eNeurologicalSci 18 (2020) 100214

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Letter to the Editor

Leigh Syndrome with atypical cerebellum imaging features

We appreciate the received letter and thank the opportunity to clarify the issues raised over our article “Leigh Syndrome with atypical cerebellar lesions” [1].

The cerebellar lesions were interpreted as microbleeds based on basic MR semiology [2]. Multiple foci of small, rounded, homogeneous, and markedly hypointense lesions on susceptibility-weighted magnetic resonance imaging, are extensively described in medical literature and regarded as microbleeds [2]. This correlation has been demonstrated by some radiologic-histopathologic studies [3,4], with demonstration of perivascular hemosiderin deposits [5].

Cerebral microbleeds present most commonly in the elderly population, being mostly related to hypertensive arteriopathy and cerebral amyloid angiopathy [2,6]. However, there are more potential causes, such as traumatic brain injury [7], posterior reversible encephalopathy syndrome (PRES) [8], cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [9], Moya-Moya [10], radiation-induced microbleeds [11]. In most of the previously stated causes for cerebral microbleeds, an underlying vasculopathy mechanism has been proved or formally proposed [2–7] [8–12].

In most of the patients, the diagnosis is presumptive, based on brain imaging semiology and other clinical findings, and not on brain biopsy [2,7].

As substantiated, there are several potential causes for microbleeds, many of them unrelated to vascular typical adult risk factors. Thus, stating the absence of the typical adult factors to refute the existence of microangiopathy is a misconception.

MELAS, MERRF, and LHON are mentioned as a proof of concept that mitochondrial diseases can present with cerebral microangiopathy, just like we propose for Leigh Syndrome [12]. The patient has a genetically proven Leigh Syndrome [1]; thus, there is no point in refuting symptoms related to other mitochondrial diseases that the index patient does not have.

The index patient is alive and has a genetically proven Leigh Syndrome [1]. A biopsy has no clinical purpose and would be unethical.

The figures reported by Muramatsu et al. [13] reinforce our recommendation of considering mitochondrial disease in the differential diagnosis of an acute cerebellar disease.

Ischemic stroke is not mentioned in the article. In fact, brain parenchymal restricted diffusion has been demonstrated in several different brain pathologies, distinctive of ischemic stroke [14]. Panels G and H from Fig. 1 show a pattern of restricted diffusion [1], which has been demonstrated in basal ganglia and thalami of Leigh Syndrome patients [15]. Perfusion imaging had no clinical indication.

As stated in the article, cytotoxic edema exists when there is a pattern of restricted diffusion, which is defined by ADC hypointensity. ADC is represented by a graphic reconstruction obtained by plotting the natural logarithm of the signal intensity versus two b values (b = 0 s/mm2 and b = 1000 s/mm2) [16] and is not a matter of the authors' opinion.

The patient did not present with stroke-like episode.

Our focus in this case report is the brain lesions since they probably underlie all the major clinical findings. On a formal neurologic examination, muscle weakness was not prominent and had not a proximal to distal gradient. The patient is thin, and the muscles are globally and moderately hypotonic, with retained reflexes. EMG was performed and demonstrated signs of mild denervation consistent with axonal neuropathy. In Leigh syndrome this finding is not very uncommon and is usually a subclinical problem [17,18]. Therefore, we used the term muscular hypotrophy, not atrophy.

We hope our answer was useful.

References

[1] M.G.A. da Veiga, C. Marecos, S.T. Duarte, J.P. Vieira, C. Conceição, Leigh syndrome with atypical cerebellar lesions, ENeurologicalSci. 16 (2019) 100197, https://doi.org/10.1016/j.ensci.2019.100197.

[2] S. Haller, M.W. Vernooij, J.P.A. Kuijer, E.M. Larsson, H.R. Jäger, F. Barkhof, Cerebral microbleeds: imaging and clinical significance, Radiology. 287 (2018) 11–28, https://doi.org/10.1148/radiol.2018170803.

[3] S. Haller, M.L. Montandon, F. Lazeyras, M. Scheffler, S. Meckel, F.R. Herrmann, P. Giannakopoulos, E. Kövari, Radiologic-histopathologic correlation of cerebral microbleeds using pre-mortem and post-mortem MRI, PLoS One 11 (2016) 1–11, https://doi.org/10.1371/journal.pone.0167743.

[4] M. Schrag, G. McAuley, J. Pomakian, A. Jiffry, S. Tung, C. Mueller, H.V. Vinters, E.M. Haacke, B. Holshouser, D. Kido, W.M. Kirsch, Correlation of hypointensities in susceptibility-weighted images to tissue histology in dementia patients with cerebral amyloid angiopathy: a postmortem MRI study, Acta Neuropathol. 119 (2010) 291–302, https://doi.org/10.1007/s00401-009-0615-z.

[5] A. Shoamanesh, C.S. Kwok, O. Benavente, Cerebral microbleeds: histopathological correlation of neuroimaging, Cerebrovasc. Dis. 32 (2011) 528–534, https://doi.org/10.1159/000331466.

[6] P.A. Yates, V.L. Villemagne, K.A. Ellis, P.M. Desmond, C.L. Masters, C.C. Rowe, Cerebral microbleeds: a review of clinical, genetic, and neuroimaging associations, Front. Neurol. (2014) 1–13, https://doi.org/10.3389/fneur.2013.00205 4 JAN.

