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ACNR

Advances in Clinical Neuroscience & Rehabilitation

REVIEW ARTICLES

Embryonic Stem Cells, Meng Li

Post-Polio Syndrome – Diagnosis and Management, Elisabeth Farbu

Conference and Society News • Journal Reviews • Diary of Events

MANAGEMENT TOPIC – The Management of Intracranial Abscesses

COGNITIVE PRIMER – Apraxia

REHABILITATION ARTICLE – Sacral Nerve Stimulation (Neuromodulation) for the Treatment of Lower Urinary Tract Symptoms in Adult Patients

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Welcome to the fifth year of ACNR. Once more this issue has a variety of articles written by authorative experts both from within the UK and abroad.

The first of our review articles is on the post-polio syndrome by Dr Elisabeth Farbu from Bergen in Norway. This condition is now relatively rare and despite being first described by Raymond and Charcot in 1875, has always been a controversial area. I certainly remember as an SHO the debates that used to rage on the Phipps (now Lane-Fox) respiratory unit at St Thomas' Hospital as to whether this was a true disorder, or simply the natural ageing of a body with weak muscles. In her article, Dr Farbu lays to rest this controversy by setting out in beautiful clarity the diagnosis (including the strict diagnostic criteria in table 1) and management of this condition. This article is complimented by a case report on the web site prepared by Alastair Wilkins of a patient with this syndrome.

Meng Li in her review article reveals the truth about embryonic stem (ES) cells, without any of the hype that often accompanies articles on these, the most versatile, of stem cells. These stem cells have attracted much publicity not only in terms of the ethical issues they raise but their biological utility to reveal answers to normal development as well as their potential therapeutic use in neurological disorders. In this last respect the need to engineer controlled differentiation of ES cells into neurons remains a high priority, as does the need to prevent them from proliferating in an uncontrolled tumourigenic fashion. Meng Li deals with these issues along with the broader topic of using mouse ES cells to make transgenic animals, which has so revolutionised modern biology. This article is succinct, packed with information and a marvellous condensation of this expanding field – an area of neurobiology that will have relevance to all those working in neuroscience and neurology.

Neurosurgery in this issue takes on the subject of intracranial abscesses. Peter Whitfield takes us through this relatively rare condition with its range of presentations and therapies – many of which are surgical and based on the approach of MacEwen from 1881 of "debridement and drainage". This article, as with all in these series, is steeped in common sense and beautifully illustrated with plenty of relevant radiographic images. This article is a superb accompaniment to the neuropathology article by Daniel du Plessis in ACNR 4(6).

The management of lower urinary tract symptoms is encountered by most neurologists and rehabilitationists, and is typically treated using anti-cholinergic drugs and/or some form of catheterisation. In the article by Simon Harrison and colleagues in this issue, we are given a state of the art discussion on the use of sacral nerve stimulators - a procedure that is not without difficulties, but which also appears to be of great value to some selected groups of patients. Although this technique is expensive and still being developed, the article should at least raise the profile of this procedure which was certainly new to me.

Neuropathology considers head injury (HI), and Colin Smith takes us through the different types of HI and how they evolve over time. This touches upon other topics we have covered in the past, including states of persistently altered consciousness (see Zeman ACNR 3(3)) and dementia. This article contains the usual educational plethora of histological images.

Andrew Larner tells us that no sign in neurology is to be believed!! He discusses the topographical anatomy of false-localising signs, starting with Colliers paper in Brain in 1904, in which he observed that 12.4% of patients with brain tumours had false-localising signs. This short account by Andrew is, as always, beautifully written (unlike most of my editorials) and is a real education.

In the cognitive primer series, Sebastian Crutch discusses Apraxia. This inability to perform purposeful voluntary movements in the presence of intact motor and sensory systems is one of the most fascinating and memorable deficits in neurological practice. This article comprehensively takes us through the range of different types of dyspraxia, and how they can be recognised and tested for along with their neural basis.

In drugs in neurology, Wendy Phillips and myself discuss tetrabenazine – the drug most commonly prescribed for chorea and related movement disorders. This drug, with its long history of use in neurology and psychiatry, is still not especially well-known to many practitioners because of its relatively selective indications.

As usual there are the journal, conference and book reviews. So as ACNR enters 2005, do keep the feedback coming and thanks for all your support and encouragement over the last 4 years with this exciting and evolving project.

Roger Barker, Co-Editor,
Email: roger@acnr.co.uk

A new drug has been licensed in the US

There is a new potential treatment for multiple sclerosis: natalizumab, given by IV infusion once a month. We know this drug better by the name Antegren, although for some extraordinary reason the owners (Biogen) have renamed it Tysabri. It is a monoclonal antibody that targets an adhesion molecule (VLA-4) on lymphocytes and so prevents them from latching onto CNS endothelium and crossing the blood-brain-barrier. Its approval is based on the 12 month data from two large, two-year phase III trials. The AFFIRM trial (n> 900) people showed natalizumab reduced the relapse rate by 66 per cent compared to placebo and the SENTINEL trial (n=1,200) showed that natalizumab and interferon-beta reduce relapse rate by 54% compared to interferon alone. However, before getting too excited, we need to see the trial data. Astonishingly, the only information available at present is directly from the manufacturing pharmaceutical company. The results have not yet been published in a peer-reviewed journal. Furthermore, the critical data -on whether natalizumab impacts on the accumulation of disability in multiple sclerosis - has not been released at all. An application for the European licensing of natalizumab was submitted to the European Medicines Agency (EMEA) in June 2004 and a marketing authorisation is expected towards the end of 2005. Even if it is licensed, NICE will have to be satisfied that natalizumab offers value for money, a test which the interferons failed. And if that is successful, neurology centres are going to have to face the daunting task of administering a monthly infusion to everyone who is suitable for the treatment. For the sake of people with multiple sclerosis, who may have a lot to benefit from this exciting treatment, we need to ensure natalizumab is efficiently and critically assessed at each hurdle. Exciting times!

Alasdair Coles, Co-Editor, Email: alasdair@acnr.co.uk

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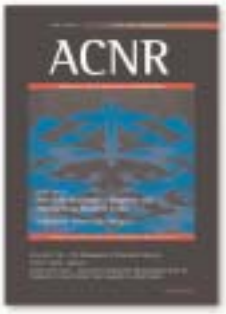
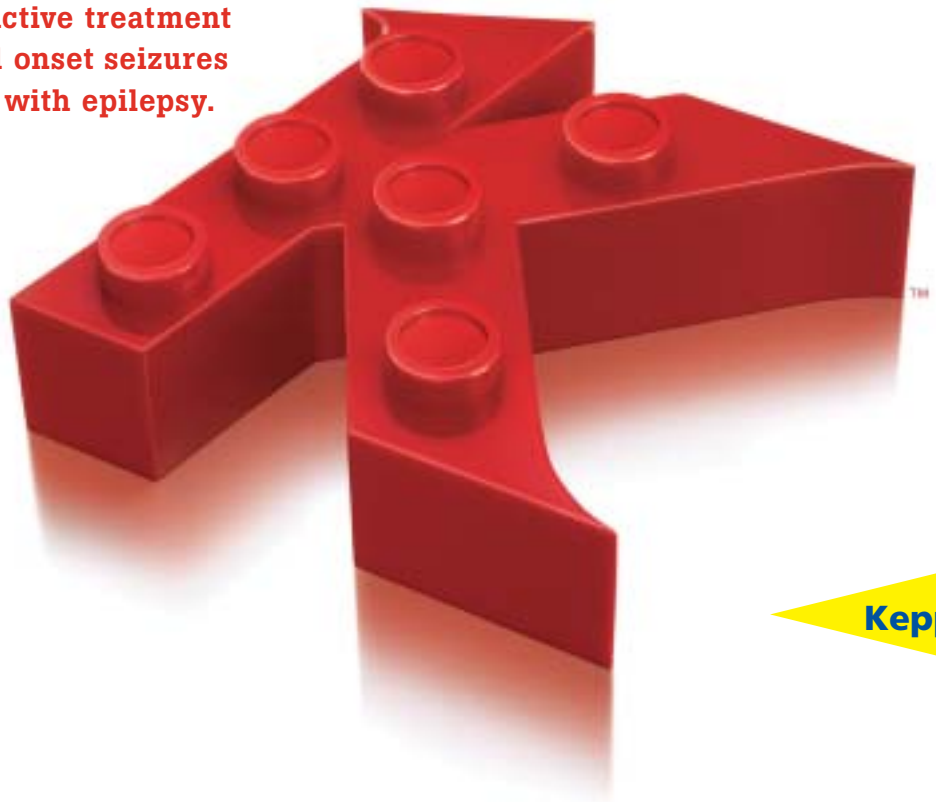


Cover picture:
Courtesy of Psychology Press, taken from Dyslexia, Reading and the Brain by Alan Beaton.
See page 45 for more information.

For adjunctive treatment of partial onset seizures in adults with epilepsy.



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Date of preparation: September 2004.

References:
1. Krakow K, Walker M, Otoul C, Sander JWAS. Long-term continuation of Levetiracetam in patients with refractory epilepsy. *Neurology.* 2001; 56: 1772-1774. **2.** Patsalos PN. Pharmacokinetic profile of Levetiracetam: toward ideal characteristics. *Pharmacol Ther.* 2000; 85: 77-85. **3.** French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. *Epilepsy Res.* 2001; 47: 77-90.

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Embryonic Stem Cells

Key properties of ES cells

Embryonic stem (ES) cells are karyotypically normal continuous cell lines isolated directly from the inner cell mass of the blastocyst embryo. ES cells are unique stem cells as they retain the developmental potency of foetal founder cells even after extended propagation and manipulation in culture. When transferred to a preimplantation mouse embryo, ES cells incorporate to the inner cell mass and generate mice that are chimeric both in somatic and germ tissues[1] (Fig 1).

ES cells were initially isolated and maintained by co-culture on feeder layers of mitotically inactivated mouse fibroblasts.[2,3] It was identified later that the fibroblast feeders express the stem cell regulator leukaemia inhibitory factor (LIF) which actively suppress differentiation.[4,5] LIF is able to completely replace feeder layers, not only in the maintenance of previously established ES cell lines, but also in the *de novo* establishment of karyotypically normal and germ line competent ES cell lines.[5] This property has enabled the culture of homogeneous population of pluripotent ES cells in the absence of contaminating fibroblasts.

Recently, it was discovered that bone morphogenic proteins (BMPs) act in combination with LIF to sustain self-renewal and preserve multilineage differentiation of ES cells in serum-free condition.[6] This fully defined culture paradigm also supports the generation of germ line competent ES cell lines. In the absence of LIF, however, BMP stimulates differentiation, suggesting that a very delicate balance of different signalling pathways regulate ES cell self-renewal versus differentiation.

Creation of designer mouse models

The capacity for germ-line colonisation means that ES cells can be exploited as vehicles for transgenic manipulation of the mouse genome, via introduction of new genetic information or the alteration of the host gene sequences. Indeed, the major use of ES cells to date is as a cellular tool for the production of mice carrying predetermined genetic modification generated by homologous recombination or gene targeting. The planned alteration of a gene is first generated in genome of ES cells in tissue culture. Genetically modified ES cells can then be injected into recipient blastocysts, where they contribute differentiated progeny to their host, resulting in the birth of genetically modified chimeric pups. Following germline transmission, mice that carry a defined mutation of a gene are generated. The genetic modification can now be designed in a sophisticated manner such that the mutation can be temporally and spatially regulated (conditional knock-out), by exploiting the Cre-loxP system and cell/tissue specific regulatory elements. Over the past decade, gene targeting by homologous recombination has revolutionised the field of mouse genetics and allowed the analysis of diverse aspects of gene function *in vivo*.

Cellular model for developmental studies

The integration of ES cells into normal embryonic development demonstrates their capacity to respond to a repertoire of developmental regulatory signals. Therefore, ES cells provide an invaluable *in vitro* system for the experimental identification and characterisation of factors that control early embryonic growth and differentiation. In particular the system is well suited to investigating the capacity of genes through 'gain of function' studies, since they permit the study of specific gene overexpression in a given differentiation lineage without having to worry about the effects of such an overexpression on the overall embryonic development. We have successfully applied this approach in determining Sox B transcription factors in neural fate choice from pluripotent stem cells, and in a functional screen of candidate neural genes following a microarray transcriptome analysis.[7,8,9] Conversely, ES cells also provide an ideal system for 'loss of function' studies either via siRNA technology (knock-down) or gene targeting of specific gene.

Therapeutic potential of ES cells

The establishment of human ES cells has sparked much interest in both the scientific and general community regarding their potential in regenerative therapies.[10,11] Cell transplantation can in principle be applied to many

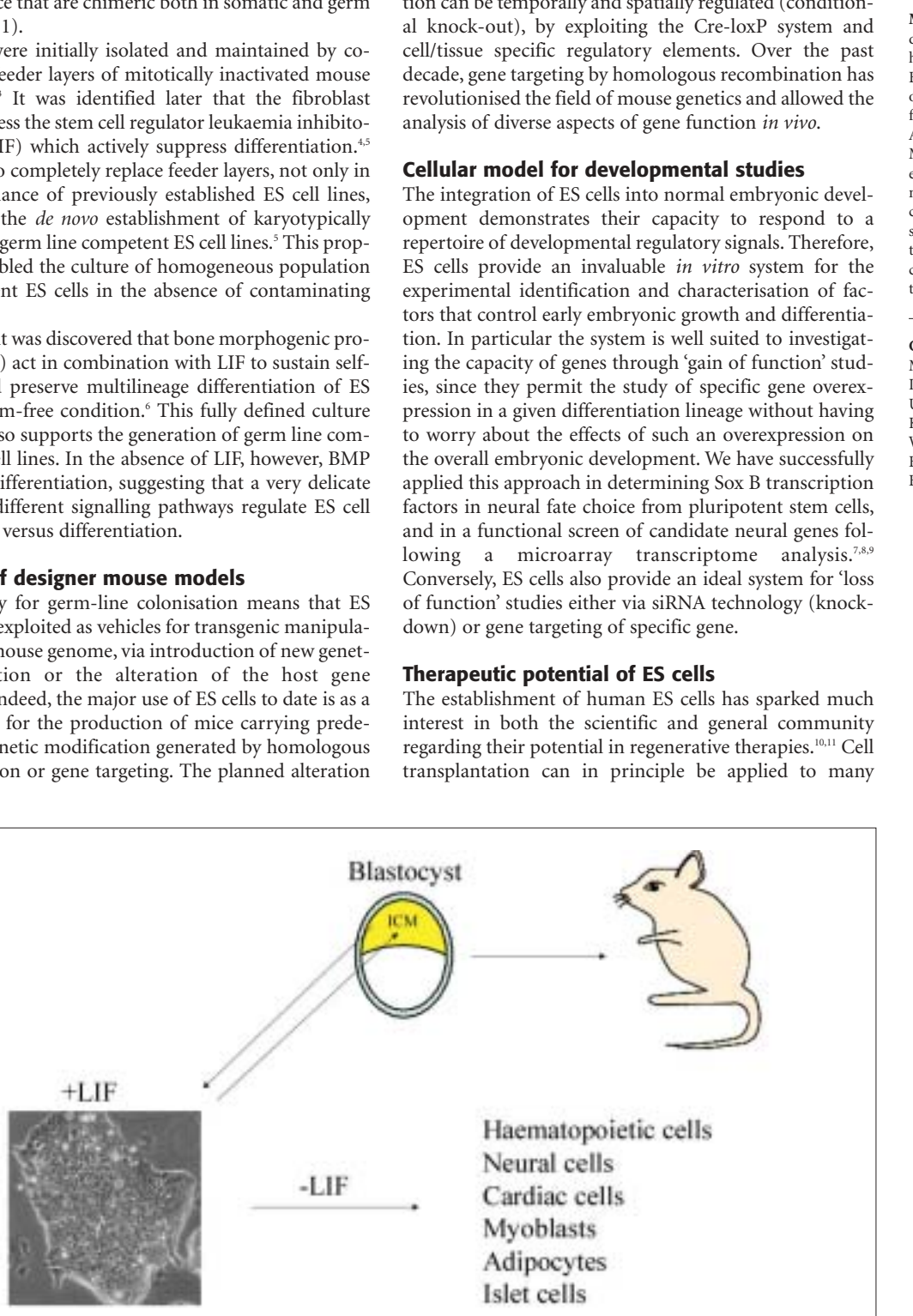

Fig 1: Diagram summarises the propagation and use of ES cells. Photograph of self-renewing mouse ES cells cultured in the presence of LIF in serum on gelatine coated plastics. Upper panel depicts the inter relationship between ES cells, the inner cell mass (ICM) cells of the blastocyst embryos, and chimeric mice. In the absence of LIF under suitable culture condition, ES cells can give rise to many differentiated somatic cell types. Photograph of the ES cells provided courtesy of QL Ying.

Meng Li completed her medical degree in Beijing University and her PhD at the University of Edinburgh. She established her own laboratory in 2000 following a Career Development Award from the UK MRC. Meng's research is focused on elucidating the cellular and molecular mechanisms that control dopaminergic neuron specification and axon connectivity, using embryonic stem cells and modern transgenic technologies.

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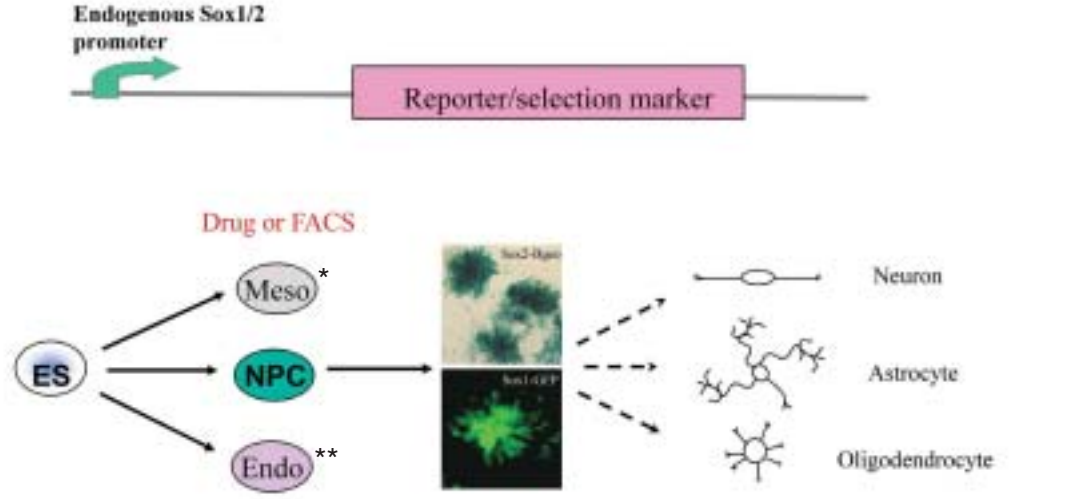

Fig 2: Neural lineage selection strategy. The approach involves firstly the generation of ES cells in which a reporter (GFP or lacZ) and/or a drug selection marker (e.g. neo) is targeted into the Sox1 or Sox2 locus via homologous recombination. Following in vitro differentiation of ES cells, either drug selection or fluorescence-activated cell sorting (FACS) can be applied to isolate cells of interest, in this application, neural stem/progenitor cells.

human diseases such as leukaemia, diabetes and some neural degenerative diseases. Many protocols have been developed to differentiate ES cells, so far mostly of mice, into a variety of cell types which includes neurons,[12] adipocytes,[13] skeletal myocytes and hematopoietic cells[14] and cardiomycytes.[15] Transplantation studies have demonstrated a certain degree of functional repair in animal models of multiple sclerosis[16] and spinal cord injury.[17]

However, our abilities to direct ES cells into specific pathways and then to support the viability and maturation of individual differentiated phenotypes in vitro remains limited. Consequently, the differentiating ES cell cultures constitute heterogeneous types of differentiated ES cell progeny with unknown phenotypes. In the absence of knowledge to instruct ES cells into a specific fate, strategies have been developed to enrich or isolate phenotypes of interest from the mix cell population. This can be achieved through selective culture condition[14] or fluorescence-activated cell sorting (FACS).[18] In addition, drug resistance or cell sorting capacity conferred by genetic manipulation in ES cells provides another way of isolating a particular cell lineage or cell types.[19,20] We have successfully applied this approach in purifying ES cell derived neural stem/progenitors based on specific expression of Sox1 and Sox2 in developing neuroepithelium[20,21] (Fig 2).

Recently, we have investigated the ability of SoxB proteins in influencing ES cell lineage choice. We found that forced expression of Sox1 or Sox2 does not impair propagation of undifferentiated ES cells, but upon release from self-renewal by LIF withdrawal promoted differentiation into neuroectoderm at the expense of mesoderm and endoderm. The efficient specification of a primary lineage by transcription factor manipulation or their down stream signalling cascade may provide a general paradigm for instructing differentiation of ES cells for biopharmaceutical screening and cell therapy applications.[9]

Conclusions

The mouse ES cells have provided us with an unprecedented opportunity to understand mammalian development and molecular mechanisms that lead to pathological situations. The development of human ES cells now offers the foundation of applying ES cell technology to the treatment of human diseases. However, much remains to be accomplished with regards to human ES cell technology before they can be used as a new form of human medicine.

References

1. Bradley A, Evans MJ, Kaufman MH, Robertson E. *Formation of germ-line chimaeras from embryo-derived teratocarcinoma cell lines.* Nature 1984;309:255-6.
2. Evans MJ, Kaufman M. *Establishment in culture of pluripotential cells from mouse embryos.* Nature 1981;292:154-6.
3. Martin GR. *Isolation of a pluripotent cell line from early mouse embryos cultured in medium conditioned by teratocarcinoma stem cells.* Proc Natl Acad Sci USA 1981;78:7634-8.
4. Gearing PD, Gough NM, King JA, Hilton DJ, Nicola NA, Simpson RJ, Nice EC, Kelso A, Metcalf D. *Molecular cloning and expression of cDNA encoding a murine myeloid leukemia inhibitory factor (LIF).* EMBO J 1987;6:3995-4002.
5. Smith AG, Heath JK, Donaldson DD, Wong GG, Moreau J, Stahl M, Rogers D. *Inhibition of pluripotential embryonic stem cell differentiation by purified polypeptides.* Nature 1988;336:688-90.
6. Ying QL, Nichols J, Chambers I, Smith A. *BMP induction of Id proteins suppresses differentiation and sustains embryonic stem cell self-renewal in collaboration with STAT3.* Cell 2003a ;115:281-92.
7. Aubert J, Dunstan H, Chambers I, Smith A. *Functional gene screening in embryonic stem cells implicates Wnt antagonism in neural differentiation.* Nat Biotechnol 2002;20:1240-45.
8. Aubert J, Stavridis MP, Tweedie S, O'Reilly M, Vierlinger K, Li M, Ghazal P, Pratt T, Mason JO, Roy D, Smith A. *Screening for mammalian neural genes via fluorescence-activated cell sorter purification of neural precursors from Sox1-gfp knock-in mice.* Proc Natl Acad Sci U S A 2003;Suppl:11836-41.
9. Zhao S, Nichols J, Smith A, Li M. *SoxB Transcription Factors Specify Neuroectodermal Lineage Choice in ES Cells.* Mol Cell Neurosci 2004;332-342.
10. Reubinoff BE, Pera MF, Fong CY, Trounson A, Bongso A. *Embryonic stem cell lines from human blastocysts: somatic differentiation in vitro.* Nat Biotechnol 2000;18:399-404.
11. Thomson JA, Odorico JS (2000) *Human embryonic stem cell and embryonic germ cell lines.* Trends Biotechnol 18:53-57.
12. Bain G, Kitchens D, Yao M, Huettner JE, Gottlieb DI. (1995) *Embryonic stem cells express neuronal properties in vitro.* Dev Biol 168:342-357.
13. Dani C, Smith AG, Dessolin S, Leroy P, Staccini L, Villageois P, Darimont C, Ailhaud G (1997) *Differentiation of embryonic stem cells into adipocytes in vitro.* J Cell Sci 110:1279-1285.
14. Wiles MV, Keller G (1991) *Multiple haematopoietic lineages develop from embryonic stem (ES) cells in culture.* Development 111:259-267.
15. Wobus A, Wallukat G, Hescheler J (1991) *pluripotent mouse embryonic stem cells are able to differentiate inot cardiomyocytes expressing chronotropic responses to adrenergic and cholinergic agents and Ca2+ channel blockers.* Differentiation 48:173-182.
16. Brustle O, Jones KN, Learish RD, Karram K, Choudhary K, Wiestler OD, Duncan ID, McKay RD (1999) *Embryonic stem cell-derived glial precursors: A source of myelinating transplants.* Science 285:754-756.
17. Liu S, Qu Y, Stewart TJ, Howard MJ, Chakrabortty S, Holekamp TF, McDonald JW (2000) *Embryonic stem cells differentiate into oligodendrocytes and myelinate in culture and after spinal cord transplantation.* Proc Natl Acad Sci U S A 97:6126-6131.
18. Nishikawa SI, Nishikawa S, Hirashima M, Matsuyoshi N, Kodama H (1998) *Progressive lineage analysis by cell sorting and culture identifies FLK1+VE-cadherin+ cells at a diverging point of endothelial and hemopoietic lineages.* Development 125:1747-1757.
19. Klug MG, Soonpaa MH, Koh GY, Field LJ (1996) *Genetically selected cardiomyocytes from differentiating embronic stem cells form stable intracardiac grafts.* J Clin Invest 98:216-224.
20. Li M, Pevny L, Lovell-Badge R, Smith A (1998) *Generation of purified neural precursors from embryonic stem cells by lineage selection.* Curr Biol 8:971-974.
21. Ying QL, Stavridis M, Griffiths D, Li M, Smith A (2003b) *Conversion of embryonic stem cells into neuroectodermal precursors in adherent monoculture.* Nat Biotechnol 21:183-86.

Post-Polio Syndrome – Diagnosis and Management

Post-polio syndrome is characterised by muscular weakness, pain, and fatigue several years after the acute polio. The first known clinical description dates back to 1875 when Raymond and Charcot reported a 19-year old tanner with previous infantile paralysis who presented with new paresis and atrophy in his shoulder. The subject was not investigated further during the next decade, as paralytic polio was considered to be a three-phase illness with acute pareses followed by a recovery period, and then a life-long stable phase. However, many patients with previous polio experienced a functional decline later on with new symptoms like pain, fatigue, muscle weakness, sleeping problems, and cold intolerance. Halstead introduced the term post-polio syndrome in 1986, describing the symptoms experienced by many polio survivors after decades with stable function. Halstead revised his criteria in 1991[1] (Table 1) where new muscle weakness was included as an obligatory criterion, with or without other symptoms like pain, cold intolerance, and fatigue.

The background and exact pathogenesis for the post-polio syndrome is still not known, although several theories have been explored. Ongoing viral replication or virus reactivation was suggested, but has not been confirmed.[2] An ongoing inflammation has been found in the spinal cord, and recent studies have shown elevated levels of inflammatory cytokines in the spinal fluid.[3] The ageing process may be a contributing factor but does not explain all clinical aspects as post-polio syndrome has been found in patients before the age of 50 years.[4] At higher age, loss of motor neurones and diminishing motor units take place at a higher rate in post-polio patients compared to patients with normal neuromuscular function.[5] Hence, the increased muscle weakness seems to be a result of both an ongoing loss of motor neurones and a diminished ability to maintain their neurogenic supply to enlarged muscle fibres.

