



Corticobasal syndrome associated with a novel 1048_1049insG progranulin mutation

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with no fibrinoid necrosis, inflammatory cell infiltration or granuloma. Macroscopic examination showed nerve hypertrophy. CIDP was diagnosed, and the patient received IVIG (400 mg/kg/day, 5 days). The dysesthesia and weakness in the four limbs decreased, and the MMT scores increased to 5. Moreover, flexion of the thoraco-lumbar spine was markedly reduced (fig 1B), and the ability to avert his back increased (fig 1D).

We performed electromyography and MRI of the paraspinal muscles during follow-up. MRI scanning from the C1 to L5 vertebrae showed no evidence of atrophy or abnormal signals in the paraspinal muscles. Electromyography of the paraspinal muscles at the levels of C6, Th4, Th6, Th8 and L4 showed high-amplitude motor unit action potentials (5 mV) at Th4 and Th6. Fibrillation potentials were present at the C6, Th4 and Th6 levels, and positive sharp waves were present at the C6 level. Non-myopathic polyphasic action potentials were noted at all levels. Denervation potentials and neuropathic motor unit potentials were noted in all four limbs.

DISCUSSION

Causative factors of camptocormia remain uncertain. In most patients with camptocormia, biopsy of paraspinal muscles shows evidence of myopathy.¹ EMG findings can be diverse and include both myogenic and neurogenic features, often with denervation, associated with positive sharp waves or fibrillation potentials.¹ CIDP and camptocormia simultaneously responded to IVIG treatment in our patient, suggesting a probable neuropathic contribution to camptocormia. In idiopathic camptocormia, chronic neuropathic denervation of paraspinal muscles is considered a contributory factor.¹ Pennison-Besnier *et al* described a patient with a 16-month history of camptocormia who showed angular atrophic fibres and fibre type grouping on lumbar paraspinal muscle biopsy.² In older people, neurogenic changes are often found on muscle biopsy, especially in the cervical and lumbar paraspinal muscles.¹ Direct impingement of paraspinal nerves has not been reported in patients with camptocormia, but Kidron *et al*³ reported spinal root involvement with paraspinal muscle denervation in a patient with mononeuritis multiplex. Our patient also showed denervation and neuropathic discharges in paraspinal muscle on EMG. CIDP can involve spinal roots, often showing enlargement on MRI. Thus, chronic denervation or neuropathic discharges of paraspinal muscles caused by involvement of spinal roots due to CIDP can contribute to camptocormia. In addition, age-related factors such as loss of muscle tone, tissue elasticity, mild kyphosis or chronic stretch are also contributory factors.¹

Various pharmacological treatments have been used to treat camptocormia, but many

patients have a poor response.¹ Steroids often improve camptocormia associated with inflammation in paraspinal muscle. IVIG treatment has had no effect on abnormal posture in patients with CIDP and dropped head⁴ or idiopathic camptocormia. However, the camptocormia in our patient responded to IVIG treatment. Dominick *et al*⁵ described a patient with progressive neck weakness and trunk extension, developing over the course of several months, that responded dramatically to IVIG treatment. The effects of IVIG treatment on camptocormia remain uncertain, but we speculate that a reduction in chronic neuropathic denervation caused by CIDP is involved. Confirmation of whether IVIG treatment is useful for the management of camptocormia must await further studies.

Neurologists should be aware that camptocormia can respond to IVIG treatment in patients with CIDP.

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Corticobasal syndrome associated with a novel 1048_1049insG progranulin mutation

Mutations in the progranulin gene (*GRN*) cause familial frontotemporal lobar degeneration (FTLD) associated with type 3 TDP-43 positive inclusions.¹ The clinical phenotype associated with progranulin mutations continues to be defined, although patients present usually with either behavioural symptoms (behavioural variant FTLD) or a

progressive aphasia. However, patients have also been described with a corticobasal syndrome (CBS), extending the pathological associations of this disorder into the TDP-43 proteinopathies.¹ Neuroanatomically, CBS is usually associated with asymmetrical frontal and parietal lobe deficits, and there is evidence that progranulin mutations are also associated with early parietal lobe involvement and asymmetrical hemispheric atrophy.² We describe a novel mutation in the *GRN* gene causing a CBS in family DRC219. This family was originally described as having “familial dementia lacking specific pathological features presenting with clinical features of corticobasal degeneration” in Brown *et al*.³

CASE REPORT

DRC219 is a family from the south of England with a history of an autosomal dominant dementia. The proband was seen and investigated at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK. Her grandmother died aged 61 and had been said to have abnormal behaviour for a few years prior to death. Her mother died aged 54, with the onset of memory and behavioural problems in her 40s, as well as a left hemiparesis. The proband's brother also had a progressive behavioural syndrome with symptoms of inappropriate social behaviour starting in his late 50s followed by obsessiveness, disinhibition and apathy as well as stereotyped behaviours and lack of insight. His speech decreased in quantity with relatively intact naming and reading, and he developed a limb apraxia. Psychometric testing at 3 years from symptom onset showed impaired visual memory but intact verbal memory, poor visuospatial skills but normal digit span.

