**Generation of prions in a test tube**

Prion diseases are a group of fatal neurodegenerative disorders, including CreutzfeldtJakob disease, which exist in sporadic, genetic or acquired forms. They are characterised by the accumulation of PrPSc, a misfolded form of the host prion protein. It is thought that PrPSc acts as a template for the conversion of PrPC to its disease-associated conformation. The exact nature of the infectious agent of prion disease has been a hotly debated topic in the field. A widely accepted theory, “protein-only hypothesis” states that the agent is solely proteinaceous. However some believe that other agents, such as nucleic acids, maybe involved in the conversion of PrPC to PrPSc. Recent work by Nobel prize-winner Stanley Prusiner lab lends further support to the “protein-only hypothesis”. They demonstrated that intracerebral inoculation of a recombinant prion induced neurodegeneration in mice, which overexpressed a fragment of PrP (amino acids 89-231) sixteen times above its normal levels. The recombinant prion was produced by expression of a truncated mouse PrP (89-231) in E.Coli. This material was purified and then polymerised into amyloid fibrils. The mice injected with PrP amyloid developed neurological dysfunction at 380 to 660 days post-inoculation, whilst the control mice remained healthy at 670 days. To demonstrate the infectious nature of the recombinant prion, the brain extracts from sick recombinant PrP mice were shown to successfully transmit disease to wild-type mice. Prusiner claims this work is convincing evidence that prions are infectious proteins and that PrPC alone is necessary and sufficient for infectivity. However, experts in the field are wary of jumping to such conclusions. John Collinge from the Institute of Neurology, London, has found that mice over-expressing PrP by 10 times wild-type levels can spontaneously develop prion disease. Moreover, the Prusiner study only involved a small number of animals. The ultimate proof of the “protein-only hypothesis” would be to use recombinant PrP to induce prion disease in wild-type mice expressing normal levels of PrP. Until this has been accomplished, the contribution of an exogenous agent in prion propagation cannot be ruled out. - LMS, SJT

Legname G, Baskakov I, Nguyen HB, Riesner D, Cohen FE, DeArmon SJ, Prusiner SB. Synthetic Mammalian Prions

SCIENCE

2004:305:673-76.

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**PARKINSON'S DISEASE: Pinky, Parky, DJ and regular Lewy Bodies**

In May this year, Nicholas Wood's group published a Science paper defining a new mutation in three families with recessive parkinsonism, which they called PINK1, bringing to four the number of genes causing mendelian inherited parkinsonism: PARK1 (alpha-synuclein), parkin, DJ-1 and PINK1. Labs all over the world reached for the PINK-1 primers and got cracking…. By the September issue of Annals, there were four papers on parkinsonism and PINK-1. An Italian group looked at 100 of their sporadic early-onset (less than 50 years old) Parkinson’s patients and found 7 with missense mutations in PINK-1. A Japanese group found 6 out of 8 of their familial parkinsonism families had PINK-1 mutations. And a Spanish group describe one case of early onset parkinsonism with the PINK-1 mutation. In the most important study, the Wood team genotyped SNPs of PINK-1 in 576 cases of regular Parkinson’s disease and 514 controls, finding no evidence that PINK-1 variants predispose to Parkinson's disease. The picture that emerges is that PINK-1 mutations cause a recessive inherited form of parkinsonism that is rather similar to the parkin and DJ1 diseases: young onset, a slow course, dyskinesia at onset and a good response to levodopa. - AJC


SCIENCE

2004:304:1158-60.

Valente EM et al. PINK1 mutations are associated with sporadic early-onset parkinsonism.

ANNALS OF NEUROLOGY


Healy DG. The gene responsible for PARK6 Parkinson’s disease, PINK1, does not influence common forms of parkinsonism.

ANNALS OF NEUROLOGY


Rohe CF et al. Homozygous PINK1 C-terminus mutation causing early-onset parkinsonism.

