The prion hypothesis of neurodegenerative disease spreads

Over recent years there has been an increasing interest in the idea that the key pathological species of protein that characterise certain neurodegenerative disorders may cause disease through a prion like process. This new theory posits that the intracellular protein aggregation spreads from cell to cell and that this then seeds pathology in the cell it has affected, in a fashion similar to that proposed for prion protein in the spongiform encephalopathies. The evidence that this is the case has been slowly accumulating although the attractiveness of the theory has often led to speculation ahead of the actual data.

Two recent papers have now added more weight to the theory. In the first of these papers, the laboratory of Virginia Lee has shown that a variety of alpha-synuclein fibrils can enter neurons via an endocytic pathway and promote recruitment of soluble endogenous alpha-synuclein. This recruitment then leads to the development of insoluble Lewy bodies and neurites, so showing that alpha-synuclein can be taken up by neurons and seed pathology. This pathology that they see in vitro, not only resembles that seen in PD, but it also leads to neuronal dysfunction and death. This is an important study because until now it has been shown that alpha-synuclein can spread from cell to cell, but has not been shown to induce any pathology. However whilst this paper provides an additional important element to the story, it should be realised that all the studies were done in vitro.

The second study is in the field of amyloid and Alzheimer’s Disease (AD). In this study the authors show that injecting AD brain extracts into animals could induce amyloid pathology at sites distal to the injection, and that this accumulation increased with time and did not occur in the absence of the inoculum. As with the study above, it again shows that pathological proteins can spread between nerve cells and induce pathology and that this may be one of the key events in how neurodegenerative disorders evolve. Of course whether this occurs in people with these diseases remains unproven, as does how one could interfere with this process if it were shown to be the case.

– Roger Barker.


Can I take my blue inhaler for my congenital myasthenia please, doc?

Well not quite, yet. We are talking of a very rare condition, which most general neurologists may never encounter in their life time. However, the awareness of rare syndromes has always fascinated neurologists. How many clinicopathological conferences have we sat through discussing the features of Histiocytosis-X, Alexander’s disease and POLG1 mutations? But nothing is better than knowing that a reasonably safe and cheap drug may be available for a genetic condition, albeit rare. Congenital myasthenic syndromes are indeed rare. Even in a specialist neuromuscular clinic you only have a handful of each of these mutations. However, more and more mutations are being identified and it is extremely useful to know that once the diagnosis is made, the treatment response is different for different mutations.

Most patients with a synaptic AChR deficiency respond reasonably well to pyridostigmine. On the other hand, Pyridostigmine is ineffective and potentially worsens the condition in those patients with endplate acetylcholinesterase deficiency (COLQ mutation), slow channel syndrome (where kinetic defects cause the channel to close very slowly), DOK7 and beta-2 laminin mutations. Patients (especially those with DOK7 mutation) may present in adult life and can be mistaken for sernonengative myasthenia (Alsheit et al 2011).

A recent open-label intention-to-treat study on patients with COLQ (n=5) or DOK7 (n=15) mutations has shown that beta-2 adrenergic agonist albuterol (US name for Salbutamol) was beneficial (Liewluck et al epub). Patients had improvement in their walking and climbing distance with corresponding reduction in their disability scores (all p<0.0001). The systemic dose used was from 4 to 12 mg/day in adults (An inhalation of standard salbutamol only delivers 100mcg per puff). The effect was persistent despite continuous use and improved the quality of life in all patients, with some patients becoming more independent and even symptom-free.

This is confirming the studies looking into other beta-2 agonists ephedrine and salbutamol in DOK7 or epsilon-subunit mutations (Lashley et al 2010, Sadeh et al 2011). We have known that sympathomimetics working through the beta-2 receptors are useful in myasthenia since the 1930s. What we don’t know is how they influence the neuromuscular transmission. Further prospective controlled trials should tell us whether the beta-2 agonists (taken systemically for the time being) are useful in this rare genetic condition.

Recently new mutations have been identified in the GFPT1 gene in patients with congenital myasthenia phenotypically similar to the DOK7 mutations – i.e. limb girdle weakness with minimal ocular or facial involvement (Guergueltcheva et al epub). These patients have been given the term congenital myasthenia with tubular aggregates (CMS-TA) in view of their muscle biopsy findings. With new mutations being identified regularly, it might not be too far before inhaled bronchodilators are carried around by some of the congenital myasthenic patients, provided we can ensure adequate systemic absorption.

