Supplementary material

Case 1 (UK1)

In retrospect, this woman first had difficulty picking up small objects in summer 1999 at age 41. Towards Christmas she had begun to have difficulty changing gear and moving her left arm. People noted difficulty catching and fixing her gaze, and her general practitioner had noted that she could not follow his finger with her eyes. Her speech became slurred. In February 2000 she began to experience abrupt loss of balance, with a tendency to fall backwards, and started to fall. She then progressively slowed down generally, and developed periods of inappropriate laughter.

When first seen at the National Hospital for Neurology and Neurosurgery in July 2000, she was in a wheelchair. Swallowing was slightly affected with occasional choking spells. During the interview she complained that her right hand was slowing down and mentioned that her left arm, and now her right, had become “alien”. Her memory was said to be intact, but her family had noted that she got yes mixed up with no, and that she tended to repeat both syllables and whole words or phrases at times. She had become sensitive to noise, and had also developed urinary frequency and urgency.

In her past medical history she had pulmonary sarcoidosis treated with prednisolone in 1986 for three months, but had been symptom free for more than 10 years. She had a history of depression but denied being currently depressed. She also had a history of frequent headaches for which she had been taking up to eight compound tablets of paracetamol 500mg plus
dihydrocodeine 10 mg per day. Previous investigations had revealed only a slightly elevated ANA with a nucleolar pattern in a titre of 1:40.

There was no family history of dementia, parkinsonism or any neurodegenerative disease.

On examination she was unable to initiate voluntary saccades, despite using head thrusts. The only saccadic eye movement witnessed was when she spontaneously looked to the right, with normal saccadic velocity. Smooth pursuit eye movements and Doll’s head movements were normal. She had inhibition of eyelid opening and closing. Her speech was slurred, her jaw jerk increased, and a pout reflex was present. Her left arm and hand were flexed, and she had great difficulty moving them voluntarily. She had a grasp reflex and groping on the right. Tone was increased, left more than right, with the characteristics of gegenhalten. Her movements were slow and clumsy. There was apraxia of the right, less affected, hand, but her left hand was too severely affected to test for apraxia. Her reflexes were very brisk, more on the left and both plantar responses were extensor. She walked with an akinetic-rigid gait with a left hemiplegic element.

When admitted to hospital one month later, all serum, urine and CSF examinations were either negative or normal including CSF 14-3-3 and S-100 proteins and Whipple’s disease PCR. Jejunal biopsy, chest X-ray and serum ACE were normal. Brain MRI revealed some generalized atrophy, more pronounced on the right side, particularly in the frontotemporal region. EEG showed a normal background rhythm with a very mild excess of theta seen.
over the temporal regions, right greater than left - no periodic complexes were seen. Nerve conduction studies (NCS), electromyography (EMG), visual evoked potentials (VEPs), brainstem auditory evoked potentials (AEPs) and somatosensory evoked potentials (SSEP) were normal. No giant potentials were seen. A gallium scan showed increased uptake of the tracer in the lacrimal glands bilaterally, in keeping with some degree of ongoing active sarcoidosis but no evidence of pulmonary or hilar involvement. A whole body 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan demonstrated no significant abnormal focus of uptake from neck down to proximal thighs. 3D FDG PET of the brain during the same study showed marked reduction of metabolic rates in the entire right frontal cortex affecting mainly the dorso-lateral region and the cingulate cortex; both temporal lobes, particularly the anterior pole and medial cortex of the right temporal pole; both basal ganglia, mainly the right, which showed almost absent FDG uptake; and reduced uptake in right thalamus.

Neuropsychological examination revealed a low verbal IQ of 67 and low performance IQ of 61 on the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981). Non-verbal abstract reasoning as tested by the coloured Progressive Matrices (Raven, 1965) was extremely poor (13/36). Memory function was also severely impaired. On short recognition memory testing (Warrington, 1996) verbal and visual memory were affected (Words 19/25, Faces 12/25). Her performance on an easy visual recognition memory test was at the 1st percentile (pictorial recognition memory test, 26/30) (Warrington,
Word retrieval skills were good as tested by the Oldfield Picture Naming test (25/30) (Oldfield & Wingfield, 1965), and visual perceptual functions were adequate as tested on the Incomplete Letters Test of visual perception (19/20), but space perceptual skills were weak as tested by counting random arrays of dots (5/10) (Warrington & James, 1991).

