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Letter to the Editor

Cardiac and Muscle Involvement in YARS2 Carriers Is of Prognostic Relevance

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In a recent article, Riley *et al.*, reported about a study of 14 patients (8 females, 4 males), aged 3 months to 49 years, carrying a *YARS2* mutation (Riley, L. G. *et al.*, 2018). In addition to sideroblastic anemia, 6 patients had mitochondrial myopathy and 4 patient's cardiac involvement (Riley, L. G. *et al.*, 2018). Three patients had thrombocytopenia (patients P1, P6, P8a), and two patients had facial dysmorphism (patients P9a and P9b). Two of the 14 patients died during the observational period (Riley, L. G. *et al.*, 2018). Since cardiac involvement and myopathy and therapeutic interventions had been only poorly specified, even in the supplementary data, there is a need to discuss some points regarding the influence of cardiac and muscle involvement on the diagnosis, therapy, prognosis, and outcome of *YARS2* carriers, which not only concern the hematologst but also the neurologist. There are also some other inconsistencies which raised concerns.

YARS2 mutations may not only manifest as mitochondrial myopathy, lactic acidosis, and sideroblastic anemia syndrome, but also with poor weight gain, respiratory failure due to affection of the respiratory muscles necessitating ventilatory support, hypoglycaemia, and hypertrophic cardiomyopathy (Shahni, R. *et al.*, 2013).

Cardiac involvement was also documented in several patients of the present study, such as in patients P1, P2a, P5, and P8a (Riley, L. G. *et al.*, 2018). Cardiologic manifestations included sinus tachycardia and pericardial effusion in patient P1, an atrial septal defect in patient P2a, mild cardiomyopathy in patient P5, and "dependent" edema in patient P8a (Riley, L. G. *et al.*, 2018). It should be mentioned if these cardiac abnormalities were accidentally detected or if all 14 included patients were prospectively investigated for cardiac disease. It would be interesting to know the cause of sinus tachycardia and pericardial effusion in patient P1 (Riley, L. G. *et al.*, 2018). Was this due to heart failure, myocarditis, or the anemia? Did this patient also present with cardiomyopathy? Interestingly, both patients who deceased had cardiac involvement (Riley, L. G. *et al.*, 2018). Did these two patients die from cardiac complications? Frequent types of cardiomyopathy in patients with a mitochondrial disorder are left ventricular noncompaction (Finsterer, J. 2009) and histiocytoid cardiomyopathy (Finsterer, J. 2008). Which specific type of cardiomyopathy was diagnosed in patient P5? It should be also explained what the expression "dependent edema" in table 1 stands for. In a previous study on 17 patients with *YARS2* variants, 53% had hypertrophic cardiomyopathy (Sommerville, E. W. *et al.*, 2017). This it at variance from the present investigation and remains unexplained but it can be speculated that the 14 patients from the present investigation were not systematically referred to the cardiologist.

Patient 11 is described with "enhanced trabeculations" on echocardiography (Riley, L. G. *et al.*, 2018). Did this patient fulfil the Swiss or Vienna criteria for left ventricular noncompaction / hypertrabeculation (LVHT)? In case the patient had LVHT, diagnosing this type of cardiomyopathy is prognostically relevant since it is frequently associated

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with heart failure, ventricular arrhythmias, cardiac thromboembolism, and sudden cardiac death (Finsterer, J. *et al.,* 2017). LVHT occurs in normally sized left ventricles but also in association with hypertrophic cardiomyopathy or dilated cardiomyopathy. Patients with LVHT require close follow-up not to miss the point at which anticoagulation, heart failure therapy, or implantation of an implantable cardioverter defibrillator (ICD) is indicated.

Since the respiratory muscles may be affected by myopathy due to *YARS2* variants (Shahni, R. *et al.,* 2013), we should be informed if the 14 patients from table 1 were prospectively investigated with pulse oximetry, spirometry, or other lung function tests. Particularly the six patients who were reported as having mild to severe myopathy (patients P1, P3, P5, P7, P8a, and P11) should have been prospectively investigated for affection of the respiratory muscles. It is conceivable that sinustachycardia in patient P1 not only resulted from anemia or cardiac dysfunction but also from involvement of the diaphragm or other respiratory muscles. It is warranted to explain the discrepancy between the high prevalence of respiratory insufficiency in a previous (47%) study (Sommerville, E. W. *et al.,* 2017) compared to the present study. It should be also discussed if respiratory dysfunction could have been due to involvement of the brainstem and which the MRI findings of the brain were.

Spontaneous remission of anemia was described in patient 11 and patients P4, P5, and P9a became transiently transfusion independent (Riley, L. G. *et al.,* 2018). No explanation is provided for this unusual course. Did these patients receive antioxidants, vitamin supplementation, or administration of co-factors? A therapeutic option not discussed is the ketogenic diet, which induces the production of ketone bodies, and is particularly effective in mitochondrial epilepsy or in patients with MELAS syndrome (Sort, R. *et al.,* 2013). Meanwhile an increasing body of evidence indicates that a ketogenic diet may also exhibit beneficial effects on mitochondrial myopathy (Ahola-Erkkilä, S. *et al.,* 2010). Did any of the 14 patients receive a ketogenic diet, particularly those, who showed complete or partial remission of sideroblastic anemia?

According to table 1, four patients were Lebanese (Riley, L. G. *et al.,* 2018). However, "Lebanese" is no ethnicity. It should be specified if these patients were Caucasians, Africans, or Asians. Supplementary clinical data suggest that these four patients were Caucasians.

In summary, patients carrying *YARS2* mutations need to be prospectively investigated for multisystem involvement, particularly for cardiac disease, since it is of prognostic relevance. It is also warranted that *YARS2* carriers are monitored for pulmonary dysfunction. Since a ketogenic diet has been shown to exhibit beneficial effects to certain phenotypic features of mitochondrial disease, it should be tried in *YARS2* carriers as well, particularly those with involvement of the skeletal muscles.

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