

EDITOR'S CHOICE

The neuroscience of pleasurable caresses

It remains true that close observations of patients with neurological diseases can inform basic neuroscience. Take, for instance, the case of GL, now aged 54. At the age of 31, she had several episodes, apparently, of "polyradiculitis and polyneuropathy" that has been stable ever since: presumably a form of Guillain-Barre syndrome. Curiously, the immune attack was directed only against large myelinated fibres; a sural nerve biopsy showed preservation of small myelinated and unmyelinated fibres. Interestingly, and in contrast to the predictions of the gate-control theory of pain, her appreciation of noxious stimuli was no different from controls. Another prediction would be that she could only perceive pain and temperature sensations. But this Canadian-Swedish group decided to exploit the patient's unique deficit and explore whether she –like some animal studies have claimed– had some form of tactile sensation subserved by small fibres: "C tactile afferents" which are found only in hairy skin. And indeed she could detect a soft brushing motion on hairy skin, such as the forearm, but not on the palm. She could not identify the brushing stimulus, or describe the path that brush took across her skin, or detect vibration on hairy skin. She perceived the brushing as a very faint "touch", but she strongly felt a pleasant ill-defined sensation. In a functional MRI study, stroking hairy skin activated GL's insular cortex but not the somatosensory areas. The authors suggest that the C tactile afferents are not involved in discriminative sensation, but rather subserve a system for "limbic touch" where caress-like sensations arouse pleasure. **-AJC**

Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G, Ekholm S, Strigo I, Worsley K, Vallbo AB, Bushnell MC.

Unmyelinated tactile afferents signal touch and project to insular cortex.

NATURE NEUROSCIENCE

2002 Jul 29 (E-publication on-line)

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PERIPHERAL NERVE

☆☆☆ RECOMMENDED

Hereditary neuropathies: all sorted?

The last decade has seen major advances in our understanding of the genetic basis of hereditary neuropathies. Many of us routinely request peripheral myelin protein 22 (PMP22) gene analysis in patients with an inherited severe demyelinating sensori-motor neuropathy and suspected Charcot Marie Tooth disease (CMT 1a, MIM 118200). Often the test comes back negative – so what do we do then? Boerkeol et al. in Houston have addressed this question by carrying out a thorough molecular genetic analysis of their cohort of 153 genealogically unrelated patients with a suspected inherited neuropathy. The authors acknowledge that their specialist interest in inherited disorders will have led to a biased cohort, but a similar bias probably reflects the kind of patients that UK neurologists would consider referring for genetic testing in any case. In the Houston cohort, 91% of cases had a family history suggestive of a dominant neuropathy, 3% had a family history suggestive of a recessive neuropathy, and 6% were sporadic cases. Interestingly, they did not classify their patients neurophysiologically prior to genetic testing. The results confirm that the 17p12 duplication in PMP22 is the most common cause of an inherited neuropathy (51.6% of the 153 cases). The second most common cause were mutations in the gap junction protein b1 gene (GJB1, or connexin 32, 7.2%). Point mutations in myelin protein zero (MPZ) accounted for 3.3%, and point mutations in PMP22 also accounted for 3.3%. Mutations in the other genes known to cause peripheral neuropathy were extremely rare, causing <1% each of the 153 cases (these included the genes for early growth response factor 2, EGR2; periaxin, PRX; myotubularin related protein 2, MTMR2; and N-myc downstream regulated gene, NEFL). No mutations were found in 32.7% of the 153 cases – approximately 1/3. This is an important paper, but it raises more questions than it answers. What causes the remaining 1/3 of presumed inherited neuropathies, how can we explain the extreme clinical variation between family members harbouring the same gene defect, and why can different mutations in the same gene (MPZ) cause a predominantly axonopathic picture in some and a predominantly demyelinating neuropathy in others? Finally, studies such as this one raise the provocative question: should we think about a blood test first, and reserve neurophysiology for the difficult cases? This may be unrealistic at present, but now we have identified most of the genes involved in hereditary neuropathies, we simply need to wait for high throughput molecular genetic diagnostic technology to catch up. **-PFC**

Boerkeol CF, Takashima H, Garcia CA, Olney RK, Johnson J, Berry K, Russo P, Kennedy S, Teebi AS, Scavina M, Williams LL, Mancias P, Butler LJ, Krajewski K, Shy M, Lupski JR.