ANNALS OF NEUROLOGY


**EPILEPSY: Ictal stuttering**

In this study, 230 adult patients were identified who met the criteria of seizures which were recorded with monitoring, who had a single diagnosis of epilepsy or psychogenic non-epileptic seizures (PNES) and did not suffer learning disability or interictal stuttering. 117 had PNES (17 male) and 113 had epilepsy (55 male). Ten had ictal stuttering (2 male). These patients often gesticulated in their seizures as if they were trying hard to speak but were unable to. They often struggled with the first part of the word: “ye.. ye.. ye..”. After the seizure some patients would suddenly give a burst of fluent speech that had they had been unable to express during the seizure. All these patients had non-epileptic seizures. On psychological profiling, these patients had more tendency to conversion symptoms than the remainder of the PNES group. This symptom adds to those that are useful in the diagnosis of PNES versus epilepsy, along with post-ictal tearfulness. Of course, the holy grail of the differentiating symptom between epilepsy and PNES will forever remain elusive but the fun is in the quest. Studies from 10 years ago showed a misdiagnosis rate of 20% for epilepsy in many clinics. With increasing awareness, I wonder how we are doing now? - MRAM


NEUROLOGY


**PARKINSON’S DISEASE: are new neurons really formed in the substantia nigra?**

One of the current goals of cell biology is to stimulate the endogenous stem cells that reside in our brains to repair the degenerating or damaged brain. It is now generally accepted that new neurons are formed even in the adult mammalian brain in the subventricular zone around the lateral ventricles and in the dentate gyrus of the hippocampus. However, there is considerable...
debate about whether neurogenesis persists into adulthood outside these regions, or whether, given appropriate stimulation, it could be induced. Thus considerable interest followed the report by Zhao et al that they had identified neurogenesis in the adult mouse substantia nigra: might it be possible to induce neurogenesis to replace the lost dopaminergic neurons in Parkinson’s disease (PD)? The initial report suggested a much slower rate of cell generation than that seen in the hippocampus, but none of the authors suggested that it would be sufficient to regenerate the entire population of nigral dopaminergic neurons throughout the lifespan of a mouse. Furthermore, in line with the lesion-induced neurogenesis seen in other brain regions, they reported increased nigral dopamine neuron generation after a partial lesion with MPTP (demonstrated by double labelling dividing dopaminergic cells with tyrosine hydroxylase, TH, and the thymidine analogue BrdU). However, in response to this article Frieldsberg et al reported that they could not identify any new dopaminergic neurons in the adult rodent substantia nigra (rat or mouse) either in normal animals or in hemicparkinsonian 6-hydroxydopamine-lesioned animals (a commonly used alternative to MPTP to model PD in rodents). They even failed to find convincing evidence of TH/BrdU double labelled cells after administration of brain-derived neurotrophic factor that has been shown to enhance neurogenesis in other regions of the rat brain. Other groups have failed to demonstrate the generation of new nigral dopaminergic neurons using different techniques, although they have identified dividing cells that co-express BrdU with markers of the glial cell lineage. Thus the jury is out. - AW Michell


PERIPHERAL NERVE: Lewis-Summer and all that

It is easy to forget that our taxonomy of the inflammatory peripheral neuropathies is actually quite recent: CIDP being defined in 1982 (by Dyck) and multi-focal motor neuropathy with conduction block being recognised in 1988 (Parry & Clarke). There has been much jostling of immune-mediated neuropathies between these two since. Lewis, Sumner, Brown & Asbury introduced a difficult entity in 1982: an asymmetrical neuropathy mainly affecting the arms, with multifocal conduction block. Sadly the eponymists could only cope with the first two authors... and those preferring descriptive names have caused much confusion... but seem to be settling now on "multi-focal acquired demyelinating sensory and motor neuropathy". This old-fashioned piece of descriptive neurology, a case series of 23 patients with Lewis-Summer neuropathy, comes out of the Salpêtrière. There is little surprising, as much learned from the 50 odd cases in the previous literature is confirmed: initial symptoms start in the arms in 70%, with distal muscle wasting in 50%; there was cranial nerve involvement in 25%; CSF protein is normal in 70%; and conduction block was usually found in the forearms; anti-GM1 antibodies were absent. The important point is that 33% of patients benefited from oral steroids in contrast to the dogma that multifocal motor neuropathy with conduction block is steroid-resistant. 50% of patients responded to IVIG... so you lumpers could – I suppose – just give all your immune-mediated neuropathies IVIG. I can hear finance departments groaning up and down the land... - AJC Viola K, Renie L, Maisnonobe T, Behin A, Neil J, Leger JM, Bourque P. Follow-up study and response to treatment in 23 patients with Lewis-Summer syndrome. BRAIN 2004;127:2010-7.

