C9ORF72: hammering home the clinical, genetic and pathological overlap between ALS and FTLD

Around 10% of ALS is familial (fALS), while ~40% of FTLD is familial. Mutations in over a dozen genes cause ALS, while mutations in MAPT and progranulin are major causes of fFTLD. Relatively little clinical overlap occurs in the syndromes associated with these ALS and FTLD-associated gene mutations. However, it had long been known that patients can develop both ALS and FTLD. This overlap has been of great interest, particularly since the discovery in 2006 of TDP-43 as the common pathological denominator of both conditions. Furthermore, 2006 also saw the publication of the first papers linking autosomal dominant ALS-FTLD to chromosome 9p. The race to identify the causative gene has lasted five years, finishing in 2011. This delay was a frustrating consequence of the nature of the mutation: a hugely expanded intronic hexanucleotide repeat in the C9ORF72 gene (chromosome 9 open reading frame 72). The size and 'G-C rich' nature of the expansion made it impossible to detect using conventional and next-generation sequencing technology. Good old-fashioned microsatellites and Southern blotting were needed. C9ORF72 seems to localise to synapses but has no known function. It does, however, have a mouse homologue, which bodes well for animal studies.

Recently, several groups have published clinicopathological studies of C9ORF72 cases (all with European ancestry). Hsiung et al (2012) describe 30 cases from 16 different families harbouring C9ORF72 mutations. 15 had FTLD, 8 ALS and 7 ALS-FTLD. Of the latter, 5 began with FTLD, 1 with ALS, and 1 with synchronous onset. Mean age of onset was 54y (range 34-74), age of death 61y (41-84) and disease duration 5y (1-16). Patients with ALS had markedly shorter survival (2.8y versus 8.4y without ALS). Interestingly, anticipation also appeared to occur, with a trend to earlier onset by 5-10y in younger generations.

Of their 22 cases with FTLD, the commonest dementia subtype was behavioural variant (15 cases). The others had progressive non-fluent aphasia (PNFA) with or without bvFTLD. No one had semantic dementia. In keeping with frontal predominant dementia, memory problems were only mild, and visuospatial problems and apraxia were uncommon. In patients with ALS, nearly half had prominent bulbar features, and even the FTLD patients had bulbar findings. An extrapyramidal syndrome (akinetic rigidity) was seen in 12 patients in all. Four had overt Parkinsonism with tremor. A variety of other clinical features were seen in small numbers, including ataxia, supranuclear gaze palsy and urinary incontinence, suggesting more widespread pathology. Marked clinical heterogeneity was seen between and within families and only three families demonstrated a consistent clinical phenotype (bvFTLD).

Hsiung et al also performed structural and functional imaging studies, which further confirmed predominantly frontal lobe failure (asymmetric in only one out of 21 cases imaged, with left predominant atrophy). Pathological studies of 21 cases again showed frontal atrophy (with relative sparing of the temporal lobes) and corticospinal tract degeneration. Degenerative changes were also seen in the basal ganglia in over half the cases studied. TDP-43 staining was prominent and widespread in all layers of the cortex, subcortical areas, hippocampus, white matter, brainstem motor nuclei and anterior horn of the spinal cord. These were ubiquitin positive, and thus characteristic of pure FTLD-TDP and ALS. C9ORF72 itself did not seem to colocalise with these inclusions.

It is interesting to note a couple of features that might mark C9ORF72 mutation cases out from other causes of TDP-43 proteinopathy. Firstly, ubiquitinated inclusions negative for TDP-43 are observed, most consistently in the cerebellar granule cell layer. This appears to be a characteristic signature for C9ORF72 mutation disease, originally described by Al-Sarraj et al (2011). Secondly, Snowden et al (2012) found a significant association between a psychotic presentation of FTLD and presence of C9ORF72 mutation. Prominent features included complex repetitive behaviours and delusions. More studies are needed to corroborate these findings.