Charcot-Marie-Tooth disease and related neuropathies: mutation distribution and genotype-phenotype correlation.

ANNALS OF NEUROLOGY

2002;51:190-201

How do intravenous immunoglobulins work in Guillain-Barre?

Guillain-Barre is usually envisaged as a T cell-driven autoimmune disease that leads to inflammation and demyelination of proximal nerve root and peripheral nerve. However Angela Vincent's group in Oxford, as well as the authors of this study, have shown in the past that antibodies circulating in patients with Guillain-Barre syndrome cause electrical conduction block in animal models of neuromuscular transmission. Klaus Toyka's group in Wurzburg have now investigated whether IVIG in Guillain-Barre operates on this pathogenic mechanism. They studied the effect of sera from seven patients, both before and after IVIG, on neuromuscular transmis-

sion in the mouse hemidiaphragm model. With a "macro" patch-clamp (larger than the conventional sort), the electrode can perfuse, and record from, both the pre- and post-synaptic membranes. They showed that sera from patients before IVIG reduced the quantal release of acetyl-choline and blocked neuromuscular conduction. Sera taken after IVIG did not have the same effect. Most interesting of all, mixing the pre- and post-IVIG serum samples abolished the former's blocking effect, as did incubation of the pre-infusion specimen with therapeutic-grade IVIG.

This suggests that part of the effect of therapeutic IVIG on Guillain-Barre may be the restoration of conduction at neuromuscular junctions. This should be eminently testable by serial electrophysiological analyses of patients. Perhaps this explains why some patients with Guillain-Barre improve so quickly after IVIG, far quicker than could be accounted for by a cellular repair process. -*AJC*

Buchwald B, Ahangari R, Weishaupt A, Toyka K.
Intravenous immunoglobulins neutralize blocking antibodies in Guillain-Barré syndrome.
ANNALS OF NEUROLOGY
2002 51: 673-680

NEUROGENETICS

☆☆☆ RECOMMENDED

Vanishing white matter disease

The widespread use of Magnetic Resonance Imaging has led to identification of many patients with unexplained leukodystrophies, particularly in childhood. At present it is only possible to reach a specific biochemical or molecular diagnosis in a small proportion of these cases. Vanishing white matter disease (VWM, MIM 603896, also called childhood ataxia with central hypomyelination) is one of these disorders. It is instantly recognisable by the striking appearance of the white matter on MRI, with large areas that have the same signal intensity as CSF on all pulse sequences, including proton density and FLAIR images. In sagittal section, the brain appears to have large cavities extending throughout the white matter, separated by fine septae radiating from the corpus callosum. VWM disease usually presents in childhood with ataxia, spasticity, seizures and optic atrophy with mild cognitive decline. Sudden deterioration in VWM disease is well described following head injury or in association with viral infections. Interestingly, presymptomatic young adults have been described with the disorder, and it may present in middle age with a slowly progressive dementia. The inheritance pattern of VWM is autosomal recessive, and the molecular basis has just been identified. Mutations in each of the five subunits of the eukaryotic translation initiation factor (eIF2B) gene have been described in patients with VWM disease. eIF2B initiates and regulates the translation of messenger RNA within the cytoplasm, and the mutations in patients with VWM are the first gene defects to disrupt this critical cellular process. It is intriguing why this should cause a disease that solely affects the white matter of the brain. Although VWM will probably turn out to be a rare disorder, it may present in adult life, and it is worth looking at the images in the clinical papers. Once seen – never forgotten. -*PFC*

Leegwater PA, Vermeulen G, Konst AA, Naidu S, Mulders J, Visser A, Kersbergen P, Mobach D, Fonds D, van Berkel CG, Lemmers RJ, Frants RR, Oudejans CB, Schutgens RB, Pronk JC, van der Knaap MS.

Subunits of the translation initiation factor eIF2B are mutated in leukoencephalopathy with vanishing white matter.

NATURE GENETICS
2001;29:383-388

Prass K, Bruck W, Schroder NW, Bender A, Prass M, Wolf T, Van

der Knaap MS, Zschenderlein R.
Adult-onset leukoencephalopathy with vanishing white matter presenting with dementia.

ANNALS OF NEUROLOGY
2001;50:665-668

van der Knaap MS, Leegwater PA, Konst AA, Visser A, Naidu S, Oudejans CB, Schutgens RB, Pronk JC.

Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter.

ANNALS OF NEUROLOGY
2002;51:264-270.

