Sir,

We thank Drs Bocca Vieira de Rezende Pinto and Sgobbi de Souza for their interest in our recent overview paper on a cohort of patients with leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), caused by DARS2 mutations (Van Berge et al., 2014). Their letter provides us with the opportunity to make specific points clearer.

The authors give a summary of the information published to date and pay special attention to exceptional cases, such as described by Miyake et al. (2011) and Synofzik et al. (2011). Additionally, they comment that magnetic resonance spectroscopy does not invariably reveal elevated lactate in patients with LBSL. They therefore suggest replacing the name LBSL by ‘DARS2-related conditions’ or ‘DARS2-related spectrum disorders’.

We agree that the use of an acronym as the name for a disease may suggest that all patients fulfil all letters of the acronym at all stages of the disease. What is more, we cannot exclude the possibility that patients with a different neurological or even non-neurological phenotype may have DARS2 mutations, which is not known because DARS2 has not been analysed in such patients. However, there is at present no positive evidence for the existence of an entirely different phenotype caused by DARS2 mutations and there is, therefore, at present no information that would justify the name ‘DARS2-related conditions’. On the contrary, LBSL is a rather homogeneous disease with limited variation in symptomatology. All or virtually all known patients fulfil the ‘L’ for leukoencephalopathy, the ‘B’ for brainstem abnormalities and the ‘S’ for spinal cord abnormalities (Van Berge et al., 2014). That not all patients had elevated lactate in magnetic resonance spectroscopy was known from the time that the name LBSL was coined (Van der Knaap et al., 2003). The information that has become available after the first publication (Van der Knaap et al., 2003) mainly concerns the severe variants (Miyake et al., 2011; Steenweg et al., 2012). Strikingly, especially the unusually severe cases fulfil all letters of the acronym.

For some disorders the addition of ‘spectrum’ is preferred to indicate that the clinical, MRI and histopathological variation is much wider than initially indicated, and that the original name does not cover all variants. This is, for instance, the case in ‘Zellweger syndrome’, a name associated with a severe, infantile onset, multi-organ disease (Zellweger et al., 1988). The name ‘Zellweger spectrum disorders’ was introduced to include all disorders caused by mutations in the same genes, and covers a much wider phenotypic range, in which numerous patients lack many of the abnormalities observed in the infantile variant (Poll-The and Gärtner, 2012). The variability in phenotypes related to DARS2 mutations, as far as currently known (Van Berge et al., 2014), is in our opinion insufficient to speak of ‘DARS2-related spectrum disorders’.

Changing a name of a disease also comes with negative effects. To date, only the acronym LBSL has been used. All papers on the subject can easily be found by using this acronym. The name is informative and refers to generally shared features. Weighing the pros and cons, we conclude that there is, at present, in our opinion, insufficient reason to change the name LBSL.

We would like to indicate that cantharidin is not an ‘antisense oligonucleotide’, as suggested by Bocca Vieira de Rezende Pinto and Sgobbi de Souza, but a compound that influences splicing. In our paper, we describe the influence of cantharidin on the splicing defect of the DARS2 gene in cellular assays (Van Berge et al., 2014). Cantharidin is, however, too toxic for application in humans. We propose that less toxic compounds with the same effects should be searched for, such as some of the pseudo-cantharidins described by Zhang et al. (2011). For alternative
treatment options, Drs Bocca Vieira de Rezende Pinto and Sgobbi de Souza refer to the paper of Synofzik et al. (2011), in which a single patient with exercise-induced paroxysmal gait ataxia was described with the typical MRI of LBSL and a homozygous DARS2 mutation. This patient showed an excellent dose-dependent, sustained positive response to a carbonic anhydrase inhibitor. In view of this, Bocca Vieira de Rezende Pinto and Sgobbi de Souza propose to investigate treatment of LBSL patients with acetazolamide or another carbonic anhydrase inhibitor first. Although this is an interesting option, we would like to comment that even though we know the largest cohort of LBSL patients worldwide, we have not come across another LBSL patient with exercise-induced paroxysmal ataxia. It is important to note that Synofzik et al. (2011) have not proven that the exercise-induced paroxysmal ataxia is part of the LBSL phenotype. We therefore prefer an approach directed at what is known about the basic defect.

References


