Letter

Considering the myelin-centric hypothesis: insights from Budka's historical adrenomyeloneuropathy case report

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We are writing in light of Dr. Budka's recent flashback paper on his seminal article on adrenomyeloneuropathy (AMN) [1]. Our letter aims to underscore a critical aspect that we believe Dr. Budka himself may have overlooked when revisiting his work after nearly fifty years: the likely myelin-centric nature of AMN in its early stages.

The original study by Dr. Budka et al. [2] contributed significantly to our understanding of AMN. In his flashback paper Dr. Budka provided virtual microscopy of original histological slides and discussed the historical context. Yet, there seems to be an under-appreciation of one of his most striking findings: the occurrence of demyelination independent of axonal degeneration in an early-stage case of AMN. In the original study [2], Dr. Budka et al. conducted a pathological examination on an AMN patient who exhibited the shortest duration of neurological symptoms prior to death, at the young age of 24, succumbing to acute adrenal failure only two years after the onset of neurological symptoms. This case stands in clear contrast to the average neurological history of 11.8 years (range 2-21) and the average age at death of 38.1 years (range 24-52) among the ten reported autopsied AMN males [3]. Remarkably, the index patient presented with a pattern of incomplete, symmetrical demyelination predominantly in the pyramidal tracts from the cerebral peduncles to the lumbar cord, with a pronounced involvement in the medulla oblongata's pyramids. Similar, demyelination was also noted in the medial and lateral lemnisci, brachium conjunctivum, spinocerebellar tracts, and the medial portion of the posterior columns, although less extensive than in the pyramidal tracts. Notably, the integrity of axons within these regions was maintained [2]. The pathological changes observed in the study are visually documented in Figure 2A of the original paper [2], and correspondingly in Figure 5 of the flashback paper [1].

In our opinion, this observation is not just a mere detail but a pivotal insight, suggesting that demyelination can precede and possibly initiate axonal degeneration, an aspect corroborated in humans by the work of Castellano et al., who used *in vivo* quantitative MRI techniques that align with the hypothesis of a primarily myelopathic process [4]. Furthermore, in the human brain, the AMN-causing protein ABCD1 appears to be predominantly expressed in glial cells, namely oligodendrocytes, microglia, and

astrocytes, as well as in endothelial cells, but not in most neurons [5]. Additionally, the expression of human ABCD1 in the oligodendrocytes of a zebrafish model of adrenoleukodystrophy (ALD) has been shown to be sufficient to rescue mutant phenotypes, providing additional support for this hypothesis[6].

This aspect is critical, as it shifts our understanding of AMN pathogenesis toward a focus on myelin pathology, particularly in the initial phases of the disease. The common co-occurrence of myelin pathology and axonal degeneration in more advanced cases and the data from *abcd1*-deficient mice may have blurred this perspective, leading to ambiguity regarding the primary pathological event [3,7].

To clarify this issue, we would highly encourage the study of a conditional knockout mouse model with the *abcd1* gene selectively inactivated in glial cells such as oligodendrocytes or astrocytes. This approach would provide definitive evidence on whether primary damage to glial cells leads to the axonal degeneration seen in *abcd1*-deficient mice [7], thereby reinforcing the hypothesis of a myelin-centric nature of early-stage AMN. This hypothesis, strongly suggested by Dr. Budka et al.'s study, is noteworthy. It further acknowledges the original contribution of their work and should guide future research towards a more targeted understanding of AMN pathology.

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