– Dr Saiju Jacob, Consultant Neurologist, Queen Elizabeth Neurosciences Centre, Edgbaston, Birmingham.


Expansion of the chromosome 9 story in FTD-MND: C9ORF72

Since the discovery of SOD1 in 1993, many more monogenic causes of autosomal dominant Motor Neurone Disease (MND) have been identified. Between them these account for only a quarter of all familial cases, and few sporadic cases, and so their
clinical significance has been limited. The overlap between Fronto-Temporal Dementia (FTD) and MND, most strikingly in autosomal dominant FTD-MND kindreds, has raised the possibility of shared mechanisms and genes. This new gene was located in a region of interest using more advanced genetic detective work, much of it by these authors. Linkage analysis of kindreds with autosomal dominant MND-FTD from Finland, Europe, the USA and Canada had identified the short arm of chromosome 9 as a region of interest. Genome wide association studies (GWAS) and analysis of linkage disequilibrium narrowed this down to 9p21. Both papers describe finding the repeat by sequencing this area of interest in kindreds known to have 9p21 linked disease. They independently identified a hexanucleotide repeat mutation in a non-coding region of C9ORF72, a gene of unknown function that is highly conserved across species. Both state that this new mutation is the commonest monogenic cause of MND-FTD identified to date.

Renton et al. focus on making persuasive arguments for the pathogenicity of this mutation, demonstrating co-segregation and significant association of the mutation with disease in known and newly identified kindreds with 9p21 linked MND/MND-FTD, and absence of the mutation in both matched and genetically controls. The co-incident discovery of this mutation by DeJesus-Hernandez et al., published in the same volume of Neuron, and both groups' finding of large repeat sizes in expanded repeat carriers, add weight to their claims.

DeJesus-Hernandez et al. suggest that this mutation may cause disease by impacting transcription of one of the three splice variants of the C9ORF72 gene. They found reduced variant 1 expression in frontal cortex and lymphoblasts in cases with the expanded repeat. They cite previous work showing that expanded repeats in noncoding regions can cause disease by generating RNA foci in affected cells. They demonstrate the presence of these foci in the frontal cortex and spinal cord of 25% of carriers of this repeat, but only 1% of noncarriers, suggesting a mechanistic overlap with other noncoding repeat expansion disorders including the myotonic dystrophies and several of the spinocerebellar ataxias. The same type of disease causing mutation, an intronic hexanucleotide repeat expansion, is known to cause RNA gain of function in SCA36, a genetic ataxia with motor neurone involvement sharing clinical features with MND.

This joint finding has immediate clinical significance in that it would allow improved diagnostic, predictive and prenatal testing in individuals at risk for familial MND-FTD, and is clearly relevant to sporadic cases also. There are the general benefits of new therapeutic targets and further insight into the pathogenesis of these devastating diseases, and of other multinucleotide repeat disorders.

These papers complement each other well, gaps in one being addressed in the other, but questions remain. Renton et al. describe two controls with a repeat number thought to be pathogenic, but questions remain. Renton et al. describe two controls with a repeat number thought to be pathogenic. DeJesus-Hernandez et al. describe comparative clinical data for carriers presenting with ALS and those with FTD, and no striking disparities are found, though they do not directly compare repeat lengths between the two groups. There is much more work to follow, but for now these papers describe an exciting step forward in understanding the genetics and pathogenesis of MND and FTD, and the links between them.

Stem cells come of age

There has been a revolution in the world of stem cell biology in recent years as the ability to steer cells to different fates becomes better understood. This includes the capacity to re-programme adult somatic cells to pluripotent stem cells (iPS cells) and then last year it was reported that adult somatic cells could be turned directly into neurons. This paper was initially met with some scepticism but subsequently a number of other groups have reproduced this finding, and of late this has been taken a stage further by making dopaminergic neurons from skin fibroblasts without the need of going through an iPS stage. This direct generation of functional dopaminergic neurons has now been reported in a series of papers from different groups, using slightly different approaches. However, the ability to do this seems robust and has obvious implications for Parkinson's Disease (PD).

Firstly it could allow for the study of dopaminergic neurons in vitro as a means of studying the disease process in an individual and those same cells could then be used for drug screening. Secondly, this approach could be used to generate autologous transplantable dopaminergic neurons for patients with PD, which avoids immunological and ethical concerns as well as issues on tumour genesis. These papers reveal something of the speed that new technologies can advance and whilst much still needs to be done, it gives great hope to all those involved in disease modelling and therapeutics.

– Roger Barker.