

**Supplementary table 1: Initial (round 1) investigations (on-line supplement)**

Investigation	Comments
<i>Blood</i>	
<b>FBC/ ESR/ Vitamin B12/ folate/ total homocysteine/ methylmalonic acid/ electrolytes/ liver function tests/ thyroid function/ lipids</b>	Total homocysteine and methylmalonic acid levels are a better functional indicator of B12 deficiency than B12 levels alone.
<b>Syphilis serology/ HIV/ Hepatitis B and C serology</b>	
<b>ANA/ ENA/ ANCA/ Double stranded DNA/ Lupus anticoagulant, anti-cardiolipin antibodies/ complement/ immunoglobulins- electrophoresis/ serum ACE/ anti-neuronal antibodies</b>	Neuro-inflammatory syndromes to be considered include neurosarcoidosis, neurolupus and paraneoplastic conditions.
<b>Vitamin E/ Copper, Caeruloplasmin/ lactate/ ammonia/ carbon monoxide</b>	
<i>CSF</i>	
<b>CSF: Protein, MC and S, glucose, oligoclonal bands (with matched serum), tau and A<math>\beta</math></b>	A raised tau level, and decreased A $\beta$ -42 level are seen in Alzheimer's disease, giving an increased ratio of tau to A $\beta$ -42 (lab dependent but typically >1)
<i>Imaging and other investigations</i>	
<b>MRI: standard MRI brain/ cervical spine plus Gadolinium; T2* can identify microhaemorrhages</b>	Classify the pattern of white matter change (see table 4)
<b>FDG-PET</b>	To exclude underlying inflammatory conditions (eg. sarcoidosis) and malignancy
<b>Nerve conduction studies</b>	
<b>Visual evoked potentials</b>	

**Supplementary Figure 1: (on-line supplement)**

Magnetic Resonance Imaging (MRI) of a middle-aged patient with a two-year history of gait and cognitive difficulties. Axial T2-weighted (a & b) and coronal T1-weighted acquisitions demonstrate fairly symmetrical and predominantly frontal periventricular and deep white matter T2-weighted signal hyperintensity and volume loss, particularly of the corpus callosum. Note the ex-vacuo dilatation of the lateral ventricles secondary to the atrophy.

**Supplementary Figure 2: (on-line supplement)**

Suggested algorithm for the evaluation of an adult with a suspected leukodystrophy

