



Figure e-1: The patient's right frontal lobe biopsy showed markedly abnormal white matter containing axonal spheroids (A, arrows, H&E, 400x; B, arrows, H&E, 1000x) that were highlighted by Bielschowsky stain (C, arrows, 400x) and SMI-31 immunostain (D, arrows, 400x). There was patchy myelin loss (E, LFB/PAS, 40x), and these regions contained macrophages with phagocytosed myelin debris (F, arrow, LFB/PAS, 1000x). Reactive gliosis was present (G, GFAP, 400x). There was an admixed inflammatory cell infiltrate composed predominantly of macrophages (H, CD68, 400x) and only scattered T cells (I, CD3, 400x) and rare B cells (J, CD20, 400x).

The overall findings raised the possibility of adult-onset leukoencephalopathy with axonal spheroids. However, a toxic injury preferentially involving the white matter could not be entirely excluded. Ischemic injury was not favored due to the relative preservation of axons in areas of myelin loss, absence of frank necrosis, and sparing of the gray matter. Arguing against MS or ADEM were the lack of prominent lymphoid inflammation, presence of axonal spheroids, and pattern of myelin damage (i.e. not sharply circumscribed or perivenular). In addition, an infectious process (i.e. viral) was considered unlikely given the absence of involvement of the gray matter and the relative paucity of lymphoid cells. Finally, there was no evidence of vasculitis or granulomatous inflammation.