PARKINSON’S DISEASE: What’s UPset in PD?

The aetiology of Parkinson’s disease (PD) remains unknown in the majority of cases but the recent identification of various genetic forms of Parkinsonism has pointed towards problems in the ubiquitin-proteasome system (UPS). It is in this context that this new study of McNaught et al is interesting. In this study adult rats were given chronic peripherally delivered inhibitors of the proteasome, following which they developed abnormalities akin to that seen in patients with PD. These abnormalities included behavioural motor problems with evidence of dopamine loss and pathology across a range of nuclei known to be affected in PD, which includes the formation of inclusion bodies similar to the Lewy body that characterises PD. Furthermore, it also raises the question as to what is it in patients with PD that causes proteasome inhibition, presumably something in the environment. This is of course not a new idea, and once we start to think of this we remember similar scenarios with agents such as MPTP in the 1980s and more recently rotenone. Whether UPS inhibition will take us to heart of what causes PD in the clinic, remains unproven, but watch this space. - RAB McNaught KP, Perl DR, Brownell A-L, Olanow CW. Systemic exposure to proteasome inhibitors causes a progressive model of Parkinson’s disease. ANNAS OF NEUROLOGY 2004;56:149-62.

PARANEOPLASTIC: Ma, what does it look like?

In this paper Dalmay and colleagues report their findings in 38 patients with anti-Ma2 antibody associated encephalitis, and as is common with their work the data is extensive and helpful, both in its breadth and depth. 38 patients (24M;12F) with a median age of 64 years were identified, of which two-thirds presented with their neurological symptoms ahead of their tumour diagnosis (most commonly germ cell tumours) and only in 4 was no tumour identified. 34 of the patients presented with symptoms of limbic, diencephalic or brainstem dysfunction with the remaining 4 cases having a cerebellar or spinal cord/patex presentation, and in nearly all cases the neurological disorder was monophasic. These neurological problems commonly occurred with cranial imaging abnormalities – 23 out of 33 with an initial MRI scan and 2 out of 7 having CT scans – typically in the medial temporal lobes, midbrain and thalamus/hypothalamus. CSF was abnormal in 25 out of 32 cases with increased protein and pleocytosis (5-113 cells) being the commonest abnormalities, with normal glucose and oligoclonal bands in the majority of cases where they were tested. A third of the patients improved with treatment, which was immunological with or without chemotherapy; 3 patients made a complete recovery. The 40% of patients who also had additional anti-Ma1 antibodies did less well. Pathological findings in 4 patients were as to be expected, with typically florid inflammation. This paper is a comprehensive account of a relatively rare condition, and makes the points that paraneoplastic conditions can take many forms and finding the primary tumour can be difficult. However, in the young male patients with oed encephalitic/brainstem presentations, it would be worthwhile checking for these antibodies and examining the testes, whilst in older patients it may be the first presentation of a lung cancer. – RAB Dalmay J, Graus F, Villarejo A, Posner JB, Blumenthal D, Thiessen B, Saiz A, Meneses P, Rosenfeld MR. Clinical analysis of anti-Ma-2-associated encephalitis. BRAIN 2004;127:1831-44.

