Int J Clin Exp Pathol 2016;9(6):6595-6596
www.ijcep.com /ISSN:1936-2625/IJCEP0023799

Letter to Editor

Phenotype and genotype heterogeneity of mitochondrial encephalopathy with lactic acidosis and stroke-like episodes

Josef Finsterer[1], Sinda Zarrouk-Mahjoub[2]

[1]Krankenanstalt Rudolfstiftung, Postfach, Vienna, Austria; [2]Genomics Platform, Pasteur Institute of Tunis, Tunisia

Received January 11, 2016; Accepted April 22, 2016; Epub June 1, 2016; Published June 15, 2016

With interest we read the article by Zhang et al. about a study of 524 pediatric patients with a mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)-like phenotype of whom 40 were positive for the mutation m.3243A > G [1]. From 44 of these patients, 36 carrying the mutation and 8 without the mutation, the clinical presentation was provided in more detail in table 2 of Zhang's paper [1]. We have the following comments and concerns.

The main concerns about this study are that genetic studies were carried out with mtDNA extracted from blood lymphocytes and that no heteroplasmy rates were determined. It is well established that the genotype/phenotype correlation is more reliable when mtDNA is extracted from muscle or from urine bladder epithelium [2]. It is also well established that phenotypic expression is strongly dependent on the heteroplasmy rates of mtDNA mutations in variably affected tissues [3]. Did the authors determine heteroplasmy rates and did they compare them between muscle and blood?

The authors also mention that 80% of Han Chinese MELAS patients carry the m.3253A > G mutation [1]. This is in strong contrast to published literature showing that 80% of the MELAS patients carry the m.3243A > G mutation [4]. How do they explain this discrepancy?

Though cardiac involvement in form of cardiomyopathy and arrhythmias has been repeatedly reported in patients carrying the m.3243A > G mutation respectively presenting with a MELAS phenotype [5, 6], none of the MELAS patients from the present study was reported to have cardiac disease. Which is the reason for the absence of cardiac abnormalities in the investigated cohort? Is it due to the young age of the patients, due to only subclinical cardiac manifestations, or simply because these patients were not systematically investigated for cardiac disease?

A classical hallmark of MELAS is the stroke-like episode [7]. Interestingly, none of the patients is reported to have presented with this typical phenotypic feature [1]. How many of the children underwent cerebral MRI after seizures, cognitive decline, vomiting, visual disturbances, or muscle weakness, frequently associated with stroke-like episodes, had been diagnosed? How many of the included patients underwent imaging studies at all? In this respect it would be also interesting to know how dementia, present in 68% of the patients carrying the mutation, had been diagnosed? Usually, dementia is a diagnosis of adult patients and difficult to diagnose in children.

Almost one third of the patients is reported to have developed "cerebral stroke" [1]. Do the authors mean ischemic stroke with typical MRI findings such as cytotoxic edema in the acute stage and chronic hyperintensities on T2-weighted images in the chronic stage? If they indeed mean ischemic stroke, which is the explanation that almost one third of this pediatric cohort developed ischemic stroke? Which were the classical cardiovascular risk factors in these patients? Did they present with atrial

fibrillation, arterial hypertension, heart failure, non-compaction, hyperlipidemia, or diabetes? Neither diabetes nor arterial hypertension or hyperlipidemia is mentioned [1]. Alternatively, the authors might mean with “cerebral stroke” that patients had stroke-like episodes, which is pathogenetically completely distinct from ischemic stroke.

Finally, epilepsy is a common phenotypic feature of MELAS. In the present study almost all patients carrying the m.3243A > G mutation did present with epilepsy (97%) [1]. Which type of seizures had these patients developed? Were seizures associated with the occurrence of stroke-like episodes or not? Which were the EEG findings? Which type of antiepileptic treatment did they receive? Which was the quality of seizure control? Did they also receive a ketogenic diet or L-arginine or succinate which has been previously proposed as an adjunctive treatment of peri-episodic seizures in these patients in addition to classical antiepileptic drugs [8]?

Overall, this interesting study requires a more detailed presentation of the phenotype of the included patients and the comparison with a cohort of adult MELAS patients to figure out if there is indeed a difference between these two age groups. Additionally, clarification of the inconsistencies as outlined above is needed.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Josef Finsterer, Krankenanstalt Rudolfstiftung, Postfach 20, 1180 Vienna, Austria, Europe. Tel: +43-1-71165-92085; Fax: +43-1-4781711; E-mail: fipaps@yahoo.de

References

[1] Zhang J, Guo J, Fang W, Jun Q, Shi K. Clinical features of MELAS and its relation with A3243G gene point mutation. Int J Clin Exp Pathol 2015; 8: 13411-5.

[2] Mayr JA, Moslemi AR, Förster H, Kamper A, Idriceanu C, Muss W, Huemer M, Oldfors A, Sperl W. A novel sporadic mutation G14739A of the mitochondrial tRNA (Glu) in a girl with exercise intolerance. Neuromuscul Disord 2006; 16: 874-7.

[3] McFarland R, Taylor RW, Turnbull DM. A neurological perspective on mitochondrial disease. Lancet Neurol 2010; 9: 829-40.

[4] Lin J, Zhao CB, Lu JH, Wang HJ, Zhu WH, Xi JY, Lu J, Luo SS, Ma D, Wang Y, Xiao BG, Lu CZ. Novel mutations m.3959G > A and m.3995A > G in mitochondrial gene MT-ND1 associated with MELAS. Mitochondrial DNA 2014; 25: 56-62.

[5] Hsu YR, Yogasundaram H, Parajuli N, Valtuille L, Sergi C, Oudit GY. MELAS syndrome and cardiomyopathy: linking mitochondrial function to heart failure pathogenesis. Heart Fail Rev 2015; 21: 103-16.

[6] Reato S, Spartà S, D’Este D. Intraventricular conduction disturbances and paroxysmal atrioventricular block in a young patient with MELAS. J Cardiovasc Med (Hagerstown) 2015; 16 Suppl 2: S100-3.

[7] Finsterer J. Genetic, pathogenetic, and phenotypic implications of the mitochondrial A3243G tRNALeu (UUR) mutation. Acta Neurol Scand 2007; 116: 1-14.

[8] Steriade C, Andrade DM, Faghfoury H, Tarnopolsky MA, Tai P. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) may respond to adjunctive ketogenic diet. Pediatr Neurol 2014; 50: 498-502.