The prevalence of post-polio syndrome has been reported to be between 20-80% depending on the polio population being studied and the diagnostic criteria being used.

Diagnosis

Post-polio syndrome is an exclusion diagnosis (Table 1). A careful medical history and clinical examination are necessary to rule out all other conditions that may cause the same symptoms. At clinical examination, signs of lower motor neurone involvement should be present with flaccid muscle weakness or atrophy and diminished tendon reflexes. However, patients who have lost 50% of their motor neurones within one segment can still have a normal clinical picture.[6] This means that subclinical motor neurone involvement may be present, and new muscle weakness may occur in apparently non-affected muscles. EMG can be of help to sort out other neurological and muscular illnesses, and can also establish a motor neurone involvement compatible with previous paralytic polio. However, EMG cannot distinguish between stable polio sequelae and new muscle weakness, and the major role of neurophysiology is to confirm previous polio and exclude other neuromuscular disorders.[7] Disorders not related to the patient's previous polio may be co-existing: neurological and rheumatological disorders, cardiovascular and thyroid disorders, and depression. A thorough investigation to sort out such co-existing disorders is necessary, as these disorders need specific treatment. They should be treated in the same way as in patients without a history of previous polio.

Management

Muscular weakness and fatigue

Even though post-polio syndrome affects only between 20-50% of polio survivors, it is important to have this in mind as polio patients in general report more pain, fatigue, sleeping problems and muscle weakness than healthy controls, and they rate their health lower.[8-10] This is irrespective of the presence of a post-polio syndrome or not. For all practical purposes today's management and treatment will be similar for patients with and without post-polio syndrome (PPS).

No specific medical treatment for PPS has been proven to be effective;

- Pyridostigmine and steroids have been tried in randomised studies without any positive effect with respect to muscle strength and fatigue;[11,12]
- Muscle training at aerobic levels without maximum exercise is useful to maintain muscular function and ameliorate fatigue[13] and muscular training in warm water seems to be particularly useful.[14] Systematic training programmes in a warm climate are more effective than identical training programmes in a cold climate;[15]
- Reorganisation of daily life activities with short breaks (thereby conserving energy expenditure) may help to counteract fatigue. In addition, properly fitted assistive devices (i.e. intermittent use of wheel chair) can help in this respect;
- Inactivity increases the risk of obesity, diabetes, cardiovascular, and muskuloskeletal problems and so polio patients who take part in physical activity have significantly less symptoms than physically inactive patients.[16] All polio patients with or without post-polio syndrome should therefore be advised to take part in physical activity, but they should not be performing static muscular training at maximum effort (anaerobic level) and they should allow intermittent breaks.

Disorders related to previous polio

Patients with previous polio are more prone to developing overuse symptoms and disorders like soft tissue inflammation, arthrosis, spinal degenerative disorders, and nerve entrapment due to asymmetric weight bearing. Carefully fitted orthoses, casts, splints, and other assisting devices may prevent or delay these symptoms.[10,17] If severe arthrosis is present, surgical treatment with hip or knee replacement should be considered in a similar fashion as to that done for patients without previous polio, but the post-operative rehabilitation period

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See www.acnr.co.uk/case%20report.htm for a case of post-polio syndrome.

Table 1: Criteria for the diagnosis of post-polio syndrome[1]

1.	A prior episode of paralytic polio confirmed by history, physical exam, and typical findings on EMG
2.	Standard EMG evaluation demonstrates changes consistent with prior anterior horn cell disease: increased amplitude and duration of motor unit action potentials, increased percentage of polyphasic potentials and, in weak muscles, a decrease in the number of motor units on maximum recruitment. Fibrillations and sharp waves may or may not be present.
3.	A period of neurologic recovery followed by an extended interval of functional stability preceding the onset of new problems. The interval of neurologic and functional stability usually lasts for 20 or more years.
4.	The gradual or abrupt onset of new neurogenic (non-disuse) weakness in previously affected and/or unaffected muscles. This may or may not be accompanied by other new health problems such as excessive fatigue, muscle pain, joint pain, decreased endurance, decreased function, and atrophy.
5.	Exclusion of medical, orthopaedic, and neurologic condition that might cause health problems listed above.

may be prolonged and require particular training programmes. Severe scoliosis or degenerative spine changes should be considered for surgery if the neurological and/or respiratory function is threatened. Sleeping problems can be related to the frequency and intensity of pain, and proper pain management may improve sleep.[10] Sleeping problems can also be a part of nocturnal hypoventilation and patients with chest wall deformities and respiratory muscle weakness are at risk of developing respiratory insufficiency.[17] Co-existing obesity increases the risk. Symptoms on respiratory insufficiency can manifest as daytime sleepiness, morning headache, sleeping problems, fatigue, dyspnea, recurrent respiratory tract infections, and if not treated properly, secondary right sided heart failure (cor pulmonale). If the respiratory insufficiency is due to a mechanical deficit only (i.e. muscle weakness) with intact lung tissue, the effect and prognosis for using artificial ventilatory aids is excellent. In most cases, artificial ventilation is only needed during nighttime, and non-invasive ventilators are the first choice. Biphasic positive-pressure ventilators (BIPAP) and nasal intermittent positive-pressure ventilators (NIPPV) are often used in polio-related respiratory insufficiency with good results. General precautions like stopping smoking, a reduction in weight if obese, the use of influenza- and pneumoccocal vaccines, and aggressive treatment of respiratory tract infections are particularly important for these patients.

In conclusion, PPS is an exclusion diagnosis based on a thorough investigation in a patient with a previous history of polio. Proper treatment of other disorders, both polio-related and non-polio-related, is important with the management of PPS being primarily based on physical therapy and muscular training along with intermittent ventilatory support if necessary.

References

1. Halstead LS. *Assessment and differential diagnosis for post-polio syndrome.* Orthopedics 1991;14(11):1209-1217.
2. Melchers W, de Visser M, Jongen P, van Loon A, Nibbeling R, Oostvogel P et al. *The post-polio syndrome: no evidence for poliovirus persistence.* Ann Neurol 1992;32(6):728-732.
3. Gonzalez H, Khademi M, Andersson M, Wallstrom E, Borg K, Olsson T. *Prior poliomyelitis-evidence of cytokine production in the central nervous system.* Journal of the Neurological Sciences 2002;205(1):15.
4. Chang CW, Huang SF. *Varied clinical patterns, physical activities, muscle enzymes, electromyographic and histologic findings in patients with post-polio syndrome in Taiwan.* Spinal Cord 2001;39(10):526-531.
5. Grimby G, Stalberg E, Sandberg A, Stibrant SK. *An 8-year longitudinal study of muscle strength, muscle fiber size, and dynamic electromyogram in individuals with late polio.* Muscle Nerve 1998; 21(11):1428-1437.
6. Stalberg E, Grimby G. *Dynamic electromyography and muscle biopsy changes in a 4-year follow- up: study of patients with a history of polio.* Muscle Nerve 1995;18(7):699-707.
7. Ravits J, Hallett M, Baker M, Nilsson J, Dalakas M. *Clinical and electromyographic studies of postpoliomyelitis muscular atrophy.* Muscle & Nerve 1990;13(8):667-674.
8. Farbu E, Gilhus NE. *Former poliomyelitis as a health and socioeconomic factor. A paired sibling study.* J Neurol 2002;249(4):404-409.
9. Farbu E, Gilhus NE. *Education, occupation, and perception of health amongst previous polio patients compared to their siblings.* Eur J Neurol 2002;9(3):233-241.
10. Farbu E, Rekand T, Gilhus NE. *Post polio syndrome and total health status in a prospective hospital study.* Eur J Neurol 2003;10(4):407-413.
11. Dinsmore S, Dambrosia J, Dalakas MC. *A double-blind, placebo-controlled trial of high-dose prednisone for the treatment of post-poliomyelitis syndrome.* Annals of the New York Academy of Sciences 1995;753:303-313.
12. Horemans HLD, Nollet F, Beelen A, Drost G, Stegeman DF, Zwarts MJ et al. *Pyridostigmine in postpolio syndrome: No decline in fatigue and limited functional improvement.* Journal of Neurology, Neurosurgery & Psychiatry 2003;74(12):1655-1661.
13. Agre JC, Rodriquez AA, Franke TM. *Strength, endurance, and work capacity after muscle strengthening exercise in postpolio subjects.* Archives of Physical Medicine & Rehabilitation 1997;78(7):681-686.
14. Willen C, Sunnerhagen KS, Grimby G. *Dynamic water exercise in individuals with late poliomyelitis.* Arch Phys Med Rehabil 2001;82(1):66-72.
15. Strumse YAS, Stanghelle JK, Utne L, Ahlvin P, Svendsby EK. *Treatment of patients with postpolio syndrome in a warm climate.* Disability & Rehabilitation 2003;25(2):77-84.
16. Rekand T, Korv J, Farbu E, Roose M, Gilhus NE, Langeland N et al. *Lifestyle and late effects after poliomyelitis. A risk factor study of two populations.* Acta Neurologica Scandinavica 2004;109(2):120-125.
17. Kidd D, Howard RS, Williams AJ, Heatley FW, Panayiotopoulos CP, Spencer GT. *Late functional deterioration following paralytic poliomyelitis.* QJM 1997;90(3):189-196.

The Management of Intracranial Abscesses

Most UK neurosurgeons treat 1-4 patients with an intracranial abscess each year. Intracranial abscesses can occur at any age. Contiguous spread to the intracranial cavity may occur directly or via emissary veins from infected paranasal sinuses, the middle ear and the mastoid. Such abscesses are usually located in the frontal or temporal lobes, or in the cerebellum. Haematogenous spread of infection can occur from the skin, dental sources and the lungs. Sixty percent of patients have a pre-disposing condition including an infective source (ear, sinus, teeth, lung), diabetes or an immunocompromised state. Patients with cyanotic heart disease are also at risk since circulating blood bypasses the pulmonary bacterial filter. Abscesses with a haematogenous origin are frequently located in the middle cerebral artery territory, presumably due to haemodynamic factors. Such abscesses are sometimes multiple.

Presentation

The clinical features in patients with an intracranial abscess evolve with time and depend upon the host-pathogen interactions. From a brain perspective patients have one or more of the following clinical scenarios:

1. Symptoms and signs of raised intracranial pressure (headache, impaired level of consciousness, slow mentation, nausea, vomiting, papilloedema).
2. Focal neurological deficits due to compression of neuronal pathways (e.g. hemiplegia, dysphasia, frontal symptoms and signs, cerebellar syndrome).
3. Seizures. These may by focal, Jacksonian or Grand Mal.

Constitutional symptoms and signs (pyrexia, rigors, dehydration, neck stiffness) and clinical features due to an infected source elsewhere in the body are surprisingly uncommon at the time of presentation.

Pathology

Britt and Enzmann described a canine model of Streptococcal abscess evolution with pathological phases that correlate with the clinical presentation in man.[1] An initial acute inflammatory cerebritis (days 1-9) is followed by hyperaemic capsule formation (days 10-14) and fibroblastic maturation (after day 14). Necrotic liquifaction and inflammatory exudate accumulate in the abscess cavity. During expansion of the abscess, the medial wall is usually thinner and less resistant and may result in ventriculitis. This is a poor prognostic indicator.

Microbiology

The majority of intracranial abscesses contain several mixed pathogens. In many patients, particularly those with sinus or ear infections a variety of aerobic and microaerophilic Streptococcal species are found (e.g. Strep millari; Strep pneumoniae, Strep pyogenes), often in combination with Haemophilus influenzae and Pseudomonas aeriginosa and anaerobes such as Bacteroides. In patients with a primary skin infection or an abscess complicating recent neurosurgery, Staphylococcus aureus is prevalent.

Investigations

Serial white blood cell counts, ESR and CRP levels provide useful parameters to monitor response to treatment – although not infrequently such investigations may be normal and can result in a delayed diagnosis. Blood cultures may help determine the likely pathogen. However, a CT or MRI scan of the brain +/- contrast secures the diagnosis and should always be performed before a lumbar puncture is considered. An abscess appears as a ring-enhancing, space demanding process. The ring of enhancement is usually quite linear without the heterogeneous appearances characteristic of a malignant glioma. The most frequent abscess locations are frontal, temporal or cerebellar. They are usually sub-cortical, but small abscesses may abut the grey-white matter interface in the middle cerebral artery territory. A CT or MRI scan may also reveal an infected source such as a paranasal sinus infection or an ear infection. The diagnosis is confirmed by examination of pus obtained directly from the abscess. Once an abscess has been identified, broad-spectrum antibiotics should be commenced and urgent neurosurgical referral made.

Surgical Options

Surgery is required to obtain pus from a solitary abscess. Sometimes this is non-diagnostic particularly if antibiotics have been administered. Surgery also reduces the bulk of an abscess providing symptomatic relief and minimising the risks of abscess growth (intraventricular rupture, herniation, venous sinus thrombosis). The surgical options include aspiration, craniotomy and complete excision or craniotomy and marsupialisation.

Aspiration

Image guided (CT or MRI) frameless stereotactic aspiration has recently become the most commonly utilised surgical technique to treat an abscess. For small and deep abscesses (< 2cm) a stereotactic frame increases the accuracy of the localisation technique. In patients with multiple abscesses, the largest lesion is usually aspirated and other lesions monitored with post-operative imaging.[2,3]

Craniotomy

A craniotomy can be performed as a primary procedure or if abscess re-growth occurs after initial aspiration. In the majority of patients brain swelling is prominent and mannitol should be administered intraoperatively to minimise this problem. If the abscess is located in non-eloquent brain the abscess wall is dissected from the surrounding brain permitting enucleation of the lesion. If the abscess is in an eloquent region a trans-cortical approach can be made through a 2 cm incision. An intersulcal approach shortens the distance to the lesion compared

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Image guided (CT or MRI) frameless stereotactic aspiration has recently become the most commonly utilised surgical technique to treat an abscess

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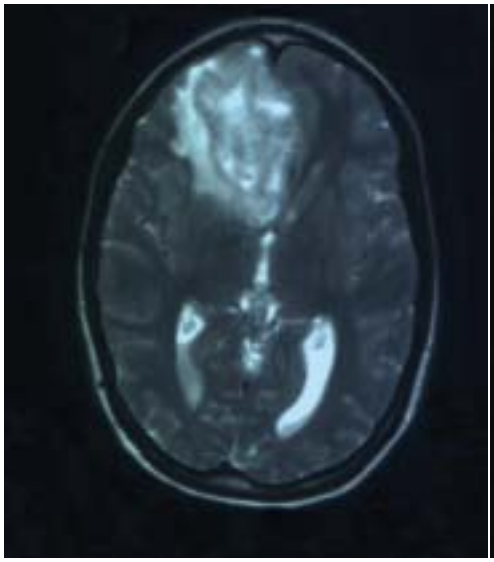


Figure 1a:
This 20 year old female presented to the neurologists with headaches and vomiting. An MRI scan showed frontal lobe cerebritis and ethmoid congestion. Note the extensive changes on this T2W image. She was treated with intravenous antibiotics for 3 weeks, improved and was discharged.

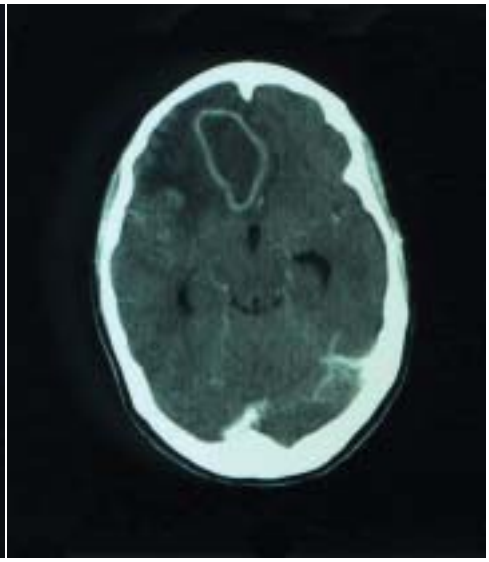


Figure 1b:
She represented 5 weeks later with similar symptoms. Her CRP and white cell count were normal. This contrast enhanced CT scan shows the characteristic appearances of an intracerebral abscess with a thin walled cavity surrounded by cerebral oedema. She underwent an emergency craniotomy to marsupialise the abscess. She also underwent bilateral sphenoidectomies and a partial ethmoidectomy to treat the infective source.

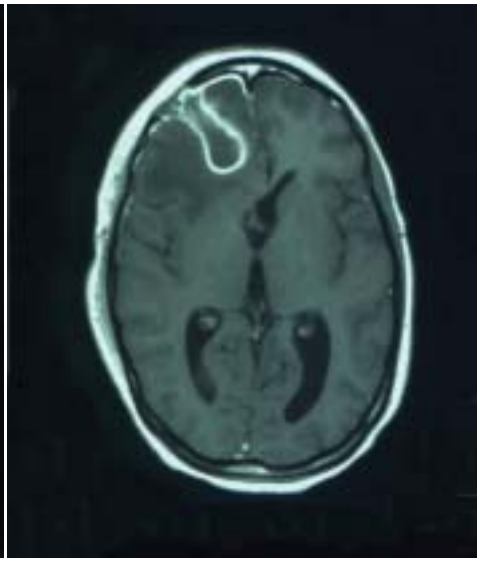


Figure 1c:
This Gadolinium enhanced MRI scan taken 4 weeks later shows involution of the abscess cavity. Intravenous ceftriaxone and metronidazole were continued for a further 3 weeks followed by 3 weeks of oral Augmentin. A repeat scan 1 month later showed further involution of the cavity.

with the more traditional transgyral corticotomy. The operative microscope is used to visualise and preserve cortical vessels within the sulcus. The abscess wall is then encountered and opened widely (marsupialisation) to permit complete aspiration of all pus (Figure 1a). The cavity is thoroughly irrigated with saline (some surgeons use a dilute solution of hydrogen peroxide). The use of haemostatic matrices (e.g. Surgicel) is limited to avoid colonisation of such materials. Following evacuation or open drainage the brain swelling has usually improved considerably permitting replacement of the bone flap during closure.

Peri-Operative Care

Several factors need to be addressed. These include the choice and duration of antibiotic treatments, the role of surveillance imaging, the treatment of any primary focus, the use of steroids and the use of prophylactic anticonvulsants.

Antibiotic Treatment

The choice of antibiotics is governed by several factors including the appearances on an initial Gram stain, the potential for mixed aerobic and anaerobic pathogens, and antibiotic penetration. Expert microbiological advice is invaluable when selecting antimicrobials. For the majority of primary abscesses initial intravenous treatment with a third generation cephalosporin and metronidazole is appropriate. Cultures may subsequently refine the choice of antibiotics.

Some antibiotics can be safely instilled during surgery (e.g. Gentamicin 10mg), but direct instillation of penicillin is unsafe and can cause seizures. The duration of antibiotic treatment is controversial. If antibiotics are administered for a short period (e.g. 2 weeks) there does appear to be an increased risk of recurrence. Provided surveillance imaging is satisfactory a 4-week course of intravenous antibiotics, supplemented by a further 2 weeks of oral treatment is recommended.

Surveillance Imaging

MRI is preferred to CT scanning to abolish the risks of radiation exposure. A post-operative MRI scan performed within 48 hours of surgery serves as a useful baseline for subsequent imaging. Provided the patient remains stable, repeating the scan at weekly intervals for 2 weeks and then at fortnightly intervals for a further 1-month enables re-accumulation of the abscess to be detected at a pre-clinical phase (Figures 1b, 1c).

Treatment of Primary Focus

To minimise the risk of recurrent or non-responsive intracranial infection any identifiable primary source requires aggressive treatment.[4] This may include surgery for paranasal, middle ear or dental sepsis, physiotherapy and antibiotics for pulmonary infection and surveillance echocardigrams in patients with a cardiac source. The timing of such interventions does not need to coincide with intracranial surgery but should be undertaken in an expert, timely fashion.

Steroid Therapy

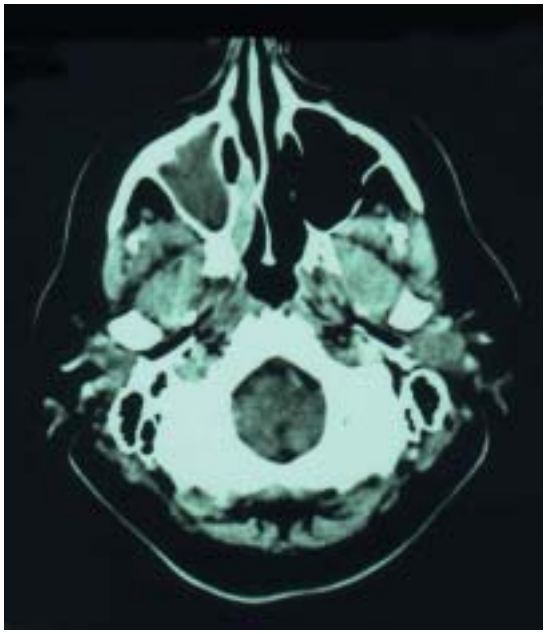
In general steroids are not used in brain abscess patients due to the immunosuppression associated with these drugs. However, extensive oedema may surround the abscess and contribute to raised intracranial pressure. In a deteriorating clinical situation steroids can improve the clinical status of patients when there appear to be few options remaining. This is probably due to a reduction in the inflammatory process reducing concomitant oedema.

Prophylactic Anticonvulsants

Between 40-50% of patients who suffer from an intracranial abscess will develop epilepsy. Prophylactic anticonvulsants should therefore be seriously considered. Patients should contact the DVLA and refrain from driving.

Prognosis

In the pre-CT era the mortality of cerebral abscesses was in the region of 30-40%. CT scanning and improved localisation techniques have reduced this to less than 5%. The use of modern treatment regimes with image-directed neurosurgery may reduce this further. Risk factors for a poor outcome include deep-seated location, intraventricular abscess rupture causing ventriculitis and a poor



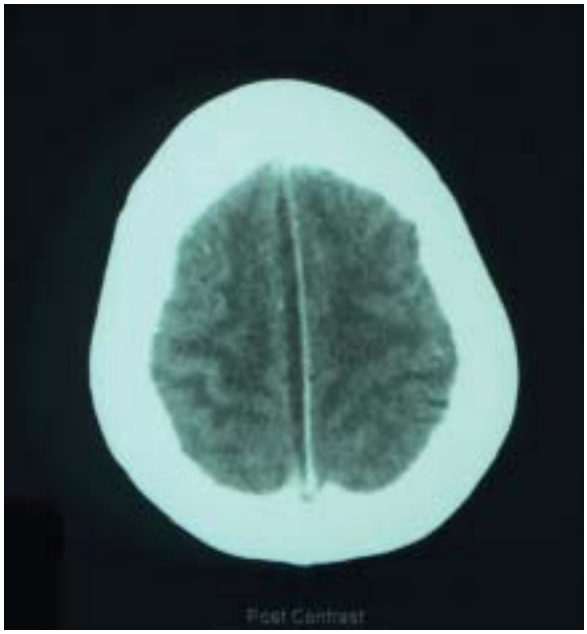


Figure 2a:
Axial CT scan showing opacification of the right maxillary sinus in a patient with a subdural empyema. This source of infection requires treatment.

Figure 2b:
Axial CT scan + contrast showing a right parasagittal subdural empyema in the same patient as figure 2a. This requires surgical drainage and is best performed through a parasagittal craniotomy taking care to preserve veins bridging from the cortex to the superior sagittal sinus.

neurological status.[5] Many patients with a neurological deficit achieve significant recovery during the rehabilitative phase of care.

Rare Intracranial Infections

Subdural empyema and extradural abscesses
These are both rare. They are usually associated with contiguous otological or sinus pathology and are identified on CT scans (Figure 2a). While extradural abscesses are readily detected, subdural empyemas typically have a subtle appearance on CT scans (Figure 2b). They are characterised by a relatively thin, low attenuation mass with minimal enhancement associated with a profound clinical picture (impaired level of consciousness, neurological deficit and fits). Symptoms and signs of infection may not be present. Early aggressive surgery targeted at the intracranial mass and any source of infection is recommended. A craniotomy is the preferred option for an empyema due to the viscous nature of the pus that is not readily washed out of the subdural space. Indeed, a fibrinous layer of tissue usually adheres to the arachnoid and is best left undisturbed after thorough irrigation under direct vision. The risk of a neurological deficit and epilepsy in patients with a subdural empyema exceeds 60%, probably due to multiple small cortical venous infarctions.[6]

Tuberculosis
TB remains common in the Indian sub-continent and cases of intracranial TB are seen in the UK. Symptoms of raised ICP and/ or epilepsy should lead to the suspicion of a tuberculoma. This is a calcified parenchymal lesion with central caeseating necrosis. TB only rarely causes a typical brain abscess appearance. Treatment options depend on the clinical status of the patient and lie between clinical surveillance, empirical anti-tuberculous treatment with follow-up scans, image-guided aspiration combined with medical treatment and rarely surgical excision.

Neurocysticercosis
This disease is endemic in most developing parts of the world. The larvae of this ingested intestinal tapeworm hatch from eggs in the intestine and migrate to a variety of tissues including brain parenchyma, muscles, subcutaneous tissues and the eye. In many cases the host immune system eliminates the parasite expeditiously. However, CT and MRI indicate that small-calcified parenchymal cystic lesions can persist. These may be multiple and may contain a mural "scolex" of larvae. Neurocysticercosis may be asymptomatic, cause epilepsy or result in a focal neurological deficit. Management is directed at seizure control.[7] Empirical treatment with the anti-helminthic agents albendazole or praziquantel is not mandatory in the late "burnt-out" phase of the disease. Surgery is only required if seizures are not controlled medically or in rare instances when space occupation is problematic.

Summary
Although the incidence of intracranial abscesses has decreased over the past 100 years the surgical principles expostulated by MacEwen in 1881, namely debridement and drainage, remain of paramount importance. Advances in neuronavigation techniques make stereotactic drainage a simple procedure that can be performed expeditiously for the majority of abscesses. The appropriate use of effective antibiotic therapy adds to the therapeutic armamentarium. Surveillance imaging with MRI scans is now the follow-up modality of choice. These changes in management have seen a significant reduction in the mortality of brain abscesses in the last 20 years.