NEGLECT: “Undercover” testing for unilateral neglect

Visual neglect is commonly tested using cancellation tests in which the subject is asked to put a pen mark through targets that are randomly spread over a page. Subjects with neglect fail to cancel targets, especially missing those on the contralesional side of the page. Such behaviour relates to impaired performance in daily living tasks. It has been proposed that spatial working memory deficits can contribute to the neglect syndrome and so in conventional cancellation tests the pen marks made can cue subjects to search a little further. If so, cancellation tests using invisible marks may be more revealing. This has proved to be the case in a study comparing cancellation performance on tests done with ink and, as the authors put it, “undercover”, using carbon paper. 23 successive cases, (average age 66 years), with suspected neglect performed a cancellation task using visible and invisible marks. This more sneaky undercover test may prove to be a very useful predictor of neglect behaviour, especially in borderline cases. However three quarters of all strokes occur in people over 65 years. It remains to be seen if elderly stroke patients can understand the more abstract undercover task and if performance is reliable. – AJT Wojcikulik E, Rorden C, Clarke K, Husain M, Driver J. Group study of an “undercover” test for visuospatial neglect: invisible cancellation can reveal more neglect than standard cancellation. J NEUROLOGY NEUROSURG PSYCHIATRY 2004;75:1356-58.
PARKINSON’S: Ergot derived dopamine agonists – What should we do?
It is well established that ergot derivatives can cause fibrosis of a variety of structures and hence their cautious use in conditions such as migraine. In Parkinson’s disease there are four ergot derived dopamine agonists – namely bromocriptine, lisuride, pergolide and cabergoline – which are widely used both in the UK and abroad. In the BNF there is a clear warning about the fact that these drugs “have been associated with pulmonary, retroperitoneal and pericardial fibrotic reactions” which is followed by some rather vague advice on what should be done in the event of development of patients on these agents. It is on this background that a series of new papers have emerged highlighting the fibrotic potential of these drugs, which has raised questions about the frequency and severity of such reactions and how we can best prevent and/or detect these side-effects. In the history of PD such stories about side-effects with commonly used drugs are not uncommon – for example, selegiline and tolcapone were both associated with major adverse effects only to re-emerge as acceptable therapies at a later time. Clearly though attention must be paid to such reports and in one of the most recent editorials in Movement Disorders, Oliver Rascol and colleagues try to help with a series of suggestions. So what should we do as prescribing clinician? I think, note the data, and be aware of these problems and be pragmatic – thinking of this with the breathed PD patient for example. I think it is premature to shift our patients away from these drugs, given the efficacy that many patients report with these agents and the paucity of data on this topic using large cohorts of unselected patients. - RAB

MIGRAINE: Left sided migraineurs display augmented parasympathetic activation when compared to right sided migraineurs
Evidence from lesion studies, stimulation studies and the Wada procedure has provided evidence that parasympathetic function is predominantly mediated by the left hemisphere and sympathetic by the right. Avnon et al have presented evidence that left sided unilateral migraineurs display augmented parasympathetic activation when compared to right sided migraineurs. They studied 15 patients with left sided and 15 patients with right sided migraine, but no non-migaineurs. Soapy water was instilled into the patient’s eyes (the same results were obtained with each eye) to elicit the trigemino-parasympathetic reflex, measured by forehead vasodilation, and somato-sympathetic reflex, measured by digital vasoconstriction. Photoplethysmography pulse sensors were placed on each subject’s forehead and index finger. This sensor consists of a light source and photo detector and detects changes in arterial blood volume by measuring changes in light reflection through tissues, such that maximal readings occur during diastole and minimum readings during systole. Heart rate response to stimulation was also recorded. Forehead vasodilation and bradycardia ie a parasympathetic response, was greater in left sided versus right sided migraineurs both during and between migraine attacks. There was no difference between the two groups in digital vasoconstriction. Several reasons were considered for this difference in parasympathetic response. Pain scores were similar between two groups so altered pain perception and processing is unlikely to account for the difference. Antidromic release of vasoactive substances was considered unlikely, as forehead vasodilation was bilateral ie not a local effect. Digital vasoconstriction was the same between the two groups, thus altered sympathetic responses are unlikely to account for the difference. The authors postulated that the ipsilateral hypothalamus may play a role in augmented parasympathetic responses to stimulation, based on animal work and human functional MRI and PET imaging data. - WP