[7] T. Imaizumi, K. Miyata, S. Inamura, I. Kohama, K. Sang Nyon, T. Nomura, The difference in location between traumatic cerebral microbleeds and microangiopathic microbleeds associated with stroke, J. Neuroimaging 21 (2011) 359–364, https://doi.org/10.1111/j.1552-6569.2011.00593.x.

[8] A.M. McKinney, B. Sarikaya, C. Gustafson, C.L. Truwit, Detection of microhemorrhage in posterior reversible encephalopathy syndrome using susceptibility-weighted imaging, Am. J. Neuroradiol. 33 (2012) 896–903, https://doi.org/10.3174/ajnr.A2886.

[9] A. Viswanathan, J.P. Guichard, A. Gschwendtner, F. Buffon, R. Cumurcuic, C. Boutron, E. Vicaut, M. Holtmannspötter, C. Pachai, M.G. Bousser, M. Dichgans, H. Chabriat, Blood pressure and haemoglobin A1c are associated with microhaemorrhage in CADASIL: a two-centre cohort study, Brain. 129 (2006) 2375–2383, https://doi.org/10.1093/brain/awl177.

[10] K. Kazumata, D. Shinbo, M. Ito, H. Shichinohe, S. Kuroda, N. Nakayama, K. Houkin, Spatial relationship between cerebral microbleeds, moyamoya vessels, and hematoma in moyamoya disease, J. Stroke Cerebrovasc. Dis. 23 (2014) 1421–1428, https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.12.007.

[11] J. Passos, H. Nzwalo, M. Valente, J. Marques, A. Azevedo, E. Netto, A. Mota, A. Borges, S. Nunes, D. Salgado, Microbleeds and cavernomas after radiotherapy for paediatric primary brain tumours, J. Neurol. Sci. 372 (2017) 413–416, https://doi.org/10.1016/j.jns.2016.11.005.

[12] J. Finsterer, S. Zarrouk-Mahjoub, Mitochondrial vasculopathy, World J. Cardiol. 8 (2016) 333, https://doi.org/10.4330/wjc.v8.i5.333.

[13] D. Muramatsu, H. Yamaguchi, K. Iwasa, M. Yamada, Cerebellar hyperintensity

https://doi.org/10.1016/j.ensci.2019.100214
Received 29 September 2019; Accepted 18 November 2019
Available online 23 November 2019

lesions on diffusion-weighted MRI in MELAS, Intern. Med. 58 (2019) 1797–1798, https://doi.org/10.2169/internalmedicine.2190-18.
[14] O. Carney, A. Falzon, A.D. MacKinnon, Diffusion-weighted MRI in paediatric neuroimaging, Clin. Radiol. 73 (2018) 999–1013, https://doi.org/10.1016/j.crad.2018.07.101.
[15] M.H. Atalar, H. Egilmez, S. Bulut, D. Icagasioglu, Magnetic resonance spectroscopy and diffusion-weighted imaging findings in a child with Leigh's disease, Pediatr. Int. 47 (2005) 601–603, https://doi.org/10.1111/j.1442-200x.2005.02112.x.
[16] P.W. Schaefer, P.E. Grant, R.G. Gonzalez, Diffusion MRbrain state of the art, Radiology. 217 (2000) 331–345, https://doi.org/10.1148/radiology.217.2.r00nv24331.
[17] Y.S. Ng, M.H. Martikainen, G.S. Gorman, A. Blain, E. Bugiardini, A. Bunting, A.M. Schaefer, C.L. Alston, E.L. Blakely, S. Sharma, I. Hughes, A. Lim, C. de Goede, M. McEntagart, S. Spinty, I. Horrocks, M. Roberts, C.E. Woodward, P.F. Chinnery, R. Horvath, V. Nesbitt, C. Fratter, J. Poulton, M.G. Hanna, R.D.S. Pitceathly, R.W. Taylor, D.M. Turnbull, R. McFarland, Pathogenic variants in MT-ATP6 : a United Kingdom–based mitochondrial disease cohort study, Ann. Neurol. 86 (2019) 310–315, https://doi.org/10.1002/ana.25525.
[18] M.P. Menezes, R.A. Ouvrier, Peripheral neuropathy associated with mitochondrial disease in children, Dev. Med. Child Neurol. 54 (2012) 407–414, https://doi.org/10.1111/j.1469-8749.2012.04271.x.

Marcos Gil Alberto da Veiga[a,*], Clara Marecos[b,c], José Pedro Vieira[b], Carla Conceição[a]
[a] *Department of Neuroradiology, Centro Hospitalar de Lisboa Central, 1150–199 Lisboa, Portugal*
[b] *Department of Neuropediatrics, Hospital Dona Estefânia – Centro Hospitalar de Lisboa Central, 1169–045 Lisboa, Portugal*
[c] *Department of Pediatrics, Hospital Professor Doutor Fernando Fonseca, EPE, IC19, 2720–276 Amadora, Portugal*
E-mail address: marcos.gil.d.veiga@gmail.com (M.G.A. da Veiga).

[*] Corresponding author at: Centro Hospitalar de Lisboa Central, Department of Neuroradiology, R. José António Serrano, 1150–199 Lisboa, Portugal.