Metabolic Brain Disease (2019) 34:1–2
https://doi.org/10.1007/s11011-018-0358-4

COMMENTARY

Silencing of *FOXRED1* in C57b1/6 mice does not generate an appropriate animal model of Leigh syndrome

Josef Finsterer[1]

Received: 8 November 2018 / Accepted: 25 November 2018 / Published online: 6 December 2018

Correspondence

With interest we read the article by Salama et al. who pretended to have developed a mouse model of Leigh syndrome by blocking the *FOXRED1* gene with small interfering RNAs (siRNA) using C57b1/6 mice (Salama et al. 2018). Neuropathological studies showed degeneration of the corpus striatum, similar to Leigh syndrome, why these animals were regarded as a putative animal model for Leigh syndrome (Salama et al. 2018). We have the following comments and concerns.

Pathognomonic for Leigh syndrome are bilaterally symmetric lesion of the basal ganglia, midbrain, brainstem, or cerebellum, which are usually hyperintens on T2-weighted images (Finsterer 2008). Thus, it would be interesting to know if C57b1/6 mice underwent imaging studies of the brain and if these typical subcortical lesions were also seen in the investigated animals.

Leigh syndrome in humans is frequently associated with epilepsy (Monden et al. 2013), which is often intractable or responds only to a ketogenic diet (Laugel et al. 2007). Thus, we should be informed how many of the 20 animals undergoing *FOXRED1* silencing developed clinical seizures during the further course or had electrical seizures or epilepsy-typical potentials on EEG. Epilepsy in Leigh syndrome significantly determines the outcome of these patients, why it is crucial that an animal model of Leigh syndrome phenotypically manifests with epilepsy.

Since some of the patients with Leigh syndrome may develop stroke-like episodes (SLEs) (Morin et al. 1999), a typical manifestation of MELAS syndrome, we should be informed if neuropathological investigations of the 20 animals showed features of a stroke-like lesion in any of them. The stroke-like lesion is the morphological equivalent of a SLE on imaging, characterised by a vasogenic edema not confined to vascular territory. Stroke-like lesions typically show dynamic increases and regressions over time.

Occasionally, extra-cerebral manifestations can be found in human Leigh syndrome (Finsterer 2008). These include polyneuropathy, myopathy, diabetes, short stature, cardiomyopathy, anemia, renal insufficiency, diarrhoea, or hypertrichosis (Finsterer 2008). Thus, we should know if any of the 20 animals undergoing *FOXRED1* silencing developed any of these extra-cerebral manifestations. Particularly affected organs in Leigh syndrome are the heart, the muscle the peripheral nerves, and the endocrine organs, why we should be informed if there were any indications for cardiomyopathy, arrhythmias, endocrine abnormalities, myopathy or neuropathy.

In summary, we do not agree with the conclusions that the data provided justify to regard C57b1/6 mice undergoing *FOXRED1* silencing as an animal model of Leigh syndrome. The value of an animal model is high if genotypic and phenotypic characteristics of the animal and human are closely similar.

✉ Josef Finsterer
fifigs1@yahoo.de

[1] Krankenanstalt Rudolfstiftung, Messerli Institute, Veterinary University of Vienna, Vienna, Austria

Author contribution JF: design, literature search, discussion, first draft.

Compliance with ethical standards

Conflict of interest There are no conflict of interest.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

Finsterer J (2008) Leigh and Leigh-like syndrome in children and adults. Pediatr Neurol 39:223–235

Laugel V, This-Bernd V, Cormier-Daire V, Speeg-Schatz C, de Saint-Martin A, Fischbach M (2007) Early-onset ophthalmoplegia in Leigh-like syndrome due to NDUFV1 mutations. Pediatr Neurol 36:54–57

Monden Y, Mori M, Kuwajima M, Goto T, Yamagata T, Momoi MY (2013) Late-onset Leigh syndrome with myoclonic epilepsy with ragged-red fibers. Brain and Development 35:582–585

Morin C, Dubé J, Robinson BH, Lacroix J, Michaud J, De Braekeleer M, Geoffroy G, Lortie A, Blanchette C, Lambert MA, Mitchell GA (1999) Stroke-like episodes in autosomal recessive cytochrome oxidase deficiency. Ann Neurol 45:389–392

Salama M, El-Desouky S, Alsayed A, El-Hussiny M, Moustafa A, Taalab Y, Mohamed W (2018) FOXRED1 silencing in mice: a possible animal model for Leigh syndrome. Metab Brain Dis. https://doi.org/10.1007/s11011-018-0334-z