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Radboud Centre for Mitochondrial Medicine Pediatric MRI score

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ABSTRACT

We developed the first user-friendly, semi-quantitative, and quick-to-perform Radboud Centre for Mitochondrial Medicine Pediatric MRI score (RCMM-PMRIS), focusing on the six most commonly described neuroimaging abnormalities in the literature. The RCMM-PMRIS was validated through individual review of 30 sets of brain MRI studies in 24 patients with genetically confirmed mitochondrial disorders by six raters. The application of RCMM-PMRIS can help to define the extent of the brain involvement and therefore to assess the radiological mitochondrial disease severity, to monitor disease progression and consequently to act as an outcome measure for treatment effects in patients with mitochondrial disease.

1. Introduction

Mitochondrial disorders (MD), with a minimal birth prevalence of 1 in 5000 births, are the most common inborn errors of metabolism caused by mutations in either the mitochondrial (mtDNA) or the nuclear (nDNA) genome leading to impaired oxidative phosphorylation (OXPHOS) (Bianchi et al., 2007; DiMauro, 2000; Skladal et al., 2003). MD represent a heterogeneous group of genetic disorders with frequent involvement of the highly energy-demanding central nervous system (Finsterer, 2006).

Magnetic resonance imaging (MRI) of the brain, with the many recent technological advances in magnetic field strength, resolution and sequencing techniques, is a sensitive diagnostic tool for MD. Its specificity is especially high for certain syndromic forms of MD such as in encephalopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, in Leigh syndrome and in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) (Haas & Dietrich, 2004). The 6 most common MRI features described in MD include bilateral symmetrical abnormalities in the deep gray matter and brainstem, diffuse white matter abnormalities, cerebral and cerebellar atrophy and stroke-like lesions in a nonvascular distribution (Haas & Dietrich, 2004; Parikh et al., 2015).

We hypothesize that MRI studies in MD are of paramount importance not only for diagnostic purposes but also for longitudinal studies rating disease progression and outcome after interventions in clinical trials and treatment. In 2004, Haas and Dietrich described how they scored MRIs for routine evaluation purposes in patients suspected for MD, rating the presence and extent of atrophy and T2 signal hyperintensities in 22 specific brain structures (Haas & Dietrich, 2004). However, up till now there is no validated and published scoring system for this highly heterogeneous and complex group of disorders.

In this study, we aim to develop and validate the first user-friendly and semi-quantitative scoring system based on the six most commonly described MRI abnormalities in patients with MD. The objective of this Radboud Centre for Mitochondrial Medicine Pediatric MRI score (RCMM-PMRIS) is to facilitate clinicians and radiologists to assess the radiological severity at a certain time point, to monitor progression of the disease and to evaluate outcome after therapeutic interventions in patients with MD. We validate the scoring system in a clinically and genetically heterogeneous cohort of pediatric MD patients who underwent MRI examinations of the brain and had their MRI studies archived in the RCMM.

Abbreviations: MD, Mitochondrial Disorders; MRI, Magnetic Resonance Imaging; MELAS, Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like Episodes; MNGIE, Mitochondrial Neurogastrointestinal Encephalomyopathy; FLAIR, Fluid-attenuated Inversion Recovery; DWI, Diffusion Weighted Imaging; IQRs, Interquartile Ranges; RCMM, Radboud Centre for Mitochondrial Medicine; RCMM-PMRIS, Radboud Centre for Mitochondrial Medicine Pediatric MRI Score.

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2. Methods

2.1. Development of RCMM-PMRIS

The aim of the RCMM-PMRIS was to provide a semi-objective, user-friendly, reproducible and quantitative method which could be performed by both clinicians and radiologists through visually assessing the MRI images of the brain that are readily available obtained by use of different commercially available MRI scanners to: (1) assess the radiological severity at a particular time point; (2) monitor the disease progression radiologically; (3) provide a radiological outcome measure for monitoring disease progression in intervention studies in children

Table 1
Patients' demographic, clinical and genetic mutation data and average total RCMM-PMRIS from 3 experienced raters