In summary, C9ORF72 mutations are clearly a major cause of FTLD. Furthermore, they may be the single most common genetic cause of fALS (accounting for 25% of familial cases). Hsiung et al found that C9ORF72 mutations accounted for 100% of their fALS-FTLD cases. However, the story is not that clear cut, as Snowden et al (2012) found that they only accounted for 8 out of their 30 fALS-FTLD cases. Thus, while C9ORF72 mutations further strengthen our understanding of ALS and FTLD as being two TDP-43 diseases on a clinical and pathological spectrum, it is clear that other ALS-FTLD genes are waiting to be discovered.

– Jemeen Sreedharan, National Hospital for Neurology and Neurosurgery, Queen Square.

Clinical and pathological features of familial frontotemporal dementia caused by C9ORF72 mutation on chromosome 9p. Hsiung GY, Dejesus-Hernandez M, Feldman HH, Sengdy P, Bouchard-Kerr P, Dwosh E, Butler R, Leung B, Fok A, Rutherford NJ, Baker M, Rademakers R, Mackenzie IR. BRAIN 2012 Feb 17.

Distinct clinical and pathological characteristics of frontotemporal dementia associated with C9ORF72 mutations. Snowden JS, Rollinson S, Thompson JC, Harris JM, Stopford CL, Richardson AM, Jones M, Gerhard A, Davidson YS, Robinson A, Gibbons L, Hu Q, Duplessis D, Neary D, Mann DM, Pickering-Brown SM. BRAIN 2012 Feb 2.

p62 positive, TDP-43 negative, neuronal cytoplasmic and intranuclear inclusions in the cerebellum and hippocampus define the pathology of C9orf72-linked FTLD and MND/ALS. Al-Sarraj S, King A, Troakes C, Smith B, Maekawa S, Bodi I, Rogelj B, Al-Chalabi A, Hortobágyi T, Shaw CE. ACTA NEUROPATHOL 2011;122(6):691-702.

(The March edition of Brain (Vol 135 issue 3) has 8 papers on C9orf72 with an editorial by John Hodges, among related papers including a CHMP2B mouse and non-human primate model of TDP-43 ALS – Ed.)

The link between iron and tau

Several lines of evidence are presented by this group into the link between loss of soluble tau in the neuronal cytoplasm in Alzheimer's disease, Parkinson's disease and tauopathies, a loss of functional iron cellular export, and iron accumulation associated with disease severity. A key finding in this paper is of prevention of onset of disease phenotype in a tau knockout mouse with iron chelation (clioquinol, fed orally for 5 months), which adds to the evidence presented in the 2003 paper by Kaur and colleagues in a mouse MPTP model of Parkinson's Disease. The paper also provides insights into disease mechanisms, with in vitro evidence of reduced soluble tau leading to decreased amyloid precursor protein (APP) cell surface trafficking and then reduced iron export.

– Mike Zandi, National Hospital for Neurology and Neurosurgery, Queen Square, London.

Lei et al. Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. NATURE MEDICINE 18, 291–295 (2012)

Kaur et al. Genetic or Pharmacological Iron Chelation Prevents MPTP-Induced Neurotoxicity In Vivo: A Novel Therapy for Parkinson's Disease. NEURON 37(6), 899–909,(2003)