References

1. Britt RH, Enzmann DR. *Clinical stages of human brain abscesses on serial CT scans after contrast infusion.* J.Neurosurg. 1983;59:972-989.
2. Boviatsis EJ, Kouyialis AT, Stranjalis G, Korfias S, Sakas DE. *CT-guided stereotactic aspiration of brain abscesses.* Neurosurgical Review 2003;26:206-209.
3. Barlas O, Sencer A, Erkan K, Eraksoy H, Sencer S, Bayindir C. *Stereotactic surgery in the management of brain abscess.* Surgical Neurology 1999;52:404-410.
4. Sennaroglu L, Sozeri B. *Otogenic brain abscess: review of 41 cases.* Otolaryngology - Head and Neck Surgery 2000;123:751-755.
5. Takechita M, Kagawa M, Izawa M, Takakura K. *Current treatment strategies and factors influencing outcome in patients with bacterial brain abscess.* Acta Neurochirurgica 1998;140:1263-1270.
6. Cowie R, Williams B. *Late seizures and morbidity after subdural empyema.* J.Neurosurg. 1983;58:569-573.
7. Sotelo J. *Neurocysticersosis.* Br Med J 2003;326:511-512.

Apraxia

The term apraxia refers to a wide variety of high-level motor disorders, characterised by an impairment of purposeful voluntary movement skill. Apraxia is only indicated if aberrant motor behaviour cannot be accounted for fully by pyramidal, extrapyramidal, cerebellar or peripheral motor deficits or sensory loss, but may be observed in association with a number of low level motor disorders (e.g. weakness, rigidity, tremor, dystonia). Equally, an apraxic deficit cannot be inferred without excluding associated cognitive deficits, for example of language or perception, as primary and sufficient explanations for the observed behaviour. The occurrence of apraxic errors is mediated greatly by the context in which the action is elicited (e.g. clinical setting or natural environment), the stimulus prompting the action (e.g. real object or verbal command), the nature of the action (e.g. meaningful or meaningless gesture), the hand with which the action is performed, and the difficulty of the action procedure (e.g. single gesture or as part of a simple or complex action sequence). Apraxic deficits may also be body-part specific; accordingly, a greater specification of upper limb, gait and trunk, and orofacial apraxias is provided below. Susequently, disorders which controversially carry the term 'apraxia' and the role of praxis in naturalistic action are considered.

Upper limb apraxia

The most commonly drawn distinction in upper limb apraxia is that between ideomotor apraxia and ideational apraxia. Individuals with ideomotor apraxia (IM) commonly show disruption in the spatial and temporal form of stored and novel gestures, which is associated with damage to the left inferior parietal operculum. Patients with ideational apraxia (IA) on the other hand tend to make well-formed movements but show a disruption of the conceptual content of action production, resulting in tool misuse, production of complete but inappropriate gestures and disorganisation of movements in an action sequence. IA typically results from left parieto-occipital lesions (just posterior to areas associated with IM), but the localising value of IA has been questioned because the condition is rarely seen in isolation. Indeed, the clinical usefulness of the distinction has been undermined by the frequent co-occurrence of IM and IA; in a study of apraxic left hemisphere brain damaged patients, 60% showed symptoms of both IM and IA.[1]

Contemporary models of upper limb praxis mirror models of language processing, with voluntary motor action involving a series of cognitive processing stages (e.g. input, output, transcoding and conceptual knowledge).[2] Such models support the notion that IM and IA actually comprise a constellation of dissociable deficits. A variety of techniques may be used to assess the integrity of differing components of the action system (for examples, see Table 1). Furthermore, given the number of terminological difficulties in this area, upper limb apraxia may be more accurately defined by the type and quality of action production errors (for a breakdown of error types, see Table 2). In evaluating the significance of praxic errors however, the specificity of gestural errors in a given context must be considered. For example, body-part-as-object errors (e.g. using the index finger to pantomime brushing teeth) have been shown to occur equally often in healthy controls as left and right hemisphere brain damaged subjects, and, in left hemisphere patients, not to be associated with severity of apraxia.[3] The modality of stimulus presentation (e.g. verbal, visual or both) for gesture production tasks must be carefully selected to maximise the likelihood that any action production errors reflect praxic dysfunction rather than concomitant cognitive deficits (e.g. misperceiving a complex, meaningless hand posture demonstrated by the clinician).

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Table 1. Techniques employed in the assessment of upper limb apraxia.

Praxic domain	Cognitive domain	Task type	Example
Reception	Praxis input	Gesture naming	Examiner performs gesture: "Tell me what I am doing"
		Gesture decision	Examiner performs real/unreal gesture: "Is this the correct way to turn a key?"
		Gesture recognition	Examiner performs a series of three gestures (one target, two foils): "Which one of these gestures is correct for using a trowel in the garden?"
Production	Praxis output	Gesture to verbal command	Examiner says: "Show me how you use a hammer to pound a nail into a wall in front of you."
		Gesture to visual tool	Examiner shows patient a tool: "Show me how you use this [hammer]."
		Gesture to tactile tool	With eyes closed/covered, patient is asked: "Show me how to use this tool [hammer] I am placing in your hand."
Imitation	Lexical/non-lexical imitation system	Gesture imitation	Examiner says: "I will produce a gesture and I want you to do it the same way I do it."
		Nonsense imitation	Examiner says: "I will produce a gesture and I want you to do it the same way I do it. It is not a real gesture like the other ones you have been doing"
Action semantics	Conceptual system	Tool selection	Patient views an object representing an incomplete action (e.g. half sawn piece of wood) and three tools (1 target e.g. saw; 2 foils): "Point to the tool which goes with the object."
		Alternative tool selection	Patient views an object representing an incomplete action (e.g. partially banged in nail) and three tools (none ideal but one with appropriate features for the task e.g. brick).
		Multiple step tasks	Examiner provides letter, envelope, stamp and pen: "Show me how to prepare a letter for posting."

Mb^hp ^ka qolrdep lcibslalm^ qebo^mv e^sb mrq if j fqp lk m^qfbkq crk`qflk+

Tebk pv j mql j p absbilm arb ql peloqbkfkd lcibslalm^,AA@F alpb bccb`qfsbkbpp p t fq`e ql Pq^ibsl ^ka pq^v fk `lkqoli+-)/

PQ>IBSL

ORION PHARMA

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Pcdcpclacq
/, J_pqcl HN *cr _j, Csp H Lcsp* 0..19/.8/15+/24,
0, Pţllc SI *cr _j, Lcspmjmew* /77693/8/1.7+/1/2,

B_rc md npcn_p_rţml8
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QR?/073

Table 2. A classification of praxic error types.[4]

Error Class	Example subtypes and descriptions
Spatial	*Internal configuration* – incorrect spatial relationship between different body parts (e.g. fingers in incorrect arrangement)
	External configuration – incorrect spatial relationship between body part and imagined tool (e.g. brushing teeth with hand too far away from the face)
	Movement – e.g. twisting pretend screwdriver from the shoulder rather than elbow
	Body part as tool – e.g. when pretending to smoke cigarette, puffing end of finger
	Amplitude – increase, decrease or irregularity in typical amplitude of a movement
Temporal	*Sequencing* – adding, deleting or transposing a movement in a multi-stage sequence
	Timing – abnormally increased, decreased or irregular rate of action production
	Occurrence – repetitive production of characteristically single movements (e.g. turn key) or reduced production of typically repetitive movements (e.g. screwdriver)
Content	*Perseverative* – response includes all or part of a previously produced pantomime
	Related – e.g. pantomime playing a trombone for the target of a bugle
	Non-related – e.g. pantomime playing a trombone for the target of shaving
	Hand – performing the action without a real or imagined tool (e.g. ripping paper by hand when asked to demonstrate use of scissors)
Other	*Concretisation* – performing pantomimed act on an inappropriate real object (e.g. when asked to saw some wood, pantomiming sawing on their leg)
	No response
	Unrecognisable – not recognisable and with no spatial or temporal features of the target

Gait, leg and trunk apraxia

Gait apraxia refers to an impaired ability to execute the highly practised, co-ordinated movements of the lower legs required for walking, but remains rather poorly specified and probably includes a number of different complex gait syndromes.[5] Disturbances of voluntary, non-routine movements of the lower limbs (leg apraxia) have also been reported in patients with gait apraxia.[6] However, it remains unclear whether leg apraxia and gait apraxia should be considered manifestations of damage to a common lower limb praxic centre, or whether leg apraxia is more closely related to the ideomotor apraxia more typically described in the upper limbs. A clearer dissociation has been described between limb apraxias and axial or trunk apraxia, in which patients may have difficulty generating body postures (e.g. stand like a boxer), rising from a lying position, rolling over or adopting a sitting position.

Orofacial apraxia

Patients with orofacial (or buccofacial) apraxia exhibit difficulties with performing voluntary meaningful and meaningless movements with facial structures including the cheeks, lips, tongue and eyebrows. Attempting to perform a pantomime to verbal command may result either in no response or often a characteristic verbal repetition of the target action (e.g. "Could you show me how to cough?" "Cough"). For some patients, imitation of an examiner's pantomime may be achieved more accurately. Orofacial apraxia may occur independently of limb apraxia, and should also be distinguished from apraxia of speech which is a disorder of articulatory integration associated with non-fluent aphasia. Orofacial apraxia is commonly associated with damage in the left frontal operculum and insula, although the left hemisphere is particularly implicated in lower face movements whilst the right hemisphere may play a role in both upper and lower face actions.[7]

Controversial apraxias

In addition to the body part-specific apraxias described above, the term apraxia has also been applied more controversially to a range of other motor disorders. Limb-kinetic (or melokinetic) apraxia refers to an inability to make precise, smooth, fine and independent movement of the fingers. The observation that the disorder can affect all types of gesture in any context irrespective of hemispheric lateralisation of damage has led to suggestions that limb-kinetic apraxia is in fact primarily a deficit of the motor system.[8] Other specialists maintain limb-kinetic apraxia is truly apractic in nature, resulting from premotor cortex damage.[9,10] The appropriateness of terms such as constructional apraxia and dressing apraxia has also been questioned, where a combination of perceptual, spatial and motor deficits may explain at least some of the action disorder.[11]

Naturalistic action disorders

Naturalistic action refers to well-established sequences of movements aimed at achieving practical goals such as food consumption or grooming activities. Naturalistic action is organised by goal hierarchies which structure behaviour over long periods of time, and is critically dependent upon cognitive processes largely subserved by the frontal lobes (e.g. planning, attention, working memory.)[12] The term frontal apraxia describes a breakdown in this sequential organisation of behaviour, and is characterised by object substitutions and misuse (e.g. spooning butter into coffee, using the wrong implements to eat or stir).[9,13] Although evidence of limb apraxia is elicited typically in a clinical setting, studies of the real world behaviour of ideomotor apraxic patients reveal a reduced frequency of tool-related action production and an increased number of tool-action errors relative to other patient groups.[14]

References

1. De Renzi E, Pieczuro A, & Vignolo LA. *Ideational apraxia: a quantitative study.* Neuropsychologia 1968;6: 41-52.
2. Rothi LG, Ochipa C & Heilman KM. *A cognitive neuropsychological model of limb praxis and apraxia.* In L.G.Rothi & K. M. Heilman (Eds). Apraxia: the neuropsychology of action. Psychology Press, Hove, UK 1997.
3. Duffy RJ, & Duffy, JR. *An investigation of body part as object (BPO) responses in normal and brain-damaged adults.* Brain Cogn 1989;10:220-236.
4. Rothi LG, Raymer AM, Ochipa C, Maher LM, Greenwald ML, & Heilman KM. Florida Apraxia Battery. Unpublished Work 1998.
5. Nutt JG, Marsden CD, & Thompson PD. *Human walking and higher level gait disorders, particularly in the elderly.* Neurology 1993; 43:268-279.
6. Meyer JS & Barron D. *Apraxia of gait: a clinico-pathological study.* Brain 1960; 83:61-84.
7. Bizzozero I, Costato D, Della Sala S, Papagno C, Spinnler H, & Venneri A. *Upper and lower face apraxia: role of the right hemisphere.* Brain 2000;123:2213-2230.
8. De Renzi E. *Apraxia.* In F.Boller & J. Grafman (Eds). Handbook of Neuropsychology; 2:245-263. Amsterdam: Elsevier 1989.
9. Luria AR. *Higher cortical functions in man.* (2nd ed.) New York: Basic Books 1980.
10. Freund HJ. *The apraxias.* In AK Asbury, GM McKhann & WI McDonald (Eds), Disease of the nervous system: clinical neurobiology: 751-767. Philadelphia: W.B. Saunders 1992.
11. McCarthy RA & Warrington EK. *Cognitive Neuropsychology:a clinical introduction.* London: Academic Press 1990.
12. Schwartz MF, & Buxbaum LJ. *Naturalistic action.* In L.G.Rothi & K. M. Heilman (Eds). Apraxia: the neuropsychology of action. Hove, UK: Psychology Press 1997.
13. Schwartz MF, Reed ES, Montgomery MW, Palmer C & Mayer MH. *The quantitative description of action disorganization after brain damage: a case study.* Cognitive Neuropsychology 1991;8:381-414.
14. Foundas AL, Macauley BL, Raymer AM, Maher LM, Heilman KM, & Gonzalez-Rothi LJ. *Ecological implications of limb apraxia: evidence from mealtime behavior.* J Int.Neuropsychol.Soc.1995;1:62-66.

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Prescribing Information UK
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Mirapexin 0.088mg, Mirapexin 0.18mg and Mirapexin 0.7mg tablets containing 0.125mg, 0.25mg and 1mg respectively of pramipexole salt (dihydrochloride monohydrate). **Indications:** The treatment of the signs and symptoms of idiopathic Parkinson's disease, alone (without levodopa) or in combination with levodopa. **Dosage and Administration:** Adults and Elderly Patients: Administration: Give tablets orally with water in equally divided doses three times per day. Initial treatment: 3 x 0.088mg base (3 x 0.125mg salt) per day for first 5 days. Then 3 x 0.18mg base (3 x 0.25mg salt) per day for 5-7 days, and then 3 x 0.35mg base (3 x 0.5mg salt) per day for 5-7 days. Increase the daily dose by 0.54mg base (0.75mg salt) at weekly intervals to a maximum dose of 3.3mg base per day (4.5mg salt per day). If necessary, increases of administration can be made at doses higher than 0.09mg base per day (0.125mg salt per day). Maintenance treatment should be in the range of 0.264mg base (0.375mg salt) up to a maximum of 3.3mg base (4.5mg salt) per day, adjust dose based on clinical response and tolerability, reduce doses used in titration and maintenance phases if necessary. Treatment discontinuation: Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Reduce dose by 0.54mg base (0.75mg salt) per day, to 0.54mg base per day (0.75mg salt per day). Thereafter reduce dose by 0.264mg base (0.37mg salt) per day. Renal impairment: See SPC for revised dosage schedules. Hepatic impairment: Dose adjustment in hepatic failure is probably not necessary. **Children:** Not recommended. **Contra-indications:** Hypersensitivity to pramipexole or any other component of the product. **Warnings and Precautions:** Reduce dose in renal impairment, inform patients that hallucinations (mostly visual) can occur. Somnolence and, uncommonly, sudden sleep onset have been reported, patients who have experienced these must refrain from driving or operating machines. A reduction of dosage or termination of therapy may be considered. If dyskinesias occur in combination with levodopa during initial titration of pramipexole in advanced Parkinson's disease, the dose of levodopa should be reduced. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweighs the risks. Ophthalmologic monitoring is recommended. If regular eye tests or if vision abnormalities occur. In cases of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. **Drug Interactions:** There is no pharmacokinetic interaction with selegiline and levodopa. Inhibitors of the cationic secretory transport system of the renal tubules such as cimetidine and amantadine may interact with pramipexole resulting in reduced clearance of either or both drugs. Consider reducing pramipexole dose when these drugs are taken concomitantly. The dosage of diuretics should be reduced, and other Parkinsonian medication kept constant, while increasing the dosage of pramipexole. Caution with other sedating medication or alcohol due to possible additive effects. Coadministration of antipsychotic drugs with pramipexole should be avoided. **Pregnancy and Lactation:** Effects in pramipexole in human pregnancy or lactation have not been studied. Pramipexole should not be used in pregnancy unless the benefit outweighs the potential risk to the foetus. Pramipexole should not be used during breastfeeding. **Undesirable Effects:** Nausea, constipation, somnolence, insomnia, hallucinations, dizziness, dyskinesia and peripheral oedema occurred more often than with placebo. Most frequent adverse reactions in combination with levodopa were dyskinesias. Constipation, nausea and dyskinesia tended to disappear with continued therapy. Hypotension may occur at the beginning of treatment in some patients, especially if Mirapexin is titrated too fast. Vertigoes has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes. **Overdose:** There is no clinical experience with massive overdosage. Expected adverse events include nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension. General symptomatic supportive measures may be required, along with gastric lavage, intravenous fluids and electrocardiogram monitoring. **Basic NHS Cost:** 0.088mg x 30 £10.00, 0.18mg x 30 £20.20, 0.18mg x 100 £66.67, 0.7mg x 30 £66.67, 0.7mg x 100 £212.24. **Legal Category:** POM. **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, D-55216 Ingelheim am Rhein, Germany. **Marketing Authorisation Number:** Mirapexin 0.088mg x 30 tablets EU/1/97/061/001, Mirapexin 0.18mg x 30 tablets EU/1/97/061/002, Mirapexin 0.35mg x 100 tablets EU/1/97/061/004, Mirapexin 0.7mg x 30 tablets EU/1/97/061/005 Mirapexin 0.7mg x 100 tablets EU/1/97/061/006. Further information is available from: Boehringer Ingelheim Ltd., Ellesfield Avenue, Bracknell, Berkshire RG12 8YS. **Date of preparation:** September 2004.

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A Topographical Anatomy of False-Localising Signs

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One hundred years ago, Dr James Collier published a paper in Brain entitled *The false localising signs of intracranial tumour.* Based on his experience of 161 clinically and pathologically examined cases of intracranial tumour seen at the National Hospital, Queen Square, London, he observed false-localising signs in 20 (12.4%).[1] The term was coined to indicate clinically observed signs that violated the expected clinico-anatomical concordance on which clinical examination is predicated.[2]

Since 1904, many examples of false-localising signs have been described. They may occur in the clinical context of raised intracranial pressure (RICP) which is symptomatic of intracranial pathology (tumour, haematoma, abscess) or idiopathic (idiopathic intracranial hypertension: IIH), and with spinal cord lesions. Associated lesions may be intra- or extraparenchymal. The course of the associated disease may be acute (cerebral haematoma) or chronic (IIH, tumour).[3]

The pathogenesis of false-localising signs remains uncertain, but their importance from a clinical standpoint is not in doubt, since they may lead to inappropriate imaging and even interventions on the wrong side (although the risk of such errors of commission is less now that neuroimaging is widely available). This article gives a brief topographical overview of false-localising signs.

Motor system

Kernohan's notch syndrome: false-localising hemiparesis

A supratentorial lesion, such as acute subdural haemaotoma, may cause transtentorial herniation of the temporal lobe, with compression of the ipsilateral cerebral peduncle against the tentorial edge; since this is above the pyramidal decussation a contralateral hemiparesis results. Occasionally, however, the hemiparesis may be ipsilateral to the lesion, and hence false-localising; this occurs when the contralateral cerebral peduncle is compressed by the free edge of the tentorium. This is the Kernohan-Woltman notch phenomenon, or Kernohan's notch syndrome.[4] There may be concurrent homolateral third nerve palsy, ipsilateral to the causative lesion.[5]

Cerebellar syndrome

Frontocerebellar pathway damage, for example as a result of infarction in the territory of the anterior cerebral artery, may result in incoordination of the contralateral limbs, mimicking cerebellar dysfunction. Suboccipital exploration to search for cerebellar tumours based on these clinical findings was known to occur before the advent of brain imaging.[6]

Brainstem compression: false-localising diaphragm paralysis

Hemidiaphragmatic paralysis with ipsilateral brainstem (medullary) compression by an aberrant vertebral artery has been described, in the absence of pathology localised to the C3-C5 segments of the spinal cord where phrenic motor neurones originate, hence a false-localising sign.[7]

Cranial nerves

Oculomotor nerve

Unilateral fixed dilated pupil (Hutchinson's pupil) may occur with an ipsilateral intracranial lesion such as an intracerebral haemorrhage, due to transtentorial herniation of the brain compressing the oculomotor nerve against the free edge of the tentorium. Because of the fascicular organisation of fibres within the oculomotor nerve, the externally placed pupillomotor fibres are most vulnerable. Very occasionally, fixed dilated pupil may occur contralateral, and hence false-localising, to intracranial pathology.[8] The exact mechanism for this clinical observation is not currently known.

Divisional third nerve palsy is usually associated with lesions at the superior orbital fissure or anterior cavernous sinus, where the superior division of the oculomotor nerve passes to the superior rectus and levator palpabrae, and the inferior division to the medial and inferior recti and inferior oblique muscles. Divisional third nerve palsies may sometimes occur with more proximal lesions, presumably as a consequence of the topographic arrangement of the fascicles within the nerve, for example with intrinsic brainstem disease (e.g. stroke)[9] or with pathology in the subarachnoid space where the nerve rootlets emerge from the brainstem (e.g. malignant infiltration).[10]

Trochlear nerve

False localising fourth nerve palsies, causing diplopia on downward and inward gaze, have occasionally been described in the context of IIH.[11,12]

Trigeminal nerve

Trigeminal nerve hypofunction (trigeminal sensory neuropathy) or hyperfunction (trigeminal neuralgia) may on occasion be false-localising, for example in association with IIH[13] or with contralateral pathology, often a tumour.[14] For example, trigeminal neuralgia has been associated with a contralateral chronic calcified subdural haematoma which caused rotational displacement of the pons, with resolution after removal of the haematoma.[15]

Abducens nerve

Sixth nerve palsies are the most common false-localising sign of raised intracranial pressure. In one series of 101 cases of IIH, 14 cases were noted, 11 unilateral and 3 bilateral.[16] Stretching of the nerve in its long intracranial course or compression against the petrous ligament or ridge of the petrous temporal bone have been suggested as the mechanism for false-localising sixth nerve palsy.[3]

Facial nerve

Lower motor neurone type facial weakness has been described in the context of IIH,[17] sometimes occurring bilaterally to cause facial diplegia,[18] usually with concurrent sixth nerve palsy or palsies. Hemifacial spasm has rarely been described with contralateral posterior fossa lesions.[14]

Vestibulocochlear nerve

Hearing loss has on occasion been reported as a complication of IIH,[19] although the commonest otological complication of IIH is tinnitus.[16]

The pathogenesis of false-localising signs remains uncertain, but their importance from a clinical standpoint is not in doubt, since they may lead to inappropriate imaging and even interventions on the wrong side

Multiple and lower cranial nerve involvement

Concurrent false-localising involvement of multiple cranial nerves has been noted on occasion, for example trigeminal, abducens and facial nerves with a contralateral acoustic neuroma,[20] and trigeminal, glossopharyngeal and vagus nerves with a contralateral laterally-placed posterior fossa meningioma.[21]

Spinal cord and roots

False localising signs within the spinal cord are well attested to. Broadly, these may be said to occur with lesions around the foramen magnum, or lower cervical/upper thoracic spinal cord.

Foramen magnum/upper cervical cord

Paraesthesia in the hands with intrinsic hand muscle wasting and distal upper limb areflexia, with or without long tract signs, suggestive of a lower cervical myelopathy may occur with lesions at the foramen magnum or upper cervical cord ("remote atrophy").[22]

Lower cervical/upper thoracic cord

Compressive lower cervical or upper thoracic myelopathy may produce spastic paraplegia with a mid-thoracic sensory level (or "girdle sensation").[23,24] For example, in one case a spastic paraplegia with a sensory level at T10 was associated with cervical compression from a herniated disc at C5/C6.[25]

Radiculopathy

False-localising radiculopathy may occur in the context of IIH and cerebral venous sinus thrombosis, manifesting as acral paraesthesias, backache and radicular pain, and less often with motor deficits,[26] which on occasion may be sufficiently extensive to mimic Guillain-Barré syndrome (flaccid-areflexic quadriplegia).[27] The postulated mechanism for such radiculopathy is mechanical root compression due to elevated CSF pressure.

Higher cognitive function

Hemineglect is much commoner with right rather than left parietal lobe lesions. An example of false-localising neglect has been encountered: in a patient with a posterior fossa meningioma causing left pontine compression, long tract signs and hydrocephalus, ipsilesional neglect was found, despite normal structural imaging of the cerebral hemispheres. The neglect resolved promptly after shunting and did not recur despite progressive brainstem compression (PC Nachev & IH Jenkins, personal communication).

Comment

As false-localising signs most often occur in the context of RICP, this seems likely to be the most important factor in the pathogenesis of these signs. Suggested mechanisms include mechanical distortion of cranial nerves with intracranial pathology and venous and/or arterial ischaemia with spinal cord pathology.[3] It is worth remembering that RICP itself may be a false localising sign when associated with spinal tumours, even in the thoracolumbar region, perhaps related to elevated CSF protein concentration.[28]

Of the various false-localising signs described, sixth nerve palsies are the most commonly observed. However, the possibility of false localisation should be borne in mind when any of the above-mentioned signs occur without obvious clinical-anatomical or clinical-radiological correlate.[2]

References

1. Collier J. *The false localising signs of intracranial tumour.* Brain 1904;27:490-508.
2. Larner AJ. *A dictionary of neurological signs. Clinical neurosemiology.* Dordrecht: Kluwer Scientific Publications, 2001.
3. Larner AJ. *False localising signs.* J Neurol Neurosurg Psychiatry 2003;74:415-418.
4. Kernohan JW, Woltman HW. I*ncisura of the crus due to contralateral brain tumor.* Arch Neurol Psychiatry 1929;21:274-287.
5. Cohen AR, Wilson J. *Magnetic resonance imaging of Kernohan's notch.* Neurosurgery 1990;27:205-207.
6. Gado M, Hanaway J, Frank R. *Functional anatomy of the cerebral cortex by computed tomography.* J Comput Assist Tomog 1979;3:1-19.
7. Schulz R, Fegbeutel C, Althoff A, Traupe H, Grimminger F, Seeger W. *Central sleep apnoea and unilateral diaphragmatic paralysis associated with vertebral artery compression of the medulla oblongata.* J Neurol 2003;250:503-505.
8. Marshman LAG, Polkey CE, Penney CC. *Unilateral fixed dilation of the pupil as a false-localizing sign with intracranial hemorrhage: case report and literature review.* Neurosurgery 2001;49:1251-1255.
9. Ksiazek SM, Repka MX, Maguire A et al. *Divisional oculomotor nerve paresis caused by intrinsic brainstem disease.* Ann Neurol 1989;26:714-718.
10. Larner AJ. *Proximal superior division oculomotor nerve palsy from metastatic subarachnoid infiltration.* J Neurol 2002;249:343-344.
11. Lee AG. *Fourth nerve palsy in pseudotumor cerebri.* Strabismus 1995;3:57-59.
12. Speer C, Pearlman J, Phillips PH et al. *Fourth nerve palsy in pediatric pseudotumor cerebri.* Am J Ophthalmol 1999;127:236-237.
13. Arsava EM, Uluc K, Nurlu G, Kansu T. *Electrophysiological evidence of trigeminal neuropathy in pseudotumor cerebri.* J Neurol 2002;249:1601-1602.
14. Matsuura N, Kondo A. *Trigeminal neuralgia and hemifacial spasm as false localizing signs in patients with a contralateral mass of the posterior cranial fossa.* J Neurosurg 1996;84:1067-1071.
15. Kandoh T, Tamaki N, Takeda N, Shirataki K, Matsumoto S. *Contralateral trigeminal neuralgia as a false localizing sign in calcified chronic subdural hematoma: a case report.* Surg Neurol 1989;32:471-475.
16. Round R, Keane JR. *The minor symptoms of increased intracranial pressure. 101 cases with benign intracranial hypertension.* Neurology 1988;38:1461-1464.
17. Davie C, Kennedy P, Katifi HA. *Seventh nerve palsy as a false localising sign.* J Neurol Neurosurg Psychiatry 1992;55:510-511.
18. Kiwak KJ, Levine SE. *Benign intracranial hypertension and facial diplegia.* Arch Neurol 1984;41:787-788.
19. Dorman PJ, Campbell MJ, Maw AR. *Hearing loss as a false localising sign in raised intracranial pressure.* J Neurol Neurosurg Psychiatry 1995;58:516.
20. Ro LS, Chen ST, Tang LM et al. *Concurrent trigeminal, abducens, and facial nerve palsies presenting as false localizing signs.* Neurosurgery 1995;37:322-324.
21. Maurice-Williams RS. *Multiple crossed false localizing signs in a posterior fossa tumour.* J Neurol Neurosurg Psychiatry 1975;38:1232-1234.
22. Sonstein WJ, LaSala PA, Michelsen WJ et al. *False localizing signs in upper cervical spinal cord compression.* Neurosurgery 1996;38:445-448.
23. Adams KK, Jackson CE, Rauch RA, Hart SF, Kleinguenther RS, Barohn RJ. *Cervical myelopathy with false localizing sensory levels.* Arch Neurol 1996;53:1155-1158.
24. Ochiai H, Yamakawa Y, Minato S, Nakahara K, Nakano S, Wakisaka S. *Clinical features of the localized girdle sensation of mid-trunk (false localizing sign) appeared [sic] in cervical compressive myelopathy patients.* J Neurol 2002;249:549-553.
25. Pego-Regiosa R, Trobajo de las Matas JE, Brañas F, Martinez-Vázquez F, Cortés-Laíño JA. *Dorsal sensory level as a false localizing sign in cervical myelopathy [in Spanish].* Rev Neurol 1998;27:86-88.
26. Moosa A, Joy MA, Kumar A. *Extensive radiculopathy: another false localising sign in intracranial hypertension.* J Neurol Neurosurg Psychiatry 2004;75:1080-1081.
27. Obeid T, Awada A, Mousali Y et al. *Extensive radiculopathy: a manifestation of intracranial hypertension.* Eur J Neurol 2000;7:549-553.
28. Ridsdale L, Moseley I. *Thoracolumbar intraspinal tumour presenting features of raised intracranial pressure.* J Neurol Neurosurg Psychiatry 1978;41:737-745.

