East African Scholars Journal of Medical Sciences
Abbreviated Key Title: East African Scholars J Med Sci
ISSN 2617-4421 (Print) | ISSN 2617-7188 (Online) |
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

DOI: 10.36349/easms.2019.v02i03.010 Volume-2 | Issue-3 | March-2019 |

Letter To The Editor

Do Urine Heteroplasmy Rates Predict the Outcome of the m.3243A>G Mutation?

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Keywords: Mitochondrial DNA, genetics, heteroplasmy, encephalomyopathy, mitochondrial disorder.

In a recent study, Fayssoil *et al.*,. investigated the relation between serum/urine heteroplasmy rates and clinical manifestations at onset and major adverse events (MAE) during follow-up in a retrospective study of 43 patients carrying the m.3243A>G mutation (Fayssoil, A., *et al.*, 2017). MAE included stroke-like episodes (SLEs), status epilepticus, heart failure, renal failure, and intestinal pseudo-obstruction (Fayssoil, A., *et al.*, 2017). We want to add some comments and concerns.

Since MAEs of the m.3243A>G mutation also include acute psychosis and ventricular arrhythmias (Anglin, R. E. *et al.*, 2012; Limongelli, G. *et al.*, 2010), it would be interesting to know how many patients developed acute psychiatric abnormalities during follow-up, how many developed mood disorders, cognitive deterioration, or an anxiety disorder, and how many patients experienced palpitations, syncope, arrhythmias on long-term ECG, or sudden cardiac death.

The number of MAEs strongly depends on the follow-up duration. The probability to develop MAE increases with disease duration. We thus should be informed about the duration of follow-up in each patient and about the variability of follow-up durations. Possibly, patients with longer follow-up also developed more frequently MAE as compared to those with short follow-up.

MAE rates also depend on age at onset or diagnosis. Patients with early onset may remain stable for a long period of time (Bouchet, C. *et al.*, 2006). Nine patients had MAE (epilepsy, SLEs) already before inclusion (Fayssoil, A., *et al.*, 2017). Possibly, heteroplasmy rates in these 9 patients were higher as compared to those without MAEs prior to inclusion. Surprisingly, the authors mention that only six patients had a "personal history of MAE" (Fayssoil, A., *et al.*, 2017). This discrepancy needs to be solved.

The authors mention that 8 patients developed fatal MAE (Fayssoil, A., *et al.*, 2017). However, table 2 in Fayssoil's article lists 9 patients with a fatal MAE (Fayssoil, A., *et al.*, 2017). This discrepancy should be explained. Table 2 also shows that one patient died from acute encephalopathy (Fayssoil, A., *et al.*, 2017). Which is the cause of death in this condition?

Heteroplasmy rates not only vary between tissues but also between different time points (Uimonen, S. *et al.*, 2001). Thus, it would be interesting to know if heteroplasmy rates were determined only once or repeatedly. In case heteroplasmy rates were repeatedly determined, it should be reported if they increased or decreased, over which time they changed, and if there was a difference in the progression between blood and urine.

Though the authors stress that clinical severity depends on heteroplasmy rates it should be added that even patients with a 100% heteroplasmy rate may not be clinically severely affected. Thus, disease modifying factors need to be considered, even for the phenotypic expression of the m.3243A>G mutation.

Patients were recruited over a 15 year period (Fayssoil, A., *et al.*, 2017). It is important to mention if the same methods were used for determining

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Journal homepage:
http://www.easpublisher.com/easjms/

Article History
Received: 18.02.2019
Accepted: 27.02.2019
Published: 14.03.2019

heteroplasmy rates throughout this time. In case, different methods were applied, it should be specified to which degree change to a new method influenced the results.

Cardiac disease is frequent among m.3243A>G mutation carriers (Hollingsworth, K. G. *et al.,* 2012). Cardiac involvement may be subclinical, why all these patients require prospective screening for heart disease (Hollingsworth, K. G. *et al.,* 2012). It should be mentioned if all patients were cardiologically investigated and how many had subclinical cardiac involvement.

In the three patients who died from heart failure, the type of treatment these patients received should be specified. It should be also mentioned if only humoral therapy was applied or if patients also received an ICD, a CRT, an assist device, or if any patient underwent heart transplantation.

Overall, this interesting study could be more meaningful if patients would have been followed up for a longer period of time, to see if the number of MAE increased with the follow-up duration, if heteroplasmy rates would have been determined repeatedly, particularly when a MAE occurred, if patients would have been prospectively investigated for subclinical or mildly manifesting involvement of organs other than the ones studied, if therapy in each patients would have been detailed, and if all inconsistencies would have been clarified.

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