During her hospitalisation she was treated with levodopa 750 mg/day plus peripheral decarboxylase inhibitor without benefit. Her diagnosis was felt to be “CBD look alike”, but unlikely to be CBD due to the rapid progression of her illness and the severe early supranuclear gaze palsy.

A follow up report from the referring neurologist in May 2001 described continued progression. She was unable to walk and now had little useful function of her right side. Her speech was declining and swallowing had become a problem. A final report in August of 2001 described her as mute, and totally immobile, with severely impaired swallowing, and she died in November 2001, less than 2½ years after her first symptom. A brain only autopsy was performed.

Case 2 (US1)

This 51-year-old right-handed woman, was referred to the Mayo Clinic in 1995 because of memory decline and headaches over the prior year. Her husband accompanied her during the interview.

She had begun to experience mild cognitive difficulties at the age of 50 years in the spring of 1994, and had recently lost her job as a dental clerk
because she was unable to adapt to changes that were occurring in the office including computerization. She was having trouble preparing meals and made mistakes in cooking because of lack of organization. Her personal hygiene had also declined and she would wear the same clothes repeatedly. She had difficulty making decisions. Her husband reported difficulties in playing cards, reduced social interactions and persistent TV viewing. She had become more dependent upon him and felt uncomfortable whenever he left her alone. In addition, she had developed obsessive compulsive-type behaviours, and would not step on cracks in floors and pavements.

She also complained of severe daily headaches of throbbing quality that began in the early mornings and would last throughout the day and were sometimes associated with nausea and vomiting.

She had a past medical history of haemochromatosis.

There was no family history of early onset dementia, parkinsonism or any neurodegenerative disease. Two maternal aunts had been diagnosed with depression. Her mother, three siblings and her two children are alive and well. Her father died at age 52 from lung and liver carcinoma.

On examination the patient scored only 24/38 on the short test of mental status (Kokmen et al., 1987), but neurological examination was otherwise unremarkable.

All serum, urine and CSF examinations were either negative or normal including CSF PCR for Whipples. A brain MRI revealed moderate frontal and temporal lobe atrophy. A HMPAO single photon emission computer
tomography (SPECT) scan showed mild decreased perfusion in the frontal lobes and possibly the anterior aspects of the temporal lobes.

Neuropsychological examination revealed a verbal IQ of 77 and performance IQ of 67 on the WAIS-R. Academic abilities (reading and arithmetic) were poor as tested by the WRAT-3 (reading 25%; arithmetic 2%) (Jastak & Wilkinson, 1984). Her attention and concentration was very poor. She had marked difficulty with the colour/word portion of the Stroop test (Jensen & Rohwer, 1966) and she was confused by the instructions for part B of the Trail Making Test (Stuss et al., 1987). Perseveration was extreme. Perceptual/spatial task status was adequate. There was mild overlap and poor attention to detail as tested by the Bender (Bender, 1946). Screening language test showed moderate compromise of language comprehension. She only named (14/50) items on the Boston Naming Test (Kaplan et al., 1983) and her letter fluency (4 words in 1 minute) and category fluency for animals, fruits and vegetables (total 13 words in 1 minute) on the phonemic/letter (i.e., FAS) and category fluency tests (Benton & Hamsher, 1989; Spreen & Strauss, 1991; Fuld, 1980). Her immediate or short-term memory was severely impaired for both verbal and nonverbal material as tested by the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987).

These findings were compatible with FTD. However, the rapidity of the progression was felt to be atypical. Her headaches were felt to be common migraines.
Over the subsequent year she continued to decline rapidly. On re-evaluation she had developed a soft voice and reduced facial expression. She exhibited echolalia and tended to wander around the house, leaving it at times. If left unsupervised she would eat sweets constantly. She continued to feed herself, and if left unattended would overeat and sometimes regurgitate. She had gained 15 lbs in the last year. She now had an occasional fecal incontinence.