The Neuropathology of Head Injury

Acute head injury

Epidemiology

In the United Kingdom more than 150,000 patients are admitted to hospital each year with an acute head injury. Of this group more than 80% are classified as having a mild head injury, as defined by the Glasgow Coma Scale (GCS).[1] Approximately 1-2% of patients admitted to hospital after traumatic brain injury die as a consequence of their injuries with the majority of fatalities being within the severe head injury group.

In the acute phase the neuropathology of blunt force head injury can be divided into two principal categories: 1) focal; and 2) diffuse[2] (see table).

Haematomas

Intracranial haemorrhage is the most common cause of clinical deterioration and death in patients who experience a lucid interval after head injury. Haematomas may act as a mass lesion and produce secondary effects. Extradural (EDH), subdural (SDH) and intracerebral (ICH) haematomas can all be associated with traumatic brain injury.[3]

EDH's are seen in some 10% of severely head injured patients, 80% being associated with skull fractures and the majority involve the middle meningeal artery with fractures of the squamous temporal bone.

SDH's tend to be more extensive than extradural lesions as blood can spread more freely within the subdural space (Figure 1). The majority are due to disruption of parasagittal bridging veins.

ICH's may be superficial, usually associated with contusions, or they may be more deeply seated, usually within the basal ganglia. When an intracerebral lesion is in continuity with a subdural haematoma the term "burst lobe" is used.

Contusions

These are seen in approximately 90% of fatal cases of traumatic brain injury, although they may be absent in some 6% of fatal cases. They are more commonly seen at the crests of the frontal and temporal gyri than within sulci and occur principally at sites where the brain comes in contact with the uneven bony surfaces of the base of the skull. Contre-coup lesions on the opposite side of the brain to the site of impact are thought to be due to negative pressures built up as the brain moves in relation to the skull at the moment of impact. Patients with contusions may show sudden clinical deterioration, particularly those with extensive bifrontal lesions.

Diffuse injury

Three forms of diffuse brain injury are seen as a consequence of trauma; diffuse ischaemic injury, which involves grey matter, diffuse traumatic axonal injury (TAI), which involves white matter, and brain swelling.

While focal infarcts are commonly seen after fatal traumatic head injury (91% in one study), usually as a consequence of raised intracranial pressure (ICP), global cerebral ischaemia is less common. Global cerebral ischaemia may be related to hypotension, e.g. after multiple injuries, or secondary to raised ICP resulting in reduced cerebral blood flow. Ischaemic neurons are widely distributed, initially following a pattern of selective vulnerability.

Diffuse traumatic axonal injury (TAI) describes a diffuse process in which there is disruption to axons in a number of white matter bundles throughout the cerebrum and brainstem (Figure 2). Axons are damaged as a consequence of rotational forces being applied to the brain, and is most frequently seen in high velocity impacts such as road traffic accidents. TAI is not a static process. A small proportion of axons may be damaged at the time of head injury (primary axotomy), but animal experiments suggest this is not the case for most of the damaged axons, which degenerate over a period of time after the head injury (secondary axotomy). The clinical impact of TAI ranges from mild diffuse injury being associated with short spells of unconciousness and possibly concussion, through to extensive diffuse TAI associated with irreversible coma and death. The structural basis of concussion is poorly defined. However, TAI has been described in mild head injury[5] and may form the basis of concussion. Post-concussive sequelae are commonly described in mild head injury and axonal damage has been demonstrated in animal models of concussion.

Brain swelling can develop either locally, such as in relation to contusions, or can be diffuse involving one or both hemispheres. In diffuse brain swelling ischaemia is the most common underlying pathology, although swelling can be associated with diffuse TAI.

Long term outcome

The outcome is modified by the type and severity of injury and may be influenced by the pre-morbid state such as age, nutritional status and pre-existing disease. Among survivors of traumatic brain injury of all grades

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Focal injuries	Diffuse Injuries
Scalp lacerations	Global ischaemia
Skull fractures	Diffuse traumatic axonal injury
Contusions	Brain swelling
Intracranial haemorrhages	
Lesions secondary to raised intracranial pressure	

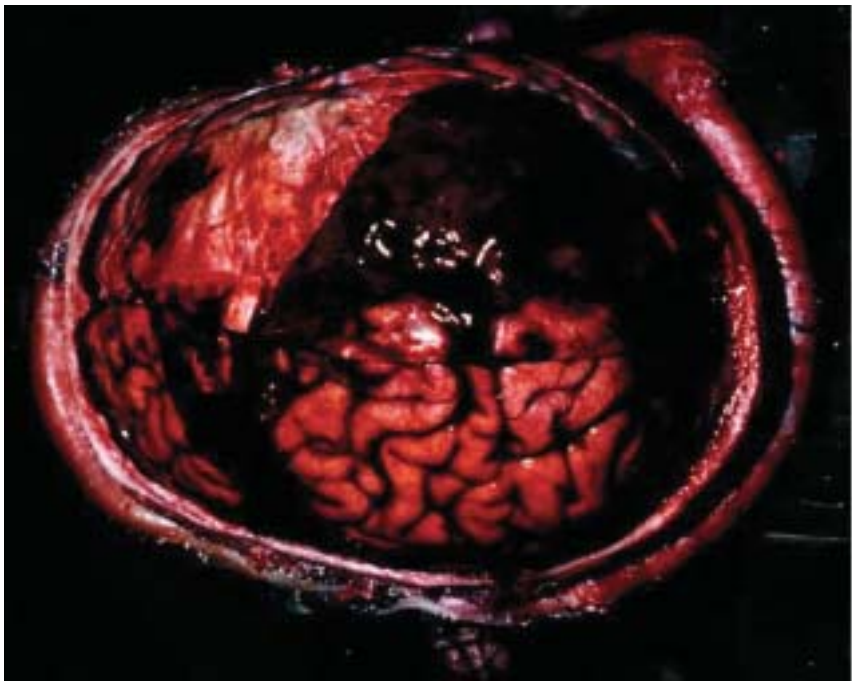

Figure 1: Subacute subdural haematoma identified at autopsy. This individual had a blunt force head injury as the result of a fall. The patient survived for two weeks post injury. The lesion extends over the surface of the right cerebral hemisphere and shows some degree of organisation.

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*Despite no PK interactions, LYRICA appears to be additive in the impairment of cognitive and gross motor function when co-administered with oxycodone. LYRICA may potentiate the effect of lorazepam and ethanol[5]

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References: 1. French JA *et al.* Neurology 2003; 60: 1631–1637. 2. Arroyo S *et al.* Epilepsia 2004; 45: 20–27. 3. Beydoun AA *et al.* Epilepsia 2000; 41(Suppl. 7): 253–254. 4. Baulac M *et al.* Poster presented at the 6th European Congress on Epileptology: Vienna, Austria; 30 May–3 June 2004. 5. LYRICA Summary of Product Characteristics.

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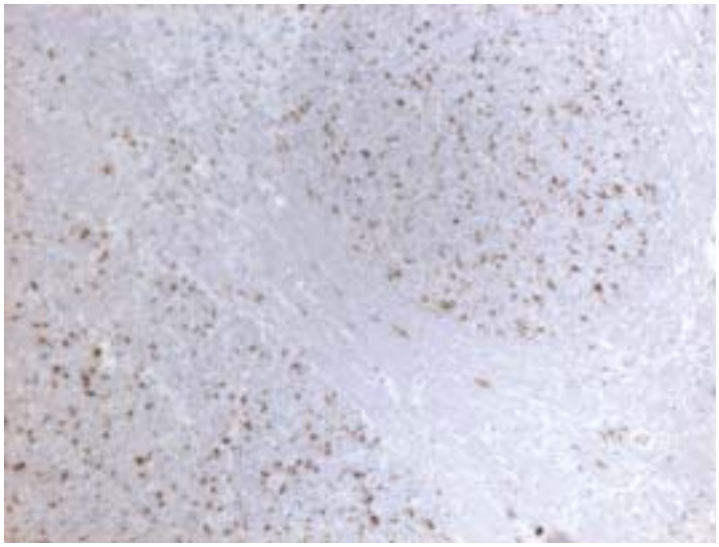

Figure 2

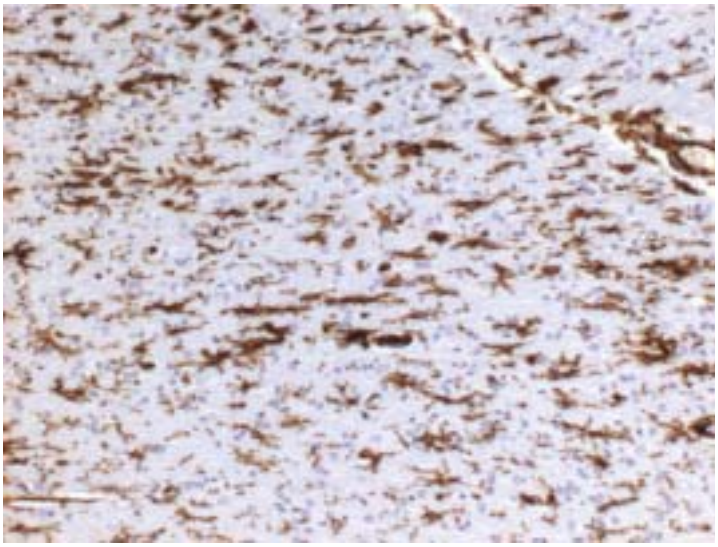

Figure 3

Figure 2: Immunocytochemistry for Amyloid Precursor Protein (b-APP)demonstrates swollen damaged axons (stained brown) within the corpus callosum from a case of diffuse traumatic axonal injury.

Figure 3: Microglial activation demonstrated in the white matter of an individual who survived for several weeks after an episode of blunt force head injury. The activated microglia are immunostained by an antibody which recognises MHC class II expression. Most cells are still ramified, the characteristic morphology of quiescent microglia, but are hypertrophied.

chronic disability may have a physical component although it is predominantly the cognitive and behavioural problems which provide the greatest challenge. Outcome may be assessed by the extended Glasgow Outcome Scale (GOS) which defines four outcome states; death/ vegetative state, severe disability, moderate disability, and good recovery.[6]

Neuropathological basis of outcome after head injury

In studies of the brains of patients who entered a vegetative state after blunt force head injury[7] diffuse pathology was common and, in particular, diffuse traumatic axonal injury was seen in more than 60% of the cases. In severe disability[8] there was a relatively equal distribution of focal and diffuse pathology between cases, while in moderate disability[9] focal lesions, particularly evacuated intracranial haematomas, accounted for the bulk of the pathology with diffuse injury being uncommon. Neuronal loss from the dorsomedial thalamic nucleus was seen in all grades of disability while additional damage to the ventral posterior nucleus was also seen in severely disabled and vegetative cases.[10]

Neurodegeneration and Dementia after head injury

Recent studies have indicated that the incidence of moderate and severe disability in young people and adults one year after mild head injury is similar to that seen in survivors of moderate and severe head injury.[11] This raises the possibility of ongoing brain damage in long-term survivors of head injury such that their cognitive function and motor function continues to deteriorate for months and possibly years after the initial injury.[12] The clinical entity of dementia pugilistica is well recognised in the setting of repetitive head injury. Epidemiological evidence looking at an association between a single episode of head injury and subsequent neurodegeneration is conflicting although meta-analysis of both retrospective and prospective studies does suggest an association.[13] Head injury and Alzheimer's disease (AD) have similarities in relation to protein and cellular responses and in genetic influences, particularly the influence of APOE polymorphisms.[14] Both cytoskeletal pathology and amyloid deposition are key pathological features of AD and have been described in animal models of head injury and studies of both fatal head injury and repetitive head injury in humans. Cholinergic dysfunction has been described in both AD and head injury: damage to key cholinergic pathways (nucleus basalis of Meynart) has been reported at autopsy in head injury and imaging studies of survivors of head injury have demonstrated damage to basal forebrain structures. Chronic neuroinflammation has been postulated as a mediator of neuronal loss in many chronic neurological diseases, including AD, and is a feature of the response to head injury (Figure 3).[15]

References

1. Teasdale G, Jennett B. *Assessment of coma and impaired consciousness: A practical scale.* Lancet 1974,304:81-4.
2. Graham DI, Smith C. (2001) *The pathology of head injury.* CPD Bulletin- Cellular Pathology 2001,3:148- 51.
3. Smith C, Graham DI. *Subdural and extradural hemorrhages. In: Olsson Y, ed. Pathology and Genetics Cerebrovascular disease.* Basel: ISN Neuropath Press, 2005.
4. Graham DI, Gennarelli TA, McIntosh TK. *Trauma.* In: Graham DI, Lantos PL, eds. Greenfield's Neuropathology. London: Arnold, 2002: 823-98.
5. Blumbergs PC, Scott G, Manavis J, Wainwright H, Simpson DA, McLean AJ. *Staining of amyloid precursor protein to study axonal damage in mild head injury.* Lancet 1994,344:1055-6.
6. Teasdale GM, Pettigrew LE, Wilson JT, Murray G, Jennett B. *Analyzing outcome of treatment of severe head injury: a review and update on advancing the use of the Glasgow Outcome Scale.* J Neurotrauma 1998,15:587-97.
7. Adams JH, Graham DI, Jennett B. *The neuropathology of the vegetative state after an acute brain insult.* Brain 2000,123:1327-38.
8. Jennett B, Adams JH, Murray LS, Graham DI. *Neuropathology in vegetative and severely disabled patients after head injury.* Neurology 2001,56:486-90.
9. Adams JH, Graham DI, Jennett B. *The structural basis of moderate disability after traumatic brain damage.* J Neurol Neurosurg Psychiatry 2001,71:521-4.
10. Maxwell WL, Pennington K, MacKinnon MA, Smith DH, McIntosh TK, Wilson JT, Graham DI. *Differential responses in three thalamic nuclei in moderately disabled, severely disabled and vegetative patients after blunt head injury.* Brain 2004,127:2470-8.
11. Thornhill S, Teasdale GM, Murray GD, McEwen J, Roy CW, Penny KI. *Disability in young people and adults one year after head injury: prospective cohort study.* BMJ 2000,320:1631-5.
12. Smith C, Nicoll JAR, Graham DI. *Head Injury and Dementia.* In: Esiri MM, Lee V M-Y, Trojanowski JQ, eds. The Neuropathology of Dementia, Cambridge University Press, Cambridge, 2004:457-71.
13. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. *Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication.* J Neurol Neurosurg Psychiatry. 2003,74:857-62.
14. Teasdale GM, Nicoll JA, Murray G, Fiddes M. *Association of apolipoprotein E polymorphism with outcome after head injury.* Lancet 1997,350:1069-71.
15. Gentleman SM, Leclercq PD, Moyes L, Graham DI, Smith C, Griffin WS, Nicoll JA. *Long-term intracerebral inflammatory response after traumatic brain injury.* Forensic Sci Int 2004,146:97-104.

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References:

1. Hart I. Myasthenia Gravis – the essentials. Eurocommunica publications.
2. Buckley C. Diagnosis and treatment of myasthenia gravis. Prescriber 2000;19
3. Sharma KR. Myasthenia gravis: a critical review. Internal Med 1996; August:47-69
4. Drachman DB. Myasthenia gravis. N Eng J Med 1994;330:1797-1810
5. Vincent A, Drachman DB. Myasthenia Gravis. In: eds Pourmand R, Harati Y, Neuromuscular Disorders, Lippincott, Williams & Wilkins, Philadelphia 2001: p159

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SPECT in Dementia (Advances in Biological Psychiatry Vol. 22)

Editors: KP Ebmeier (ed.)
Published by: Karger 2003
ISBN: 3-8055-7595-5
Price: EUR80.00

This slim tome gives details of a study entitled "SPECT in dementia", a collaborative European initiative designed to improve the use of single photon emission computed tomography in the diagnosis of dementia, involving centres in Scotland, France, Germany, Italy and Israel.

Many of the chapters are quite technical in their orientation, e.g. combining images from different clinical settings, voxel-based approaches to imaging (statisitical paramateric mapping apparently improves rater accuracy of scan reading), comparison of HMPAO-SPECT with FDG-PET, and use of novel receptor ligands. There is no specific discussion of the functional imaging signatures of different dementia syndromes (frontotemporal dementia, dementia with Lewy bodies, vascular cognitive impairment, prion disease), the focus being principally on Alzheimer's disease (AD), in which context an exhaustive systematic review (taking up more than a quarter of the book) that finds 99mTc-HMPAO-SPECT can successfully discriminate between normal controls and AD is reassuring though hardly earth-shattering.

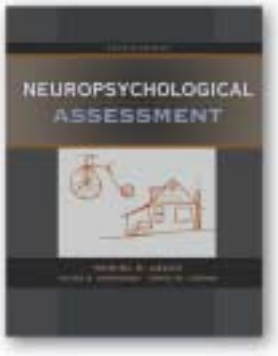
Of perhaps greater clinical impact are chapters on the use of SPECT to correlate specific cognitive and psychiatric phenomena in AD with specific patterns of regional cerebral perfusion, and, particularly topical, assessing the efficacy of cholinestrase inhibitor (ChEI) therapy in AD. Donepezil seems to preserve regional cerebral blood flow patterns in comparison to untreated AD patients, and in responders vs. non-responders. In the future, use of acetylcholine receptor ligands may also provide a surrogate measure of ChEI efficacy.

A cost-effectiveness study of SPECT in the diagnosis of AD rounds off the text, and makes interesting reading for those of us unfamiliar with the methodology of such studies. Some of the assumptions, for example monthly follow up of AD patients for 3 months before deciding whether ChEI is continued, and transfer of responders to a GP who will then prescribe the drug, caused some raising of eyebrows.

Thus, this book's appeal is largely to the cognoscenti of functional brain imaging, rather than to the clinical neurologist, but nonetheless is worth dipping into by those with an interest in dementia.

AJ Larner; Cognitive Function Clinic, WCNN, Liverpool.

Neuropsychological Assessment (Fourth Edition)



Authors: Lezak, MD; Howieson, DB & Loring, DW; with Hannay, HJ & Fischer, JS
Publisher: Oxford University Press, 2004
ISBN: 0-19-511121-4
Price: £59.50

This is an update of what for almost three decades has been the classic textbook of clinical neuropsychological assessment. The first edition appeared back in 1976, followed by updates in 1983 and 1995. The volume of what is covered in this textbook has grown significantly, perhaps reflecting the exponential developement of knowledge in this exciting field.

As before, the basic scientific knowledge underpinning the practice of neuropsychological assessment is covered in great depth before discussing implications for clinical practice. It is both striking and reassuring that often there is not a single, definitive answer to clinical dilemmas. A good example of this is the question of how to determine pre-morbid ability (Chapter 4) where a critical appraisal of the different methods is followed by providing a pragmatic solution to this perennial problem in neuropsychological assessment. A general theme emphasising the need to be "clinically streetwise" permeates the text. Indeed, the point is made that it is now harder than ever to be a good clinician (page 102).

In general, there is now more on neuro-imaging and a better integration of insights from cognitive neuropsychology. The limitations of findings from neuro-imaging studies are however highlighted throughout (For example, page 287). A particular strength remains the provision of strong links between research findings and clinical practice. There is also more on the implications of neuropsychological assessment for the practice of neuropsychological rehabilitation, in effect removing the rather artificial barrier between assessment and rehabilitation.

The basic structure of the book is, as before, that the first few chapters address the core, scientific basis of clinical neuropsychological assessment (Chapters 1 – 8), before proceeding to review a truly wide range of tests, rating scales and inventories (Chapters 9 – 19). Finally, a new chapter on response bias has been added (Chapter 20). The application of computers in neuropsychological assessment is not covered. It is likely that the first eight chapters will as before be the "must know" part of the book, while the section on tests will probably be used more as a reference source.

A vast array of tests are comprehensively reviewed, including some of the new versions of existing, widely used tests such as the Wechsler Adult Intelligence Scale – III, the Wechsler Memory Scale – III and the Rivermead Behavioural Memory Test - E. Newer tests that are now being used in practice, for example the Delis-Kaplan Executive Function System and the Behavioural Assessment of the Dysexecutive Syndrome, as well as tests that have been around for several decades, for example the Porteus mazes, are reviewed. The tests are critically reviewed regarding reliability, validity and other neuropsychological findings, providing essential guidance to the practitioner. As is often the case in neuroscience, a lot of the answers are not straightforward. Indeed, the point is made that it remains unclear what many tests measure (page108).

Are there any gaps in this truly phenomenal textbook? The short answer is no. Perhaps bedside cognitive assessment and psychopharmacology could have been covered in a bit more depth, but there are textbooks specifically dedicated to these topics. The chapters on rating scales, inventories and questionnaires used in neuropsychological assessment (Chapters 18 & 19) could possibly have included more instruments, for example the European Brain Injury Questionnaire and the Brain Injury Community Rehabilitation Outcome scale, but then again, it is simply not possible to include every test or questionnaire currently in use. Neuropsychological Assessment (Fourth Edition) represents a monumental achievement by the authors and remains the most important text on clinical neuropsychological assessment. No practitioner or researcher should be without it.

Rudi Coetzer, North Wales Brain Injury Service, Conwy & Denbighshire NHS Trust.

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The Multiple Sclerosis Society of Great Britain and Northern Ireland

MS is the most common disabling neurological disorder affecting young adults. It is estimated that around 85,000 people in the UK have MS. Approximately 50 people are diagnosed with MS every week.

The MS Society is the UK's largest charity dedicated to supporting everyone whose life is affected by MS. It is dedicated to funding the very best research into the cause, cure and care of people affected by MS, and is currently the largest funder of MS research in the UK. Research is essential to all aspects of the Society's work. It ensures those affected are provided with evidence-based information, enabling them to make informed decisions and manage their condition. It also helps professionals to develop their services and to provide effective treatment and care.

MS Society Research Programme

The MS Society currently funds around 55 research projects with aims of finding the causes of MS, investigating ways to stop progression, alleviating symptoms, and also improving services to better meet the needs of people affected by MS. In addition to short-term innovative projects, PhD studentships, Fellowships, and Project grants, the MS Society currently supports three Programme grants. These long-term commitments include the UK MS Tissue Bank at Imperial College, the NMR MRI Unit at University College London, and the MS Society Cambridge Centre for Myelin Repair at Cambridge University.

Consumer Involvement

The MS Society has a policy of involving consumers at every stage of its research programme to ensure Society funded research is relevant, and reflects the needs and interests of those who live with the condition. So far, 150 people affected by MS have been integrated into the research programme, taking part in activities ranging from grant review, reporting on the progress of funded research, raising awareness about MS, and contributing to the MS Society's research strategy.

After consultation with people affected by MS and researchers in 2002, the MS Society has agreed some research priorities to run alongside its open grant round, to ensure funds are focused further. Initial priorities include a Symptom Research Programme with the first symptom to be addressed being fatigue, and research into nerve damage and repair.

MS Professional Network

The MS Society Professional Network is a group of health and social care professionals with a common interest in sharing good practice and information to improve services for people affected by MS. Membership is free and includes regular newsletters, conferences and learning events. To join email msnetwork@mssociety.org.uk or call 020 8438 0765.

MS Frontiers 2005

MS Frontiers is the Society's key research conference, which aims to bring together researchers and healthcare professionals within the MS field to share ideas and identify key challenges for the future. It is also a great opportunity for students and younger researchers currently studying MS to take part in what has consistently proven to be an extremely interesting and enjoyable event. This year's programme focuses on neuroprotection, and sessions covering:

- a UK MS clinical trial network
- evolving MS services
- epidemiology
- translational research in neurology

The event in 2005 will be held in Edinburgh on the 25th & 26th May at Heriot-Watt University. For further details or to obtain a booking form please contact frontiers@mssociety.org.uk or tel: 020 8438 0809.

