Administrative note: The provided document contains a letter to the editor discussing the absence of beta-amyloid deposition in the central nervous system of a transgenic mouse model of distal myopathy with rimmed vacuoles.

**Absence of beta-amyloid deposition in the central nervous system of a transgenic mouse model of distal myopathy with rimmed vacuoles**

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Distal myopathy with rimmed vacuoles (DMRV) is an autosomal recessive disorder characterised by early adult-onset (15–40 years), slowly progressive myopathy with preferential weakness of the tibialis anterior and sparing of the quadriceps femoris muscles [1]. The muscle biopsy shows rimmed vacuoles containing deposits immunoreactive for β-amyloid (Aβ) and other proteins. DMRV is due to mutations in the GNE gene, which encodes a bifunctional enzyme (uridine diphosphate-N-acetylmuramaldehyde 2-epimerase/N-acetylmannosamine kinase) in the sialic acid synthetic pathway. A recently developed mouse model of DMRV that expresses the human GNE D176V mutation in a Gne knockout background reproduces the clinical, pathological and biochemical features of human DMRV [2].

In the 30 aged DMRV mice examined there was no evidence of Aβ deposits in the brains or spinal cords (Figure 1B). However, Aβ deposits were detected in the skeletal muscles of all these animals. The deposits were usually linear, beaded and found in the central part of the fibres (Figure 1C, D). Occasionally, these deposits were associated with vacuoles found in the central part of the fibres (Figure 1C, D).

Brain and skeletal muscle tissue sections from 30 DMRV mice older than 40 weeks were harvested, formalin-fixed, processed and paraffin embedded. Sixteen spinal cords were also available for examination. Tissues sections were stained by hematoxylin and eosin for light microscopy. Immunohistochemistry (IHC) to detect Aβ was performed using a mouse monoclonal primary antibody (clone 6E/10; Covance, Princeton, NJ) and the Envision method with minor modifications [3]. As a positive IHC control, we used tissues from an established mouse model of AD, the Tg2576 transgenic mouse (Taconic, Germantown, NY) that expresses the Swedish mutation of amyloid precursor protein. Brain tissue sections from a human case of AD were also included as a positive control. For negative controls, sections were incubated with normal goat serum to replace the primary antibody.

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Although the aged DMRV mouse model demonstrated convincing Aβ deposition in skeletal muscles, there was no Aβ deposition in the CNS. This suggests that amyloidogenesis in AD and DMRV may be different. Amyloidogenesis in AD is mainly associated with post-translational proteolytic processing of amyloid precursor protein by α-, β- and γ-secretases. However, hyposialylation is an important factor in the pathogenesis of the disease and amyloidogenesis in DMRV. Hyposialylation of several important muscle glycoproteins...
such as neprilysin, a membrane proteinase involved with the normal breakdown of Aβ has been observed [4,5]. In DMRV, reduced muscle neprilysin activity may cause toxic Aβ accumulation in vulnerable fibres and a failure in repair or regeneration of muscle fibres possibly through modulation of the insulin-like growth factor I-dependent pathways [5]. In addition, it was demonstrated that reduced neprilysin activity in the DMRV mice was restored after treatment with sialic acid analogues [6]. Interestingly, the DMRV mouse brain showed normal sialylation levels [2,7], although the other organs showed hyposialylation. This is attributed to a strong sialic acid uptake mechanism in neuronal cells. It was suggested that sialin, a lysosomal sialic acid transporter protein, is involved in the uptake of exogenous sialic acid to maintain normal cellular sialylation in the brain [8]. This may be the reason there is no abnormal Aβ deposition in the DMRV mouse brain. This is also supported by the finding that sialic acid levels in the cerebrospinal fluid of the DMRV mice remain unaltered (Malicdan and Noguchi, unpublished data). In the DMRV mouse brain, normal levels of sialic acid could actually mitigate Aβ toxicity, if Aβ levels were to increase [6]. The level of sialic acid in brains of human DMRV is unknown and further investigations are needed. If there is no hyposialylation in the brains of DMRV patients, Aβ deposition may not occur. Nonetheless, based on current findings, we speculate that brain Aβ deposition is unlikely to be increased in human DMRV and hence, an increased incidence of AD in these patients is also probably unlikely.

**Declaration of interest**

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**References**