On examination, she paced the room and clung to her husband. She responded minimally to verbal commands. She was hypophonic and hypomimic. Her reflexes were brisk, but symmetric, with flexor plantar responses. Muscle tone, gait and arm swing were normal. Laboratory studies were again normal with the exception of a slightly elevated thyroid stimulating hormone (TSH) level of 5.3 (normal: 0.3-5.0) and a thyroid microsomal antibody titre of 1:25600. A repeat brain MRI showed relatively marked frontal and temporal lobe atrophy that had progressed significantly since her previous scan in 1995.

When seen in July of 1997, she was mute, incontinent of urine and feaces, and was unable to ambulate. She was fed pureed foods by her husband who had also mentioned that for the past couple of months there was a reduction in left side movements with increasing stiffness of her left side.

On examination she had cervical torticollis. She was bradykinetic, with rigidity on the left. Reflexes were brisk bilaterally but more so on the left. Her plantar reflexes remained flexor.
She was placed in a nursing home a few months after where she remained until 1998 when she died 4 years after disease onset. A brain only autopsy was performed.

Case 3 (US2)
This 47-year-old right-handed man, presented to the Mayo Clinic in late 1997 with a 3-year history of a rapidly progressive neurological disorder.

The onset of his illness dated back to July 1994, age 44, when he had noticed reduced dexterity of the right hand and a tendency to “fumble with a pen”. He described slowed voluntary movements of the right hand and fingers but denied any change in the size of his handwriting. He also denied any history of bowel, bladder, sexual or other autonomic dysfunction. Neurological examination in July 1994 revealed hypomimia, rigidity and mild apraxia in his right arm, and reduced right arm swing on walking. His deep tendon reflexes were brisker in the right arm. It was felt that the patient had an atypical form of parkinsonism, possibly CBD, and levodopa treatment in increasing dosage, was initiated without benefit.

At a follow-up consultation in December 1994 significant worsening of symptoms and signs was noted.

By early 1996 he complained of right hand weakness. NCS were normal while EMG demonstrated occasional complex repetitive discharges, without evidence of denervation.
In January 1997 serum studies revealed an elevated ANA titre 1:2560 (normal <1: 30) and he was treated with high dose pulse methylprednisolone therapy for three days followed by daily oral steroids. Follow up examination in February 1997 revealed continued progression, now with bilateral facial weakness. He also was noted to favour keeping both his arms in a flexed posture with a dystonic-like grip in flexion of both hands. The ANA titre was 1:80 and the steroids were tapered off.

In March 1997 he walked with both upper extremities in a persistent flexed posture, with cortical thumbs. Examination revealed bilateral spasticity, rigidity and dystonic posturing of the hands. He now had marked difficulty speaking, and some difficulty swallowing.

In November 1997 he was referred to the Mayo Clinic. By this time he was mute and non-ambulatory, but his family gave additional history. In his past medical history Raynaud’s syndrome had been diagnosed, on the basis of “blue hands” many years prior to the onset of his neurological illness, and he had also been told of a “tendency towards lupus”. His father had been diagnosed as having idiopathic Parkinson’s disease in his early 50’s, but a few years later developed dementia. His father in turn had died in his mid 50’s, without a post-mortem. The rest of the family history on his father’s side of the family was unknown to the patient’s wife. The maternal family history was unremarkable. His siblings and children are alive and well.

Neurological examination revealed parkinsonism, and dystonia. Of note, he had increased muscle tone throughout, more so in the arms and neck.
compared to the lower extremities. He had diffuse hyper-reflexia with bilateral sustained ankle clonus. He was only able to take a few short steps with support. His eye movements were full. He was unable to cooperate to determine more specific abnormalities, and mental status testing was not possible. He was asked to blink once for yes and twice for no but was unable to do so. He had some moaning but nothing that confirmed he understood.

All serum, urine and CSF examinations were either negative or normal. EEG revealed non-specific slowing and MRI brain scan demonstrated frontotemporal atrophy.