For further information about the MS Society's research programme, email researchadmin@mssociety.org.uk, call 020 8438 0770, or visit the Society's website http://www.mssociety.org.uk/research/index.html

To list your event in this diary, e-mail brief details to: Rachael@acnr.co.uk

2005

March

The Visual System - RSM Clinical Neurosciences Section
3 March, 2005; London, UK
Tel. 20 7290 2984/2982, E. cns@rsm.ac.uk

Royal College of Psychiatry: Old Age Psychiatry
3-4 March, 2005; UK. http://www.rcpsych.ac.uk/conferences/diary/index.htm

13th Annual Conference - Association of Cognitive Analytic Therapy: Body, Brain and Beyond CAT
4-5 March, 2005, London, UK
Tel. 020 7188 0692, E. conference@acat.me.uk

Standardised Assessment in Occupational Therapy with special emphasis on Dementia, Part 2
March, 2005; London, UK. Tel. 020 7834 3181

9th International Congress of Parkinson's Disease and Movement Disorders
5-8 March, 2005; New Orleans, US
E. congress@movementdisorders.org

GCNN 2, 2nd Global College of Neuroprotection and Neuroregeneration Annual Conference
7-10 March, 2005; Innsbruck, Austria
E. info@gcnpnr.org

The British Pain Society Annual Meeting
8-11 March, 2005; Edinburgh, UK
Tel. 020 7631 8870,
E. meetings@britishpainsociety.org

7th International Conference on Progress in Alzheimer's and Parkinson's Disease
9 - 13 March, 2005; Sorrento, Italy
Fax. 08451 275 687, E. adpd@kenes.com

The Electrophysiological Technologists' Association Scientific Meeting
10-12 March, 2005; Glasgow, UK
E. epta@execbs.com

Advances in Otology and Neurotology
11-12 March, 2005; Houston, US
E. cme@bcm.tmc.edu

Advances in the Management of People in a Vegetative and Minimally Conscious State
16 March, 2005; Newcastle, UK
Linda Eldred, Tel. 0870 1500 100,
E. eldredl@irwinmitchell.co.uk

Tuberous Sclerosis Association: Professional Study Day
17 March, 2005; Birmingham, UK
Tel. 01527 871898, Fax. 01527 579452.

1st Joint International Meeting on Degos Disease
18-19 March, 2005; Berlin, Germany
E. judith@degosdisease.com

Essential Skills in Neurosurgery
22 March, 2004; London, UK
0207 4053 474, E. international@rcseng.ac.uk

ABN Spring Meeting
30 March - 1 April; Belfast, UK
Tel. 020 7405 4060, E. info@theabn.org

BPS 2005 Quinquennial Conference
30 March - 2 April, 2005; Manchester, UK
www.bps.org.uk/events/AC2005

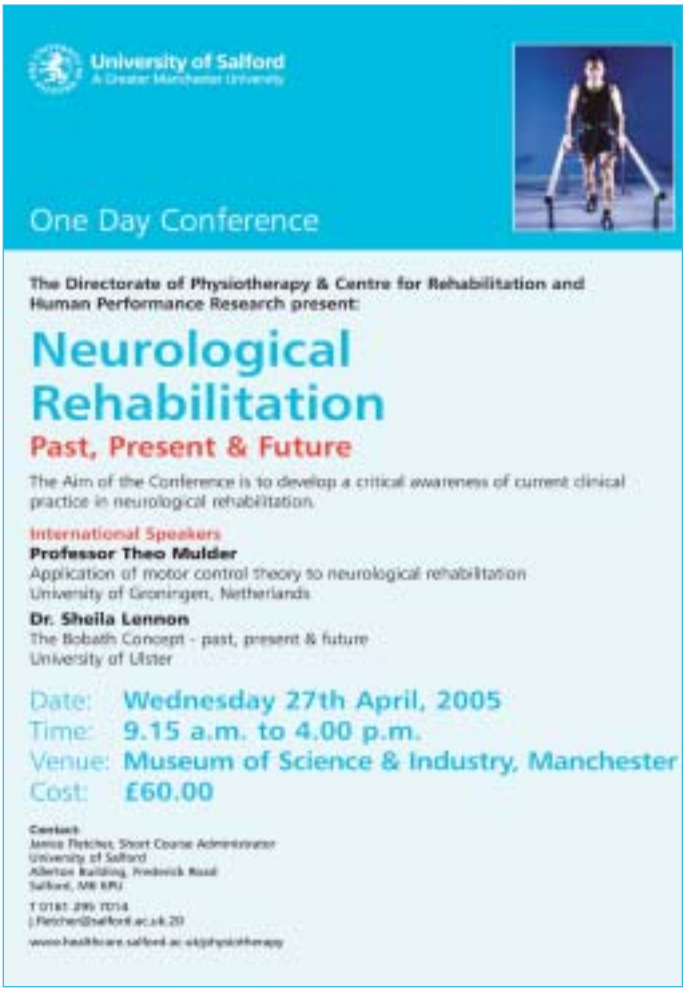
April

Pain Management: The Online Series, Assessing and Treating Neuropathic Pain
1-30 April, 2005
E. mark_evans@ama-assn.org

7th Neurochemistry Winter Conference
2-7 April, 2005; Sölden, Austria
www.sambax.com/nwc2005/

18th National Meeting of the BNA
3-6 April, 2005; Brighton, UK
www.bna.org.uk

Clinical Neurophysiology BSCN Course
3-8 April, 2005; Oxford, UK
E. robin.kennett@orh.nhs.uk



International Psychogeriatric Association
5-8 April, 2005; Rotorua, New Zealand
Fax. +1 847 663 0591, Tel. +1 847 663 0574,
E. info@ipa-online.org

Independent Living Scotland
6-7 April, 2005; Glasgow, UK
Tel. 020 7874 0200.

27th Advanced Clinical Neurology Course
6-8 April, 2005; Edinburgh, UK
E. events@acnr.co.uk

Do Corticosteroids Damage the Brain? Symposium in honour of Prof Joe Herbert
7 April, 2005; Cambridge, UK
Michael Hastings, E. mha@mrc-lmb.cam.ac.uk,
Tel. 01223 402307/402411.

Introduction to Neuropsychological Rehabilitation
7-8 April; 2005; Ely, UK
E.alison.gamble@ozc.nhs.uk

Neurology for Neuroscientists XI
7-8 April, 2005; Oxford, UK
E. nneurosc@ion.ucl.ac.uk

Insight Following Brain Injury
8 - 9 April, 2005; Gatwick Hilton, Sussex

Brain Tree Training,
E. enquiries@BrainTreeTraining.co.uk
Tel. 01276 472 369.

American Academy of Neurology (AAN) Annual Meeting
9-16 April, 2005; Florida, US
http://am.aan.com/

Cognitive Neuroscience Society (CNS) Meeting
10-12 April, 2005; New York, US
E. cnsinfo@cogneurosociety.org
www.cogneurosociety.org/content/meeting

3rd World Congress Of The ISPRM
10-14 April, 2005; San Paulo, Brazil
E. ispmr2005@isprm.org
UK MS Week 2005
10-17 April, 2005, UK. E. info@msif.org

International Parkinson's Disease Conference
11 April, 2005; Luxembourg
Register by 11 March - FREE.
www.epda.eu.com/worldPDDay-2005.shtm

Certificate Course in Neurological Rehabilitation
11-29 April, 2005, Newcastle, UK
Tel/Fax. 0191 2195695,
E. traceymole@actionfordisability.co.uk

Neuro-Ophthalmology Clinical Course
11-15 April, 2005; Dubline, Ireland
Tel. +353 1 809 2609 or +353 1 803 2876

2005 International Conference on Posture & Wheeled Mobility
11-15 April 2005; Exeter, UK
E. info@mobility2005.org, Tel: 0845 1301 674

Neurodegeneration - RSM Clinical Neurosciences Section
14 April, 2005; London, UK
Tel. 20 7290 2984/2982, E. cns@rsm.ac.uk

Tuberous Sclerosis Association: Professional Study Day - the adult perspective
14 April, 2005; Birmingham, UK
E. support@tuberous-sclerosis.org,
Tel. 01527 871898

RCP Live: Current Issues in the Management of Parkinson's Disease
14 April, 2005; Online
E. conferences@rcplondon.ac.uk,
www.rcplondon.ac.uk

British Sleep Society Spring Meeting
14-15 April, 2005; Newcastle, UK
Jane Orgill, Lung Function Unit, St George's Hospital, Tooting SW17 0QT.

BGS Spring Meeting
14-15 April, 2005; Birmingham, UK
British Geriatric Society, Tel. 0207 6081369

Evolving MS Services
15 April, 2005; Wales. E. CBray@mssociety.org.uk

ESH-EBMT-EUROCORD Euroconference on Stem Cell Research
15-18 April, 2005; Cascais, Portugal
E. ghyslaine@chu-stlouis.fr

73rd Annual Meeting of the American Association of Neurological Surgeons
16-21 April, 2005; New Orleans, US
www.aans.org/annual/2005/

Second International Neuroacanthocytosis Symposium "Expanding the Spectrum of Choreatic Syndromes"
17-20 April, 2005; Montreal, Canada
Tel. 0207 937 2938; E. gingerirvine@usa.net

The Management of Blackouts and Misdiagnosis of Epilepsy and Falls
19 April, 2005; London, UK
Tel. 0207 9351 174, Fax. 0207 4875 218,
E. conferences@rcplondon.ac.uk

Action in Neuro-Rehab
21 April, 2005; Newbury, UK
Tel. 01635 202 605, E. neuroconf@aol.com

Neuroanaesthesia Society of Great Britain and Ireland, Annual Update
21-22 April, 2005; Bristol, UK
E. John.carter@north-bristol.swest.nhs.uk / samantha.shinde@north-bristol.swest.nhs.uk

III International Conference on Metals and the Brain: From Neurochemistry to Neurodegeneration
20-22 April, 2005; Cape Town, South Africa
www.unistel.co.za/neuro2005

Understanding Brain Injury
22 April, 2005; Ely, UK
E. alison.gamble@ozc.nhs.uk

Otoneurologia 2005
23-24 April, 2005; Azores Portugal
otoneuro2005@mail.pt, www.otoneuro.pt

Neurological Rehabilitation: Past, Present & Future
27 April, 2005; Manchester, UK
Tel. 0161 295 7014, E. j.fletcher@salford.ac.uk

May

Short Courses : Neuro-Medical / Surgical Nursing
May, 2005; Cambridge, UK
E. wood@health-homerton.ac.uk

6th World Congress on Brain Injury
1 - 4 May, 2005; Melbourne, Australia
E. braininjury@icms.com.au

Aspects of the Neurological Examination - RSM Clinical Neurosciences Section
Tel. 20 7290 2984/2982, E. cns@rsm.ac.uk

Annual Meeting of the German, Austrian, Swiss section of the International League Against Epilepsy
5-7 May, 2005; Innsbruck, Austria
Tel. +43 512 5043879,
E: iris.unterberger@uibk.ac.at

2nd quadrennial meeting of the World Federation of Neuro-Oncology EANO VI
5-7 May, 2005; Edinburgh, UK
E. EANO6@fecs.be, Tel. 32 27 750 205,
Fax. 32 27 750 200.

4th BASP Thrombolysis Training Day
6 May, 2005; Nottingham, UK
Pamela Nicholson, sec to Professor Lees,
E. pcn1w@clinmed.gla.ac.uk, Tel. 0141 211 2176.

Neurochirurgie 2005
7-11 May, 2005; Strasbourg, France
Fax. +49 3 028 449 911,
E. nch2005@porstmann-kongresse.de

12th European Congress of Clinical Neurophysiology
8-12 May, 2005; Stockholm, Sweden
E. secretary@ec-ifcn.org /weerd@ipe.nl

Inaugural Meeting of the Vocational Rehabilitation Special Interest Group
13 May, 2005; London, UK
E. admin@bsrm.co.uk

Alzheimer's Disease: Update on Research, Treatment, & Care
19-20 May, 2005; San Diego, US
E. jcollier@ucsd.edu

Traumatic Brain Injury – The Road to Recovery

6 December, 2004; London, UK.

This was a one-day conference organised by the Royal College of Physicians and British Society of Rehabilitation Medicine held at the Royal College of Physicians, London. The main theme of the meeting was to enable professionals involved in the care of patients with brain injury to have a clear understanding of the scope as well as the complexities involved in rehabilitation of this patient group.

Professor Carol Black, President of the Royal College of Physicians gave the welcome address and was pleased that so many people involved in brain injury rehabilitation, not only from the statutory services but also from the voluntary and charitable sectors, had come to this meeting. She went on to say that the meeting covered a topic that has not received the attention it deserves in the past. The meeting was conducted in four sessions.

1. Morning sessions

Chair: Dr Vera Neumann,
President of the British Society of Rehabilitation Medicine

1.1. The patient journey

Title: National Service Framework (NSF) for long term conditions: Guidance and evidence for traumatic brain injury (TBI) rehabilitation
Speaker: Professor Lynne Turner-Stokes, Vice-Chair – External Reference Group of the NSF for long term conditions
Take home messages:
1. There is an urgent need for further research in traumatic brain injury (TBI) rehabilitation
2. Users' and carers' views must be fully taken into account in further development of TBI rehabilitation
3. A new research typology has been developed with information on classification of design, quality rating and grades of evidence and recommendations

Title: Robin's story – one family's experience of brain injury
Speakers: Steve and Ann Harris, Robin's parents
Take home messages:
1. Good practice in post brain injury rehabilitation has been rather patchy
2. There needs to be better co-operation and co-ordination of services for those with brain injury in the community

1.2. Clinical conundrums

Title: Management of agitation and challenging behaviour
Speaker: Dr Simon Fleminger, Consultant Neuropsychiatrist
Take home messages:
1. Managing restless, agitated and aggressive patients following brain injury requires a team approach
2. The medication to control these problems must be used judiciously in conjunction with psychological and behavioural management programmes

Title: Profound brain damage: locked in or vegetative state
Speaker: Dr Keith Andrews, Director – Institute of Complex Neuro-disability
Take home messages:
1. There is still much confusion among the clinicians between locked in, minimally conscious and vegetative states
2. It is important to be aware of potential pitfalls in diagnosis as well as problematic presentations

2. Afternoon sessions

Chair: Professor Lynne Turner-Stokes

2.1. Brain injury rehabilitation services

Title: Acute care and the interface with rehabilitation
Speaker: Professor John Pickard, Consultant Neurosurgeon
Take home messages:
1. The interface between acute care and rehabilitation services are far from ideal
2. Head injury co-ordinators are essential in ensuring smooth movement of patients through acute care, rehabilitation and support in the community

Title: Specialist rehabilitation service networks – a model of care
Speaker: Dr Kyaw Nyein, Consultant in Rehabilitation Medicine
Take home messages:
1. Network of specialist rehabilitation services are essential to ensure appropriate and timely care for patients with brain injury
2. There needs to be an ever closer collaboration between the specialist rehabilitation services and the district and community services in delivering a seamless service to patients with severe complex disability in the community

2.2. Living with brain injury

Title: Longer term community support and case management
Speaker: Maggie Campbell, Brain Injury Co-ordinator
Take home message:
1. Need to promote an interdisciplinary client centred approach in practical service delivery
2. Professionals should work in collaboration with service users to achieve realistic personalised goals

Title: Back to work following brain injury
Speaker: Dr Andy Tyerman, Consultant Clinical Neuropsychologist
Take home message:
1. Supported work re-entry programmes are effective in reintegrating the brain injury population to their workplace
2. Need to develop local inter-agency protocols
He then launched the inter-agency guidelines on vocational assessment and rehabilitation after acquired brain injury, which was well received.

There was widespread agreement among those who attended the one-day conference that the highlight of the meeting was Steve and Ann Harris's powerful presentation of their son Robin's journey following his brain injury.The trials and tribulations that they encountered as well as the triumphs that they achieved with able support from many of the professionals involved in Robin's care left a powerful and indelible impression on those who attended the meeting as to the importance of patient centred care.

Dr Andrew Thu, Dr Charlie Nyein, Regional Rehabilitation Unit, Northwick Park Hospital, London.

15th International ALS/MND Symposium

2-4 December 2004; Philadelphia, USA

Doctors, nurses and professionals allied to medicine (PAM's) gathering in a northern city in a temperate weather zone in early winter? – it must be the ALS/MND symposium. All those with a significant interest in motor neurone disease (MND) or amyotrophic lateral sclerosis (ALS), gathered in Philadelphia. For a relatively uncommon condition, MND generates disproportionate interest, probably because most health care workers recognise the awful truth of this disease.

This year more that 750 delegates gathered to present, discuss, debate and exchange the most recent advances in the fields of MND basic science research and clinical care. Each year the size of this meeting increases, reflecting the impact that MND has upon patients, their families and professional carers alike. The symposium proper was preceded by several days of satellite sessions and an allied professionals meeting for the day immediately preceding the opening plenary session. The format of opening and closing joint plenary sessions, separated by parallel sessions covering basic science research and clinical care is well established. Most clinical academics are forced to make difficult choices between key sessions covering important areas of scientific advance and those concentrating on important issues of care provision.

One of the major themes highlighted this year was the similarity of MND to many other neurodegenerative conditions. Several keynote speakers emphasised this point with reference to Parkinson's disease, Alzheimer's disease and some of the tri-nucleotide repeat disorders. It is now more that ten years since the first report that mutations in Cu/Zn superoxide dismutase (SOD1) are causal in approximately 20% of familial MND cases. Finally, mutated SOD1 is starting to give up its aetiological secrets. Several elegant scientific presentations put forward evidence that, in common with other neurodegenerative conditions, mutant SOD1 associated familial MND appears to be a disorder caused by protein mis-folding, failed degradation and ultimate pathological aggregation. These problems appear fundamental to motor neurone cell loss in mutant SOD1 associated MND, and may well be of great importance in sporadic MND, where protein aggregation was first reported and remains one of the most widespread neuropathological abnormalities.

At last year's symposium (in a cold and dank Milan) the first reports of the vascular endothelial growth factor (VEGF) gene acting as a risk factor (modifier) for the development of MND were presented. This year several scientific presentations showed how this novel information is being exploited in new therapeutic approaches to MND. VEGF administered to transgenic mice carrying human SOD1 mutations and which develop a form of MND, improved survival of these animals. Moreover, novel delivery systems using viral vectors, conveying VEGF genes to motor neurons were also shown to slow the degenerative process in both in vitro and in vivo models of MND.

A novel therapeutic option, again employing our understanding of the role of mutant SOD1 was reported by Don Cleveland's group (USA). They have developed anti-sense RNA oligonucleotides to several SOD1 mutants, which down regulate those specific SOD1 RNAs in vitro. This may offer a therapeutic pathway for familial MND sufferers with identified SOD1 mutations.

Although stem cell therapies in MND were not prominent at this year's symposium, Stanley Appel's group (USA) presented evidence that bone marrow derived haematopoietic stem cells may be able to cross the blood brain barrier, with sustained levels of donor-derived DNA present in the spinal cords of allogenic bone marrow transplanted MND patients. Caution in the interpretation of these very early and limited results must remain, particularly given the use of a high-risk strategy such as bone marrow transplantation.

The clinical sessions included brief reports of trials conducted in human MND patients. Three of these reported trials were small and preliminary in nature. Sadly, the two large and well conducted trials presented, examining the drugs celecoxib and pentoxyfilline respectively, both reported negative results in terms of improved survival.

MND care centres around the world are still wrestling with the problems associated with the appropriate timing of various interventions such as gastrostomy and ventilation for MND patients. Increasing evidence supports the use of some form of pressure measurement as the most accurate monitor of respiratory function (maximum inspiratory or expiratory pressure, nasal sniff pressure, peak cough flow), with overnight oxygen saturation and forced vital capacity being relatively insensitive indicators of the need for some form of ventilatory intervention.

A clinical session was devoted to non-invasive ventilation (NIV). Several groups reported the results of their experience in the use of NIV for their MND patients, and factors which influenced successful and compliant use of NIV. The Newcastle (UK) group reported the results of the only positive therapeutic trial presented at the symposium. More than 40 MND patients fulfilling predetermined criteria for NIV were randomly allocated to receive NIV or "standard" conservative management of their respiratory insufficiency. A significant overall survival benefit, but more importantly a highly significant and sustained improvement in quality of life was detected in patients receiving NIV.

The symposium closed with two excellent presentations on differing epidemiological studies of MND. Dr Chio (Italy) reported on the high incidence of MND amongst professional footballers in Italy, supporting the widely held but largely anecdotal view that MND is over represented in high performing sports men and women. The mechanisms behind this apparent finding remain elusive. Dr Cox (USA) presented what appears to be the answer to a near 100-year-old conundrum – the very high incidence ALS / Parkinsonism / dementia complex (ALS/PDC) affecting the Chamorro peoples of Guam. Nearly 20 years ago this disorder was linked to an environmental toxin ß-methyl-amino-L-alanine (BMAA), found in cycad seeds, a staple of the Chamorro diet. However, the level of BMAA appeared to low in the flour derived from these seeds. It now appears that BMAA is concentrated in flying foxes (fruit bats), a delicacy highly sought after by the Chamorro peoples, the ingestion of which led to their toxic exposure to BMAA and the development of ALS/PDC. Intriguingly, Dr Cox presented preliminary data indicating the presence of BMAA in the brain tissue of Alzheimer's disease patients in Canada (who had no association with Guam) raising the possibility that such toxins are present in other parts of the world and may even contribute to neurodegeneration.

Suitably enthused, and having had ample opportunity to reinforce old collaborations and forge new ones, delegates left with plenty of new scientific and clinical information to digest, and thoughts of a temperate Dublin next December in their minds.

Dr Timothy Williams,
Consultant Neurologist & MND Care Centre
Medical Director, Newcastle.

See www.acnr.co.uk/pdfs/volume2issue3/v2i3interview.pdf for an interview with Oliver Sacks, "Flying Bats in Guam - the cause of the complex".
For a response to that article by Dr Huw Morris, see www.acnr.co.uk/pdfs/volume2issue3/v2i3specfeaturebats.pdf

American Epilepsy Society Annual Meeting

3-7 December, 2004; New Orleans, USA

Following the heavy snow in Boston last year, balmy New Orleans was a welcome change. Genetics was the topic for the annual course. The number of single gene epilepsies identified continues to increase. As in other clinical areas, there is a "many-to-many relationship"; the same clinical syndrome may be associated with different genes and abnormalities of the same gene may be associated with different clinical syndromes. For example, SCN1A truncating mutations cause severe myoclonic epilepsy of infancy and missense mutations cause generalised epilepsy with febrile seizures plus (GEFS+), which may also be associated with mutations of the SCN1B, SCN2A and GABA receptor gene mutations. Lennox and Lennox demonstrated a concordance of 80% in MZ twins for IGE syndromes half a century ago and this has been almost exactly replicated by Berkovic and colleagues. In rare IGE families with a dominant pedigree, abnormalities of the GABA receptor have been identified. However, the genetic bases of commoner idiopathic epilepsies remain elusive. A late onset form of idiopathic generalised absence epilepsy has been recognised for some years but recent studies have shown that up to a quarter of IGE has onset over the age of 20. If your patient has tonic clonic seizures with no aura, triggered by fatigue or alcohol, and a family history, think IGE.

Another major session was devoted to neuronal development. Since the 1970's it has been known that the cortical neurons arise from the ependymal zone and then migrate along radial glial fibres. Arnold Kriegstein from San Francisco, used labelling methods to show how glial cells at the ventricular zone start to produce their radial fibre then divide asymmetrically to produce another glial cell and a neuron which then migrates up the glial fibre. Some of the molecules that help to determine the fate of either cell, are being identified. By contrast divisions of cells slightly further along their route, in the subventricular zone, are symmetric, giving two neurons. Some radial cells have GABAA receptors and studies show that GABA active drugs can influence neurogenesis; of significance as we consider antiepileptic drugs in pregnancy. When radial glial cells reach the cortex they change into astrocytes, which may retain some stem cell activity. Pat Levitt from Vanderbilt University pointed out that interneurons are only 10% of neurons and so changes in pathological states may be difficult to detect. He described how in the rat they arise from the ventral telencephalon and then migrate into the cortex by a mechanism dependent on hepatocyte growth factor (HGF). A knockout mouse with reduced HGF has fewer interneurons and increased susceptibility to seizures. They are also less social and more sensitive to diazepam. He speculated that altered functional anatomy of cortical columns may cause these changes and that they may be a model for autistic spectrum disorders. Amy Brooks from Pennsylvania addressed the question of why young animals are particularly susceptible to seizures. In immature neurons there is a higher intracellular chloride concentration than in mature neurons. Consequently, chloride fluxes controlled by GABA receptors move in the opposite direction and are depolarising rather than hyperpolarising. She also described how A and B type GABA subunits switch during development to alter their functional properties such that young mice are particularly prone to seizures in the postnatal period. Glutamate receptor function is also enhanced from postnatal day 5-15 in the mouse. In addition the response of the brain to seizures appears to be different at different ages. After status in neonatal mice there is an upregulation of GABAA with an increased sensitivity to benzodiazepines, which is not seen after status in adults. All adults in these studies developed spontaneous seizures within 4 days of status whereas neonates did not. If similar factors operate in humans, they may clearly be significant in designing and using drugs in young children rather than in adults

In the annual Lennox lecture, Dr Pitkänen from Denmark emphasised an increasing theme that current therapies treat seizures and we should be looking at factors that underly the development of epilepsy. She argued that current models may not be representative of human epilepsy and suggested different models and the use of surrogate markers in assessing the severity of acute brain injury such as 14-3-3 protein levels in the CSF. She showed how the adrenergic blocker atipamezole may make established seizures worse but is anti-epileptogenic; if given early after injury may reduce the severity of subsequent epilepsy by 90%.

One session was devoted to evidence-based guidelines in the drug treatment of epilepsy. The background was set with a talk that described the evolution over 20-30 years from expert opinion through consensus statements to evidence-based medicine, a process driven partly by cost considerations. Dr Ben Menachem chaired an ILAE team which analysed all the existing drug trials in different forms of epilepsy, used to inform the current guidelines of the ILAE. In monotherapy studies of focal epilepsy, only 1 trial (from 1985) was considered to be of class 1a quality and only 10 of 33 studies were in the top tier. The panel adopted the view that only where a good quality trial had been conducted could firm conclusions be drawn. So if you conduct a good study on a mediocre drug it gets in the guidelines and if you conduct a bad study on a good drug it doesn't. Recommended first line treatment for focal epilepsy in adults is carbamazepine, oxcarbazepine, topiramate and valproate (men) with alternative treatments gabapentin, lamotrigine, phenytoin (downgraded by toxicity) and valproate (women). There are no ILAE recommended drugs for childhood absence epilepsy because there are no good trials and sulthiame (not available for decades in the UK) is the only recommended drug for benign rolandic epilepsy as it is the only one subjected to a decent clinical trial. This approach emphasises the need for more carefully conducted trials. But where none is available, taking the evidence-based principle to extremes denies a wealth of clinical experience, implies that opinion and consensus are worthless and results in guidelines that are frankly bizarre – better no guidelines at all. As the leading international epilepsy organisation the voice of the ILAE has an authority which it risks losing if it generates guidelines to which nobody will adhere.

The issues around pregnancy and epilepsy continue to figure largely. Whether maternal seizures contribute to major foetal malformations remains uncertain but the various registers give useful and sometimes disturbing information about AED's, with valproate remaining the villain of the piece. Carbamazepine and lamotrigine data are more reassuring.

A recent Cochrane review concluded that

Dancing in the street in New Orleans.

Single gene mutations and epilepsy syndromes have a many-to-many relationship

there is insufficient evidence of the benefit of specialist nurse intervention. Insufficient evidence of efficacy does not imply absence of efficacy and a US study using the QOLIE-89 demonstrated that nurses do provide significant quality of life improvements for their patients.