Age (years) when MRI was performed	Gender	Clinical features	nDNA or mtDNA	Genetic defect	Gene function	Average total RCMM-PMRIS from 3 experienced raters
1	M	Leigh syndrome	mtDNA	*m.8993T>G*	OXPHOS structure: complex V (*MT-ATP6*)	5.3
9	M	Leigh syndrome	mtDNA	*m.8993T>C*	OXPHOS structure: complex V (*MT-ATP6*)	3.3
10	M	Leigh syndrome	mtDNA	*m.8993T>G*	OXPHOS structure: complex V (*MT-ATP6*)	4
6	M	Leigh syndrome	mtDNA	*m.09185T>C*	OXPHOS structure: complex V (*MT-ATP6*)	3
4	M	Leigh syndrome	mtDNA	*m.12490A>G*	OXPHOS structure: complex I (*MT-ND5*)	2.3 10.3 8.3
4	M	Leigh syndrome	mtDNA	*m.14459G>A*	OXPHOS structure: complex I (*MT-ND6*)	9.3
14	M	Cerebellar syndrome, muscle cramps, bradykinesia	mtDNA	*m.8993T>C*	OXPHOS structure: complex V (*MT-ATP6*)	7.3
3	M	Cerebellar sign	mtDNA	*m.8993T>C*	OXPHOS structure: complex V (*MT-ATP6*)	7
17	M	Mental retardation, ptosis, cerebellar sign, peripheral neuropathy, dystonia	mtDNA	*m.12490A>G*	OXPHOS structure: complex I (*MT-ND5*)	7
7	M	Stroke episode, ptosis, dystonia	mtDNA	*m.03697G>A*	OXPHOS structure: complex I (*MT-ND1*)	8.3
11	M	Failure to thrive, ptosis, ophthalmoplegia, exercise intolerance	mtDNA	*m.3243A>G*	Mitochondrial protein translation (*MT-TL 1*)	6
4	F	Congenital hip dysplasia, food refusal, long term tube feeding, motor delay, exercise intolerance	mtDNA	*m.3243A>G*	Mitochondrial protein translation (*MT-TL 1*)	3.3
12	M	Failure to thrive, exercise intolerance, motor delay, mild hypertrophic cardiomyopathy, sensorineural hearing loss	mtDNA	*m.3243A>G*	Mitochondrial protein translation (*MT-TL 1*)	1.7
16	F	Mild mental retardation, short stature, exercise intolerance	mtDNA	*m.3243A>G*	Mitochondrial protein translation (*MT-TL 1*)	4.3
3	M	Sensorineural hearing impairment, exercise intolerance, behavior problem	mtDNA	*m.7507A>G*	Mitochondrial protein translation (*MT-TS 1*)	2.7
11	M	Psychomotor retardation, movement disorder, dystonia, ataxia	nDNA	*SDHA*	OXPHOS structure: complex II	1.3
5	M	Hypotonia, central apnoea	nDNA	*NDUFS7*	OXPHOS structure: complex I	2.7
14	F	Severe psychomotor retardation, deafness, cataracts, progressive pyramidal gait disturbance and movement disorder, calcinosis cu tis, cystinuria without kidney stones	nDNA	*CEP89*	OXPHOS structure: complex IV	2.7
12	M	Leigh syndrome	nDNA	*NDUFS7*	OXPHOS structure: complex I	0.7
2	F	Leigh syndrome	nDNA	*SURF1*	OXPHOS structure: complex IV	3
3 1	F	Psychomotor retardation, cerebellar sign, peripheral neuropathy, visual impairment	nDNA	*OPA1*	Mitochondrial membrane homeostasis	3 1.7
13 8	M	Psychomotor retardation, bradykinesia, mask face, ophthalmoplegia, atxia	nDNA	*MTFMT*	Mitochondrial protein translation	2 0
14 11 7	F	3-methylglutaconic aciduria with deafness, encephalopathy and Leigh like (MEGDEL) syndrome	nDNA	*SERAC1*	Mitochondrial membrane homeostasis	0 2 0
0	M	Severe global delay, hypotonia, facial dysmorphism, hyperlaxity, epilepsy	nDNA	*FBXL4*	MtDNA replication	4.7