☆☆☆ RECOMMENDED

Huntington's disease-like 2 - how common is this?

There are an ever-growing number of patients who develop what looks like Huntington's disease but don't have the appropriate CAG repeat in the huntingtin gene. These cases represent a heterogeneous group of patients, some of whom display clear inheritance. In 2001 Margolis et al (*Ann.Neurol.* 50:373-380) described an HD like disorder that mapped to chromosome 16 and was associated with a CAG/CTG repeat in the gene coding for junctophilin-3. This condition has been termed Huntington disease-like 2 and to date has only been found in families of African origin. In order to ascertain how common it is in Europe, Bauer et al report their findings in a short letter to the *Annals of Neurology* (which is easy to overlook) on the frequency of this gene defect in the cohort of patients from Austria and Germany who have "gene negative" HD. This group consists of a staggering 1,600 patients referred by neurologists for HD testing that were negative for the gene, in so much as they had a CAG repeat length in exon 1 of huntingtin of less than 37. On testing, none of the patients had an expanded allele in the junctophilin-3 gene, which explains its reporting as a letter rather than a full report.

This paper is important for those involved in HD, as it means that this gene defect is unlikely to be of significance in individuals of a non-African background who present with an HD like illness. It is also important in highlighting the fact that negative results can often be overlooked because they are deemed to be low priority publications, and as such biases can be left in the literature and so in clinical practice - *RAB*.

Bauer J, Gencik M, Laccione F, Peters H, Weber BH, Feder EH, Weirich H, Morris-Rosendahl DJ, Rolfs A, Gencikova A, Bauer P, Wenning GK, Epplen JT, Holmes SE, Margolis RL, Ross CA, Riess O.

Trinucleotide repeat expansions in the junctophilin-3 gene are not found in Caucasian patients with a Huntington's disease-like phenotype.

ANNALS OF NEUROLOGY
2002 51:662.

☆☆☆ RECOMMENDED

Copy a flower or draw a clock?

Unilateral neglect is common after right hemisphere stroke and is associated with poor functional outcome. It is therefore important to identify the problem early and monitor it. However screening is often haphazard. Clinicians may choose a single quick and easy bedside test such as asking the patient to draw a flower or to spot a wiggling finger, when they are examined on admission, but very often the neglect is discovered later by observation from staff. Choosing the best early detection test is a problem, since there are many and the tests' sensitivities are often unknown.

19 centres in France and Belgium have collaborated to assess the sensitivity of a battery of tests for spatial neglect and compare

the results with performance on a behavioural test comprising 10 daily living tasks. 206 consecutive patients suffering from first ever unilateral right hemisphere stroke were included. Most were in rehabilitation settings. The patients were tested on pencil and paper tests: bells cancellation test, figure copying, clock drawing, line bisection and writing, a reading test, recognition of overlapping figures as well as assessments to determine gaze orientation, the ability to find the left hand using the right and bilateral finger wiggling for extinction. In two of the participating centres a standardised behavioural assessment was also performed.

According to the behavioural assessment, neglect was considered as clinically significant in about one third of cases but detection of neglect varied greatly between the pencil and paper tests. The proportion of patients who scored below normal ranged from 19-50%. More than 85% of patients presented with some degree of neglect on at least one test. The bell's test was found to be the most sensitive, in particular the measurement of the patient's starting point of cancellation. The line bisection test was the least sensitive. The presence of neglect was found to be task dependent and the results of this study support the view that neglect is not a simple unitary disorder. It follows then that several tests done by the bedside are more likely than a single test to detect neglect that will affect behavioural performance. Following the results of multiple regression from this large study the French Study Group suggest that the bells cancellation test, figure copying and clock drawing used together as a battery would pick up neglect in the majority of cases. -AJT

Azouvi P, Samuel C, Louis-Dreyfus A et al., for the French Collaborative Study Group on Assessment of Unilateral Neglect Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke.

JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY
2002; 73: 160-66

Chiropractic Manipulation And Stroke

There are many reports of posterior circulation stroke secondary to vertebral artery dissection seemingly provoked by chiropractic manipulation of the neck. However these are generally anecdotal cases or small series. Thus the true relationship of chiropractic manipulation as a cause of stroke is open to publication, selection and recall bias. This study seeks to determine whether, and if so with what risk, chiropractic manipulation of the neck really does lead to vertebrobasilar infarction.