It is always somewhat mind-numbing to work round 1000 posters in two sessions. There was of course basic science that we didn't understand and the usual posters telling how different new drugs really do work quite well in this or that form of epilepsy in which they haven't been tried before. Here is a baker's dozen highlights that struck us: 1) intravenous furosemide or mannitol suppressed interictal spike activity as measured by intraoperative EEG spike recording during epilepsy surgery. 2) Over 90% of 75 patients with JME identified lifestyle as seizure triggers (sleep deprivation 77%, stress 83%, menstruation 33%, alcohol 11% - an underestimate I think – and various cognitive tasks in a small number each), important factors to consider in your patients. 3) Late-onset non-tumoral temporal lobe epilepsy in 20 patients was associated with very high antithyroid antibodies, 18 of whom did not fulfil criteria for diagnosis of Hashimoto's encephalopathy. This may need to be added to the list of autoimmune causes including paraneoplastic and voltage-gated-potassium channel antibodies. 4) Pre-ictal headache affected 11 of 100 consecutive patients and lasted more than 30 minutes in 4. In 9 patients it was ipsilateral to the seizure focus (nb headache is often a prodrome of psychogenic non-epileptic seizures. 5) There is always a little hesitancy in using baclofen in patients with epilepsy but in one study of 42 children with cerebral palsy, intrathecal baclofen at least, did not increase seizures. 6) When do you decide when to abandon trial of a new drug in your patient? A study from Alabama suggests that the strategy varies from drug to drug; they found topiramate has a ceiling response at around 400mg and gabapentin at 2400mg per day. Higher doses yielded few new responders. By contrast, oxcarbazepine had a more linear dose-response, all the way to the maximum recommended 2400mg. 7) Lamotrigine levels start to fall only 3 days after withdrawing concomitant valproate. In women with catamenial epilepsy lamotrigine levels peak at ovulatory day 10-13, with up to 31% reduction premenstrually. 8) One study reported good efficacy but poor tolerability of bromides in 17 patients with refractory epilepsy. Plus ça change! 9) Beware stopping AED in seizure-free patients; in an analysis of 12 studies where treatment was reinstituted, it took up to 1 year for half of patients to become seizure free and 10% never regained seizure-freedom. 10) Confusion is such a common presentation in the elderly that it is easy to forget the occasional patient presenting with non-convulsive status. Even those who had previously suffered a bout were not diagnosed for 29 hours on average. 11) Of 10 patients in one study with unexplained syncope, 9 had psychogenic pseudosyncope; "swoons" are rarely organic. 12) Rapidly titrated levetiracetam has been used successfully in the treatment of refractory focal status. MRAM also has found it valuable in this indication and would be interested to hear from others with similar experience. 13) Depression in TLE patients was associated with inferior frontal hypometabolism on FDG-PET. Hypometabolism developed in similar areas in those who developed depression after temporal lobectomy; an organic cause is implied.

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Sacral Nerve Stimulation (Neuromodulation) for the Treatment of Lower Urinary Tract Symptoms in Adult Patients

Sacral nerve stimulation (SNS) has become established in recent years as a treatment option for two groups of patients seen within urological practice. Firstly, it can be used for patients with idiopathic detrusor over-activity leading to symptoms of urinary frequency, urgency and urge incontinence.[1] The second group are women with urinary retention due to either an unknown cause or abnormalities of the distal urethral sphincter (Fowler's syndrome). Other indications are now being evaluated as interest and research into this exciting treatment modality gains momentum.

Origins of the technique

Electrical stimulation of the peripheral nervous system has long been known to influence lower urinary tract symptoms (LUTS) and perception of pelvic pain, whether delivered transcutaneously or by implanted devices. Historically, stimulation has been applied using anal, vaginal, bladder wall and cutaneous electrodes. In the modern era, anal and vaginal stimulation probes have been used to treat stress incontinence, while transcutaneous electrical nerve stimulation (TENS) has been successfully used to treat chronic pain. While treating such patients, investigators observed that electrical stimulation also had a beneficial effect on urinary urgency and urge incontinence.[2,3] Both anogenital and transcutaneous stimulation techniques have since been used to treat bladder overactivity. However, the short hangover effect, combined with the intensity of the treatment schedules themselves, have prevented widespread acceptance of these non-invasive techniques.

A more invasive approach using direct electrical stimulation of the third (and sometimes fourth) sacral nerves was first described experimentally in 1988[4] and is now the most prominent and well established of the so-called neuromodulation techniques. In contrast to the non-invasive methods, sacral nerve neuromodulation uses continuous stimulation and close nerve contact. This requires surgical implantation of a pulse generator and electrode.

Theoretical basis of sacral neuromodulation

The aim of sacral neuromodulation is to relieve bladder symptoms by rebalancing micturition control. However, the exact neurophysiological basis for this action is still unclear. Everyday clinical experience shows that bladder contractions can be suppressed by external sphincter and pelvic floor contractions, and therefore it is not surprising that electrical stimulation of the sacral nerves causes bladder inhibition in both animals and man.[2,5] However, when mixed S3 nerves are stimulated at the level of the sacral foramina it is not always clear whether therapeutic neuromodulation is the result of direct activation of the sensory nerves, or indirectly by activation of the striated external sphincter and pelvic floor muscles leading to reflex detrusor relaxation. Both mechanisms have been considered and researchers now conclude that it is the afferent pathways, causing inhibition at either spinal or supraspinal level, which play the crucial role.[6-8] The most direct evidence supporting an afferent mechanism comes from the fact that neuromodulation effects can be demonstrated with stimulation of the (purely sensory) dorsal penile and clitoral nerves.[2]

Indications

The main indications for SNS are detrusor overactivity and female urinary retention as mentioned above. However, there is also some evidence that neuromodulation may be useful in patients with voiding disorders of neurological origin: it has been used successfully in patients with multiple sclerosis and incomplete spinal cord lesions.[9,10] However, the numbers of such reported cases are small. Painful bladder disorders, notably interstitial cystitis, have also been studied in small case series with some, but not all, investigators finding favourable responses.[11]

S3 sacral neuromodulation received FDA approval in the USA for the treatment of urge incontinence in 1997 and for urgency/frequency and non-obstructive urinary retention in 1999. However, within the UK current National Institute for Clinical Excellence (NICE) guidelines exist only for patients with urge/frequency syndrome and urge incontinence.[1]

Pre-operative patient work-up

All patients who are considered for sacral neuromodulation should have their diagnosis defined as clearly as possible by urodynamic assessment. They should have undergone rigorous trials of conservative treatments such as lifestyle modification, pelvic floor exercises and anticholinergic therapy. It is also important to document the severity of patient symptoms using frequency/volume charts which document fluid intake and urine output over several days.

Not every patient will gain benefit from sacral neuromodulation and it is now accepted practice that every patient considered for this technique should undergo a trial period of temporary stimulation known as percutaneous nerve evaluation (PNE). The test electrode is placed in either the right or left S3 posterior sacral foramen using local anaesthesia. Surface markings identify the site of the posterior sacral foramen and a hollow needle is used to allow the electrode to be threaded into position. Correct positioning of the electrode is determined by both motor and sensory responses. Once well positioned, the temporary electrode is held in place with an adhesive dressing and an external pulse generator provides stimulation for three to five days. The patient provides subjective information regarding their response to the PNE, while objective data comes from accurately completed frequency/volume charts.

Only those patients who gain significant benefit from the PNE proceed to neuromodulator implantation. The PNE is generally considered successful when there is at least 50% improvement in the main voiding symptom. Although results vary between studies in the literature in general approximately 50% of patients will respond well to the trial stimulation and go on to receive a definitive sacral neuromodulator implant.

The implant technique

Implantation of a sacral neuromodulator is performed under either general or local anaesthesia. The original open surgical approach to the sacrum[12] has been superseded by a minimally invasive percutaneous alternative.[13] A quad electrode with four independent stimulation electrodes is positioned under radiological control. Once in place, an outer sheath is removed and plastic tines spring out and fix the assembly in place (Figure 1). The electrode is tunnelled to a subcutaneous pocket in the upper outer quadrant of the buttock area where the pulse generator is implanted (Figure 2).

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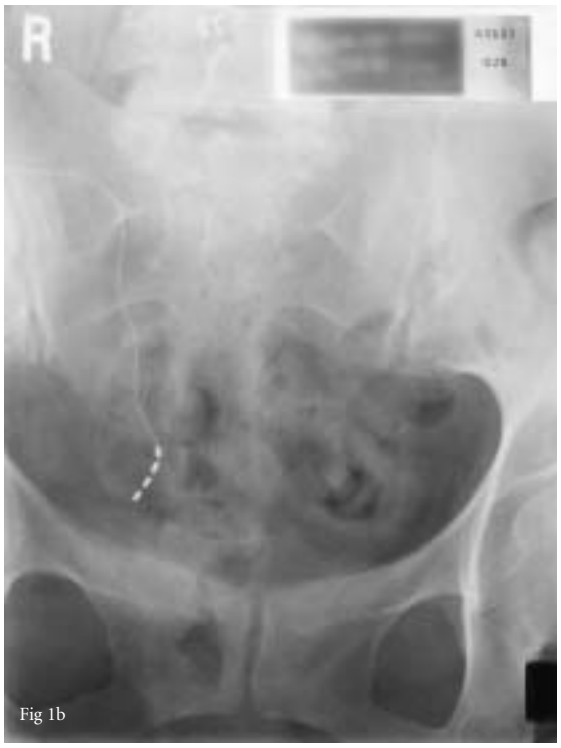
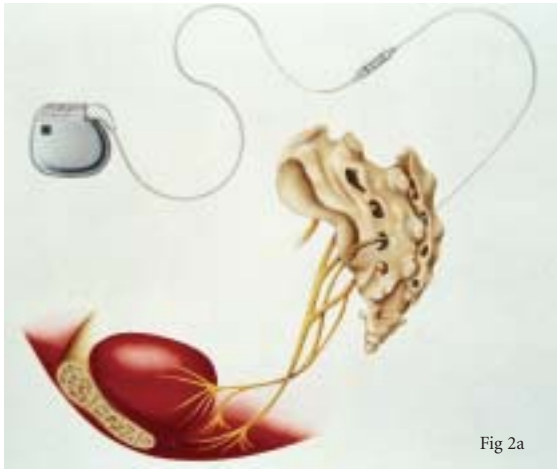


Figure 1. (a) The tined lead.
(b) X-ray showing the tined lead in position.



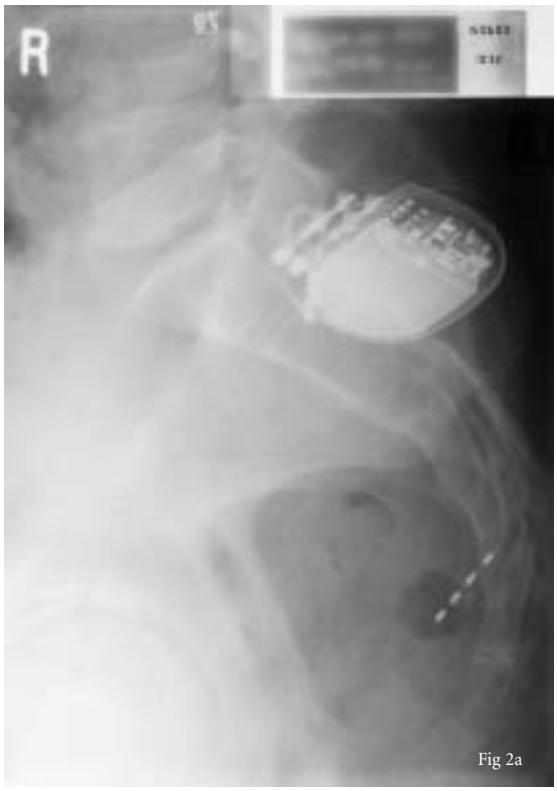


Figure 2: (a)The sacral neuromodulation circuit.
(b) X-ray showing the neuromodulation circuit in situ.

A key feature of the technology is that the pulse generator can be adjusted using an external computer and telemetry link. The system is extremely flexible and familiarity with its options and capabilities is essential; successful initial programming and subsequent adjustment is critical to the success of an implant programme.

Results and complications

Efficacy data from both randomised controlled trials and case series studies show that about 70% of the patients who received sacral neuromodulators for urge/frequency and urge incontinence became dry or showed improvement in their main incontinence symptoms.[1,14-16] This compared with 4% in the control groups in randomised studies. Fewer episodes of leakage, fewer pads used and fewer voids per day were also reported post-implantation. The data concerning female patients with non-obstructive urinary retention are less extensive but shows that 69% eliminated catheterisation at six months and a further 14% had a 50% or greater reduction in the catheter volume per catheterisation.[17]

There is no evidence that the safety profile for sacral neuromodulation differs according to patients' clinical indications for implantation. Overall surgical revision rate is approximately 33%. The most common complications are pain (24%), lead migration (16%), wound problems (7%), adverse effect on bowel function (6%), infection (5%), and generator problems (5%). 15% of patients require replacement or relocation of the implanted pulse generator and some (9%) have required permanent explantation.[1]

Over the past eight years 55 patients with a variety of lower urinary tract dysfunctions have received permanent SNS implants at our centre. Our experience in these patients largely mirrors that reported in the literature, although we believe that medium and long-term benefit will be achieved in about 60% of patients if one is dealing with highly symptomatic subjects. One of the major problems that we encounter is that there is a group of patients whose symptoms return within the first few months after implantation; this relapse occurs despite the system continuing to produce typical sensory and motor responses for S3 stimulation and is resistant to reprogramming efforts. It is our belief that this picture represents central nervous system adaptation to the stimulus and this might be analogous to the loss of efficacy that can be seen when neural stimulators are used to treat chronic pain.

Conclusion

Sacral neuromodulation is an exciting and valuable technique which has the ability to transform the quality of life of some patients with severe LUTS which are refractory to more conservative measures. The simplicity of the surgical technique and its associated safety are key issues for patients who are considering this form of treatment and set it apart from alternative approaches such as augmentation cystoplasty. The widespread adoption of SNS in the UK remains hampered by funding and cost issues (each implant costs in the order of £6,750). However, we feel that its proven utility and the lack of acceptable alternative treatment options should lead to the establishment of regional centres which would provide a neuromodulation implant service.

There is every indication that neural stimulation will become an important modality in the treatment of some patients with LUTS. However, future research and technological developments are likely to demonstrate that current practice will come to be seen as the beginning of an era rather than the definitive delivery of this form of therapy.

References

1. Brazzelli M, Murray A, Fraser C, Grant A. *Systematic review of the efficacy and safety of sacral nerve stimulation for urinary urge incontinence and urgency-frequency.* Aberdeen: Review Body for Interventional Procedures; 2003. Commissioned by the National Institute for Clinical Excellence. Available from: www.nice.org.uk/ip082systematicreview
2. Craggs M, McFarlane J. *Neuromodulation of the lower urinary tract.* Experimental Physiology 1999;84:149-160.
3. Thon WF, Baskin LS, Jonas U et al. *Neuromodulation of voiding dysfunction and pelvic pain.* World J Urol 1991;9:138-141.
4. Tanagho EA, Schmidt RA. *Electrical stimulation in the clinical management of the neurogenic bladder.* J Urol 1988;140:1331-1339.
5. Bemelmans BLH, Mundy AR, Craggs MD. *Neuromodulation by implant for treating lower urinary tract symptoms and dysfunction.* Eur Urol 1999;36:81-91.
6. Malaguti S, Spinelli M, Giardiello G et al. *Neurophysiological evidence may predict the outcome of sacral neuromodulation.* J Urol 2003;170(6, Part 1 of 2):2323-2326.
7. Groen J, Bosch JLHR. *Neuromodulation techniques in the treatment of the overactive bladder.* BJU Int 2001;87:723-731.
8. Brubaker L. *Electrical stimulation in overactive bladder.* Urology 2000;55(supp 5A):17-23.
9. Bosch JLHR, Groen J. *Treatment of refractory urge urinary incontinence with sacral spinal nerve stimulation in multiple sclerosis patients.* Lancet 1996;348:717-719.
10. Bosch JLHR, Groen J. *Neuromodulation: urodynamic effects of sacral (S3) spinal nerve stimulation in patients with detrusor instability or detrusor hyperflexia.* Behav Brain Res 1998;92:141-150.
11. Comiter CV. *Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study.* J Urol 2003;169(4):1369-1373.
12. Siegel SW. *Management of voiding dysfunction with an implantable neuroprosthesis.* Urol Clin North America 1992;19(1):163-170.
13. Spinelli M, Giardiello G, Gerber M et al. *New sacral neuromodulation lead for percutaneous implantation using local anaesthesia: description and first experience.* J Urol 2003;170(5):1905-1907.
14. Schmidt RA, Jonas U, Oleson KA. *Sacral nerve stimulation for the treatment of refractory urge incontinence.* J Urol 1999;162:352-357.
15. Hassouna MM, Siegel SW, Lycklama a Nijeholt AAB et al. *Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicentre study on efficacy and safety.* J Urol 2000;163:1849-1854.
16. Spinelli M, Bertapelle P, Cappellano F et al. *Chronic sacral neuromodulation in patients with lower urinary tract symptoms: results from a national register.* J Urol 2001;166:541-545.
17. Jonas U, Fowler CJ, Chancellor MB et al. *Efficacy of sacral nerve stimulation for urinary retention: Results 18 months after implantation.* J Urol 2001;165(1):15-19.

Deep Brain Stimulation for Post Traumatic Tremor

Introduction

After severe head injury a significant number of survivors will suffer from crippling movement disorders of which tremor is particularly disabling. In a survey of 289 severely head injured children significant tremor was noted in 45% within 18 months of follow up. However, in half the cases the tremor improved with time.[1]

In those patients with severe post traumatic tremor one common finding is of lesions in the projections from the cerebellum to the thalamus typically in the mid brain.[2] The tremors are of a violent nature and often affect the shoulder and arm. The shoulder tremor is usually of a wide displacement rendering the patient unable to do anything and can also make nursing virtually impossible.

Medical therapy is rarely helpful but it is worth trying L Dopa in all such patients as occasionally there are some responders.[3] However, in such patients surgery is the best hope of alleviation.

In the past, lesioning the thalamus was the therapy of choice.[4] Although the results reported have been good there are many disadvantages. In an injured brain, to cause further damage by a lesion runs the risk of high side effects, also many such patients may have bilateral tremor and bilateral lesions would be at high risk particularly to speech and swallowing. We therefore feel that deep brain stimulation is the treatment of choice.

Patient selection

People with head injuries will also quite commonly have problems with ataxia or inco-ordination in addition to tremor. This will affect the response to surgery which will only help tremor. To better select candidates for surgery we have used visually guided tasks.

VISUALLY GUIDED WRIST RAMP TRACKING TASK

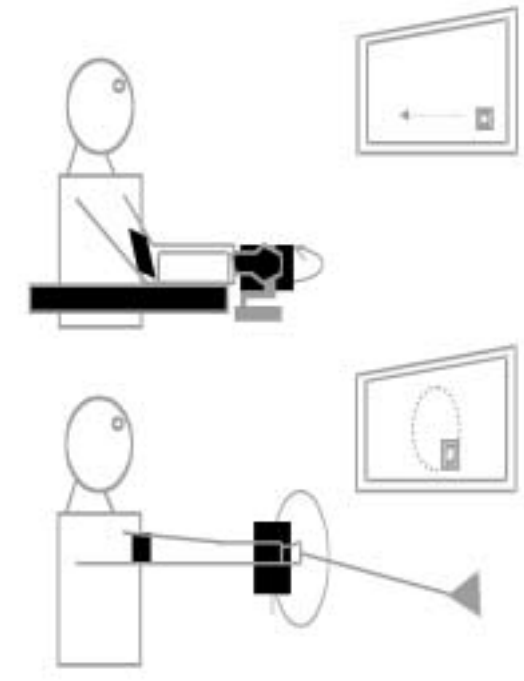


Figure 1: Wrist tracking (top), shoulder tracking below
As illustrated (Fig 1), patients are sat comfortably in front of a screen and use a joy stick to track a target moving across the screen. Movements of the forearm for distal tremor and whole arm for shoulder tremor can be recorded. We found that patients with a distal tremor with a single frequency responded better to thalamic surgery targeted at the VOP nucleus than patients with irregular jerky movements. Proximal single frequency tremor responds to stimulation deeper in the zona incerta.

Case report

We illustrate this with the case of a man aged 26 years. At the age of 18 years he was hit by a car suffering severe head and chest injuries. He was left with a right hemiparesis although the left side was functional. 12 months after his injuries he began to develop tremor of his left arm which progressed to a severe almost ballistic movement disorder, at which time, he was referred for consideration of deep brain stimulation. An MRI scan of his brain showed a lesion of the left cerebellar peduncle consistent with his symptoms.

He underwent visual guided tracking which showed there was a tremor with frequency of 5 Hz (Fig 2). He was then offered surgery and a right VOP/ZI electrode was implanted stereotactically (Fig 3) with good suppression of the tremor during the operation (Fig 2).

He remains well, with functional use of his left arm. He is able to feed himself, drink but unable to perform fine tasks two years after surgery.

Conclusions

Post traumatic tremor is an extremely disabling condition and is generally resistant to medical therapy. We feel that carers of such patients should seek help from specialist centres for consideration of deep brain stimulation.

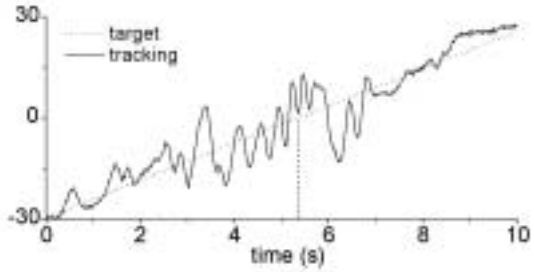
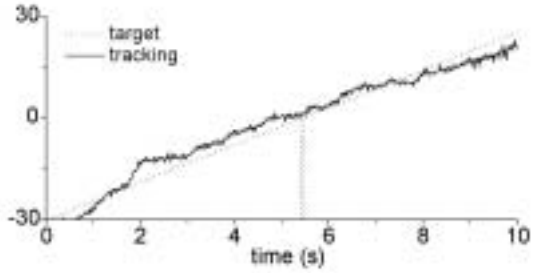


Figure 2: Above - Preoperative tracking. Below - Post-operative tracking. The traces from the visual guided tracking task illustrates the virtual loss of tremor after deep brain stimulation.



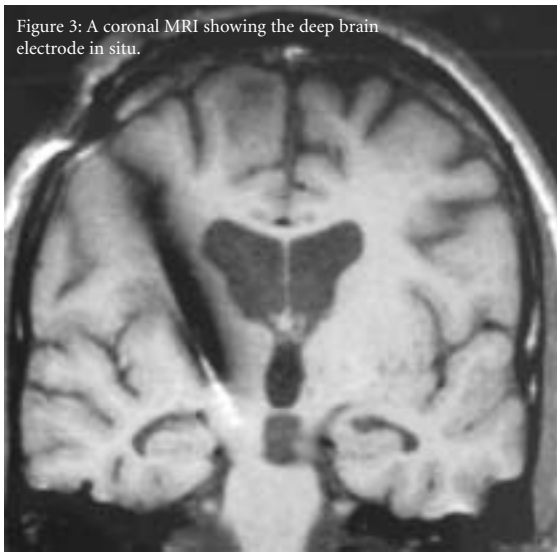


Figure 3: A coronal MRI showing the deep brain electrode in situ.

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References

1. Johnson SL, Hall DM. *Post-traumatic tremor in head injured children.* Arch Dis Child. 1992 Feb;67(2):227-8.
2. Harmon RL, Long DF, Shirtz J. *Treatment of post-traumatic midbrain resting-kinetic tremor with combined levodopa/carbidopa and carbamazepine.* Brain Inj. 1991 Apr-Jun;5(2):213-8.
3. Krauss JK, Wakhloo AK, Nobbe F, Trankle R, Mundinger F, Seeger W. *Lesion of dentatothalamic pathways in severe post-traumatic tremor.* Neurol Res. 1995 Dec;17(6):409-16.
4. Marks PV. *Stereotactic surgery for post-traumatic cerebellar syndrome: an analysis of seven cases.* Stereotact Funct Neurosurg. 1993;60(4):157-67.

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The Use of Tetrabenazine in Movement Disorders

Introduction

Tetrabenazine (TBZ) is a relatively safe and effective treatment for a wide variety of hyperkinetic movement disorders, particularly tardive dyskinesia (TD) and chorea. It has been subject to a number of studies including double blind placebo controlled crossover trials, although there have been no randomised controlled trials and no studies in patients with pre-existing depression.

The mechanism of action of tetrabenazine

TBZ is a synthetic benzoquinolizine derivative[1] which binds to vesicular monamine transporters (VMATs). Monoamines are concentrated from the cytoplasm into vesicles by VMATs (Figure). The transporters exchange protons for monoamines, using a proton electrochemical gradient generated by a vacuole ATP-dependent H^+ pump.[2,3] Many compounds bind to VMATs but three drugs bind selectively: TBZ, reserpine (from the Indian *Rauwolfia* plant) and ketanserin.[4] Two human isoforms of VMAT exist and have been cloned; $VMAT_1$[5] and $VMAT_2$.[6] $VMAT_2$ is located predominantly in the brain and in sympathetic neurones, and $VMAT_1$ in peripheral endocrine and paracrine cells.[7] TBZ binds with high affinity to $VMAT_2$ but with low affinity to $VMAT_1$.[8] Reserpine binds with different characteristics and, on the basis of displacement studies, it has been proposed that they bind to the same site on the VMAT but to different conformations.[9] Reserpine binds irreversibly whereas TBZ displays reversible binding. TBZ thus inhibits the uptake of monoamines into synaptic vesicles and so diminishes their output at synapses.

TBZ additionally blocks postsynaptic dopamine receptors.[10,11] Despite this, there have been no reports of TD, thus conferring significant advantages over neuroleptics in the treatment of hyperkinetic movement disorders.

Pharmacokinetics

TBZ has a low and erratic bioavailability and is metabolised by first pass metabolism.[12]

Clinical use and adverse effects

Indications

TBZ has been used in a wide range of movement disorders and more recently as a positron emission tomography (PET) ligand.[13,14,15,16]

Case reports and open label studies

Many case reports and open label studies have reported benefits of TBZ.[17,18,19,20] For example, Ondo and colleagues in 1999, showed that scores on the Abnormal Involuntary Movement Scale (AIMS) were reduced by 54% in twenty patients with TD post TBZ administration.[26] Others, however, have described adverse effects, including oculogyric crises, retrocollis[21] and neuroleptic malignant syndrome.[22, 23, 24]

Retrospective studies

A recent, retrospective study showed that TBZ was moderately effective for a large variety of hyperkinetic movement disorders and highly effective for Huntington's disease (HD) chorea, and patients with facial dystonia and dyskinesia.[25] A retrospective chart review was conducted in three tertiary care centres and 118 patients were followed up for a mean of twenty-two months with the Clinical Global Impression of Change (CGIC) scale used to assess response to TBZ.