A blast from the past

In the UK, the driving regulations for an ordinary (type 1) licence are based on a calculation of a risk of seizures of 20% in a year. Less than this and you are allowed behind the wheel, more and then the keys go back on the hook. Consequently the epidemiological data informing these decisions is crucial and a central pin has been the MRC drug withdrawal study which has celebrated its 21st birthday. With its coming of age is a further analysis of the data within the study and an analysis of related studies. The broad brush figures which we have known for a long time are that after two years of seizure freedom, the risk of seizures is 22% in the next two years if a patient continues on treatment and 41% if they do not (30% in the first year). The current analysis looked at patients over 16 (potential drivers) and asked the question: "what is the risk of seizures in the next 12 months at various points" in their course. They found that if a patient was seizure free for three months after completion of a six month drug withdrawal, then their risk of seizures in the subsequent 12 months was 15% (CI 10-19%) and at six months, the risk was 9% (CI 5-13%). 127 patients had a seizure following drug withdrawal and reinstated treatment. The risk of a further seizure from 3-15 months after reinstatement was 26% and the risk from 6-18 months, if seizure free for the first 6 months was 18%. Five other studies looking at recurrence risk in the 12 months following drug withdrawal found 12-30% but methods and cohorts differ. These data suggest that the DVLA guidelines recommending six months off driving

after withdrawal are not too far off the mark, although may be a little conservative with the annualised risk falling below 20% at three months. Equally ensuring seizure freedom for six months after reinstatement of treatment may be long enough off driving, although the numbers from the MRC study are too small to be sure.

– Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospital NHS Trust, Bedford.

Seizure recurrent after anti-epileptic drug withdrawal and the implications for driving: further results from the MRC antiepileptic drug withdrawal study and a systematic review. Bonnett LJ, Shukralla A, Tudor-Smith C, Williamson PR, Marson AG. JNNP 2011;82:1328-33.

Deep brain stimulation for amnesia?

Suthana and colleagues from the University of California, Los Angeles and Tel Aviv University, implanted intracranial depth electrodes in seven subjects with pharmacological treatment refractory epilepsy to plan for epilepsy surgery, and noted improvement in a virtual spatial navigation memory task with entorhinal cortex stimulation at a low level, compared to no stimulation. This stimulation was associated with resetting of the phase of the theta rhythm of the hippocampal EEG. Direct hippocampal stimulation was ineffective. A repeated measures block design was used for statistical analysis and the p values are quite modest (0.03). Clearly the studies require replication and then a relevant trial in disorders with amnesia in which the risks of DBS may be allowable, for instance herpes simplex encephalitis or Alzheimer's disease. Even small gains in memory encoding ability may be clinically meaningful and aid to quality of life. This study adds to the potential roles of DBS in neuropsychiatric diseases including the so far studied obsessive compulsive disorder and major depression in which perhaps the acceptable risks are smaller.

– Mike Zandi, National Hospital for Neurology and Neurosurgery, Queen Square, London.

Memory Enhancement and Deep-Brain Stimulation of the Entorhinal Area. Suthana et al. NEJM 2012;366:502-10.

So much for history

This is quite a small study of just 35 patients with 120 seizures from a telemetry unit. Twelve patients had 36 non-epileptic seizures and eighty six seizures were recorded from the remaining patients, mostly partial seizures. The videos were compared against witnesses' histories of the seizures. At least half of witnesses reported more than 30% of signs incorrectly. The six signs which were found on video-telemetry to discriminate most clearly between epilepsy and non-epileptic seizures were reported incorrectly by 37-62% of witnesses. The signs, on video telemetry, which most clearly predicted non-epileptic attacks were preserved awareness, eyelid fluttering, evidence of seizure activity changing in response to observers. Those most clearly predicting epileptic attacks were eye opening/widening, abrupt onset and post-ictal confusion or sleep. This study re-emphasises the problems inherent in epilepsy diagnosis from the history. This diagnostic minefield has high error rates for all of us. Marcus Reuber has shown us that it is not just what you say but also how you say it and this can be used to augment diagnostic accuracy but in the end, diagnostic proof requires video telemetry. Yet only a fraction of patients who might benefit from telemetry can avail themselves of it. How many other serious conditions have such poor access to diagnostic tests?

– Mark Manford, Addenbrooke's Hospital, Cambridge and Bedford Hospital NHS Trust, Bedford.

Can semiology predict psychogenic non-epileptic seizures? A prospective study. Syed TU, LaFrance WC, Kahriman ES et al. ANN NEUROL 2011;69:997-1004.