Each of 582 patients with a posterior circulation infarct admitted to hospital in Ontario were identified retrospectively and matched to 4 controls from the local population. Public health billing records were used to identify all persons having chiropractic manipulation prior to the event date.

Patients under the age of 45 were five times (95% CI 1.32-43.87) more likely to have undergone chiropractic manipulation than controls in the week before stroke onset and were five times as likely (95% CI 1.34-18.57) to have made 3 or more visits to a chiropractor for neck manipulation in the previous month. There was no association for patients over the age of 45 yrs.

This is the first population based control study to test the association between chiropractic manipulation and vertebrobasilar stroke and does demonstrate an association for young people. The results correspond to an incidence of 1.3 cases of stroke within 1 week of manipulation per 100 000 (greater than the 1 per million previously suggested). However biases do exist - patients who may have had a subarachnoid haemorrhage from intracranial extension of the vertebral dissection and patients with carotid dissections were excluded. The vertebrobasilar strokes were not all proven dissections. The visit to the chiropractor may have been due to the initial neck pain of a spontaneous dissection and the manipulation was not actually the cause of the dissection (although may have aggravated it). Clearly a large prospective population based case control study is the only way to eliminate

such bias but this would require a long study period. Meantime the neurologist who sees a patient with a posterior circulation stroke needs to consider a dissection as a likely cause, patients who have had a previous spontaneous dissection should probably avoid chiropractors and chiropractors should refer on any patient who develops neurological symptoms between or after treatment sessions. Should they warn patients of the risk? Since it is 1:100 000 presumably not. -PM

Rothwell DM, Bondy SJ, Williams JI.

Chiropractic manipulation and stroke: a population-based case-control study.

STROKE
2001;32:1054-1059

DEMENTIA

BACE: a therapeutic target in Alzheimer's disease

The amyloid b-peptide (Ab) that accumulates in the plaques in Alzheimer's disease (AD) brain is derived from the amyloid precursor protein (APP) by sequential activity of b- and g-secretases. A novel transmembrane aspartyl protease, b-site APP cleaving enzyme or BACE, also known as Asp2, has been characterised as b-secretase. This study examined BACE in human brain (sporadic AD, normal, and neurological controls).

BACE immunoreactivity in Western blots was quantified by image densitometry. Compared to b-tubulin, whose signal did not differ between AD and the control groups, BACE showed a 2.7 fold increase in expression in AD brain, and a 2.5 fold increase compared to a-synuclein. Consistent with increased BACE expression, there was a 1.8 fold increase in the signal for b-CTF/b-tubulin; b-CTF is the C-terminal fragment of APP produced by b-secretase cleavage, and the direct precursor of Ab.

Competitive reverse transcription polymerase chain reaction was used to quantify BACE mRNA levels. Similar results were found in AD and controls, suggesting no increase in message expression. Hence an alteration in protein metabolism would seem to be the cause of increased BACE expression.

Although the precise mechanism of increased BACE expression in AD brain is unknown, this study does suggest that BACE is a logical target for AD treatment. BACE knockout animals are viable and normal although devoid of Ab generation. Patents claiming BACE inhibitors for the treatment of AD have already been filed.

-AJL

Holsinger RMD, McLean CA, Beyreuther K, Masters CL, Evin G. Increased expression of the amyloid precursor b-secretase in Alzheimer's disease.

ANNALS OF NEUROLOGY
2002;51(6):783-786

MULTIPLE SCLEROSIS

☆☆☆ RECOMMENDED

How pregnancy protects mum in MS

It has long been recognized that women with multiple sclerosis experience fewer relapses during the third trimester of pregnancy compared to any other time. In a small study, in which two pregnant women with MS underwent serial MRI scans, a parallel reduction in T2-weighted lesions was demonstrated in the third trimester. A recent prospective study, published in the New England Journal of Medicine (1998) by Christian Confavreux, followed over 200 women with MS through their pregnancies and confirmed a statistically significant reduction in relapse rate during pregnancy, and an equal increase immediately afterwards.