Cross-over studies

Several placebo controlled cross over studies have been described. McLellan, Chalmers and Johnson[27] in 1974 published the first double blind crossover trial of TBZ, thiopropazate and placebo, using ten patients with chorea, nine of whom had HD. Each phase of treatment lasted two weeks and assessment was clinical, cinematographic (videos watched by eight neurologists) and with manual dexterity tasks. The authors found that TBZ produced the most effective improvement of chorea. They noted that side effects could occur for the first time after several weeks of treatment.

Jankovic[28] in 1982 published a double blind crossover trial of TBZ versus placebo using nineteen patients with a variety of movement disorders. The trial design was similar and again, TBZ significantly reduced the patient's score on the hyperkinesia scale, particularly in patients with TD.

Long term data

Jankovic and colleagues have published open label long-term data on the use of TBZ.[29,30] In the more recent larger study,[29] 526 patients were treated with TBZ and 400 analysed. Among those who were not analysed, seventeen discontinued TBZ within the first two weeks of treatment due to intolerable adverse effects and fourteen discontinued due to lack of efficacy. Most patients had been tried on a variety of other medication but their symptoms were poorly controlled. The drug was

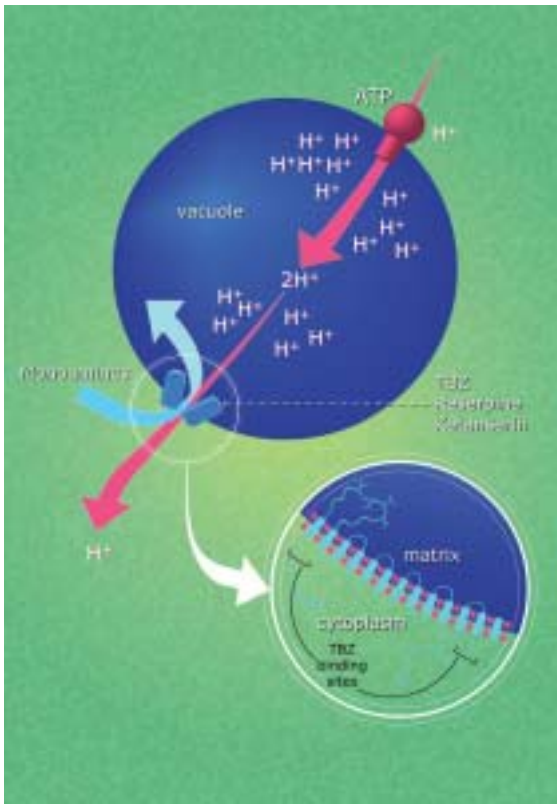

Figure: An ATP-dependent H^+ pump on the vesicle membrane generates a proton electrochemical gradient. This gradient drives the entry of cytoplasmic monoamines into the vesicle via the VMAT (monoamine/$2H^+$ exchange). TBZ binds reversibly and reserpine, irreversibly, to the VMAT, preventing the vesicular accumulation of monoamines. TBZ also blocks postsynaptic dopamine receptors. The VMAT has 12 transmembrane domains, with the C and N terminals in the cytoplasm, and three putative glycosylation sites in the vesicular lumen. TBZ binds to transmembrane domains I and II, and X and XII.

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Roger Barker is co-editor of ACNR, and is Honorary Consultant in Neurology at The Cambridge Centre for Brain Repair. His main area of research is into neurodegenerative and movement disorders, in particular Parkinson's and Huntington's disease. He is also the university lecturer in Neurology at Cambridge where he continues to develop his clinical research into these diseases along with his basic research into brain repair using neural transplants.

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started at 25 mg once a day and increased until the movement disorder was controlled or adverse effects appeared. Most patients determined their long-term response within the first six weeks of treatment. Responses were graded on a 5-point scale, evaluated by the same neurologist, patient and relatives, 1 being an excellent response. Mean follow up was 28.9 +/- 31.1 months. Patients with TD responded best (89.3% with a grade of 1) although in all groups but the HD patients, the score had reduced slightly at the end of evaluation (e.g. to 84.9% in the case of TD). 82.8% of HD patients scored 1, as did 62.9% of dystonia patients; but patients with Tourette's syndrome responded least well (57.4% scored grade 1).

Side effects were common (81.8%) although this may have reflected the author's strategy of increasing the dose to the maximum recommended, or until side effects were experienced, or complete control achieved. 36.5% of patients experienced drowsiness, 28.5% Parkinsonism, 15% depression, 11% insomnia, 10.3% anxiety, 2.3% acute dystonic reaction and lesser numbers of side effects including confusion, orthostatic hypotension, and hallucinations. Seventy-three patients reported no side effects at all, and all the side effects were dose related, reversible upon reduction of the dose or cessation of the drug (which occurred in 23% of patients). Interestingly, lithium enhanced the action of TBZ in 67.6% of the thirty-four patients in whom it was tried.

Kazamatsuri, Chien and Cole[17] noted in a long-term study in 1973, that the beneficial effect of TBZ may decline within a few days or weeks. Other long term studies have been published and, for example, shown benefit from TBZ with mild infrequent side effects.[18, 25]

Use of TBZ in HD

Most of the published evidence has shown that TBZ significantly improves TD and the chorea in HD. Over 90% of patients with HD will display chorea at some stage of the illness, particularly in the early phase but other more disabling movement disorders are common, and tend to develop later in the illness, displacing chorea.[31] The decision to treat chorea with TBZ must be balanced against the risk of developing more disabling Parkinsonism (albeit at high doses) and depression, both of which are common in HD. These effects can be ameliorated by TBZ withdrawal. Pragmatically, TBZ should be avoided in patients with pre-existing depression.

Anti-choreic medication, if indicated at all, should be tailored to the individual patient and antipsychotic medication, for example, may be a more appropriate choice in patients with concomitant psychiatric disorders.

References

1. Pletscher A, Brossi A, Gey KF. *Benzoquinoline derivatives: a new class of monoamine depleting drug with psychotropic action.* Int Rev. Neurobiol. 1962;4:275-306.
2. Kanner BI, Schuldiner S. *Mechanism of storage and transport of neurotransmitters.* CRC Crit. Rev. Biochem,1987;22:1-38.
3. Johnson RG. *Accumulation of biological amines into chromaffin granules: a model for hormone and neurotransmitter transport.* Physiol. Rev, 1988;68:232-307.
4. Scherman D, Henry JP. *Effect of drugs on the ATP-induced and pH-gradient-driven monoamine transport by bovine chromaffin granules.* Biochem Pharmacol. 1980 Jul 1;29(3):1883-90.
5. Liu Y, Peter D, Roghani A, Schuldiner S, Prive GG, Eisenberg D, Brecha N, Edwards RH. *A cDNA that suppresses MPP+ toxicity encodes a vesicular amine transporter.* Cell. 1992 Aug 21;70(4):539-51.
6. Erickson JD, Eiden LE, Hoffman BJ. *Expression cloning of a reserpine-sensitive vesicular monoamine transporter.* Proc. Natl. Acad. Sci. USA. 1992;89:10993-7.
7. Erickson JD, Schafer MKH, Bonner TI, Eiden LE, Weihe E. *Distinct pharmacological properties and distribution in neurones and endocrine cells of two isoforms of the human vesicular monoamine transporter.* Proc. Natl. Acad. Sci. USA. 1996;93:5166-71.
8. Henry JP, Scherman D. *Radioligands of the vesicular monoamine transporter and their use as markers of monoamine storage vesicles.* Biochem Pharmacol. 1989 Aug 1;38(15):2395-404.
9. Darchen F, Scherman D, Henry JP. *Reserpine binding to chromaffin granules suggests the existence of two conformations of the monoamine transporter.* Biochemistry. 1989 Feb 21;28(4):1692-7.
10. Login IS, Cronin MJ, MacLeod RM. *Tetrabenazine has properties of a dopamine receptor antagonist.* Ann Neurol. 1982 Sep;12(3):257-62.
11. Reches A, Burke RE, Kuhn CM, Hassan MN, Jackson VR, Fahn S. *Tetrabenazine, an amine-depleting drug, also blocks dopamine receptors in rat brain.* J Pharmacol Exp Ther. 1983 Jun;225(3):515-21.
12. Roberts MS, McLean S, Millingen KS, Galloway HM. *The pharmacokinetics of tetrabenazine and its hydroxy metabolite in patients treated for involuntary movement disorders.* Eur J Clin Pharmacol. 1986;29(6):703-8.
13. Scherman D, Desnos C, Darchen F, Pollak P, Javoy-Agid F, Agid Y. *Striatal dopamine deficiency in Parkinson's disease: role of aging.* Ann Neurol. 1989 Oct;26(4):551-7.
14. DaSilva JN, Kilbourn MR, Domino EF. *In vivo imaging of monoaminergic nerve terminals in normal and MPTP-lesioned primate brain using positron emission tomography (PET) and [11C]tetrabenazine.* Synapse. 1993 Jun;14(2):128-31.
15. Frey KA, Koeppe RA, Kilbourn MR, Vander Borght TM, Albin RL, Gilman S, Kuhl DE. *Presynaptic monoaminergic vesicles in Parkinson's disease and normal ageing.* Ann Neurol. 1996 Dec;40(6):873-84.
16. Gilman S, Frey KA, Koeppe RA, Junck L, Little R, Vander Borght TM, Lohman M, Martorello S, Lee LC, Jewett DM, Kilbourn MR. *Decreased striatal monoaminergic terminals in olivopontocerebellar atrophy and multiple system atrophy demonstrated with positron emission tomography.* Ann Neurol. 1996 Dec;40(6):885-92.
17. Kazamatsuri H, Chien CP, Cole JO. *Long-term treatment of tardive dyskinesia with haloperidol and tetrabenazine.* Am J Psychiatry. 1973 Apr;130(4):479-83.
18. Mikkelsen BO. *Tolerance of tetrabenazine during long-term treatment.* Acta Neurol Scand. 1983 Jul;68(1):57-60.
19. Bartels M, Zeller E. *Tetrabenazine (Nitoman) therapy of chronic spontaneous oral dyskinesia. A video- and EMG-controlled study.* Eur Arch Psychiatry Neurol Sci. 1984;234(3):172-4.
20. Watson MW, Skelton D, Jamali F. *Treatment of tardive dyskinesia: preliminary report on use of tetrabenazine.* Can J Psychiatry. 1988 Feb;33(1):11-3.
21. Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S. *Tetrabenazine induces acute dystonic reactions.* Ann Neurol. 1985 Feb;17(2):200-2.
22. Petzinger GM, Bressman SB. *A case of tetrabenazine-induced neuroleptic malignant syndrome after prolonged treatment.* Mov Disord. 1997 Mar;12(2):246-8.
23. Mateo D, Munoz-Blanco JL, Gimenez-Roldan S. *Neuroleptic malignant syndrome related to tetrabenazine introduction and haloperidol discontinuation in Huntington's disease.* Clin Neuropharmacol. 1992 Feb;15(1):63-8.
24. Ossemann M, Sindic CJ, Laterre C. *Tetrabenazine as a cause of neuroleptic malignant syndrome.* Mov Disord. 1996 Jan;11(1):95.
25. Paleacu D, Giladi N, Moore O, Stern A, Honigman S, Badarny S. *Tetrabenazine treatment in movement disorders.* Clin Neuropharmacol. 2004 Sep-Oct;27(5):230-3.
26. Ondo WG, Hanna PA, Jankovic J. *Tetrabenazine treatment for tardive dyskinesia: assessment by randomized videotape protocol.* Am J Psychiatry. 1999 Aug;156(8):1279-81.
27. McLellan DL, Chalmers RJ, Johnson RH. *A double-blind trial of tetrabenazine, thiopropazate, and placebo in patients with chorea.* Lancet. 1974 Jan 26;1(7848):104-7.
28. Jankovic J. *Treatment of hyperkinetic movement disorders with tetrabenazine: a double-blind crossover study.* Ann Neurol. 1982 Jan;11(1):41-7.
29. Jankovic J, Orman J. *Tetrabenazine therapy of dystonia, chorea, tics, and other dyskinesias.* Neurology. 1988 Mar;38(3):391-4.
30. Jankovic J, Beach J. *Long-term effects of tetrabenazine in hyperkinetic movement disorders.Neurology.* 1997 Feb;48(2):358-62.
31. Bates G, Harper P, Jones L. Huntington's disease (third edition). 2002.

Wendy Philips received an honorarium from Cambridge Laboratories for writing this article. However, the views expressed are those of the authors.

EDITOR'S CHOICE

Alcoholism is linked to disruption of the biological clock

Alcohol and drug addiction are complex disorders with environmental, drug-induced and genetic components. It is likely that multiple genes contribute to the development of an addictive disease. There is a growing body of evidence implicating circadian clock genes in mechanisms of drug-abuse related behaviours. The clock genes, including, *Per1, Per2, Cry1* and *Cry2*, underlie the ability of the biological clock to provide endogenous rhythms of physiological functions with a periodicity of 24 hours, without any environmental cues. These genes regulate oscillations in the levels of the transcription factor complex, CLOCK-BMAL1, in the suprachiasmatic nucleus of the hypothalamus. Such oscillations are generated by inhibitory feedback loops, in which the protein products of the clock genes down-regulate their own transcription. This study by Spanagel focuses on one such clock gene, *Per2*, and its role in alcoholism. They investigated a $Per2^{Brdm1}$ mutant mouse, in which the *Per2* protein is rendered non-functional. As a result, neurochemically these mutant mice exhibited serious disturbances in the glutamatergic system. A significant reduction in the astrocytic expression of the EAAT1 glutamate transporter, which clears glutamate from the synaptic cleft, produced a three-fold increase in extracellular glutamate in the ventral striatum. On a behavioural level, the $Per2^{Brdm1}$ mutant mice voluntarily consumed more alcohol compared to wild-type mice. On administration of acamprosate, an anti-relapse drug, the $Per2^{Brdm1}$ mutants showed a reduction in augmented extracellular glutamate levels in the nucleus accumbens and their alcohol consumption was normalised to below wild-type levels. This latter finding lends support to the theory that acamprosate acts by reducing the hyperglutamatergic state in alcohol-dependents. In humans Spanagel found that the *Per2* gene had an analogous function in the regulation of alcohol consumption. By sequencing the *Per2* gene of alcohol-dependents, they identified a haplotype of four gene variants associated specifically with the subjects with low alcohol consumption. In summary, Spanagel identifies glutamate to be the link between disruption of the *Per2* and increased alcohol consumption. It is proposed that glutamate alters the alcohol reinforcement processes in the brain, most likely via modulation of the dopamine reward pathways. In the clinic, acamprosate increases abstinence rates in just 10-20% of cases compared to placebo. Further research is required to determine if certain polymorphisms in the *Per2* gene confer a positive acamprosate response. Thus it would be possible to predict if a patient would benefit from this therapy. - ***LMS & SJT***

Spanagel R, Pendyala, Abarca C, Zghoul T, Sanchis-Segura C, Magnone M, Lascorz J, depner M, Holzberg D, Soyka M, Schreiber S, Matsuda F, Lathrop M, Schumann G, Albrecht U.
The clock gene Per 2 influences the glutamatergic system and modulates alcohol consumption.
NATURE MEDICINE
2005;11:35-42.

MOTORNEURON DISEASE: VEGF treatment of ALS

★★★ RECOMMENDED

Amyotrophic lateral sclerosis (ALS) is a paralysing progressive disorder that kills within five years of onset. It can present in one of two forms: the first is limb-onset ALS, which is characterised by initial muscle weakness of extremities and the second, more aggressive form is bulbar-onset ALS, in which patients have difficulty swallowing and breathing. This disease results from selective loss of motor neurons in the spinal cord and brainstem but the underlying pathogenic mechanism has not yet been identified. Furthermore, there is currently no cure for this devastating illness. To date, neurotrophin treatment of motor neuron degeneration, although rational, has proved unsuccessful in prolonging survival of ALS patients. Storkebaum and colleagues have now published very encouraging data indicating that vascular endothelial factor (VEGF) may be an effective therapy for ALS. In a mutant SOD1 transgenic rat model, which mimics the more severe bulbar-onset disease, they have found that continuous intracerebroventricular (i.c.v) delivery of recombinant VEGF improves motor performance compared to controls. When administered before onset of symptoms, onset of paralysis was delayed by 17 days and survival was improved by 22 days. They demonstrate that through their novel mode of delivery VEGF diffuses from the site of delivery in the CSF to spinal motorneurons, where it is anterogradely transported in axons. Whilst they show that VEGF prolongs motorneuron survival via a direct neurotrophic action, it is proposed that VEGF is a more effective therapy compared to other neurotrophic factors due to its additional angiogenic activity whereby increasing blood flow to the microenvironments of the brain and spinal cord. I.c.v. VEGF administration offers protection to cervical neurons in particular and thus represents an ideal therapy for bulbar-onset ALS and final stage limb-onset disease. This route of administration offers advantages, in that dosing and duration of treatment can be controlled. Whilst these results are highly promising, it must be noted that only a modest improvement in survival was observed when i.c.v VEGF was administered at the time of disease onset. - ***LMS & SJT***

Storkebaum E, Lambrechts D, Dewerchin M, Moreno-Murciano M-P, Appelmans S, Oh H, Van Damme P, Rutten B, Man W, De Mol M, Wyns S, Manka D, Vermeulen K, Van Den Bosch L, Mertens N, Schmitz, Robberecht W, Conway EM, Collen D, Moons L, Carmeliet P.
Treatment of Motorneuron Degeneration by Intracerebroventricular delivery of VEGF in rat model of ALS.
NATURE NEUROSCIENCE
2005;8:85-92.

COGNITIVE IMMUNOLOGY: The cortical control of thymic function

★★★ RECOMMENDED

There is a lot of very poor science in the field of neuro-endocrine-immune interactions and, accordingly, it is given a wide berth by most respectable laboratories. But no less a figure than Norman Geschwind drew attention in the 1980s, with Peter Behan, to the possible lateralisation of neocortical control over the immune system. Vahe Amassian, in New York, has been working up this story for more than a decade and now has produced a compelling animal study. Amassian's group studied rats in whom a permanent stimulating electrode had been placed over either tempero-parietal cortex. A permanent catheter in the right atrium allowed frequent blood sampling. A four hour stimulation of the left cortex increased circulating T and B lymphocyte numbers; whilst exactly the opposite occurred with stimulation of the right tempero-parietal cortex. This difference was most marked during periods of increased behavioural activity, such as at night. The effect of cortical stimulation was abolished by thymectomy or lesions of the cord above T7. These data suggest there is an anatomical pathway from the cortex through the

upper thoracic spinal cord to the thymus which controls lymphocyte generation. Furthermore, there is cortical lateralisation of function of this pathway…. But, what on earth does this mean? Frustratingly, the authors have not revealed whether there is any difference in phenotype of the newly generated lymphocytes. (I am sure they will have looked). Nor do they say if the altered lymphocyte numbers lead to any difference in immune responses. - ***AJC***

Moshel YA, Durkin HG, Amassian VE.

Lateralized neocortical control of T lymphocyte export from the thymus I. Increased export after left cortical stimulation in behaviorally active rats, mediated by sympathetic pathways in the upper spinal cord.

JOURNAL OF NEUROIMMUNOLOGY

2005;158:3-13.

NEUROIMMUNOLOGY: Inflammation in the brain is good for you

Much effort is spent suppressing inflammation in the brains of people with multiple sclerosis. Yet there has always been a kernel of sceptics who have cautioned that this may be throwing out the baby with the bathwater, because inflammation promotes remyelination. It is true that, in the 1990s, it was shown that remyelination is often found close to inflammatory lesions. And, experimentally, remyelination is impaired in the absence of T cells, Class II expression or the cytokines IL-1 and TNF-a. Yet who can really argue that the dominant effect of cerebral inflammation in multiple sclerosis is bad? Robin Franklin at the Vet School in Cambridge has studied the beneficial effects of inflammation by using a model in which demyelination is induced by a toxin, with any inflammation therefore being a secondary response. He has previously shown that depletion of macrophages from the animals, using clodronate-liposome, impaired oligodendrocyte remyelination. Now his group has adopted a different approach. They studied the effect of minocycline treatment on the repair of demyelinated cerebellar lesions induced by ethidium bromide. Minocycline is an antibiotic, but it also has multiple anti-inflammatory actions. These were confirmed in this study by the reduced activation of microglia (as shown by reduced Class II and Ox42 expression) in the minocycline-treated animals. The crucial results were that oligodendrocyte precursor numbers in the lesion were also reduced in these animals, accompanied by reduced histological remyelination. What makes this study so interesting is that minocycline is being trialled in the treatment of multiple sclerosis, having shown promising efficacy in suppressing EAE. Whilst minocycline might effectively reduce the immune attack on myelin (which of course is deliberately missing from the Franklin model), it might also reduce repair. Indeed might suppressed remyelination be a generic problem with anti-inflammatory treatments of multiple sclerosis? Having said which, an hour or two in a MS clinic soon brings home the indisputable point that leaving inflammation unchecked in the brain is not a good thing. Clearly the way forward is to dissect from the complex mechanisms of inflammation those that promote repair and those that are harmful. - ***AJC***

Li WW, Setzu A, Zhao C, Franklin RJ.

Minocycline-mediated inhibition of microglia activation impairs oligodendrocyte progenitor cell responses and remyelination in a non-immune model of demyelination.

JOURNAL OF NEUROIMMUNOLOGY

2005;158:58-66.

REHABILITATION: Functional electrical stimulation for stroke recovery

Treatment methods in rehabilitation can take decades to develop, test and become part of clinical practice. Functional Electrical Stimulation (FES) has been advocated by a passionate few as a method for improving walking since the 1960s. Over the last decade support has become more widespread. Sophisticated stimulating systems being researched for the benefit of people with spinal cord injuries have received attention in the press and it is becoming more common for therapists to use simple systems in clinical practice as a gait training tool after stroke. 2005 sees evidence, from a good randomised controlled trial, of the benefit of FES used as a treatment early after stroke. Yan, Hui-Chan and Li recruited 46 patients from a single centre in Hong Kong. The patients were within 3 weeks of stroke (mean 9 days) and only 5 were able to walk before the treatment. They were randomly allocated using a minimisation method to either standard rehabilitation plus FES, 30 minutes a day, 5 days a week for 3 weeks, or to a placebo group who had sham stimulation for 60 minutes a day plus standard rehabilitation, or to a control group who received standard rehabilitation only. The stimulation was carried out not during gait training but with the patient positioned on their side lying with the affected leg in a sling. Quadriceps, hamstrings, tibialis anterior and gastrocnemius were stimulated using an activation sequence that mimicked the gait cycle. Spasticity, isometric strength of the ankle dorsiflexors and plantar flexors and the amount of their co-contraction was measured along with walking ability weekly during the treatment period and also at a follow up 8 weeks after stroke. The assessor was blinded to the individual subject's intervention. Significantly greater improvements in impairment level outcomes were found in the FES group compared with the other two groups. Significantly more subjects in the FES group were able to walk after treatment than in the other two groups. These differences were evident at week 2, 3 of the treatment and 8 weeks after stroke. Patients in the FES group were also able to start walking in the hospital an average of two days earlier than those in the other two groups. This trial shows that sensorimotor stimulation requiring no active participation on the part of the patient but which mimics the gait cycle can help prepare patients for walking early after stroke. The adoption of FES as a treatment in clinical practice is restricted in part by the cost of stimulators and of training therapists in their use, but also by lack of evidence of its effect from good quality randomised controlled trials. The results of this study should increase the support for a treatment that has been forty years in the making. - ***AJT***

Yan T, Hui-Chan CWY, Li LSW.

Functional Electrical Stimulation improves motor recovery of the lower extremity and walking ability of subjects with first acute stroke.

STROKE

2005:36:80-5.

COGNITION: Better than one for the phrenologists

Most people acquire a 'collection' of one sort or another during their lives. Animals ranging from crows to hamsters may also accumulate non-food items, often shiny ones. Experimental lesion studies implicate a number of subcortical sites in this behaviour. In humans, however, it is thought that the drive to collect is modulated by cognitive processes presumably occurring in the cortex. Several clinical conditions are associated with maladaptive collecting behaviour including schizophrenia, obsessive-compulsive disorder and various dementias. Famously, after suffering frontal lobe trauma, Phineas Gage developed a 'great fondness' for animals and souvenirs. Collectors of cortical areas to which a function has been ascribed will enjoy the study by Anderson and colleagues in the January issue of *Brain*. The key data-sets are profiles of collecting behaviour, and maps of static cortical lesions in a group of 63 subjects. Nine were deemed to have abnormal collecting behaviour. Perhaps surprisingly, in view of the varied nature of collections in general, independent raters showed 100% agreement when deciding on the normality or otherwise of an individual's collecting behaviour. General neuropsychological testing confirmed that global impairment was not present; the 'collectors' scored somewhat better on tests of executive function and worse on tests of memory. The study draws upon an important resource, already used in a language study (*Damasio et al, 2004*). Structural MR images of all patients have been reconstructed such that the lesions are mapped to allow voxel-by-voxel comparison of overlaps. The resulting anatomical data can be analysed alongside any cognitive or behavioural indices. In this instance, maximal lesion overlap in 'collectors' versus 'non-collectors' was the mesial and inferior prefrontal region bilaterally, which included anterior cingulate cortex and extended to involve the frontal pole on the right. There was no evidence of damage in subcortical structures associated with acquisition behaviour in rodents. The inference is that activity in mesial prefrontal structures is necessary for regulation of collecting tendencies that originate in subcortical bioregulatory nuclei and that the normal operation of this multitiered system underlies the ubiquitous tendency of humans to create socially acceptable collections. Comparison of Anderson's paper and a single case study that showed impairment of mentalising abilities with bilateral anterior cingulate lesions (*Bird et al, Brain 2004, also reviewed in ACNR*) highlights the burgeoning literature on localisation of cerebral function and the need for care in its assimilation. - ***RRD***

Anderson SW, Damasio H, Damasio AR.

A neural basis for collecting behaviour in humans.

BRAIN

2005;128:201-12.

PARKINSON'S DISEASE: A stimulating new approach

The surgical treatment of Parkinson's disease (PD) has concentrated on either neural transplantation (*see ACNR 2(6)*) or deep brain stimulation (*ACNR 2(6)*). However there is an emerging realisation that many of the features of PD may occur through alterations of synchronised oscillatory neuronal activities in corticostriatal circuits. With this in mind, Drouot et al

posed the unusual hypothesis that direct interference of the basal ganglia associated motor cortical areas, by using implanted electrodes adjacent to the cortex, may actually lead to functional recovery in PD. This they investigated using the chronic MPTP primate model of PD, and a high frequency stimulating epidural electrode placed unilaterally on the motor cortex, but at an intensity below that required for producing muscle twitching in the contralateral muscles. Amazingly this approach worked, with a significant bilateral improvement in bradykinesia, in association with an increase in metabolic activity in the supplementary motor area (SMA) using FDG-PET – an area that is known to be underactive in the bradykinesia of PD. In addition there was a normalisation of firing rates from neurons within the output nuclei of the basal ganglia and a reduction in synchronised oscillatory activities between the cortex and basal ganglia. All of this was achieved without side-effects. Of course whether this is the whole story behind its actions is not known, but the authors attribute the success of their approach to the normalisation of aberrant neuronal activity downstream of the striatum. Whatever the mechanism, this approach is exciting and may lead to a radical rethink of the surgical treatment of movement disorders as well as the role of cortical stimulation in other basal ganglia related disorders. - ***RAB***

Drouot X, Oshino S, Jarraya B, Besret L, Kishima H, Remy P, Dauguet J, Lefaucheur JP, Dolle F, Conde F, Bottlaender M, Peschanski M, Keravel Y, Hantraye P, Palfi S.

