healthy children. This highlights the role of neuropsychological assessment in the patient's diagnosis and management of selective cognitive deficits, as short cognitive screening is unlikely to document cognitive impairment and traditional intelligence testing does not show the patient's cognitive profile (Lezak, 1988; Ardila, 1999), which is needed for making recommendations in the context of patients' education.

Selective slowing in verbal learning and low verbal fluency seem to prove slight language impairment. This profile is consistent with the earlier misdiagnosis of developmental dyslexia as the other areas of cognition were well preserved. In previous reports of patients with mitochondrial disorders, language function was either not reported (Lang et al, 1995; Turconi, 1999; Kauffman, 2004) or impaired in some cases (Kartsounis, 1992; Sartor, 2002; Bosbach, 2003).

Attention deficits were attributed to the patients with MID in most of previous reports (Kartsounis, 1992; Lang, 1995; Turconi, 1999; Sartor, 2002; Bosbach, 2003).

However, most of the tasks used in those studies were time- and (oculo)motor-dependent and (e.g. Trail Making Test A, d2 or Coding from WISC-R). In our patient, better performance on BVRT than Corsi task was noted, which may suggest no visual distractibility, but poor eye tracking. This is consistent with the visuospatial test performance. Our patient performed well on most visuo-perceptual tasks, but failed on task requiring angle comparison (JOLO), which is in line with Turconi et al.'s results (1999). Few studies reported impaired construction in MID (Lang, 1995; Bosbach, 2003); in our patient construction tasks were not administered due to severity of motor symptoms and the fact that test results would have been difficult to interpret.

Memory seems to have been better preserved in our patient than in previously reported cases, in whom both immediate (Lang, 1995; Turconi, 1999; Sartor, 2002; Bosbach, 2003) and delayed recall (Bosbach, 2003) as well as recognition impairments (Kartsounis, 1992; Lang, 1995) were noted. To our knowledge, none of the previous studies compared verbal and visual material learning in patients with MID. Furthermore, visual memory was assessed either by tasks requiring construction (Turconi, 1999; Sartor, 2002) or only in the recognition format with no repeated exposure of stimuli. In our patient selective problems with verbal learning were observed in the context of preserved visuospatial learning.

Previous studies with MID patients failed to assess multiple domains of executive functions. Impaired performance on Wisconsin Card Sorting Test was noted (Sartor, 2002; Bosbach, 2003). However, this task is very demanding visually. Not only does it require tracking 4 stimuli cards, 4 cards previously arranged and the card at hand, but it also requires fine discrimination between light yellow stars and crosses which are perceptually similar. In our patient, The Brixton Spatial Anticipation Test, with much lower visual demands, did not document deficits. Similarly, planning was within normal range, when motor demands were minimized.

The impact of antiepileptic drugs on cognitive function in our patient needs to be taken into consideration. Valproic acid (VPA) used as a first drug before the final diagnosis of MERFF is rarely reported to cause cognitive problems (Gillham et al., 1991), however, studies performed on monotherapy in adult and adolescents populations are rather sparse. Recently, the major interest was on the disruptive effects of VPA on cognitive functions of children born from mothers suffering

from epilepsy treated with VPA (Meador et al., 2009) but that was not an issue in this study. Levetiracetam (Koo et al., 2013) shows also very favourable cognitive profile. In contrast clobazam (Patat et al., 1991) is known to cause memory impairment in healthy volunteers (at the dose of 30 mg). In patients with epilepsy the data are conflicting because CLB use in drug resistant epilepsies entailed cognitive improvement due to significant seizures reduction; in some studies it is highlighted that the cognitive side-effect profile of CLB is similar to other benzodiazepines but with substantially decreased sedation and increased psychomotor performance (Wheless and Phelps, 2013). In our opinion it is unlikely that observed cognitive deficits were due to antiepileptic drugs particularly since some of those deficits had already been present prior to the introduction of these antiepileptic drugs.

CONCLUSION

The present patient report questions the utility of the term „mitochondrial dementia” in MERFF. However, we present data that indicate a probability of association between MERRF and some mental deterioration. Neuropsychological results in MIDs are frequently motor-biased and cognitive impairments may be overestimated due to inadequate choice of assessment tools. Comprehension neuropsychological assessment is crucial in MIDs so as to allow the provision of useful recommendations for education planning.

CONFLICT OF INTEREST DISCLOSURE

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