MULTIPLE SCLEROSIS: Assessing muscle strength and motor fatigue
Reliable tests to measure muscle strength and motor fatigue will enable physiotherapists and other clinicians to gauge how a person responds to ongoing therapy or treatment. Weakness and fatigue are characteristic symptoms of Multiple Sclerosis. Knee dynamometry is often used to measure muscular tone thereby enabling quantification of muscle strength and motor fatigue. Typically a patient is asked to extend or flex their leg against a hydraulic lever and required to hold this position while the applied force is measured. Muscle strength is measured over five seconds, whereas fatigue is calculated from the force-time curve over longer durations. Carried out in Finland, this small study tested the reliability of measuring isometric torque and a new fatigue index in 28 volunteers with mild-moderate MS. Repeated measurements of isometric torque in knee extension or flexion were gathered and indices of muscle fatigue were calculated. Subjective fatigue was recorded using the Fatigue Severity Scale. Measurements were repeated one week later. Isometric torque measurements assessed maximum muscle strength and areas under the force versus time curve provided the basis for calculating motor fatigue. Maximal isometric torque was reliably measured using the knee dynamometer. The authors conclude that their new index (calculated using the time of peak muscle strength as the starting point) is a reliable measure of motor fatigue in MS patients. They point out that previous indices include the rise to maximal strength (ie non-fatiguing time) in the calculations or omit the initial 5 seconds (where in MS fatigue may start). Interestingly, the subjective questionnaire data did not correlate well with the quantitative measures of motor fatigue. This undermines the importance of helping patients and clinicians communicate subtleties effectively. Developing objective and subjective measures in tandem would help to support this. – LAJ

EPILEPSY: A shocking pain in the neck
Vagus nerve stimulation (VNS) has become increasingly popular as a treatment for epilepsy in the USA and more centres in the UK are also undertaking or planning to undertake the procedure. It involves inserting electrodes...
Most children can expect their condition to be self-limiting. That focal epilepsy and certain rarer syndromes are more refractory. Overall, most childhood epilepsy can be well controlled and is a benign condition but greater than one year, 19% with two drugs and 9% with three or more. At 5 years, treatment cannot be assessed in a scientific fashion. However, 388 (86%) data although 25% improved from 2 to 5 years. This is an observational study at 5 years. Generally the outcome at 5 years was predictable from the two year only 6% of patients with good control at 2 years deteriorated to poor control. They had previously reported this cohort at 2 years follow-up and found that there are no useful selection criteria but as someone brought up on rigourous work-up for epilepsy surgery, this makes me uncomfortable. The results are modest but these patients are desperate and VNS seems to be safe, if expensive. I suspect that only history will judge if this is a passing fad. - MRAM


EPILEPSY: childhood epilepsy

In this study the authors recruited 466 children with new onset epilepsy. This was about 75% of the number of children expected from previous epidemiological studies to develop epilepsy in the recruitment period. Follow-up was nearly complete; eight died and 3 were lost to follow-up. The primary outcome measure was terminal remission at 5 years, which is the duration of seizure freedom at 5 years since onset. They divided children into bands according to duration of remission at 5 years: 5 years (14%), >5 years (27%), 3-4 years (14%), 2-3 years (9%), 1-2 years (12%), <1 year (ie not in remission, 24%). About 25% achieved terminal remission within 2 months of onset. The authors performed a multivariate analysis to identify the factors which predicted refractoriness. Factors relating to the seizure syndrome were the only ones which predicted a poor outcome at a level of P<0.001 and included infantile spasms, myoclonic and atonic seizures; and focal epilepsy (except the idiopathic group). Unclassifiable epilepsy was associated with a significantly better prognosis than other groups. A wide variety of other factors were not related to refractoriness, including gender, age at onset, other seizure types neurological signs, EEG, imaging, family history and history of febrile convulsions. They had previously reported this cohort at 2 years follow-up and found only 6% of patients with good control at 2 years deteriorated to poor control at 5 years. Generally the outcome at 5 years was predictable from the two year data although 25% improved from 2 to 5 years. This is an observational study and treatment cannot be assessed in a scientific fashion. However, 388 (86%) children received medication; 206 a single therapy, 46% achieved a remission greater than one year, 19% with two drugs and 9% with three or more. At 5 years only 161 were still using medication. This study confirms the view that most childhood epilepsy can be well controlled and is a benign condition but that focal epilepsy and certain rarer syndromes are more refractory. Overall, most children can expect their condition to be self-limiting. - MRAM