Functional recovery in a primate model of Parkinson's disease following motor cortex stimulation.

NEURON

2004;44:769-78.

EPILEPSY: Out of Africa

In a region with a population approaching 1 billion, there are 75 EEG machines and 25 CT scanners, roughly equivalent to 1 scanner for the population of England and at any one time many are broken. Half the population are under the age of 15 and life expectancy is 45. Mortality below age 5 is 16.4%. Against this setting, with little health care infrastructure, simple epidemiological questions are difficult to answer. This review of epidemiology relied only on door-to-door surveys. The prevalence of epilepsy in two studies of villages 20km apart in Nigeria, with similar ethnic and age structures were 0.5% and 3.7% - population sizes were admittedly small. Reviewing all the studies from this part of the world the prevalence ranges from 0.5-7.4% with most studies falling out at 1-2% (cf Western populations around 0.5%). Some of these may be underestimates as young women especially have to hide their epilepsy in order to get married. There are less data on the mortality of epilepsy but in a small study in Ethiopia it has been estimated to be 3.16% (cf 1.64% without epilepsy) with status epilepticus and burns being the modes of death attributed directly to seizures. I imagine that SUDEP goes unrecognised in this society. Seizures start below the age of 20 in 60% of the population, but this may reflect the population structure of the region. Treatment (usually phenobarbital) is effective in this environment, but compliance is poor and may contribute to later relapse. In small studies where investigation has allowed epilepsy classification, 40% have focal seizures, half generalised seizures, usually from a focal onset and 9% were unclassifiable. Perinatal factors are important in the aetiology of epilepsy in all countries but are difficult to evaluate in this region as studies rely on personal recall by patients' mothers. The real significance of cysticercosis is difficult to establish as few patients will have a CT scan, but prevalence of seropositivity ranges is 0.3% in predominantly Muslim areas but much more in other regions. In a case control study from Burundi, an association was found with seizures but seropositivity was 35.1% of controls as well. Other postulated but unproven associations include malaria (the commonest cause of febrile seizures), filariasis and onchocerciasis. Eradication of Taenia solium could give a 50% reduction of epilepsy in this region. As in the history of health care in the developed world, a single public health care measure can do much more than thousands of doctors and prescriptions and is probably cheaper, but requires a more coordinated effort. - ***MRAM***

Preux PM and Druet-Cabanac M.

Epidemiology and aetiology of epilepsy in sub-Saharan Africa.

LANCET NEUROLOGY

2005;4:21-31.

MULTIPLE SCLEROSIS & DEVIC'S DISEASE: Defined by a new antibody

★★★ RECOMMENDED

A monophasic neurological disease characterised by bilateral optic nerve involvement and myelitis occurring in rapid succession was first described by Eugene Devic in the late 19th century. Since then a relapsing form of the illness has been identified and there has been much philosophising about whether this represents a variant of multiple sclerosis, or whether it is a distinct disease. To the cynics' "so what?" came the important rebuttal in the late 1990s from the Mayo clinic, that attacks of Devic's disease, but not multiple sclerosis, may respond to plasma exchange (*Keegan, M. Neurology 2002;58:143-6*). This discovery led the hunt for an antibody that might mediate Devic's… and here it is. Brian Weinshenker's group at the Mayo has managed the extraordinary feat of collecting serum from 45 patients with Devic's disease and 35 with "forme frustes" of the disease: recurrent transverse myelitis or optic neuritis. They compared these to serum from 22 people with classical multiple sclerosis, found an antibody and then tested it out in two other cohorts. They discovered that serum from most Devic's patients (33/45) contains a distinct immunoglobulin they called "NMO-IgG", that was found in only 2/22 multiple sclerosis controls and in higher proportions of those with recurrent transverse myelitis (14/27) or optic neuritis (2/8). NMO-IgG bound to mouse pia and subpia, outlined the Virchow-Robin space and microvessels in white and grey matter, and also to subependymal white matter and the subpial layer of midbrain. Co-labelling showed that the antibody bound to the abluminal face of microvessels and in extracellular matrix protein in pial and perivascular locations. These findings correlate nicely with the vasculocentric pattern of immunoglobulin and complement deposition seen in the spinal cords of people with Devic's. The crucial questions are: what is the molecular target of the antibody and why does it pick on the optic nerves and spinal cord? If the Mayo team know the answers, they are certainly not telling… - ***AJC***

Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG.

A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis.

LANCET

2004 Dec 11;364(9451):2106-12.

PARKINSON'S DISEASE: What you eat is important

There is no doubt that modifying the environment can have effects on neurological disorders and this has perhaps been most explored clinically in rehabilitation therapy and in the laboratory with enrichment of the animal environment. However whilst attempts to manipulate the environment for the good of the individual are well known, how this is achieved at the cellular level has been less well explored. In this paper, Maswood et al have shown that in MPTP treated monkeys, dietary caloric restriction (CR) had a significant effect on the toxicity of the MPTP on the nigrostriatal dopaminergic network such that it afforded a degree of protection which was accompanied by an improvement in motor deficits. These investigators then demonstrated that this CR had a significant effect of the levels of GDNF in the caudate nucleus – implying that this may be the explanation for the observed recovery. However, in PD the greatest area of dopaminergic loss is the putamen rather than the caudate nucleus – a structure that is more associated with the cognitive, than motor, deficits of PD. Furthermore patients with PD often have difficulty maintaining their weight because of the difficulties with swallowing coupled to the increased metabolic rates induced by the movement disorder of this condition. Thus recommending CR in this patient group is not straightforward. However this study once more highlights the complex relationship that exists between our environment (including diet) and the state of our brain in health and disease. A relationship that is worth remembering when you are trying to lose those extra pounds from 2004, through your 2005 New Year resolutions. - ***RAB***

Maswood N, Young J, Tilmont E, Zhang Z, Gash DM, Gerhardt GA, Grondin R, Roth GS, Mattison J, Lane MA, Carson RE, Cohen RM, Mouton PR, Quigley C, Mattson MP, Ingram DK.

Caloric restriction increases glial cell line derived neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease.

PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, USA.

2004;101:18171-6.

EPILEPSY: Stepping attacks

Unusual cases of epilepsy are curiosities but also give insights into the function of the brain. A 33-year-old man had a history of sudden falls. These were often precipitated by distractions such as unexpected loud noises or seeing a change in the floor material. His only symptom during the attacks was the sensation of loss of connection with his left lower limb. During the attacks, which were videoed, he would try to step over an obstacle with his right foot, but never his left foot, and then fall. Ictal scalp EEG revealed a midline 10-12Hz frontocentral discharge, lasting 1-3 seconds. He underwent intracranial

EEG and simultaneous EMG. The EMG showed no alteration in muscle activity or resting tone during attacks. Attacks were reproduced by stimulation of the right posterior parietal region and spontaneous discharges were also recorded from this area. The patient decided against resective surgery but underwent multiple pial transection, which was unsuccessful. The clinical manifestations of epilepsy never cease to amaze. I always ask myself in these sort of cases whether I would have thought of the diagnosis. - ***MRAM***

So EL and Schaüble BS.
Ictal asomatoagnosia as a cause for epileptic falls. Simultaneous video, EMG and invasive EEG.
NEUROLOGY
2004;63:2153-4.

EPILEPSY: Anticonvulsants in the garden

Valerian is a perennial, widely distributed in Europe and North America. It is distinctive by its unpleasant smell and taste, so should make a good medicine. It was probably first used in the treatment of epilepsy by Fabio Colonna (1567-1650) of Naples, who himself suffered from epilepsy. He searched for a herb to help him and wrote a classic work "Phytobasanos" in which he described the efficacy of Valerian for his own condition. Willis only cited Valerian as an ingredient in one of his anticonvulsant concoctions in his work "Pathology of the Brain and Nervous stock: On convulsive diseases". Tissot in the 1770's described it as the best drug available for epilepsy and other European noteworthies also used it with success, such that it was in popular usage in the 18th and 19th centuries. John Cooke of London wrote in 1823 that valerian had "very little power" but Robert Bentley Todd (1849) thought more highly of it. Soon after it was superseded by the bromides and was not mentioned by Gowers in his monograph in 1885. It was used in WWII to relieve the stress of air-raids in London and is now used as a nocturnal sedative. In this role there have been a number of clinical trials, including one comparing it favourably with oxazepam but none of these is very satisfactory technically. Among the chemical ingredients of the plant are valepotriates, which may yield isovaleric acid, chemically related to valproic acid. Valerian extracts contain GABA and also valerenic acid, which inhibits GABA transaminase. So when the nth AED fails and you and your patient don't know where to go, you might try the garden. - ***MRAM***

Eadie MJ.
Could Valerian have been the first anticonvulsant?
EPILEPSIA
2004;45:1338-1343.
(with help from http://ods.od.nih.gov/factsheets/Valerian.asp)

EPILEPSY: Fracture risk

In Denmark all fractures are recorded on a central register, providing a unique opportunity to identify risk factors. From 1977 only inpatients were recorded but from 1995 outpatients were included. Medications prescribed and bought are also registered centrally to enable reimbursement of patients. For AEDs the amount taken by each patient from 1996-2000 could also be calculated. This study was conducted as a case-control study with fractures as the outcome and AED use as the variable. A further analysis was conducted to take account of different seizure types including generalised tonic clonic and focal seizures, IGE absences and status epilepticus. From Jan 01 2000 to Dec 31 2000 there were 124,655 fractures and for each case, three age and gender-matched controls were selected from a national database. The following factors were associated with a slight but significantly increased risk of fracture: lower income; divorced or unmarried status; being out of work or retired; more regular GP visits or ever having taken corticosteroids. Not surprisingly factors associated with a considerably higher risk were previous fracture or use of any treatment for osteoporosis such as HRT or biphosphonates. 2.5% of patients who had sustained a fracture had epilepsy, and 5.7% were taking AEDs compared with 1.3% of controls with epilepsy and 2.9% taking AEDs; these were particularly spine (10.3%) and hip fractures (9.9%). Odds ratios for specific drugs were calculated and a dose-response was sought. An increased risk of fracture was associated with carbamazepine, oxcarbazepine, clonazepam, valproate and phenobarbitone, but only phenobarbitone was associated with an increased risk of spine fracture. The increased risk, as measured by an adjusted odds ratio, was modest (1.18 for carbamazepine and 1.79 for Phenobarbital, which had the greatest effect). A clear dose-response effect with duration of drug exposure ($P<0.01$) was seen only with carbamazepine and phenobarbital. This is a large study and important because it is population-based and likely to suffer little from failure of case ascertainment. A limitation of the study is the unknown duration of AED exposure before 1996; a reasonable hypothesis is that the longer a drug is taken the higher the risk of fracture. Also the study did not differentiate between epilepsy in remission and active epilepsy. Some other factors were not included such as smoking and alcohol history which impact on bone density and differ between epilepsy patients and controls. Nevertheless it provides evidence that there is a clear, if limited contribution to fractures in patients taking carbamazepine or phenobarbital. As evidence of this kind accumulates, we shall have to start to advise patients about bone protection, especially as we discharge them into the community on long-term treatment, without specialist follow-up. NICE guidelines also recommend bone densitometry for patients taking enzyme-inducing AED. -***MRAM***

Vestergaard P, Rejnmark L and Mosekilde L.
Fracture risk associated with the use of anti-epileptic drugs.
EPILEPSIA
2004;11:1330-7.

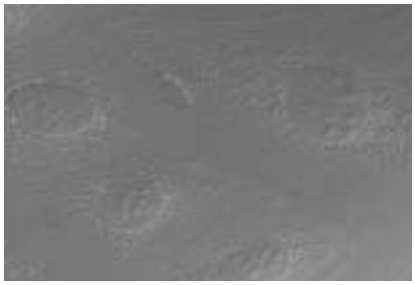
Motorised Stage and Ergo Controller for Eclipse 90i

Researchers can now view, manipulate and digitally capture their samples from a remote location with the Motorised Stage and Ergo Controller accessories for the Nikon Eclipse 90i. When combined with Nikon's Digital Imaging Heads and Digital Sight Camera systems, the user can adjust the focus, move the stage, switch observation techniques and capture images, as if they were seated in front of the microscope. This could be extremely beneficial if it is necessary to simultaneously perform other tasks at the PC, particularly if the microscope is to be sited in an isolated area.

Preference settings can also be recorded for each individual user. For simplicity and efficiency of operation, buttons on the front panel of the Ergo Controller can be assigned to the control functions that are most frequently used.

For more information Email discover@nikon.co.uk

New Standards in DIC Imaging



Nikon Instruments Europe is completely redesigning its DIC system for the Eclipse TE2000, 90i and 80i research microscopes. With enhanced resolution researchers can visualise minute structures with superb clarity and contrast. Three types of DIC are now available providing researchers a choice of standard, high contrast or high resolution DIC, allowing them to tailor imaging capabilities depending on their application.

The DIC prism is the key to creating the 3-D effect in DIC imaging. By making changes to the material composition of the prism, Nikon have been able to generate uniformly crisp images that demonstrate high contrast and high resolution – even at low magnifications.

The 3-D effect of DIC imaging can also be adjusted and optimised on Eclipse 90i and 80i upright models equipped with a rotatable stage by altering the shear direction of the DIC image. The result is sharper imaging revealing more structural information about the specimen under observation.

For more information Email discover@nikon.co.uk

New Era of Flexibility and Performance to Digital Fluorescence Microscopy

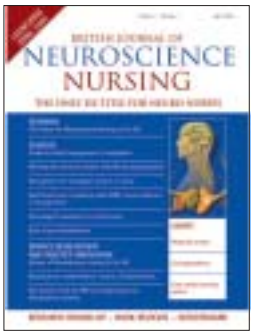
The Carl Zeiss Axio Imager is an innovative modular system for digital fluorescence microscopy, featuring advanced flexibility and application versatility. New IC2S objectives (Infinity Contrast & Colour Corrected System) optimise image quality and maximise contrast in all techniques while special fluorescence filters reduce exposure and image acquisition time by up to 50% for superior 3D imaging.

The 'Intelligent Stand' is the basis for each of the four models, ranging from manual entry-level to fully automated high-end systems. It incorporates an award-winning complex of software elements that automatically recognise components as they are added, such as filter wheels and objectives. In addition, the embedded "contrast manager" ensures simple changes between contrasting techniques. Standard interfaces permit communication via USB and TCP/IP, making integration into a network or complete remote control quick and simple. For the first time, defined interfaces in the reflected and transmitted-light beam paths allow coupling of additional optical components.

The vibration-free Imaging Cell is isolated within the stand for stable observation and unparalleled precision. An apochromatic fluorescence beam path ensures optimum colour correction over the entire wavelength range. Axio Imager also introduces special fluorescence filters with a significantly improved signal-to-noise ratio, which permit excitation intensity up to 70% higher than normal to reduce exposure times by up to 50%.

For further information, contact Carl Zeiss Ltd., PO Box 78, Woodfield Road, Welwyn Garden City, Hertfordshire, AL7 1LU.

British Journal of Neuroscience Nursing



This new journal, launching in April 2005, brings together clinical updates, research reports and policy developments in the rapidly evolving field of neuroscience nursing. It is an invaluable tool for nurses who want to keep up to date and improve their practice. Other members of the health care team will also find it of great benefit.

The journal addresses all aspects of neuroscience nursing in an intelligent, helpful and accessible way. Prevention, primary care, acute and critical care, rehabilitation and palliative care are all covered.

For information on how to subscribe to the only UK journal dedicated to neuroscience nursing please call the Freephone 0800 137 201.

To register an interest in contributing to the journal please contact the editor-in-chief, Sue Woodward, programme leader for critical care and post-registration education at Kings College London (sue.woodward@kcl.ac.uk) or the editor, Ruth Laughton (ruth@markallengroup.com).

Handheld Pulse Oximeter from Tyco Healthcare

The Critical Care Division of Tyco Healthcare has launched the OxiMAX NPB40, an enhanced version of the existing handheld Nellcor NPB-40 oximeter.

The OxiMAX NPB40 handheld pulse oximeter encompasses fifth generation OxiMax technology and is intended for non-invasive spot check measurement of functional arterial oxygen saturation (SpO2) and the pulse rates of adults, paediatric and neonatal patients. It can be used for attended monitoring in hospital, emergency, transport and mobile environments, as well as at home. It is compatible with all OxiMax sensors, and its event data is readable on other OxiMax monitors with the ability to display event data.

Compared to the earlier NPB-40 oximeter, the OxiMAX NPB40 features a 7-button configuration membrane panel, a real-time clock and a bi-directional IrDA capability. It is launched with an LCD display for SpO2 and BPM (beats per minute) readings, together with tactile feedback membrane buttons and a number of LCD indicators. These include alarm silence, pulse search, low battery, motion and print indicators.

For information please telephone the Tyco Healthcare customer care team on 01329 224306.

Residential Units for People with Acquired Brain Injury

Specialist care provider Voyage is to open the third of their residential units for people with acquired brain injury in May 2005. The purpose-built, eight place home in Dudley in the West Midlands offers a spacious, homely environment, and features ensuite rooms with kitchenette facilities.

The home is equipped to be able to support individuals with significant physical disabilities, including a specialist bathroom and the use of ceiling tracking, but will also admit people who only have cognitive needs. The emphasis of the care and support that will be provided will be on enabling people to increase their independence and pursue an individual programme of activities in the community, and there will be a high level of staffing to facilitate this.

Voyage's other units are in Gloucester and Burnley. The contact to discuss referrals is Steve Ball, Associate Development Director, on Tel. 01543 442540.

Tyco Healthcare ECG Electrodes serve all applications

The Critical Care Division of Tyco Healthcare manufacturers a range of solid hydrogel, stress testing, multipurpose and long-term monitoring electrodes, plus the liquid gel electrodes for up to 24-hour, short term monitoring.

The complete range of Tyco Healthcare ECG electrodes incorporate:

- A range of round, oval and square electrodes for easy application to a variety of anatomical sites.
- A broad scope of backing materials to suit all patient skin types, including foam, cloth, micropore, and vinyl.
- Patented gel formulas which exceed AAMI electrical standards.
- Non-sensitising and non-irritating adhesives, designed to be 'kind' to patients skin and minimise allergic reactions.
- Individual packaging and a two-year shelf life.

A comprehensive brochure on all the Tyco Healthcare ECG electrodes is available. It also features an indication chart, full list of monitoring accessories and a look at the latest TAB/SNAP Universal Connector. Complementary skin preparation products are also listed.

For more information please telephone 01329 224187.

Greater Dose Flexibility for Treatment of Schizophrenia

Bristol-Myers Squibb Pharmaceuticals Ltd and Otsuka Pharmaceuticals (UK) Ltd launched a 5mg dose of Abilify (aripiprazole) for the treatment of schizophrenia.

Dr Helen Millar, consultant psychiatrist at the Carseview Centre, Dundee said, "The availability of a 5mg dose of Abilify allows more flexibility in prescribing for the clinician and therefore treatment can be tailored to meet the needs of sensitive populations such as the elderly."

Abilify works in a new way to currently available antipsychotics. It is thought that an imbalance in dopamine may account for the symptoms of schizophrenia. Abilify is a dopamine system stabiliser. This means that it preserves or enhances dopaminergic neurotransmission where it is too low and reduces dopaminergic transmission where it is too high. This results in sustained efficacy against the positive (delusions, hallucinations and hostility), negative (lack of motivation and social interaction) and cognitive (memory loss and poor attention) symptoms of schizophrenia. Clinical trials have demonstrated the short- and long-term efficacy of Abilify in acute psychosis.

Clinicians now have the choice of further dose flexibility, with the availability of a 5mg once-a-day tablet.

For more information contact BMS on Tel. 020 8754 3519.

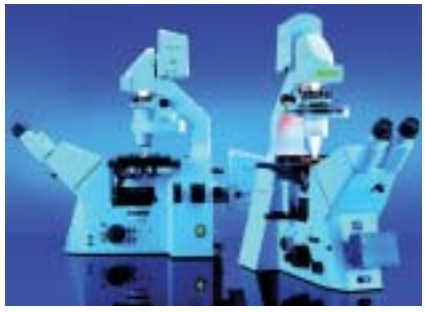
A Sourcebook of Psychological and Biological Research

Dyslexia, Reading And The Brain: Despite the wealth of literature available on the subject of dyslexia, there is little that explores the subject beyond a single theoretical framework. The need for a comprehensive review of the literature by both researchers and practitioners from different fields and theoretical backgrounds is the central motivation behind Dyslexia, Reading and the Brain. By combining the existing fragmented and one-sided accounts, Alan Beaton has created a sourcebook that provides the much-needed basis for a more integrated and holistic approach to dyslexia.

The comprehensive coverage and impartial approach mean that this sourcebook will prove an invaluable resource for anyone involved in study, research or practice in the fields of reading and dyslexia.

To order please contact Thomson Publishing Services, Tel. 01264 343 071, Email book.orders@tandf.co.uk

Carl Zeiss purchases P.A.L.M. Microlaser Technologies



Carl Zeiss has announced the acquisition of German-based P.A.L.M. Microlaser Technologies (PALM). The move brings together PALM's proprietary Laser Microdissection and Pressure Catapulting (LMPC) technology and Carl Zeiss' award-winning laser scanning microscopes.

"Carl Zeiss laser scanning microscopes are setting new standards in research imaging instrumentation," says Dr Ulrich Simon, head of the microscopy business group at Carl Zeiss and Chairman of the PALM supervisory board. "Our microscope stands are not just the keystone of our own integrated imaging solutions but the preferred choice for many partners, including PALM. The uniting of Carl Zeiss and PALM will open the way to new, highly integrated biomedical application solutions."

"Adding the superior global infrastructure of Carl Zeiss to the technological leadership of the PALM products will double our size over the next three years, even within a strongly competitive market," says Reinhard Müller-Späth, CEO of PALM. "This union is the logical consequence of a very successful partnership."

For further information, contact Carl Zeiss Ltd, PO Box 78, Woodfield Road, Welwyn Garden City, Hertfordshire, AL7 1LU.

DR. ALOIS ALZHEIMER

Aricept Significantly Improves Behavioural Symptoms[1-3]

Compared to untreated AD patients

Aricept® donepezil hydrochloride

BEFORE HIM,
THE DISEASE DIDN'T HAVE A NAME

BEFORE ARICEPT,
IT DIDN'T HAVE A REALISTIC TREATMENT

Aricept® donepezil hydrochloride

CONTINUING COMMITMENT TO ALZHEIMER'S

ABBREVIATED PRESCRIBING INFORMATION
ARICEPT® (donepezil hydrochloride)
Please refer to the SmPC before prescribing ARICEPT 5 mg or ARICEPT 10 mg. **Indication:** Symptomatic treatment of mild to moderately severe Alzheimer's dementia. **Dose and administration:** ***Adults/elderly;*** 5 mg daily which may be increased to 10 mg once daily after at least one month. No dose adjustment necessary for patients with renal impairment. Dose escalation, according to tolerability, should be performed in patients with mild to moderate hepatic impairment. ***Children;*** Not recommended. **Contra-Indications:** ***Pregnancy.*** Hypersensitivity to donepezil, piperidine derivatives or any excipients used in ARICEPT. ***Lactation:*** Excretion into breast milk unknown. Women on donepezil should not breast feed. **Warnings and Precautions:** Initiation and supervision by a physician with experience of Alzheimer's dementia. A caregiver should be available to monitor compliance. Regular monitoring to ensure continued therapeutic benefit, consider discontinuation when evidence of a therapeutic effect ceases. Exaggeration of succinylcholine-type muscle relaxation. Avoid concurrent use of anticholinesterases, cholinergic agonists, cholinergic antagonists. Possibility of vagotonic effect on the heart which may be particularly important with "sick sinus syndrome", and supraventricular conduction conditions. There have been reports of syncope and seizures - in such patients the possibility of heart block or long sinusal pauses should be considered. Careful monitoring of patients at risk of ulcer disease including those receiving NSAIDs. Cholinomimetics may cause bladder outflow obstruction. Seizures occur in Alzheimer's disease and cholinomimetics have the potential to cause seizures and they may also have the potential to exacerbate or induce extrapyramidal symptoms. Care in patients suffering asthma and obstructive pulmonary disease. As with all Alzheimer's patients, routine evaluation of ability to drive/operate machinery. No data available for patients with severe hepatic impairment. **Drug Interactions:** Experience of use with concomitant medications is limited, consider possibility of as yet unknown interactions. Interaction possible with inhibitors or inducers of Cytochrome P450; use such combinations with care. Possible synergistic activity with succinylcholine-type muscle relaxants, beta-blockers, cholinergic or anticholinergic agents. **Side effects:** Most commonly diarrhoea, muscle cramps, fatigue, nausea, vomiting, and insomnia. Common effects (>1/100, <1/10): common cold, anorexia, hallucinations, agitation, aggressive behaviour, syncope, dizziness, insomnia, diarrhoea, vomiting, nausea, abdominal disturbance, rash, pruritis, muscle cramps, urinary incontinence, headache, fatigue, pain, accident. Uncommon effects (>1/1,000, <1/100): seizure, bradycardia, gastrointestinal haemorrhage, gastric & duodenal ulcers, minor increases in serum creatine kinase. Rare (>1/10,000, <1/1,000): extrapyramidal symptoms, sino-atrial block, atrioventricular block, liver dysfunction including hepatitis. **Presentation and basic NHS cost:** Blister packed in strips of 14. ARICEPT 5 mg; white, film coated tablets marked 5 and Aricept, packs of 28 £68.32. ARICEPT 10 mg; yellow, film coated tablets marked 10 and Aricept, packs of 28 £95.76. **Marketing authorisation numbers:** ARICEPT 5 mg; PL 10555/0006. ARICEPT 10 mg; PL 10555/0007. **Marketing authorisation holder:** Eisai Ltd. **Further Information from/Marketed by:** Eisai Ltd, Hammersmith International Centre, 3 Shortlands, London, W6 8EE and Pfizer Limited, Walton Oaks, Dorking Road, Tadworth, Surrey KT20 7NS. **Legal category:** POM
Date of preparation: January 2002.

References: 1. Gauthier S, Feldman H, Hecker J, *et al. Curr Med Res Opin* 2002; **18** (6): 347-354. **2.** Holmes C, Wilkinson D, Dean C, *et al. Neurology* 2004; **63**: 214-219. **3.** Cummings JL, Donohue JA, Brooks RL. *Am J Geriatr Psychiatry* 2000; **8:2:** 134-140.

Eisai Pfizer

A735-ARI572-09-04