Online Resource 2 Case histories

**Patient 1** was the first known affected family member who was born in 1906 and had a 2 year history of progressive paralysis with dysarthria, dysphagia and parkinsonian features. She died aged 45. Her death certificate lists bulbar paralysis and progressive muscular atrophy.

**Patient 2** presented at the age of 40 with 9 year history of progressive immobility, dysarthria and falls. Later in the disease course she developed signs of poor self care and cognitive decline. She had facial immobility, rigidity of all four limbs, intermittent tremor, bradykinesia and normal reflexes. She died aged 43.

**Patient 3** presented at the age of 52 with a three month history of poor insight, cognitive impairment, emotional lability, dysarthria and clumsiness. Over the following 18 months she developed dysphagia, anarthria and progressive quadraparesis. On examination she had a severe pseudobulbar palsy, tongue fasciculations, a supranuclear gaze palsy, bilateral facial weakness and emotional disinhibition. Mixed upper and lower motor neuron signs were seen in all four limbs with extensor plantars. She died aged 53.

**Patient 4** died at the age of 43 following a one year history of asymmetrical weakness initially involving lower limbs and then upper limbs. There was no memory impairment at presentation although later in the disease she developed some mild emotional lability and personality change. She had bilateral facial weakness with predominantly distal weakness and muscle wasting in all four limbs. As her disease progressed she developed proximal muscle fasciculations and hyporeflexia in all four limbs. She had preserved bulbar function, sensation and cognition. EMG examination showed evidence of chronic partial denervation in upper and lower limbs with widespread fibrillations throughout. Her CK was normal as was her CSF other than a mildly elevated protein. She had diffuse cerebral atrophy on a CT scan and non-specific minor EEG abnormalities.

**Patient 5** became slower and more withdrawn from the age of 38. This was initially thought to be due to depression. However, by the age of 42 she was showing signs of Parkinsonism with hypomimia, bradykinesia and asymmetrically reduced arm swing. She had no insight into her difficulties. She remained orientated with intact memory. Her condition progressed over the next 3 years with increasing paucity of speech, immobility and falls. She became withdrawn and unable to look after herself or her affairs. In the last year of her life she developed dysarthria, dysphagia, urinary incontinence and marked cognitive decline with prominent loss of executive function. At this late stage of the disease she developed mild muscle weakness, wasting and hyporeflexia in all four limbs with increased tone and extensor plantar responses. She died aged 46.
Patient 6 presented aged 46 with a 2 year history of progressive asymmetrical weakness and spreading from her upper limbs to her lower limbs. At presentation she had been wheelchair bound for 3 months and had more recently developed dysarthria, dysphagia and personality change. Her MMSE was 25. She had hypermetric saccades, pseudobulbar palsy, spastic tetraparesis, hypereflexia, wasting of the intrinsic hand muscles, extensor plantars and no sensory abnormalities. Neuropsychological assessment found emotional lability, executive dysfunction and poor concentration but relatively preserved memory. Attention, visuospatial and constructional skills were particularly severely impaired. Neuropsychological assessment in was performed using a standardised tests where she scored as follows. RBANS: Immediate memory - 7th percentile, Visuospatial/Constructional Skills low – 1st percentile, Language – 21st percentile, Attention 0.2nd percentile, Delayed memory – 30th. There was also severe impairment on tests of executive function: Stroop Colour Word Task, Letter and Category Fluency, Delis Kaplin Over the next year she developed dystonic limb posturing, head drop, dysphagia and anarthria. Her CSF was unremarkable. An MRI of her brain and cervical spine showed diffuse cerebral and cerebellar atrophy. Electrophysiologically she had decreased compound muscle action potentials, fibrillation potentials and other signs of denervation. She died 15 months after presentation at the age of 47.

Patient 7 at the age of 45 was admitted to a psychiatric hospital with agitation, low mood, poor appetite and delusions that her food was being poisoned. She was treated with antidepressants and antipsychotics. Within a few weeks she was noted to be more withdrawn with fine tremor, bradykinesia and hypomimia. She was treated with a course of electro-convulsive therapy with minimal benefit. Within two months she had features of cognitive decline and progressive ataxia. She was then walking unaided but had an MMSE of 11/30, broken saccades, cerebellar signs, mild spastic quadraparesis, normal reflexes and flexor plantars. Neuropsychological assessment demonstrated severely impaired visuospatial and constructional skills with perseveration such that she was unable to complete a six piece puzzle or draw a simple human figure. CSF examination was normal. An EEG showed an increase in both fast and slow wave activity and her CT head revealed generalised cerebral atrophy. She subsequently declined rapidly over a four month period, developed myoclonic jerks and died at the age of 45.
Patient 8 presented with a one year history of increasing difficulties managing her affairs and a three month history of cognitive decline, impaired manual dexterity and slowness of speech and gait. She had asymmetrical limb rigidity, weakness and bradykinesia as well as pathologically brisk reflexes in all four limbs, dysarthria, hypomimia, personality change and impaired verbal fluency. Eight months after presentation she entered institutional care showing impulsive and compulsive tendencies and has also developed psychotic delusions and auditory hallucinations. On neuropsychological assessment using a battery of standardised tests she was markedly impaired on tests of executive function and also visuo-constructional skills. Specifically when assessing visuospatial function she was unable to draw a clock face and scored extremely low on the ‘WASI Block Design’ test. Her function on verbal and visual memory tests was also impaired (10th to 25th centile) but this was felt to be, at least in part, a reflection of her executive difficulties. Visuo-perceptual and language skills were relatively preserved. Nerve conduction studies and EMG were normal. Her MRI brain scan revealed frontotemporal atrophy (Figure 2). Two years into the disease course she developed increasing wasting of the small muscles of the hand with brisk reflexes followed by a progressive pseudobulbar palsy with dysarthria and dysphagia.

Patient 9 presented at the age of 40 with 2 months of dysarthria and left hand weakness. She had pseudobulbar palsy, bilateral lower motor neurone facial weakness and an asymmetrical spastic quadraparesis. There were no cerebellar signs, sensory abnormalities or parkinsonian features. Her MMSE was 30/30, with only mildly impaired verbal fluency. Over the next six months her quadraparesis progressed and she became anarthric. She developed dysphagia requiring PEG feeding, intrinsic hand muscle wasting and respiratory muscle weakness leading to her death at the age of 41.