ALZHEIMER’S DISEASE: donepezil treatment

The acetylcholine esterase inhibitors (donepezil, rivastigmine and galantamine) represent the only specific treatment modality for that overwhelmingly common condition, Alzheimer’s disease. Although approved by the National Institute of Clinical Excellence, there remains a great deal of uncertainty about their value in real clinic populations over the medium to long-term. This independent, large, multicentre trial with broad inclusion criteria and follow-up for five years provides important, if disheartening, insights. It confirms the modest cognitive improvements reported by other, usually less rigorous, trials and documents continued efficacy of donepezil over two years. They key message, however, is that the primary outcome measures of time to institutionalisation and ‘disability’ (by the Bristol activities of daily living scale) did not differ significantly between the placebo and treatment groups. The many secondary endpoints, including carer-related indices, were similarly unimpressive. A run-in phase with its own randomisation is adopted as a prelude to the main randomisation and ongoing trial. Patients not completing the run-in did not proceed to the main trial; drop-out from long term follow-up was thereby kept to a minimum whilst retaining data on early intolerance. Although adverse events are noted to have occurred a little more frequently among those receiving donepezil, few details are given. A criticism of the trial is that far too much was statistically included that had originally been envisaged (500 v. 2-3000). The explanation offered was that the poor availability of donepezil throughout the NHS from 2001 limited recruitment; this is rather unconvincing given that the trial started in 1998. Perhaps more centres were needed. The eventual size of the sample gave a power of 90% to detect a delay to institutionalisation of 6 months. The conclusion that ‘donepezil … benefits (are) below minimally relevant thresholds’ is very forthright. It is difficult to imagine the withdrawal of these agents without alternatives being available. None, however, would disagree that the acetylcholine esterase inhibitors scarcely begin to address the need for effective treatment in Alzheimer’s disease. - RBD


BASAL GANGLIA: The ventral striatum mediates recognition of anger

The authors postulated that the ventral striatum (VS) is involved in anger recognition, based on previously described observations and animal work. Four patients with lesions of the VS were recruited and compared with four patients with dorsal basal ganglia damage and neurologically normal controls. Baseline IQ and audiometry were performed. Patients completed a number of tasks including visual recognition of emotion, vocal recognition (sounds and prosody of spoken digits), and questionnaires pertaining to the personal experience of anger. Patients with VS lesions scored poorly on anger recognition tasks, particularly visual recognition. The authors felt that this was a specific deficit, particularly as it is fear that is lost non-specifically with ageing and non-specific brain injury. One VS patient reported an increased experience of anger, another a reduced experience, and the remaining two reported no change. Scores fluctuated across different questionnaires. The authors postulated that this result could represent an erratic aggression system in patients with VS lesions, and drew parallels with Huntington’s disease (HD) patients. Previous studies have shown that disgust perception is particularly impaired in HD patients although anger perception is also impaired. The authors hypothesised that impaired recognition of disgust could result from degeneration in the insula while striatal dysfunction and degeneration could account for impaired recognition of anger. Based on functional MRI studies, it has been postulated that the amygdala, which mediates fear perception, may also be involved in defensive aggression (which is partly fear mediated). The authors concluded that the VS and frontostriatal circuitry is involved with competitive aggression, and acquiring resources, which requires recognition of anger in others. - WP