Uncovering the mechanism by which relapses are reduced in late pregnancy would reveal a potential treatment that is more

effective than any of the currently licensed disease modifying drugs. To identify the mechanism by which pregnancy reduces disease activity in MS, Langer-Gould et al from Stanford used a mouse model of relapsing remitting multiple sclerosis (Relapsing Remitting Experimental Autoimmune Encephalitis – EAE). They then explored the effect of pregnancy on (i) the susceptibility to EAE; (ii) relapse rate; and (iii) the phenotype of the T cells driving the autoimmune process. They clearly demonstrated a reduction in relapse rate in late pregnancy as expected, and also a marked reduction in disease susceptibility if induction was attempted during mid/late pregnancy. (Interestingly, it has been observed that women whose first MS relapse is during pregnancy tend to follow a more benign disease course.) On the analysis of T cell function from pregnant 'protected' mice compared with virgin mice the group found no difference. They demonstrated the T cells had a Th1-cytotoxic-phenotype irrespective of whether or not the animal was pregnant. This was a surprise: hitherto the explanation for the protective effect of pregnancy had been a shift in the phenotype of T cells from Th1 to Th2. However, when serum from a pregnant mouse was added to cells from a virgin or pregnant mouse there was a reduction in the cytotoxicity of cells from both pregnant and non-pregnant mice. This phenomenon was not seen when serum was used from the non-pregnant mice. They concluded that a substance present in the serum during pregnancy was responsible for preventing the cytotoxic T cells from causing inflammation in the central nervous system.

The hunt is now on to identify the pregnancy related serum factor that keeps the self-reactive T cells in check. If it can be bottled, a treatment significantly more effective than currently available disease modifying drugs may emerge.

Langer-Gould A, Garren H, Slansky A, Ruiz PJ, Steinman L.

Late pregnancy suppresses relapses in experimental autoimmune encephalomyelitis: evidence for a suppressive pregnancy-related serum factor.

JOURNAL OF IMMUNOLOGY
2002 Jul 15;169(2):1084-91.

EPILEPSY

Towards a mechanism of antiepileptic drug teratogenicity:

Any article involving the human ether-a-go-go-related gene (HERG) is bound to draw my attention. Though sadly not related to the Moulin Rouge, this article provides an insight into a possible mechanism of antiepileptic drug teratogenicity, an issue faced daily by most neurologists. The gene encodes the major human

cardiac repolarisation channel (Ikr). During weeks 5-9 of development, class III anti-arrhythmics (blocking Ikr), trimethadione and phenytoin will induce identical embryonic arrhythmias at concentrations not affecting the maternal heart. Episodic hypoxia causes similar teratogenic changes and it is proposed that arrhythmia-induced hypoxia underlies the teratogenicity of these drugs. The pathological changes of vascular disruption and haemorrhage into the palate are similar for phenytoin and induced episodic hypoxia.

The current experiment was to explore the teratogenic properties of dimethadione (DMO), the active metabolite of the antiepileptic drug trimethadione. DMO was given intraperitoneally to mice on gestational day 9-16 at 1000mg/Kg, to identify the sensitive period. DMO was given at 125-1000mg/kg on day 12, which seemed to be the most sensitive day, to test dose effect relationships. Some mice were pre-treated with α -phenyl-N-tert-butyl-nitron (BPN) a scavenger of reactive oxygen species. A placebo arm received just saline. Mice were sacrificed 24-28hrs after the dose of DMO. Observations on the mice included heart rate measurements, patch clamping to assess prolongation of the Q-T interval, which is a measure of abnormal cardiac repolarisation. Pathological examinations were made including somite number and assessment for palatal haemorrhage. In this study DMO caused early embryonic deaths in 16%, late foetal deaths in 9% and cleft palate. The main effect of PBN was to reduce cleft palate in a dose dependent fashion with a less clear effect on embryonic deaths.

The effect of DMO on heart rate was dramatic, with dose-dependent bradycardia (69% reduction in HR at the highest dose) and arrhythmia (29% at the highest dose), without affecting maternal heart rate. DMO had a clear dose-dependent effect on Ikr although the effect of TMO was less clear. The maximal effect of these drugs was at gestational day 12 and it disappeared after GD 13. These data support the view that DMO interferes with foetal heart rate. The timing of this effect coincides with the timing of development of cleft palate and corresponds to the appropriate period in humans. Although this effect is commoner in animals treated with trimethadione than phenytoin, it is fundamentally similar. Real progress is being made towards our understanding of foetal abnormalities with this group of drugs, which may help in anticipating problems with other drugs, if they can be tested against this model. -**MRAM**

Azarbayjani F and Danielsson BR.

Embryonic arrhythmia by inhibition of HERG channels: a common hypoxia-related teratogenic mechanism for antiepileptic drugs.

EPILEPSIA
2002;43:457-268

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