At his last neurological evaluation prior to death in February 1998 it was commented that he would only track movement with his eyes, seemed to prefer to “watch TV all day long”, and would cry for hours at a time. He died of bronchopneumonia in May 1998 less than 3 ½ years after onset. A complete autopsy was performed revealing testicular atrophy.

Case 4 (D1)
(Patient still alive) This 43-year old woman first presented to a memory disorder centre in August 2001 for evaluation of rapid progressive dementia.

Besides hemicrania she had been healthy.

She had been well up until autumn 1999 when she developed depression, successfully treated with serotonin specific reuptake inhibitors. In autumn 2000 she began complaining of a rapidly progressive memory loss associated with loss of initiative and personality changes. She lost interest in
her job and was unable to plan and execute her work. She was later sent home on sick leave in the spring of 2001 and later fired. Her family noted progressive memory loss associated with loss of initiative. She developed a taste for sweets and soft drinks and eventually gained weight of 10kg. Later she became sexually disinhibited. From summer 2000 her gait became slow and unsteady, she had a tendency to fall and her speech became dysarthric. There was also a report of her not being able to stop laughing once she started.

There was no family history of early onset dementia, parkinsonism or any other neurodegenerative disease. Both parents are alive and well. Her mother and maternal grandfather had episodes of depression only. Her paternal grandmother had late onset (unknown) liver disease and some memory problems and died at age 77.

On examination September 2001 she was apathetic, disinhibited, and demonstrated a lack of social awareness and mental rigidity. Her speech was slow and dysarthric. There was the presence of stimulus-bound behaviour, motor perseveration with reduced executive functions, abstraction and bradyphrenia. Her facial expression was decreased with a low blink frequency. She had very active primitive reflexes. Her eye movements were normal. There was increased tone in the limbs, legs more than arms, with mild axial rigidity, but power was normal. Her reflexes were hyperactive and her plantar responses were extensor. Rapid alternating movements were bradykinetic. There was no evidence of tremor, ataxia, fasciculation, or other involuntary movements. Her gait was slow and balance poor.
All serum, urine and CSF examinations were either negative or normal. EEG initially revealed low-frequency activity (3-5Hz) periodically in the left temporal area, with a few sharp waves; however, subsequent EEGs were normal. Initial brain MRI in June 2001 and follow up in September 2001 revealed bilateral increased T2 weighted signal in the striatum with mild frontotemporal atrophy. An FDG-PET scan demonstrated considerable decreased glucose uptake in the right frontal lobe, and asymmetric uptake in the basal ganglia and thalami most decreased on the right. There was also moderate decreased uptake in the rest of the cerebral cortex of the right hemisphere, left temporal lobe and left cerebellar hemisphere (diaskisis). An 18F fluoro-dopa PET scan demonstrated 80% reduction in F-Dopa conversion to dopamine in both basal ganglia most pronounced on the right.

Neuropsychological examination demonstrated normal intelligence. In the complex arithmetic problems of Luria (Luria, 1973), she was right in only 3 of 5 and did not check her results. Psychomotor speed was decreased. Trail making A was completed in 36 seconds and in Trail making B she was markedly slow, 90 seconds, and needed guiding several times. In verbal fluency tests she produced 7 words starting with the letter S and 12 animals in 1 minute with several animals repeated. Visual and auditory learning and memory was impaired. Out of 10 words only 5 were learned after 5 attempts. Visuospatial problem solving was normal, however slow.

Genetic testing for Huntington’s disease, dentatorubral-pallidoluysian atrophy and prion protein mutation was negative.
The patient underwent a brain biopsy in October 2001.

Since then her condition has deteriorated and from May 2002 she has been completely mute. In September 2002 her gait became increasingly spastic and she became wheelchair bound. In December 2002 her swallowing deteriorated and after pneumonia she had a percutaneous gastrostomy tube inserted. On examination January 2003 she is spastic with complete paralysis of left arm and legs. She only moves her right arm. Reflexes remain hyperactive. Her eye movements are full without gaze palsy.