The proband was right-handed and worked as a dressmaker. She initially developed symptoms at the age of 64 years old with difficulties using her left arm and a tremor in the left hand. She had difficulties using scissors, writing and dressing herself. She gave a history of a possible alien limb phenomenon in the left arm, with the hand appearing to move on its own, grasping at things and interfering with the movement of the right hand. A few months later, she developed symptoms in her left leg, dragging it when walking. Over a similar period, she developed behavioural symptoms, becoming disinhibited, distractible and restless, often wandering about. These problems deteriorated with later development of aggression and delusions. Neurological examination at 1 year from symptom onset revealed an asymmetric parkinsonian syndrome, worse on the left side, with a postural tremor, rigidity and bradykinesia. There was dystonic posturing of the left hand and a limb apraxia bilaterally. She had mild pyramidal weakness on the left, and cortical sensory loss (dysgraphaesthesia) was noted in the left hand. Saccadic eye movements were

abnormal with slowing of initiation. Psychometry at 1 year from symptom onset showed a discrepancy between verbal IQ (97) and performance IQ (79) with deterioration in non-verbal skills. On testing of specific cognitive domains, there was mild impairment of executive function, scoring poorly on verbal fluency and with concrete interpretation of proverbs. She scored between the 25th and 50th percentile on tests of verbal and visual episodic memory. She scored well on other aspects of cognitive testing: face recognition (50th percentile on a test of famous faces), naming (75th percentile), visuospatial and visuo-perceptual skills (above the 50th percentile), spelling and calculation. Brain imaging with CT showed asymmetrical hemispheric atrophy, worse on the right side. She continued to deteriorate over the next 2 years and died 3 years after symptom onset at the age of 67.

GENETIC ANALYSIS

All 13 exons of the *GRN* gene were sequenced in the proband in at least one direction. Analysis of the electropherogram traces revealed a c.1048_1049insG mutation in exon 10 on the reverse complement strand. Translation of the mutant allele would lead to a p.Ala350GlyfsX18 abnormal progranulin protein. In keeping with a large mutation spectrum at the *GRN* locus¹ the frameshift mutation reported here would be expected to be a functionally null allele, as it results in a premature stop codon and possibly nonsense mediated decay. However, this mutation was not found in her brother. We confirmed that these patients were likely to be siblings with a relatedness analysis using ML-relate software:⁴ using 10 microsatellite markers from the Promega PowerPlex16 STR marker set, the results of this analysis demonstrated that the relationships of half-sibling, full-sibling and parent/offspring were consistent with genetic data, and the hypothesis of unrelatedness was rejected at $p < 10^{-15}$. These individuals shared a total of 12 alleles across the 10 markers tested.

Although originally described as lacking specific pathological features, review of the proband's neuropathological postmortem findings revealed the presence of type 3 TDP-43 pathology with ubiquitin-positive, TDP-43 positive intranuclear inclusions,⁵ consistent with that described in other patients with *GRN* mutations.

DISCUSSION

We have described the presence of a novel *GRN* mutation in family DRC219 in which the proband has a corticobasal syndrome associated with behavioural symptoms. Other members of the family had progressive behavioural symptoms and personality change consistent with behavioural variant FTLD. However, it is of interest that although the brother developed a fronto-

temporal dementia syndrome, he was not found to have the mutation. Explanations for a phenocopy syndrome in the brother are speculative: possibilities include a chance occurrence of sporadic behavioural variant FTLD, which we favour, or alternatively these findings are also compatible with a somatic reversion from the mutant allele to the wild-type in the proband's brother's white blood cells. Of note, an FTLD phenocopy syndrome has also been described in a Calabrian *GRN* kindred where four members of the family were found to be negative for the mutation.⁶

The proband in DRC219 was noted to have asymmetrical cerebral atrophy, more marked on the right side. While some studies have suggested a heterogeneous clinical presentation of *GRN* mutations,¹ there does appear to be a strong correlation with the presence of parietal lobe deficits and asymmetrical atrophy,² independent of the type of mutation, consistent with the fact that all *GRN* mutations known to be pathogenic are null mutations causing an effect by haploinsufficiency. The combination of these features in the presence of a family history should be a strong indication for sequencing the progranulin gene.

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Treatment of musical hallucinosis with acetylcholinesterase inhibitors

Patients diagnosed with musical hallucinosis (MH) report hearing songs, melodies or orchestral music in the absence of a source of sound. Typically there is no delusional interpretation of the hallucinations.¹

Because of the rareness of the disorder, reports of successful therapy have mostly been case studies. These have described treatment with neuroleptics, antidepressants and antiepileptics.

There is some evidence that a cholinergic deficit is likely to play a role in different hallucinatory syndromes. Based on this evidence we treated two cases of MH with cholinergic drugs.

CASE REPORTS

Case No 1

A 54-year-old male patient reported MH since the age of 34 years. The hallucinations took the form of different songs sung by a male voice which he could not attribute to anyone known to him. The melodies were partly accompanied by the sounds of a piano or guitar. Sometimes the patient would also hear orchestral music. The hallucinations were predominantly perceived on the right-hand side.

The patient described an increased intensity of the MH after a stroke at the age of 52 years. He had suffered infarctions of the left and right medial cerebral artery territories at the ages of 52 and 54 years, respectively. While no clinical symptoms remained of the infarction in the left hemisphere, the infarction in the right hemisphere had resulted in left hemiparesis. The patient had hearing loss in the left ear since birth. In the right ear, hearing loss which had meanwhile become severe had been induced by otosclerosis beginning at the age of 35 years. In addition, the patient suffered from bilateral tinnitus, the noise of which was clearly distinguishable from the hallucinated music.

There were no psychopathological findings apart from the MH. No delusions were present.